

Research article

Open Access

## Polymorphisms in the interleukin-10 gene cluster are possibly involved in the increased risk for major depressive disorder

Tanel Traks\*<sup>1,2</sup>, Kati Koido<sup>1,2</sup>, Triin Eller<sup>2,3</sup>, Eduard Maron<sup>3,4,5</sup>, Külli Kingo<sup>2,6</sup>, Veiko Vasar<sup>2,3</sup>, Eero Vasar<sup>1,2</sup> and Sulev Kõks<sup>1,2,7</sup>

Address: <sup>1</sup>Department of Physiology, University of Tartu, Ravila 19, 50411 Tartu, Estonia, <sup>2</sup>Centre of Molecular and Clinical Medicine, University of Tartu, Tartu, Estonia, <sup>3</sup>Department of Psychiatry, University of Tartu, Tartu, Estonia, <sup>4</sup>Research Department of Mental Health, The North Estonian Regional Hospital, Psychiatry Clinic, Tallinn, Estonia, <sup>5</sup>Estonian Genome Foundation, University of Tartu, Tartu, Estonia, <sup>6</sup>Department of Dermatology and Venerology, University of Tartu, Tartu, Estonia and <sup>7</sup>Institute of Veterinary Medicine and Animal Sciences, Estonian University of Life Sciences, Tartu, Estonia

Email: Tanel Traks\* - tanel.traks@ut.ee; Kati Koido - kati.koido@ut.ee; Triin Eller - triin.eller@kliinikum.ee; Eduard Maron - eduard.maron@kliinikum.ee; Külli Kingo - kylli.kingo@kliinikum.ee; Veiko Vasar - veiko.vasar@kliinikum.ee; Eero Vasar - eero.vasar@ut.ee; Sulev Kõks - sulev.koks@ut.ee

\* Corresponding author

Published: 16 December 2008

Received: 28 July 2008

BMC Medical Genetics 2008, 9:111 doi:10.1186/1471-2350-9-111

Accepted: 16 December 2008

This article is available from: <http://www.biomedcentral.com/1471-2350/9/111>

© 2008 Traks et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

### Abstract

**Background:** Innate immune inflammatory response is suggested to have a role in the pathogenesis of major depressive disorder (MDD). Interleukin (IL)-10 family cytokines IL-10, IL-19, IL-20, and IL-24 are all implicated in the inflammatory processes and polymorphisms in respective genes have been associated with various immunopathological conditions. This study was carried out to investigate whether single-nucleotide polymorphisms (SNPs) in these genes are also associated with MDD.

**Methods:** Case-control association study was performed with seven SNPs from the *IL10* gene cluster. 153 patients with MDD and 277 healthy control individuals were recruited.

**Results:** None of the selected SNPs were individually associated with MDD. The linkage disequilibrium (LD) analysis indicated the existence of two recombination sites in the *IL10* gene cluster, thus confirming the formerly established LD pattern of this genomic region. This also created two haplotype blocks, both consisting of three SNPs. Additionally, the haplotype analysis detected a significantly higher frequency of block 2 (*IL20* and *IL24* genes) haplotype TGC in the patients group compared to healthy control individuals ( $P = 0.0097$ ).

**Conclusion:** Our study established increased risk for MDD related to the *IL20* and *IL24* haplotype and suggests that cytokines may contribute to the pathogenesis of MDD. Since none of the block 2 SNPs were individually associated with MDD, it is possible that other polymorphisms linked to them contribute to the disease susceptibility. Future studies are needed to confirm the results and to find the possible functional explanation.

## Background

Major depression (MD or major depressive disorder, MDD) is a complex disease that not only affects the lives of the patients but also their family members and is one of the major causes of disability worldwide, ranking 4th according to a recent survey of global burden of disease and estimated to become 2nd by 2030 [1]. To date, the most popular explanation of the cause has been the monoamine hypothesis which only encompasses a part of the disturbances producing the disease. Hence, many new theories and prospects for pharmacotherapy are currently being developed [2]. Among these, considerable effort has been made to elucidate the role of the innate immune inflammatory response in depression with elevated pro-inflammatory cytokines influencing neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and information processing [3].

