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- Dardiotis E, Fountas K, Dardiotti M, Xiromerisiou G, Kapsalaki E, Tasiou A, Hadjigeorgiou G. **Genetic Association Studies in Patients with Traumatic Brain Injury**. Neurosurgical focus. 2010;28(1):E9
- Dardiotis E, Dardiotti M, Hadjigeorgiou GM, Paterakis K. **Lack of association between the IL1A gene (-889) polymorphism and outcome after head injury**. Surg Neurol. 2006;66(3):334-5.
- Hadjigeorgiou GM, Paterakis K, Dardiotis E, Dardiotti M, Aggelakis K, Tasiou A, Xiromerisiou G, Komnos A, Zintzaras E, Scarneas N, Papadimitriou A, Karantanias A. **IL-1RN and IL-1B gene polymorphisms and cerebral hemorrhagic events after traumatic brain injury**. Neurology. 2005;65(7):1077-82.
- μ , , , μ , μ , μ μ μ . 2007, 14(2):59-67.

3. M. Dardioti, E. Dardiotis, K. Aggelakis, K. Paterakis, A. Komnos, A. Karantanas, A.Tasiou, G. Xiromerissiou, G. Hadjigeorgiou: **Interleukin 2 (+114) gene polymorphism and traumatic brain injury**. Sixteenth Meeting of the European Neurological Society, 27-31 May 2006, Lausanne, Switzerland. Journal of Neurology, Volume 253, Suppl.2, May 2006: II/53.

4. M. Dardioti, E. Dardiotis, K. Aggelakis, A. Komnos, A.Tasiou, K. Paterakis, G. Noulas, A. Papadimitriou, G.M. Hadjigeorgiou: **Interleukin 2 (-384) gene polymorphism and traumatic brain injury**. 2006 EFNS. European Journal of Neurology, Volume 13, Supplement 2, September 2006, p150.

5. E. Dardiotis, M. Dardioti, A. Komnos, K. Paterakis, G. Noulas, G. Xiromerissiou, K. Aggelakis, A.Tasiou, I. Gabranis, S. Ralli, A. Karantanas, A. Papadimitriou, G. Hadjigeorgiou: **Interleukin 6 (-174) gene polymorphism and traumatic brain injury**. Seventeenth Meeting of the European Neurological Society, 16-20 June 2007, Rhodes, Greece. Journal of Neurology, Volume 254, Suppl.3, May 2007: III/71

6. M. Dardioti, E. Dardiotis, K. Aggelakis, K. Paterakis, A. Komnos, A. Karantanas, A.Tasiou, G. Xiromerissiou, G. Hadjigeorgiou: **Interleukin 6 (-174) gene polymorphism and traumatic brain injury**. 2006 EFNS. European Journal of Neurology, Volume 13, Supplement 2, September 2006, p150.

7. M. Dardioti, E. Dardiotis, K. Aggelakis, K. Paterakis, A. Komnos, A. Karantanas, A.Tasiou, G. Xiromerissiou, G. Hadjigeorgiou: **Interleukin 6 (-174) gene polymorphism and traumatic brain injury**. 2006 EFNS. European Journal of Neurology, Volume 13, Supplement 2, September 2006, p150.

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Abstract	. 12
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-1 (IL-1)	. 70
-2 (IL-2)	. 84
-6 (IL-6)	. 92
	. 100
μ	. 101
μ	. 102
	. 108
μ	. 140
	. 166
	. 180

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 μ μ μ μ μ -
 μ μ μ μ μ
 μ μ IL-1 (-511C/T, rs16944), IL-1 (+3953C/T, rs1143634), IL-1 (-889C/T, rs1800587), IL-1RA (VNTR 2, rs2234663), IL-2(+114G/T, rs2069763), IL-2(-384 /G, rs2069762) IL-6(-174G/C, rs1800795).
 : μ 365 μ (60 [16.4%]).
 μ μ , μ μ μ
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 μ .
 μ DNA μ μ ,
 μ μ μ PCR/RFLP μ .
 Hardy-Weinberg μ Fisher exact test.
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 Bonferroni: μ μ μ
 p=0.007 (0.05/7=0.007)
 μ : μ
 μ μ IL-1 (-511C/T), IL-1 (+3953C/T), IL-1 (-889C/T), IL-2 (-384T/G) IL-6(-174G/C).
 μ μ IL-2(+114G/T)
 μ μ . μ ,

μ μ μ μ GCS 3-8 μ μ
 GCS 13-15 μ μ (μ [μ
 μ] 0.57 [0.38-0.80], $p=0.002$) μ
 μ μ μ (0.53 [0.31-0.81], $p=0.009$)
 μ μ μ (2.32 [1.18-5.12], $p=0.02$).
 μ μ IL-1RA (VNTR)
 μ 2 4.5 μ μ -
 μ μ (4.57 [1.67-12.96], $p=0.004$). μ μ -
 μ (0.26 [0.14-
 0.71], $p=0.003$). , μ 2 μ
 : GCS 3-8 μ
 GCS 9-12 (μ 0.32 [0.12-0.90], $p=0.030$ μ
 0.32 [0.16-0.83], $p=0.02$) GCS 3-8 μ
 GCS 13-15 (μ 0.37 [0.19-0.78], $p=0.02$ μ
 0.45 [0.25-0.91], $p=0.017$). , 6 μ ,
 μ 2 μ :
 μ 0.39 [0.19-0.89], $p=0.011$ μ μ 0.43 [0.19-
 0.86], $p=0.035$.
 μ μ
 IL-1 (IL-1 -889C/T, IL-1 +3953C/T, IL-1 -511C/T, IL-1RA VNTR) IV
 (1-1-2-2) μ μ
 (0.16 (0.05-0.51), $p=0.0005$) μ μ (0.40 (0.20-0.78),
 $p=0.0058$). , VIII (2-2-2-1) μ μ
 (9.79 (2.74-34.98), $p=2.64 \times 10^{-5}$),
 VI (2-1-1-1) μ μ μ 6 μ
 3.01 [1.59-5.69], $p=0.0004$).
 μ μ IL-2 (IL-2 +114G/T IL-2 -384T/G)
 II (2-1) μ μ (0.55
 (0.39-0.78), $p=0.00087$).
 μ μ : μ μ
 μ μ ,
 μ μ μ . ,
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 μ μ μ .

ABSTRACT

Introduction: Traumatic Brain Injury (TBI) triggers inflammatory processes the extent of which determines the degree of acute and chronic neuronal cell death and patient's clinical outcome. Interleukins, which are the main mediators of inflammation, were found to play a central role in the pathophysiology of TBI. We conducted a prospective study to investigate possible influence of genetic polymorphisms of the interleukin genes in the clinical severity, 6 months outcome and hemorrhagic events in patients with TBI. In particular, we tested the IL-1 (-511C/T, rs16944), IL-1 (+3953C/T, rs1143634), IL-1 (-889C/T, rs1800587), IL-1RA (VNTR, rs2234663), IL-2(+114G/T, rs2069763), IL-2(-384T/G), rs2069762) and IL-6(-174G/C, rs1800795) polymorphisms.

Patient-Methods: 365 (women=60 [16.4%]) prospectively recruited patients with TBI were evaluated. Initial neurological status and six-month outcome were assessed by means of the Glasgow Coma Score and Glasgow Outcome Scale respectively. Based on computed tomography findings at admission patients were stratified according to the presence and type of haemorrhagic event.

DNA was extracted using the salting out method, while SNPs genotypes were determined using standard PCR/RFLP methods

The Hardy–Weinberg equilibrium was assessed by means of the Fisher's exact test. For comparisons between categorical variables we used the χ^2 test. Multivariable logistic regression analysis was used to control for possible confounding factors. Analysis for dominant recessive and allele contrast models of inheritance was performed. Linkage disequilibrium between SNPs was examined and haplotype estimation was performed by an expectation-maximization algorithm. Control for multiple comparisons was performed using Bonferroni's correction for 7 polymorphisms. The level of significance (p) was equal to 0.007 ($0.05/7=0.007$).

Results: No statistically significant difference was found for IL-1 (-511C/T), IL-1 (+3953C/T), IL-1 (-889C/T), IL-2 (-384T/G) and IL-6(-174G/C) polymorphisms.

Allele T of IL-2(+114G/T) polymorphism was associated with more severe clinical presentation at admission. There was a significant association between patients with GCS 3-8 and those with GCS 13-15 when considering allele contrast model (odds ratios [confidence interval] 0.57 [0.38-0.80], $p=0.002$) and a trend for association for dominant model (0.53 [0.31-0.81], $p=0.009$) and recessive model of inheritance (2.32 [1.18-5.12], $p=0.02$).

Compared to noncarriers, IL-1RA allele 2 carriers had 4.5 times higher odds of having cerebral hemorrhages after TBI (4.57 [1.67-12.96], $p=0.004$). Similar results

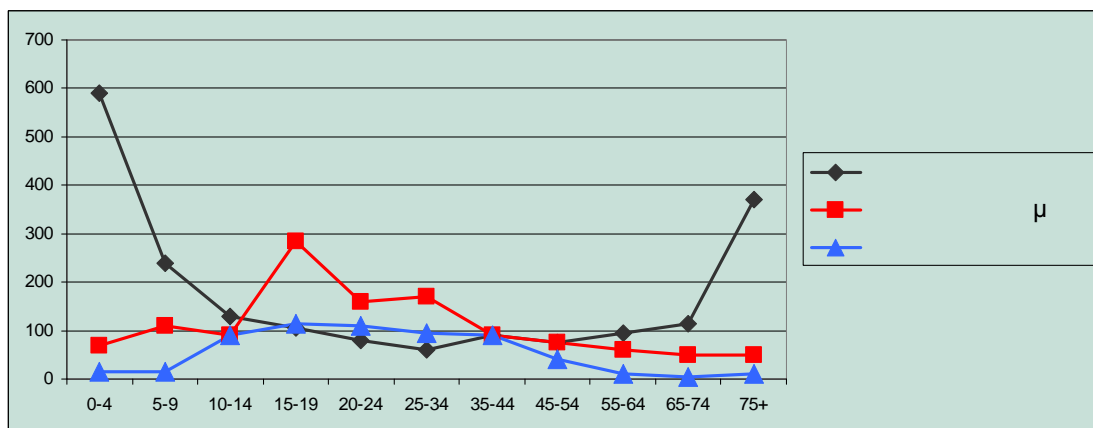
were obtained when comparing allele contrast frequencies (0.26 [0.14-0.71], $p=0.003$). In allele 2 carriers there was also a trend towards severe clinical presentation at admission: GCS at admission 3-8 vs GCS 9-12 (dominant genetic model 0.32 [0.12-0.90], $p=0.030$ and allele contrast model 0.32 [0.16-0.83], $p=0.02$) and GCS at admission 3-8 vs GCS 13-15 (dominant model 0.37 [0.19-0.78], $p=0.02$ and allele contrast model 0.45 [0.25-0.91], $p=0.017$). Finally, an opposite trend towards favourable 6 month's outcome was found for IL-1RA allele 2 (dominant model 0.39 [0.19-0.89], $p=0.011$ and allele contrast genetic model 0.43 [0.19-0.86], $p=0.035$).

Haplotype analysis of IL-1 SNPs (IL-1 -889C/T, IL-1 +3953C/T, IL-1 -511C/T, IL-1RA VNTR) revealed that haplotype IV (1-1-2-2) was associated with increased risk for more severe clinical presentation at admission [0.16 (0.05-0.51), $p=0.0005$] and hemorrhagic events [0.40 (0.20-0.78), $p=0.0058$]. Haplotype VIII (2-2-2-1) was associated with higher likelihood for milder clinical presentation at admission [9.79 (2.74-34.98), $p=2.64 \times 10^{-5}$], while haplotype VI (2-1-1-1) was linked to unfavourable 6month outcome [3.01 (1.59-5.69), $p=0.0004$]. Haplotype analysis of IL-2 SNPs (IL-2 +114G/T, IL-2 -384T/G) revealed that haplotype II (2-1) was associated with increased risk for more severe clinical presentation at admission [0.55 (0.39-0.78), $p=0.00087$].

Conclusions: Our study provides evidence of an implication of interleukins genetic polymorphisms in the clinical presentation at admission, 6 months outcome and hemorrhagic events of TBI patients. However, further studies are needed to confirm these associations and investigate underlying pathogenetic mechanisms.

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μ , 500.000
μ μ ,
75.000 μ 90.000 , μ μ
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μ μ [1].
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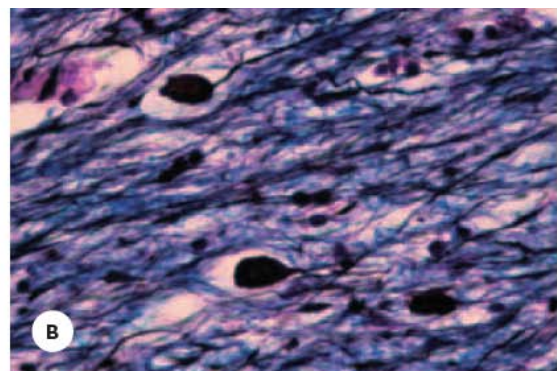
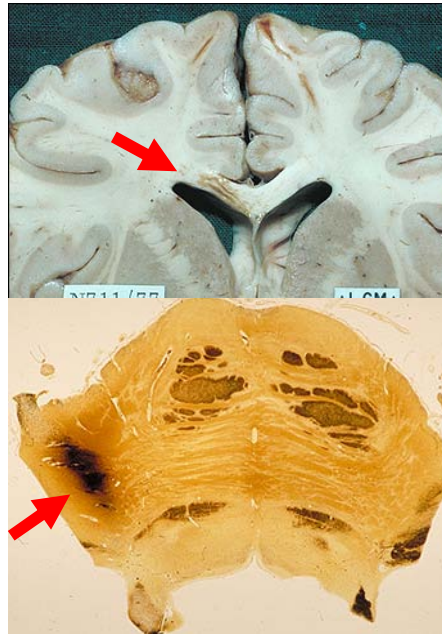
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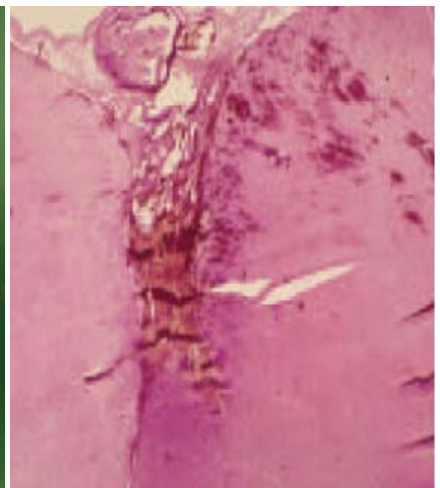
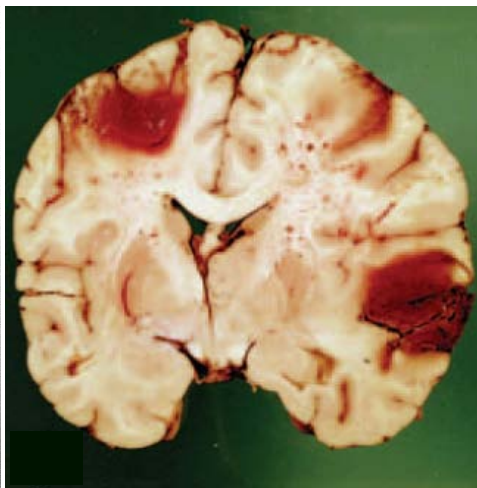
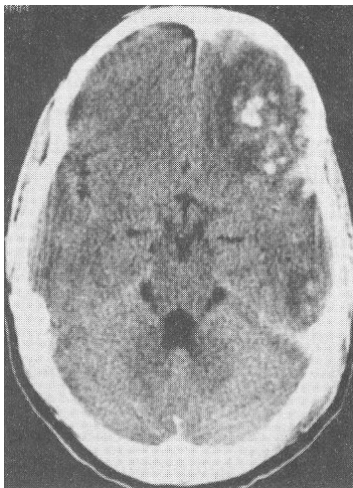


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[illegible]

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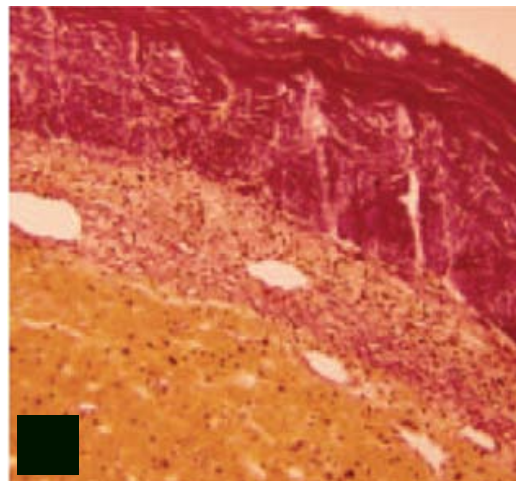

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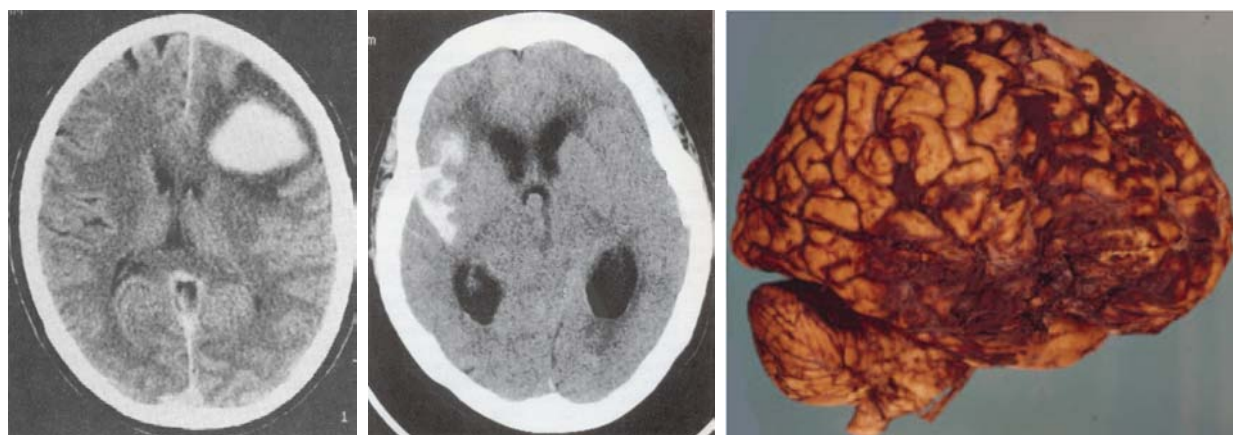
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(GCS: Glasgow Coma Scale)
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Becker . [7],
, μ : : 32%,
/ : 11%, μ / : 57%.
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μ μ .
μ μ μ
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μ
μ (punch-drunk boxer's syndrome), μ -
μ μ .
μ -
μ . μ
. 80%
μ 3 μ 4,
54% GCS 5 μ 7, 27%
8 μ 10 6% μ (11-
15).
μ
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μ , μ 65%
μ CT (mass lesion) 82% μ
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60%. μ 50% μ .
μ , (. .).
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μ , μ

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μ (μ , μ).

(μ μ) μ

μ :

μ μ

μ μ , μ ,

μ .

, μ (>40mmHg)

μ μ

μ μ - .

μ .

μ μ μ μ (cerebral perfusion pressure), μ 50 mmHg-150 mmHg. , μ μ μ , μ μ (μ μ μ μ) μ (μ μ μ μ). , μ μ 18 ml/100gm μ μ - μ [8]. , μ μ μ μ . , 3 μ μ , μ μ μ μ [9]. μ μ μ μ μ μ .

μ μ

μ μ . , μ μ μ μ . (hyperglycolysis), μ μ μ μ [10], μ μ μ μ [11, 12]. - - (N-acetyl-aspartate) μ . μ - μ μ [13, 14]. μ μ μ c (cytochrome c oxidase II) [15]. , μ μ μ μ - . , μ μ μ μ

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μ
 . μ μ μ μ
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 . μ (50
), μ
 μ [27].

 , μ (protease
 calpain) [28, 29]. μ - μ μ
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 [30, 31].

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 [32-35].
 μ NGF (nerve growth factor)
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 (vasogenic edema) (cytotoxic edema).To μ
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[38]. μ μ μ μ μ

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[39]. VEGF (vascular endothelial growth factor) μ μ μ μ

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(<90 mmHg) (PaO₂<60 mmHg).

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μ μ 50 mmHg. ,

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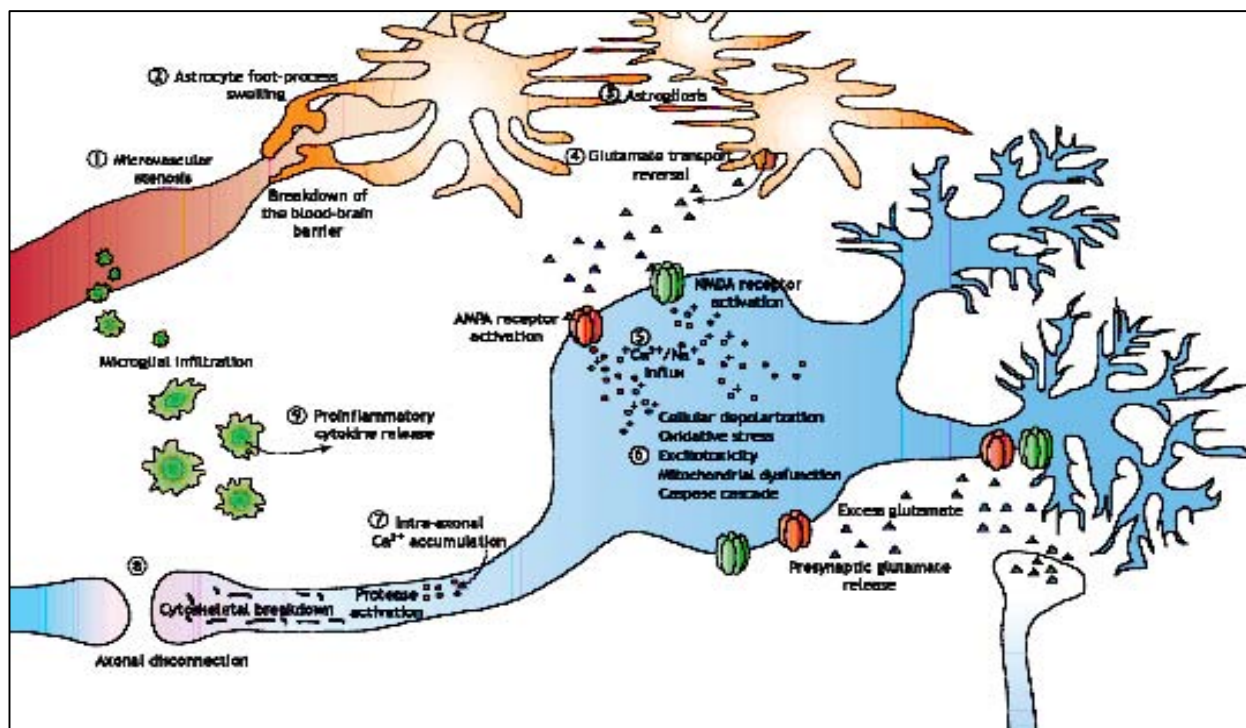
μ - μ [40]. ,

μ μ μ μ

μ μ . ,

μ μ (>60 mmHg)

μ [41]. μ μ μ μ



: μ μ μ
 μ (1) μ , μ -
 μ (2). -
 μ (" ") (3)
 μ (4)
 μ (excitotoxic) μ μ .
 μ , Ca (5) μ μ
 μ Ca Zn μ AMPA NMDA -
 μ (6), μ
 μ , Ca (7) μ μ μ
 μ (8). , μ μ μ
 μ , μ (9) -
 μ -
 [43].

ΚΡΑΝΙΟΕΓΚΕΦΑΛΙΚΗ ΚΑΚΩΣΗ

ΑΝΟΣΟΛΟΓΙΚΗ

- Ενεργοποίηση συμπληρώματος
- Απελευθέρωση κυτοκινών
- Απελευθέρωση χυμοκινών

ΜΗΧΑΝΙΚΗ

- Βλάβες αγγείων, κυττάρων, κυτταροσκελετού, αξόνων

ΧΗΜΙΚΗ

- Διατροφική ανεπάρκεια, διαταραχή ισορροπίας ιόντων, οξειδωτική βλάβη, κυτταροτοξικά

Δευτεροπαθής εγκεφαλική βλάβη

Πρωτοπαθής εγκεφαλική βλάβη

Νέκρωση

Συσσώρευση λευκοκυττάρων

Ατροφία εγκεφάλου
Απώλεια νευρώνων

Παρατεταμένη φλεγμονή

Απόπτωση

Απελευθέρωση κυτοχρώματος C
Ενεργοποίηση κασπασών
Έκφραση προ αποπτωτικών μεσολαβητών

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 (Ca^{2+} , ,
 , corticotropin releasing factor) -
 [51-54]. ,
 μ [55, 56] μ
 μ μ [57]. μ -
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), μ μ μ
 μ μ [58],
 (μ μ - μ , 1- μ [59], μ
 [60]) - μ [61]. , μ
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 μ μ
 μ μ μ μ
 μ μ (immediate early genes,
 IEGs) μ (heat shock proteins).
 IEGs μ - c-fos c-jun [62,
 63]. μ μμ
 μ . -
 NGF (Nerve Growth Factor) [64] -
 μ μ - μ (APP) [65]. , μ IEGs
 , c-fos c-jun, μ μ μ
 [66, 67]. IEGs (c-fos, c-jun, jun)
 μ μ μ (mRNA μ
) μ
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μ . μ 6h μ
μ , μ μ 12-24h μ
[73, 74]. , μ
μ . μ
μ μ μ μ .
μ μ , , ,
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μ . μ , IL-
1 GABA (g-aminobutyric acid)
[75]. , IL-1
μ μ μ (long-term potentiation) [76].
μ
μ
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μ μ μ .
-1 (IL-1)
IL-1 μ
[77, 78] [72]. μ
IL-1 (-
μ) μ μ
(mRNA μ 15min 1h) μ 6
[79, 80]. μ , μ
mRNA IL-1 15min μ
μ [81].

μ μ μ IL-1
 μ IL-1
 μ μ μ
 μ μ ,
[82].
IL-1 μ μ
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, μ μ / μ . , μ μ
[83]
IL-1 μ .
IL-1 μ μ μ IL-1 μ IL-1
, μ ,
IL-1 μ μ μ μ -
 μ [84]. μ
 μ μ IL-1 IL-1 μ [85,
86]. IL-1 , IL-1 ,
, μ , μ [87].

mRNA	μ , μ μ , μ , μ , μ , μ	Fan et al. [88](1995), Shohami et al(1997), Szaflarski et al[89] (1995) Yan et al. [90] (1992) Woodroffe et al. [91] (1991) Wang et al. [92] (1997) Rostworowski et al. [93] (1997) Herx et al. [94] (2000)
	, μ , μ , μ , μ , μ	Taupin et al (1993) Tchelingerian et al. (1993) Fagan and Gage [95] (1990) Yan et al. (1992) Wang et al. (1997)

: IL-1 μ μ
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IL-1 , IL-1RA IL-1 μ

μ .

μ μ μ

mRNA IL-1 mRNA IL-1RA 6h μ μ 5 μ

[96]. IL-1RA μ .

mRNA IL-1 μ .

IL-1 -

(IL-1RI) μ μ

(IL-1RII) 3h μ

[97].

-6 (IL-6)

μ

IL-6 6-8h μ [61].

μ μ μ μ μ μ , μ

IL-6 μ μ μ [98].

μ μ μ IL-6

(IL-6R) μ . μ -

IL-6 μ / . μ -

NGF

(nerve growth factor) [99]. , IL-6

μ μ .

IL-6 μ μ , μ , μ

μ μ [90, 100]. ,

IL-6 (IL-6R) .

$\mu\mu$ μ
 -1
 μ IL-1 $\mu\mu$
 μ [101]. , IL-1 μ
 μ [84, 102]. , in vivo, μ IL-1
 μ [103-105].
 μ IL-1 [103]
ICE (IL-1 converting enzyme) [106] μ
IL-1 μ μ μ , μ
 μ
[37]. , Knockout IL-1 IL-1
 μ
 μ . , μ
 μ μ [107].
IL-1RA
 μ IL-1RA μ
 μ [108, 109].
 μ IL-1RA [110] -
 μ ,
[111-113].
IL-1RA μ IL-1
 μ
[114]. μ , IL-1RA μ
 μ (fluid percussion injury)
[112]. μ μ , μ IL-1RA μ
 μ [109]. , IL-1RA
 μ [115].
 μ
 μ IL-1RA
[116].

IL-6

[117] μ . μ μ , μ

μ μ μ μ

μ . μ , Knockout

μ μ μ

IL-6 (wild type mice) [118].

μ IL-1 IL-18,
IFN- γ (Interferon-gamma). ,
 μ μ , μ μ
 μ [77, 119-121]. μ
 μ IL-18
[122, 123] μ . ' μ ,
 μ μ IL-18 μ -
 , IL-18BP (IL-18 binding protein). , μ IL-18BP
 μ μ μ . μ , μ
 μ IL-18 , μ
 μ μ μ [122].

IL-12 μ - μ ,
IFN- [124]. , μ
[125]. μ
 μ . , μ
IL-12 , μ
 , μ [126], [127],
[128]. , IL-12
 μ 14 μ μ , μ
 μ μ μ .

, - μ IL-1 μ .

, μ IL-1 $\mu\mu$ μ .

μ (IL-4, IL-10 [129, 130] IL-1RA) μ μ IL-6 (-

μ μ μ IL-1), μ - μ .

μ , μ μ IL-6

μ [131, 132]. ,

IL-6 [133]. IL-6

μ .

IL-1 μ

IL-1 IL-1RA μ

μ μ μ , μ μ μ

IL-1 μ IL-1 (μ) .

μ , IL-1RA [116] μ μ ,

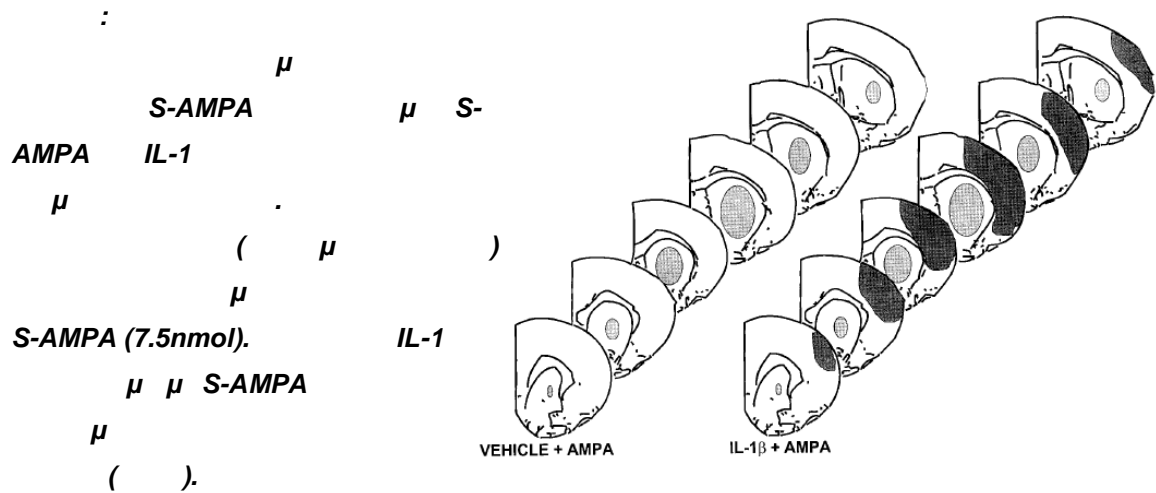
IL-1 μ μ S-AMPA (-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid: -

μ μ AMPA/kainate)

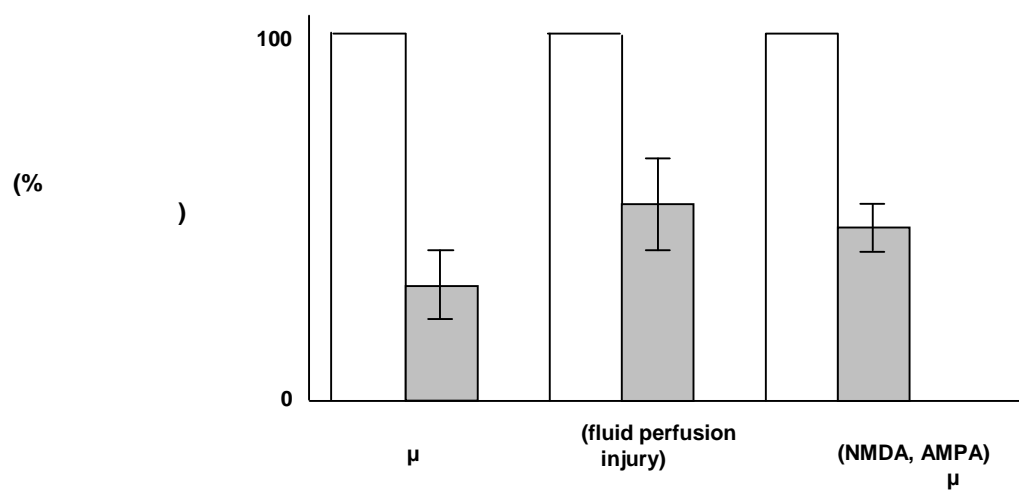
μ μ .

, IL-1 -

.



μ IL-1 IL-1RA
 μ ().
 μ (. .)
 μ , μ -
 μ μ μ .

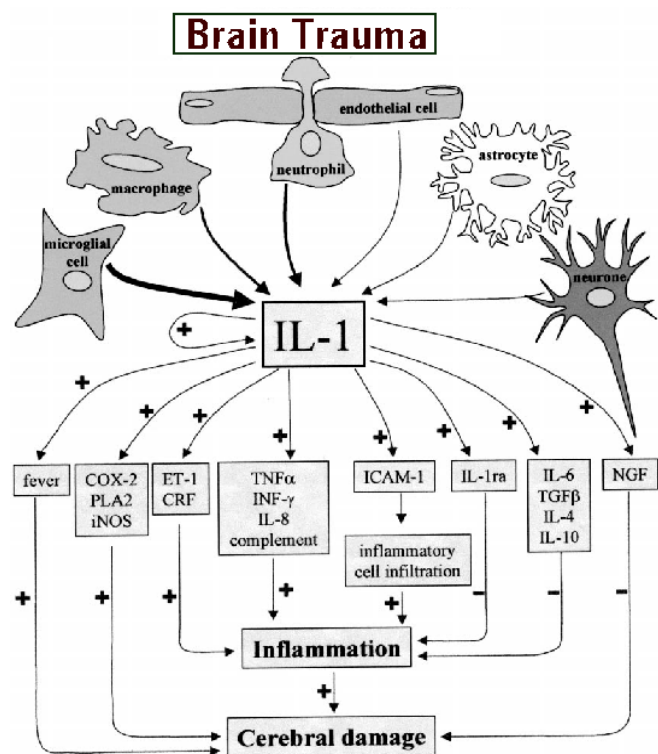


μ IL-1RA
 μ (μ)
 , -
 (lateral fluid perfusion injury, -
 10 μ g IL-1RA),
 10 μ g IL-1RA),
 NMDA AMPA
 μ (5 μ g IL-1RA μ).

[illegible]

μ , IL-1
 μ NGF (nerve growth factor)
 [141], μ IL-1RA [110]. μ ,
 IL-1 [142] [143] μ
 μ μ $\mu\mu$
 [78, 144]. , μ o
 μ [145-147]. , -
 $\mu\mu$ μ -
 [148] μ [149, 150]. μ μ
 [151] μ
 , NO NMDA [152].
 μ , μ IL-1
 , IL-1
 μ .

: μ IL-1
 μ ,
 μ
 . COX-2: cyclo-
 oxygenase 2, PLA2: phospholipase 2,
 iNOS: inducible NO synthase, ET-1:
 endothelin 1, CRF: corticotropin
 releasing factor, TNF α : tumor necrosis
 factor, INF γ : interferon gamma, ICAM-
 1: intercellular cell adhesion molecule
 1, IL-1RA: interleukin-1 Receptor
 Antagonist, IL-6: interleukin-6, TGF :
 transforming growth factor, IL-4:
 interleukin-4, IL-10: interleukin-10,
 NGF: nervous growth factor.



IL-1 μ
 IL-1 μ
 μ [153]. ,
 μ
 IL-1

IL-1 (5ng) μ μ -

μ μ μ [104].

IL-1 μ (2.5ng)

μ [154].

IL-1 μ -

μ , IL-1

μ μ -

IL-1RA -

μ ICE μ μ ,

[111, 115, 155]. μ IL-1RA

μ ICE μ μ .

IL-1 μ

IL-1 μ (CBF:cerebral blood flow) μ -

μ μ [156]. ,

IL-1 μ μ

μ [97]. μ μ

IL-1 ()

μ , [157,

158]. , IL-1 (

) [159]. μ , IL-1

μ μ μ

, μ μ

μ μ IL-1RA μ μ

μ ICE. μ IL-1RA

μ ICE

μ μ [160].

IL-1

IL-1 μ Ca^{2+} [161],
 μ [162], μ iNOs (inducible nitric oxide
 synthase) NO [163],
 [164] CRF (corticotropin releasing factor) [165],
 μ μ - μ [166, 167],
 μ [168]. , IL-1
 . μ ,
 Ca^{2+} , GABA ,
 . μ , μ IL-1
 . , IL-1
 μ μ μ
 μ [78].

IL-1

μ
 IL-1 μ
 , ,
 Parkinson, μ Down ,
 , IL-1 μ Alzheimer.
 μ , IL-1 , μ -
 μ [55, 169].
 μ μ Alzheimer (AD) IL-1
 APP [170] (amyloid precursor protein) -
 μ μ - μ (A) μ μ μ -
 . , IL-1
 tau [171] () $\mu\mu$
 μ .
 μ μ μ -
 IL-1 (IL-1 IL-1) μ
 Alzheimer [172, 173]. , μ μ μ μ
 IL-1 μ AD.
 , μ

IL-6 μ

, μ μ -

IL-6 μ μ

. μ , IL-6

μ ,

μ .

μ μ μ μ

μ , IL-6 μ

[178].

μ (μ IL-1 , TNF-) [179, 180] -

μ - - (HPA axis: hypothalamic-pituitary-adrenal axis), μ -

μ , ,

.

, μ IL-6 μ μ -

μ , μ ,

. , TNF (tumor

necrosis factor, - μ), NGF (nerve

growth factor), ,

NMDA (N-methyl-D-

aspartate) [57]. , IL-6

μ

μ ,

.

μ μ

μ μ μ μ

μ , μ .

