Connexin 50 gene on human chromosome 1q21 is associated with schizophrenia in matched case-control and family-based studies

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Background: The gap junction subunit connexin permits direct intercellular exchange of ions and molecules including glutamate, and plays an important role in the central nervous system. The connexin 40 (Cx40) and connexin 50 (Cx50) genes are located on chromosome 1q21.1, a region strongly linked with schizophrenia. These lines of evidence suggest that Cx40 and Cx50 may play a role in schizophrenia.

Methods: Using an allele-specific PCR assay, four polymorphisms each were genotyped for Cx40 and Cx50 in 190 Caucasian patients with schizophrenia and 190 controls matched for sex, age and ethnicity. Following up, Cx50 rs989192 and rs4950495 were investigated in 99 Canadian and 163 Portuguese trios and nuclear families with schizophrenia probands. Hardy–Weinberg equilibrium and linkage disequilibrium (LD) block identification was carried out with HaploView, and association analysis for alleles and haplotypes with a permutation test of 10 000 simulations was carried out using the UNPHASED software program.

Results: Distributions of genotype frequencies of all markers were in Hardy–Weinberg equilibrium in Caucasian patients, controls and families. One rs989192-rs4950495 LD block was found in patients but not in controls. We found a significant association between the Cx50 rs989192-rs4950495 haplotype and schizophrenia ($\chi^2=29.55$, $p<0.01$). The A-C haplotype had a higher frequency in patients ($\chi^2=7.153$, $p<0.01$). Family studies also showed that the A-C haplotype was transmitted more often to patients with schizophrenia ($\chi^2=8.43$, $p<0.01$). No association of Cx40 with schizophrenia was found for allele, genotype or haplotype analyses.

Conclusions: Our matched case-control and family study indicate that Cx50, but not Cx40, may play a role in the genetic susceptibility to schizophrenia.

Gap junctions (GJs) are channel-forming structures in contacting plasma membranes. Two hemichannels, each built of six connexin subunits, can dock to each other to form conduits between cells. GJs allow direct metabolic and electrical communication between almost all cell types in the mammalian brain.¹ These small molecules involve second messengers (inositol triphosphate (IP3), cyclic nucleotides and Ca²⁺), neurotransmitters (glutamate, adenosine triphosphate and nitric oxide) and metabolites.^{2,3} During development, there is extensive regulation of the spatial and temporal expression of connexins, this regulation being implicated in the control of differentiation and growth.⁴ Injection of antibodies to connexins into blastomeres of amphibian or rodent embryos, or transgenic mice with altered connexin expression results in severe developmental anomalies.⁵ Differentiation of neurons and astrocytes from embryonal carcinoma cells is accompanied

by decreased connexin 43 expression and loss of coupling.⁶ This differentiation is significantly attenuated if gap junction intercellular communication (GJIC) is blocked.⁷ Therefore, gap junctions play very important roles in mammalian neural development.^{1,8} Schizophrenia has generally been considered to be a neurodevelopmental disorder.⁹ Moreover, an increasing number of reports have demonstrated that gamma-aminobutyric acid (GABA)ergic interneurons themselves are interconnected through electrical synapses.² These interconnections, if impaired, may be involved in the aetiology of schizophrenia. Furthermore, changes in GJIC between neurons have been observed in vivo after applying treatment with antipsychotic drugs or withdrawal of amphetamine.^{2,10} Taking these data together, connexin genes can be considered as potential candidates in the development of schizophrenia. In fact, Cx36 was tested in a large catatonic schizophrenia pedigree, but no association was found.¹¹

A genome-wide scan for schizophrenia susceptibility loci provided considerable evidence of linkage to chromosome 1q21-q22.¹² The linkage of chromosome 1q with schizophrenia was replicated in several other reports.^{13–16} Two connexin genes, Cx50 (GJA8) and Cx40 (GJA5), are located at 1q21. To our knowledge, studies on the genetic association of Cx50 and Cx40 in schizophrenia are lacking. Therefore, we genotyped four polymorphisms for each of these two connexin genes in a matched case-control sample from Toronto, Canada, and found a significant association between the Cx50 rs989192-rs4950495 haplotypes and schizophrenia. This association was confirmed in an independent study of Portuguese families with probands with schizophrenia.

