Association between 5q23.2-located polymorphism of \textit{CTXN3} gene (Cortexin 3) and schizophrenia in European-Caucasian males; implications for the aetiology of schizophrenia

Omar Šerý$^{1,2,*}$, Jan Lochman$^1$, Jana Povová$^3$, Vladimír Janout$^3$, Jiří Plesník$^1$ and Vladimir J Balcar$^4$

Abstract

Background: The objective of the study was to examine several polymorphisms in \textit{DISC1} and \textit{CTNX3} genes as possible risk factors in schizophrenia. \textit{DISC1} (disrupted-in-schizophrenia 1) has been studied extensively in relation to mental disease while \textit{CTXN3}, has only recently emerged as a potential "candidate" gene in schizophrenia. \textit{CTXN3} resides in a genomic region (5q21-34) known to be associated with schizophrenia and encodes a protein cortexin 3 which is highly enriched in brain.

Methods: We used ethnically homogeneous samples of 175 male patients and 184 male control subjects. All patients were interviewed by two similarly qualified psychiatrists. Controls were interviewed by one of the authors (O.S.). Genotyping was performed, following amplification by polymerase chain reaction (PCR), using fragment analysis in a standard commercial setting (Applied Biosystems, USA).

Results: We have found a statistically significant association between rs6595788 polymorphism of \textit{CTXN3} gene and the risk of schizophrenia; the presence of AG genotype increased the risk 1.5-fold. Polymorphisms in \textit{DISC1} gene showed only marginally statistically significant association with schizophrenia (rs17817356) or no association whatsoever (rs821597 and rs980989) while two polymorphisms (rs9661837 and rs3737597) were found to be only slightly polymorphic in the samples.

Conclusion: Evidence available in the literature suggests that altered expression of cortexin 3, either alone, or in parallel with changes in \textit{DISC1}, could subtly perturb GABAergic neurotransmission and/or metabolism of amyloid precursor protein (APP) in developing brain, thus potentially exposing the affected individual to an increased risk of schizophrenia later in life.

Keywords: \textit{DISC1}, SLC12A2, NKCC1, GABAergic neurotransmission, Amyloid precursor protein (APP), Alzheimer’s disease

Background

There are numerous reports in the literature, including those on genome-wide association studies (GWAS), proposing putative links between particular genes and mental diseases such as schizophrenia. \textit{DISC1} (Disrupted-in-Schizophrenia 1) is one such "candidate" gene (reviews: [1,2]) and this is so despite extensive investigations having produced, to date, little evidence for a direct association between any structural changes in \textit{DISC1} and a specific disease (review: [3]). However, the protein which \textit{DISC1} encodes (DISC1) is known to be involved in the development of the central nervous system; neural proliferation and migration as well as neurite outgrowth are among the most often cited targets of \textit{DISC1} [2,4].

In contrast to \textit{DISC1}, \textit{CTXN3}, a three-exon (exons 1a, 1b, 2 and 3) gene spread over a 9.6-kb region of human chromosome 5q23.2, has been known and studied for only a few years [5-8]. In humans, \textit{CTXN3} translates into a protein (cortexin 3 also known as KABE: “Kidney And Brain Expressed” protein) which is present mainly in kidney and brain, including foetal brain tissue [5].
Recently, Panichareon et al. [6] described an association between two \textit{CTXN3} polymorphisms and schizophrenia in a sample of Thai Asian population. This finding is intriguing for a variety of reasons. Panichareon et al. [6] noted a linkage disequilibrium (albeit a moderate one) between SNP's in \textit{CTXN3} and \textit{SLC12A2}; both these genes are within the 5q23 region that has been identified as a “locus of vulnerability” or a “candidate region” with respect to genetic risk of schizophrenia [9-11]. Furthermore, genetic studies have associated a gene-interplay between \textit{SLC12A2} and \textit{DISCI} with an altered risk of schizophrenia [12]. In fact, \textit{SLC12A2} has been linked to \textit{DISCI}, also as a result of \textit{in vitro} experiments [12] and following \textit{in vivo} measurements of hippocampal activity in humans [13]. By analogy with the putative role of \textit{DISCI}, the above observations can be taken as implying that altered genetics of \textit{CTXN3}, either individually or in conjunction with changes in \textit{DISCI}, might represent a significant risk factor in schizophrenia. This conjecture forms the basis for our current hypothesis.