μ μ μ

μ , μ

, , -

, μ μ μ -

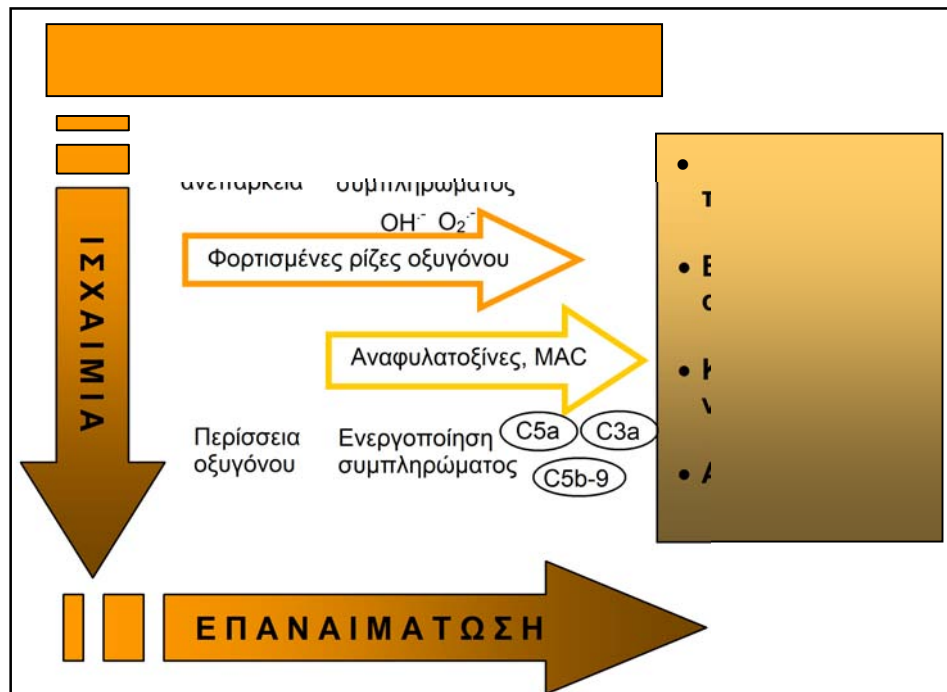
μ μ μ [181, 182]. μ

, ,

The diagram illustrates the complement system activation pathways. It shows the classical pathway (C1-C4) and the alternative pathway (C3-C5) leading to the formation of the C5b-9 MAC complex. The classical pathway is initiated by Ag/Ab complexes, while the alternative pathway is initiated by C3. Both pathways converge at C3, which is cleaved into C3a and C3b. C3b then cleaves C5 into C5a and C5b. C5b, along with C6, C7, C8, and C9, forms the C5b-9 MAC complex, which is shown as a large purple structure on the right.

μ C3a, μ μ . μ C3a μ C3a
 (C3a receptor: C3aR). C5a μ C5a
 C5 μ C5 . μ C5a
 (C5a receptor: C5aR). μ , μ C5a
 μ , μ μ , μ μ ,
 , μ , μ μ ,
 . μ μ - μ
 stress μ
 μ - μ stress μ
 μ μ [50, 196, 197]. μ
 μ , μ μ ,
 μ , μ . μ ,
 μ , μ , μ
 (reactive oxygen
 intermediates) [198]. μ μ
 μ , μ .
 , μ , μ , μ
 μ , μ , μ μ , μ
 μ . μ μ
 stress μ
 [199-201]. , μ μ
 , μ μ μ / μ
 , μ
 stress [197]. μ

μ μ μ , - . μ
 μ μ μ μ
 μ μ [200, 202]. , μ
 μ
 μ [203].



7: μ / μ
 μ . μ μ μ
 μ μ . μ
 (nutritive failure) μ
 (ATP: adenosine triphosphate), μ μ
 . μ , μ
 μ , μ μ
 μ μ , C3a C5a, μ MAC
 (membrane attack complex)/C5b-9. , μ / μ
 μ μ
 , , .

IL-1

IL-1. IL-1RA, (IL-1) , Ca^{2+} , NO). (IL-1) , IL-1RA , 8-12h [204].

IL-6

μ μ μ

μ $\mu\mu$, μ μ -

IL-6 (sIL-6R),

μ IL-6. , sIL-6R

μ μ IL-6

μ . , IL-6 [205, 206]

μ [207, 208]

IL-6 μ

μ

IL-6, μ $\mu\mu$ μ

IL-6 μ

, μ μ

μ

IL-6

μ μ - μ , μ

μ - μ , μ -

μ μ μ μ -

IL-6 μ μ

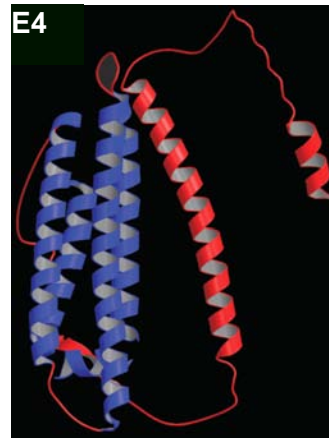
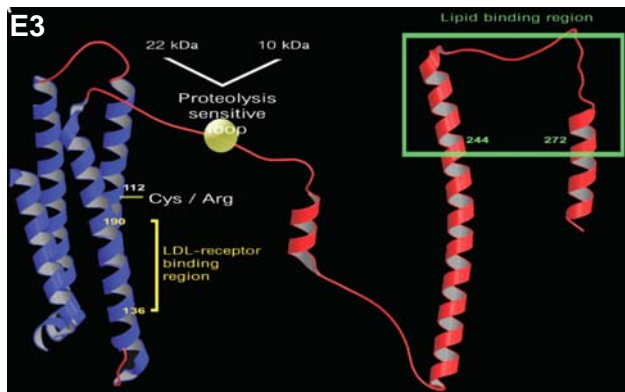


μ μ μ ,
μ μ
μ . μ
μ
μ , COMT
(catechol-o-methyltransferase), neprilysin, DRD2 (dopamine
D2 receptor), , p53 , ACE
CACNA1A μ .

(ApoE)

apoE

APOE μ 3.7Kb, 4
μ μ μ 19 [209]. apo μ
(=34KDa) 299 μ μ
μ μ μ [210].
3 μ apoE: 2, 3 4 3
: 2, 3 4. μ
(cys) (arg) 112 158
μ , 2 cys¹¹²cys¹⁵⁸, 3
cys¹¹²arg¹⁵⁸ 4 arg¹¹²arg¹⁵⁸. μ apoE μ -
μ 7% (2), 78% (3) 15% (4) μ [211].
μ μ APOE :
3 μ (APOE 2/2, APOE 3/3, APOE 4/4) 3
(APOE 2/3, APOE 3/4, APOE 2/4). μ
APOE 2/3, APOE 3/3, APOE 3/4.
4
Alzheimer (AD) [212-214], μ μ
μ [215] μ [216],
μ μ μ
[217, 218].



: μ 3 4 μ apoE

.

apoE

, apoE

μ

,

,

μ

.

μ

.

μ

, μ

μ

- ,

-

.

μ

μ

apoE,

. apoE

μ

μ

μ μ

,

μ

[219],

,

.

apoE

μ

.

μ

μ ,

apo

LDL (low

density lipoprotein)

μ

μ

,

apo

LDL, μ

μ

apoE

μ

.

apoE

apoE

μ

,

μ

μ

μ

[220].

μ

μ

apoE

μ

μ

μ

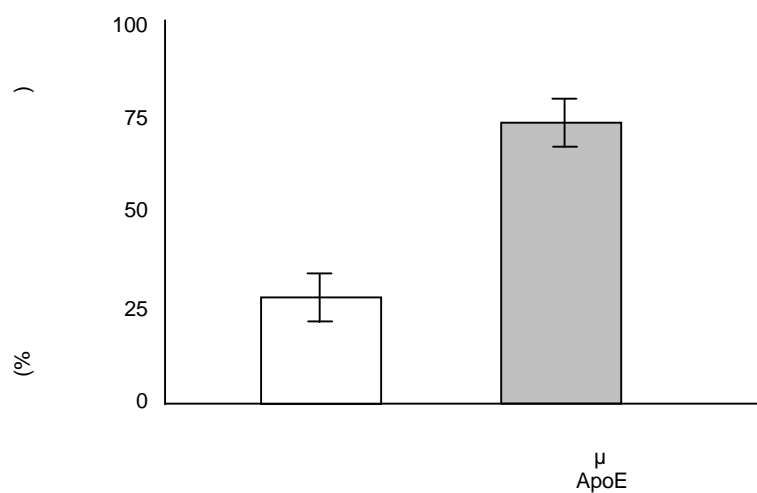
.

μ

APOE

apoE μ

[222].

[illegible]

μ .
 μ
 μ
 μ

μ μ apoE

μ - μ μ μ

μ AD [223]. ,

μ 30%

μ [224]. , μ μ

apoE μ μμ

μ AD apoE

AD. μ μ APOE 4

4 μ

μ 4 [225].

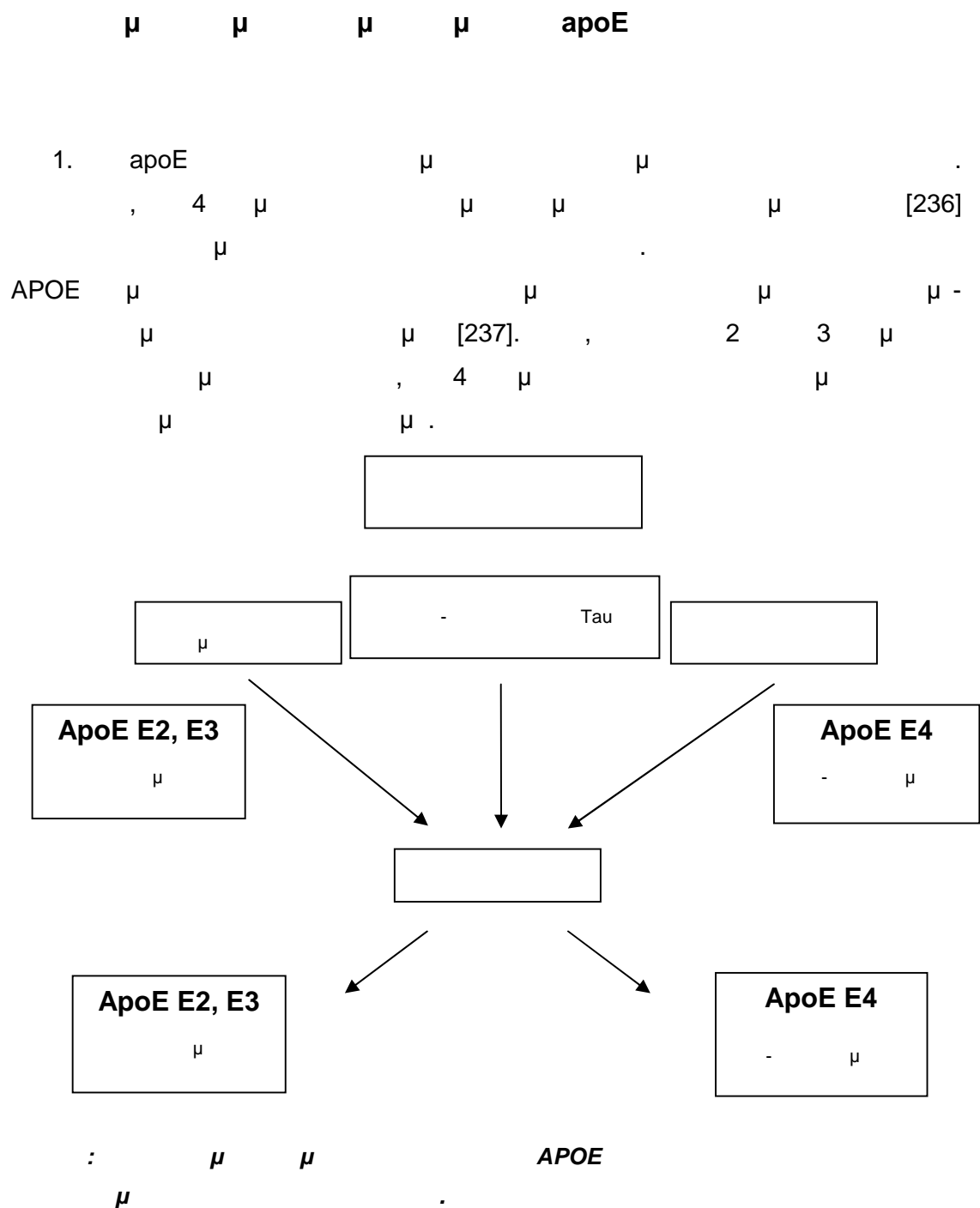
μ μ APOE 4

μ μ . μ

[218] μ (n=93) 57% μ 4

μ (, , μ μ

μ) 6 μ μ μ 27%
 μ 4 μ . μ
 μ ,
 μ (μ μ , [GCS] μ
 μ . , μ 4
 μ (μ GCS) μ .
 μ μ μ
 μ [226].
 μ μ apoE μ μ μ
 μ μ , μ μ
 μ 4 [227].
 μ , APOE
 μ μ . μ μ [217]
 μ 4 μ -
 μ μ μ μ (>7 μ).
 μ , μ μ μ μ -
 μ 4 μ -
 μ [228]. , 4
 μ μ μ μ [229],
 μ μ μ [230].
 μ APOE -
 μ μ μ . μ ,
 μ 4 μ
 μ μ μ μ -
 μ [231]. μ , μ μ [232] μ
 μ 4
 μ μ μ μ - . ,
 μ 4 μ
 μ μ μ μ [233] μ μ - .
 μ , μ μ 77 μ
 μ 4 μ
 μ μ μ μ -
 μ [234].
 μ APOE
 μ , μ
 μ [235].
APOE μ μ ,



2. apoE

(lipid peroxidation),

[238].

3. apoE
 $\mu\mu$. 4
 $\mu\mu$ [239] μ
 [240].
 4. , apoE
 $\mu\mu$ μ .
 3 μ $\mu\mu\mu$ μ
 μ tau (μ
 μ) μ -
 $\mu\mu$, 4 μ
 μ tau [241].

PO

APOE
 $\mu\mu$. μ ,
 G/T $\mu\mu$ -219 A/T $\mu\mu$ -491 .
 μ -219 -
 169% . , -
 μ -491 μ 63%
 [242]. μ , -
 μ AD. μ ,
 G-219T $\mu\mu$ -491 μ -
 μ AD [243]
 μ μ AD [244, 245]. μ
 μ μ [246] μ
 μ . μ ,
 G-219T $\mu\mu$
 μ GG GT . μ -491 /
 $\mu\mu$.

Neprilysin

- μ μ μ
 $\mu\mu$ μ
 μ . μ , μ
 Alzheimer

μ neprilysin [247]. μ AD
neprilysin
μ μ [248, 249]. , knockout μ
μ neprilysin μ
μ [247]. , neprilysin
μ μ μ μ
μ μ μ [250]. , neprilysin
μ μ μ μ
μ μ μ [251].
μ μ GT neprilysin
μ μ μ μ
μ AD [252, 253]. μ μ
μ neprilysin
μ DNA, μ
μ μ μ . ,
μ μ μ 81 , μ μ
3.45 μ . μ μ
GT μ μ μ [254].
μ μ neprilysin μ -
μ μ μ μ .

COMT

COMT (catechol-o-methyltransferase), μ
μ (DA) (NE),
μ μ : (COMT Val/Val, COMT Val/Met, COMT Met/Met).
μ μ
DA [255], μ
DA [256, 257]. μ μ [258] μ μ COMT
Val158Met μ .
μ , μ
(Val/Val μ μ), μ DA ,
μ μ μ μ
(Wisconsin Card Sorting Test, WCST), μ μ
μ (Met/Met) DA
μ . μ , μ μ 39 μ 27 μ

IL-1 , IL-1 , IL-1 Receptor Antagonist (IL-1RA). IL-1 IL-1 -
 μ IL-1A IL-1B ,
 μ μ μ
2 [262]. IL-1RA IL-1 IL-1 ,
IL1RN [263]. μ μ 5
 μ IL-1A , -889 [262]. μ IL-
1A*2 μ μ μ μ AD [172, 173,
264, 265]. IL-1B μ .
 μ μ 5 IL-1B , +3953.
 μ 2 μ μ
IL-1 μ μ 1
[266]. μ μ IL-1B
, -511 [267]. , IL1RN
 μ μ 2
 μ (variable number of tandem repeats). μ μ
5 , μ IL-1R 2 μ μ
IL-1 in vivo. , μ μ IL-1B +3953,
IL-1B-511 IL-1RA μ μ μ AD [173, 268].
 μ μ μ
. μ μ [269] μ μ μ
IL-1B μ . μ , 14
25 (56%) IL-1B(+3953)*2 μ -
 μ 8 44 (18.1%) μ - 2. , 20
28 (71.4%) IL-1B(-511)*2 μ -
 μ 2% (2 41) μ - 2 (P=0.005).
, IL-1A (-889) μ μ μ μ
[270].
-6 (IL-6) μ μ -
 μ μ .
 μ IL-6 μ μ
 μ [271, 272]. , μ μ
IL-6 (-174) μ μ ,
 μ [272].

p53

μ μ [37]. p53
 μ [273] μ μ
 (pro) (arg) μ 72 -
 [274]. μ μ
 , Arg/Arg μ
 [275]. μ μ [276] Arg72Pro
 μ μ μ μ . μ
 μ μ - , Arg/Arg -
 (69%) μ Arg/Pro Pro/Pro (31%).
 , Arg/Arg μ μ (2.9)
 μ - μ . μ ,
 μ μ p53 μ .

Angiotensin converting enzyme (ACE)

μ μ (ACE)
 μ - , μ μ .
 ACE μ μ ,
 [277]. ACE μ
 μ μ μ 17 17q23.
 μ μ / (I/D: insertion/deletion)
 16 ACE (II, ID DD),
 ACE μ [278]. μ ,
 ACE μ μ μ DD
 [279]. , I μ μ
 μ AD [280, 281], D μ μ -
 μ [282-284] μ μ
 74 [285].
 μ μ [286] μ ACE I/D μ μ
 μ KEK.
 D μ μ
 μ (Grooved Pegboard Trial
 Making Tests) μ I . μ μ

ACE μ μ μ μ μ
 . , μ
 / μ μ
 μ μ μ μ .
 , ACE μ μ μ ,
 μ
 [287].

CACNA1A

μ μ (missense) μ
 CACNA1A ,
 Ca²⁺ (CACNA1A calcium channel subunit gene), μ μ
 μ μ [288].
 μ , 3 μ μ μ
 , μ μ CACNA1A
 (S) (L) 218 (S218L). ,
 μ μ μ
 μ CACNA1A μ
 μ .

		μ μ		μ μ		μ	
		μ μ	μ	μ	μ	μ	
Nicoll et al (1995)[225]	APOE	2/ 3/ 4	90 μ (23 A +)	μ		APOE4	, p<0.00001
Sorbi et al (1995)[228]	APOE	2/ 3/ 4	16 μ	μ μ		APOE4	, p<0.01
Mayeux et al (1995)[174]	APOE	2/ 3/ 4	236 μ μ μ	μ AD		μ AD μ	APOE4
Katzman et al (1996)[289]	APOE	2/ 3/ 4	160 μ μ AD, 69 μ	μ AD		APOE4 μ AD, OR 13.5, 95% CI 2.63-69.12, p=0.0018	
Teasdale et al (1997)[218]	APOE	2/ 3/ 4	89 μ	- μ		APOE4	, OR 0.23, 95% CI 0.06-0.82, p=0.024
Jordan et al (1997)[227]	APOE	2/ 3/ 4	30 μ	(CBI μ)		μ APOE4	p<0.01
Friedman et al (1999)[217]	APOE	2/ 3/ 4	69 μ	μ		APOE4	
Mehta et al (1999)[290]	APOE	2/ 3/ 4	797 μ μ	μ AD μ 2.1 μ		-	
Plassman et al (2000)[291]	APOE	2/ 3/ 4	46 μ AD, 356 AD, μ	μ AD		-	
Lichtman et al (2000)[292]	APOE	2/ 3/ 4	31 μ μ	μ μ μ μ 6 μ		μ APOE4 μ μ μ	, p=0.05
Guo et al (2000)[293]	APOE	2/ 3/ 4	942 μ AD μ , 327 μ	μ AD		μ AD APOE4	, OR 3.3, 95%CI 2.0-5.5
Kutner et al (2000)[294]	APOE	2/ 3/ 4	53	μ		μ APOE4 μ μ μ	p=0.004
Liaquat et al (2002)[229]	APOE	2/ 3/ 4	129 μ	μ μ μ GOS μ 6 μ		μ E4 μ μ μ	, p=0.0056
Crawford et al (2002)[233]	APOE	2/ 3/ 4	110 μ	μ μ μ μ 6 μ μ		μ APOE4 μ μ μ	, p=0.015
Liberman et al (2002)[231]	APOE	2/ 3/ 4	87 μ μ	μ 3 6		μ APOE4 μ μ μ	
Chiang et al (2003)[226]	APOE	2/ 3/ 4	100 μ	μ GOS μ 6 μ		APOE4	, OR 3.01, 95%CI 1.02-8.88, p=0.04
Nathoo et al (2003)[235]	APOE	2/ 3/ 4	110 μ , μ	μ GOS μ 6 μ		-	

Diaz-Arrastia et al (2003)[230]	APOE	2/ 3/ 4	106 μ μ	μ GOS μ 6 μ		μ E4 , OR 2.41, 95%CI 1.15-5.07, p=0.03
Millar et al (2003)[295]	APOE	2/ 3/ 4	396 μ	GOS μ 6 μ , 18		-
Kerr et al (2003)[296]	APOE	2/ 3/ 4	91 μ	μ (- , μ () μ / ()		μ μ APOE4 / μ
Chamelian et al (2004)[297]	APOE	2/ 3/ 4	90 μ μ	GOS,		-
Sundstrom et al (2004)[232]	APOE	2/ 3/ 4	34 μ μ	μ		APOE4 μ μ μ μ μ
Quinn et al (2004)[199]	APOE	2/ 3/ 4	106 μ 2-19	μ		-
Koponen et al (2004)[298]	APOE	2/ 3/ 4	60 μ	μ μ 30		APOE4 μ , p=0.028
Teasdale et al (2005)[299]	APOE	2/ 3/ 4	1094 μ	GOS 6 μ		E4 μ μ - μ <15 , OR 3.06, 95%CI 1.22- 7.65, p=0.07
Leclercq et al (2005)[300]	APOE	2/ 3/ 4	88 μ μ	μ		E4 μ μ , p=0.021
Ariza et al (2006)[234]	APOE	2/ 3/ 4	77 μ	6 μ μ		APOE4
Smith et al (2006)[301]	APOE	2/ 3/ 4	239	μ		APOE4 , p=0.05 p=0.08
Jiang et al (2006)[302]	APOE	2/ 3/ 4	110 μ	(<7 μ μ)		APOE4 , OR 4.84, 95%CI 1.44-16.21, p=0.011
Isoniemi et al (2006)[303]	APOE	2/ 3/ 4	58 μ	μ , 31.3 μ		-
Kerr et al (2006)[296]	APOE	2/ 3/ 4	54 μ	Xe-CT μ μ μ 24h μ		APOE4 μ μ μ μ
Ponsford et al (2007)[304]	APOE	2/ 3/ 4	120 μ μ	6, 12 μ 3,		-
Han et al (2007)[305]	APOE	2/ 3/ 4	78 μ μ	1 μ		APOE4 μ
Alexander et al (2007)[9]	APOE	2/ 3/ 4	123 μ	GOS 3, 6, 12 24 μ		APOE4 μ

Hiekkanen et al (2007)[306]	APOE	2/ 3/ 4	33 μ μ -	μ μ MRI μ 1 μ		-
Zhou et al (2008)[307]	APOE	2/ 3/ 4	- : 14 μ μ 2427 μ μ	GCS μ GOS 6 μ		- APOE4, RR 1.36, 95%CI 1.04-1.78
Willemse-van Son et al (2008)[308]	APOE	2/ 3/ 4	79 μ μ	GOS 3, 6, 12, 18, 24, 36 μ μ		APOE4, OR 0.26, 95% CI 0.02-0.51, p=0.037
Tanriverdi et al (2008)[309]	APOE	2/ 3/ 4	93 μ μ , 27 μ μ	μ		μ APOE3/E3 μ , OR 0.29, 95% CI 0.11-0.78, p=0.01
Brichtova et al (2008)[310]	APOE	2/ 3/ 4	70 μ	GCS , GOS 1		μ APOE4 μ -
Luukinen et al (2008)[311]	APOE	2/ 3/ 4	134 μ μ >70 , 28 μ μ ,	μ 9		μ ApoE4 , OR 2.70, 95% CI 1.02-7.16
Ost et al (2008)[312]	APOE	2/ 3/ 4	96 μ	μ 1 μ		- APOE4 μ (p=0.0079)
Rapoport et al (2008)[313]	APOE	2/ 3/ 4	49 μ μ , 68 μ μ	μ 1 2		-
Kristman et al (2008)[314]	APOE	2/ 3/ 4	318 (28 μ)			-
Ashman et al (2008)[87]	APOE	2/ 3/ 4	54 μ μ , 40 μ μ	2-5 μ ,		-
Han et al (2009)[315]	APOE	2/ 3/ 4	46 μ μ	μ		APOE4 μ
Muller et al (2009)[264]	APOE	2/ 3/ 4	59 μ	6 μ μ		ApoE4 μ μ , p=0.046
Hiekkanen et al (2009)[316]	APOE	2/ 3/ 4	33 μ	1 μ μ μ , GOS		-
Lo et al (2009)[317]	APOE	2/ 3/ 4	65 μ	μ (CPP)		μ μ μ CPP ApoE4 μ μ - , p=0.03
Lendon et al (2003)[246]	APOE	-219G/T -491A/T -427C/T	92 μ	GOS 6 μ		μ - μ μ
Jiang et al (2007)[318]	APOE	-219G/T -491A/T -427C/T	110 μ	(<7 μ μ)		- -491AA μ APOE4
Jiang et al (2008)[319]	APOE	-219G/T -491A/T -427C/T	110 μ	(<7 μ μ CT)		- - -
Terrell et al (2008)[320]	APOE	2/ 3/ 4	195			-

	Tau APOE	His47Tyr Ser53Pro -219G/T	72 μ μ μ 8			- - TT , OR 2.7, 95% CI 1.1-6.8, p=0.03
Johnson et al. (2009)[254]	Neprilysin	GT	81 μ μ μ	μ μ A		μ μ GT p=0.0001 >41, OR 10.1, 95% CI 3.1-32.5,
Martinez et al (2005)[276]	p53	Arg72Pro	90 μ	μ GOS μ GOS 6 μ		Arg/Arg, OR 2.9, 95% CI 1.05-8.31, p=0.039
Ariza et al (2006)[286]	ACE	I/D	73 μ μ	μ μ μ μ		D μ
Uzan et al. (2005)[321]	IL-1b	+3953 C/T -511 A/G	69 μ	μ GOS 6 μ μ GOS 6 μ		Allele 2, OR 0.25, 95% CI 0.12-0.55, p= 0.0004 Allele 2, p=0.005
Hadjigeorgiou (2005)[322]	IL-1RA IL-1b	VNTR -511 A/G	151 μ	μ		Allele 2, OR 4.57, 95% CI 1.67-12.96, p = 0.004 -
Tanriverdi et al (2006)[270]	IL-1a	-889 C/T	71 μ	GOS 6 μ		-
Dardiotis et al. (2006)[323]	IL-1a	-889 C/T	215 μ	GOS 6 μ		-
Minambres et al (2003)[272]	IL-6	-174 C/G	62 μ	GOS 6 μ		-
McAllister et al (2005)[261]	ANKK1	rs1800497	39 27 μ μ	(SD=24.4) μ μ 38.4 μ		T μ μ μ
McAllister et al (2008)[261]	ANKK1 NCAM DRD2	31 polymorphisms	93 μ 21	(SD=15.8) μ μ 43.1 μ		T SNPs (rs1800497) μ ANKK1
Lipsky et al (2005)[258]	COMT	Val158Met	113 μ	μ		Val μ
Chan et al (2008)[324]	SLC6A4	5-HTTLPR rs25531	174 μ			-

-1 (IL-1)

IL-1 IL-1

IL-1 3 3
: IL-1 IL-1 , IL-1RA (IL-1
Receptor Antagonist) IL-1. IL-1 IL-1
μ μ . μ
() μ μ 31KD. μ
μ μ 17KD μ μ
IL-1RA (secreted IL-
1RA: sIL-1RA) μ μ
μ .
IL-1 (IL-1R): I (IL-1RI)
μ , II (IL-1RII) -
μ IL-1 μ μ .
IL-1 I μ , μ
AcP (IL-1R-accessory protein) [325]. μ μ μ -
IL-1RI μ IL-1R-AcP μ
μ μ . -
IL-1RI (IL-1sRI) IL-1RII (IL-1sRII) μ IL-1 , IL-1
IL-1RA.

IL-1

IL-1
IL-1 μ
μ μ 4.200 (bp)
μ μ 200bp
[326].
IL-1
μ IL-1 μ
17KD. μ μ IL-1 (proIL-1) 31KD -
μ μ (μ) , μ
μ [327]. proIL-1

μ , μ proIL-1
 μ μ , -
 . , proIL-1 -
 [177]. ,
 proIL-1 (calcium-
 dependent, membrane-associated cysteine proteases-calpains) [177, 328]. -
 μ Ca^{2+} ,
 μ μ IL-1 . , μ
 IL-1 μ [329].

IL-1
 proIL-1 μ μ μ
 , . ,
 IL-1 μ .
 IL-1 μ μ μ
 . , μ
 μ [329].

μ IL-1
 In vitro μ proIL-1
 , μ - μ .
 10-15% IL-1 μ μ [330] μ
 [331]. μ μ (myristoylation)
 μ μ . μ μ IL-
 1 μ μ μ μ
 μ , μ
 [332]. μ μ IL-1
 μ IL-1 (anti-IL-1) . , μ μ
 IL-1 (anti-IL-1) μ μ IL-
 1 .

IL-1

μ μ IL-1 IL-1
 μ μ
 [333, 334]. μ μ (μ

mRNA (splicing),
 μ mRNA, 3 μ - μ μ .

ICE (IL-1 converting enzyme)

μ μ , [15]
 μ μ IL-1 116-117 μ -
 (asp-ala), μ μ - , μ μ IL-
 1 .

IL-1R (IL-1 Receptor)

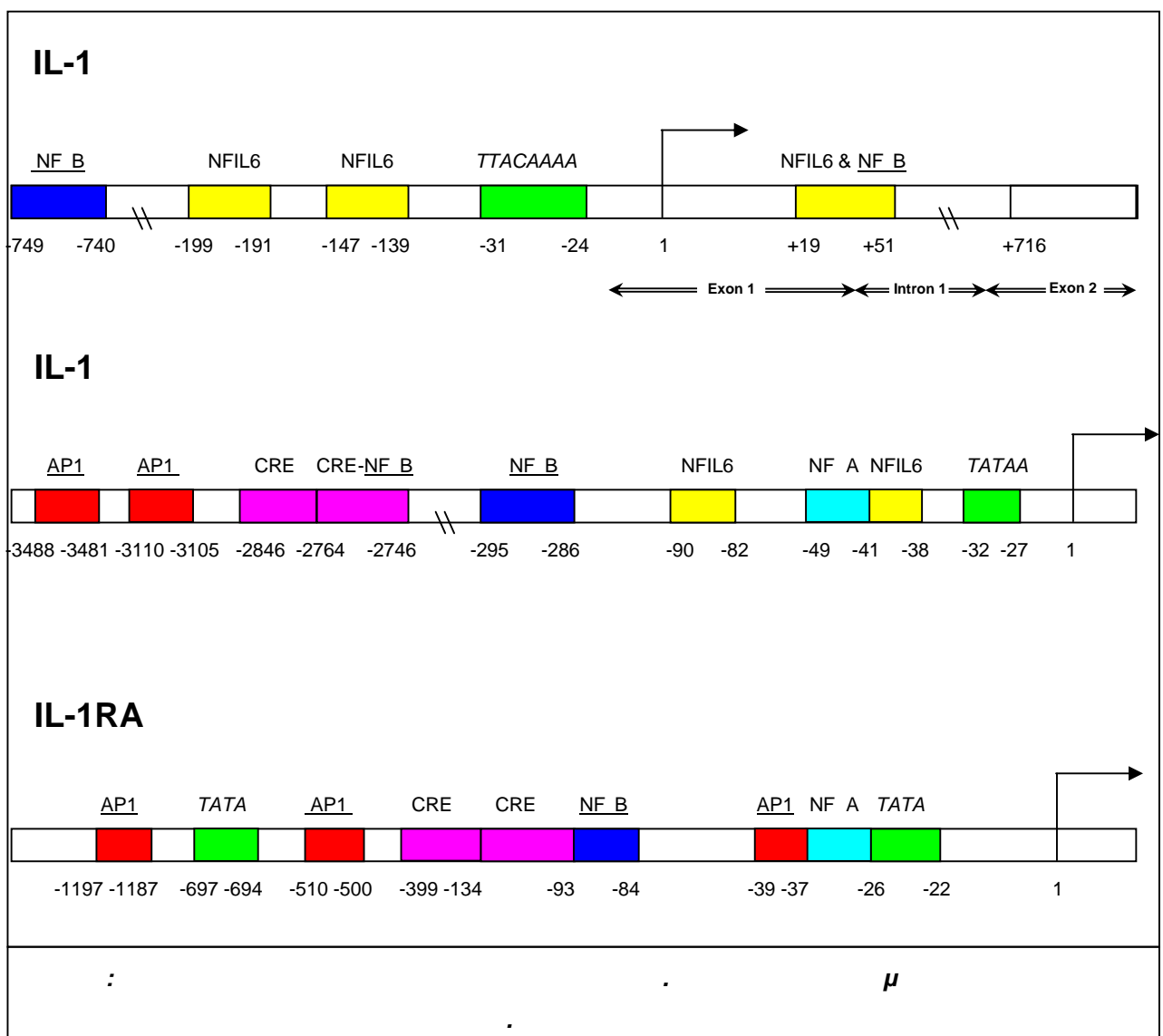
μ IL-1:
 I (IL-1RI) II (IL-1RII).
 μ (Ig) 3
 μ μ , μ μ [325, 341, 342].
 , IL-1RI IL-1RII
 μ μ μ 2 [343].

IL-1

IL-
 1 [344] 1984. μ
 μ IL-1 [345] IL-1 [346]. ,
 IL-1 μ 10 Kbp, IL-1
 7 Kbp. IL-1
 μ μ 2 (2q13) [347]. , IL-1 IL-1
 . ,
 μ
 μ [346].
 IL-1 IL-1 7 .
 μ 5 μ - μ μ mRNA
 . , μ μ
 IL-1. -
 IL-1
 [348]. , IL-

1 , IL-1 μ
 μ μ (repetitive sequence elements), μ
 Alu . IL-1 μ
 IL-1
 μ μ GRE (glucocorticoid response element)
 (TGTYCT). ,
 μ IL-1 . μ
 3 μ - μ μ (3 UTR),
 o - . 3 UTR
 IL-1 IL-1 AU,
 ATTTA μ .
 μ ,
 mRNAs - [349].

IL-1



IL-1 motif), IL-1 NFkB, IL-1RA, CREB (cAMP response element binding protein), [350].

IL-1 TATA (TATA box IL-1RA. IL-1 NFbA

IL-1 (promoter) IL-1 -511 (single nucleotide polymorphism, SNP) [267] (rs16944).

IL-1 [351-353].

IL-1B-511*1	
✓	μ [354]
✓	μ [355]
✓	μ [356]
✓	Parkinson [357] μ [358].
✓	[359]
✓	[360]
✓	μ μ Alzheimer [361]
IL-1B-511*2	
✓	[362].
✓	μ μ [363]
✓	μ Sjogren [364].
✓	μ [365].
✓	μ [366]
✓	Parkinson [367, 368]
✓	μ μ [369]
: μ μ IL-1 (-511 C/T) (rs16944)	

IL-1 -889 μ

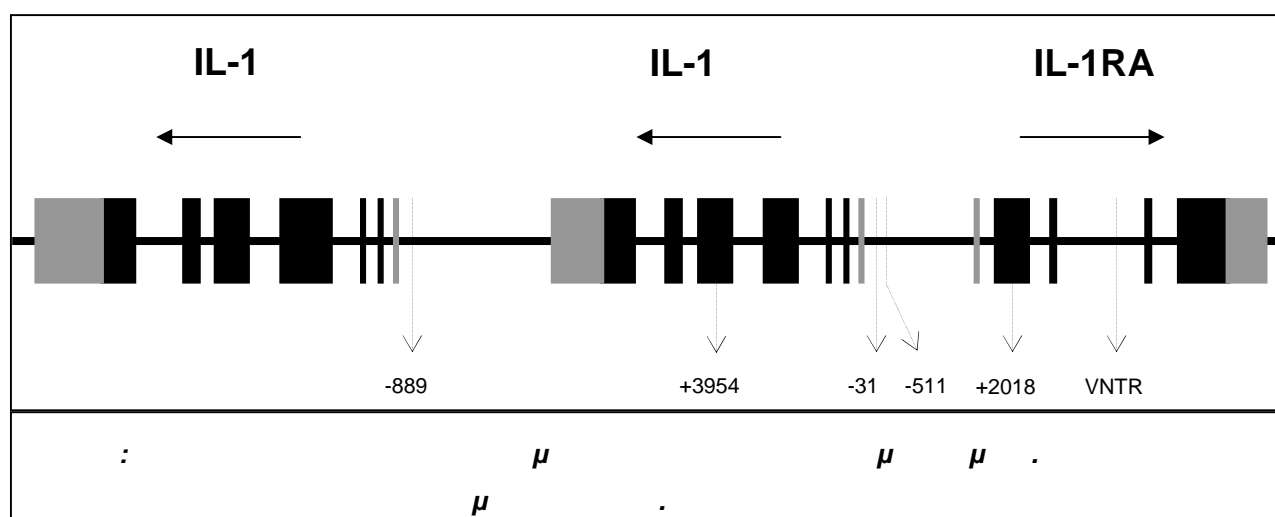
μ C/T μ μ μ [370].

μ μ 2

IL-1 (-889) μ IL-1 [371],

μ , $2/2$ μ ,
 μ IL-1 [372]. ,
 μ μ μ μ . μ μ
 μ μ μ μ μ μ
 μ μ -92 -82,
-889 [373]. ,
 μ μ μ , +4845,
pro-IL-1 IL-1 . μ -
 μ IL-1 (-889) μ μ
IL-1 (-889)*2 (IL-1 (+4845)*2) μ
 μ IL-1 [373].

IL-1 -889*1	
✓	μ μ [363]
✓	μ -Behcet [374]
✓	[375]
✓	[376]
✓	μ μ [377]
IL-1 -889*2	
✓	μ Alzheimer [378]
✓	μ [379]
✓	μ [380]
✓	μ [381]
✓	μ [370]
:	μ μ IL-1 (-889 C/T)



IL-1

IL-1

μ μ μ μ μ in vitro

μ μ in vivo .

μ μ μ

μ IL-1 μ μ

μ , μ

Ca^{2+} [382],

μ [218], (long-term

potentiation) [383] GABA (- μ) [384]. ,

IL-1 in vivo μ

2 (COX2) (inducible

nitric oxide synthase) (iNOS) [385]. , IL-1

μ CRF (corticotrophin releasing factor),

μ μ μ μ [154].

IL-1

IL-1

, μ [147]. ,

,

[386], (μ

- μ 1- μ) [59] μ μ [58].

IL-1 μ , -

, [387].

IL-1

μ μ (caspase) μ -

μ μ . -

IL-1 $\mu\mu$. μ ,

1 [160] (μ IL-1)

[155] μ μ

.

IL-1

IL-1 μ

μ IL-1 -

μ , μ -

[388] μ

μ [84], [389]. ,

μ μ [390]

, μ

μ [388]. IL-1 μ

μ [391].