Interleukin (IL)-10 and its recently discovered paralogs IL-19, IL-20, and IL-24 are all implicated in the inflammatory processes and act on the Th1/Th2 cytokine balance [4]. All of their genes are located in the *IL10* gene cluster in a 200 kb region of chromosome 1 within the locus q31-32. In accordance with the proposed role of these cytokines in various inflammatory diseases, the polymorphisms in respective genes have also been associated with many immunopathological conditions, especially psoriasis [5-7]. In addition, while elevated pro-inflammatory cytokines such as IL-1, IL-6 and TNF- $\alpha$  (tumor necrosis factor  $\alpha$ ) have been associated with MDD, IL-10 as a counteractive anti-inflammatory cytokine has been studied directly in reference to MDD. Results describing the relationship between MDD and IL-10 production have so far been inconsistent, showing increased [8,9], unchanged [10] or decreased [11] levels of IL-10 in depressed patients, and also differentiating between depressive subtypes [12]. It has been suggested that in case of the increased IL-10 it may indicate a compensatory anti-inflammatory response against generalized inflammatory state in MDD [13]. Furthermore, antidepressants have been shown to stimulate the production of IL-10 along with the reduction of the general pro-inflammatory/anti-inflammatory cytokine ratio [14]. In respect to neurotransmitter metabolism, IL-10 inhibits the nearly ubiquitously expressed indoleamine 2,3-dioxygenase (IDO), an enzyme responsible for directing tryptophan degradation along the kynurenine pathway [15], thus possibly increasing the availability of tryptophan for serotonin synthesis and decreasing the levels of neurotoxic *N*-methyl-D-aspartate (NMDA) receptor agonist quinolinic acid and NMDA antagonist kynurenic acid [16]. Finally, astrocytes which release IL-10 in the central nervous system and are especially sensitive to the apoptotic effects of quinolinic acid, have been observed to be reduced in MDD [16,17].

Considering the active role of *IL10* cluster cytokines in inflammatory processes and the impaired immune function in MDD, and also the specific evidences linking IL-10 to MDD, the present study was aimed to investigate the possible association between genetic variations in these genes and MDD. We selected seven SNPs from the *IL10* gene cluster to determine their individual and haplotype associations with MDD. It should also be noted that the genome-wide linkage analysis has identified the chromosome 1q31-32 region that contains the *IL10* gene cluster as one of the susceptibility loci to bipolar disorder, known for its high comorbidity with MDD [18].

## Methods

### Study sample

Unrelated patients ( $n = 153$ ; 38 males; 115 females; mean age  $\pm$  SD:  $40.5 \pm 13.4$  yr) with MDD were recruited in the study along with healthy control individuals ( $n = 277$ ; 70 males; 206 females; mean age  $\pm$  SD:  $39.4 \pm 14.0$  yr) from the Estonian population. Diagnoses of patients were substantiated by psychiatric interview and verified by Mini International Neuropsychiatric Interview (M.I.N.I. 5.0.0) based on DSM-IV [19]. The case group consisted of patients with only MDD and patients with MDD and comorbid anxiety disorders (panic disorder, generalized anxiety disorder, obsessive compulsive disorder, social phobia). Controls were evaluated using M.I.N.I. to exclude those with psychiatric morbidity, and with a family history interview to exclude those with a known history of major psychiatric disorders in first-degree relatives. Patients were recruited among consecutive outpatients and in-patients at the Clinic of Psychiatry of Tartu University Hospital and controls were recruited by newspaper advertisement in Tartu, Estonia. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Review Committee on Human Research of the University of Tartu approved the study protocol. Each subject provided written informed consent.

### Marker selection and genotyping

In our previous study, we identified two haplotype blocks within the *IL10* gene cluster encompassing thirteen SNPs from *IL19*, *IL20*, and *IL24* genes [6]. Among these, six tag SNPs (three from both blocks) were selected for this study using the Haploview Tagger program [20]. The selected SNPs of block 1 were rs2243188 and rs2243193 of *IL19* (intron 6, 3' UTR) and rs2981572 of *IL20* (5' near gene) and SNPs of block 2 were rs1518108 of *IL20* (3' UTR), rs1150253 and rs1150258 of *IL24* (intron 2, exon 5). Additionally, we included rs1800872 of *IL10* (5' UTR) that lies within the putative STAT 3 binding site and has been associated with IL-10 expression [21,22]. All selected SNPs had a minor allele frequency above 20% and were separated by more than 1000 bp.