As we have previously carried out several successful case-control association studies between schizophrenia and SNP's in \textit{OPRM1}, \textit{DRD3}, \textit{SNAP-25}, \textit{MTHFR} and \textit{ADRA2A} genes in samples of typical European population [14-16] we decided to use a similar approach to test the present hypothesis and include both \textit{CTXN3} and \textit{DISCI} gene polymorphisms in our investigation. We now report on the rs6595788 polymorphism of \textit{CTXN3} gene and the rs17817356, rs821597, rs9661837, rs980989 and rs3737597 polymorphisms of \textit{DISCI} gene and discuss them as possible risk factors for pathophysiology of schizophrenia in a group of male patients and controls. All these polymorphisms have been studied by other authors in associations studies related to psychiatric diseases [17-21].

\section*{Methods}

\subsection*{Subjects}

In order to eliminate from our data possible confounding influence of sex-differences in the aetiology of schizophrenia [22], we used all-male samples of both patients and controls. The total of 359 males of Czech nationality (Caucasians) entered the study. The group of patients with schizophrenia included 175 males (mean age 35.5 ± 10.9) hospitalized at the Department of Psychiatry, Faculty Hospital, Brno and the Psychiatric Hospital, Jihlava. The patients were diagnosed according to ICD-10 criteria (International Classification of Diseases, 10th Edition) and according to DSM-IV criteria (APA, 1994). All patients underwent structured interviews with qualified psychiatrists (cf. Acknowledgments). Patients with psychiatric comorbidities were excluded from the study.

The control group included 184 males (mean age 48.2 ± 13.8). They were volunteers recruited from blood donors at Blood Bank Brno, patients treated for erectile dysfunction at Trauma Hospital Brno, among employees of private companies in Brno, agriculture farms in the area around Brno, university academics and employees of National Theatre in Brno. The Mini-International Neuropsychiatric Interview (M.I.N.I.) was performed with each member of the control group [23]. Any individuals suspected of not being fully mentally healthy were excluded from the group. In order to minimize personal bias, all screening and interviewing was done by only two psychiatrists with similar backgrounds who closely communicated with each other, or, in the case of control subject, by one of the authors (O.S.) assisted by a qualified psychologist.

All participants, whether they entered as patients or controls, signed an informed consent to participate in the study. Genotypes of the participants were analysed only after the interviews with psychiatrists had been completed. The project was approved by the Ethical Committee of the Faculty Hospital, Brno.

\section*{Genotyping}

DNA was extracted from 200 mL of EDTA-anticoagulated whole blood using an UltraClean Blood DNA Isolation Kit (Mobio, USA). Six SNPs (rs6595788, rs17817356, rs821597, rs9661837, rs980989 and rs3737597) were assayed using multiplexed polymerase chain reaction (PCR) amplification, followed by single base extension (SNaPshot, Applied Biosystems, USA). The primers used for multiplexed PCR and the SNaPshot method are listed in Table 1. Each multiplex polymerase chain reaction was done in a final volume of 20 mL. The reaction mixture consisted of 2 mL of DNA template (50 ng/mL), 0.2 mM primers (Table 1) and 2 x Kappa 2G FAST Ready Mix (Kappa Biosystems). After initial denaturation at 95°C for 3 min, samples were amplified through 40 cycles (95°C for 10 sec, 60°C for 20 sec with 50% ramp, 72°C for 50 sec), followed by holding at 72°C for 10 min in a Veriti thermal cycler (Applied Biosystems, USA). After purification with PCR ExoSAP (Fermentas, Lithuania), PCR products were mixed and 1 mL of mixture was added to SNaPshot reaction mix (Applied Biosystems, USA) in a total volume of 10 mL. Cycling conditions were set up according to the manufacturer's instruction manual. After the SNaPshot reaction, SAP (Fermentas, Lithuania) treatment was carried out for 30 min at 37°C. One microliter of each sample was then added to 9 mL of deionized formamide and 0.4 mL of standard size LIZ 120 (Applied Biosystems, USA) before analysis on a 3100 DNA Fragment Analysis System (Applied Biosystems, USA) in a 36 cm capillary array using the POP-7 polymer.
Statistical analysis
The CSS Statistica software (StatSoft, USA) was used for statistical evaluation of the results. The chi-square test was used for the comparison of genotype frequencies in the studied groups. Odds ratios (OR's) and 95% confidence intervals (95% CI) as estimates of relative risk for the schizophrenia associated with the genotypes were calculated using logistic regression. To minimize false-positive results potentially caused by multiple testing, we applied the Bonferroni correction for three independent loci genotyped. The level of statistical significance was adjusted to \( P = 0.008 \). Hardy-Weinberg equilibrium was tested by chi\(^2\) test.

