



HAL
open science

Toxoplasma gondii exposure may modulate the influence of TLR2 genetic variation on bipolar disorder: a gene–environment interaction study

José Oliveira, Rémi Kazma, Edith Le Floch, Meriem Bennabi, Nora Hamdani, Djaouida Bengoufa, Mehdi Dahoun, Céline Manier, Frank Bellivier, Rajagopal Krishnamoorthy, et al.

► To cite this version:

José Oliveira, Rémi Kazma, Edith Le Floch, Meriem Bennabi, Nora Hamdani, et al.. Toxoplasma gondii exposure may modulate the influence of TLR2 genetic variation on bipolar disorder: a gene–environment interaction study. International Journal of Bipolar Disorders, 2016, 4 (1), pp.11. 10.1186/s40345-016-0052-6 . cea-04557509

HAL Id: cea-04557509

<https://cea.hal.science/cea-04557509>

Submitted on 24 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

RESEARCH

Open Access



Toxoplasma gondii exposure may modulate the influence of *TLR2* genetic variation on bipolar disorder: a gene–environment interaction study

José Oliveira^{1,2†}, Rémi Kazma^{3†}, Edith Le Floch³, Meriem Bennabi^{1,2}, Nora Hamdani^{2,4,5,6}, Djaouida Bengoufa⁷, Mehdi Dahoun⁷, Céline Manier¹, Frank Bellivier^{8,9}, Rajagopal Krishnamoorthy¹, Jean-François Deleuze³, Robert Yolken^{10,11}, Marion Leboyer^{2,4,5,6†} and Ryad Tamouza^{1,2,7,8*†}

Abstract

Background: Genetic vulnerability to environmental stressors is yet to be clarified in bipolar disorder (BD), a complex multisystem disorder in which immune dysfunction and infectious insults seem to play a major role in the pathophysiology. Association between pattern-recognition receptor coding genes and BD had been previously reported. However, potential interactions with history of pathogen exposure are yet to be explored.

Methods: 138 BD patients and 167 healthy controls were tested for serostatus of *Toxoplasma gondii*, CMV, HSV-1 and HSV-2 and genotyped for *TLR2* (*rs4696480* and *rs3804099*), *TLR4* (*rs1927914* and *rs11536891*) and *NOD2* (*rs2066842*) polymorphisms (SNPs). Both the pathogen-specific seroprevalence and the *TLR/NOD2* genetic profiles were compared between patients and controls followed by modelling of interactions between these genes and environmental infectious factors in a regression analysis.

Results: First, here again we observed an association between BD and *Toxoplasma gondii* ($p = 0.045$; OR = 1.77; 95 % CI 1.01–3.10) extending the previously published data on a cohort of a relatively small number of patients (also included in the present sample). Second, we found a trend for an interaction between the *TLR2 rs3804099* SNP and *Toxoplasma gondii* seropositivity in conferring BD risk ($p = 0.017$, uncorrected).

Conclusions: Pathogen exposure may modulate the influence of the immunogenetic background on BD. A much larger sample size and information on period of pathogen exposure are needed in future gene–environment interaction studies.

Keywords: Bipolar disorder, Innate immunity, Pathogen recognition receptor, Genetic diversity, Infection, Gene–environment interaction

Background

Bipolar disorder (BD) is a heritable chronic psychiatric illness standing among the leading causes of disability worldwide (Collins et al. 2011; Gore et al. 2011;

Whiteford et al. 2013). The aetiology of BD is multifactorial and results from complex interactions between genetic determinants and a number of known and yet to be uncovered environmental factors (Kerner 2014). The index bipolar diagnosis is often delayed by many years as longitudinal natural history is one among the components of diagnosis (Leboyer and Kupfer 2010). Currently, objective biomarkers that could lead to early and specific diagnosis of BD are lacking and identification of such markers along with objectively assessed environmental

*Correspondence: tamouza.ryad@gmail.com

†José Oliveira and Rémi Kazma are co-first authors

Marion Leboyer and Ryad Tamouza are co-senior authors

⁷ Laboratoire Jean Dausset and LabEx Transplantex, Hôpital Saint Louis, Paris, France

Full list of author information is available at the end of the article

factors could assist in tailoring reasoned preventive and therapeutic approaches for BD.