Genomic DNA was extracted from the whole blood and the SNPs rs2243193, rs2981572, and rs1150253 were analyzed by the tetra-primer ARMS-PCR method as described previously [6,23,24]. For the SNPs rs1800872, rs2243188, rs1518108, and rs1150258 the Applied Biosystems (Foster City, California) SNPlex™ assay was used [25]. This method is based on the oligonucleotide ligation/polymerase chain reaction assay (OLA/PCR) using allele-specific ZipCode™ probes and adaptors followed by hybridization of fluorescently labelled ZipChute™ probes that allow the detection of genotypes by capillary electrophoresis. The probes were detected with an Applied Biosystems 3730 DNA Analyzer, and data interpretation was performed with the Applied Biosystems Genemapper v4.0 software.

**Statistical analyses**

Single marker association analysis and multimarker haplotype association tests between groups of patients and controls and Hardy-Weinberg equilibrium calculations in both groups were performed using the Haploview v4.0 software [20]. Analysis of genotype frequencies was performed using the web version of Genepop [26]. The Solid Spine of linkage disequilibrium (LD) method was used to define the haplotype blocks and the resulting blocks were used in the haplotype association test. The extent of disequilibrium was demonstrated by the standardized D' characteristic that was multiplied by 100 in the LD illustration generated in Haploview. One thousand permutations were used to correct P-values for multiple testing error in haplotype analysis.

**Results**

Seven SNPs of the genomic region of *IL10*, *IL19*, *IL20*, and *IL24* genes (*IL10* cluster) were analyzed in 153 Estonian

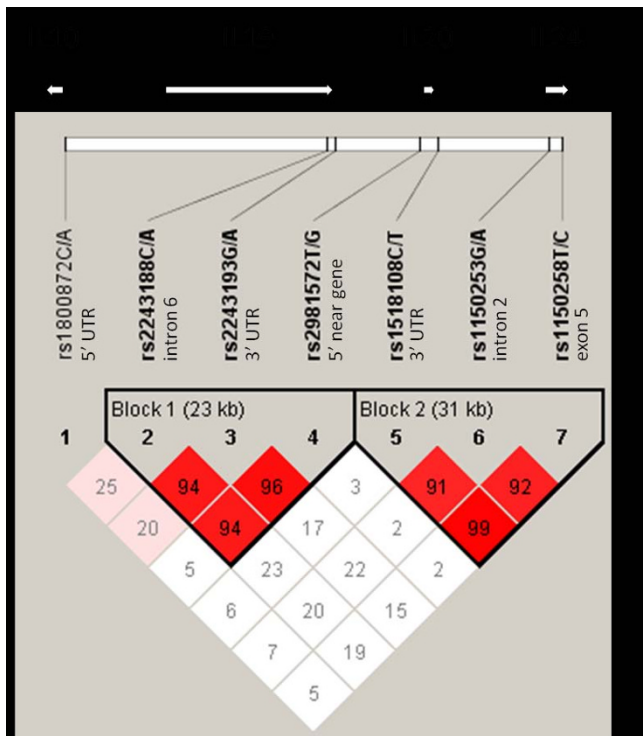
patients with MDD and 277 healthy control subjects. Genotype frequencies of these polymorphisms did not deviate significantly from the Hardy-Weinberg equilibrium in neither of the groups. Comparing genotype and allele frequencies between MDD patients and controls, none of the analyzed seven SNPs showed statistically significant association with susceptibility to MDD (Table 1).