Results
Allele and genotype frequencies of all analysed polymorphisms are displayed in Table 2. Preliminary statistical evaluation indicated no genetic linkages among the studied DISC1 gene polymorphisms (data not shown). We found a statistically significant association between schizophrenia and rs6595788 polymorphism of CTXN3 gene. The frequency of G allele is significantly higher in schizophrenic patients in comparison with control subjects (\( p = 0.0018 \)). Genotype frequencies are significantly different between patients and controls (\( p = 0.004 \)). The presence of G allele in the genotype increased the risk of schizophrenia (Odds Ratio = 1.6923; 95% CI of OR = 1.2231 - 2.3414, Risk Ratio = 1.1674; 95 % CI of OR = 1.0602 - 1.2855).

Only a marginal statistically significant difference between patients and controls was noted in rs17817356 polymorphism of DISC1 gene, with AG genotype apparently more frequent in patients (\( p = 0.01 \)). When analysing rs9661837 polymorphism, we found no GG genotype in either schizophrenics or controls. AG genotype was present in 6 schizophrenic patients and in only one control subject and the statistical significance of difference in allele frequencies (\( p = 0.06 \)) and in genotype frequencies (\( p = 0.048 \)) could be considered as marginal at best. For rs9661837 and rs3737597 polymorphisms we did not perform OR and RR analyses because of too low minor allele frequencies. We detected no relationship between schizophrenia and rs821597, rs980989 and rs3737597 polymorphisms of the DISC1 gene.

Genotypic frequency of rs17817356 polymorphism (DISC1) in schizophrenic patients but not in the controls deviated from Hardy-Weinberg equilibrium (\( p < 0.03 \)). The interaction between rs6595788 and rs17817356 polymorphisms appeared significant, too (\( p < 0.002 \)); the genotype AGAG having been found to be about 2x more frequent in schizophrenic patients than in control subjects (Table 3). This genotype alone could, therefore, contribute to a higher risk of schizophrenia.

Discussion
There have been two previous attempts to establish an association between polymorphisms of CTXN3 gene and schizophrenia. One was performed in the United States using brain in vivo imaging as a quantitative trait (QT) enhancement of statistical power in a genome-wide association study (QT-GWAS; [7]), the other one was a case-control association analysis of a group of Thai Asians [6]. The present study is, therefore, the first one of its kind carried out entirely within Europe on a sample of typical European-Caucasian population [24]. It is also, to date, the largest case-control study, in terms of the number of subjects surveyed, of association between a CTXN3 polymorphism and any mental disease.

Cortxin 3 belongs to “cortxin family” that includes three proteins: cortxin 1, cortxin 2 and cortxin 3. Cortxin 3 displays amino acid sequences very similar (about 43% homology in humans) to those found in a protein cortxin 1 (encoded by CTXNI gene), previously identified in the cerebral cortex [25]. Human CTXNI
gene is located on the chromosome 19p13.2 and it has 2 exons, CTXN2 with 5 exons is located in 15q21.1 chromosome region (according to recent information from GenBank). Two alternative variants of CTXN3 cDNA sequences differ in the 5’ untranslated region implying a possibility of alternative splicing regulating tissue-specific expression of the gene. Indeed, in silico cloning has indicated that brain and kidney each express own forms of cortexin 3 which differ from one another, particularly in the region encoded by exon 1 [5]. Additional theoretical considerations [5] indicated that cortexin 3 could be an integral membrane protein involved in extracellular or intracellular signalling.

Using expressed sequence tag (EST) analyses of cDNA libraries, orthologs of cortexin 3 with highly conserved sequences have been identified in mouse, rat, cow, dog, zebrafish, chicken, chimpanzee, Rhesus monkey and frog ([5]; cf. GenBank). Non-human forms of cortexin 3 have species-characteristic tissue distributions but seem to be always enriched in brain. Cortexins 1-3 should not be confused with another "cortexin" ("(r)-cortexin"), a 43 kDa nitric oxide synthase activating protein from kidney, studied mostly in the context of blood pressure regulation and related disorders [26,27]. "Cortexin" may promote growth of neurites [28] and it has been claimed that it can restore cognition after ischemic stroke [29].

While we found little or no association between the status of the subjects and polymorphisms in DISC1, in the case of CTXN3, there was a clear, statistically significant, albeit quantitatively modest, link between rs6595788 and schizophrenia. This observation could have implications for the aetiology of schizophrenia, at least for the male form(s) of the disease. What would be the most likely responsible mechanism(s)?