Studies on gene–environment interactions in psychiatric disorders essentially focus on early-life psychosocial stressors as the environmental risk factor and to a limited extent on the infectious history of the mother (during pregnancy) or the foetus/neonate (Uher 2014). For example, in BD, an interaction between *BDNF* gene polymorphisms and stressful life events seems to confer relatively higher risk for depressive episodes (Hosang et al. 2010). Similarly, maternal herpes simplex virus 2 (HSV-2) and cytomegalovirus (CMV) infectious history appears to interact, respectively, with *GRIN2B* and *CTNNA3* gene polymorphisms to raise the risk of schizophrenia (SZ) (Børglum et al. 2014; Demontis et al. 2011). While the assessment of early-life stress may be subject to recall bias, history of infections is relatively amenable to objective evaluation. Indeed, in recent studies, infectious agents emerged as a group of well-defined environmental risk factors in psychiatric disorders and in particular in BD (Canetta et al. 2014; Dickerson et al. 2004; Hamdani et al. 2013; Parboosing et al. 2013). These studies not only stress the importance of studying infectious events but also, by decreasing the sample heterogeneity, allow to capture the environmental influence on genetic liability (Kazma et al. 2011). Genetic susceptibility to infections is mediated by the inter-individual variability of immune responses, the first line defence being the innate immune system (Kotb et al. 2002; Pandey et al. 2014).

In this regard, genetic polymorphism of the pattern-recognition receptors (PRRs) is of interest as PRRs recognize the pathogen-associated molecular patterns (PAMPs) (bacterial, viral, fungal or parasite-derived) as well as host-derived danger signals to provide optimal protection (Akira et al. 2006). We recently provided evidence for associations between BD and genetic variants of *TLR2*, *TLR4* and *NOD2* genes, all encoding for pivotal PRRs (Oliveira et al. 2014a, b, c). The membrane-bound *TLR2* and *TLR4* and the cytoplasmic *NOD2* receptors are widely expressed on immune cells, intestinal epithelial cells and more importantly in microglia that actively participate in the central nervous system (CNS) homeostasis and immune surveillance (Akira et al. 2006; Berrebi et al. 2003; Hanke and Kielian 2011; Lala et al. 2003; Olson and Miller 2004; Rivest 2009; Sterka and Marriott 2006).

Although genetic associations between *TLR2*, *TLR4* and *NOD2* polymorphisms with susceptibility to infections on the one hand (Schröder and Schumann 2005; Tekin et al. 2012; van Well et al. 2013), and BD (as discussed above) on the other have been independently reported in the literature, the influence of interaction

between a particular infection and variability of the innate immune system on BD phenotype remains to be tested.

In order to explore possible gene–environment interactions, the present study evaluates the effect of interactions between serologically documented exposure to *Toxoplasma gondii*, CMV, HSV-1 or HSV-2 and polymorphisms of *TLR2*, *TLR4* and *NOD2* genes in a sample of patients with BD.

Methods

Subjects

This study included 138 cases (in- and out-patients) meeting the DSM-IV criteria (American Psychiatric Association 1994) for BD [type I, II or not otherwise specified (NOS)], from two French university-affiliated psychiatry departments (Mondor Hospital, Créteil, University Paris-Est and Fernand Widal Hospital, Paris, University Paris Diderot).

Patients were interviewed with the French version of the “Diagnostic Interview for Genetic Studies” (DIGS) for the assessment of lifetime clinical characteristics of BD as well as for demographic characteristics (i.e. number of years of education, working status, place of birth) (Nurnberger et al. 1994). Ongoing treatments as well as hospitalization status were recorded. Manic and depressive symptoms were assessed using, respectively, the Young Mania Rating Scale (Young et al. 1978) and the Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg 1979). In addition, 167 healthy controls were enrolled through a clinical investigation centre (Centre for Biological Resources, Mondor Hospital, Créteil, France). Only subjects without any personal or family history of psychotic disorders, affective disorders, addictive or suicidal behaviour, or auto-immune diseases were included in the present study. Patients and controls were submitted to serological screening and were negative for HIV-1/-2, Hepatitis A, B and C and had no known recent inflammatory, auto-immune or infectious event or a neurological disease. Knowing that *Toxoplasma gondii* infection incidence highly varies according to geographical location and assuming that potential early-life influences of *Toxoplasma gondii* may thus vary according to place of birth, a subsample including only individuals born in Metropolitan France was selected to study the association between this parasite and BD. Indeed, to refine the genetic association analysis, a homogeneous subgroup of 76 cases and 67 controls, with French ancestry (at least 3 grandparents born in mainland France), was selected. Written informed consent was obtained from all participating subjects and the institutional ethical committee approved the research protocol.