Haplotype analysis of the *IL10*, *IL19*, *IL20*, and *IL24* genes was performed according to the pairwise linkage disequilibrium pattern observed within each of these genes (cases + controls, n = 429). The LD analysis indicated the existence of two recombination sites in the *IL10* gene cluster, the first between rs1800872 of *IL10* and rs2243188 of *IL19* ( $|D'| = 0.25$ ) and the second between rs2982572 and rs1518108 of *IL20* ( $|D'| = 0.03$ ; Figure 1). This also created two haplotype blocks, one containing rs2243188, rs2243193, and rs2981572 (the first two SNPs from *IL19* and the third SNP from *IL20* gene;  $|D'| 0.94-0.96$ ) and the other containing rs1518108, rs1150253, and rs1150258 (the first SNP from *IL20* and the rest from *IL24* gene;  $|D'| 0.91-0.99$ ; Figure 1). Four common haplotypes with an estimated frequency  $\geq 1\%$  were identified in both blocks, together comprising 98.6% and 99.1% of all haplotypes in block 1 and block 2, respectively. Additionally, the haplotype analysis provided one haplotype significantly associated with increased disease susceptibility. Namely, the block 2 haplotype TGC frequency was significantly higher in patients with MDD compared to the control group ( $P = 0.0097$ ; OR 3.45; 95% CI 1.28-9.32; Table 2) and the result remained statistically significant after permutations ( $P_{adj} = 0.042$ ; Table 2). However, the overall frequency of this haplotype was only 2.1% in the pooled group of patients and controls.

**Table 1: Genotype and allele frequencies of SNPs from the *IL10* gene cluster in MDD patients (n = 153) and control individuals (n = 277)**

SNP ID	Alleles		Genotypes				Alleles		
	I/2*	Groups	I I	I 2	2 2	P-value	I	2	P-value
rs1800872	C/A	Controls	51.0	41.3	7.7	0.5460	71.6	28.4	0.5238
		Patients	53.2	41.0	5.8		73.7	26.3	
rs2243188	C/A	Controls	65.8	30.7	3.5	0.1790	81.1	18.9	0.1820
		Patients	57.1	40.0	2.9		77.1	22.9	
rs2243193	G/A	Controls	62.8	33.1	4.1	0.4803	79.3	20.7	0.4636
		Patients	59.2	35.9	4.9		77.1	22.9	
rs2981572	T/G	Controls	48.4	42.9	8.7	0.6789	69.9	30.1	0.6406
		Patients	46.4	43.6	10.0		68.2	31.8	
rs1518108	C/T	Controls	27.5	56.6	15.9	0.8755	55.8	44.2	0.8251
		Patients	29.5	51.1	19.4		55.0	45.0	
rs1150253	G/A	Controls	27.1	55.2	17.7	0.8855	54.7	45.3	0.8657
		Patients	31.9	46.8	21.3		55.3	44.7	
rs1150258	T/C	Controls	27.0	56.4	16.6	0.8741	55.2	44.8	0.8227
		Patients	29.9	48.9	21.2		54.4	45.6	

\* 1 represents the major allele, 2 represents the minor allele



**Figure 1**  
**The selected single-nucleotide polymorphisms (SNPs) of the *IL10* gene cluster.** The relative positions and transcriptional orientation of the *IL10*, *IL19*, *IL20*, and *IL24* genes are shown. The extent of linkage disequilibrium (LD) is demonstrated by the  $D'$  characteristic multiplied by 100 and haplotypes identified using the Solid Spine of LD method are boxed.

**Discussion**

Numerous studies have established statistical associations of the *IL10* gene cluster polymorphisms with various inflammatory diseases [5-7] and the innate immune inflammatory response is suggested to have a role in the etiology of MDD [3]. Deriving from that, the present study was intended to determine the associations between seven selected SNPs from the aforementioned genomic region and MDD.

The results indicated that none of the SNPs were individually associated with MDD. On the part of the *IL10* gene, this was in line with a previous report also finding no association between the *IL10* gene and MDD, analyzing a promoter polymorphism at position -819 in that case [27]. Other studies investigating the association between cytokine gene polymorphisms and MDD have lead to diverse results. No significant associations were found between the polymorphisms from *IL1B* [28], *IL6* [29] and *TNFB* [30] genes and MDD, although there was a trend for patients who were homozygous for the -511T allele of the *IL1B* gene to have less severity depressive symptoms and

more favourable fluoxetine therapeutic response than -511C carriers [28]. However, polymorphisms from *TNFA* [31] and *CCL2* [32] genes were associated with MDD. Also, single polymorphisms and seven haplotypes from inflammation-related genes involved in T-cell functioning *PSMB4* and *TBX21* were associated with MDD susceptibility [33].