**Table 2 Genotype frequencies of CTXN3 and DISC1 gene polymorphisms among cases and controls**

| Genes | SNP | Genotype | Controls (N = 184) | Patients (N = 175) | OR (95% CI) | P value |
|-------|-----|----------|-------------------|-------------------|------------|---------|
|       |     | Number   | (%)              | Number            | (%)        |         |
| CTXN3 | rs6595788 | AA       | 106 (57.6)       | 70 (40.2)         | 1.00 (-)   | - (-)   |
|       |     | AG       | 67 (36.4)        | 86 (49.4)         | 1.94 (1.52-3.02) | 0.003 |
|       |     | GG       | 11 (6.0)         | 18 (10.4)         | 2.48 (1.10-5.65) | 0.025 |
|       |     | AG+GG    | 78 (42.4)        | 104 (59.8)        | 2.02 (1.33-3.08) | 0.001 |
| DISC1 | rs17817356 | GG       | 74 (40.2)        | 50 (28.9)         | 1.00 (-)   | - (-)   |
|       |     | AG       | 80 (43.5)        | 99 (57.2)         | 1.83 (1.15-2.91) | 0.010 |
|       |     | AA       | 30 (16.3)        | 24 (13.9)         | 1.18 (0.62-2.26) | 0.609 |
|       |     | AG+AA    | 110 (59.8)       | 123 (71.1)        | 1.65 (1.06-2.57) | 0.025 |
| DISC1 | rs821597 | GG       | 74 (40.2)        | 70 (40.2)         | 1.00 (-)   | - (-)   |
|       |     | AG       | 89 (48.4)        | 78 (44.8)         | 0.93 (0.59-1.45) | 0.737 |
|       |     | AA       | 21 (11.4)        | 26 (15.0)         | 1.31 (0.68-2.54) | 0.424 |
|       |     | AG+AA    | 110 (59.8)       | 104 (59.8)        | 1.00 (0.66-1.53) | 0.998 |
| DISC1 | rs980989 | CC       | 123 (66.9)       | 108 (62.1)        | 1.00 (-)   | - (-)   |
|       |     | AC       | 53 (28.8)        | 59 (33.9)         | 1.27 (0.81-1.99) | 0.303 |
|       |     | AA       | 8 (4.3)          | 7 (4.0)           | 1.00 (0.35-2.84) | 0.995 |
|       |     | AC+AA    | 61 (33.1)        | 66 (37.9)         | 1.23 (1.80-1.90) | 0.345 |
| DISC1 | rs9661837 | AA       | 183 (99.5)       | 169 (96.6)        | NC*        |         |
|       |     | AG       | 1 (0.5)          | 6 (3.4)           | - (-)      |         |
|       |     | GG       | 0 (0.0)          | 0 (0.0)           | - (-)      |         |
|       |     | AG+GG    | 1 (0.5)          | 6 (3.4)           | - (-)      |         |
| DISC1 | rs3737597 | CC       | 171 (92.9)       | 166 (95.4)        | NC**       |         |
|       |     | CT       | 13 (7.1)         | 7 (4.0)           | - (-)      |         |
|       |     | TT       | 0 (0.0)          | 1 (0.6)           | - (-)      |         |
|       |     | CT+TT    | 13 (7.1)         | 8 (4.6)           | - (-)      |         |

All chi-squared tests are two-tailed. Alpha value is adjusted by Bonferroni correction and statistically significant results (P<0.008) are marked bold.
NC – minor allele frequency too low to calculate precise OR and P values.
*the statistical significance of difference in allele frequencies by Fisher's exact test is p = 0.06.
**the statistical significance of difference in allele frequencies by Fisher's exact test is p = 0.4.
region linked to the schizophrenia in a meta-analytical study by Lewis et al. [10]. It is also within the region linked to neurocognitive traits associated with higher risk of schizophrenia as reported by Almasy et al. [30]. According to our in silico analysis, both polymorphism described by Panichareon [6] as associated with the schizophrenia (rs 698172 and rs245178) are located in an intergenic region adjacent to CTXN3 gene that has recently been shown to contain a sequence corresponding to a non-coding RNA of unknown function. The rs6595788 polymorphism, which is a subject of our study, is located directly at 5’-end of CTXN3 gene, its precise locus being at a distance of 16787 bp from the proximate polymorphism studied by Panichareon [6] (rs698172) found in the intergenic region at the opposite side of the CTXN3 sequence i.e. downstream of 3’-end of the gene.