Serological analysis

Solid-phase enzyme microplate immunoassay methods were used to measure the IgG and IgM class antibodies to *Toxoplasma gondii*, CMV, HSV-1 and HSV-2 in blood samples using previously described methods (Yolken et al. 2001). Assay reagents were obtained from IBL America (Minneapolis, Minnesota, USA). The results were expressed as a ratio between the reactivity of the sample and a standard sample run on each microplate. Seropositivity was defined as a *T. gondii* IgG ratio ≥ 0.8 , equivalent to ≥ 10 international units. All antibody measurements were carried out at the Stanley Laboratory of Developmental Neurovirology, Baltimore, MD, USA. All samples were coded to ensure anonymity and the laboratory did not have access to diagnostic or clinical information.

TLR2, TLR4 and NOD2 genotyping

Genomic DNA was extracted from EDTA-treated peripheral blood sample using a standard procedure. Selection of analysed single-nucleotide polymorphisms (SNPs) of *TLR2* (*rs4696480* and *rs3804099*), *TLR4* (*rs1927914* and *rs11536891*) and *NOD2* (*rs2066842*) were based on previous positive genetic association findings with BD subsets (Oliveira et al. 2014a, b, c). All SNPs were analysed by a pre-developed TaqMan[®] 5'-nuclease assay kits (Applied Biosystems[®], Foster City, CA, USA) using allele-specific fluorogenic oligonucleotide probes as described earlier (Oliveira et al. 2014a, b, c).

Statistical analysis

The comparison of demographic/clinical characteristics and *Toxoplasma gondii*, CMV, HSV-1 and HSV-2 serological status between cases and controls was performed using Chi-square tests for categorical variables and Mann–Whitney *U* tests for continuous variables. To correct for multiple testing (four serological markers), we used the Bonferroni approach to determine the significance threshold ($0.05/4 = 0.0125$). According to these results, a multiple logistic regression analysis was further performed to test the association between *Toxoplasma gondii* seropositivity and BD diagnosis adjusting for age at inclusion and level of education (higher education vs other). This logistic regression analysis was similarly performed in the subsample of individuals born in France.

Allelic frequency comparisons between cases and controls and testing for deviation from Hardy–Weinberg proportions in controls were performed using the Chi-square tests. Fisher's exact test was used wherever appropriate.

To test for the potential gene–environment interaction between the studied SNPs of *TLR2*, *TLR4* and *NOD2* and *Toxoplasma gondii* serostatus, we modelled a multiple

logistic regression incorporating an interaction term, also adjusting for age at inclusion and level of education. The number of minor alleles was included in the model as a continuous variable, in our additive genetic model. To correct for multiple testing (five SNPs), we used the Bonferroni approach to determine the significance threshold ($0.05/5 = 0.01$). All associations were first tested for the whole sample and in a second step using only the subsample of individuals of French ancestry (as described above). All statistical analyses were performed using the SPSS v20.0.0 and the WINPEPI v11.43 software packages (Abramson 2011).

Results

Demographic/clinical characteristics and allele distributions in cases and controls are given, respectively, in Tables 1 and 3. The distribution of all the studied SNPs complied with the expected Hardy–Weinberg proportions.

We found a statistically significant association between BD and *Toxoplasma gondii* IgG seropositivity (univariate *p* value = 0.002) which was additionally confirmed by a multiple logistic regression analysis adjusting for age at inclusion and level of education (*p* value = 0.049;

Table 1 Clinical and demographic characteristics of bipolar and control subjects

	BD (n = 138)	HC (n = 167)	<i>p</i> value
Mean \pm SD			
Age at inclusion (years)	43.6 \pm 13.50	39.5 \pm 13.77	0.009
Age at onset (years) (n = 135) ^a	26.3 \pm 10.51	–	–
<i>n</i> (%)			
Gender (female)	71 (51.4)	90 (53.9)	0.671
Diagnoses (DSM-VI)			
BD-I	98 (71.0)	–	–
BD-II	37 (26.8)	–	–
BD-NOS	3 (2.2)	–	–
Place of birth (Metropolitan France)	113 (81.9)	137 (82.0)	0.973
Education level (higher education)	78 (56.5)	72 (43.1)	0.020
Working status (currently active)	72 (52.2)	93 (55.7)	0.540
Serum anti-pathogen IgG (positive)			
<i>Toxoplasma gondii</i>	103 (74.6)	97 (58.1)	0.002
CMV	84 (60.9)	107 (64.1)	0.565
HSV-1	34 (24.6)	47 (28.1)	0.490
HSV-2	87 (63.0)	119 (71.3)	0.127