SUBJECTS AND METHODS

Subjects

Informed consent was obtained from each participant. For the case-control study, 190 Caucasian patients and 190 controls matched for age and sex (115 men, 75 women; mean (SD) age 43.5 (10.3) years) were analysed. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was administered by trained research assistants to each patient. The controls were screened for major psychiatric disorders or substance misuse, and excluded if either was detected, either current or in the past. We also investigated 99 Canadian Caucasian families from Toronto (40 triads and 59 diads) with probands diagnosed by the *Diagnostic and statistical manual of mental disorders*, 4th edition (DSM-IV) criteria (72 male and 27 female probands), among whom 33 patients overlapped with the case-control study. Another 163 Portuguese trios and nuclear families with probands with DSM-IV schizophrenia

Abbreviations: Cx40, connexin 40; Cx50, connexin 50; GABA, gamma-aminobutyric acid; GJ, gap junction; GJIC, inositol triphosphate; LD, linkage disequilibrium; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; SNP, single nucleotide polymorphism; T/U, transmitted/untransmitted ratio

Figure 1 Polymorphisms and linkage disequilibrium (LD) in Cx40 and Cx50. Only Caucasian patients with schizophrenia and their controls are shown in the LD diagram. The numbers in the squares are D' values ($\times 100$).

(105 male and 58 female probands, all Caucasians) from both mainland Portugal (Coimbra) and the Azores islands were investigated. The collection of patient samples from Portugal occurred within the framework of a NIMH-sponsored grant to four of the authors (CP, MP, JLK, MA). The diagnosis was confirmed using the Diagnostic Interview for Genetic Studies. In all samples from Canada and Portugal, a consensus-based best estimate procedure provided the final decision for the diagnostic classification of the patients. Schizoaffective disorder was included.

Genotyping

Genotypes for the single nucleotide polymorphisms (SNPs) rs989192, rs4950495, rs3766503 and rs1532399 in Cx50, and rs1043806, rs1692141, rs791277 and rs1495956 in Cx40 were assessed by the 5'-exonuclease activity (TaqMan) assay¹⁷ using an automated sequence detection system (ABI Prism 7000; Applied Biosystems, Foster City, California, USA). Figure 1 shows the locations of these polymorphisms.

Statistical analyses

Statistical power of the sample size was calculated using the program QUANTO 1.1 for matched case-control and family-based studies.¹⁸ The program HaploView V3.2 was used to test for concordance with Hardy-Weinberg equilibrium, calculate D' between SNP pairs, and identify linkage disequilibrium (LD) blocks, which were defined with confidence intervals.¹⁹ The program UNPHASED V3.0.6 was used for an association analysis for alleles and haplotypes, with the rare haplotype being set to 0.05.²⁰ The p values for each marker and haplotype were adjusted from permutation test with 10 000 simulations. Comparison of genotype frequencies between patients and controls was performed using the χ^2 test. Odds ratios (OR) with 95% CI were estimated for the effects of high-risk alleles.²¹

RESULTS

Matched case-control study

Our 190 patients and 190 matched controls had 80% power to detect a relative risk as low as 1.89 if the significance was set at 0.05. For Caucasian patients and controls, distributions of genotype frequencies of the eight polymorphisms in Cx40 and Cx50 were all in Hardy-Weinberg equilibrium ($p > 0.10$). The polymorphisms rs1043806 and rs1692141 in Cx40 were tightly

linked in one LD block in both patients and controls. However, rs989192 and rs4950495 in Cx50 formed another LD block only in patients with schizophrenia, but not in controls (fig 1).

We did not find any significant differences between patients with schizophrenia and controls ($p > 0.05$) for the allele and genotype frequencies for each individual marker in Cx40 and Cx50 (table 1). Performing haplotype analyses using two-marker pairs, we found that the rs989192-rs4950495 haplotypes were significantly associated with schizophrenia ($\chi^2 = 29.55$, $p = 0.001$; table 2). Compared with controls, patients had a higher frequency of an A-C haplotype ($\chi^2 = 7.153$, $p < 0.01$, OR = 1.91, 95% CI = 1.17 to 3.13) and low frequencies of a G-C haplotype ($\chi^2 = 33.44$, $p < 0.001$, OR = 5.51, 95% CI = 2.54 to 11.96). Cx50 haplotypes from all four markers showed a significant association with schizophrenia ($\chi^2 = 28.02$, $p < 0.01$), but Cx40 did not ($\chi^2 = 0.87$, $p > 0.58$).