, IL-1RA , μ

μ , μ IL-1

, μ μ

μ [392]. μ

-

μ IL-1RA μ μ μ

apoE^{-/-} [393]. , μ knockout

μ IL-1 IL-1RA

apoE^{-/-} μ [394-398]. , μ IL-1RA ^{+/-}

μ μ μ μ [396].

, μ μ μ

[399] knockout IL-1RA. μ

μ , ,

μ μ

.

μ μ μ μ , μ

-

μ μ μ μ .

μ ,

μ μ μ

-

. μ μ μ

-

μ μ

μ . , μ ,

μ - μ

IL-1RA μ

IL-1, μ .

IL-1 μ

$\mu\mu$ μ

. IL-1 μ

μ μ : μ μ [400]. IL-1

[401]

μ , μ μ

μ μ . , IL-1 μ μ -

C [400]. μ C μ -

μ μ thrombomodulin. IL-1 -

,

C. , μ IL-1 $\mu\mu$

μ [402]. μ IL-1

μ μ [403].

IL-1 :

IL-1 in vivo

, in vitro μ IL-1

, . , μ

IL-1

μ NGF (nerve growth factor) [387]. μ , IL-1

[142] [143] μ μ -

μ $\mu\mu$ [144]. ,

μ IL-1

, , IL-1

μ .

IL-1 (IL-1RA)

IL-1RA 18% μ μ μ IL-1 26% μ

μ IL-1 . IL-1RA μ μ μ (sIL-

1RA) μ (icIL-1RA1,2,3) [404].

μ , sIL-1RA μ 17KDa,

177 μ μ (leader sequence),

μ .

sIL-1RA 4 3 .

, icIL-1RA μ 18KDa (icIL-

1RA1) 159 μ . μ IL-1RA

μ (splicing), $\mu\mu$
 icIL-1RA 9.4Kb upstream
 sIL-1RA. μ μ
 icIL-1RA sIL-1RA, 3
 μ (signal peptide). ,
 icIL-1RA μ , icIL-1RA
 μ μ .
 icIL-1RA μ μ , -
 . ,
 μ μ μ .
 sIL-1RA IL-1, μ
 (icIL-1RA).
 , μ , ,
 , μ IL-1RA sIL-1RA
 μ mRNA
 μ IL-1RA, [405].
 μ IL-1RA
 [406]. μ μ μ 25KDa icIL-1RA2.
 mRNA icIL-1RA2 μ 63bp
 μ icIL-1RA.
 μ 3 N 2^- μ μ icIL-1RA,
 μ μ μ 21 μ . mRNA icIL-1RA2
 μ , μ ,
 . , icIL-1RA2
 , mRNA μ μ in vivo.
 μ μ μ μ 16KDa icIL-1RA3 [407].
 μ μ , μ ,
 . μ μ μ
 μ . , μ μ
 IL-1 μ μ IL-1RA.
 μ μ IL-1 μ
 μ sIL-1RA.
 μ IL-1RA -
 $\mu\mu$ -
 [404].
 IL-1RA μ ,
 , [408],

in vivo μ μ

μ [404].

IL-1RA μ

μ μ ,

μ (lg)

3 μ μ . IL-1 -

μ μ μ

IL-1RA. IL-

1 in vivo μ . ,

IL-1RA μ μ

μ IL-1.

IL-1 IL-1RA μ -

[404]; μ

IL-1RA

μ , μ ,

1 2 IL-1 IL-1 μ

μ , IL-1RA μ . ,

3 μ

[409].

IL-1RA

IL-1RA (IL1RN) μ

μ μ 2, q14-q21 [410]. IL-

1 (IL-1), IL-1 (IL-1) IL-1RA , μ μ μ

430Kb: IL-1 μ +0 +35Kb, IL-1 μ +70

+110Kb IL1RN μ +330 +430Kb.

μ

μ μ 2,

.

μ μ IL-1RA

μ μ 2

IL-1RA μ (2-6)

86bp [410]. 5 μ -

μ

,

μ μ .

atcctggggaaagtgagggaaatatggacatcacatggaacaacatccaggagactcaggcct ctaggagtaactgggtagtgtgc					
:	86	μ	5	μ ²	VNTR
μ	μ	IL-1RN (rs2234663).			

μ

μ :

μ	μ	
1	4	μ
2	2	μ μ μ
3	3	
4	5	
5	6	

: μ IL-1RA μ

.

μ μ 1
73%, μ 2 μ 21%.

μ μ μ .

μ μ μ μ IL-1RA

μ μ IL1RN*2 μ μ
, μ μ μ

IL-1RA IL-1 .
IL1RN*2 μ μ IL-1 μ

μ μ IL-1 [351]. ,

μ 2 μ μ

IL-1RA in vitro [411]. , μ

sIL-1RA μ μ - . , IL1RN*2 μ

μ μ icIL-1RA1 [404]

[412] μ 2 μ μ μ

[404].

icIL-1RA1

[illegible]

μ

$\mu\mu$ μ μ μ CD4⁺T

, Th1 Th2. Th1 IL-2, IL-12 INF- . Th2

μ μ μ IL-4, IL-6

IL-10. , μ ,

μ μ

μ μ μ . , -

μ - μ . Th1 (IL-2, IL-12,

IFN-) - μ , Th2 (IL-4, IL-6, IL-10)

μ .

IL-2 μ μ 4 - (four-bundle -helical

cytokine) μ - μ

μ

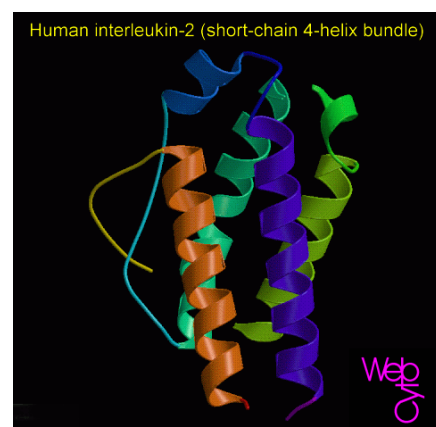
(IL-2R). IL-2 μ μ - μ

, μ , μ μ -

μ , μ μ μ μ μ .

IL-2 63% μ

μ .



IL-2 (IL-2R)

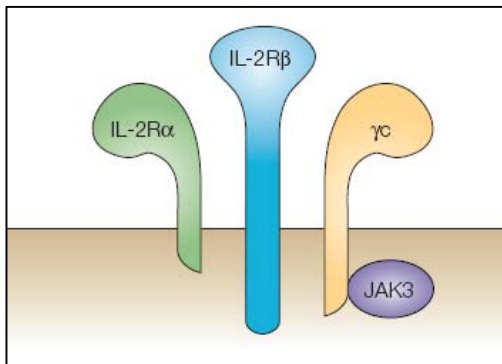
IL-2 (IL-2R)

[413].

μ - μ (T cells).

3 μ - (IL-2R CD25), -
(IL-2R CD122) - (c CD132), μ

$\mu\mu$ IL-2 [414].



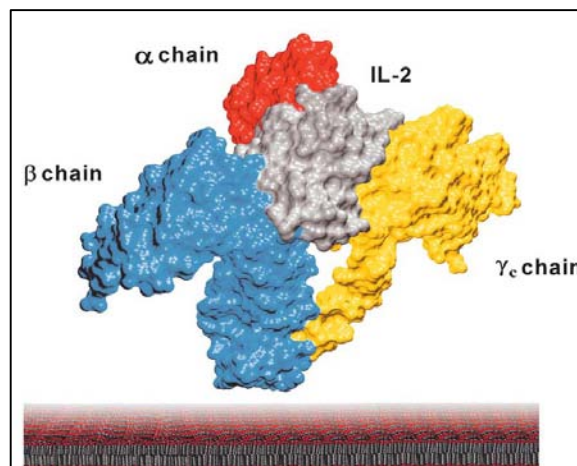
:
IL-2 (IL-2R) 3
: - (IL-2R), -
(IL-2R) - (c).
IL-2, IL-2R
 μ .

μ

IL-2/IL-2R

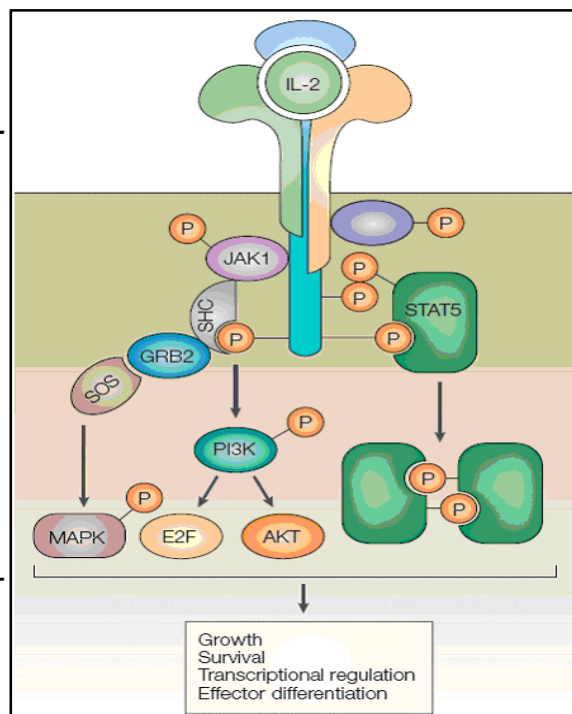
- IL-2R -
IL-2/IL-2R. IL-2
 μ IL-2/IL-2R, μ -
 μ μ μ [415].
 μ IL-2R
IL-2 [301, 416]. μ IL-2
 μ ,
 μ μ μ IL-2 4
- , μ
- , μ μ (
 μ). IL-2 μ
IL-2 - IL-2R. IL-2,
- μ μ , μ μ
- , μ μ
 μ μ .

IL-2/IL-2R



IL-2R

IL-2R



JAK3 [417, 418] (Janus activated kinase 3)

SHC (SRC-homology-2-domain-containing transforming protein C) STAT5 μ (signal transducer and activator of transcription) IL-2R .

, μ SHC MAPK (mitogen activated protein kinase) [419] PI3K-AKT μ (phosphatidylinositol 3-kinase) [420]. , tyr STAT5 μ -

, μ μ μ μ μ -

, μ

‘ - ’ [421].

IL-2

IL-2 , μ

μ , μ μ

(T cell tolerance). IL-2

CD4+ CD8+ T μ μ ,

μ S

[422, 423]. , IL-2 μ

CD4+CD25+T μ (μ_{reg}) [424, 425],

(AICD: activation-induced cell death) [426]. , IL-2

μ NK (natural killer cells) ,

μ μ [427]. ,

IL-2 μ μ [428,

429].

IL-2 $\mu\mu$ μ ,

, μ μ , μ , -

,

IL-2 μ . μ

IL-2 μ ,

μ , μ -

μ (lymphoid hyperplasia) μ -

- μ , , μ

μ , μ [430] μ -

, [431, 432]. ,

IL-2 μ CD4+CD25+T μ

(μ_{reg}) μ (AICD),

μ - μ [426, 433]. μ ,
 IL-2 μ μ
 μ (peripheral tolerance).
 μ IL-2 μ -
 μ , μ
 μ (EAE-experimental autoimmune encephalomyelitis)
 [434], Crohn [435], μ [436],
 [437], μ μ (SLE-systemic
 lupus erythematosus) [438]. , μ μ -
 . , μ IL-2 μ μ
 μ , μ μ
 μ μ 1,
 μ (HTLV-I-human T cell leukemia virus type 1)[439],[383].

IL-2

IL-2 μ ,
 .
 μ μ NK (natural killer cells) [440],
 - [441]. , IL-2 μ
 μ ,
 μ μ [442].
 , IL-2 μ μ ,
 μ μ ,
 . , μ IL-2
 μ
 [443], μ μ
 μ .

μ IL-2

IL-2. IL-2 μ μ μ

μ [346] μ . μ
 μ , μ IL-2
 μ μ [444]. , μ
 EAE (experimental autoimmune encephalomyelitis)
 μ IL-2 (mRNA μ)
 μ μ
 μ [445, 446]. , μ μ
 IL-2
 () μ [346]. ,
 μ IL-2 μ ,
 μ ,
 [447, 448].

IL-2

IL-2 μ
 μ μ 4, q26-q27 [449]. μ IL-2,
 μ μ
 , μ μ μ
 , NF-AT (nuclear factor of activated T cells) , AP-1
 (activated protein-1), NF-kB (nuclear factor kB), -
 μ 1 (Oct-1)[450]. IL-2
 , μ
 NF-AT [451].
 μ μ μ μ
 NF-AT μ Jun Fos . μ μ
 c-Jun μ c-Jun/c-Fos
 NF-AT DNA. μ -
 μ μ IL-2,
 μ μ μ
 (TcR).
 PLC 1 μ (phospholipase C- -1) [452, 453],
 μ G- p21^{ras} [454, 455], μ
 μ NF-AT , μ
 μ IL-2 [450].
 IL-2 (IL-2R) 8 ,
 μ μ 25Kb μ μ 10. 2 4

μ [456]. ,
IL-2R μ μ 10,
p15.1, IL-2R μ μ 22, q13,
IL-2R μ μ ,
q13 [457].

μ μ IL-2

μ μ IL-2
-384 IL-2 [458],
(G) μ (). μ μ
μ IL-
2. : G (), T
(μ). μ μ μ
μ , μ G (G/G)
-384 IL-2 IL-2
μ G/T μ T/T [361].
μ μ 1
IL-2, +114 [459].
: G (), T (μ).
μ μ , μ μ
μ μ ,
μ .
μ ,
μ μ IL-2 73%,
G μ 27% [458, 460]. , μ
.

μ μ IL-2 μ

μ μ μ
IL-2 μ μ
. μ , μ μ μ ,
(T/G, T/T) μ μ -384
IL-2 μ μ
μ μ [461].

μ

(\quad / \quad) -384 μ μ μ μ

μ μ μ Helicobacter pylori

μ μ μ [462].

, μ μ -

[463]. μ μ

G -384 μ μ μ

μ μ (graft-versus-host-disease) μ

μ [464]. , μ

μ μ

IL-2 μ μ

[465].

6 (IL-6)

μ

μ

μ

IL-6. CNTF

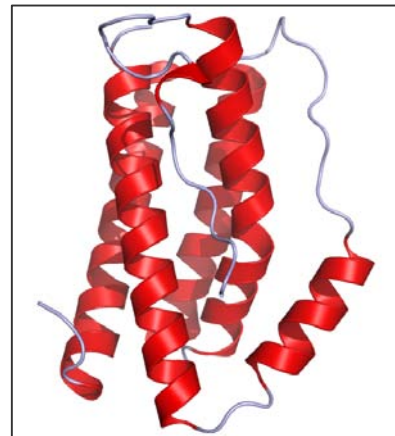
(ciliary neurotrophic factor), LIF (leukemia inhibitory factor),

activity), IL-6 IL-11 [466]. IL-6, μ

20-24KDa μ - μ μ . μ μ

μ μ 30%. , -

μ μ μ



μ IL-6

μ

μ μ

μ μ μ -

[467].

μ μ IL-6

IL-6

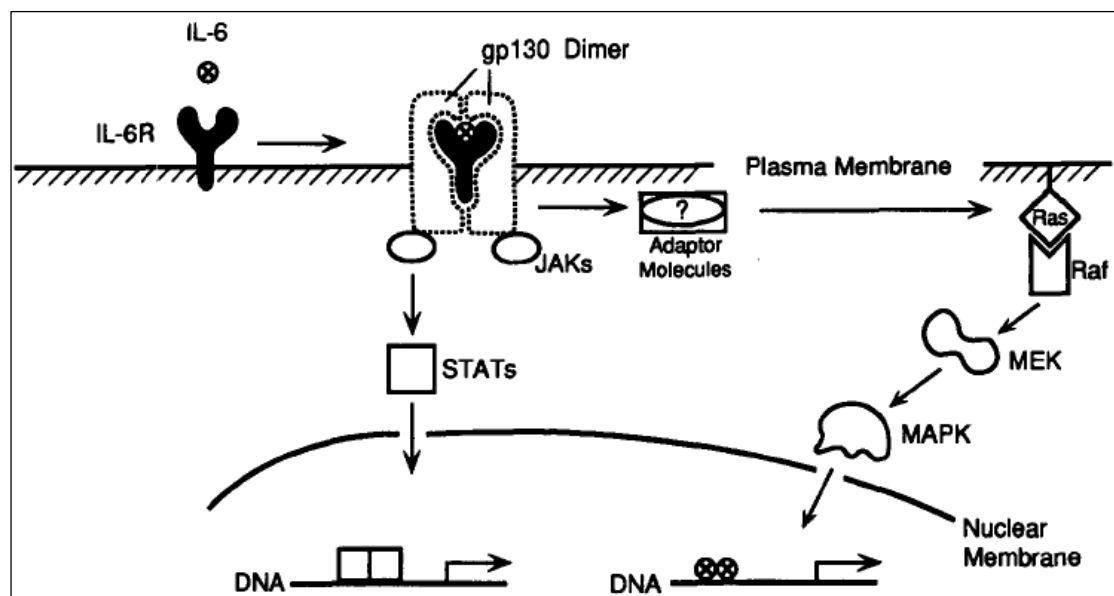
μ -

μ μ - - -

(WSXWS) μ μ

μ III (fibronectin III) [466].

IL-6 binds to the IL-6 receptor (IL-6R) and gp130 (a Janus kinase, JAKs). JAKs are associated with gp130 and STAT (signal transducers and activators of transcription). IL-6 binding to gp130 activates JAKs, which then phosphorylate STATs. This leads to the activation of transcription factors like G-proteins, Ras, and MAPKs (mitogen-activated protein kinases).



IL-6 binds to the IL-6R and gp130. JAKs are associated with gp130 and STATs. IL-6 binding to gp130 activates JAKs, which then phosphorylate STATs. This leads to the activation of transcription factors like G-proteins, Ras, and MAPKs (mitogen-activated protein kinases).

IL-6

μ μ μ μ IL-6
 , μ μ
 μ [471-473]. μ ,
 μ μ IL-6 μ .
 μ , μ IL-6/
 μ gp130 μ - ,
 μ μ IL-6. μ ,
 gp130 μ μ ,
 IL-6, μ μ
 IL-6/IL-6 (trans-signalling pathway).

IL-6

IL-6 μ
 [90, 474-478]. μ mRNA
 IL-6 μ , ,
 [476]. , IL-6
 [478]. mRNA IL-6
 μ
 [474, 475]. μ , ,
 μ μ μ ,
 μ μ mRNA
 . , mRNAs -
 , μ μ . ,
 IL-6 .

μ IL-6

_____ : μ μ mRNA IL-6
 IL-1 TNF- . ,
 - - μ IL-1RA
 μ TNF- , [479].
 _____ :
 IL-6 [480]. ,
 μ IL-6 . μ , IL-1 ,

vivo μ IL-6 μ [495]. μ , in
 NMDA (N-methyl-D-aspartate)
 μ [131]. μ μ IL-6
 IL-6 μ μ μ Ca^{2+} μ
 [496, 497].
 _____: μ in vitro μ , IL-6
 μ ,
 μ NGF (nerve growth factor) [498]. ,
 IL-6 μ NGF ,
 [499-501].
 _____: IL-6 μ
 in vitro [502] in vivo [133, 503-505]. , IL-6
 IL-6 -
 NGF [506].
 IL-6 μ μ _____: IL-6 μ
 [178].
 μ (μ IL-1 , TNF-) [179, 180] -
 μ - (HPA axis: hypothalamic-pituitary-adrenal axis), μ -
 μ , ,
 [507].
 IL-6 _____: IL-6
 μ , / IL-
 6 μ μ μ μ
 [508].

:

IL-6

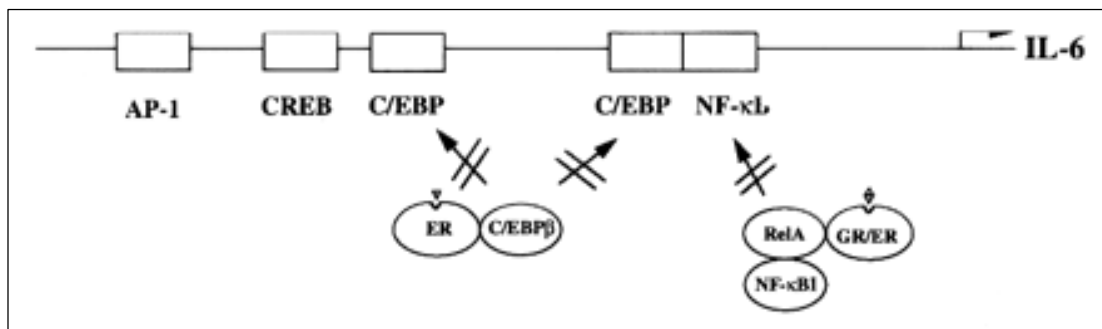
μ μ μ Ca^{2+}

μ

HPA

IL-6

IL-6
 μ μ 7, p21-p15. 5 4 ,
 μ μ [509]. μ ,
 IL-6 μ NF-IL6
 (C/EBP), C/EBP , NF- κ B, μ
 μ [510, 511].



1: μ μ IL-6. -
 μ μ IL-6, μ GR -
 (glucocorticoid receptor) μ Re1A μ NF- κ B μ -
 (estrogen receptor)/C/EBP β ER/NF- κ B μ IL-6, μ μ ER
 . AP-1:AP-1 site, CREB:cyclic
 adenosine 5'-monophosphate-response element binding site, C/EBP:C/EBP binding
 site, NF- κ B:NF- κ B binding site.
 μ .

IL-6 (IL-6R)
 μ μ μ 1, q21-q22.

μ μ IL-6
 μ μ (SNP)
 IL-6, -174 [512]. μ -
 μ μ IL-6 μ in vivo [369, 513]
 μ μ IL-6 [514]. 2 :
 C (), G ().
 CC μ μ IL-6 μ
 μ , GG IL-6

μ [515, 516]. , μ μ C
IL-6 [517], μ
IL-6 μ CC [518].
μ . μ ,
μ - μ , G μ μ
0.87-1.0, μ μ 0.54-0.62 [519-521].
, GG μ -
μ (80-100%), μ
μ (30-45%). , μ μ
μ GG
(38%), μ CC
(18%) [512].

μ μ IL-6 μ

μ μ IL-6
/
IL-6, μ .

IL6-174G

✓ μ 2 [522]
✓ μ μ μ
[523]
✓ μ μ μ [524]
✓ μ μ [525]
✓ μ μ μ [295]
✓ μ μ , μ μ
μ [526]
✓ μ μ - μ μ [527]
✓ μ μ μ Kaposi μ μ μ HIV (Human
Immunodeficiency Virus) [528] μ μ Hodgkin
[529]

IL6-174C

✓ μ [512]
✓ μ μ / μ μ
μ [530]
✓ μ μ μ [531]

: μ μ IL-6 (-174G/C)

, μ μ -
 μ . μ
 μ ,
 μ , μ
 μ
 μ .
 μ μ
 (insertions), (deletions), μ (duplications),
 μ μ (single nucleotide polymorphisms, SNPs)
 . μ μ μ
 μ μ μ μ
 . μ μ μ
 , μ ,
 μ μ μ .
 μ μ μ μ μ
 μ μ μ μ μ . μ
 μ , (μ μ)
 μ) μ) μ ,
 μ μ μ μ μ μ (stratification bias)
 μ , (linkage disequilibrium) μ μ
 μ μ μ μ
 μ .
 μ μ ,
 μ μ μ μ , μ -
 , μ
 .
 μ μ μ μ μ
 μ μ , μ
 (odds ratio) 1.2 1.4. ,
 μ (μ

μ GCS: 3-8, 9-12 13-15, ,
μ

3. μ μ .

4. μ μ μ ,
μ , μ μ -
, μ , μ μ ,
μ , μ
μ μμ . μ μ μ
(, ,) μ
μ μ μ ABC/2.

5. μ μ
μ μ .

6. μ μ μ DN (μ
) μ μ

DNA μ μ .

7. μ 6 μ μ
μ μ
(Glasgow Outcome Scale: GOS).
μ : (GOS= μ
(G) μ (MD)), -
μ μ μ
(GOS= μ (SD)
(V) (D)).

μ μ

μ DNA μ μ μ
μ [532]. -
DNA.

μ μ IL-1RA

μ PCR VNTR μ μ -
 IL-1RA. μ μ [533]
 28681 μ 28970 (Gene Bank Accession Number U65590).
 μ μ (2%)
 μ (EtBr) μ .

μ μ IL-1 (-511)

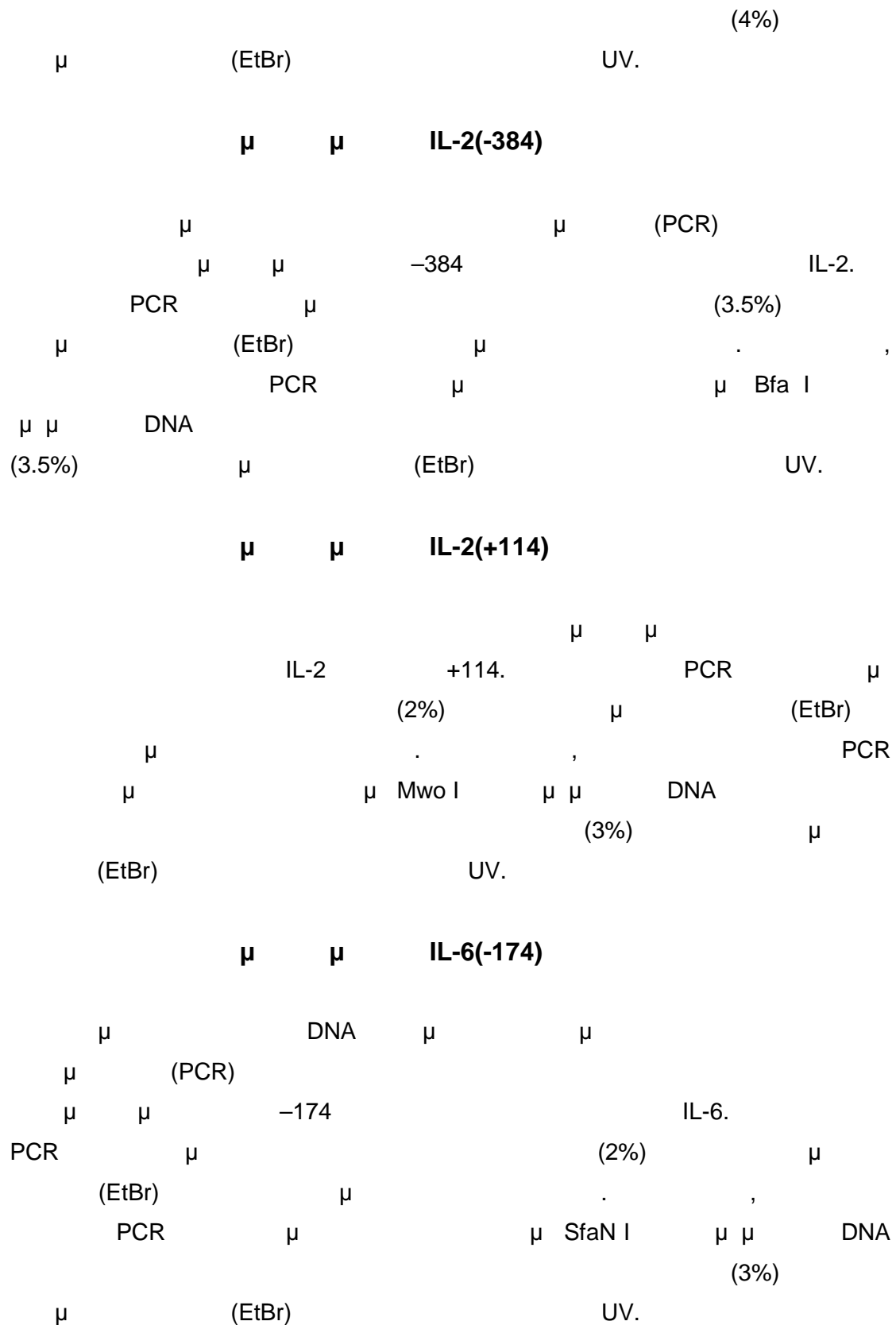
μ μ -511
 IL-1 . PCR μ
 (2.5%) μ (EtBr) μ
 . , PCR μ
 μ Ava I μ μ DNA
 (2.5%) μ (EtBr)
 UV.

μ μ IL-1 (+3953)

μ μ 5⁰
 IL-1 . PCR μ
 (1.5%) μ (EtBr) μ
 . , PCR μ
 μ Taq I μ μ DNA
 (2%) μ (EtBr)
 UV.

μ μ IL-1 (-889)

μ DNA μ μ
 μ (PCR)
 μ μ -889 IL-1 .
 PCR μ (4%) μ
 (EtBr) μ
 PCR μ μ Nco I μ μ DNA



Hardy-Weinberg (H-W) test online (power analysis) Fisher exact test

(Institute of Human Genetics, Technical University Munich, Munich, Germany, <http://ihg.gsf.de/cgibin/hw/hwa1.pl>). CaTS (CaTS Power Calculator for Genetic Studies (Center for Statistical Genetics, University of Michigan, Ann Arbor, MI <http://www.sph.umich.edu/csg/abecasis/cats/>).

GCS (Genetic Case-Control Study) (logistic regression), (odds ratio) (95% confidence intervals). GCS (3-8, 9-12, 13-15)

IL-1 -889C/T (rs1800587), IL-1 +3953C/T (rs1143634), IL-1 -511C/T (rs16944), IL-1RA VNTR (rs2234663)] IL-2 [IL-2 +114G/T (rs2069763), IL-2 -384T/G (rs2069762)]

4. 174G/C (rs1800795) IL-6
 7, .
 (maximum-likelihood estimation).
 shesis (<http://analysis.bio-x.cn/SHEsisMain.htm>),
 permutation tests,
 Freeman-Tukey proportion tests.
 (D r²)
 JLIN
 (<http://www.genepi.com.au/projects/jlin>).
 SPSS v.12.0 (Chicago, IL) SAS v.6.12 (Cary, NC).
 Bonferroni
<http://www.quantitativeskills.com/sisa/calculations/bonfer.htm>,

μ DNA
 μ DNA , μ ,
 μ μ μ μ μ .
 μ μ μ DNA
DNA . μ DNA
 μ μ μ μ μ .
 μ μ μ DNA.
 μ ,
 μ , DNA μ
 μ μ . μ μ μ μ
 μ . μ μ DNA μ
 μ () . μ
10ml μ , Na₂EDTA.
 μ μ μ DNA
:

- μ
- Lysis I: NH₄Cl (155mM), KHCO₃ (10mM), EDTA (1mM), pH=7.4
- Lysis II: Tris (10mM), NaCl (400mM), di-Na EDTA (2mM), pH=8.2
- μ (10mg/ml)
- μ 10% w/v SDS (sodium dodecyl sulfate:)
- μ μ NaCl (6M)
-
- CH₃COONa (3M)
- 1%

μ DNA μ μ
:

1 μ

1. 12ml μ ddH₂O (μ). 15ml μ (μ).
2. μ 15min, 3500rpm, 4°C (μ).
3. , μ μ ddH₂O 12ml μ vortex.
4. μ 15min, 3500rpm, 4°C.
5. μ μ μ μ . μ μ lysis μ 12ml.
6. μ 15min, 3500rpm, 4°C.
7. μ μ 5 6 μ lysis .
8. μ μ μ μ μ . μ μ lysis I μ 6ml (μ lysis I lysis I μ μ DNA. , EDTA μ (Ca²⁺, Mg²⁺) . , μ , DNA). μ μ 15-30min, μ μ .
9. μ 750μl SDS (10% w/v) 100μl (10mg/ml) (SDS μ μ , μ μ . , μ , μ DNA). μ 37°C 16-18hrs (overnight-O/N).

2 μ

1. μ 2ml 6M μ μ NaCl. μ 15sec (μ μ μ).
2. μ 15min, 3500rpm, 4°C.

3. μ DNA. μ μ
4. μ 15min, 3500rpm, 4°C.
5. μ μ 50ml μ
6. μ .
 μ , μ 2 (2 μ μ
 μ) CH_3COONa μ 1/10
 μ . μ μ
 μ CH_3COONa
7. -20°C O/N.

3 μ

1. μ 50min, 3500rpm, 4°C.
2. μ μ . DNA « » μ μ
70% eppendorf (μ μ
 μ μ
 μ).
3. μ 30min, 12000rpm, 4°C.
4. μ μ 2 , μ
20min.
5. μ μ () , (μ μ μ -
DNA) μ μ μ , μ μ
 μ (μ μ
6. μ).
7. DNA 4°C () -20°C (μ
 μ).

μ DNA
 .
 (1%) μ DNA μ (EtBr) DNA μ
 UV.
 DNA.
 .
 μ DNA
 μ DNA
 μ μ μ μ μ .
 DNA
 μ μ 260nm.
 μ , μ (OD) μ DNA
 (μ μ DNA 1:100) μ μ 260nm 280 nm
 μ μ 1cm. 260nm
 μ , 280 nm
 μ μ μ .
 DNA μ μ OD_{260}/OD_{280} μ
 μ 1,7 1,9 DNA, μ μ
 1,7 μ DNA , μ
 μ 1,9 μ μ RNA.
 μ μ 260nm μ OD μ 1
 50 μ g/ml DNA. μ μ
 DNA μ μ :

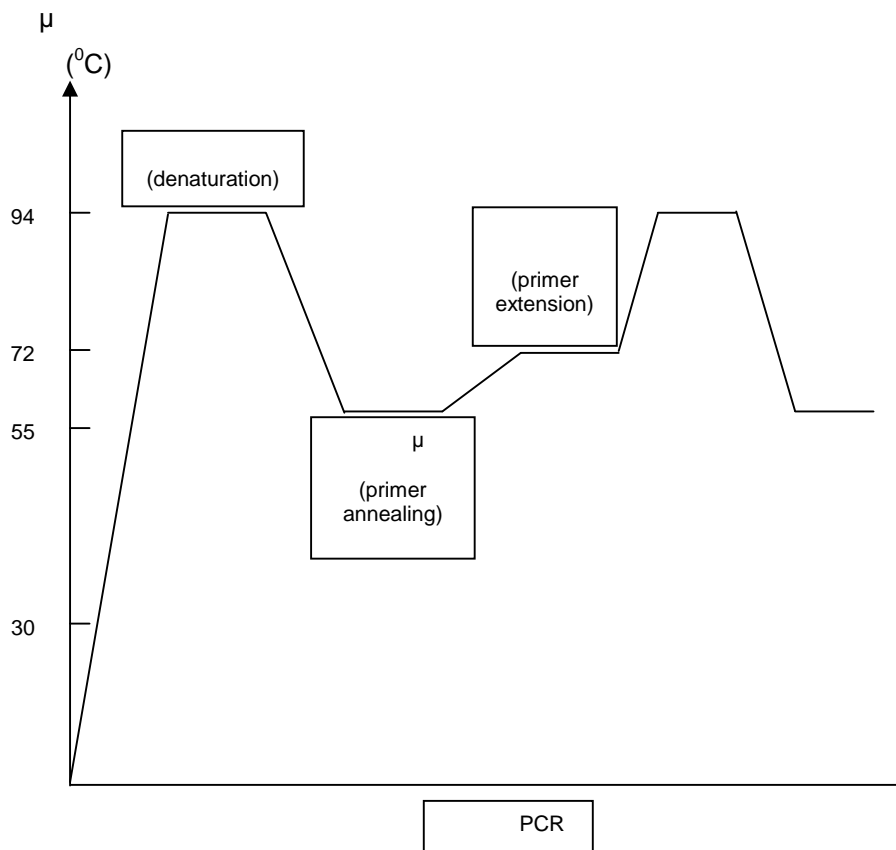
$\text{DNA } (\mu\text{g/ml}) = \quad \times 50 \times \mu \text{ } OD_{260}$

μ μ DNA
 μ 0,2 μ g DNA/ml μ .

μ (PCR: Polymerase Chain Reaction)

μ in vitro μ DNA (DNA-)
μ . PCR μ
DNA: DNA μ
μ DNA μ -
DNA
Taq DNA μ . μ DNA
μ μ μ DNA.
μ DNA
μ ,
μ μ
μ (primer). μ ,
μ μ DNA
- μ μ
μ DNA μ μ -
. PCR μ μ .
PCR μ μ
in vitro eppendorf μ μ
. DNA- μ , DNA
μ μ (denaturation)
2 : , μ
μ μ DNA- (primer annealing)
3 : DNA, Taq DNA μ dNTPs,
μ μ 3 μ
DNA- μ
(extension). DNA 5 → 3 .
μ μ , PCR
μ μ μ μ μ μ
μ DNA, μ μ
μ μ μ DNA- μ
μ μ .

PCR:



PCR (thermal cycler),

PCR.

DNA.

G+C.

G+C

3

2

).

114

μ : :

➤	DNA	μ	(Taq DNA	μ)
➤				μ	-
	μ	-	(primers)		
➤		μ	5		-
			(dNTPs)		
➤			μ	MgCl ₂	
➤	μ		μ	Taq DNA	μ
➤		DNA		μ	- μ

μ , :

μ DNA- PCR

μ DNA-

μ DNA. , μ

DNA, μ PCR. -

μ ,

μ DNA

μ DNA- ,

μ G+C, μ 40% μ 60%.

μ , μ 15 μ 30

μ μ 3

μ μ 0.1-0.2μ .

μ - μ μ (primer-

dimers) μ DNA- ,

DNA-

μ (T_m, melting temperature), μ , μ

(T_a, annealing temperature). μ

DNA μ

μ μ

μ :

$$m = (4^* \mu \text{ G+C}) + (2^* \mu \text{ A+T})$$

μ T_m μ μ 55-65°C.
Taq DNA- μ μ ,
 Thermus aquaticus, μ μ μ
 DNA,
 μ μ PCR. , μ ,
 μ μ μ μ
 . Taq DNA μ
 μ 1-5U\100 μ l. μ μ -
 , μ
 μ μ . μ
 μ (temperature optimum) μ 72°C.
 , 5 (dNTPs) -
 DNA. dNTPs (dATP, dTTP, dCTP dGTP)
 μ μ μ
 μ , μ μ
 μ . ,
 dNTPs μ 20-200 μ .
 PCR μ (Mg²⁺).
 Mg²⁺ μ - ,
 μ DNA μ .
 Mg²⁺ 1,5-2mM.
 Mg²⁺ μ
 μ .
 , μ μ ,
 PCR μ μ (buffer). μ μ
Tris-HCl pH μ 8,3 8,9.
 μ μ μ IL-1RA VNTR
 μ μ μ μ -
 :

Primer F: 5' **GCC CCT CAG CAA CAC TCC TAT** 3'

Primer R: 5' **CCC TGG TCC CCA CAA AAC TA** 3'

PCR

:

PCR _____:

95°C	7min	}	32
95°C	30sec		
56°C	30sec		
72°C	90sec		
72°C	7min		
4°C	∞		

DNA (200ng/μl)	2.50 μl	0.02μgr
10× PCR buffer	2.50μl	1x
dNTPs (40mM)	0.50μl	0.8mM
Primer F (10μM)	0.25μl	0.1μ
Primer R (10μM)	0.25μl	0.1μ
MgCl ₂ (50mM)	1.00μl	2mM
Taq DNA Polymerase (5u/μl)	0.25μl	0.05u
dd ₂	17.75μl	-
(V .)	25.00μl	

50μl.