BD bipolar disorder; HC healthy controls; NOS not otherwise specified; SD standard deviation; CMV cytomegalovirus; HSV-1 herpes simplex virus 1; HSV-2 herpes simplex virus 2; NS non-significant

^a Data were missing for three patients

OR = 1.77; 95 % CI 1.00–3.11) (Table 2). We also observed this association in the subgroup of patients born in France, similarly adjusting for age at inclusion and level of education (p value = 0.009; OR = 2.34; 95 % CI 1.23–4.43) (Table 2). This result confirms and extends the previously published data on a smaller set of French patients belonging to the same cohort and included in the present study (101 BD patients and 95 healthy controls in common) (Hamdani et al. 2013).

None of the five SNPs studied in *TLR2*, *TLR4* and *NOD2* were significantly associated with BD, using an allelic or genotype model after accounting for multiple testing and remained non-significant for the French ancestry subset (data not shown).

A trend for an interaction between *TLR2* rs3804099 and *Toxoplasma gondii* influencing the risk for BD was noted, although no longer significant after correction for multiple testing (Table 3). This SNP has an odds ratio below one in the *Toxoplasma gondii* seropositive group and the opposite in the seronegative group as assessed by separate logistic regression analyses with an additive model (Table 4).

Discussion

Inherited immune vulnerability to environmental risk factors may explain the association between BD and exposure to a variety of infections early in life, during a critical neurodevelopmental window (Canetta et al. 2014;

Table 2 Association between *Toxoplasma gondii* and bipolar disorder adjusted for age and level of education in the whole sample

	Entire sample					Individuals born in France				
	β	OR	CI 95 %	df	p value	β	OR	CI 95 %	df	p value
Age	0.016	1.016	0.996–1.036	1	0.110	0.009	1.009	0.988–1.031	1	0.403
Level of education	0.629	1.876	1.172–3.003	1	0.009	0.656	1.928	1.144–3.248	1	0.014
<i>Toxoplasma gondii</i>	0.568	1.765	1.002–3.108	1	0.049	0.850	2.339	1.234–4.433	1	0.009

Level education = higher education vs other level of education

OR odds ratio; CI confidence interval; df degrees of freedom

Table 3 *TLR2*, *TLR4* and *NOD2* polymorphisms in bipolar patients and healthy controls: genotype distribution

Polymorphism		MAF		p value	HWE p value
		BD ($n = 138$)	Controls ($n = 167$)		
<i>TLR2</i> rs4696480	T > A	0.46	0.51	0.178	0.929
<i>TLR2</i> rs3804099	T > C	0.46	0.44	0.610	0.804
<i>TLR4</i> rs1927914	A > G	0.41	0.39	0.601	0.671
<i>TLR4</i> rs11536891	T > C	0.17	0.14	0.265	0.588
<i>NOD2</i> rs2066842	C > T	0.25	0.25	0.898	0.656

TLR2 Toll-like receptor 2; *TLR4* Toll-like receptor 4; *NOD2* nucleotide-binding oligomerization domain containing 2; *BD* bipolar disorder; *NS* non-significant; *MAF* minor allele frequency; *HWE* Hardy–Weinberg equilibrium in controls

Table 4 SNP x *Toxoplasma gondii* interaction

Polymorphism		TG positive		TG negative		p value (GxE)	OR TG (+) (CI 95 %)	OR TG (–) (CI 95 %)
		MAF BD	MAF HC	MAF BD	MAF HC			
<i>TLR2</i> rs4696480	T/A	0.47	0.53	0.44	0.49	0.923	0.760 (0.51–1.14)	0.805 (0.44–1.47)
<i>TLR2</i> rs3804099	T/C	0.42	0.45	0.59	0.43	0.021	0.894 (0.62–1.30)	2.289 (1.15–4.58)
<i>TLR4</i> rs1927914	A/G	0.40	0.37	0.46	0.42	0.992	1.102 (0.76–1.60)	1.154 (0.65–2.05)
<i>TLR4</i> rs11536891	T/C	0.17	0.11	0.17	0.18	0.341	1.546 (0.91–2.64)	0.944 (0.42–2.14)
<i>NOD2</i> rs2066842	C/T	0.25	0.28	0.24	0.20	0.408	0.875 (0.56–1.37)	1.300 (0.64–2.63)