Family study

The sample size for the family study had 80% power to detect a relative risk as low as 1.67 if significance was set at 0.05. We selected two polymorphisms in Cx50, rs989192 and rs4950495, based on the significant results from our matched case-control study. The distributions of genotype frequencies of these two polymorphisms in both the Canadian and Portuguese families were in Hardy-Weinberg equilibrium ($p > 0.05$). These two markers also formed one LD block in the families. In the Portuguese families, the rs989192A allele was transmitted more often to patients with schizophrenia (transmitted:untransmitted (T:U) = 62:36.54, $\chi^2 = 5.248$, $p = 0.022$, OR = 1.79, 95% CI = 1.17 to 2.75). There was also a difference between the transmitted and untransmitted ratio of the rs4950495C allele (T:U = 76:40.39, $\chi^2 = 8.823$, $p = 0.003$, OR = 2.03, 95% CI = 1.36 to 3.04) (fig 2). Haplotype analysis for these two markers showed a significant association between Cx50 and schizophrenia ($\chi^2 = 8.707$, $p = 0.037$). The A-C haplotype was transmitted more often ($\chi^2 = 6.096$, $p = 0.014$, OR = 1.9, 95% CI = 1.23 to 2.95) and the G-T haplotype less often ($\chi^2 = 6.218$, $p = 0.013$, OR = 1.77, 95% CI = 1.2 to 2.6) to patients with schizophrenia (table 3). In the Canadian families, we found a trend towards significance for rs989192 (A allele T:U = 30:16.92, $\chi^2 = 3.236$, $p = 0.072$) (fig 2), but no association

Table 1 Comparison of allele and genotype frequencies of eight markers in Cx40 and Cx50 in 190 Canadian Caucasian patients with schizophrenia and age and sex matched healthy controls

Markers	Allele or genotype	Patients	Controls	LRS	p Value*
rs1043806	C	301 (0.79)	305 (0.80)	0.130	0.74
	T	79 (0.21)	75 (0.20)		
	C/C	121 (0.64)	124 (0.65)	0.124	0.94
	C/T	59 (0.31)	57 (0.30)		
	T/T	10 (0.05)	9 (0.05)		
rs1692141	A	299 (0.79)	303 (0.80)	0.128	0.73
	G	81 (0.21)	77 (0.20)		
	A/A	119 (0.63)	122 (0.64)	0.123	0.94
	A/G	61 (0.32)	59 (0.31)		
	G/G	10 (0.05)	9 (0.05)		
rs791277	C	4 (0.01)	10 (0.03)	0	1
	G	376 (0.99)	370 (0.97)		
	C/G	4 (0.02)	10 (0.05)	2.670	0.10
	G/G	186 (0.98)	180 (0.95)		
rs1495956	C	96 (0.25)	95 (0.25)	0.007	0.95
	T	284 (0.75)	285 (0.75)		
	C/C	12 (0.06)	13 (0.07)	0.123	0.94
	C/T	72 (0.38)	69 (0.36)		
rs989192	T/T	106 (0.56)	108 (0.57)		
	A	50 (0.13)	39 (0.10)	1.543	0.19
	G	330 (0.87)	341 (0.90)		
	A/A	3 (0.02)	1 (0.01)	1.880	0.39
	A/G	44 (0.23)	37 (0.20)		
rs4950495	G/G	143 (0.75)	152 (0.80)		
	C	58 (0.15)	66 (0.17)	0.617	0.41
	T	322 (0.85)	314 (0.83)		
	C/C	3 (0.02)	7 (0.04)	1.660	0.44
	C/T	52 (0.27)	52 (0.27)		
rs3766503	T/T	135 (0.71)	131 (0.69)		
	A	364 (0.96)	355 (0.93)	2.104	0.09
	G	16 (0.04)	25 (0.07)		
	A/A	174 (0.92)	166 (0.87)	1.788	0.18
	A/G	16 (0.08)	23 (0.12)		
rs1532399	G/G	0 (0)	1 (0.01)		
	G	83 (0.22)	97 (0.26)	1.428	0.20
	T	297 (0.78)	283 (0.74)		
	G/G	7 (0.04)	9 (0.05)	1.592	0.45
	G/T	69 (0.36)	79 (0.42)		
	T/T	114 (0.60)	102 (0.54)		