μ μ IL-1 -511 (-511C/T)
μ μ μ

:

Primer F: ⁵ TGG CAT TGA TCT GGT TCA TC³

Primer R: ⁵ GTT TAG GAA TCT TCC CAC TT³

PCR

:

PCR _____:

95°C	3min	}	35
95°C	1min		
55°C	1min		
74°C	1min		
74°C	6min		
4°C	∞		

50μl.

DNA (200ng/μl)	5.00 μl	0.02μgr
10× PCR buffer	5.00μl	1x
dNTPs (40mM)	1.50μl	1.2mM
Primer F (10μM)	1.00μl	0.2μ
Primer R (10μM)	1.00μl	0.2μ
MgCl ₂ (50mM)	2.00μl	2mM
Taq DNA Polymerase (5u/μl)	0.50μl	0.05u
dd H ₂ O	34.00μl	-
(V _{total})	50.00μl	

μ μ IL-1 +3953
 (+3953C/T) μ μ μ
 :

Primer F: 5' **GCC ACA GTG AGC AGT AAT AGA** 3'
 Primer R: 5' **CAA CAA CAG GAA GAG AGA ACC** 3'

PCR :

PCR :	
95°C	7min
95°C	30sec
55°C	30sec
72°C	90sec
72°C	7min
4°C	∞

32

,
50μl.

DNA (200ng/μl)	5.00 μl	0.02μgr
10× PCR buffer	5.00μl	1x
dNTPs (40mM)	1.50μl	1.2mM
Primer F (10μM)	1.00μl	0.2μ
Primer R (10μM)	1.00μl	0.2μ
MgCl ₂ (50mM)	2.00μl	2mM
Taq DNA Polymerase (5u/μl)	0.50μl	0.05u
dd ₂	34.00μl	-
(V .)	50.00μl	

μ μ IL-1 -889 (-889C/T)
μ μ μ -

:

Primer F: ⁵ **GTT CTA CCA CCT GAA CTA GGC**³

Primer R: ⁵ **TTA CAT ATG AGC CTT CCA TG**³

PCR :

PCR _____:	
94 ⁰ C	7min
94 ⁰ C	1min
50 ⁰ C	1min
72 ⁰ C	1min
72 ⁰ C	10min
4 ⁰ C	∞

,

50μl.

DNA (200ng/μl)	5.00 μl	0.02μgr
10× PCR buffer	5.00μl	1x
dNTPs (40mM)	1.00μl	0.8mM
Primer F (10μM)	1.00μl	0.2μ
Primer R (10μM)	1.00μl	0.2μ
MgCl ₂ (50mM)	1.50μl	1.5mM
Taq DNA Polymerase (5u/μl)	0.50μl	0.05u
dd ₂	35.00μl	-
(V .)	50.00μl	

μ μ IL-2 -384 (-384T/G)
μ μ μ -

:

Primer F: ⁵CTC TTT GTT ACA TTA GCC CAC ACT TAG GTG³

Primer R: ⁵CAC AAT ATG CTA TTC ACA TGT TCA GTG TAG³

PCR :

PCR		:
94 ⁰ C	2min	
94 ⁰ C	20sec	} 35
66 ⁰ C	40sec	
72 ⁰ C	20sec	
72 ⁰ C	10min	
4 ⁰ C	∞	

,

50μl.

DNA (200ng/μl)	5.00 μl	0.02μgr
10× PCR buffer	5.00μl	1x
dNTPs (40mM)	1.50μl	1.2mM
Primer F (10μM)	1.00μl	0.2μ
Primer R (10μM)	1.00μl	0.2μ
MgCl ₂ (50mM)	3.00μl	3mM
Taq DNA Polymerase (5u/μl)	0.50μl	0.05u
dd ₂	33.00μl	-
(V .)	50.00μl	

$\mu \mu$ IL-2 +114
 (+114G/T) $\mu \mu \mu$
 :

Primer F: ⁵ **ATG TAC AGG ATG CAA CTC CT**³

Primer R: ⁵ **TGG TGA GTT TGG GAT TCT TG**³

PCR :

PCR :	
94 ⁰ C	2min
94 ⁰ C	20sec
52 ⁰ C	40sec
72 ⁰ C	20sec
72 ⁰ C	10min
4 ⁰ C	∞

,
50μl.

DNA (200ng/μl)	5.00 μl	0.02μgr
10× PCR buffer	5.00μl	1x
dNTPs (40mM)	1.50μl	1.2mM
Primer F (10μM)	1.00μl	0.2μ
Primer R (10μM)	1.00μl	0.2μ
MgCl ₂ (50mM)	3.00μl	3mM
Taq DNA Polymerase (5u/μl)	0.50μl	0.05u
dd ₂	33.00μl	-
(V .)	50.00μl	

μ μ IL-6 -174 (-174G/C)
μ μ μ -

:

Primer F: ⁵ **CAG AAG AAC TCA GAT GAC TGG**³

Primer R: ⁵ **GCT GGG CTC CTG GAG GGG**³

PCR :

PCR _____:	
95 ⁰ C	5min
95 ⁰ C	1min
63 ⁰ C	1min
72 ⁰ C	2min
72 ⁰ C	10min
4 ⁰ C	∞

,

25μl.

DNA (200ng/μl)	2.50 μl	0.02μgr
10× PCR buffer	2.50μl	1x
dNTPs (40mM)	0.50μl	0.8mM
Primer F (10μM)	0.50μl	0.2μ
Primer R (10μM)	0.50μl	0.2μ
MgCl ₂ (50mM)	0.75μl	1.5mM
Taq DNA Polymerase (5u/μl)	0.50μl	0.1u
dd ₂	17.25μl	-
(V .)	25.00μl	

$$v = E \times z / f$$

, z , E , f .

DNA μ μ .

DNA. μ , μ μ μ .

DNA, μ μ .

, μ , $\mu\mu$.

O D- 3,6- -L- μ 1→4 μ . , μ μ μ .

, μ μ μ .

μ μ .

.

μ μ μ . O μ μ .

μ Tris- -EDTA (1× : 10mM Tris, 0.09M , 0.5M EDTA) μ pH 8, μ μ .

μ .

μ - μ .

μ : () μ μ , () μ , () μ .

, μ μ DNA μ μ : 100mM EDTA , 20% w/v Ficoll, 1%Bromophenol blue).

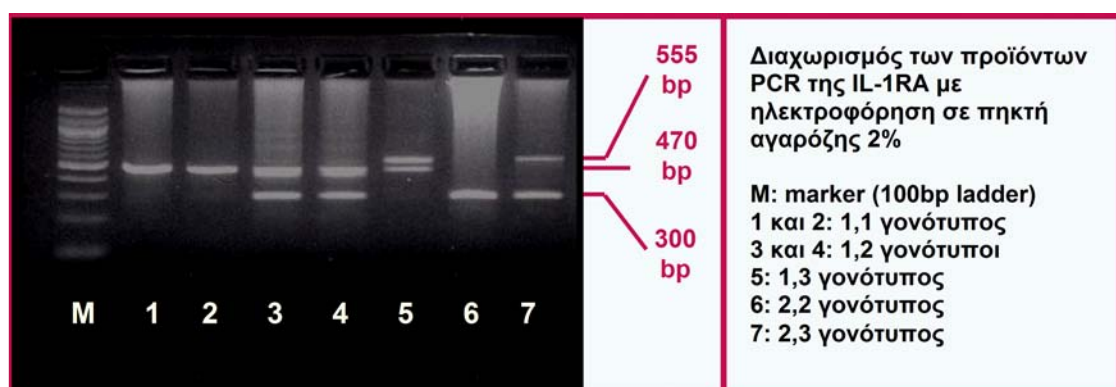
μ (« ») . , μ

(90-100V) μ , DNA
DNA μ
pH, μ .
DNA
DNA μ .
 μ μ μ .
DNA.
UV, DNA ,
 μ .
DNA.
 μ μ ,
DNA μ ,
PCR .

IL-1RA

T PCR μ (2%)
 μ (1 μ g/ml) μ .
 μ PCR μ
 μ μ DNA (100bp DNA Ladder).
 μ μ :

Allele 1	4 repeats of 86bp	470bp
Allele 2	2 repeats	300bp
Allele 3	5 repeats	555bp
Allele 4	3 repeats	385bp
Allele 5	6 repeats	740bp



IL-1 (-511)

To PCR μ (2.5%)
 μ (1 μ g/ml) μ .
 μ PCR μ
 μ μ DNA (100bp DNA Ladder).
 PCR μ μ , 304bp. ,
 , μ
 (2.5%) UV.
 μ μ :

Allele 1	PCR 2 μ μ	190 114bp
Allele 2	μ PCR	304bp

IL-1 (+3953)

To PCR μ (1.5%)
 μ (1 μ g/ml) μ .
 μ PCR μ
 μ μ DNA (100bp DNA Ladder).
 PCR μ μ , 731bp. ,
 , μ
 (2%) UV.
 μ μ :

Allele C	PCR 2 μ μ	497 234bp
Allele T	μ PCR	731bp

IL-1 (-889)

To PCR μ (4%)
 μ (1 μ g/ml) μ .
 μ PCR μ
 μ μ DNA (174 DNA/Hinf I Marker).

PCR μ μ , 99bp. ,
 μ
 (4%) UV.
 μ μ :

Allele T	μ PCR	99bp
Allele C	PCR 2 μ μ	83 16bp

IL-2(-384)

To PCR μ (3.5%)
 μ (1 μ g/ml) μ .
 μ PCR μ
 μ μ DNA (Low molecular weight DNA
 ladder). PCR μ μ , 169bp. ,
 μ , μ
 (3.5%) UV.
 μ μ :

Allele 1	μ PCR	169bp
Allele 2	PCR 2 μ μ	137 32bp

IL-2(+114)

To PCR μ (2%)
 μ (1 μ g/ml) μ .
 μ PCR μ
 μ μ DNA (Low molecular weight DNA
 ladder). PCR μ μ , 262bp. ,
 μ , μ
 (3%) UV.
 μ μ :

Allele G	μ PCR	262bp
Allele T	PCR 2 μ μ	151 111bp

IL-6(-174)

To μ PCR μ (2%)
μ (1μg/ml) μ .
μ PCR μ
μ μ DNA (100bp DNA ladder).
PCR μ μ , 611bp. ,
, μ
(3%) UV.
μ μ :

Allele G	μ PCR	611bp
Allele C	PCR 2 μ μ	367 244bp

5 G↓AATTC3
3 CTTAA↑G5

Hae III

5 GG↓CC3

3 CC↑GG5

5 GG CC3

3 CC GG5

Eco RI

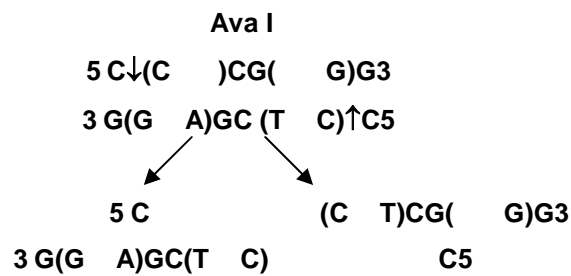
5 G↓AATTC3
3 CTTAA↑G5

5' G AATTC 3'
3' CTTAA G 5'

μ , μ μ μ μ μ
μ μ -
12 μ 15°C.

IL-1 (-511)

PCR μ μ μ Ava I. To
Ava I μ μ Anabaena
variabilis. Ava I, μ , μ
:




μ PCR
40μl.

PCR product	30.00 μl	
μ Ava I (10u/μl)	1.00 μl	0.25u
10x NE Buffer 2	4.00 μl	1x
dd ₂	5.00 μl	-
(V)	40.00 μl	

16-18hrs (O/N) 37°C, μ μ DNA
2.5%
μ (1μg/ml) μ μ 100V
UV. μ
μ μ DNA (100bp
DNA Ladder).
μ μ :

Ηλεκτροφόρηση του PCR προϊόντος της IL-1 β (-511) σε 2.5% πηκτή αγαρόζης μετά από πέψη με το *NotI* περιοριστικό ένζυμο.

M: marker (100bp DNA ladder)
1 και 4: 2,2 γονότυπος
2, 3, 5, 6: 1,1 γονότυπος
7: 1,2 γονότυπος



Lane	Genotype	Band(s) (bp)
M	Marker	304, 190, 114
1	2,2	190
2	1,1	114
3	1,1	114
4	2,2	190
5	1,1	114
6	1,1	114
7	1,2	190, 114

Taq I PCR Escherichia Coli. Taq I.

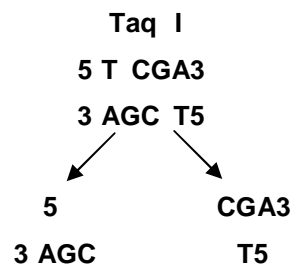
μ μ μ - ,

μ

.

Taq I, μ , μ

:



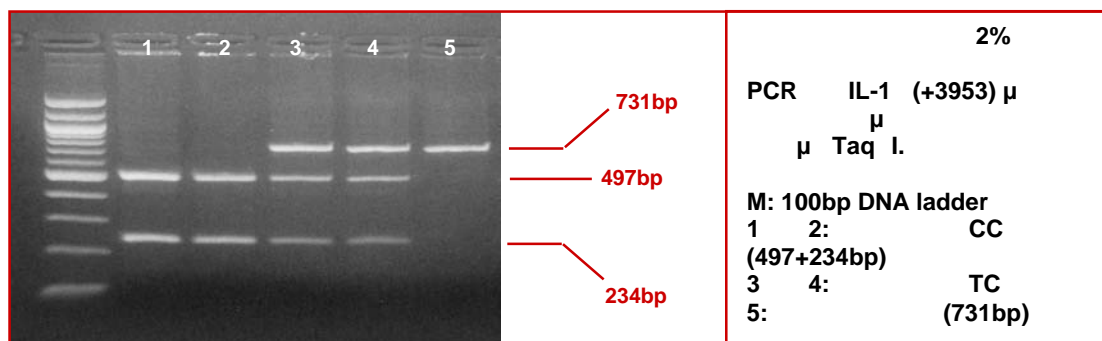
Institutional Repository - Library & Information Centre - University of Thessaly
15/10/2023 16:36:36 EEST - 167.114.118.212

PCR product	30.00 μ l	
μ Taq I (20u/ μ l)	1.00 μ l	0.5u
10x NE Buffer 3	4.00 μ l	1x
100x BSA [*]	0.40 μ l	1x
dd ₂	4.60 μ l	-
(V)	40.00 μ l	

* BSA (Bovine Serum Albumin: μ)

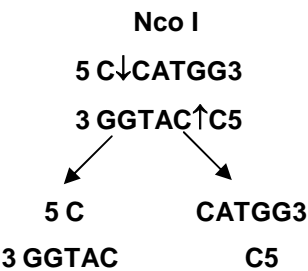
μ , , μ .
 16-18hrs (O/N) 65°C, μ μ DNA
 2%
 μ (1 μ g/ml) μ μ 100V
 UV. μ
 μ μ μ DNA (100bp
 DNA ladder).

μ μ :
 ➤ IL1B+3953*C (-C +3953 5
 IL-1B): μ Taq I μ
 PCR μ , 2 μ μ (497 234bp).
 ➤ IL1B+3953* (μ -T +3953 5
 IL-1B): μ Taq I μ
 PCR (731bp).



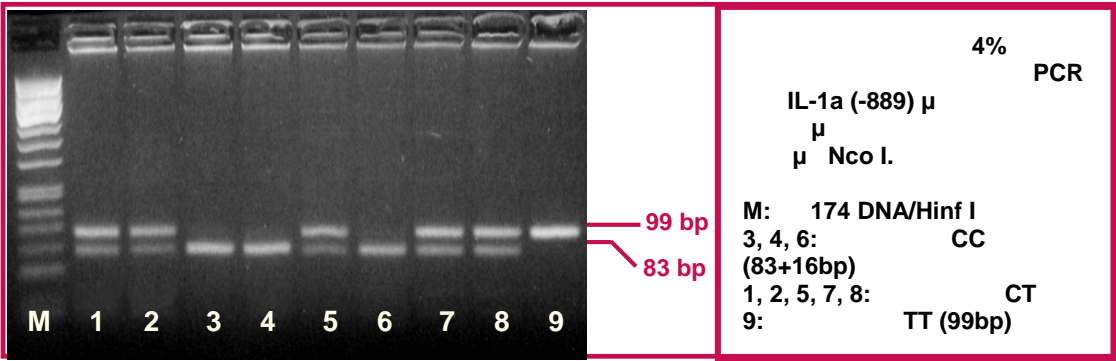
IL-1 (-889)

PCR μ μ μ Nco I. To
 Nco I μ μ Nocardia corallina.

Nco I, μ , μ
 :

 μ PCR
 45 μ l.

PCR product	35.00 μ l	
μ Nco I (10u/ μ l)	1.50 μ l	0.33u
10x NE Buffer 4	4.50 μ l	1x
dd ₂	4.00 μ l	-
(V)	45.00 μ l	

16-18hrs (O/N) 37°C, μ μ DNA
 4%
 μ (1 μ g/ml) μ μ 100V
 UV. μ
 μ μ μ DNA (174
 DNA/Hinf I Marker).
 μ μ :
 >IL1A-889*C (-C -889
 IL-1A): μ Nco I μ
 PCR μ , 2 μ μ (83 16bp).
 >IL1A-889*T (μ -T -889
 IL-1A): μ Nco I μ
 PCR (99bp).
 μ μ 16bp μ μ 83 bp
 μ IL1A-889*C.



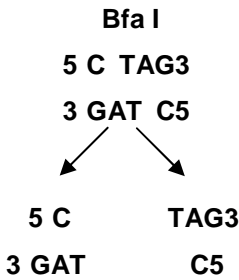
IL-2(-384)

PCR μ μ μ Bfa I. To Bfa

I μ μ Bacteroides fragilis.

Bfa I, μ , μ

:



μ PCR

40 μ l.

PCR product	30.00 μ l	
μ Bfa I (5u/ μ l)	3.00 μ l	0.38u
10x NE Buffer 4	4.00 μ l	1x
dd ₂	3.00 μ l	-
(V)	40.00 μ l	

16-18hrs (O/N) 37⁰C, μ μ DNA

3.5%

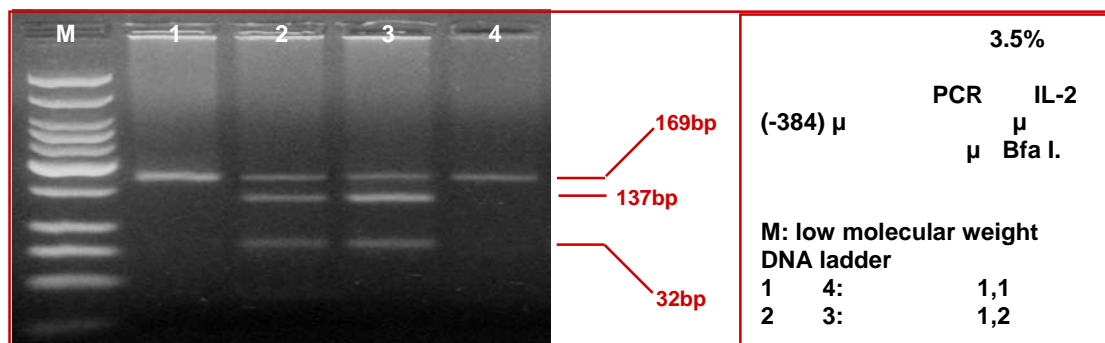
μ (1 μ g/ml) μ μ 100V

UV. μ

μ μ μ DNA (Low

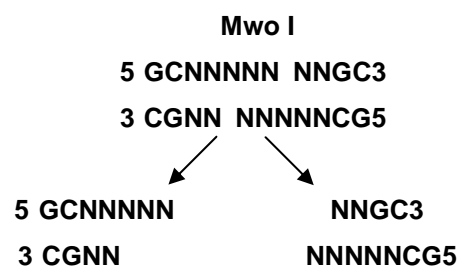
molecular weight DNA ladder).

μ μ :
 μ -T -384 IL-
 2): μ Bfa I μ PCR
 (169bp).
 μ -G -384
 IL-2): μ fa I μ PCR
 μ , 2 μ μ (137 32bp).
 μ , μ μ 32bp . , μ
 μ μ 137bp μ IL2-384*2.



IL-2(+114)

PCR μ μ μ Mwo I. To
 Mwo I μ μ Methanobacterium
 wolfeii. Mwo I, μ , μ
 :



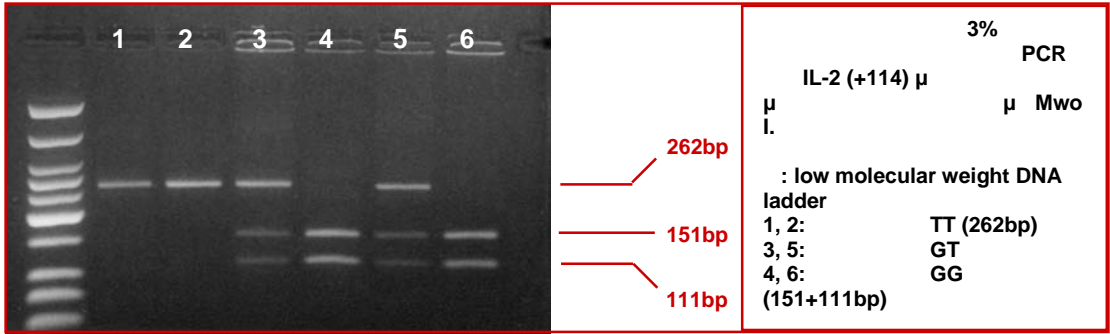
* :

μ PCR
 40 μ l.

PCR product	30.00 µl	
µ Mwo I (5u/µl)	1.00 µl	0.13u
10x NE Buffer 3	4.00 µl	1x
dd ₂	5.00 µl	-
(V)	40.00 µl	

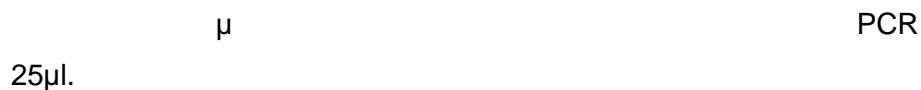
16-18hrs (O/N) 60°C, µ µ DNA
3%
µ (1µg/ml) µ µ 100V
UV. µ
µ µ DNA (Low
molecular weight DNA ladder).

µ µ :
➤ IL2+114*G (-G +114 1
IL-2): µ Mwo I µ
PCR µ , 2 µ µ (151 111bp).
➤ IL2+114*T (µ -T +114 1
IL-2): µ Mwo I µ
PCR (262bp).

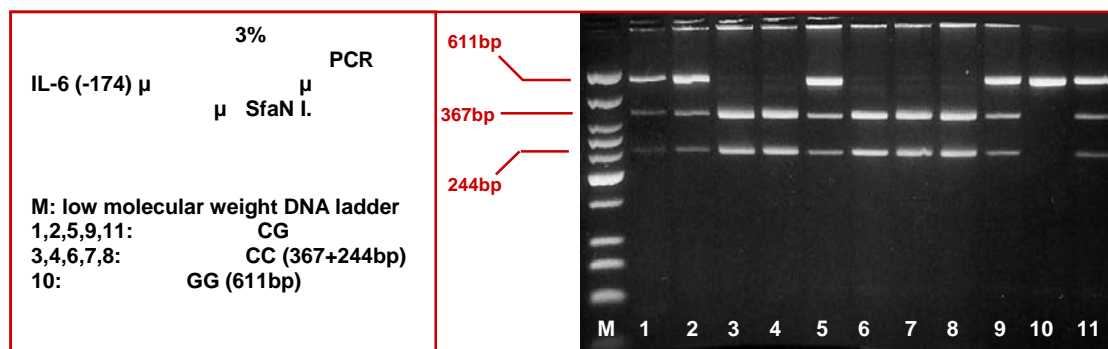


IL-6(-174)

PCR µ µ SfaN I. To
SfaN I µ µ Streptococcus
faecium. SfaN I, µ , µ
:



16-18hrs (O/N) 37°C, μ μ DNA 3% 100V μ (1μg/ml) μ UV. μ DNA (Low molecular weight DNA ladder). μ : ➤IL6-174*G (-G -174 IL-6): μ SfaN I μ PCR (611bp). ➤IL6-174*C (-C -174 IL-6): μ SfaN I μ PCR μ , 2 μ μ (367 244bp).



μ 365
 μ , 305 60 (5:1). μ
 (mean) 40.06±20,99 μ
 μ . μ -
 , μ
 [1].
 μ μ μ (GCS). μ GCS
 μ 10.99±3.85. GCS
 34.24% (GCS 8), 15,34% μ
 μ 9-12 50.41%
 μ (GCS 13-15).
 μ μ
 μ μ .
 , 78 (21.37%) μ
 . 287 (78.63%) μ .
 μ , 167 (45.75%) μ , 40 -
 (10.95%) μ μ , 185 (50.68%)
 μ , 91 (24.93%) μ μ ,
 24 (6.57%) μ 44
 (12.05%) μ .
 , μ μ -
 (GOS) μ 6 μ μ .
 μ , 242 (66.30%) , 54
 (14.79%) μ , 33 (9.04%)
 , 21 (5.75%)
 15 μ (4.11%) μ 6 μ
 μ μ .
 , μ GOS 6μ μ -
 μ . μ ,
 μ 5 4
 GOS, μ , μ -
 6 μ μ , μ
 3, 2 1 GOS. , , 296 μ

(81.09%) μ ,
(18.91%) μ .

69

μ	μ μ
	365
	305 (83.6%)
	60 (16.4)
(\pm SD)	40.06 \pm 20.99
(%)	57 (15.61%)
(%)	17 (4.65%)
	26 (7.12%)
μ (%)	45 (12.32%)
μ (%)	48 (13.15%)
(%)	109 (29.86%)
GCS (μ \pm SD)	10.99 \pm 3.85
GCS: 3-8	125 (34.24%)
GCS: 9-12	56 (15.34%)
GCS: 13-15	184 (50.41%)
6 μ	
(5)	242 (66.30%)
(4)	54 (14.79%)
(3)	33 (9.04%)
(2)	21 (5.75%)
(1)	15 (4.11%)
(4-5)	296 (81.09%)
μ (1-3)	69 (18.91%)
μ	
μ	78 (21.37%)
μ	287 (78.63%)
μ	167 (45.75%)
μ μ	40 (10.95%)
μ	185 (50.68%)
μ μ	55 (15.06%)
μ μ	91 (24.9%)

μ	24 (6.57%)
μ	44 (12.05%)
SD= , GCS= μ μ	

μ μ μ μ : IL-1 -511C/T (rs16944), IL-1 +3953C/T (rs1143634), IL-1 -889C/T (rs1800587), IL-1RA VNTR 2 (rs2234663), IL-2 +114G/T (rs2069763), IL-2 -384T/G (rs2069762) IL-6 -174G/C (rs1800795).

μ μ μ μ , μ μ μ μ Hapmap (<http://hapmap.ncbi.nlm.nih.gov>, Protocol: Phase3 _Draft2).

	SNP	μ rs	μ μ			Minor allele frequency μ
1.	IL-1 (-889C/T)	rs1800587	113259431 (chr 2)	IL-1	μ	0.252
2.	IL-1 (+3953C/T)	rs1143634	113306861 (chr 2)	5	Coding-synonymous	0.208
3.	IL-1 (-511C/T)	rs16944	113311338 (chr 2)	IL-1	μ	0.358
4.	IL-1RA (VNTR)	rs2234663	113604577 (chr 2)	2	No-coding	No data
5.	IL-2(+114G/T)	rs2069763	123596932 (chr 4)	1	Coding-synonymous	0.342
6.	IL-2(-384T/G)	rs2069762	123597430 (chr 4)	IL-2	μ	0.273
7.	IL-6(-174G/C)	rs1800795	22733170 (chr 7)	IL-6	μ	0.465

(1-7) μ - μ μ : μ , μ μ μ . $\mu\mu$ Fisher exact test μ μ Hardy-Weinberg (H-W) . μ μ IL-1 (-511C/T, rs16944), IL-1 (+3953C/T, rs1143634), IL-1 (-889C/T, rs1800587), IL-1RA (VNTR, rs2234663), IL-2(+114G/T, rs2069763), IL-6(-174G/C, rs1800795) H-W (p>0.05), μ μ μ μ

μ μ IL-2 (-384T/G, rs2069762)
 H-W (p<0.01).
 μ μ μ μ GG,
 TG (59.18%), μ
 μ . μ
 μ GG [534]. ,
 μ . μ μ μ
 GG μ μ ,
 μ .
 8-14
 μ μ μ : 1)
 μ GCS, 2)
 6 μ μ GOS 3) μ μ
 . μ
 μ μ μ - μ
 (allele contrast). , μ
 μ μ μ (logistic regression analysis)
 μ . ,
 , , μ , μ μ
 μ . 6 μ
 μ GCS
 μ . , μ
 μ , GCS μ
 μ μ .
 μ 7 SNPs μ Bonferroni
 μ 0.05 0.007. , μ -
 μ μ μ μ 0.007.
 μ μ IL-1 (-511C/T, rs16944), IL-
 1 (+3953C/T, rs1143634), IL-1 (-889C/T, rs1800587), IL-2 (-384T/G
 rs2069762) IL-6(-174G/C, rs1800795)
 μ .
 μ μ IL-2(+114G/T, rs2069763)
 μ 2 () μ μ

μ GCS 3-8 μ GCS 13-15 μ μ
 ([μ μ] 0.57 [0.38-0.80], $p=0.002$)
 μ μ (0.53 [0.31-0.81], $p=0.009$). μ
 μ μ μ Bonferroni μ
 μ $p=0.02$ 2.32 μ μ
 μ 1.18 5.12.
 μ μ IL-1RA (VNTR, rs2234663)
 μ 2 (μ) 4.5 μ
 μ μ μ μ (μ μ)
 [μ μ] 4.57 [1.67-12.96], $p=0.004$). μ μ
 μ μ (0.26 [0.14-
 0.71], $p=0.003$).
 μ 2 μ
 μ : GCS 3-8 μ GCS 9-12
 (μ 0.32 [0.12-0.90], $p=0.030$ μ
 0.32 [0.16-0.83], $p=0.02$) GCS 3-8 μ GCS 13-15
 (μ 0.37 [0.19-0.78], $p=0.02$ μ -
 μ 0.45 [0.25-0.91], $p=0.017$).
 μ 6 μ , μ 2 μ
 μ : μ 0.39 [0.19-0.89], $p=0.011$
 μ μ 0.43 [0.19-0.86], $p=0.035$.

1: μ											
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2:	μ	μ	μ	μ	IL-2 (-384T/G rs2069762)						
								μ			
	1.1 (TT)	%	1.2 (TG)	%	2.2 (GG)	%		1 (T)	%	2 (G)	%
(n=365)	149	40,82%	216	59,18%	0	0,00%		514	70,41%	216	29,59%
(n=296)	120	40,54%	176	59,46%	0	0,00%		416	70,27%	176	29,73%
(n=69)	29	42,03%	40	57,97%	0	0,00%		98	71,01%	40	28,99%
GCS 3-8 (n=125)	56	44,80%	69	55,20%	0	0,00%		181	72,40%	69	27,60%
GCS 9-12 (n=56)	22	39,29%	34	60,71%	0	0,00%		78	69,64%	34	30,36%
GCS 13-15 (n=184)	71	38,59%	113	61,41%	0	0,00%		255	69,29%	113	30,71%
μ μ (n=287)	116	40,42%	171	59,58%	0	0,00%		403	70,21%	171	29,79%
μ (n=78)	33	42,31%	45	57,69%	0	0,00%		111	71,15%	45	28,85%

IL-2 (+114G/T rs2069763)												
3:	μ	μ	μ	μ								
								μ				
		1.1 (GG)	%	1.2 (GT)	%	2.2 (TT)		%	1 (G)	%	2 (T)	%
(n=365)		183	50,14%	145	39,73%	37		10,14%	511	70,00%	219	30,00%
(n=296)		150	50,68%	115	38,85%	31		10,47%	415	70,10%	177	29,90%
(n=69)		33	47,83%	30	43,48%	6		8,70%	96	69,57%	42	30,43%
GCS 3-8 (n=125)		51	40,80%	55	44,00%	19		15,20%	157	62,80%	93	37,20%
GCS 9-12 (n=56)		27	48,21%	23	41,07%	6		10,71%	77	68,75%	35	31,25%
GCS 13-15 (n=184)		105	57,07%	67	36,41%	12		6,52%	277	75,27%	91	24,73%
μ μ (n=287)		145	50,52%	112	39,02%	30		10,45%	402	70,03%	172	29,97%
μ (n=78)		38	48,72%	33	42,31%	7		8,97%	109	69,87%	47	30,13%

4:	μ	μ	μ	μ	IL-6 (-174C/G rs1800795)						
								μ			
	1.1 (CC)	%	1.2 (CG)	%	2.2 (GG)	%		1 (C)	%	2 (G)	%
(n=365)	225	61,64%	126	34,52%	14	3,84%		576	78,90%	154	21,10%
(n=296)	181	61,15%	103	34,80%	12	4,05%		465	78,55%	127	21,45%
(n=69)	44	63,77%	23	33,33%	2	2,90%		111	80,43%	27	19,57%
GCS 3-8 (n=125)	81	64,80%	41	32,80%	3	2,40%		203	81,20%	47	18,80%
GCS 9-12 (n=56)	29	51,79%	26	46,43%	1	1,79%		84	75,00%	28	25,00%
GCS 13-15 (n=184)	115	62,50%	59	32,07%	10	5,43%		289	78,53%	79	21,47%
μ μ (n=287)	177	61,67%	97	33,80%	13	4,53%		451	78,57%	123	21,43%
μ (n=78)	48	61,54%	29	37,18%	1	1,28%		125	80,13%	31	19,87%

5: μ μ μ μ IL-1RN (VNTR rs2234663)																		
													μ					
μ μ IL-1RA	1.1	%	1.3	%	1.2	%	2.2	%	2.3	%	1		%	2	%	3	%	
(n=151)	81	53,64%	6	3,97%	51	33,77%	12	7,95%	1	0,66%	219		72,52%	76	25,17%	7	2,32%	
(n=119)	60	50,42%	3	2,52%	44	36,97%	11	9,24%	1	0,84%	167		70,17%	67	28,15%	4	1,68%	
(n=32)	21	65,63%	3	9,38%	7	21,88%	1	3,13%	0	0,00%	52		81,25%	9	14,06%	3	4,69%	
GCS 3-8 (n=59)	24	40,68%	1	1,69%	27	45,76%	7	11,86%	0	0,00%	76		64,41%	41	34,75%	1	0,85%	
GCS 9-12 (n=24)	15	62,50%	2	8,33%	7	29,17%	0	0,00%	0	0,00%	39		81,25%	7	14,58%	2	4,17%	
GCS 13-15 (n=68)	42	61,76%	3	4,41%	17	25,00%	5	7,35%	1	1,47%	104		76,47%	28	20,59%	4	2,94%	
(n=117) μ μ	55	47,01%	4	3,42%	46	39,32%	11	9,40%	1	0,85%	160		68,38%	69	29,49%	5	2,14%	
(n=34) μ	26	76,47%	2	5,88%	5	14,71%	1	2,94%	0	0,00%	59		86,76%	7	10,29%	2	2,94%	

6: μ μ μ μ IL-1 (-511C/T rs16944)											
								μ			
	1.1 (CC)	%	1.2 (CT)	%	2.2 (TT)	%		1 (C)	%	2 (T)	%
(n=151)	51	33,77%	83	54,97%	17	11,26%		185	61,26%	117	38,74%
(n=119)	42	33,33%	69	54,76%	15	11,90%		153	60,71%	99	39,29%
(n=32)	9	36,00%	14	56,00%	2	8,00%		32	64,00%	18	36,00%
GCS 3-8 (n=59)	20	33,90%	36	61,02%	3	5,08%		76	64,41%	42	35,59%
GCS 9-12 (n=24)	9	37,50%	11	45,83%	4	16,67%		29	60,42%	19	39,58%
GCS 13-15 (n=68)	22	32,35%	36	52,94%	10	14,71%		80	58,82%	56	41,18%
A μ (n=117)	36	30,77%	67	57,26%	14	11,97%		139	59,40%	95	40,60%
X μ (n=34)	15	44,12%	16	47,06%	3	8,82%		46	67,65%	22	32,35%

7:	μ	μ	μ	μ	IL-1 (-889 C/T rs1800587)		μ				
		1.1 (CC)	%	1.2 (CT)	%	2.2 (TT)	%	1 (C)	%	2 (T)	%
(n=215)		107	49,77%	84	39,07%	24	11,16%	298	69,30%	132	30,70%
(n=185)		93	50,27%	72	38,92%	20	10,81%	258	69,73%	112	30,27%
(n=30)		14	46,67%	12	40,00%	4	13,33%	40	66,67%	20	33,33%
GCS 3-8 (n=64)		34	53,13%	24	37,50%	6	9,38%	92	71,88%	36	28,13%
GCS 9-12 (n=27)		9	33,33%	12	44,44%	6	22,22%	30	55,56%	24	44,44%
GCS 13-15 (n=124)		64	51,61%	48	38,71%	12	9,68%	176	70,97%	72	29,03%
μ μ (n=168)		82	48,81%	69	41,07%	17	10,12%	233	69,35%	103	30,65%
μ (n=47)		25	53,19%	15	31,91%	7	14,89%	65	69,15%	29	30,85%

8: μ μ IL-1 (+3953C/T rs1143634)				
[2] vs [1]				
	2 ()	1 (C)	OR (95%CI)	p-value
(n=296)	148	444	-	
(n=69)	35	103	1.03 [0.68-1.71] [†]	p=0.91
GCS 3-8 (n=125)	58	192	-	
GCS 9-12 (n=56)	33	79	1.35 [0.87-2.35]*	p=0.22
GCS 13-15 (n=184)	92	276	1.15 [0.69-1.73]*	p=0.65
μ (n=287)	144	430	-	
μ (n=78)	39	117	0.98 [0.68-1.53] [†]	p=0.96
μ 2 [12+22] vs [11]				
	[12+22] (/-)	[11] (CC)	OR (95%CI)	p-value
(n=296)	124	172	-	
(n=69)	30	39	1.01 [0.68-1.84] [†]	p=0.82
GCS 3-8 (n=125)	49	76	-	
GCS 9-12 (n=56)	27	29	1.49 [0.73-2.77]*	p=0.28
GCS 13-15 (n=184)	78	106	1.16 [0.76-1.84]*	p=0.61
μ (n=287)	120	167	-	
μ (n=78)	34	44	1.03 [0.61-1.81] [†]	p=0.75
μ 2 [22] vs [11+12]				
	[22] ()	[11+12] (C/-)	OR (95%CI)	p-value
(n=296)	24	272	-	
(n=69)	5	64	1.16 [0.43-3.03] [†]	p=0.84
GCS 3-8 (n=125)	9	116	-	
GCS 9-12 (n=56)	6	50	0.68 [0.27-1.98]*	p=0.46
GCS 13-15 (n=184)	14	170	0.99 [0.41-2.63]*	p=0.85
μ (n=287)	24	263	-	
μ (n=78)	5	73	1.37 [0.46-3.66] [†]	p=0.54