SNP single-nucleotide polymorphism; *TG* *Toxoplasma gondii*; *MAF* minor allele frequency; *BD* bipolar disorder; *HC* healthy controls; *GxE* gene–environment interaction; *OR* odds ratio; *CI* confidence interval

Foldager et al. 2014; Graham et al. 2014; Hamdani et al. 2013; Mazaheri-Tehrani et al. 2014; Parboosing et al. 2013). Herein, we explored the interaction between infectious stigma and genetic variants of the innate arm of the immune response in a sample of adult BD patients.

First, we confirmed the influence of *Toxoplasma* infection in BD by analysing a much larger sample than in a previous study (Table 1) and also by stringently selecting those born in France for sample homogeneity (Hamdani et al. 2013). Second, we did not find a genetic association between individual *TLR2*, *TLR4* and *NOD2* alleles and BD, as compared to our previous positive findings of association in a distinct study cohort (Oliveira et al. 2014a, b, c). Such discrepancy could possibly be related to differences in the study design. The present study involves a relatively smaller sample size, specifically when considering only individuals of French ancestry, 76 cases and 67 controls. Such differing study setting may not necessarily have the power to detect the previously observed genetic associations, involving approximately 550 and 200 cases and controls, respectively, and stringently selected for their genetic homogeneity (at least three generations from mainland France) (Oliveira et al. 2014a, b, c). However, it must be noted that the referred SNPs were not associated with BD in the large GWAS by the Psychiatric Genomics Consortium (7481 patients and 9250 controls) (Sklar et al. 2011). Third, in the gene–environment interaction analysis, the *TLR2* *rs3804099*/*Toxoplasma* interaction shows a trend in that the *TLR2* genetic variation may modulate the relationship between *Toxoplasma gondii* exposure and BD.

Indeed, *TLR2* molecules have been implicated: (i) in the perpetuation of inflammatory responses in the CNS after pro-inflammatory stimulation of astrocytes (Henn et al. 2011); (ii) in triggering neuro-inflammation in the presence of endogenous molecules such as α -synuclein and amyloid β -peptide, respectively, in Parkinson and Alzheimer disorders (Kim et al. 2013; Liu et al. 2012); and (iii) in sustaining neuro-inflammation due to HSV-1 infection (Aravalli et al. 2005). Besides these observations, association of *TLR2* genetic diversity either with Alzheimer's disease (Yu et al. 2011) or with cognitive function in SZ (Kang et al. 2013) suggests that inter-individual liability to modulate neuro-inflammation may be genetically driven. Yet direct evidence for the involvement of *TLR2* in susceptibility to *Toxoplasma gondii* and neuro-inflammation is lacking. Nevertheless, a role for *TLR2* is highly probable since higher loads of *Toxoplasma gondii* in brain tissue were observed in *TLR2*-deficient mice following infection with *Toxoplasma gondii* cysts (Mun et al. 2003).

We have recently described a combined effect of both *TLR2* *rs3804099* TT genotype and reported childhood sexual abuse on the age at onset of BD, a proxy of disease

severity (Oliveira et al. 2015). Additionally, in a murine model, prenatal immune priming (through the *TLR3* pathway) combined to peripubertal stress were shown to synergistically induce behavioural changes, unbalanced neurotransmitter levels, enhanced expression of markers of inflammation and microglia activation in stress-sensitive brain areas of mice (Giovannoli et al. 2013). We may thus hypothesize that aberrant encounters viz infectious insults and/or psychosocial stress early in life may affect neurodevelopmental processes in genetically vulnerable individuals through a common mechanism involving inherited defective innate immune responses (Dickerson et al. 2014; Foldager et al. 2014).