The LD analysis indicated the existence of two recombination sites in the *IL10* gene cluster, the first between rs1800872 and rs2243188 ( $|D'| = 0.25$ ) and the second between rs2982572 and rs1518108 ( $|D'| = 0.03$ ), thus confirming the formerly established LD pattern of this genomic region [6,34]. The resulting two haplotype blocks consisted of rs2243188, rs2243193, and rs2982572 ( $|D'| 0.94-0.96$ ); and rs1518108, rs1150253, and rs1150258 ( $|D'| 0.91-0.99$ ). Additionally, the haplotype analysis revealed that the frequency of the block 2 haplotype TGC was significantly higher among patients compared to controls and was therefore associated with susceptibility to MDD ( $P = 0.0097$ ; OR 3.45; 95% CI 1.28-9.32). However, this result should be approached with caution, as the overall frequency of this haplotype was only 2.1% in the pooled group of patients and controls. The block 2 contained one SNP from the *IL20* gene and two from the *IL24* gene and since these SNPs weren't individually associated with MDD, it is possible that the polymorphisms contributing to the increased disease susceptibility are linked to them in the same haplotype block. Considering the elevated levels of inflammatory mediators in MDD and the mainly pro-inflammatory nature of *IL-20* and *IL-24* cytokines, these functional polymorphisms could affect the immunological states in the context of MDD. In addition, the block 2 extends further from the *IL24* gene in 3' direction and includes the genes *FAIM3*, *PIGR*, and *FCAMR* (HapMap, genome build 35), that could also be affected by alternative haplotypes. Unfortunately, specific causal explanations connecting SNPs and MDD are beyond the scope of this research and could be established in functional studies.

**Conclusion**

The present study established increased risk for MDD related to the *IL20* and *IL24* haplotype and suggests that cytokines may contribute to the pathogenesis of MDD. Since none of the block 2 SNPs were individually associated with MDD, it is possible that other polymorphisms linked to them contribute to the disease susceptibility. The main limitation in this case was the small sample size that hinders the detection of small effects. Confirmative study with increased number of the SNPs and a larger sample is needed.

**Competing interests**

The authors declare that they have no competing interests.

**Table 2: Haplotype analysis of SNPs from the IL10 gene cluster with major depressive disorder.**

	Controls (n = 277)	Patients (n = 153)	P-value nom	P-value adj	OR (95% CI)
Block 1 haplotypes (IL19 and IL20 genes)					
CGT	68.6	67.3	0.7093	1.0000	0.94 (0.69–1.28)
AAG	17.9	21.4	0.2297	0.8840	1.25 (0.87–1.79)
CGG	10.1	8.4	0.4168	0.9890	0.81 (0.49–1.35)
CAG	2.3	1.1	0.2506	0.9180	0.49 (0.14–1.68)
Block 2 haplotypes (IL20 and IL24 genes)					
CGT	53.3	51.6	0.6459	1.0000	0.94 (0.70–1.25)
TAC	42.8	40.8	0.5768	1.0000	0.92 (0.69–1.23)
CAT	1.9	2.8	0.4109	0.9890	1.47 (0.58–3.74)
TGC	1.2	3.9	<b>0.0097</b>	<b>0.0420</b>	3.45 (1.28–9.32)

P-values ≤0.05 are in bold; P-value nom: nominal P-value; P-value adj: permutation adjusted P-value; OR: odds ratio; CI: confidence interval

**Authors' contributions**

TT participated in the molecular genetic studies, performed the statistical analyses and drafted the manuscript. KK participated in the design of the study and the molecular genetic studies, performed the statistical analyses and helped to revise the draft. TE and EM coordinated the collection of the blood samples of the study participants and performed their psychiatric testing. KK participated in the design of the study and helped to revise the draft. VV, EV, and SK conceived the study, participated in its coordination and draft revision. All authors have read and approved the final manuscript.