(*) GCS , , μ , μ μ .(†) μ GCS / μ

9: μ μ IL-2 (-384T/G rs2069762)				
[2] vs [1]				
	2 (G)	1 (T)	OR (95%CI)	p-value
(n=296)	176	416	-	
(n=69)	40	98	0.92 [0.68-1.90] [†]	p=0.84
GCS 3-8 (n=125)	69	181	-	
GCS 9-12 (n=56)	34	78	1.12 [0.79-1.81]*	p=0.52
GCS 13-15 (n=184)	113	255	1.15 [0.79-1.68]*	p=0.45
μ (n=287)	171	403	-	
μ (n=78)	45	111	0.98 [0.61-1.44] [†]	p=0.85
μ 2 [12+22] vs [11]				
	[12+22] (G/-)	[11] TT)	OR (95%CI)	p-value
(n=296)	176	120	-	
(n=69)	40	29	0.92 [0.59-1.83] [†]	p=0.87
GCS 3-8 (n=125)	69	56	-	
GCS 9-12 (n=56)	34	22	1.21 [0.63-2.37]*	p=0.46
GCS 13-15 (n=184)	113	71	1.45 [0.73-2.28]*	p=0.21
μ (n=287)	171	116	-	
μ (n=78)	45	33	0.91 [0.54-1.58] [†]	p=0.78
μ μ 2 [22] vs [11+12]				
	[22] (GG)	[11+12] (T/-)	OR (95%CI)	p-value
(n=296)	0	296	-	
(n=69)	0	69	0.21 [0.004-12.10] [†]	p=1.00
GCS 3-8 (n=125)	0	125	-	
GCS 9-12 (n=56)	0	56	0.42 [0.007-23.41]*	p=1.00
GCS 13-15 (n=184)	0	184	1.46 [0.035-77.63]*	p=1.00
μ (n=287)	0	287	-	
μ (n=78)	0	78	0.24 [0.004-16.45] [†]	p=1.00

10:	μ	μ	IL-2 (+114G/T rs2069763)	
[2] vs [1]				
	2 (T)	1 (G)	OR (95%CI)	p-value
(n=296)	177	415	-	
(n=69)	42	96	1.03 [0.67-1.57] [†]	p=0.93
GCS 3-8 (n=125)	93	157	-	
GCS 9-12 (n=56)	35	77	0.767 [0.477-1.234]*	p=0.27371
GCS 13-15 (n=184)	91	277	0.57 [0.38-0.80]*	p=0.002
μ (n=287)	172	402	-	
μ (n=78)	47	109	1.04 [0.67-1.51] [†]	p=0.94
μ 2 [12+22] vs [11]				
	[12+22] (T/-)	[11] (GG)	OR (95%CI)	p-value
(n=296)	146	150	-	
(n=69)	36	33	1.17 [0.61-1.92] [†]	p=0.64
GCS 3-8 (n=125)	74	51	-	
GCS 9-12 (n=56)	29	27	0.72 [0.36-1.41]*	p=0.37
GCS 13-15 (n=184)	79	105	0.53 [0.31-0.81]*	p=0.009
μ (n=287)	142	145	-	
μ (n=78)	40	38	1.12 [0.68-1.79] [†]	p=0.75
μ 2 [22] vs [11+12]				
	[22] (TT)	[11+12] (G/-)	OR (95%CI)	p-value
(n=296)	31	265	-	
(n=69)	6	63	1.27 [0.46-2.88] [†]	p=0.61
GCS 3-8 (n=125)	19	106	-	
GCS 9-12 (n=56)	6	50	1.45 [0.58-3.52]*	p=0.48
GCS 13-15 (n=184)	12	172	2.32 [1.18-5.12]*	p=0.02
μ (n=287)	30	257	-	
μ (n=78)	7	71	1.17 [0.48-2.55] [†]	p=0.65

(*) GCS , , μ , μ μ .(†) μ GCS / μ

11:	μ	μ	IL-6 (-174C/G rs1800795)	
[2] vs [1]				
	2 (G)	1 (C)	OR (95%CI)	p-value
(n=296)	127	465	-	
(n=69)	27	111	0.87 [0.52-1.55] [†]	p=0.68
GCS 3-8 (n=125)	47	203	-	
GCS 9-12 (n=56)	28	84	1.41 [0.87-2.32]*	p=0.19
GCS 13-15 (n=184)	79	289	1.167 [0.75-1.73]*	p=0.43
μ (n=287)	123	451	-	
μ (n=78)	31	125	0.93 [0.54-1.42] [‡]	p=0.68
μ 2 [12+22] vs [11]				
	[12+22] (G/-)	[11] (CC)	OR (95%CI)	p-value
(n=296)	115	181	-	
(n=69)	25	44	0.87 [0.53-1.59] [†]	p=0.66
GCS 3-8 (n=125)	44	81	-	
GCS 9-12 (n=56)	27	29	1.74 [0.92-3.01]*	p=0.096
GCS 13-15 (n=184)	69	115	1.12 [0.67-1.81]*	p=0.67
μ (n=287)	110	177	-	
μ (n=78)	30	48	1.05 [0.64-1.71] [‡]	p=0.96
μ μ 2 [22] vs [11+12]				
	[22] (GG)	[11+12] (C/-)	OR (95%CI)	p-value
(n=296)	12	284	-	
(n=69)	2	67	1.42 [0.32-5.88] [†]	p=0.63
GCS 3-8 (n=125)	3	122	-	
GCS 9-12 (n=56)	1	55	1.31 [0.12-12.96]*	p=0.76
GCS 13-15 (n=184)	10	174	0.43 [0.12-1.60]*	p=0.21
μ (n=287)	13	274	-	
μ (n=78)	1	77	3.63 [0.47-25.28] [‡]	p=0.19

12:	μ	μ	IL-1RN (VNTR rs2234663)	
[2] vs [1]				
	2	1	OR (95%CI)	p-value
(n=119)	67	167	-	
(n=32)	9	52	0.43 [0.19-0.86][†]	p=0.035
GCS 3-8 (n=59)	41	76	-	
GCS 9-12 (n=24)	7	39	0.32 [0.16-0.83]*	p=0.02
GCS 13-15 (n=68)	28	104	0.45 [0.25-0.91]*	p=0.017
A μ (n=117)	69	160	-	
X μ (n=34)	7	59	0.26 [0.14-0.71][‡]	p=0.003
μ 2 [12+22] vs [11]				
	Allele 2 carrier	Allele 2 non-carrier	OR (95%CI)	p-value
(n=119)	56	63	-	
(n=32)	8	24	0.37 [0.19-0.78][†]	p=0.02
GCS 3-8 (n=59)	34	25	-	
GCS 9-12 (n=24)	7	17	0.32 [0.12-0.90]*	p=0.030
GCS 13-15 (n=68)	23	45	0.39 [0.19-0.89]*	p=0.011
A μ (n=117)	58	59	-	
X μ (n=34)	6	28	4.57 [1.67-12.96][‡]	p=0.004
μ μ 2 [22] vs [11+12]				
	[22]	[11+12+1.3+2.3]	OR (95%CI)	p-value
(n=119)	11	108	-	
(n=32)	1	31	2.83 [0.28-25.13] [†]	p=0.31
GCS 3-8 (n=59)	7	52	-	
GCS 9-12 (n=24)	0	24	6.31 [0.37-110.1]*	p=0.11
GCS 13-15 (n=68)	5	63	1.68 [0.514-5.52]*	p=0.47
A μ (n=117)	11	106	-	
X μ (n=34)	1	33	3.21 [0.53-25.6] [†]	p=0.25

13: μ μ IL-1 (-511C/T rs16944)				
[2] vs [1]				
	2 (T)	1 (C)	OR (95%CI)	p-value
(n=119)	99	153	-	
(n=32)	18	32	0.82 [0.49-1.60] [†]	p=0.65
GCS 3-8 (n=59)	42	76	-	
GCS 9-12 (n=24)	19	29	1.17 [0.56-2.12]*	p=0.65
GCS 13-15 (n=68)	56	80	1.23 [0.77-1.98]*	p=0.38
A μ (n=117)	95	139	-	
X μ (n=34)	22	46	0.73 [0.36-1.11] [†]	p=0.29
μ 2 [12+22] vs [11]				
	[12+22] (T/-)	[11] (CC)	OR (95%CI)	p-value
(n=119)	84	42	-	
(n=32)	16	9	0.87 [0.33-1.96] [†]	p=0.63
GCS 3-8 (n=59)	39	20	-	
GCS 9-12 (n=24)	15	9	0.86 [0.32-2.29]*	p=0.755
GCS 13-15 (n=68)	46	22	1.00 [0.48-2.10]*	p=0.993
A μ (n=117)	80	37	-	
X μ (n=34)	19	15	1.71 [0.78-3.73] [†]	p=0.087
μ μ 2 [22] vs [11+12]				
	[22] (TT)	[11+12] (C/-)	OR (95%CI)	p-value
(n=119)	15	111	-	
(n=32)	2	23	1.51 [0.37-7.6] [†]	p=0.54
GCS 3-8 (n=59)	3	56	-	
GCS 9-12 (n=24)	4	20	0.23 [0.17-1.44]*	p=0.12
GCS 13-15 (n=68)	10	58	0.311 [0.151-1.22]*	p=0.10
A μ (n=117)	14	103	-	
X μ (n=34)	3	31	1.48 [0.31-4.88] [†]	p=0.65

(*) GCS , , μ . ([†]) , μ μ , μ . ([†]) GCS / μ

15 16. μ μ μ μ

μ μ >0.05 . μ μ (μ

μ μ μ SNPs) Bonferroni.

μ μ

IL-1 (IL-1 -889C/T, IL-1 +3953C/T, IL-1 -511C/T, IL-1RA VNTR)

μ 6μ 6 μ μ

μ >0.05 . VI (2-1-1-1, -

μ SNP IL-1 -889 C/T μ) -

μ μ μ 6μ μ (

[μ μ] 3.01 [1.59-5.69], $p=0.0004$). Global test

μ ($p=0.0025$).

μ μ GCS 3-8 μ GCS 9-12

μ IV (1-1-2-2) μ μ -

(0.16 (0.05-0.51), $p=0.0005$),

μ VIII (2-2-2-1) μ μ

GCS 9-12 (9.79 (2.74-34.98), $p=2.64*10^{-5}$). Global test

μ ($p=0.0001$).

μ μ GCS 3-8 μ μ GCS 13-15

μ .

μ μ μ μ

μ μ IV (1-1-2-2) μ

μ μ μ (0.40 (0.20-0.78), $p=0.0058$). Global

test μ ($p=0.015$, - μ

Bonferroni 0.008). μ μ IL-1

(Linkage Disequilibrium) (17) μ

μ μ D (0,77840) μ μ μ μ

IL-1 -889C/T IL-1 +3953C/T.

μ μ IL-2 (IL-2

+114G/T IL-2 -384T/G) μ μ

μ GCS 3-8 GCS 9-12. , μ μ μ μ GCS

3-8 μ μ GCS 13-15 II (2-1)

μ μ (0.55 (0.39-0.78),
 $p=0.00087$). Global test μ ($p=0.0032$).
 (Linkage Disequilibrium) LD
 μ μ μ 18

15: μ μ IL-1								
Haplotype	IL-1 (-889C/T) rs1800587	IL-1 (+3953C/T) rs1143634	IL-1 (-511C/T) rs16944	IL-1RA (VNTR) rs2234663	% μ	% μ μ	Fisher's p-value	OR (95%CI) [†]
I	1	1	1	1	26.5	23.7	0.58	0.88 (0.56-1.38)
II	2	2	1	1	16.3	12.0	0.22	0.70 (0.40-1.24)
III	1	1	2	1	15.8	21.2	0.09	1.49 (0.92-2.40)
IV	1	1	2	2	13.2	7.6	0.07	0.54 (0.27-1.07)
V	1	1	1	2	7.6	5.5	0.40	0.71 (0.32-1.58)
VI	2	1	1	1	4.7	12.5	0.0004	3.01(1.59-5.69)
				Global $\chi^2=18.4$	Global Fisher's p-value=0.0025			
Haplotype	IL-1 (-889C/T) rs1800587	IL-1 (+3953C/T) rs1143634	IL-1 (-511C/T) rs16944	IL-1RA (VNTR) rs2234663	% μ GCS 3-8	% μ GCS 9-12	Fisher's p-value	OR (95%CI)*
I	1	1	1	1	25.6	23.6	0.57	0.86 (0.51-1.45)
II	2	2	1	1	15.2	16.4	0.85	1.06 (0.57-1.95)
III	1	1	2	1	14.3	18.3	0.38	1.31 (0.71-2.38)
IV	1	1	2	2	15.0	2.9	0.0005	0.16 (0.05-0.51)
V	1	1	1	2	9.1	7.9	0.64	0.82 (0.36-1.86)
VI	2	1	1	1	7.1	8.3	0.73	1.15 (0.50-2.64)
VII	2	1	2	2	3.3	5.0	0.46	1.49 (0.50-4.47)
VIII	2	2	2	1	1.2	11.4	2.64*10 ⁻⁵	9.79 (2.74-34.98)
				Global $\chi^2= 29.05$	Global Fisher's p-value=0.0001			

(*) GCS , , μ , μ μ μ .(†)

15 (): μ μ IL-1								
Haplotype	IL-1 (-889C/T) rs1800587	IL-1 (+3953C/T) rs1143634	IL-1 (-511C/T) rs16944	IL-1RA (VNTR) rs2234663	% μ GCS 3-8	% μ GCS 13-15	Fisher's p-value	OR (95%CI)*
I	1	1	1	1	25.6	28.1	0.44	1.15 (0.79-1.68)
II	2	2	1	1	15.2	15.4	0.92	1.02 (0.65-1.61)
III	1	1	2	1	14.3	18.2	0.17	1.36 (0.86-2.13)
IV	1	1	2	2	15.0	13.3	0.54	0.86 (0.54-1.38)
V	1	1	1	2	9.1	5.7	0.10	0.59 (0.32-1.11)
VI	2	1	1	1	7.1	5.1	0.31	0.70 (0.36-1.38)
				Global $\chi^2=5.55$	Global Fisher's p-value=0.35			
Haplotype	IL-1 (-889C/T) rs1800587	IL-1 (+3953C/T) rs1143634	IL-1 (-511C/T) rs16944	IL-1RA (VNTR) rs2234663	% μ μ	% μ	Fisher's p-value	OR (95%CI)†
I	1	1	1	1	24.6	34.5	0.08	1.41 (0.95-2.08)
II	2	2	1	1	14.5	18.6	0.46	1.19 (0.74-1.91)
III	1	1	2	1	15.6	19.2	0.59	1.13 (0.71-1.80)
IV	1	1	2	2	13.9	6.9	0.0058	0.40 (0.20-0.78)
V	1	1	1	2	7.9	3.8	0.038	0.40 (0.17-0.97)
VI	2	1	1	1	5.3	8.1	0.31	1.42 (0.71-2.82)
				Global $\chi^2=14.06$	Global Fisher's p-value=0.015			

(*) , μ GCS / , μ μ μ . (†) ,

16: μ μ IL-2						
Haplotype	IL-2 (+114G/T) rs2069763	IL-2 (-384T/G) rs2069762	% μ	% μ μ	Fisher's p-value	OR (95%CI) [†]
I	1	1	40.4	40.6	0.96	1.01 (0.69-1.47)
II	2	1	29.9	30.4	0.90	1.02 (0.68-1.53)
III	1	2	29.7	29.0	0.86	0.96 (0.64-1.45)
		Global $\chi^2=0.032$	Global Fisher's p-value=0.98			
Haplotype	IL-2 (+114G/T) rs2069763	IL-2 (-384T/G) rs2069762	% μ GCS 3-8	% μ GCS 9-12	Fisher's p-value	OR (95%CI)*
I	1	1	35.2	38.4	0.55	1.14 (0.72-1.82)
II	2	1	37.2	31.2	0.27	0.76 (0.47-1.23)
III	1	2	27.6	30.4	0.59	1.14 (0.70-1.86)
		Global $\chi^2=1.19$	Global Fisher's p-value=0.54			
Haplotype	IL-2 (+114G/T) rs2069763	IL-2 (-384T/G) rs2069762	% μ GCS 3-8	% μ GCS 13-15	Fisher's p-value	OR (95%CI)*
I	1	1	35.2	44.6	0.02	1.48 (1.06-2.06)
II	2	1	37.2	24.7	0.00087	0.55 (0.39-0.78)
III	1	2	27.6	30.7	0.41	1.16 (0.81-1.65)
		Global $\chi^2=11.47$	Global Fisher's p-value=0.0032			
Haplotype	IL-2 (+114G/T) rs2069763	IL-2 (-384T/G) rs2069762	% μ μ	% μ	Fisher's p-value	OR (95%CI) [†]
I	1	1	40.2	41.0	0.86	1.03 (0.72-1.48)
II	2	1	30.0	30.1	0.96	1.01 (0.68-1.48)
III	1	2	29.8	28.8	0.81	0.95 (0.64-1.41)
		Global $\chi^2=0.056$	Global Fisher's p-value=0.97			

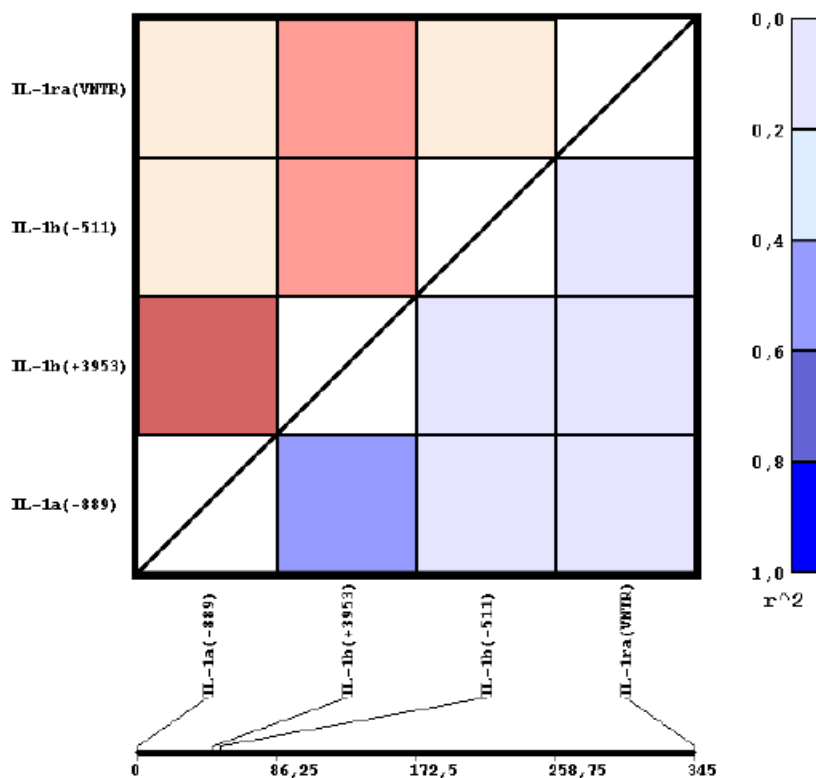
(*)
GCS

, , μ . (†) , μ μ , , μ . (†)
 μ GCS / μ

17: (Linkage Disequilibrium, LD) μ -

IL-1RA (VNTR)	0,38520	0,51583	0,34572	
IL-1b (-511)	0,35454	0,42757		0,06464
IL-1b (+3953)	0,77840		0,03784	0,02978
IL-1a (-889)		0,43222	0,03655	0,02345
D' r^2	IL-1a (-889)	IL-1b (+3953)	IL-1b (-511)	IL-1RA (VNTR)

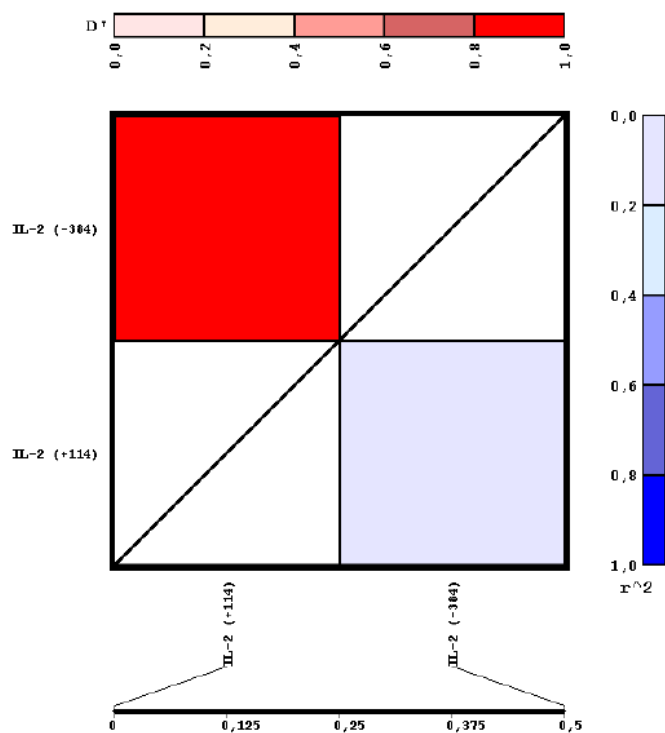
μ : μ μ μ (D r^2) μ IL-1 (chr 2).



18: **IL-2 (chr 4)** (Linkage Disequilibrium, LD) r^2

IL-2 (-384)	1,00000	
IL-2 (+114)		0,18010
D'	r^2	IL-2 (+114) IL-2 (-384)

r^2 : r^2 r^2 (D' r^2) r^2



[illegible]

μ μ ,
 μ μ μ , μ
 μ μ
. μ IL-1 , IL-1 , IL-
1RA, IL-2 IL-6, μ μ -
 μ . μ -
 μ μ , μ
 μ μ
 μ .
 μ
 μ μ μ μ
IL-1 (-511C/T, rs16944), IL-1 (+3953C/T, rs1143634), IL-1 (-889C/T, rs1800587), IL-6(-174G/C, rs1800795).
, μ $\mu\mu$ μ μ
IL-1RA VNTR (rs2234663) IL-2 +114G/T (rs2069763)
 μ . μ , VNTR (rs2234663) μ μ IL-1RA
, 6μ
 μ μ . ,
+114G/T (rs2069763), μ μ IL-2
 μ . μ
 μ Bonferroni
 μ 0.007, μ μ .
 μ μ μ
 μ , IL-1 (IL-1 -889C/T, IL-1 +3953C/T,
IL-1 -511C/T, IL-1RA VNTR) IV (1-1-2-2)
 μ μ μ . ,
VIII (2-2-2-1) VI (2-1-1-1)
 6μ .
 μ μ IL-2 (IL-2 +114G/T IL-2 -384T/G)
II (2-1) μ μ
.

IL-1RA VNTR (rs2234663)

IL-1: IL-1RA, 1 1 . (VNTR, rs2234663) IL-1RA

IL-1 IL-1

[404].

IL-1RA (VNTR, rs2234663) 2 ()

4.5 ([4.57 [1.67-12.96], p=0.004).

(0.26 [0.14-0.71], p=0.003).

2 GCS 3-8 GCS 9-12

(0.32 [0.12-0.90], p=0.030 0.32 [0.16-0.83], p=0.02) GCS 3-8 GCS 13-15

(0.37 [0.19-0.78], p=0.02 0.45 [0.25-0.91], p=0.017).

6 2 0.39 [0.19-0.89], p=0.011

0.43 [0.19-0.86], p=0.035.

1. IL-1RA VNTR (rs2234663)

VNTR IL-1RA

IL-1RA

2 IL-1RA [322].

IL-1RA

2 IL-1RA IL-1RA

IL-1 IL-1RA [351, 411]. IL-1RA (sIL-1RA)

2. μ μ IL-1RA VNTR (rs2234663)

171

0.91], $p=0.017$).

μ 2 IL-1RA μ μ μ GCS 3-8, GCS 9-12
GCS 13-15, μ μ μ -
2 34,75% 14,58% 20,59% .
[71]

μ , , μ ,
(mRNA μ 15min 1h). , μ IL-1
 μ IL-1 [542] μ
.
 μ IL-1RA μ
 μ , IL-1 .
 μ , IL-1
 , μ , μ
 μ μ (pmoles) [78]. ,
 , μ IL-1
 μ μ μ
[85].
 , μ IL-1RA μ
 μ μ , , μ
 μ . μ μ
(μ),
 μ μ 1
 μ 4 [543].
 μ μ [544], sIL-1RA
 μ μ μ
50% μ μ μ
 μ . μ , -
 ,
[108].
 μ μ
 μ . , μ IL-1RA
 μ μ μ ,
[115],

174

μ μ μ , μ μ

μ (long-term potentiation) [558].

μ IL-1 μ μ

μ μ 2 IL-1RA

μ μ μ .

μ 2 IL-1RA - μ

μ μ IL-1 μ μ

icIL-1RA1., μ 2 IL-1RA μ

- μ

μ μ μ μ ,

μ -

μ , μ μ -

. , μ -

μ .

μ ,
 IV (1-1-2-2) μ μ
 (0.16 (0.05-0.51), $p=0.0005$) μ VIII (2-2-2-1)
 μ μ GCS 9-12 (9.79 (2.74-34.98),
 $p=2.64 \times 10^{-5}$). μ
 μ 2 VNTR μ μ IL-1RA IV

μ VIII. μ , IV
 (1-1-2-2) μ 2 VNTR μ μ IL-1RA
 μ μ μ (0.40 (0.20-0.78), $p=0.0058$). , μ -
 μ VI (2-1-1-1) μ -
 μ μ 6 μ μ (
 [μ μ] 3.01 [1.59-5.69], $p=0.0004$).

μ μ **IL-2 +114 (rs2069763) -384**
(rs2069762)

μ μ μ μ μ IL-2 .
 IL-2 μ - μ μ
 . μ (natural Killer)
 Th1 (T-helper 1) [346]. -
 IL-2.
 IL-2 μ μ μ
 μ [346]. μ μ μ
 μ IL-2 μ μ
 [444].
 μ μ IL-2 μ μ , μ μ
 -384 [458],
 IL-2 [361] μ
 [461]. O μ μ
 +114 [459]. μ
 μ , μ
 μ μ . μ μ μ
 -384 μ μ .
 , μ μ +114G/T (rs2069763) IL-2
 μ 2 () μ μ
 . μ , μ
 μ μ μ GCS 3-8 μ GCS 13-15 μ
 μ ([μ μ] 0.57 [0.38-0.80],
 $p=0.002$) μ μ (0.53 [0.31-0.81], $p=0.009$).
 μ μ μ μ Bonferroni
 μ μ $p=0.02$, μ 2.32
 μ μ 1.18 5.12.

μ μ μ GCS 3-8 μ GCS 9-12,
 μ . , μ
 μ μ μ GCS 3-8, GCS 9-
12 GCS 13-15, μ μ
 μ 37,20% 31,25% 24,73% (3, 143).
 μ μ μ μ -
 μ μ GCS 3-8 μ GCS 9-12.
 μ μ +114G/T (rs2069763) IL-2
1 μ (CTG CTT, Leu Leu 38)
 μ . μ
mRNA μ -
 μ (Linkage Disequilibrium) μ
 μ μ μ μ ,
. μ
 μ μ IL-2 (IL-2 +114G/T IL-2 -384T/G).
II (2-1) μ μ
(GCS 3-8 μ GCS 9-12: OR (95%C.I.) 0.55 (0.39-0.78),
p=0.00087). μ
 μ μ +114G/T μ μ -384T/G.
 μ 1 () μ μ -384T/G μ μ
IL-2 μ μ 2 (G) [361]. , μ μ
 μ IL-2 μ .
IL-2 μ
. (Linkage Disequilibrium) μ
 μ μ LD block (D =1.00 μ
 $r^2=0,18$).

μ μ IL-6 -174G/C (rs1800795)

μ μ μ
 μ μ -174G/C (rs1800795) IL-6. IL-6 μ
 μ . IL-6 μ , μ -
 μ
[356].

IL-6 μ μ μ

[559]. , IL-6

,

μ IL-6 [77].

μ IL-6 ,

IL-6 μ [560].

μ μ μ μ μ -174G/C (rs1800795) IL-6.

μ μ μ IL-6 μ in vivo

[369, 512, 513] μ μ IL-6 [514].

2 : C (), G (

). CC μ μ IL-6

μ μ , GG

IL-6 μ [515, 516]. , μ μ

C IL-6 [517],

μ IL-6 μ CC [518].

μ μ . μ , μ -

μ , G μ μ 0.87-

1.0, μ , μ 0.54-0.62 [519-521].

μ μ -174G/C (rs1800795) IL-6 μ μ -

/

μ . IL-6,

μ . , μ μ μ

μ [272],

μ μ μ μ .

μ μ :

μ μ $\mu\mu$

, μ μ

μ μ μ

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μ μ μ .

μ .

μ μ ,

μ μ μ

. μ μ μ
 . μ , μ
 μ μ , μ
 μ μ μ
 μ μ μ
 μ , apoE μ
 μ μ μ
 apoE μ -
 μ bapineuzumab, μ
 μ Alzheimer, μ APOE .
 μ IL-1RA, μ
 μ [535].
 μ ,
 μ ,
 μ μ , μ
 - μ (proinflammatory) - μ (anti-inflammatory) -
 , μ μ μ μ .
 μ μ
 μ μ μ
 μ [561].
 , μ
 μ μ μ (genetic
 manipulation), μ μ
 (promoters) [562]. -
 mRNA,
 μ μ [563].
 , μ μ μ μ
 μ
 . μ μ (pharmacogenomics)
 μ μ
 μ , μ
 μ μ μ
 [564]. μ μ
 μ μ μ μ ,
 μ μ μ .

1. Ghajar J. Traumatic brain injury. *Lancet* 2000; 356:923-9.
2. Ommaya AK, Grubb RL, Jr., Naumann RA. Coup and contre-coup injury: observations on the mechanics of visible brain injuries in the rhesus monkey. *J Neurosurg* 1971; 35:503-16.
3. Adams JH, Graham DI, Murray LS, Scott G. Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases. *Ann Neurol* 1982; 12:557-63.
4. Labadie EL, Glover D. Physiopathogenesis of subdural hematomas. Part 1: Histological and biochemical comparisons of subcutaneous hematoma in rats with subdural hematoma in man. *J Neurosurg* 1976; 45:382-92.
5. Annegers JF, Grabow JD, Groover RV, Laws ER, Jr., Elveback LR, Kurland LT. Seizures after head trauma: a population study. *Neurology* 1980; 30:683-9.
6. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 1998; 338:20-4.
7. Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R. The outcome from severe head injury with early diagnosis and intensive management. *J Neurosurg* 1977; 47:491-502.
8. Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. *J Neurosurg* 1991; 75:685-93.
9. Martin NA, Patwardhan RV, Alexander MJ, Africk CZ, Lee JH, Shalmon E, Hovda DA, Becker DP. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. *J Neurosurg* 1997; 87:9-19.
10. Bergsneider M, Hovda DA, Shalmon E, Kelly DF, Vespa PM, Martin NA, Phelps ME, McArthur DL, Caron MJ, Kraus JF, Becker DP. Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *J Neurosurg* 1997; 86:241-51.
11. Verweij BH, Muizelaar JP, Vinas FC, Peterson PL, Xiong Y, Lee CP. Mitochondrial dysfunction after experimental and human brain injury and its possible reversal with a selective N-type calcium channel antagonist (SNX-111). *Neurol Res* 1997; 19:334-9.
12. Verweij BH, Muizelaar JP, Vinas FC, Peterson PL, Xiong Y, Lee CP. Impaired cerebral mitochondrial function after traumatic brain injury in humans. *J Neurosurg* 2000; 93:815-20.
13. Signoretti S, Marmarou A, Tavazzi B, Lazzarino G, Beaumont A, Vagnozzi R. N-Acetylaspartate reduction as a measure of injury severity and mitochondrial dysfunction following diffuse traumatic brain injury. *J Neurotrauma* 2001; 18:977-91.
14. Sinson G, Bagley LJ, Cecil KM, Torchia M, McGowan JC, Lenkinski RE, McIntosh TK, Grossman RI. Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: correlation with clinical outcome after traumatic brain injury. *AJNR Am J Neuroradiol* 2001; 22:143-51.
15. Harris LK, Black RT, Golden KM, Reeves TM, Povlishock JT, Phillips LL. Traumatic brain injury-induced changes in gene expression and functional activity of mitochondrial cytochrome C oxidase. *J Neurotrauma* 2001; 18:993-1009.
16. Menzel M, Döppenberg EM, Zauner A, Soukup J, Reinert MM, Bullock R. Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. *J Neurosurg* 1999; 91:1-10.
17. Magnoni S, Ghisoni L, Locatelli M, Caimi M, Colombo A, Valeriani V, Stocchetti N. Lack of improvement in cerebral metabolism after hyperoxia in severe head injury: a microdialysis study. *J Neurosurg* 2003; 98:952-8.
18. Reinert M, Barth A, Rothen HU, Schaller B, Takala J, Seiler RW. Effects of cerebral perfusion pressure and increased fraction of inspired oxygen on brain tissue oxygen, lactate and glucose in patients with severe head injury. *Acta Neurochir (Wien)* 2003; 145:341-9; discussion 349-50.
19. Faden AI, Demediuk P, Panter SS, Vink R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science* 1989; 244:798-800.
20. Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg* 1990; 73:889-900.

21. Palmer AM, Marion DW, Botscheller ML, Swedlow PE, Styren SD, DeKosky ST. Traumatic brain injury-induced excitotoxicity assessed in a controlled cortical impact model. *J Neurochem* 1993; 61:2015-24.
22. Globus MY, Alonso O, Dietrich WD, Busto R, Ginsberg MD. Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia. *J Neurochem* 1995; 65:1704-11.
23. Marklund N, Clausen F, Lewander T, Hillered L. Monitoring of reactive oxygen species production after traumatic brain injury in rats with microdialysis and the 4-hydroxybenzoic acid trapping method. *J Neurotrauma* 2001; 18:1217-27.
24. Kontos HA, George E. Brown memorial lecture. Oxygen radicals in cerebral vascular injury. *Circ Res* 1985; 57:508-16.
25. Kontos HA. Oxygen radicals in CNS damage. *Chem Biol Interact* 1989; 72:229-55.
26. Kontos HA, Povlishock JT. Oxygen radicals in brain injury. *Cent Nerv Syst Trauma* 1986; 3:257-63.
27. Bullock R, Zauner A, Woodward JJ, Myseros J, Choi SC, Ward JD, Marmarou A, Young HF. Factors affecting excitatory amino acid release following severe human head injury. *J Neurosurg* 1998; 89:507-18.
28. Kampfl A, Posmantur R, Nixon R, Grynspan F, Zhao X, Liu SJ, Newcomb JK, Clifton GL, Hayes RL. μ -calpain activation and calpain-mediated cytoskeletal proteolysis following traumatic brain injury. *J Neurochem* 1996; 67:1575-83.
29. Saatman KE, Graham DI, McIntosh TK. The neuronal cytoskeleton is at risk after mild and moderate brain injury. *J Neurotrauma* 1998; 15:1047-58.
30. Saatman KE, Murai H, Bartus RT, Smith DH, Hayward NJ, Perri BR, McIntosh TK. Calpain inhibitor AK295 attenuates motor and cognitive deficits following experimental brain injury in the rat. *Proc Natl Acad Sci U S A* 1996; 93:3428-33.
31. Posmantur R, Kampfl A, Siman R, Liu J, Zhao X, Clifton GL, Hayes RL. A calpain inhibitor attenuates cortical cytoskeletal protein loss after experimental traumatic brain injury in the rat. *Neuroscience* 1997; 77:875-88.
32. Rink A, Fung KM, Trojanowski JQ, Lee VM, Neugebauer E, McIntosh TK. Evidence of apoptotic cell death after experimental traumatic brain injury in the rat. *Am J Pathol* 1995; 147:1575-83.
33. Yakovlev AG, Knoblach SM, Fan L, Fox GB, Goodnight R, Faden AI. Activation of CPP32-like caspases contributes to neuronal apoptosis and neurological dysfunction after traumatic brain injury. *J Neurosci* 1997; 17:7415-24.
34. Conti AC, Raghupathi R, Trojanowski JQ, McIntosh TK. Experimental brain injury induces regionally distinct apoptosis during the acute and delayed post-traumatic period. *J Neurosci* 1998; 18:5663-72.
35. Clark RS, Kochanek PM, Chen M, Watkins SC, Marion DW, Chen J, Hamilton RL, Loeffert JE, Graham SH. Increases in Bcl-2 and cleavage of caspase-1 and caspase-3 in human brain after head injury. *Faseb J* 1999; 13:813-21.
36. Sinson G, Perri BR, Trojanowski JQ, Flamm ES, McIntosh TK. Improvement of cognitive deficits and decreased cholinergic neuronal cell loss and apoptotic cell death following neurotrophin infusion after experimental traumatic brain injury. *J Neurosurg* 1997; 86:511-8.
37. Raghupathi R, Graham DI, McIntosh TK. Apoptosis after traumatic brain injury. *J Neurotrauma* 2000; 17:927-38.
38. Barzo P, Marmarou A, Fatouros P, Hayasaki K, Corwin F. Contribution of vasogenic and cellular edema to traumatic brain swelling measured by diffusion-weighted imaging. *J Neurosurg* 1997; 87:900-7.
39. Sansing LH, Kaznatcheeva EA, Perkins CJ, Komaroff E, Gutman FB, Newman GC. Edema after intracerebral hemorrhage: correlations with coagulation parameters and treatment. *J Neurosurg* 2003; 98:985-92.
40. Gopinath SP, Robertson CS, Contant CF, Hayes C, Feldman Z, Narayan RK, Grossman RG. Jugular venous desaturation and outcome after head injury. *J Neurol Neurosurg Psychiatry* 1994; 57:717-23.
41. Juul N, Morris GF, Marshall SB, Marshall LF. Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. *J Neurosurg* 2000; 92:1-6.