In our study, it must be noted that the *TLR2* *rs3804099*/*Toxoplasma gondii* interaction term in the regression analysis was not statistically significant after correction for multiple comparisons. However, the trend found for the *Toxoplasma gondii* \times *TLR2* interaction and the observation that the *TLR2* *rs3804099* demonstrated an OR of 0.894 in the seropositive group and of 2.289 in the seronegative one emphasizes the pertinence of considering environmental risk factors when evaluating the genetic risk of BD and warrant replication using a much larger cohort. Another limitation of the present study is the absence of information regarding the ‘time window’ of exposure to *Toxoplasma gondii* as we only have data on IgG antibodies.

Conclusions

We extend previously published data confirming the association between *Toxoplasma gondii* and BD on a much larger sample size and suggest that history of *Toxoplasma* exposure may modulate the influence of *TLR2* polymorphism on BD. A much larger sample size and better characterization of environmental risk exposure containing information on type, intensity and period of pathogen exposure are needed in future studies. If infections were ever to play a significant role in BD pathogenesis in interaction with host genetic liability, one would expect that appropriate and timely interventions on the environmental insults must be able to prevent or reduce the pathogenic load of BD highlighting the importance of gene-environment studies.

Authors' contributions

JO, RK (Rajagopal Krishnamoorthy), ML and RT coordinated the study and wrote the manuscript. RK (Rémi Kazma), ELF and JFD did the statistical analyses. NH and FB contributed to the patients' inclusion. RY did the analysis of infectious stigma. All authors read and approved the final manuscript.

Author details

¹ INSERM, U1160, Hôpital Saint Louis, Paris, France. ² Fondation FondaMental, Créteil, France. ³ Centre National de Génotypage, CEA, Evry, France. ⁴ Faculté de Médecine, Université Paris-Est, Créteil, France. ⁵ AP-HP, DHU PePSY, Pôle de Psychiatrie, Hôpitaux Universitaires Henri Mondor, Créteil, France. ⁶ INSERM, U955, Psychiatrie Translationnelle, Créteil, France. ⁷ Laboratoire

Jean Dausset and LabEx Transplantex, Hôpital Saint Louis, Paris, France. ⁸ Sorbonne Paris-Cité, Université Paris Diderot, Paris, France. ⁹ INSERM UMR-S1144-VariaPsy, Hôpital Fernand Widal, Paris, France. ¹⁰ Stanley Laboratory of Developmental Neurovirology, Johns Hopkins University Medical Center, Baltimore, USA. ¹¹ Stanley Research Program, Sheppard Pratt, Baltimore, MD, USA.

Acknowledgements

We thank patients with bipolar disorders and controls who agreed to participate in this study. We thank the Cochin Hospital cell repository, the Clinical Centre of Investigations, the Biological Resources Centre of Mondor Hospital, and the blood bank Centre of EFS Créteil (for technical assistance). We thank the FondaMental Foundation.

We thank Agence Nationale de la Recherche (ANR) (Samenta Project V.I.P. ANR-08-MNPS-041), INSERM and AP-HP (DHU PePsy).

J. Oliveira acknowledges the financial support of the Foundation for Science and Technology (Portugal) doctoral degree Grant (SFRH/BD/76170/2011).

Competing interests

The authors declare that they have no competing interests.

Funding

This project was funded the Foundation FondaMental (www-fondation-fondamental.org), *Institut National de la Santé et de la Recherche Médicale* (INSERM), AP-HP (Assistance Publique des Hôpitaux de Paris), and by the *Investissements d'Avenir* program managed by the ANR under reference ANR-11-IDEX-0004-02 and ANR-10-COHO-10-01.