**Acknowledgements**

This study was supported by Estonian Science Foundation grants 5688, 6576, and 7034 and Estonian Ministry of Science and Education grants SF0180125s08, SF0182584Bs03, and SF0180043s07. We thank the patients and volunteers for participation.

**References**

- Mathers CD, Loncar D: **Projections of global mortality and burden of disease from 2002 to 2030.** *PLoS medicine* 2006, **3**:e442.
- Berton O, Nestler EJ: **New approaches to antidepressant drug discovery: beyond monoamines.** *Nature reviews* 2006, **7**:137-151.
- Raison CL, Capuron L, Miller AH: **Cytokines sing the blues: inflammation and the pathogenesis of depression.** *Trends in immunology* 2006, **27**:24-31.
- Pestka S, Krause CD, Sarkar D, Walter MR, Shi Y, Fisher PB: **Interleukin-10 and related cytokines and receptors.** *Annual review of immunology* 2004, **22**:929-979.
- Hollegaard MV, Bidwell JL: **Cytokine gene polymorphism in human disease: on-line databases, Supplement 3.** *Genes and immunity* 2006, **7**:269-276.
- Koks S, Kingo K, Vabrit K, Ratsep R, Karelson M, Silm H, Vasar E: **Possible relations between the polymorphisms of the cytokines IL-19, IL-20 and IL-24 and plaque-type psoriasis.** *Genes and immunity* 2005, **6**:407-415.
- Kingo K, Mossner R, Koks S, Ratsep R, Kruger U, Vasar E, Reich K, Silm H: **Association analysis of IL19, IL20 and IL24 genes in palmoplantar pustulosis.** *Br J Dermatol* 2007, **156**:646-652.
- Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H: **Cytokine production and serum proteins in depression.** *Scandinavian journal of immunology* 1995, **41**:534-538.
- Kubera M, Kenis G, Bosmans E, Zieba A, Dudek D, Nowak G, Maes M: **Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: comparison**

- between the acute state and after remission.
- Polish journal of pharmacology* 2000, **52**:237-241.
- Huang TL, Lee CT: **T-helper 1/T-helper 2 cytokine imbalance and clinical phenotypes of acute-phase major depression.** *Psychiatry and clinical neurosciences* 2007, **61**:415-420.
- Parisis JT, Adamopoulos S, Rigas A, Kostakis G, Karatzas D, Venetsanou K, Kremastinos DT: **Comparison of circulating proinflammatory cytokines and soluble apoptosis mediators in patients with chronic heart failure with versus without symptoms of depression.** *The American journal of cardiology* 2004, **94**:1326-1328.
- Rothermundt M, Arolt V, Fenker J, Gutbrodt H, Peters M, Kirchner H: **Different immune patterns in melancholic and non-melancholic major depression.** *European archives of psychiatry and clinical neuroscience* 2001, **251**:90-97.
- Simon NM, McNamara K, Chow CW, Maser RS, Papakostas GI, Pollack MH, Nierenberg AA, Fava M, Wong KK: **A detailed examination of cytokine abnormalities in Major Depressive Disorder.** *Eur Neuropsychopharmacol* 2008, **18**:230-233.
- Kenis G, Maes M: **Effects of antidepressants on the production of cytokines.** *The international journal of neuropsychopharmacology/official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)* 2002, **5**:401-412.
- Weiss G, Murr C, Zoller H, Haun M, Widner B, Ludescher C, Fuchs D: **Modulation of neopterin formation and tryptophan degradation by Th1- and Th2-derived cytokines in human monocyte cells.** *Clinical and experimental immunology* 1999, **116**:435-440.
- Muller N, Schwarz MJ: **The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression.** *Mol Psychiatry* 2007, **12**:988-1000.
- Guillemin GJ, Wang L, Brew BJ: **Quinolinic acid selectively induces apoptosis of human astrocytes: potential role in AIDS dementia complex.** *Journal of neuroinflammation* 2005, **2**:16.
- Deterra-Wadleigh SD, Badner JA, Berrettini VH, Yoshikawa T, Goldin LR, Turner G, Rollins DY, Moses T, Sanders AR, Karkera JD, et al: **A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2.** *Proceedings of the National Academy of Sciences of the United States of America* 1999, **96**:5604-5609.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: **The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.** *The Journal of clinical psychiatry* 1998, **59**(Suppl 20):22-33.
- Barrett JC, Fry B, Maller J, Daly MJ: **Haploview: analysis and visualization of LD and haplotype maps.** *Bioinformatics (Oxford, England)* 2005, **21**:263-265.
- Kube D, Platzer C, von Knethen A, Straub H, Bohlen H, Hafner M, Tesch H: **Isolation of the human interleukin 10 promoter. Characterization of the promoter activity in Burkitt's lymphoma cell lines.** *Cytokine* 1995, **7**:1-7.