42. Stein SC, Chen XH, Sinson GP, Smith DH. Intravascular coagulation: a major secondary insult in nonfatal traumatic brain injury. *J Neurosurg* 2002; 97:1373-7.
43. Park E, Bell JD, Baker AJ. Traumatic brain injury: can the consequences be stopped? *Cmaj* 2008; 178:1163-70.
44. Eisenberg HM, Gary HE, Jr., Aldrich EF, Saydjari C, Turner B, Foulkes MA, Jane JA, Marmarou A, Marshall LF, Young HF. Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. *J Neurosurg* 1990; 73:688-98.
45. Bayir H, Clark RS, Kochanek PM. Promising strategies to minimize secondary brain injury after head trauma. *Crit Care Med* 2003; 31:S112-7.
46. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, Jane JA, Marmarou A, Foulkes MA. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993; 34:216-22.
47. Golding EM. Sequelae following traumatic brain injury. The cerebrovascular perspective. *Brain Res Brain Res Rev* 2002; 38:377-88.
48. Wahl M, Schilling L, Unterberg A, Baethmann A. Mediators of vascular and parenchymal mechanisms in secondary brain damage. *Acta Neurochir Suppl (Wien)* 1993; 57:64-72.
49. Rosomoff HL, Kochanek PM, Clark R, DeKosky ST, Ebmeyer U, Grenvik AN, Marion DW, Obrist W, Palmer AM, Safer P, White RJ. Resuscitation from severe brain trauma. *Crit Care Med* 1996; 24:S48-56.
50. Leker RR, Shohami E. Cerebral ischemia and trauma-different etiologies yet similar mechanisms: neuroprotective opportunities. *Brain Res Brain Res Rev* 2002; 39:55-73.
51. Raghupathi R, McIntosh TK, Smith DH. Cellular responses to experimental brain injury. *Brain Pathol* 1995; 5:437-42.
52. Hayes RL, Yang K, Raghupathi R, McIntosh TK. Changes in gene expression following traumatic brain injury in the rat. *J Neurotrauma* 1995; 12:779-90.
53. McIntosh TK. Neurochemical sequelae of traumatic brain injury: therapeutic implications. *Cerebrovasc Brain Metab Rev* 1994; 6:109-62.
54. McIntosh TK, Smith DH, Meaney DF, Kotapka MJ, Gennarelli TA, Graham DI. Neuropathological sequelae of traumatic brain injury: relationship to neurochemical and biomechanical mechanisms. *Lab Invest* 1996; 74:315-42.
55. Perry VH, Bolton SJ, Anthony DC, Betmouni S. The contribution of inflammation to acute and chronic neurodegeneration. *Res Immunol* 1998; 149:721-5.
56. Holmin S, Soderlund J, Biberfeld P, Mathiesen T. Intracerebral inflammation after human brain contusion. *Neurosurgery* 1998; 42:291-8; discussion 298-9.
57. Morganti-Kossmann MC, Rancan M, Otto VI, Stahel PF, Kossmann T. Role of cerebral inflammation after traumatic brain injury: a revisited concept. *Shock* 2001; 16:165-77.
58. Bellander BM, von Holst H, Fredman P, Svensson M. Activation of the complement cascade and increase of clusterin in the brain following a cortical contusion in the adult rat. *J Neurosurg* 1996; 85:468-75.
59. Kordula T, Bugno M, Rydel RE, Travis J. Mechanism of interleukin-1- and tumor necrosis factor alpha-dependent regulation of the alpha 1-antichymotrypsin gene in human astrocytes. *J Neurosci* 2000; 20:7510-6.
60. Wong D, Dorovini-Zis K. Upregulation of intercellular adhesion molecule-1 (ICAM-1) expression in primary cultures of human brain microvessel endothelial cells by cytokines and lipopolysaccharide. *J Neuroimmunol* 1992; 39:11-21.
61. Taupin V, Toulmond S, Serrano A, Benavides J, Zavala F. Increase in IL-6, IL-1 and TNF levels in rat brain following traumatic lesion. Influence of pre- and post-traumatic treatment with Ro5 4864, a peripheral-type (p site) benzodiazepine ligand. *J Neuroimmunol* 1993; 42:177-85.
62. Larsson LG, Gray HE, Totterman T, Pettersson U, Nilsson K. Drastically increased expression of MYC and FOS protooncogenes during in vitro differentiation of chronic lymphocytic leukemia cells. *Proc Natl Acad Sci U S A* 1987; 84:223-7.
63. Sheng M, Greenberg ME. The regulation and function of c-fos and other immediate early genes in the nervous system. *Neuron* 1990; 4:477-85.
64. D'Mello SR, Heinrich G. Multiple signalling pathways interact in the regulation of nerve growth factor production in L929 fibroblasts. *J Neurochem* 1991; 57:1570-6.

65. Quitschke WW, Goldgaber D. The amyloid beta-protein precursor promoter. A region essential for transcriptional activity contains a nuclear factor binding domain. *J Biol Chem* 1992; 267:17362-8.
66. Dragunow M, Young D, Hughes P, MacGibbon G, Lawlor P, Singleton K, Sirimanne E, Beilharz E, Gluckman P. Is c-Jun involved in nerve cell death following status epilepticus and hypoxic-ischaemic brain injury? *Brain Res Mol Brain Res* 1993; 18:347-52.
67. Smeyne RJ, Vendrell M, Hayward M, Baker SJ, Miao GG, Schilling K, Robertson LM, Curran T, Morgan JI. Continuous c-fos expression precedes programmed cell death in vivo. *Nature* 1993; 363:166-9.
68. Pelham HR. Speculations on the functions of the major heat shock and glucose-regulated proteins. *Cell* 1986; 46:959-61.
69. Gonzalez MF, Shiraishi K, Hisanaga K, Sagar SM, Mandabach M, Sharp FR. Heat shock proteins as markers of neural injury. *Brain Res Mol Brain Res* 1989; 6:93-100.
70. Lowenstein DH, Thomas MJ, Smith DH, McIntosh TK. Selective vulnerability of dentate hilar neurons following traumatic brain injury: a potential mechanistic link between head trauma and disorders of the hippocampus. *J Neurosci* 1992; 12:4846-53.
71. Hopkins SJ, Rothwell NJ. Cytokines and the nervous system. I: Expression and recognition. *Trends Neurosci* 1995; 18:83-8.
72. Rothwell NJ, Hopkins SJ. Cytokines and the nervous system II: Actions and mechanisms of action. *Trends Neurosci* 1995; 18:130-6.
73. Giulian D, Chen J, Ingeman JE, George JK, Noponen M. The role of mononuclear phagocytes in wound healing after traumatic injury to adult mammalian brain. *J Neurosci* 1989; 9:4416-29.
74. Moreno-Flores MT, Bovolenta P, Nieto-Sampedro M. Polymorphonuclear leukocytes in brain parenchyma after injury and their interaction with purified astrocytes in culture. *Glia* 1993; 7:146-57.
75. Miller LG, Fahey JM. Interleukin-1 modulates GABAergic and glutamatergic function in brain. *Ann N Y Acad Sci* 1994; 739:292-8.
76. Bellinger FP, Madamba S, Siggins GR. Interleukin 1 beta inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus. *Brain Res* 1993; 628:227-34.
77. Allan SM, Rothwell NJ. Cytokines and acute neurodegeneration. *Nat Rev Neurosci* 2001; 2:734-44.
78. Rothwell N, Allan S, Toulmond S. The role of interleukin 1 in acute neurodegeneration and stroke: pathophysiological and therapeutic implications. *J Clin Invest* 1997; 100:2648-52.
79. Higgins GA, Olschowka JA. Induction of interleukin-1 beta mRNA in adult rat brain. *Brain Res Mol Brain Res* 1991; 9:143-8.
80. Shohami E, Gallily R, Mechoulam R, Bass R, Ben-Hur T. Cytokine production in the brain following closed head injury: dexamethasone (HU-211) is a novel TNF-alpha inhibitor and an effective neuroprotectant. *J Neuroimmunol* 1997; 72:169-77.
81. Minami M, Kuraishi Y, Yabuuchi K, Yamazaki A, Satoh M. Induction of interleukin-1 beta mRNA in rat brain after transient forebrain ischemia. *J Neurochem* 1992; 58:390-2.
82. Knoblach SM, Faden AI. Cortical interleukin-1 beta elevation after traumatic brain injury in the rat: no effect of two selective antagonists on motor recovery. *Neurosci Lett* 2000; 289:5-8.
83. Blasi F, Riccio M, Brogi A, Strazza M, Taddei ML, Romagnoli S, Luddi A, D'Angelo R, Santi S, Costantino-Ceccarini E, Melli M. Constitutive expression of interleukin-1beta (IL-1beta) in rat oligodendrocytes. *Biol Chem* 1999; 380:259-64.
84. Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood* 1996; 87:2095-147.
85. Patel HC, Boutin H, Allan SM. Interleukin-1 in the brain: mechanisms of action in acute neurodegeneration. *Ann N Y Acad Sci* 2003; 992:39-47.
86. Lu KT, Wang YW, Yang JT, Yang YL, Chen HI. Effect of interleukin-1 on traumatic brain injury-induced damage to hippocampal neurons. *J Neurotrauma* 2005; 22:885-95.
87. Benveniste EN. Inflammatory cytokines within the central nervous system: sources, function, and mechanism of action. *Am J Physiol* 1992; 263:C1-16.
88. Fan L, Young PR, Barone FC, Feuerstein GZ, Smith DH, McIntosh TK. Experimental brain injury induces expression of interleukin-1 beta mRNA in the rat brain. *Brain Res Mol Brain Res* 1995; 30:125-30.

89. Szaflarski J, Burtrum D, Silverstein FS. Cerebral hypoxia-ischemia stimulates cytokine gene expression in perinatal rats. *Stroke* 1995; 26:1093-100.
90. Yan HQ, Banos MA, Herregodts P, Hooghe R, Hooghe-Peters EL. Expression of interleukin (IL)-1 beta, IL-6 and their respective receptors in the normal rat brain and after injury. *Eur J Immunol* 1992; 22:2963-71.
91. Woodroffe MN, Sarna GS, Wadhwa M, Hayes GM, Loughlin AJ, Tinker A, Cuzner ML. Detection of interleukin-1 and interleukin-6 in adult rat brain, following mechanical injury, by in vivo microdialysis: evidence of a role for microglia in cytokine production. *J Neuroimmunol* 1991; 33:227-36.
92. Wang CX, Olschowka JA, Wrathall JR. Increase of interleukin-1beta mRNA and protein in the spinal cord following experimental traumatic injury in the rat. *Brain Res* 1997; 759:190-6.
93. Rostworowski M, Balasingam V, Chabot S, Owens T, Yong VW. Astrogliosis in the neonatal and adult murine brain post-trauma: elevation of inflammatory cytokines and the lack of requirement for endogenous interferon-gamma. *J Neurosci* 1997; 17:3664-74.
94. Herx LM, Rivest S, Yong VW. Central nervous system-initiated inflammation and neurotrophism in trauma: IL-1 beta is required for the production of ciliary neurotrophic factor. *J Immunol* 2000; 165:2232-9.
95. Fagan AM, Gage FH. Cholinergic sprouting in the hippocampus: a proposed role for IL-1. *Exp Neurol* 1990; 110:105-20.
96. Wang X, Barone FC, Aiyar NV, Feuerstein GZ. Interleukin-1 receptor and receptor antagonist gene expression after focal stroke in rats. *Stroke* 1997; 28:155-61; discussion 161-2.
97. Sairanen TR, Lindsberg PJ, Brenner M, Siren AL. Global forebrain ischemia results in differential cellular expression of interleukin-1beta (IL-1beta) and its receptor at mRNA and protein level. *J Cereb Blood Flow Metab* 1997; 17:1107-20.
98. Frati A, Salvati M, Mainiero F, Ippoliti F, Rocchi G, Raco A, Caroli E, Cantore G, Delfini R. Inflammation markers and risk factors for recurrence in 35 patients with a posttraumatic chronic subdural hematoma: a prospective study. *J Neurosurg* 2004; 100:24-32.
99. Kossmann T, Hans VH, Imhof HG, Stocker R, Grob P, Trentz O, Morganti-Kossmann C. Intrathecal and serum interleukin-6 and the acute-phase response in patients with severe traumatic brain injuries. *Shock* 1995; 4:311-7.
100. Gruol DL, Nelson TE. Physiological and pathological roles of interleukin-6 in the central nervous system. *Mol Neurobiol* 1997; 15:307-39.
101. Zhao B, Schwartz JP. Involvement of cytokines in normal CNS development and neurological diseases: recent progress and perspectives. *J Neurosci Res* 1998; 52:7-16.
102. Ott L, McClain CJ, Gillespie M, Young B. Cytokines and metabolic dysfunction after severe head injury. *J Neurotrauma* 1994; 11:447-72.
103. Yamasaki Y, Matsuura N, Shozuhara H, Onodera H, Itoyama Y, Kogure K. Interleukin-1 as a pathogenetic mediator of ischemic brain damage in rats. *Stroke* 1995; 26:676-80; discussion 681.
104. Loddick SA, Rothwell NJ. Neuroprotective effects of human recombinant interleukin-1 receptor antagonist in focal cerebral ischaemia in the rat. *J Cereb Blood Flow Metab* 1996; 16:932-40.
105. Lawrence CB, Allan SM, Rothwell NJ. Interleukin-1beta and the interleukin-1 receptor antagonist act in the striatum to modify excitotoxic brain damage in the rat. *Eur J Neurosci* 1998; 10:1188-95.
106. Hara H, Friedlander RM, Gagliardini V, Ayata C, Fink K, Huang Z, Shimizu-Sasamata M, Yuan J, Moskowitz MA. Inhibition of interleukin 1beta converting enzyme family proteases reduces ischemic and excitotoxic neuronal damage. *Proc Natl Acad Sci U S A* 1997; 94:2007-12.
107. Boutin H, LeFeuvre RA, Horai R, Asano M, Iwakura Y, Rothwell NJ. Role of IL-1alpha and IL-1beta in ischemic brain damage. *J Neurosci* 2001; 21:5528-34.
108. Garcia JH, Liu KF, Relton JK. Interleukin-1 receptor antagonist decreases the number of necrotic neurons in rats with middle cerebral artery occlusion. *Am J Pathol* 1995; 147:1477-86.

109. Sanderson KL, Raghupathi R, Saatman KE, Martin D, Miller G, McIntosh TK. Interleukin-1 receptor antagonist attenuates regional neuronal cell death and cognitive dysfunction after experimental brain injury. *J Cereb Blood Flow Metab* 1999; 19:1118-25.
110. Dinarello CA, Thompson RC. Blocking IL-1: interleukin 1 receptor antagonist in vivo and in vitro. *Immunol Today* 1991; 12:404-10.
111. Relton JK, Rothwell NJ. Interleukin-1 receptor antagonist inhibits ischaemic and excitotoxic neuronal damage in the rat. *Brain Res Bull* 1992; 29:243-6.
112. Toulmond S, Rothwell NJ. Interleukin-1 receptor antagonist inhibits neuronal damage caused by fluid percussion injury in the rat. *Brain Res* 1995; 671:261-6.
113. Relton JK, Martin D, Thompson RC, Russell DA. Peripheral administration of Interleukin-1 Receptor antagonist inhibits brain damage after focal cerebral ischemia in the rat. *Exp Neurol* 1996; 138:206-13.
114. Rothwell NJ, Relton JK. Involvement of cytokines in acute neurodegeneration in the CNS. *Neurosci Biobehav Rev* 1993; 17:217-27.
115. Betz AL, Yang GY, Davidson BL. Attenuation of stroke size in rats using an adenoviral vector to induce overexpression of interleukin-1 receptor antagonist in brain. *J Cereb Blood Flow Metab* 1995; 15:547-51.
116. Loddick SA, Wong ML, Bongiorno PB, Gold PW, Licinio J, Rothwell NJ. Endogenous interleukin-1 receptor antagonist is neuroprotective. *Biochem Biophys Res Commun* 1997; 234:211-5.
117. Penkowa M, Moos T, Carrasco J, Hadberg H, Molinero A, Bluethmann H, Hidalgo J. Strongly compromised inflammatory response to brain injury in interleukin-6-deficient mice. *Glia* 1999; 25:343-57.
118. Clark WM, Rinker LG, Lessov NS, Hazel K, Hill JK, Stenzel-Poore M, Eckenstein F. Lack of interleukin-6 expression is not protective against focal central nervous system ischemia. *Stroke* 2000; 31:1715-20.
119. Fassbender K, Mielke O, Bertsch T, Muehlhauser F, Hennerici M, Kurimoto M, Rossol S. Interferon-gamma-inducing factor (IL-18) and interferon-gamma in inflammatory CNS diseases. *Neurology* 1999; 53:1104-6.
120. Hedtjarn M, Leverin AL, Eriksson K, Blomgren K, Mallard C, Hagberg H. Interleukin-18 involvement in hypoxic-ischemic brain injury. *J Neurosci* 2002; 22:5910-9.
121. Jander S, Schroeter M, Stoll G. Interleukin-18 expression after focal ischemia of the rat brain: association with the late-stage inflammatory response. *J Cereb Blood Flow Metab* 2002; 22:62-70.
122. Yatsiv I, Morganti-Kossmann MC, Perez D, Dinarello CA, Novick D, Rubinstein M, Otto VI, Rancan M, Kossmann T, Redaelli CA, Trentz O, Shohami E, Stahel PF. Elevated intracranial IL-18 in humans and mice after traumatic brain injury and evidence of neuroprotective effects of IL-18-binding protein after experimental closed head injury. *J Cereb Blood Flow Metab* 2002; 22:971-8.
123. Menge T, Jander S, Stoll G. Induction of the proinflammatory cytokine interleukin-18 by axonal injury. *J Neurosci Res* 2001; 65:332-9.
124. Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nat Rev Immunol* 2003; 3:133-46.
125. Constantinescu CS, Frei K, Wysocka M, Trinchieri G, Malipiero U, Rostami A, Fontana A. Astrocytes and microglia produce interleukin-12 p40. *Ann N Y Acad Sci* 1996; 795:328-33.
126. Kornelisse RF, Hack CE, Savelkoul HF, van der Pouw Kraan TC, Hop WC, van Mierlo G, Suur MH, Neijens HJ, de Groot R. Intrathecal production of interleukin-12 and gamma interferon in patients with bacterial meningitis. *Infect Immun* 1997; 65:877-81.
127. Balashov KE, Smith DR, Khoury SJ, Hafler DA, Weiner HL. Increased interleukin 12 production in progressive multiple sclerosis: induction by activated CD4+ T cells via CD40 ligand. *Proc Natl Acad Sci U S A* 1997; 94:599-603.
128. Stahel PF, Kossmann T, Joller H, Trentz O, Morganti-Kossmann MC. Increased interleukin-12 levels in human cerebrospinal fluid following severe head trauma. *Neurosci Lett* 1998; 249:123-6.
129. Spera PA, Ellison JA, Feuerstein GZ, Barone FC. IL-10 reduces rat brain injury following focal stroke. *Neurosci Lett* 1998; 251:189-92.

130. Knoblach SM, Faden AI. Interleukin-10 improves outcome and alters proinflammatory cytokine expression after experimental traumatic brain injury. *Exp Neurol* 1998; 153:143-51.
131. Toulmond S, Vige X, Fage D, Benavides J. Local infusion of interleukin-6 attenuates the neurotoxic effects of NMDA on rat striatal cholinergic neurons. *Neurosci Lett* 1992; 144:49-52.
132. Loddick SA, Turnbull AV, Rothwell NJ. Cerebral interleukin-6 is neuroprotective during permanent focal cerebral ischemia in the rat. *J Cereb Blood Flow Metab* 1998; 18:176-9.
133. Campbell IL, Abraham CR, Masliah E, Kemper P, Inglis JD, Oldstone MB, Mucke L. Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6. *Proc Natl Acad Sci U S A* 1993; 90:10061-5.
134. Hartl R, Schurer L, Schmid-Schonbein GW, del Zoppo GJ. Experimental antileukocyte interventions in cerebral ischemia. *J Cereb Blood Flow Metab* 1996; 16:1108-19.
135. Hong L, Imeri L, Opp MR, Postlethwaite AE, Seyer JM, Krueger JM. Intercellular adhesion molecule-1 expression induced by interleukin (IL)-1 beta or an IL-1 beta fragment is blocked by an IL-1 receptor antagonist and a soluble IL-1 receptor. *J Neuroimmunol* 1993; 44:163-70.
136. Allan SM, Lawrence CB, Rothwell NJ. Interleukin-1 beta and interleukin-1 receptor antagonist do not affect glutamate release or calcium entry in rat striatal synaptosomes. *Mol Psychiatry* 1998; 3:178-82.
137. Jander S, Kraemer M, Schroeter M, Witte OW, Stoll G. Lymphocytic infiltration and expression of intercellular adhesion molecule-1 in photochemically induced ischemia of the rat cortex. *J Cereb Blood Flow Metab* 1995; 15:42-51.
138. Soriano SG, Lipton SA, Wang YF, Xiao M, Springer TA, Gutierrez-Ramos JC, Hickey PR. Intercellular adhesion molecule-1-deficient mice are less susceptible to cerebral ischemia-reperfusion injury. *Ann Neurol* 1996; 39:618-24.
139. Yang GY, Mao Y, Zhou LF, Gong C, Ge HL, Betz AL. Expression of intercellular adhesion molecule 1 (ICAM-1) is reduced in permanent focal cerebral ischemic mouse brain using an adenoviral vector to induce overexpression of interleukin-1 receptor antagonist. *Brain Res Mol Brain Res* 1999; 65:143-50.
140. Allan SM. The role of pro- and antiinflammatory cytokines in neurodegeneration. *Ann N Y Acad Sci* 2000; 917:84-93.
141. Strijbos PJ, Rothwell NJ. Interleukin-1 beta attenuates excitatory amino acid-induced neurodegeneration in vitro: involvement of nerve growth factor. *J Neurosci* 1995; 15:3468-74.
142. Brenneman DE, Schultzberg M, Bartfai T, Gozes I. Cytokine regulation of neuronal survival. *J Neurochem* 1992; 58:454-60.
143. Sastry PS, Rao KS. Apoptosis and the nervous system. *J Neurochem* 2000; 74:1-20.
144. Csuka E, Hans VH, Ammann E, Trentz O, Kossmann T, Morganti-Kossmann MC. Cell activation and inflammatory response following traumatic axonal injury in the rat. *Neuroreport* 2000; 11:2587-90.
145. Benveniste EN. Cytokines: influence on glial cell gene expression and function. *Chem Immunol* 1992; 52:106-53.
146. Thery C, Mallat M. Influence of interleukin-1 and tumor necrosis factor alpha on the growth of microglial cells in primary cultures of mouse cerebral cortex: involvement of colony-stimulating factor 1. *Neurosci Lett* 1993; 150:195-9.
147. Giulian D, Vaca K, Corpuz M. Brain glia release factors with opposing actions upon neuronal survival. *J Neurosci* 1993; 13:29-37.
148. Gadiant RA, Cron KC, Otten U. Interleukin-1 beta and tumor necrosis factor-alpha synergistically stimulate nerve growth factor (NGF) release from cultured rat astrocytes. *Neurosci Lett* 1990; 117:335-40.
149. Goss JR, O'Malley ME, Zou L, Styren SD, Kochanek PM, DeKosky ST. Astrocytes are the major source of nerve growth factor upregulation following traumatic brain injury in the rat. *Exp Neurol* 1998; 149:301-9.
150. Eng LF, Yu AC, Lee YL. Astrocytic response to injury. *Prog Brain Res* 1992; 94:353-65.
151. Giulian D. Reactive glia as rivals in regulating neuronal survival. *Glia* 1993; 7:102-10.
152. Merrill JE. Effects of interleukin-1 and tumor necrosis factor-alpha on astrocytes, microglia, oligodendrocytes, and glial precursors in vitro. *Dev Neurosci* 1991; 13:130-7.

153. Murakami N, Sakata Y, Watanabe T. Central action sites of interleukin-1 beta for inducing fever in rabbits. *J Physiol* 1990; 428:299-312.
154. Stroemer RP, Rothwell NJ. Exacerbation of ischemic brain damage by localized striatal injection of interleukin-1beta in the rat. *J Cereb Blood Flow Metab* 1998; 18:833-9.
155. Loddick SA, MacKenzie A, Rothwell NJ. An ICE inhibitor, z-VAD-DCB attenuates ischaemic brain damage in the rat. *Neuroreport* 1996; 7:1465-8.
156. Zhang Z, Chopp M, Goussev A, Powers C. Cerebral vessels express interleukin 1beta after focal cerebral ischemia. *Brain Res* 1998; 784:210-7.
157. Shibata M, Leffler CW, Busija DW. Recombinant human interleukin 1 alpha dilates pial arterioles and increases cerebrospinal fluid prostanoids in piglets. *Am J Physiol* 1990; 259:H1486-91.
158. Osuka K, Suzuki Y, Watanabe Y, Dogan A, Takayasu M, Shibuya M, Yoshida J. Vasodilator effects on canine basilar artery induced by intracisternal interleukin-1 beta. *J Cereb Blood Flow Metab* 1997; 17:1337-45.
159. Katabami T, Shimizu M, Okano K, Yano Y, Nemoto K, Ogura M, Tsukamoto T, Suzuki S, Ohira K, Yamada Y, et al. Intracellular signal transduction for interleukin-1 beta-induced endothelin production in human umbilical vein endothelial cells. *Biochem Biophys Res Commun* 1992; 188:565-70.
160. Schielke GP, Yang GY, Shivers BD, Betz AL. Reduced ischemic brain injury in interleukin-1 beta converting enzyme-deficient mice. *J Cereb Blood Flow Metab* 1998; 18:180-5.
161. Campbell VA, Segurado R, Lynch MA. Regulation of intracellular Ca²⁺ concentration by interleukin-1beta in rat cortical synaptosomes: an age-related study. *Neurobiol Aging* 1998; 19:575-9.
162. Murray CA, Clements MP, Lynch MA. Interleukin-1 induces lipid peroxidation and membrane changes in rat hippocampus: An age-related study. *Gerontology* 1999; 45:136-42.
163. Beasley D, Schwartz JH, Brenner BM. Interleukin 1 induces prolonged L-arginine-dependent cyclic guanosine monophosphate and nitrite production in rat vascular smooth muscle cells. *J Clin Invest* 1991; 87:602-8.
164. Hartung HP, Schafer B, Heininger K, Toyka KV. Recombinant interleukin-1 beta stimulates eicosanoid production in rat primary culture astrocytes. *Brain Res* 1989; 489:113-9.
165. Xia L, Matera C, Ferin M, Wardlaw SL. Interleukin-1 stimulates the central release of corticotropin-releasing hormone in the primate. *Neuroendocrinology* 1996; 63:79-84.
166. Yang GY, Liu XH, Kadoya C, Zhao YJ, Mao Y, Davidson BL, Betz AL. Attenuation of ischemic inflammatory response in mouse brain using an adenoviral vector to induce overexpression of interleukin-1 receptor antagonist. *J Cereb Blood Flow Metab* 1998; 18:840-7.
167. Yang Y, Quitschke WW, Brewer GJ. Upregulation of amyloid precursor protein gene promoter in rat primary hippocampal neurons by phorbol ester, IL-1 and retinoic acid, but not by reactive oxygen species. *Brain Res Mol Brain Res* 1998; 60:40-9.
168. Giulian D, Young DG, Woodward J, Brown DC, Lachman LB. Interleukin-1 is an astroglial growth factor in the developing brain. *J Neurosci* 1988; 8:709-14.
169. Rothwell NJ, Luheshi G, Toulmond S. Cytokines and their receptors in the central nervous system: physiology, pharmacology, and pathology. *Pharmacol Ther* 1996; 69:85-95.
170. Goldgaber D, Harris HW, Hla T, Maciag T, Donnelly RJ, Jacobsen JS, Vitek MP, Gajdusek DC. Interleukin 1 regulates synthesis of amyloid beta-protein precursor mRNA in human endothelial cells. *Proc Natl Acad Sci U S A* 1989; 86:7606-10.
171. Hardy J, Duff K, Hardy KG, Perez-Tur J, Hutton M. Genetic dissection of Alzheimer's disease and related dementias: amyloid and its relationship to tau. *Nat Neurosci* 1998; 1:355-8.
172. Grimaldi LM, Casadei VM, Ferri C, Veglia F, Licastro F, Annoni G, Biunno I, De Bellis G, Sorbi S, Mariani C, Canal N, Griffin WS, Franceschi M. Association of early-onset Alzheimer's disease with an interleukin-1alpha gene polymorphism. *Ann Neurol* 2000; 47:361-5.
173. Nicoll JA, Mrak RE, Graham DI, Stewart J, Wilcock G, MacGowan S, Esiri MM, Murray LS, Dewar D, Love S, Moss T, Griffin WS. Association of interleukin-1 gene polymorphisms with Alzheimer's disease. *Ann Neurol* 2000; 47:365-8.

174. Mayeux R, Ottman R, Tang MX, Noboa-Bauza L, Marder K, Gurland B, Stern Y. Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and their first-degree relatives. *Ann Neurol* 1993; 33:494-501.
175. Gentleman SM, Graham DI, Roberts GW. Molecular pathology of head trauma: altered beta APP metabolism and the aetiology of Alzheimer's disease. *Prog Brain Res* 1993; 96:237-46.
176. Holmin S, Mathiesen T. Long-term intracerebral inflammatory response after experimental focal brain injury in rat. *Neuroreport* 1999; 10:1889-91.
177. Hoshino S, Tamaoka A, Takahashi M, Kobayashi S, Furukawa T, Oaki Y, Mori O, Matsuno S, Shoji S, Inomata M, Teramoto A. Emergence of immunoreactivities for phosphorylated tau and amyloid-beta protein in chronic stage of fluid percussion injury in rat brain. *Neuroreport* 1998; 9:1879-83.
178. Rothwell NJ, Busbridge NJ, Lefevre RA, Hardwick AJ, Gauldie J, Hopkins SJ. Interleukin-6 is a centrally acting endogenous pyrogen in the rat. *Can J Physiol Pharmacol* 1991; 69:1465-9.
179. Luheshi G, Miller AJ, Brouwer S, Dascombe MJ, Rothwell NJ, Hopkins SJ. Interleukin-1 receptor antagonist inhibits endotoxin fever and systemic interleukin-6 induction in the rat. *Am J Physiol* 1996; 270:E91-5.
180. Shalaby MR, Waage A, Aarden L, Espevik T. Endotoxin, tumor necrosis factor-alpha and interleukin 1 induce interleukin 6 production in vivo. *Clin Immunol Immunopathol* 1989; 53:488-98.
181. Barnum SR. Complement in central nervous system inflammation. *Immunol Res* 2002; 26:7-13.
182. Gasque P, Dean YD, McGreal EP, VanBeek J, Morgan BP. Complement components of the innate immune system in health and disease in the CNS. *Immunopharmacology* 2000; 49:171-86.
183. Morgan BP, Gasque P. Expression of complement in the brain: role in health and disease. *Immunol Today* 1996; 17:461-6.
184. Barnum SR. Inhibition of complement as a therapeutic approach in inflammatory central nervous system (CNS) disease. *Mol Med* 1999; 5:569-82.
185. van Beek J, Elward K, Gasque P. Activation of complement in the central nervous system: roles in neurodegeneration and neuroprotection. *Ann N Y Acad Sci* 2003; 992:56-71.
186. Elward K, Gasque P. "Eat me" and "don't eat me" signals govern the innate immune response and tissue repair in the CNS: emphasis on the critical role of the complement system. *Mol Immunol* 2003; 40:85-94.
187. Stahel PF, Barnum SR. Bacterial meningitis: complement gene expression in the central nervous system. *Immunopharmacology* 1997; 38:65-72.
188. Emmerling MR, Watson MD, Raby CA, Spiegel K. The role of complement in Alzheimer's disease pathology. *Biochim Biophys Acta* 2000; 1502:158-71.
189. Stahel PF, Morganti-Kossmann MC, Kossmann T. The role of the complement system in traumatic brain injury. *Brain Res Brain Res Rev* 1998; 27:243-56.
190. Kaczorowski SL, Schiding JK, Toth CA, Kochanek PM. Effect of soluble complement receptor-1 on neutrophil accumulation after traumatic brain injury in rats. *J Cereb Blood Flow Metab* 1995; 15:860-4.
191. Keeling KL, Hicks RR, Mahesh J, Billings BB, Kotwal GJ. Local neutrophil influx following lateral fluid-percussion brain injury in rats is associated with accumulation of complement activation fragments of the third component (C3) of the complement system. *J Neuroimmunol* 2000; 105:20-30.
192. Nataf S, Stahel PF, Davoust N, Barnum SR. Complement anaphylatoxin receptors on neurons: new tricks for old receptors? *Trends Neurosci* 1999; 22:397-402.
193. Stahel PF, Morganti-Kossmann MC, Perez D, Redaelli C, Gloor B, Trentz O, Kossmann T. Intrathecal levels of complement-derived soluble membrane attack complex (sC5b-9) correlate with blood-brain barrier dysfunction in patients with traumatic brain injury. *J Neurotrauma* 2001; 18:773-81.
194. Singhrao SK, Neal JW, Rushmere NK, Morgan BP, Gasque P. Spontaneous classical pathway activation and deficiency of membrane regulators render human neurons susceptible to complement lysis. *Am J Pathol* 2000; 157:905-18.

195. Bellander BM, Singhrao SK, Ohlsson M, Mattsson P, Svensson M. Complement activation in the human brain after traumatic head injury. *J Neurotrauma* 2001; 18:1295-311.
196. Redl H, Gasser H, Schlag G, Marzi I. Involvement of oxygen radicals in shock related cell injury. *Br Med Bull* 1993; 49:556-65.
197. Evans PH. Free radicals in brain metabolism and pathology. *Br Med Bull* 1993; 49:577-87.
198. Granger DN. Role of xanthine oxidase and granulocytes in ischemia-reperfusion injury. *Am J Physiol* 1988; 255:H1269-75.
199. Tyurin VA, Tyurina YY, Borisenko GG, Sokolova TV, Ritov VB, Quinn PJ, Rose M, Kochanek P, Graham SH, Kagan VE. Oxidative stress following traumatic brain injury in rats: quantitation of biomarkers and detection of free radical intermediates. *J Neurochem* 2000; 75:2178-89.
200. Shohami E, Gati I, Beit-Yannai E, Trembovler V, Kohen R. Closed head injury in the rat induces whole body oxidative stress: overall reducing antioxidant profile. *J Neurotrauma* 1999; 16:365-76.
201. Beit-Yannai E, Kohen R, Horowitz M, Trembovler V, Shohami E. Changes of biological reducing activity in rat brain following closed head injury: a cyclic voltammetry study in normal and heat-acclimated rats. *J Cereb Blood Flow Metab* 1997; 17:273-9.
202. Shohami E, Beit-Yannai E, Horowitz M, Kohen R. Oxidative stress in closed-head injury: brain antioxidant capacity as an indicator of functional outcome. *J Cereb Blood Flow Metab* 1997; 17:1007-19.
203. Bayir H, Kagan VE, Tyurina YY, Tyurin V, Ruppel RA, Adelson PD, Graham SH, Janesko K, Clark RS, Kochanek PM. Assessment of antioxidant reserves and oxidative stress in cerebrospinal fluid after severe traumatic brain injury in infants and children. *Pediatr Res* 2002; 51:571-8.
204. Touzani O, Boutin H, Chuquet J, Rothwell N. Potential mechanisms of interleukin-1 involvement in cerebral ischaemia. *J Neuroimmunol* 1999; 100:203-15.
205. Brakenhoff JP, de Hon FD, Fontaine V, ten Boekel E, Schooltink H, Rose-John S, Heinrich PC, Content J, Aarden LA. Development of a human interleukin-6 receptor antagonist. *J Biol Chem* 1994; 269:86-93.
206. Savino R, Lahm A, Salvati AL, Ciapponi L, Sporeno E, Altamura S, Paonessa G, Toniatti C, Ciliberto G. Generation of interleukin-6 receptor antagonists by molecular-modeling guided mutagenesis of residues important for gp130 activation. *Embo J* 1994; 13:1357-67.
207. Gijbels K, Brocke S, Abrams JS, Steinman L. Administration of neutralizing antibodies to interleukin-6 (IL-6) reduces experimental autoimmune encephalomyelitis and is associated with elevated levels of IL-6 bioactivity in central nervous system and circulation. *Mol Med* 1995; 1:795-805.
208. Suzuki H, Yasukawa K, Saito T, Goitsuka R, Hasegawa A, Ohsugi Y, Taga T, Kishimoto T. Anti-human interleukin-6 receptor antibody inhibits human myeloma growth in vivo. *Eur J Immunol* 1992; 22:1989-93.
209. Houlston RS, Snowden C, Green F, Alberti KG, Humphries SE. Apolipoprotein (apo) E genotypes by polymerase chain reaction and allele-specific oligonucleotide probes: no detectable linkage disequilibrium between apo E and apo CII. *Hum Genet* 1989; 83:364-8.
210. Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* 1988; 240:622-30.
211. Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer's disease. *Annu Rev Med* 1996; 47:387-400.
212. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; 261:921-3.
213. Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993; 43:1467-72.
214. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. Apolipoprotein E: high-avidity binding to beta-amyloid and increased

- frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A* 1993; 90:1977-81.
215. Alberts MJ, Graffagnino C, McClenny C, DeLong D, Strittmatter W, Saunders AM, Roses AD. ApoE genotype and survival from intracerebral haemorrhage. *Lancet* 1995; 346:575.
 216. Couderc R, Mahieux F, Bailleul S, Fenelon G, Mary R, Fermanian J. Prevalence of apolipoprotein E phenotypes in ischemic cerebrovascular disease. A case-control study. *Stroke* 1993; 24:661-4.
 217. Friedman G, Froom P, Sazbon L, Grinblatt I, Shochina M, Tsenter J, Babaey S, Yehuda B, Groswasser Z. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. *Neurology* 1999; 52:244-8.
 218. Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet* 1997; 350:1069-71.
 219. Graham DI, Horsburgh K, Nicoll JA, Teasdale GM. Apolipoprotein E and the response of the brain to injury. *Acta Neurochir Suppl* 1999; 73:89-92.
 220. Herz J. Lipoprotein receptors: beacons to neurons? *Trends Neurosci* 2001; 24:193-5.
 221. Horsburgh K, Kelly S, McCulloch J, Higgins GA, Roses AD, Nicoll JA. Increased neuronal damage in apolipoprotein E-deficient mice following global ischaemia. *Neuroreport* 1999; 10:837-41.
 222. Horsburgh K, McCulloch J, Nilsen M, McCracken E, Large C, Roses AD, Nicoll JA. Intraventricular infusion of apolipoprotein E ameliorates acute neuronal damage after global cerebral ischemia in mice. *J Cereb Blood Flow Metab* 2000; 20:458-62.
 223. Mortimer JA, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Rocca WA, et al. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int J Epidemiol* 1991; 20 Suppl 2:S28-35.
 224. Roberts GW, Gentleman SM, Lynch A, Graham DI. beta A4 amyloid protein deposition in brain after head trauma. *Lancet* 1991; 338:1422-3.
 225. Nicoll JA, Roberts GW, Graham DI. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. *Nat Med* 1995; 1:135-7.
 226. Chiang MF, Chang JG, Hu CJ. Association between apolipoprotein E genotype and outcome of traumatic brain injury. *Acta Neurochir (Wien)* 2003; 145:649-53; discussion 653-4.
 227. Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. *Jama* 1997; 278:136-40.
 228. Sorbi S, Nacmias B, Piacentini S, Repice A, Latorraca S, Forleo P, Amaducci L. ApoE as a prognostic factor for post-traumatic coma. *Nat Med* 1995; 1:852.
 229. Liaquat I, Dunn LT, Nicoll JA, Teasdale GM, Norrie JD. Effect of apolipoprotein E genotype on hematoma volume after trauma. *J Neurosurg* 2002; 96:90-6.
 230. Diaz-Arrastia R, Gong Y, Fair S, Scott KD, Garcia MC, Carlile MC, Agostini MA, Van Ness PC. Increased risk of late posttraumatic seizures associated with inheritance of APOE epsilon4 allele. *Arch Neurol* 2003; 60:818-22.
 231. Liberman JN, Stewart WF, Wesnes K, Troncoso J. Apolipoprotein E epsilon 4 and short-term recovery from predominantly mild brain injury. *Neurology* 2002; 58:1038-44.
 232. Sundstrom A, Marklund P, Nilsson LG, Cruts M, Adolfsson R, Van Broeckhoven C, Nyberg L. APOE influences on neuropsychological function after mild head injury: within-person comparisons. *Neurology* 2004; 62:1963-6.
 233. Crawford FC, Vanderploeg RD, Freeman MJ, Singh S, Waisman M, Michaels L, Abdullah L, Warden D, Lipsky R, Salazar A, Mullan MJ. APOE genotype influences acquisition and recall following traumatic brain injury. *Neurology* 2002; 58:1115-8.
 234. Ariza M, Pueyo R, Matarin Mdel M, Junque C, Mataro M, Clemente I, Moral P, Poca MA, Garnacho A, Sahuquillo J. Influence of APOE polymorphism on cognitive and behavioural outcome in moderate and severe traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2006; 77:1191-3.
 235. Nathoo N, Chettry R, van Dellen JR, Connolly C, Naidoo R. Apolipoprotein E polymorphism and outcome after closed traumatic brain injury: influence of ethnic and regional differences. *J Neurosurg* 2003; 98:302-6.
 236. Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, Pericak-Vance MA, Goldgaber D, Roses AD. Increased amyloid beta-peptide deposition in

- cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proc Natl Acad Sci U S A* 1993; 90:9649-53.
237. Strittmatter WJ, Weisgraber KH, Huang DY, Dong LM, Salvesen GS, Pericak-Vance M, Schmechel D, Saunders AM, Goldgaber D, Roses AD. Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. *Proc Natl Acad Sci U S A* 1993; 90:8098-102.
 238. Miyata M, Smith JD. Apolipoprotein E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and beta-amyloid peptides. *Nat Genet* 1996; 14:55-61.
 239. Arendt T, Schindler C, Bruckner MK, Eschrich K, Bigl V, Zedlick D, Marcova L. Plastic neuronal remodeling is impaired in patients with Alzheimer's disease carrying apolipoprotein epsilon 4 allele. *J Neurosci* 1997; 17:516-29.
 240. Poirier J, Delisle MC, Quirion R, Aubert I, Farlow M, Lahiri D, Hui S, Bertrand P, Nalbantoglu J, Gilfix BM, Gauthier S. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. *Proc Natl Acad Sci U S A* 1995; 92:12260-4.
 241. Fleming LM, Weisgraber KH, Strittmatter WJ, Troncoso JC, Johnson GV. Differential binding of apolipoprotein E isoforms to tau and other cytoskeletal proteins. *Exp Neurol* 1996; 138:252-60.
 242. Artiga MJ, Bullido MJ, Sastre I, Recuero M, Garcia MA, Aldudo J, Vazquez J, Valdivieso F. Allelic polymorphisms in the transcriptional regulatory region of apolipoprotein E gene. *FEBS Lett* 1998; 421:105-8.
 243. Lambert JC, Araria-Goumidi L, Myllykangas L, Ellis C, Wang JC, Bullido MJ, Harris JM, Artiga MJ, Hernandez D, Kwon JM, Frigard B, Petersen RC, Cumming AM, Pasquier F, Sastre I, Tienari PJ, Frank A, Sulkava R, Morris JC, St Clair D, Mann DM, Wavrant-DeVrieze F, Ezquerra-Trabalon M, Amouyel P, Hardy J, Haltia M, Valdivieso F, Goate AM, Perez-Tur J, Lendon CL, Chartier-Harlin MC. Contribution of APOE promoter polymorphisms to Alzheimer's disease risk. *Neurology* 2002; 59:59-66.
 244. Lambert JC, Mann D, Goumidi L, Harris J, Amouyel P, Iwatsubo T, Lendon C, Chartier-Harlin MC. Effect of the APOE promoter polymorphisms on cerebral amyloid peptide deposition in Alzheimer's disease. *Lancet* 2001; 357:608-9.
 245. Lambert JC, Mann D, Richard F, Tian J, Shi J, Thaker U, Merrot S, Harris J, Frigard B, Iwatsubo T, Lendon C, Amouyel P. Is there a relation between APOE expression and brain amyloid load in Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2005; 76:928-33.
 246. Lendon CL, Harris JM, Pritchard AL, Nicoll JA, Teasdale GM, Murray G. Genetic variation of the APOE promoter and outcome after head injury. *Neurology* 2003; 61:683-5.
 247. Iwata N, Tsubuki S, Takaki Y, Shirotani K, Lu B, Gerard NP, Gerard C, Hama E, Lee HJ, Saido TC. Metabolic regulation of brain Abeta by neprilysin. *Science* 2001; 292:1550-2.
 248. Maruyama M, Higuchi M, Takaki Y, Matsuba Y, Tanji H, Nemoto M, Tomita N, Matsui T, Iwata N, Mizukami H, Muramatsu S, Ozawa K, Saido TC, Arai H, Sasaki H. Cerebrospinal fluid neprilysin is reduced in prodromal Alzheimer's disease. *Ann Neurol* 2005; 57:832-42.
 249. Russo R, Borghi R, Markesbery W, Tabaton M, Piccini A. Neprilysin decreases uniformly in Alzheimer's disease and in normal aging. *FEBS Lett* 2005; 579:6027-30.
 250. Mohajeri MH, Wollmer MA, Nitsch RM. Abeta 42-induced increase in neprilysin is associated with prevention of amyloid plaque formation in vivo. *J Biol Chem* 2002; 277:35460-5.
 251. Mohajeri MH, Kuehnle K, Li H, Poirier R, Tracy J, Nitsch RM. Anti-amyloid activity of neprilysin in plaque-bearing mouse models of Alzheimer's disease. *FEBS Lett* 2004; 562:16-21.
 252. Sakai A, Ujike H, Nakata K, Takehisa Y, Imamura T, Uchida N, Kanzaki A, Yamamoto M, Fujisawa Y, Okumura K, Kuroda S. Association of the Neprilysin gene with susceptibility to late-onset Alzheimer's disease. *Dement Geriatr Cogn Disord* 2004; 17:164-9.
 253. Yamada M, Sodeyama N, Itoh Y, Takahashi A, Otomo E, Matsushita M, Mizusawa H. Association of neprilysin polymorphism with cerebral amyloid angiopathy. *J Neurol Neurosurg Psychiatry* 2003; 74:749-51.