Received: 20 January 2016 Accepted: 5 May 2016

Published online: 20 May 2016

References

- Abramson JH. WINPEPI updated: computer programs for epidemiologists, and their teaching potential. *Epidemiol Perspect Innov*. 2011;8:1.
- Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell*. 2006;124(4):783–801.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Paris: Masson; 1994.
- Aravalli RN, Hu S, Rowen TN, Palmquist JM, Lokensgard JR. Cutting edge: TLR2-mediated proinflammatory cytokine and chemokine production by microglial cells in response to herpes simplex virus. *J Immunol*. 2005;175(7):4189–93.
- Berrebi D, Maudinas R, Hugot JP, Chamaillard M, Chareyre F, De Lagaussie P, et al. Card15 gene overexpression in mononuclear and epithelial cells of the inflamed Crohn's disease colon. *Gut*. 2003;52(6):840–6.
- Børglum AD, Demontis D, Grove J, Pallesen J, Hollegaard MV, Pedersen CB, et al. Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci. *Mol Psychiatry*. 2014;19(3):325–33.
- Canetta SE, Bao Y, Co MD, Ennis FA, Cruz J, Terajima M, et al. Serological documentation of maternal influenza exposure and bipolar disorder in adult offspring. *Am J Psychiatry*. 2014;171(5):557–63.
- Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, et al. Grand challenges in global mental health. *Nature*. 2011;475(7354):27–30.
- Demontis D, Nyegaard M, Buttenschøn HN, Hedemand A, Pedersen CB, Grove J, et al. Association of GRIN1 and GRIN2A-D with schizophrenia and genetic interaction with maternal herpes simplex virus-2 infection affecting disease risk. *Am J Med Genet B Neuropsychiatr Genet*. 2011;156B(8):913–22.
- Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Cole S, Krivogorsky B, et al. Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder. *Biol Psychiatry*. 2004;55(6):588–93.
- Dickerson F, Stallings C, Origoni A, Katsafanas E, Schweinfurth LA, Savage CL, et al. Pentraxin 3 is reduced in bipolar disorder. *Bipolar Disord*. 2014;17(4):409–14.
- Foldager L, Köhler O, Steffensen R, Thiel S, Kristensen AS, Jensenius JC, et al. Bipolar and panic disorders may be associated with hereditary defects in the innate immune system. *J Affect Disord*. 2014;164:148–54.
- Giovanoli S, Engler H, Engler A, Richetto J, Voget M, Willi R, et al. Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. *Science*. 2013;339(6123):1095–9.
- Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. *Lancet*. 2011;377(9783):2093–102.
- Graham KL, Carson CM, Ezeoke A, Buckley PF, Miller BJ. Urinary tract infections in acute psychosis. *J Clin Psychiatry*. 2014;75(4):379–85.
- Hamdani N, Daban-Huard C, Lajnef M, Richard J-R, Delavest M, Godin O, et al. Relationship between *Toxoplasma gondii* infection and bipolar disorder in a French sample. *J Affect Disord*. 2013;148(2–3):444–8.
- Hanke ML, Kielian T. Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. *Clin Sci (Lond)*. 2011;121(9):367–87.
- Henn A, Kirner S, Leist M. TLR2 hypersensitivity of astrocytes as functional consequence of previous inflammatory episodes. *J Immunol*. 2011;186(5):3237–47.
- Hosang GM, Uher R, Keers R, Cohen-Woods S, Craig I, Korszun A, et al. Stressful life events and the brain-derived neurotrophic factor gene in bipolar disorder. *J Affect Disord*. 2010;125(1–3):345–9.
- Kang WS, Park JK, Lee SM, Kim SK, Park HJ, Kim JW. Association between genetic polymorphisms of Toll-like receptor 2 (TLR2) and schizophrenia in the Korean population. *Gene*. 2013;526(2):182–6.
- Kazma R, Babron M-C, Génin E. Genetic association and gene-environment interaction: a new method for overcoming the lack of exposure information in controls. *Am J Epidemiol*. 2011;173(2):225–35.
- Kerner B. Genetics of bipolar disorder. *Appl Clin Genet*. 2014;7:33–42.
- Kim C, Ho D-H, Suk J-E, You S, Michael S, Kang J, et al. Neuron-released oligomeric α -synuclein is an endogenous agonist of TLR2 for paracrine activation of microglia. *Nat Commun*. 2013;4:1562.
- Kotb M, Norrby-Teglund A, McGeer A, El-Sherbini H, Dorak MT, Khurshid A, et al. An immunogenetic and molecular basis for differences in outcomes of invasive group A streptococcal infections. *Nat Med*. 2002;8(12):1398–404.
- Lala S, Ogura Y, Osborne C, Hor SY, Bromfield A, Davies S, et al. Crohn's disease and the NOD2 gene: a role for paneth cells. *Gastroenterology*. 2003;125(1):47–57.
- Leboyer M, Kupfer DJ. Bipolar disorder: new perspectives in health care and prevention. *J Clin Psychiatry*. 2010;71(12):1689–95.
- Liu S, Liu Y, Hao W, Wolf L, Kiliaan AJ, Penke B, et al. TLR2 is a primary receptor for Alzheimer's amyloid β peptide to trigger neuroinflammatory activation. *J Immunol*. 2012;188(3):1098–107.
- Mazaheri-Tehrani E, Maghsoudi N, Shams J, Soori H, Atashi H, Motamedi F, et al. Borna disease virus (BDV) infection in psychiatric patients and healthy controls in Iran. *Viral J*. 2014;1:161.
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–9.
- Mun HS, Aosal F, Norose K, Chen M, Piao LX, Takeuchi O, et al. TLR2 as an essential molecule for protective immunity against *Toxoplasma gondii* infection. *Int Immunol*. 2003;15(9):1081–7.
- Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry*. 1994;51(11):849–59 (**discussion 863–864**).
- Oliveira J, Busson M, Etain B, Jamain S, Hamdani N, Boukouaci W, et al. Polymorphism of Toll-like receptor 4 gene in bipolar disorder. *J Affect Disord*. 2014a;152–154:395–402.
- Oliveira J, Etain B, Lajnef M, Hamdani N, Bennabi M, Bengoufa D, et al. Combined effect of TLR2 Gene polymorphism and early life stress on the age at onset of bipolar disorders. *PLoS One*. 2015;10(3):e0119702.
- Oliveira J, Hamdani N, Busson M, Etain B, Bennabi M, Amokrane K, et al. Association between toll-like receptor 2 gene diversity and early-onset bipolar disorder. *J Affect Disord*. 2014b;165:135–41.
- Oliveira J, Hamdani N, Etain B, Bennabi M, Boukouaci W, Amokrane K, et al. Genetic association between a "standing" variant of NOD2 and bipolar disorder. *Immunobiology*. 2014c;219(10):766–71.