22. Howell WM, Rose-Zerilli MJ: **Cytokine gene polymorphisms, cancer susceptibility, and prognosis.** *The Journal of nutrition* 2007, **137**:194S-199S.
23. Kingo K, Koks S, Nikopensius T, Silm H, Vasar E: **Polymorphisms in the interleukin-20 gene: relationships to plaque-type psoriasis.** *Genes and immunity* 2004, **5**:117-121.
24. Koks S, Kingo K, Ratsep R, Karelson M, Silm H, Vasar E: **Combined haplotype analysis of the interleukin-19 and -20 genes: relationship to plaque-type psoriasis.** *Genes and immunity* 2004, **5**:662-667.
25. Tobler AR, Short S, Andersen MR, Paner TM, Briggs JC, Lambert SM, Wu PP, Wang Y, Spoonde AY, Koehler RT, et al.: **The SNPlex genotyping system: a flexible and scalable platform for SNP genotyping.** *J Biomol Tech* 2005, **16**:398-406.
26. Raymond M, Rousset F: **GENEPOP (Version 1.2): Population Genetics Software for Exact Tests and Ecumenicism.** *J Hered* 1995, **86**:248-249.
27. Jun TY, Pae CU, Chae JH, Bahk WM, Kim KS, Han H: **Report on IL-10 gene polymorphism at position -819 for major depression and schizophrenia in Korean population.** *Psychiatry and clinical neurosciences* 2002, **56**:177-180.
28. Yu YW, Chen TJ, Hong CJ, Chen HM, Tsai SJ: **Association study of the interleukin-1 beta (C-511T) genetic polymorphism with major depressive disorder, associated symptomatology, and antidepressant response.** *Neuropsychopharmacology* 2003, **28**:1182-1185.
29. Hong CJ, Yu YW, Chen TJ, Tsai SJ: **Interleukin-6 genetic polymorphism and Chinese major depression.** *Neuropsychobiology* 2005, **52**:202-205.
30. Jun TY, Pae CU, Chae JH, Bahk WM, Kim KS, Pyo CW, Han H: **Tumor necrosis factor-beta gene polymorphism may not be associated with major depressive disorder in the Korean population.** *Psychiatry and clinical neurosciences* 2003, **57**:31-35.
31. Jun TY, Pae CU, Hoon H, Chae JH, Bahk WM, Kim KS, Serretti A: **Possible association between -G308A tumour necrosis factor-alpha gene polymorphism and major depressive disorder in the Korean population.** *Psychiatric genetics* 2003, **13**:179-181.
32. Pae CU, Yu HS, Kim TS, Lee CU, Lee SJ, Jun TY, Lee C, Serretti A, Paik IH: **Monocyte chemoattractant protein-1 (MCP1) promoter -2518 polymorphism may confer a susceptibility to major depressive disorder in the Korean population.** *Psychiatry research* 2004, **127**:279-281.
33. Wong ML, Dong C, Maestre-Mesa J, Licinio J: **Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response.** *Mol Psychiatry* 2008, **13**:800-812.
34. Oleksyk TK, Thio CL, Truelove AL, Goedert JJ, Donfield SM, Kirk GD, Thomas DL, O'Brien SJ, Smith MW: **Single nucleotide polymorphisms and haplotypes in the IL10 region associated with HCV clearance.** *Genes and immunity* 2005, **6**:347-357.

### Pre-publication history

The pre-publication history for this paper can be accessed here:

<http://www.biomedcentral.com/1471-2350/9/111/pre-pub>