254. Johnson VE, Stewart W, Stewart JE, Graham DI, Praestgaard AH, Smith DH. A Neprilysin Polymorphism and Amyloid-beta Plaques Following Traumatic Brain Injury. *J Neurotrauma* 2009.
255. Weinshilboum RM, Otterness DM, Szumlanski CL. Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annu Rev Pharmacol Toxicol* 1999; 39:19-52.
256. Akil M, Kolachana BS, Rothmond DA, Hyde TM, Weinberger DR, Kleinman JE. Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. *J Neurosci* 2003; 23:2008-13.
257. Diaz-Asper CM, Weinberger DR, Goldberg TE. Catechol-O-methyltransferase polymorphisms and some implications for cognitive therapeutics. *NeuroRx* 2006; 3:97-105.
258. Lipsky RH, Sparling MB, Ryan LM, Xu K, Salazar AM, Goldman D, Warden DL. Association of COMT Val158Met genotype with executive functioning following traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 2005; 17:465-71.
259. Ritchie T, Noble EP. Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. *Neurochem Res* 2003; 28:73-82.
260. Small GW, Noble EP, Matsuyama SS, Jarvik LF, Komo S, Kaplan A, Ritchie T, Pritchard ML, Saunders AM, Conneally PM, Roses AD, Haines JL, Pericak-Vance MA. D2 dopamine receptor A1 allele in Alzheimer disease and aging. *Arch Neurol* 1997; 54:281-5.
261. McAllister TW, Rhodes CH, Flashman LA, McDonald BC, Belloni D, Saykin AJ. Effect of the dopamine D2 receptor T allele on response latency after mild traumatic brain injury. *Am J Psychiatry* 2005; 162:1749-51.
262. Murzin AG, Lesk AM, Chothia C. beta-Trefoil fold. Patterns of structure and sequence in the Kunitz inhibitors interleukins-1 beta and 1 alpha and fibroblast growth factors. *J Mol Biol* 1992; 223:531-43.
263. Nicklin MJ, Weith A, Duff GW. A physical map of the region encompassing the human interleukin-1 alpha, interleukin-1 beta, and interleukin-1 receptor antagonist genes. *Genomics* 1994; 19:382-4.
264. Du Y, Dodel RC, Eastwood BJ, Bales KR, Gao F, Lohmuller F, Muller U, Kurz A, Zimmer R, Evans RM, Hake A, Gasser T, Oertel WH, Griffin WS, Paul SM, Farlow MR. Association of an interleukin 1 alpha polymorphism with Alzheimer's disease. *Neurology* 2000; 55:480-3.
265. Rainero I, Bo M, Ferrero M, Valfre W, Vaula G, Pinessi L. Association between the interleukin-1alpha gene and Alzheimer's disease: a meta-analysis. *Neurobiol Aging* 2004; 25:1293-8.
266. Pociot F, Molvig J, Wogensen L, Worsaae H, Nerup J. A TaqI polymorphism in the human interleukin-1 beta (IL-1 beta) gene correlates with IL-1 beta secretion in vitro. *Eur J Clin Invest* 1992; 22:396-402.
267. di Giovine FS, Takhsh E, Blakemore AI, Duff GW. Single base polymorphism at -511 in the human interleukin-1 beta gene (IL1 beta). *Hum Mol Genet* 1992; 1:450.
268. Yucesoy B, Peila R, White LR, Wu KM, Johnson VJ, Kashon ML, Luster MI, Launer LJ. Association of interleukin-1 gene polymorphisms with dementia in a community-based sample: the Honolulu-Asia Aging Study. *Neurobiol Aging* 2006; 27:211-7.
269. Uzan M, Tanriverdi T, Baykara O, Kafadar A, Sanus GZ, Tureci E, Ozkara C, Uysal O, Buyra N. Association between interleukin-1 beta (IL-1beta) gene polymorphism and outcome after head injury: an early report. *Acta Neurochir (Wien)* 2005; 147:715-20; discussion 720.
270. Tanriverdi T, Uzan M, Sanus GZ, Baykara O, Is M, Ozkara C, Buyra N. Lack of association between the IL1A gene (-889) polymorphism and outcome after head injury. *Surg Neurol* 2006; 65:7-10; discussion 10.
271. Winter CD, Pringle AK, Clough GF, Church MK. Raised parenchymal interleukin-6 levels correlate with improved outcome after traumatic brain injury. *Brain* 2004; 127:315-20.
272. Minambres E, Cemborain A, Sanchez-Velasco P, Gandarillas M, Diaz-Reganon G, Sanchez-Gonzalez U, Leyva-Cobian F. Correlation between transcranial interleukin-6 gradient and outcome in patients with acute brain injury. *Crit Care Med* 2003; 31:933-8.
273. Fisher DE. The p53 tumor suppressor: critical regulator of life & death in cancer. *Apoptosis* 2001; 6:7-15.

274. Ara S, Lee PS, Hansen MF, Saya H. Codon 72 polymorphism of the TP53 gene. *Nucleic Acids Res* 1990; 18:4961.
275. Dumont P, Leu JI, Della Pietra AC, 3rd, George DL, Murphy M. The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. *Nat Genet* 2003; 33:357-65.
276. Martinez-Lucas P, Moreno-Cuesta J, Garcia-Olmo DC, Sanchez-Sanchez F, Escribano-Martinez J, del Pozo AC, Lizan-Garcia M, Garcia-Olmo D. Relationship between the Arg72Pro polymorphism of p53 and outcome for patients with traumatic brain injury. *Intensive Care Med* 2005; 31:1168-73.
277. Erdos EG, Skidgel RA. The angiotensin I-converting enzyme. *Lab Invest* 1987; 56:345-8.
278. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990; 86:1343-6.
279. Tiret L, Rigat B, Visvikis S, Breda C, Corvol P, Cambien F, Soubrier F. Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. *Am J Hum Genet* 1992; 51:197-205.
280. Narain Y, Yip A, Murphy T, Brayne C, Easton D, Evans JG, Xuereb J, Cairns N, Esiri MM, Furlong RA, Rubinsztein DC. The ACE gene and Alzheimer's disease susceptibility. *J Med Genet* 2000; 37:695-7.
281. Elkins JS, Douglas VC, Johnston SC. Alzheimer disease risk and genetic variation in ACE: a meta-analysis. *Neurology* 2004; 62:363-8.
282. Amouyel P, Richard F, Cottel D, Amant C, Codron V, Helbecque N. The deletion allele of the angiotensin I converting enzyme gene as a genetic susceptibility factor for cognitive impairment. *Neurosci Lett* 1996; 217:203-5.
283. Richard F, Berr C, Amant C, Helbecque N, Amouyel P, Alperovitch A. Effect of the angiotensin I-converting enzyme I/D polymorphism on cognitive decline. The EVA Study Group. *Neurobiol Aging* 2000; 21:75-80.
284. Stewart R, Powell J, Prince M, Mann A. ACE genotype and cognitive decline in an African-Caribbean population. *Neurobiol Aging* 2004; 25:1369-75.
285. Richard F, Fromentin-David I, Ricolfi F, Ducimetiere P, Di Menza C, Amouyel P, Helbecque N. The angiotensin I converting enzyme gene as a susceptibility factor for dementia. *Neurology* 2001; 56:1593-5.
286. Ariza M, Matarin MD, Junque C, Mataro M, Clemente I, Moral P, Antonia Poca M, Garnacho A, Sahuquillo J. Influence of Angiotensin-converting enzyme polymorphism on neuropsychological subacute performance in moderate and severe traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 2006; 18:39-44.
287. Hu J, Igarashi A, Kamata M, Nakagawa H. Angiotensin-converting enzyme degrades Alzheimer amyloid beta-peptide (A beta); retards A beta aggregation, deposition, fibril formation; and inhibits cytotoxicity. *J Biol Chem* 2001; 276:47863-8.
288. Kors EE, Terwindt GM, Vermeulen FL, Fitzsimons RB, Jardine PE, Heywood P, Love S, van den Maagdenberg AM, Haan J, Frants RR, Ferrari MD. Delayed cerebral edema and fatal coma after minor head trauma: role of the CACNA1A calcium channel subunit gene and relationship with familial hemiplegic migraine. *Ann Neurol* 2001; 49:753-60.
289. Katzman R, Galasko DR, Saitoh T, Chen X, Pay MM, Booth A, Thomas RG. Apolipoprotein-epsilon4 and head trauma: Synergistic or additive risks? *Neurology* 1996; 46:889-91.
290. Mehta KM, Ott A, Kalmijn S, Slioter AJ, van Duijn CM, Hofman A, Breteler MM. Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam Study. *Neurology* 1999; 53:1959-62.
291. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, Phillips C, Gau BA, Welsh-Bohmer KA, Burke JR, Guralnik JM, Breitner JC. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology* 2000; 55:1158-66.
292. Lichtman SW, Seliger G, Tycko B, Marder K. Apolipoprotein E and functional recovery from brain injury following postacute rehabilitation. *Neurology* 2000; 55:1536-9.
293. Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, Green RC, Sadovnick AD, Duara R, DeCarli C, Johnson K, Go RC, Growdon JH, Haines JL, Kukull WA,

- Farrer LA. Head injury and the risk of AD in the MIRAGE study. *Neurology* 2000; 54:1316-23.
294. Kutner KC, Erlanger DM, Tsai J, Jordan B, Relkin NR. Lower cognitive performance of older football players possessing apolipoprotein E epsilon4. *Neurosurgery* 2000; 47:651-7; discussion 657-8.
 295. Harding D, Dhamrait S, Millar A, Humphries S, Marlow N, Whitelaw A, Montgomery H. Is interleukin-6 -174 genotype associated with the development of septicemia in preterm infants? *Pediatrics* 2003; 112:800-3.
 296. Darnell JE, Jr., Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science* 1994; 264:1415-21.
 297. Chamelian L, Reis M, Feinstein A. Six-month recovery from mild to moderate Traumatic Brain Injury: the role of APOE-epsilon4 allele. *Brain* 2004; 127:2621-8.
 298. Koponen S, Taiminen T, Kairisto V, Portin R, Isoniemi H, Hinkka S, Tenovuo O. APOE-epsilon4 predicts dementia but not other psychiatric disorders after traumatic brain injury. *Neurology* 2004; 63:749-50.
 299. Teasdale GM, Murray GD, Nicoll JA. The association between APOE epsilon4, age and outcome after head injury: a prospective cohort study. *Brain* 2005; 128:2556-61.
 300. Leclercq PD, Murray LS, Smith C, Graham DI, Nicoll JA, Gentleman SM. Cerebral amyloid angiopathy in traumatic brain injury: association with apolipoprotein E genotype. *J Neurol Neurosurg Psychiatry* 2005; 76:229-33.
 301. Stauber DJ, Debler EW, Horton PA, Smith KA, Wilson IA. Crystal structure of the IL-2 signaling complex: paradigm for a heterotrimeric cytokine receptor. *Proc Natl Acad Sci U S A* 2006; 103:2788-93.
 302. Jiang Y, Sun X, Xia Y, Tang W, Cao Y, Gu Y. Effect of APOE polymorphisms on early responses to traumatic brain injury. *Neurosci Lett* 2006; 408:155-8.
 303. Isoniemi H, Kurki T, Tenovuo O, Kairisto V, Portin R. Hippocampal volume, brain atrophy, and APOE genotype after traumatic brain injury. *Neurology* 2006; 67:756-60.
 304. Ponsford J, Rudzki D, Bailey K, Ng KT. Impact of apolipoprotein gene on cognitive impairment and recovery after traumatic brain injury. *Neurology* 2007; 68:619-20.
 305. Han SD, Drake AI, Cessante LM, Jak AJ, Houston WS, Delis DC, Filoteo JV, Bondi MW. Apolipoprotein E and traumatic brain injury in a military population: evidence of a neuropsychological compensatory mechanism? *J Neurol Neurosurg Psychiatry* 2007; 78:1103-8.
 306. Hiekkanen H, Kurki T, Brandstack N, Kairisto V, Tenovuo O. MRI changes and ApoE genotype, a prospective 1-year follow-up of traumatic brain injury: a pilot study. *Brain Inj* 2007; 21:1307-14.
 307. Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA. Meta-analysis of APOE4 allele and outcome after traumatic brain injury. *J Neurotrauma* 2008; 25:279-90.
 308. Willemse-van Son AH, Ribbers GM, Hop WC, van Duijn CM, Stam HJ. Association between apolipoprotein-epsilon4 and long-term outcome after traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2008; 79:426-30.
 309. Tanriverdi F, Taheri S, Ulutabancan H, Caglayan AO, Ozkul Y, Dundar M, Selcuklu A, Unluhizarci K, Casanueva FF, Kelestimur F. Apolipoprotein E3/E3 genotype decreases the risk of pituitary dysfunction after traumatic brain injury due to various causes: preliminary data. *J Neurotrauma* 2008; 25:1071-7.
 310. Brichtova E, Kozak L. Apolipoprotein E genotype and traumatic brain injury in children--association with neurological outcome. *Childs Nerv Syst* 2008; 24:349-56.
 311. Luukinen H, Jokelainen J, Kervinen K, Kesaniemi YA, Winqvist S, Hillbom M. Risk of dementia associated with the ApoE epsilon4 allele and falls causing head injury without explicit traumatic brain injury. *Acta Neurol Scand* 2008; 118:153-8.
 312. Ost M, Nylen K, Csajbok L, Blennow K, Rosengren L, Nellgard B. Apolipoprotein E polymorphism and gender difference in outcome after severe traumatic brain injury. *Acta Anaesthesiol Scand* 2008; 52:1364-9.
 313. Rapoport M, Wolf U, Herrmann N, Kiss A, Shammi P, Reis M, Phillips A, Feinstein A. Traumatic brain injury, Apolipoprotein E-epsilon4, and cognition in older adults: a two-year longitudinal study. *J Neuropsychiatry Clin Neurosci* 2008; 20:68-73.
 314. Kristman VL, Tator CH, Kreiger N, Richards D, Mainwaring L, Jaglal S, Tomlinson G, Comper P. Does the apolipoprotein epsilon 4 allele predispose varsity athletes to concussion? A prospective cohort study. *Clin J Sport Med* 2008; 18:322-8.

315. Han SD, Suzuki H, Drake AI, Jak AJ, Houston WS, Bondi MW. Clinical, cognitive, and genetic predictors of change in job status following traumatic brain injury in a military population. *J Head Trauma Rehabil* 2009; 24:57-64.
316. Hiekkanen H, Kurki T, Brandstack N, Kairisto V, Tenovuo O. Association of injury severity, MRI-results and ApoE genotype with 1-year outcome in mainly mild TBI: a preliminary study. *Brain Inj* 2009; 23:396-402.
317. Lo TY, Jones PA, Chambers IR, Beattie TF, Forsyth R, Mendelow AD, Minns RA. Modulating effect of apolipoprotein E polymorphisms on secondary brain insult and outcome after childhood brain trauma. *Childs Nerv Syst* 2009; 25:47-54.
318. Jiang Y, Sun X, Gui L, Xia Y, Tang W, Cao Y, Gu Y. Correlation between APOE -491AA promoter in epsilon4 carriers and clinical deterioration in early stage of traumatic brain injury. *J Neurotrauma* 2007; 24:1802-10.
319. Jiang Y, Sun XC, Gui L, Tang WY, Zhen LP, Gu YJ, Wu HT. Lack of association between apolipoprotein E promoters in epsilon4 carriers and worsening on computed tomography in early stage of traumatic brain injury. *Acta Neurochir Suppl* 2008; 105:233-6.
320. Terrell TR, Bostick RM, Abramson R, Xie D, Barfield W, Cantu R, Stanek M, Ewing T. APOE, APOE promoter, and Tau genotypes and risk for concussion in college athletes. *Clin J Sport Med* 2008; 18:10-7.
321. Uzan M, Tanriverdi T, Baykara O, Kafadar A, Sanus GZ, Tureci E, Ozkara C, Uysal O, Buyra N. Association between interleukin-1 beta (IL-1beta) gene polymorphism and outcome after head injury: an early report. *Acta Neurochir (Wien)* 2005; 147:715-20.
322. Hadjigeorgiou GM, Paterakis K, Dardiotis E, Dardioti M, Aggelakis K, Tasiou A, Xiomerisiou G, Komnos A, Zintzaras E, Scarmeas N, Papadimitriou A, Karantanis A. IL-1RN and IL-1B gene polymorphisms and cerebral hemorrhagic events after traumatic brain injury. *Neurology* 2005; 65:1077-82.
323. Dardiotis E, Dardioti M, Hadjigeorgiou GM, Paterakis K. Re: Lack of association between the IL1A gene (-889) polymorphism and outcome after head injury. Tanriverdi T et al. *Surg Neurol* 2006;65:7-10; discussion 10. *Surg Neurol* 2006; 66:334-5.
324. Chan F, Lanctot KL, Feinstein A, Herrmann N, Strauss J, Sicard T, Kennedy JL, McCullagh S, Rapoport MJ. The serotonin transporter polymorphisms and major depression following traumatic brain injury. *Brain Inj* 2008; 22:471-9.
325. Greenfeder SA, Nunes P, Kwee L, Labow M, Chizzonite RA, Ju G. Molecular cloning and characterization of a second subunit of the interleukin 1 receptor complex. *J Biol Chem* 1995; 270:13757-65.
326. Mora M, Carinci V, Bensi G, Raugei G, Buonamassa DT, Melli M. Differential expression of the human IL-1 alpha and beta genes. *Prog Clin Biol Res* 1990; 349:205-16.
327. Stevenson FT, Torrano F, Locksley RM, Lovett DH. Interleukin 1: the patterns of translation and intracellular distribution support alternative secretory mechanisms. *J Cell Physiol* 1992; 152:223-31.
328. Miller AC, Schattenberg DG, Malkinson AM, Ross D. Decreased content of the IL1 alpha processing enzyme calpain in murine bone marrow-derived macrophages after treatment with the benzene metabolite hydroquinone. *Toxicol Lett* 1994; 74:177-84.
329. Watanabe N, Kobayashi Y. Selective release of a processed form of interleukin 1 alpha. *Cytokine* 1994; 6:597-601.
330. Stevenson FT, Bursten SL, Fanton C, Locksley RM, Lovett DH. The 31-kDa precursor of interleukin 1 alpha is myristoylated on specific lysines within the 16-kDa N-terminal propiece. *Proc Natl Acad Sci U S A* 1993; 90:7245-9.
331. Kurt-Jones EA, Beller DI, Mizel SB, Unanue ER. Identification of a membrane-associated interleukin 1 in macrophages. *Proc Natl Acad Sci U S A* 1985; 82:1204-8.
332. Brody DT, Durum SK. Membrane IL-1: IL-1 alpha precursor binds to the plasma membrane via a lectin-like interaction. *J Immunol* 1989; 143:1183-7.
333. Labriola-Tompkins E, Chandran C, Varnell TA, Madison VS, Ju G. Structure-function analysis of human IL-1 alpha: identification of residues required for binding to the human type I IL-1 receptor. *Protein Eng* 1993; 6:535-9.
334. Grutter MG, van Oostrum J, Priestle JP, Edelmann E, Joss U, Feige U, Vosbeck K, Schmitz A. A mutational analysis of receptor binding sites of interleukin-1 beta: differences in binding of human interleukin-1 beta muteins to human and mouse receptors. *Protein Eng* 1994; 7:663-71.

335. Rubartelli A, Cozzolino F, Talio M, Sitia R. A novel secretory pathway for interleukin-1 beta, a protein lacking a signal sequence. *Embo J* 1990; 9:1503-10.
336. Fenton MJ, Vermeulen MW, Clark BD, Webb AC, Auron PE. Human pro-IL-1 beta gene expression in monocytic cells is regulated by two distinct pathways. *J Immunol* 1988; 140:2267-73.
337. Jarrous N, Kaempfer R. Induction of human interleukin-1 gene expression by retinoic acid and its regulation at processing of precursor transcripts. *J Biol Chem* 1994; 269:23141-9.
338. Serkkola E, Hurme M. Synergism between protein-kinase C and cAMP-dependent pathways in the expression of the interleukin-1 beta gene is mediated via the activator-protein-1 (AP-1) enhancer activity. *Eur J Biochem* 1993; 213:243-9.
339. Jobling SA, Auron PE, Gurka G, Webb AC, McDonald B, Rosenwasser LJ, Gehrke L. Biological activity and receptor binding of human prointerleukin-1 beta and subpeptides. *J Biol Chem* 1988; 263:16372-8.
340. Bakouche O, Brown DC, Lachman LB. Subcellular localization of human monocyte interleukin 1: evidence for an inactive precursor molecule and a possible mechanism for IL 1 release. *J Immunol* 1987; 138:4249-55.
341. Sims JE, March CJ, Cosman D, Widmer MB, MacDonald HR, McMahan CJ, Grubin CE, Wignall JM, Jackson JL, Call SM, et al. cDNA expression cloning of the IL-1 receptor, a member of the immunoglobulin superfamily. *Science* 1988; 241:585-9.
342. McMahan CJ, Slack JL, Mosley B, Cosman D, Lupton SD, Brunton LL, Grubin CE, Wignall JM, Jenkins NA, Brannan CI, et al. A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types. *Embo J* 1991; 10:2821-32.
343. Sims JE, Painter SL, Gow IR. Genomic organization of the type I and type II IL-1 receptors. *Cytokine* 1995; 7:483-90.
344. Auron PE, Webb AC, Rosenwasser LJ, Mucci SF, Rich A, Wolff SM, Dinarello CA. Nucleotide sequence of human monocyte interleukin 1 precursor cDNA. *Proc Natl Acad Sci U S A* 1984; 81:7907-11.
345. Furutani Y, Notake M, Fukui T, Ohue M, Nomura H, Yamada M, Nakamura S. Complete nucleotide sequence of the gene for human interleukin 1 alpha. *Nucleic Acids Res* 1986; 14:3167-79.
346. Amick JE, Yandora KA, Bell MJ, Wisniewski SR, Adelson PD, Carcillo JA, Janesko KL, DeKosky ST, Carlos TM, Clark RS, Kochanek PM. The Th1 versus Th2 cytokine profile in cerebrospinal fluid after severe traumatic brain injury in infants and children. *Pediatr Crit Care Med* 2001; 2:260-264.
347. Lafage M, Maroc N, Dubreuil P, de Waal Malefijt R, Pebusque MJ, Carcassonne Y, Mannoni P. The human interleukin-1 alpha gene is located on the long arm of chromosome 2 at band q13. *Blood* 1989; 73:104-7.
348. Bensi G, Mora M, Raugei G, Buonamassa DT, Rossini M, Melli M. An inducible enhancer controls the expression of the human interleukin 1 beta gene. *Cell Growth Differ* 1990; 1:491-7.
349. Caput D, Beutler B, Hartog K, Thayer R, Brown-Shimer S, Cerami A. Identification of a common nucleotide sequence in the 3'-untranslated region of mRNA molecules specifying inflammatory mediators. *Proc Natl Acad Sci U S A* 1986; 83:1670-4.
350. Stylianou E, Saklatvala J. Interleukin-1. *Int J Biochem Cell Biol* 1998; 30:1075-9.
351. Santtila S, Savinainen K, Hurme M. Presence of the IL-1RA allele 2 (IL1RN*2) is associated with enhanced IL-1beta production in vitro. *Scand J Immunol* 1998; 47:195-8.
352. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, Herrera J, Lissowska J, Yuan CC, Rothman N, Lanyon G, Martin M, Fraumeni JF, Jr., Rabkin CS. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000; 404:398-402.
353. Hall SK, Perregaux DG, Gabel CA, Woodworth T, Durham LK, Huizinga TW, Breedveld FC, Seymour AB. Correlation of polymorphic variation in the promoter region of the interleukin-1 beta gene with secretion of interleukin-1 beta protein. *Arthritis Rheum* 2004; 50:1976-83.
354. Licastro F, Chiappelli M, Caldarera CM, Tampieri C, Nanni S, Gallina M, Branzi A. The concomitant presence of polymorphic alleles of interleukin-1beta, interleukin-6 and apolipoprotein E is associated with an increased risk of myocardial infarction in elderly men. Results from a pilot study. *Mech Ageing Dev* 2004; 125:575-9.

355. Nishimura M, Kawakami H, Komure O, Maruyama H, Morino H, Izumi Y, Nakamura S, Kaji R, Kuno S. Contribution of the interleukin-1beta gene polymorphism in multiple system atrophy. *Mov Disord* 2002; 17:808-11.
356. Morganti-Kossmann MC, Rancan M, Stahel PF, Kossmann T. Inflammatory response in acute traumatic brain injury: a double-edged sword. *Curr Opin Crit Care* 2002; 8:101-5.
357. Mattila KM, Rinne JO, Lehtimäki T, Roytta M, Ahonen JP, Hurme M. Association of an interleukin 1B gene polymorphism (-511) with Parkinson's disease in Finnish patients. *J Med Genet* 2002; 39:400-2.
358. Nishimura M, Mizuta I, Mizuta E, Yamasaki S, Ohta M, Kuno S. Influence of interleukin-1beta gene polymorphisms on age-at-onset of sporadic Parkinson's disease. *Neurosci Lett* 2000; 284:73-6.
359. Reich K, Mossner R, König IR, Westphal G, Ziegler A, Neumann C. Promoter polymorphisms of the genes encoding tumor necrosis factor-alpha and interleukin-1beta are associated with different subtypes of psoriasis characterized by early and late disease onset. *J Invest Dermatol* 2002; 118:155-63.
360. Zanardini R, Bocchio-Chiavetto L, Scassellati C, Bonvicini C, Tura GB, Rossi G, Perez J, Gennarelli M. Association between IL-1beta -511C/T and IL-1RA (86bp)n repeats polymorphisms and schizophrenia. *J Psychiatr Res* 2003; 37:457-62.
361. Hoffmann SC, Stanley EM, Darrin Cox E, Craighead N, DiMercurio BS, Koziol DE, Harlan DM, Kirk AD, Blair PJ. Association of cytokine polymorphic inheritance and in vitro cytokine production in anti-CD3/CD28-stimulated peripheral blood lymphocytes. *Transplantation* 2001; 72:1444-50.
362. Nemetz A, Nosti-Escanilla MP, Molnar T, Kope A, Kovacs A, Feher J, Tulassay Z, Nagy F, Garcia-Gonzalez MA, Pena AS. IL1B gene polymorphisms influence the course and severity of inflammatory bowel disease. *Immunogenetics* 1999; 49:527-31.
363. Parks CG, Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS, Pandey JP. Systemic lupus erythematosus and genetic variation in the interleukin 1 gene cluster: a population based study in the southeastern United States. *Ann Rheum Dis* 2004; 63:91-4.
364. Muraki Y, Tsutsumi A, Takahashi R, Suzuki E, Hayashi T, Chino Y, Goto D, Matsumoto I, Murata H, Noguchi E, Sumida T. Polymorphisms of IL-1 beta gene in Japanese patients with Sjogren's syndrome and systemic lupus erythematosus. *J Rheumatol* 2004; 31:720-5.
365. Virta M, Hurme M, Helminen M. Increased frequency of interleukin-1beta (-511) allele 2 in febrile seizures. *Pediatr Neurol* 2002; 26:192-5.
366. Kanemoto K, Kawasaki J, Miyamoto T, Obayashi H, Nishimura M. Interleukin (IL)1beta, IL-1alpha, and IL-1 receptor antagonist gene polymorphisms in patients with temporal lobe epilepsy. *Ann Neurol* 2000; 47:571-4.
367. Schulte T, Schols L, Müller T, Woitalla D, Berger K, Krüger R. Polymorphisms in the interleukin-1 alpha and beta genes and the risk for Parkinson's disease. *Neurosci Lett* 2002; 326:70-2.
368. McGeer PL, Yasojima K, McGeer EG. Association of interleukin-1 beta polymorphisms with idiopathic Parkinson's disease. *Neurosci Lett* 2002; 326:67-9.
369. Endler G, Marsik C, Joukhadar C, Marculescu R, Mayr F, Mannhalter C, Wagner OF, Jilma B. The interleukin-6 G(-174)C promoter polymorphism does not determine plasma interleukin-6 concentrations in experimental endotoxemia in humans. *Clin Chem* 2004; 50:195-200.
370. McDowell TL, Symons JA, Ploski R, Forre O, Duff GW. A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1 alpha polymorphism. *Arthritis Rheum* 1995; 38:221-8.
371. Shirodaria S, Smith J, McKay IJ, Kennett CN, Hughes FJ. Polymorphisms in the IL-1A gene are correlated with levels of interleukin-1alpha protein in gingival crevicular fluid of teeth with severe periodontal disease. *J Dent Res* 2000; 79:1864-9.
372. Hulkkonen J, Laippala P, Hurme M. A rare allele combination of the interleukin-1 gene complex is associated with high interleukin-1 beta plasma levels in healthy individuals. *Eur Cytokine Netw* 2000; 11:251-5.
373. Kawaguchi Y, Hara M, Kamatani N, Wright TM. Identification of an IL1A gene segment that determines aberrant constitutive expression of interleukin-1 alpha in systemic sclerosis. *Arthritis Rheum* 2003; 48:193-202.

374. Karasneh J, Hajeer AH, Barrett J, Ollier WE, Thornhill M, Gul A. Association of specific interleukin 1 gene cluster polymorphisms with increased susceptibility for Behcet's disease. *Rheumatology (Oxford)* 2003; 42:860-4.
375. Hutyrova B, Pantelidis P, Drabek J, Zurkova M, Kolek V, Lenhart K, Welsh KI, Du Bois RM, Petrek M. Interleukin-1 gene cluster polymorphisms in sarcoidosis and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2002; 165:148-51.
376. Ravindran JS, Owen P, Lagan A, Lewis J, Korendowych E, Welsh K, McHugh N. Interleukin 1alpha, interleukin 1beta and interleukin 1 receptor gene polymorphisms in psoriatic arthritis. *Rheumatology (Oxford)* 2004; 43:22-6.
377. Sciacca FL, Ferri C, Veglia F, Andreetta F, Mantegazza R, Cornelio F, Franciotta D, Piccolo G, Cosi V, Batocchi AP, Evoli A, Grimaldi LM. IL-1 genes in myasthenia gravis: IL-1A -889 polymorphism associated with sex and age of disease onset. *J Neuroimmunol* 2002; 122:94-9.
378. Dominici R, Cattaneo M, Malferrari G, Archi D, Mariani C, Grimaldi LM, Biunno I. Cloning and functional analysis of the allelic polymorphism in the transcription regulatory region of interleukin-1 alpha. *Immunogenetics* 2002; 54:82-6.
379. Um JY, Moon KS, Lee KM, Yun JM, Cho KH, Moon BS, Kim HM. Association of interleukin-1 alpha gene polymorphism with cerebral infarction. *Brain Res Mol Brain Res* 2003; 115:50-4.
380. Hutyrova B, Lukac J, Bosak V, Buc M, du Bois R, Petrek M. Interleukin 1alpha single-nucleotide polymorphism associated with systemic sclerosis. *J Rheumatol* 2004; 31:81-4.
381. Combarros O, Infante J, Llorca J, Berciano J. Interleukin-1A (-889) genetic polymorphism increases the risk of multiple system atrophy. *Mov Disord* 2003; 18:1385-6.
382. Plata-Salaman CR, Ffrench-Mullen JM. Interleukin-1 beta depresses calcium currents in CA1 hippocampal neurons at pathophysiological concentrations. *Brain Res Bull* 1992; 29:221-3.
383. Tsuda H, Huang RW, Takatsuki K. Interleukin-2 prevents programmed cell death in adult T-cell leukemia cells. *Jpn J Cancer Res* 1993; 84:431-7.
384. Zeise ML, Madamba S, Siggins GR. Interleukin-1 beta increases synaptic inhibition in rat hippocampal pyramidal neurons in vitro. *Regul Pept* 1992; 39:1-7.
385. Serou MJ, DeCoster MA, Bazan NG. Interleukin-1 beta activates expression of cyclooxygenase-2 and inducible nitric oxide synthase in primary hippocampal neuronal culture: platelet-activating factor as a preferential mediator of cyclooxygenase-2 expression. *J Neurosci Res* 1999; 58:593-8.
386. Boje KM, Arora PK. Microglial-produced nitric oxide and reactive nitrogen oxides mediate neuronal cell death. *Brain Res* 1992; 587:250-6.
387. Carman-Krzan M, Vige X, Wise BC. Regulation by interleukin-1 of nerve growth factor secretion and nerve growth factor mRNA expression in rat primary astroglial cultures. *J Neurochem* 1991; 56:636-43.
388. Tamaru M, Tomura K, Sakamoto S, Tezuka K, Tamatani T, Narumi S. Interleukin-1beta induces tissue- and cell type-specific expression of adhesion molecules in vivo. *Arterioscler Thromb Vasc Biol* 1998; 18:1292-303.
389. Bevilacqua MP, Pober JS, Wheeler ME, Cotran RS, Gimbrone MA, Jr. Interleukin-1 activation of vascular endothelium. Effects on procoagulant activity and leukocyte adhesion. *Am J Pathol* 1985; 121:394-403.
390. Ohsuzu F. The roles of cytokines, inflammation and immunity in vascular diseases. *J Atheroscler Thromb* 2004; 11:313-21.
391. Moyer CF, Sajuthi D, Tulli H, Williams JK. Synthesis of IL-1 alpha and IL-1 beta by arterial cells in atherosclerosis. *Am J Pathol* 1991; 138:951-60.
392. Tedgui A, Mallat Z. Anti-inflammatory mechanisms in the vascular wall. *Circ Res* 2001; 88:877-87.
393. Elhage R, Maret A, Pieraggi MT, Thiers JC, Arnal JF, Bayard F. Differential effects of interleukin-1 receptor antagonist and tumor necrosis factor binding protein on fatty-streak formation in apolipoprotein E-deficient mice. *Circulation* 1998; 97:242-4.
394. Isoda K, Shiigai M, Ishigami N, Matsuki T, Horai R, Nishikawa K, Kusuhashi M, Nishida Y, Iwakura Y, Ohsuzu F. Deficiency of interleukin-1 receptor antagonist promotes neointimal formation after injury. *Circulation* 2003; 108:516-8.