- Olson JK, Miller SD. Microglia initiate central nervous system innate and adaptive immune responses through multiple TLRs. *J Immunol*. 2004;173(6):3916–24.
- Pandey S, Kawai T, Akira S. Microbial sensing by Toll-like receptors and intracellular nucleic acid sensors. *Cold Spring Harb Perspect Biol*. 2014;7(1):a016246.
- Parboosing R, Bao Y, Shen L, Schaefer CA, Brown AS. Gestational influenza and bipolar disorder in adult offspring. *JAMA Psychiatry*. 2013;70(7):677–85.
- Rivest S. Regulation of innate immune responses in the brain. *Nat Rev Immunol*. 2009;9(6):429–39.
- Schröder NW, Schumann RR. Single nucleotide polymorphisms of Toll-like receptors and susceptibility to infectious disease. *Lancet Infect Dis*. 2005;5(3):156–64.
- Sklar P, Ripke S, Scott LJ, Andreassen OA, Cichon S, Craddock N, et al. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet*. 2011;43(10):977–83.
- Sterka D Jr, Marriott I. Characterization of nucleotide-binding oligomerization domain (NOD) protein expression in primary murine microglia. *J Neuroimmunol*. 2006;179(1–2):65–75.
- Tekin D, Dalgic N, Kayaalti Z, Soylemezoglu T, Diler B, Kutlubay BI. Importance of NOD2/CARD15 gene variants for susceptibility to and outcome of sepsis in Turkish children. *Pediatr Crit Care Med*. 2012;13(2):e73–7.
- Uher R. Gene-environment interactions in severe mental illness. *Front Psychiatry*. 2014;5:48.
- Van Well GTJ, Sanders MS, Ouburg S, Kumar V, van Furth AM, Morré SA. Single nucleotide polymorphisms in pathogen recognition receptor genes are associated with susceptibility to meningococcal meningitis in a pediatric cohort. *PLoS One*. 2013;8(5):e64252.
- Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. *Lancet*. 2013;382(9904):1575–86.
- Yolken RH, Bachmann S, Ruslanova I, Lillehoj E, Ford G, Torrey EF, et al. Antibodies to *Toxoplasma gondii* in individuals with first-episode schizophrenia. *Clin Infect Dis*. 2001;32(5):842–4.
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429–35.
- Yu JT, Mou SM, Wang LZ, Mao CX, Tan L. Toll-like receptor 2–196 to –174 del polymorphism influences the susceptibility of Han Chinese people to Alzheimer's disease. *J Neuroinflammation*. 2011;8:136.

Submit your manuscript to a SpringerOpen[®] journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Immediate publication on acceptance
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► springeropen.com