SLC12A2 encodes a transporter which co-transport sodium, chloride, and potassium (Na+, Cl−, and K+). NKCC1 and KCC2 (SLC12A5) are involved in the regulation of neuronal network development [32]. Tran-

Table 3 Frequencies of the most important haplotypes in patients with Schizophrenia versus Control Subjects

| Genes     | SNPs                  | p-value (chi-squared test) | SNPs alleles | Estimated frequencies |
|-----------|-----------------------|----------------------------|--------------|-----------------------|
| CTXN3*DISC1 | rs6595788 * rs17817356 | 0.002                      | AG*AG        | 0.283                 | 0.125                |
|           |                       |                            | AA*GG        | 0.116                 | 0.201                |
|           |                       |                            | GG*AG        | 0.075                 | 0.022                |

difference in the developmental timing of the depolarization/hyperpolarization switch [35]. If this difference translates into sex-specific effects on the brain development (and a sex-specific effect on the risk of schizophrenia), our choice of all male population increased homogeneity of the sample and could have significantly improved the statistical power of the present study.

Presence of another potentially relevant mechanism involving cortexin 3 has been indicated by a recent report by Chouraki et al. [36]. They performed a genome-wide association meta-analysis on more than three thousand healthy subjects studying plasma levels of amyloid beta (Aβ) peptides. They established that the plasma levels of Aβ 1-42 were most closely associated with the rs11241936 polymorphism of CTXN3 gene. Subsequent in vitro studies showed that cortexin 3 interfered with amyloid precursor protein (APP) metabolism and decreased the secretion of Aβ-fragments. Involvement of APP and Aβ fragments in Alzheimer’s disease is well known (reviews: [37-39]) but their role in the normal brain, particularly during the development, has been given less attention [40]. In fact, APP is present in growth cones and it has a role in the formation of neurites and synaptogenesis [41]. Mice lacking APP displayed dramatically altered brain morphology [42] possibly as a result of disrupted migration of neural precursor cells in the developing cortex [43]. DISC1 has also been studied in the context of neuronal development and migration and shown to interact with APP [4] thus providing another biochemical locus where cortexin 3 and DISC1 could act together.

APP has also been shown to influence the expression of NR1, a protein subunit of critical importance in the formation of functional NMDA receptors [44]. Changes in cortexin 3/DISC1/APP interactions could, therefore, result in altered expression and distribution of NMDA receptors as has been observed in schizophrenia [45] (review: [46]). Any such relationships are, however, likely to be extremely complex and involve additional genetic (or epigenetic) mechanisms [45]; their detection may depend on the development and application of new analytical technologies (review: [47]).

In conclusion, we report a strong association between schizophrenia and a single nucleotide polymorphism in
the CTXN3 gene (cortexin 3) in an ethnically homogenous group of male patients. In contrast, we found only weak or no associations between schizophrenia and several polymorphisms in DISC1 gene. Available evidence suggests that cortexin 3 is involved in brain ontogeny, particularly in the development of GABAergic neurotransmission and metabolism of APP which could, in turn, impact on neuronal maturation, migration and synaptogenesis. Taking into account the developmental hypothesis of schizophrenia, we conjecture that any genetic variations in the CTXN3 gene affecting expression and/or characterist of cortexin 3 protein would have a potential to contribute to the aetiology of complex mental diseases.

Competing interests
The authors declare that they have no competing interests with respect to the authorship and/or publication of this article.

Authors' contributions
OS designed the study, interviewed controls subjects, supervised the genotyping, performed statistical evaluation of the data and drafted the manuscript; JL and JPlenšek performed DNA isolation and analysis; JPovová and Vli initiated the study, helped with its design and supervised selection of participants; VlBi contributed to the interpretation of data in the context of developmental and synaptic neurochemistry and helped to prepare the final draft of the manuscript. All authors read and approved the final manuscript.

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Author details
1Laboratory of Neurobiology and Molecular Psychiatry, Laboratory of Molecular Physiology, Department of Biochemistry, Faculty of Science, Masaryk University, Kotlářská 2, 611 37, Brno, Czech Republic. 2Institute of Animal Physiology and Genetics, Academy of Sciences, Veveri 97, 602 00, Brno, Czech Republic. 3Department of Epidemiology and Public Health, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic. 4Laboratory of Neurochemistry, Bosch Institute and Discipline of Anatomy and Histology, School of Medical Sciences, Sydney Medical School, The University of Sydney, Sydney, 2006 Sydney, NSW, AUSTRALIA.

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