395. Devlin CM, Kuriakose G, Hirsch E, Tabas I. Genetic alterations of IL-1 receptor antagonist in mice affect plasma cholesterol level and foam cell lesion size. *Proc Natl Acad Sci U S A* 2002; 99:6280-5.
396. Isoda K, Sawada S, Ishigami N, Matsuki T, Miyazaki K, Kusuhara M, Iwakura Y, Ohsuzu F. Lack of interleukin-1 receptor antagonist modulates plaque composition in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 2004; 24:1068-73.
397. Kirii H, Niwa T, Yamada Y, Wada H, Saito K, Iwakura Y, Asano M, Moriwaki H, Seishima M. Lack of interleukin-1 β decreases the severity of atherosclerosis in ApoE-deficient mice. *Arterioscler Thromb Vasc Biol* 2003; 23:656-60.
398. Chi H, Messas E, Levine RA, Graves DT, Amar S. Interleukin-1 receptor signaling mediates atherosclerosis associated with bacterial exposure and/or a high-fat diet in a murine apolipoprotein E heterozygote model: pharmacotherapeutic implications. *Circulation* 2004; 110:1678-85.
399. Nicklin MJ, Hughes DE, Barton JL, Ure JM, Duff GW. Arterial inflammation in mice lacking the interleukin 1 receptor antagonist gene. *J Exp Med* 2000; 191:303-12.
400. Esmon CT. Possible involvement of cytokines in diffuse intravascular coagulation and thrombosis. *Baillieres Best Pract Res Clin Haematol* 1999; 12:343-59.
401. Bevilacqua MP, Pober JS, Majeau GR, Cotran RS, Gimbrone MA, Jr. Interleukin 1 (IL-1) induces biosynthesis and cell surface expression of procoagulant activity in human vascular endothelial cells. *J Exp Med* 1984; 160:618-23.
402. Schorer AE, White JG. Interleukin 1 enhances arterial thrombogenicity in vitro. *Thromb Res* 1989; 56:515-22.
403. Osnes LT, Westvik AB, Joo GB, Okkenhaug C, Kierulf P. Inhibition of IL-1 induced tissue factor (TF) synthesis and procoagulant activity (PCA) in purified human monocytes by IL-4, IL-10 and IL-13. *Cytokine* 1996; 8:822-7.
404. Arend WP. The balance between IL-1 and IL-1Ra in disease. *Cytokine Growth Factor Rev* 2002; 13:323-40.
405. Malyak M, Smith MF, Jr., Abel AA, Hance KR, Arend WP. The differential production of three forms of IL-1 receptor antagonist by human neutrophils and monocytes. *J Immunol* 1998; 161:2004-10.
406. Muzio M, Polentarutti N, Sironi M, Poli G, De Gioia L, Introna M, Mantovani A, Colotta F. Cloning and characterization of a new isoform of the interleukin 1 receptor antagonist. *J Exp Med* 1995; 182:623-8.
407. Malyak M, Guthridge JM, Hance KR, Dower SK, Freed JH, Arend WP. Characterization of a low molecular weight isoform of IL-1 receptor antagonist. *J Immunol* 1998; 161:1997-2003.
408. Gabay C, Smith MF, Eidlen D, Arend WP. Interleukin 1 receptor antagonist (IL-1Ra) is an acute-phase protein. *J Clin Invest* 1997; 99:2930-40.
409. Greenfeder SA, Varnell T, Powers G, Lombard-Gillooly K, Shuster D, McIntyre KW, Ryan DE, Levin W, Madison V, Ju G. Insertion of a structural domain of interleukin (IL)-1 β confers agonist activity to the IL-1 receptor antagonist. Implications for IL-1 bioactivity. *J Biol Chem* 1995; 270:22460-6.
410. Tarlow JK, Blakemore AI, Lennard A, Solari R, Hughes HN, Steinkasserer A, Duff GW. Polymorphism in human IL-1 receptor antagonist gene intron 2 is caused by variable numbers of an 86-bp tandem repeat. *Hum Genet* 1993; 91:403-4.
411. Danis VA, Millington M, Hyland VJ, Grennan D. Cytokine production by normal human monocytes: inter-subject variation and relationship to an IL-1 receptor antagonist (IL-1Ra) gene polymorphism. *Clin Exp Immunol* 1995; 99:303-10.
412. Dewberry R, Holden H, Crossman D, Francis S. Interleukin-1 receptor antagonist expression in human endothelial cells and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2000; 20:2394-400.
413. Robb RJ, Munck A, Smith KA. T cell growth factor receptors. Quantitation, specificity, and biological relevance. *J Exp Med* 1981; 154:1455-74.
414. Nelson BH, Willerford DM. Biology of the interleukin-2 receptor. *Adv Immunol* 1998; 70:1-81.
415. Rickert M, Boulanger MJ, Goriatcheva N, Garcia KC. Compensatory energetic mechanisms mediating the assembly of signaling complexes between interleukin-2 and its α , β , and γ (c) receptors. *J Mol Biol* 2004; 339:1115-28.
416. Wang X, Rickert M, Garcia KC. Structure of the quaternary complex of interleukin-2 with its α , β , and γ (c) receptors. *Science* 2005; 310:1159-63.

417. Nelson BH, Lord JD, Greenberg PD. Cytoplasmic domains of the interleukin-2 receptor beta and gamma chains mediate the signal for T-cell proliferation. *Nature* 1994; 369:333-6.
418. Russell SM, Johnston JA, Noguchi M, Kawamura M, Bacon CM, Friedmann M, Berg M, McVicar DW, Witthuhn BA, Silvennoinen O, et al. Interaction of IL-2R beta and gamma c chains with Jak1 and Jak3: implications for XSCID and XCID. *Science* 1994; 266:1042-5.
419. Zmuidzinas A, Mamon HJ, Roberts TM, Smith KA. Interleukin-2-triggered Raf-1 expression, phosphorylation, and associated kinase activity increase through G1 and S in CD3-stimulated primary human T cells. *Mol Cell Biol* 1991; 11:2794-803.
420. Moon JJ, Rubio ED, Martino A, Krumm A, Nelson BH. A permissive role for phosphatidylinositol 3-kinase in the Stat5-mediated expression of cyclin D2 by the interleukin-2 receptor. *J Biol Chem* 2004; 279:5520-7.
421. Moriggl R, Topham DJ, Teglund S, Sexl V, McKay C, Wang D, Hoffmeyer A, van Deursen J, Sangster MY, Bunting KD, Grosveld GC, Ihle JN. Stat5 is required for IL-2-induced cell cycle progression of peripheral T cells. *Immunity* 1999; 10:249-59.
422. Crabtree GR. Contingent genetic regulatory events in T lymphocyte activation. *Science* 1989; 243:355-61.
423. Gesbert F, Moreau JL, Theze J. IL-2 responsiveness of CD4 and CD8 lymphocytes: further investigations with human IL-2Rbeta transgenic mice. *Int Immunol* 2005; 17:1093-102.
424. Malek TR. The main function of IL-2 is to promote the development of T regulatory cells. *J Leukoc Biol* 2003; 74:961-5.
425. Maloy KJ, Powrie F. Fueling regulation: IL-2 keeps CD4+ Treg cells fit. *Nat Immunol* 2005; 6:1071-2.
426. Schimpl A, Berberich I, Kneitz B, Kramer S, Santner-Nanan B, Wagner S, Wolf M, Hunig T. IL-2 and autoimmune disease. *Cytokine Growth Factor Rev* 2002; 13:369-78.
427. Gaffen SL, Liu KD. Overview of interleukin-2 function, production and clinical applications. *Cytokine* 2004; 28:109-23.
428. Wang H, Diamond RA, Yang-Snyder JA, Rothenberg EV. Precocious expression of T cell functional response genes in vivo in primitive thymocytes before T lineage commitment. *Int Immunol* 1998; 10:1623-35.
429. Yang-Snyder JA, Rothenberg EV. Developmental and anatomical patterns of IL-2 gene expression in vivo in the murine thymus. *Dev Immunol* 1993; 3:85-102.
430. Sadlack B, Merz H, Schorle H, Schimpl A, Feller AC, Horak I. Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. *Cell* 1993; 75:253-61.
431. Reya T, Bassiri H, Biancaniello R, Carding SR. Thymic stromal-cell abnormalities and dysregulated T-cell development in IL-2-deficient mice. *Dev Immunol* 1998; 5:287-302.
432. Sadlack B, Lohler J, Schorle H, Klebb G, Haber H, Sickel E, Noelle RJ, Horak I. Generalized autoimmune disease in interleukin-2-deficient mice is triggered by an uncontrolled activation and proliferation of CD4+ T cells. *Eur J Immunol* 1995; 25:3053-9.
433. Kneitz B, Herrmann T, Yonehara S, Schimpl A. Normal clonal expansion but impaired Fas-mediated cell death and anergy induction in interleukin-2-deficient mice. *Eur J Immunol* 1995; 25:2572-7.
434. Petitto JM, Streit WJ, Huang Z, Butfiloski E, Schiffenbauer J. Interleukin-2 gene deletion produces a robust reduction in susceptibility to experimental autoimmune encephalomyelitis in C57BL/6 mice. *Neurosci Lett* 2000; 285:66-70.
435. Radford-Smith G, Jewell DP. Cytokines and inflammatory bowel disease. *Baillieres Clin Gastroenterol* 1996; 10:151-64.
436. Pawlik A, Kurzawski M, Florczak M, Gawronska Szklarz B, Herczynska M. IL1beta+3953 exon 5 and IL-2 -330 promoter polymorphisms in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23:159-64.
437. Eerligh P, Koeleman BP, Dudbridge F, Jan Bruining G, Roep BO, Giphart MJ. Functional genetic polymorphisms in cytokines and metabolic genes as additional genetic markers for susceptibility to develop type 1 diabetes. *Genes Immun* 2004; 5:36-40.
438. Crispin JC, Alcocer-Varela J. Interleukin-2 and systemic lupus erythematosus--fifteen years later. *Lupus* 1998; 7:214-22.

439. Niinuma A, Higuchi M, Takahashi M, Oie M, Tanaka Y, Gejyo F, Tanaka N, Sugamura K, Xie L, Green PL, Fujii M. Aberrant activation of the interleukin-2 autocrine loop through the nuclear factor of activated T cells by nonleukemogenic human T-cell leukemia virus type 2 but not by leukemogenic type 1 virus. *J Virol* 2005; 79:11925-34.
440. Kochanek PM, Clark RS, Ruppel RA, Adelson PD, Bell MJ, Whalen MJ, Robertson CL, Satchell MA, Seidberg NA, Marion DW, Jenkins LW. Biochemical, cellular, and molecular mechanisms in the evolution of secondary damage after severe traumatic brain injury in infants and children: Lessons learned from the bedside. *Pediatr Crit Care Med* 2000; 1:4-19.
441. Smith KA. Interleukin-2: inception, impact, and implications. *Science* 1988; 240:1169-76.
442. Hanisch UK, Quirion R. Interleukin-2 as a neuroregulatory cytokine. *Brain Res Brain Res Rev* 1995; 21:246-84.
443. Su HC, Cousens LP, Fast LD, Slifka MK, Bungiro RD, Ahmed R, Biron CA. CD4+ and CD8+ T cell interactions in IFN-gamma and IL-4 responses to viral infections: requirements for IL-2. *J Immunol* 1998; 160:5007-17.
444. Truettner JS, Suzuki T, Dietrich WD. The effect of therapeutic hypothermia on the expression of inflammatory response genes following moderate traumatic brain injury in the rat. *Brain Res Mol Brain Res* 2005; 138:124-34.
445. Jensen MA, Arnason BG, Toscas A, Noronha A. Global inhibition of IL-2 and IFN-gamma secreting T cells precedes recovery from acute monophasic experimental autoimmune encephalomyelitis. *J Autoimmun* 1996; 9:587-97.
446. Kennedy MK, Torrance DS, Picha KS, Mohler KM. Analysis of cytokine mRNA expression in the central nervous system of mice with experimental autoimmune encephalomyelitis reveals that IL-10 mRNA expression correlates with recovery. *J Immunol* 1992; 149:2496-505.
447. Gallo P, Piccinno M, Pagni S, Tavolato B. Interleukin-2 levels in serum and cerebrospinal fluid of multiple sclerosis patients. *Ann Neurol* 1988; 24:795-7.
448. Merrill JE. Interleukin-2 effects in the central nervous system. *Ann N Y Acad Sci* 1990; 594:188-99.
449. Degrave W, Tavernier J, Duerinck F, Plaetinck G, Devos R, Fiers W. Cloning and structure of the human interleukin 2 chromosomal gene. *Embo J* 1983; 2:2349-53.
450. Jain J, Loh C, Rao A. Transcriptional regulation of the IL-2 gene. *Curr Opin Immunol* 1995; 7:333-42.
451. Brabletz T, Pietrowski I, Serfling E. The immunosuppressives FK 506 and cyclosporin A inhibit the generation of protein factors binding to the two purine boxes of the interleukin 2 enhancer. *Nucleic Acids Res* 1991; 19:61-7.
452. Secrist JP, Karnitz L, Abraham RT. T-cell antigen receptor ligation induces tyrosine phosphorylation of phospholipase C-gamma 1. *J Biol Chem* 1991; 266:12135-9.
453. Weiss A, Koretzky G, Schatzman RC, Kadlecsek T. Functional activation of the T-cell antigen receptor induces tyrosine phosphorylation of phospholipase C-gamma 1. *Proc Natl Acad Sci U S A* 1991; 88:5484-8.
454. Downward J, Graves J, Cantrell D. The regulation and function of p21ras in T cells. *Immunol Today* 1992; 13:89-92.
455. Izquierdo Pastor M, Reif K, Cantrell D. The regulation and function of p21ras during T-cell activation and growth. *Immunol Today* 1995; 16:159-64.
456. Kronke M, Leonard J, Depper M, Greene W. Structure and function of the human interleukin 2 receptor gene. *Behring Inst Mitt* 1987:60-72.
457. Gaffen SL. Signaling domains of the interleukin 2 receptor. *Cytokine* 2001; 14:63-77.
458. John S, Turner D, Donn R, Sinnott P, Worthington J, Ollier WE, Hutchinson IV, Hajeer AH. Two novel biallelic polymorphisms in the IL-2 gene. *Eur J Immunogenet* 1998; 25:419-20.
459. Matesanz F, Delgado C, Fresno M, Alcina A. Allelic selection of human IL-2 gene. *Eur J Immunol* 2000; 30:3516-21.
460. Reynard MP, Turner D, Navarrete CV. Allele frequencies of polymorphisms of the tumour necrosis factor-alpha, interleukin-10, interferon-gamma and interleukin-2 genes in a North European Caucasoid group from the UK. *Eur J Immunogenet* 2000; 27:241-9.

461. Matesanz F, Fedetz M, Collado-Romero M, Fernandez O, Guerrero M, Delgado C, Alcina A. Allelic expression and interleukin-2 polymorphisms in multiple sclerosis. *J Neuroimmunol* 2001; 119:101-5.
462. Togawa S, Joh T, Itoh M, Katsuda N, Ito H, Matsuo K, Tajima K, Hamajima N. Interleukin-2 gene polymorphisms associated with increased risk of gastric atrophy from *Helicobacter pylori* infection. *Helicobacter* 2005; 10:172-8.
463. Scarel-Caminaga RM, Trevisatto PC, Souza AP, Brito RB, Line SR. Investigation of an IL-2 polymorphism in patients with different levels of chronic periodontitis. *J Clin Periodontol* 2002; 29:587-91.
464. MacMillan ML, Radloff GA, Kiffmeyer WR, DeFor TE, Weisdorf DJ, Davies SM. High-producer interleukin-2 genotype increases risk for acute graft-versus-host disease after unrelated donor bone marrow transplantation. *Transplantation* 2003; 76:1758-62.
465. Fedetz M, Matesanz F, Caliz R, Ferrer MA, Collado MD, Alcina A, Martin J. Lack of association between -384 and 114 IL-2 gene polymorphisms and rheumatoid arthritis. *J Rheumatol* 2003; 30:435-7.
466. Kishimoto T, Akira S, Narazaki M, Taga T. Interleukin-6 family of cytokines and gp130. *Blood* 1995; 86:1243-54.
467. Richards CD, Gauldie J. *The acute-phase protein response. Textbook of Immunopharmacology*. Eds M. M. Dale, J. C. Foreman and T. P. Fan Blackwell Scientific Publications: Oxford, 1994.
468. Hirano T, Matsuda T, Nakajima K. Signal transduction through gp130 that is shared among the receptors for the interleukin 6 related cytokine subfamily. *Stem Cells* 1994; 12:262-77.
469. Ihle JN, Witthuhn BA, Quelle FW, Yamamoto K, Silvennoinen O. Signaling through the hematopoietic cytokine receptors. *Annu Rev Immunol* 1995; 13:369-98.
470. Kishimoto T, Taga T, Akira S. Cytokine signal transduction. *Cell* 1994; 76:253-62.
471. Heaney ML, Golde DW. Soluble cytokine receptors. *Blood* 1996; 87:847-57.
472. Mackiewicz A, Wiznerowicz M, Roeb E, Karczewska A, Nowak J, Heinrich PC, Rose-John S. Soluble interleukin 6 receptor is biologically active in vivo. *Cytokine* 1995; 7:142-9.
473. Rose-John S, Heinrich PC. Soluble receptors for cytokines and growth factors: generation and biological function. *Biochem J* 1994; 300 (Pt 2):281-90.
474. Gadiant RA, Otten U. Differential expression of interleukin-6 (IL-6) and interleukin-6 receptor (IL-6R) mRNAs in rat hypothalamus. *Neurosci Lett* 1993; 153:13-16.
475. Gadiant RA, Otten U. Expression of interleukin-6 (IL-6) and interleukin-6 receptor (IL-6R) mRNAs in rat brain during postnatal development. *Brain Res* 1994; 637:10-4.
476. Gadiant RA, Otten U. Identification of interleukin-6 (IL-6)-expressing neurons in the cerebellum and hippocampus of normal adult rats. *Neurosci Lett* 1994; 182:243-6.
477. Schobitz B, Voorhuis DA, De Kloet ER. Localization of interleukin 6 mRNA and interleukin 6 receptor mRNA in rat brain. *Neurosci Lett* 1992; 136:189-92.
478. Schobitz B, de Kloet ER, Sutanto W, Holsboer F. Cellular localization of interleukin 6 mRNA and interleukin 6 receptor mRNA in rat brain. *Eur J Neurosci* 1993; 5:1426-35.
479. Ringheim GE, Burgher KL, Heroux JA. Interleukin-6 mRNA expression by cortical neurons in culture: evidence for neuronal sources of interleukin-6 production in the brain. *J Neuroimmunol* 1995; 63:113-23.
480. Labourdette GaS, M. *Growth factors and their receptors in the central nervous system. In: Neuroglia*, 1995.
481. Norris JG, Tang LP, Sparacio SM, Benveniste EN. Signal transduction pathways mediating astrocyte IL-6 induction by IL-1 beta and tumor necrosis factor-alpha. *J Immunol* 1994; 152:841-50.
482. Sawada M, Suzumura A, Marunouchi T. TNF alpha induces IL-6 production by astrocytes but not by microglia. *Brain Res* 1992; 583:296-9.
483. Wesselingh SL, Gough NM, Finlay-Jones JJ, McDonald PJ. Detection of cytokine mRNA in astrocyte cultures using the polymerase chain reaction. *Lymphokine Res* 1990; 9:177-85.
484. Benveniste EN, Sparacio SM, Norris JG, Grenett HE, Fuller GM. Induction and regulation of interleukin-6 gene expression in rat astrocytes. *J Neuroimmunol* 1990; 30:201-12.

485. Lee SC, Liu W, Dickson DW, Brosnan CF, Berman JW. Cytokine production by human fetal microglia and astrocytes. Differential induction by lipopolysaccharide and IL-1 beta. *J Immunol* 1993; 150:2659-67.
486. Gitter BD, Regoli D, Howbert JJ, Glasebrook AL, Waters DC. Interleukin-6 secretion from human astrocytoma cells induced by substance P. *J Neuroimmunol* 1994; 51:101-8.
487. Gottschall PE, Tatsuno I, Arimura A. Regulation of interleukin-6 (IL-6) secretion in primary cultured rat astrocytes: synergism of interleukin-1 (IL-1) and pituitary adenylate cyclase activating polypeptide (PACAP). *Brain Res* 1994; 637:197-203.
488. Grimaldi M, Pozzoli G, Navarra P, Preziosi P, Schettini G. Vasoactive intestinal peptide and forskolin stimulate interleukin 6 production by rat cortical astrocytes in culture via a cyclic AMP-dependent, prostaglandin-independent mechanism. *J Neurochem* 1994; 63:344-50.
489. Norris JG, Benveniste EN. Interleukin-6 production by astrocytes: induction by the neurotransmitter norepinephrine. *J Neuroimmunol* 1993; 45:137-45.
490. Righi M, Mori L, De Libero G, Sironi M, Biondi A, Mantovani A, Donini SD, Ricciardi-Castagnoli P. Monokine production by microglial cell clones. *Eur J Immunol* 1989; 19:1443-8.
491. Sebire G, Emilie D, Wallon C, Hery C, Devergne O, Delfraissy JF, Galanaud P, Tardieu M. In vitro production of IL-6, IL-1 beta, and tumor necrosis factor-alpha by human embryonic microglial and neural cells. *J Immunol* 1993; 150:1517-23.
492. Hama T, Miyamoto M, Tsukui H, Nishio C, Hatanaka H. Interleukin-6 as a neurotrophic factor for promoting the survival of cultured basal forebrain cholinergic neurons from postnatal rats. *Neurosci Lett* 1989; 104:340-4.
493. Hama T, Kushima Y, Miyamoto M, Kubota M, Takei N, Hatanaka H. Interleukin-6 improves the survival of mesencephalic catecholaminergic and septal cholinergic neurons from postnatal, two-week-old rats in cultures. *Neuroscience* 1991; 40:445-52.
494. Kushima Y, Hatanaka H. Interleukin-6 and leukemia inhibitory factor promote the survival of acetylcholinesterase-positive neurons in culture from embryonic rat spinal cord. *Neurosci Lett* 1992; 143:110-4.
495. Yamada M, Hatanaka H. Interleukin-6 protects cultured rat hippocampal neurons against glutamate-induced cell death. *Brain Res* 1994; 643:173-80.
496. Qiu Z, Parsons KL, Gruol DL. Interleukin-6 selectively enhances the intracellular calcium response to NMDA in developing CNS neurons. *J Neurosci* 1995; 15:6688-99.
497. Holliday J, Parsons K, Curry J, Lee SY, Gruol DL. Cerebellar granule neurons develop elevated calcium responses when treated with interleukin-6 in culture. *Brain Res* 1995; 673:141-8.
498. Satoh T, Nakamura S, Taga T, Matsuda T, Hirano T, Kishimoto T, Kaziro Y. Induction of neuronal differentiation in PC12 cells by B-cell stimulatory factor 2/interleukin 6. *Mol Cell Biol* 1988; 8:3546-9.
499. Marz P, Herget T, Lang E, Otten U, Rose-John S. Activation of gp130 by IL-6/soluble IL-6 receptor induces neuronal differentiation. *Eur J Neurosci* 1997; 9:2765-73.
500. Sterneck E, Kaplan DR, Johnson PF. Interleukin-6 induces expression of peripherin and cooperates with Trk receptor signaling to promote neuronal differentiation in PC12 cells. *J Neurochem* 1996; 67:1365-74.
501. Wu YY, Bradshaw RA. Synergistic induction of neurite outgrowth by nerve growth factor or epidermal growth factor and interleukin-6 in PC12 cells. *J Biol Chem* 1996; 271:13033-9.
502. Selmaj KW, Farooq M, Norton WT, Raine CS, Brosnan CF. Proliferation of astrocytes in vitro in response to cytokines. A primary role for tumor necrosis factor. *J Immunol* 1990; 144:129-35.
503. Chiang CS, Stalder A, Samimi A, Campbell IL. Reactive gliosis as a consequence of interleukin-6 expression in the brain: studies in transgenic mice. *Dev Neurosci* 1994; 16:212-21.
504. Fattori E, Lazzaro D, Musiani P, Modesti A, Alonzi T, Ciliberto G. IL-6 expression in neurons of transgenic mice causes reactive astrogliosis and increase in ramified microglial cells but no neuronal damage. *Eur J Neurosci* 1995; 7:2441-9.
505. Steffensen SC, Campbell IL, Henriksen SJ. Site-specific hippocampal pathophysiology due to cerebral overexpression of interleukin-6 in transgenic mice. *Brain Res* 1994; 652:149-53.

506. Frei K, Malipiero UV, Leist TP, Zinkernagel RM, Schwab ME, Fontana A. On the cellular source and function of interleukin 6 produced in the central nervous system in viral diseases. *Eur J Immunol* 1989; 19:689-94.
507. Schobitz B, De Kloet ER, Holsboer F. Gene expression and function of interleukin 1, interleukin 6 and tumor necrosis factor in the brain. *Prog Neurobiol* 1994; 44:397-432.
508. Oka T, Oka K, Hosoi M, Hori T. Intracerebroventricular injection of interleukin-6 induces thermal hyperalgesia in rats. *Brain Res* 1995; 692:123-8.
509. Sehgal PB. Regulation of IL6 gene expression. *Res Immunol* 1992; 143:724-34.
510. Matsusaka T, Fujikawa K, Nishio Y, Mukaida N, Matsushima K, Kishimoto T, Akira S. Transcription factors NF-IL6 and NF-kappa B synergistically activate transcription of the inflammatory cytokines, interleukin 6 and interleukin 8. *Proc Natl Acad Sci U S A* 1993; 90:10193-7.
511. Akira S, Isshiki H, Nakajima T, Kinoshita S, Nishio Y, Hashimoto S, Natsuka S, Kishimoto T. A nuclear factor for the IL-6 gene (NF-IL6). *Chem Immunol* 1992; 51:299-322.
512. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *J Clin Invest* 1998; 102:1369-76.
513. Bennermo M, Held C, Stemme S, Ericsson CG, Silveira A, Green F, Tornvall P. Genetic predisposition of the interleukin-6 response to inflammation: implications for a variety of major diseases? *Clin Chem* 2004; 50:2136-40.
514. Terry CF, Loukaci V, Green FR. Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. *J Biol Chem* 2000; 275:18138-44.
515. Zheng C, Huang DR, Bergenbrant S, Sundblad A, Osterborg A, Bjorkholm M, Holm G, Yi Q. Interleukin 6, tumour necrosis factor alpha, interleukin 1beta and interleukin 1 receptor antagonist promoter or coding gene polymorphisms in multiple myeloma. *Br J Haematol* 2000; 109:39-45.
516. Olomolaiye O, Wood NA, Bidwell JL. A novel NlaIII polymorphism in the human IL-6 promoter. *Eur J Immunogenet* 1998; 25:267.
517. Bennet AM, Prince JA, Fei GZ, Lyrenas L, Huang Y, Wiman B, Frostegard J, Faire U. Interleukin-6 serum levels and genotypes influence the risk for myocardial infarction. *Atherosclerosis* 2003; 171:359-67.
518. Brull DJ, Montgomery HE, Sanders J, Dhamrait S, Luong L, Rumley A, Lowe GD, Humphries SE. Interleukin-6 gene -174g>c and -572g>c promoter polymorphisms are strong predictors of plasma interleukin-6 levels after coronary artery bypass surgery. *Arterioscler Thromb Vasc Biol* 2001; 21:1458-63.
519. Cox ED, Hoffmann SC, DiMercurio BS, Wesley RA, Harlan DM, Kirk AD, Blair PJ. Cytokine polymorphic analyses indicate ethnic differences in the allelic distribution of interleukin-2 and interleukin-6. *Transplantation* 2001; 72:720-6.
520. Meenagh A, Williams F, Ross OA, Patterson C, Gorodezky C, Hammond M, Leheny WA, Middleton D. Frequency of cytokine polymorphisms in populations from western Europe, Africa, Asia, the Middle East and South America. *Hum Immunol* 2002; 63:1055-61.
521. Hassan MI, Aschner Y, Manning CH, Xu J, Aschner JL. Racial differences in selected cytokine allelic and genotypic frequencies among healthy, pregnant women in North Carolina. *Cytokine* 2003; 21:10-6.
522. Kristiansen OP, Mandrup-Poulsen T. Interleukin-6 and diabetes: the good, the bad, or the indifferent? *Diabetes* 2005; 54 Suppl 2:S114-24.
523. Greisenegger S, Endler G, Haering D, Schillinger M, Lang W, Lalouschek W, Mannhalter C. The (-174) G/C polymorphism in the interleukin-6 gene is associated with the severity of acute cerebrovascular events. *Thromb Res* 2003; 110:181-6.
524. Rauramaa R, Vaisanen SB, Luong LA, Schmidt-Trucksass A, Penttila IM, Bouchard C, Toyry J, Humphries SE. Stromelysin-1 and interleukin-6 gene promoter polymorphisms are determinants of asymptomatic carotid artery atherosclerosis. *Arterioscler Thromb Vasc Biol* 2000; 20:2657-62.
525. Burzotta F, Iacoviello L, Di Castelnuovo A, Gliaca F, Luciani N, Zamparelli R, Schiavello R, Donati MB, Maseri A, Possati G, Andreotti F. Relation of the -174 G/C polymorphism of interleukin-6 to interleukin-6 plasma levels and to length of hospitalization after surgical coronary revascularization. *Am J Cardiol* 2001; 88:1125-8.

526. Fernandez-Real JM, Broch M, Vendrell J, Richart C, Ricart W. Interleukin-6 gene polymorphism and lipid abnormalities in healthy subjects. *J Clin Endocrinol Metab* 2000; 85:1334-9.
527. Hefler LA, Grimm C, Ackermann S, Malur S, Radjabi-Rahat AR, Leodolter S, Beckmann MW, Zeillinger R, Koelbl H, Tempfer CB. An interleukin-6 gene promoter polymorphism influences the biological phenotype of ovarian cancer. *Cancer Res* 2003; 63:3066-8.
528. Foster CB, Lehrnbecher T, Samuels S, Stein S, Mol F, Metcalf JA, Wyvill K, Steinberg SM, Kovacs J, Blauvelt A, Yarchoan R, Chanock SJ. An IL6 promoter polymorphism is associated with a lifetime risk of development of Kaposi sarcoma in men infected with human immunodeficiency virus. *Blood* 2000; 96:2562-7.
529. Cozen W, Gill PS, Ingles SA, Masood R, Martinez-Maza O, Cockburn MG, Gauderman WJ, Pike MC, Bernstein L, Nathwani BN, Salam MT, Danley KL, Wang W, Gage J, Gundell-Miller S, Mack TM. IL-6 levels and genotype are associated with risk of young adult Hodgkin lymphoma. *Blood* 2004; 103:3216-21.
530. Jones KG, Brull DJ, Brown LC, Sian M, Greenhalgh RM, Humphries SE, Powell JT. Interleukin-6 (IL-6) and the prognosis of abdominal aortic aneurysms. *Circulation* 2001; 103:2260-5.
531. Landi S, Moreno V, Gioia-Patricola L, Guino E, Navarro M, de Oca J, Capella G, Canzian F. Association of common polymorphisms in inflammatory genes interleukin (IL)6, IL8, tumor necrosis factor alpha, NFKB1, and peroxisome proliferator-activated receptor gamma with colorectal cancer. *Cancer Res* 2003; 63:3560-6.
532. Sambrook, Fritsch, . Molecular cloning, A Laboratory Manual. Second Edition ed. Vol Book 2: Cold Spring Harbor Laboratory Press, 1989.
533. Kantarci OH, Atkinson EJ, Hebrink DD, McMurray CT, Weinshenker BG. Association of two variants in IL-1beta and IL-1 receptor antagonist genes with multiple sclerosis. *J Neuroimmunol* 2000; 106:220-7.
534. Campos MI, Godoy dos Santos MC, Trevilatto PC, Scarel-Caminaga RM, Bezerra FJ, Line SR. Interleukin-2 and interleukin-6 gene promoter polymorphisms, and early failure of dental implants. *Implant Dent* 2005; 14:391-6.
535. Rothwell N. Interleukin-1 and neuronal injury: mechanisms, modification, and therapeutic potential. *Brain Behav Immun* 2003; 17:152-7.
536. Carter DB, Deibel MR, Jr., Dunn CJ, Tomich CS, Laborde AL, Slightom JL, Berger AE, Bienkowski MJ, Sun FF, McEwan RN, et al. Purification, cloning, expression and biological characterization of an interleukin-1 receptor antagonist protein. *Nature* 1990; 344:633-8.
537. Haskill S, Martin G, Van Le L, Morris J, Peace A, Bigler CF, Jaffe GJ, Hammerberg C, Sporn SA, Fong S, et al. cDNA cloning of an intracellular form of the human interleukin 1 receptor antagonist associated with epithelium. *Proc Natl Acad Sci U S A* 1991; 88:3681-5.
538. Worrall BB, Azhar S, Nyquist PA, Ackerman RH, Hamm TL, DeGraba TJ. Interleukin-1 receptor antagonist gene polymorphisms in carotid atherosclerosis. *Stroke* 2003; 34:790-3.
539. Francis SE, Camp NJ, Dewberry RM, Gunn J, Syrris P, Carter ND, Jeffery S, Kaski JC, Cumberland DC, Duff GW, Crossman DC. Interleukin-1 receptor antagonist gene polymorphism and coronary artery disease. *Circulation* 1999; 99:861-6.
540. Kastrati A, Koch W, Berger PB, Mehilli J, Stephenson K, Neumann FJ, von Beckerath N, Bottiger C, Duff GW, Schomig A. Protective role against restenosis from an interleukin-1 receptor antagonist gene polymorphism in patients treated with coronary stenting. *J Am Coll Cardiol* 2000; 36:2168-73.
541. Francis SE, Camp NJ, Burton AJ, Dewberry RM, Gunn J, Stephens-Lloyd A, Cumberland DC, Gershlick A, Crossman DC. Interleukin 1 receptor antagonist gene polymorphism and restenosis after coronary angioplasty. *Heart* 2001; 86:336-40.
542. McClain CJ, Cohen D, Ott L, Dinarello CA, Young B. Ventricular fluid interleukin-1 activity in patients with head injury. *J Lab Clin Med* 1987; 110:48-54.
543. Rothwell NJ. Sixteenth Gaddum Memorial Lecture December 1996. Neuroimmune interactions: the role of cytokines. *Br J Pharmacol* 1997; 121:841-7.
544. Tehranian R, Andell-Jonsson S, Beni SM, Yatsiv I, Shohami E, Bartfai T, Lundkvist J, Iverfeldt K. Improved recovery and delayed cytokine induction after closed head injury

- in mice with central overexpression of the secreted isoform of the interleukin-1 receptor antagonist. *J Neurotrauma* 2002; 19:939-51.
545. Yang GY, Zhao YJ, Davidson BL, Betz AL. Overexpression of interleukin-1 receptor antagonist in the mouse brain reduces ischemic brain injury. *Brain Res* 1997; 751:181-8.
 546. Yang GY, Mao Y, Zhou LF, Ye W, Liu XH, Gong C, Lorriss Betz A. Attenuation of temporary focal cerebral ischemic injury in the mouse following transfection with interleukin-1 receptor antagonist. *Brain Res Mol Brain Res* 1999; 72:129-37.
 547. Scherbel U, Raghupathi R, Nakamura M, Saatman KE, Trojanowski JQ, Neugebauer E, Marino MW, McIntosh TK. Differential acute and chronic responses of tumor necrosis factor-deficient mice to experimental brain injury. *Proc Natl Acad Sci U S A* 1999; 96:8721-6.
 548. Rothwell NJ, Strijbos PJ. Cytokines in neurodegeneration and repair. *Int J Dev Neurosci* 1995; 13:179-85.
 549. Spranger M, Lindholm D, Bandtlow C, Heumann R, Gnahn H, Naher-Noe M, Thoenen H. Regulation of Nerve Growth Factor (NGF) Synthesis in the Rat Central Nervous System: Comparison between the Effects of Interleukin-1 and Various Growth Factors in Astrocyte Cultures and in vivo. *Eur J Neurosci* 1990; 2:69-76.
 550. DeKosky ST, Goss JR, Miller PD, Styren SD, Kochanek PM, Marion D. Upregulation of nerve growth factor following cortical trauma. *Exp Neurol* 1994; 130:173-7.
 551. DeKosky ST, Styren SD, O'Malley ME, Goss JR, Kochanek P, Marion D, Evans CH, Robbins PD. Interleukin-1 receptor antagonist suppresses neurotrophin response in injured rat brain. *Ann Neurol* 1996; 39:123-7.
 552. Carlson NG, Wieggl WA, Chen J, Bacchi A, Rogers SW, Gahring LC. Inflammatory cytokines IL-1 alpha, IL-1 beta, IL-6, and TNF-alpha impart neuroprotection to an excitotoxin through distinct pathways. *J Immunol* 1999; 163:3963-8.
 553. Ide CF, Scriptor JL, Coltman BW, Dotson RS, Snyder DC, Jelaso A. Cellular and molecular correlates to plasticity during recovery from injury in the developing mammalian brain. *Prog Brain Res* 1996; 108:365-77.
 554. Scriptor JL, Ko J, Kow K, Arimura A, Ide CF. Regulation by interleukin-1beta of formation of a line of delimiting astrocytes following prenatal trauma to the brain of the mouse. *Exp Neurol* 1997; 145:329-41.
 555. Appel E, Kolman O, Kazimirsky G, Blumberg PM, Brodie C. Regulation of GDNF expression in cultured astrocytes by inflammatory stimuli. *Neuroreport* 1997; 8:3309-12.
 556. Bizette C, Chan-Chi-Song P, Fontaine M, Tadie M. [Expression of mRNA, interleukin-1 beta, interleukin 6 and tumor necrosis factor-alpha during regeneration of the sciatic nerve in rats after tissue loss]. *Chirurgie* 1996; 121:474-81.
 557. Wang J, Bankiewicz KS, Plunkett RJ, Oldfield EH. Intrastriatal implantation of interleukin-1. Reduction of parkinsonism in rats by enhancing neuronal sprouting from residual dopaminergic neurons in the ventral tegmental area of the midbrain. *J Neurosurg* 1994; 80:484-90.
 558. Schneider H, Pitossi F, Balschun D, Wagner A, del Rey A, Besedovsky HO. A neuromodulatory role of interleukin-1beta in the hippocampus. *Proc Natl Acad Sci U S A* 1998; 95:7778-83.
 559. Penkowa M, Giralt M, Carrasco J, Hadberg H, Hidalgo J. Impaired inflammatory response and increased oxidative stress and neurodegeneration after brain injury in interleukin-6-deficient mice. *Glia* 2000; 32:271-85.
 560. Chiaretti A, Antonelli A, Mastrangelo A, Pezzotti P, Tortorolo L, Tosi F, Genovese O. Interleukin-6 and nerve growth factor upregulation correlates with improved outcome in children with severe traumatic brain injury. *J Neurotrauma* 2008; 25:225-34.
 561. Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. *Cochrane Database Syst Rev* 2005:CD000196.
 562. Hurley LH, Von Hoff DD, Siddiqui-Jain A, Yang D. Drug targeting of the c-MYC promoter to repress gene expression via a G-quadruplex silencer element. *Semin Oncol* 2006; 33:498-512.
 563. Bonetta L. RNA-based therapeutics: ready for delivery? *Cell* 2009; 136:581-4.
 564. Cacabelos R. Pharmacogenomics in Alzheimer's disease. *Methods Mol Biol* 2008; 448:213-357.