*The p value for allele analysis has been adjusted from permutation test (10 000 simulations).
LRS, likelihood ratio statistic.

between the Cx50 haplotype and schizophrenia ($\chi^2 = 2.671$, $p = 0.263$) (table 3). Combining the data from the Canadian and Portuguese families together, we found that the rs989192A

and rs4950495C alleles were transmitted significantly more often to patients with schizophrenia (T:U = 92:53.73, $\chi^2 = 8.271$, $p = 0.004$, OR = 1.82, 95% CI = 1.28 to 2.59 and T:U = 114:69.1,

Table 2 Analysis of Cx40 and Cx50 haplotypes in 190 Caucasian patients with schizophrenia and 190 matched healthy controls

Haplotype	Haplotype	Patients	Controls	χ^2	p Value	LRS	p Value*
rs1043806-rs1692141	C-A	299 (0.79)	303 (0.80)	0.123	0.726	0.131	0.74
	T-G	79 (0.21)	75 (0.20)	0.124	0.725		
rs1692141-rs791277	A-G	295 (0.78)	294 (0.77)	0.054	0.816	0.134	0.90
	G-G	81 (0.21)	76 (0.20)	0.057	0.811		
rs791277-rs1495956	G-C	96 (0.25)	95 (0.25)	0.002	0.964	0.002	0.98
	G-T	280 (0.74)	275 (0.74)	0.002	0.966		
rs1495956-rs989192	C-G	88 (0.23)	92 (0.24)	0.077	0.781	0.570	0.70
	T-A	42 (0.11)	36 (0.11)	0.595	0.441		
rs989192-rs4950495	T-G	242 (0.64)	249 (0.65)	0.047	0.828		
	A-C	50 (0.13)	27 (0.07)	7.153	0.007	29.55	0.001
rs4950495-rs3766503	G-C	8 (0.02)	39 (0.10)	33.44	7.34e-9		
	G-T	322 (0.85)	302 (0.79)	1.211	0.271		
rs3766503-rs1532399	C-A	55 (0.15)	56 (0.15)	0.059	0.808	1.511	0.81
	T-A	309 (0.81)	299 (0.79)	0.047	0.828		
	A-G	76 (0.20)	77 (0.20)	0.055	0.815	5.648	0.05
	A-T	288 (0.76)	278 (0.73)	1.418	0.234		
	G-G	7 (0.02)	20 (0.05)	6.233	0.013		

Bold signifies $p < 0.05$.

*The p value has been adjusted from permutation test (10 000 simulations).

LRS, likelihood ratio statistic.

Figure 2 Transmission disequilibrium test (TDT) with Cx50 rs989192 and rs4950495 in Canadian and Portuguese families.

$\chi^2 = 9.316$, $p = 0.002$, OR = 1.77, 95% CI = 1.29 to 2.44, respectively) (fig 2). We also found an association between the Cx50 rs989192-rs4950495 haplotype and schizophrenia ($\chi^2 = 10.315$, $p = 0.012$). The A-C haplotype was transmitted 90.98 times and not transmitted 52.61 times ($\chi^2 = 8.433$, $p = 0.004$, OR = 1.83, 95% CI = 1.28 to 2.62) and the G-T haplotype was transmitted less often to patients (T:U = 608:649.7, $\chi^2 = 7.876$, $p = 0.005$, OR = 1.67, 95% CI = 1.22 to 2.28) (table 3). No significant differences in maternal and paternal transmission were detected in our family studies (data not shown).

DISCUSSION

For the first time, to our knowledge, an association between the Cx genes on chromosome 1q21 and schizophrenia has been investigated, and we found a significant association between the Cx50 rs989192-rs4950495 haplotype and schizophrenia. Compared with controls, patients with schizophrenia had a higher frequency of an A-C haplotype ($p = 0.007$). In the Canadian and Portuguese families, the A-C haplotype was transmitted more often to patients with schizophrenia ($p = 0.004$). No association of Cx40 with schizophrenia was found for allele, genotype or haplotype analyses. Our matched case-control and family studies indicate that Cx50, but not Cx40, may play a role in the genetic susceptibility to schizophrenia.

The rs989192A-rs4950495C haplotype shows a significant association with schizophrenia. Whether this intronic haplotype can affect Cx50 gene expression or link to other functional

markers is unknown. Although other rs989192-rs4950495 haplotypes show different results between our matched case-control and family studies, we found that the haplotype frequencies were similar in Canadian patients and in the frequency of transmission patients in families, particularly compared with the frequencies in controls (tables 2 and 3). Population stratification in this study can be excluded to a certain extent because the patients and controls were matched for sex, age and ethnicity, and this association is replicated in the family study. However, we should consider effects from genotyping error and rare haplotypes,²² although the rare haplotype was set to 0.05. The results from the Canadian Caucasian families showed no association with schizophrenia although there was a trend towards significance with rs989192. The result may mainly be due to the small sample size of only 40 triads and 59 diads.

Compared with other connexins, Cx50 channels are among the most CO₂-sensitive connexin channels.^{23 24} At negative voltages, Cx50 currents do not deactivate completely, in contrast, to Cx46 currents, which do.²⁵ These characteristics of Cx50 may indicate its physiological functions and pathology in brain. It has been reported that Cx50 is not present in rat brain tissues,²⁶ other than as some unexplained non-punctate labelling in the choroid plexus.²⁷ However, from the Allen brain atlas (www.brain-map.org) we can see that Cx50 is expressed in the brain, including the hippocampus, lateral ventricle, prefrontal cortex, amygdala and cerebellum. In addition, using real-time

Table 3 Transmission disequilibrium test with Cx50 rs989192-rs4950495 haplotypes in 99 Canadian Caucasian and 163 Portuguese families with schizophrenia.

Population	Haplotype	Transmitted	Untransmitted	χ^2	p Value	LRS	p Value
Canadian	A-C	30 (0.15)	18.1 (0.09)	2.624	0.105	2.671	0.26
	G-C	9 (0.05)	8.6 (0.04)	0.007	0.932		
	G-T	163 (0.81)	175.2 (0.88)	2.145	0.143		
Portuguese	A-C	61 (0.12)	33.9 (0.07)	6.096	0.014	8.707	0.04
	A-T	1 (0.00)	3.8 (0.01)	1.212	0.271		
	G-C	15 (0.03)	8.8 (0.02)	1.222	0.269		
Total	G-T	445 (0.85)	475.5 (0.91)	6.218	0.013	10.315	0.01
	A-C	91 (0.13)	52.6 (0.07)	8.433	0.004		
	A-T	1 (0.00)	3.5 (0.01)	1.041	0.308		
	G-C	24 (0.03)	18.2 (0.03)	0.64	0.424		
	G-T	608 (0.84)	649.7 (0.90)	7.876	0.005		

Significant values are in bold.
LRS, likelihood ratio statistic.

KEY POINTS

- The connexin genes Cx40 and Cx50 are considered candidates for schizophrenia because of their functions in the brain and their chromosomal location at 1q21, a region strongly linked with schizophrenia.
- We found that the Cx50 rs989192-rs4950495 haplotype was associated with schizophrenia in matched case-control samples from Toronto, Canada, and this result was replicated in a Portuguese family study.
- No association between Cx40 and schizophrenia was found for allele, genotype or haplotype analyses.

PCR, we have detected Cx50 expression in the brain of rats undergoing a conditioned avoidance response test, and in yoked and untrained controls (data not shown). Cx40 is expressed in the conduction system and atria,²⁸ and in neurons,²⁹ astrocytes³⁰ and neuronal precursors.³¹ The Cx40 gene is close to Cx50, at a distance of 129.5 kb. Although no significant association of Cx40 with schizophrenia was found in the present study, Cx40 markers can be considered a good null controls.³²

Further and more detailed studies are necessary to elucidate the role of Cx50 in schizophrenia. We also have checked a marker in the promoter region of Cx50, rs7536277; unfortunately, no variant was found in our samples. Cx expression and GJIC in astrocytes and in neurons are targets for a number of neurotransmitters, growth factors, peptides, cytokines and endogenous bioactive lipids.² Although few reports have been published, Cx50 may interact with GABA receptors (GABRA5, GABRB3 and GABRG2; <http://string.embl.de/>). Insights into the interactions between connexins and neurotransmitters will advance our knowledge about connexins in the aetiology of schizophrenia.

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