The Complement Control-Related Genes *CSMD1* and *CSMD2* Associate to Schizophrenia

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Background: Patients with schizophrenia often suffer from cognitive dysfunction, including impaired learning and memory. We recently demonstrated that long-term potentiation in rat hippocampus, a mechanistic model of learning and memory, is linked to gene expression changes in immunity-related processes involved in complement activity and antigen presentation. We therefore aimed to examine whether key regulators of these processes are genetic susceptibility factors in schizophrenia.

Methods: Analysis of genetic association was based on data mining of genotypes from a German genome-wide association study and a multiplex GoldenGate tag single nucleotide polymorphism (SNP)-based assay of Norwegian and Danish case–control samples (Scandinavian Collaboration on Psychiatric Etiology), including 1133 patients with schizophrenia and 2444 healthy control subjects.

Results: Allelic associations were found across all three samples for eight common SNPs in the complement control-related gene *CSMD2* (*CUB and Sushi Multiple Domains 2*) on chromosome 1p35.1-34.3, of which rs911213 reached a statistical significance comparable to that of a genome wide threshold (p value $= 4.0 \times 10^{-8}$; odd ratio $= .73$, 95% confidence interval $= .65–.82$). The second most significant gene was *CSMD1* on chromosome 8p23.2, a homologue to *CSMD2*. In addition, we observed replicated associations in the complement surface receptor *CD46* as well as the major histocompatibility complex genes *HLA-DMB* and *HLA-DOA*.

Conclusions: These data demonstrate a significant role of complement control-related genes in the etiology of schizophrenia and support disease mechanisms that involve the activity of immunity-related pathways in the brain.

Key Words: Complement cascade, csmd1, csmd2, human leukocyte antigen (HLA), immunity, schizophrenia

Schizophrenia is a serious psychotic disorder with high heritability (1), and a recent population-wide Swedish national health register study covering 9 million individuals and 35,985 families with schizophrenia estimated that 64% of the disease risk could be attributed to inheritance (2–4). Still, there has been a remarkable lack of replicated genetic susceptibility factors, and it has been debated whether schizophrenia is caused by common alleles of small effect or multiple rare alleles of larger effect, or a combination of both (for review see McClellan *et al.* [5] and Owen *et al.* [6]). The last alternative has now been verified, exemplified by the association of rare genomic variations such as microdeletions with markedly higher risk of schizophrenia (7–9) as well as the demonstration of polygenic models and replicated susceptibility alleles with small effect (10–12).

Some of these common risk alleles of small effect cover the human leukocyte antigen (HLA)-complex (the human major histocompatibility complex) and its adjacent regions on chromosome 6p21.3-22.1 (10–12). These findings potentially correlate different gene sets, including immunologic factors, olfactory receptors, and/or chromatin remodeling to the risk of schizophrenia. In support of a correlation between immune responses and disease risk, higher prevalence of psychiatric disorders including schizophrenia is repeatedly reported in patients with certain autoimmune disorders (reviewed in Ortega-Hernandez *et al.* [13]). Some studies have also pointed at a possible link between maternal exposure to infections during pregnancy and higher prevalence of schizophrenia in the offspring (reviewed in Brown *et al.* [14]).

In recent years, cognitive dysfunction, including learning and memory, has been recognized as a primary and enduring core deficit in schizophrenia that occurs at an early stage, and possibly before the first psychotic episode (15). Memory is a quantitative trait with high heritability, and revealing underlying mechanisms could disclose new candidate genes for memory performance and dysfunction (16). To identify such relevant genetic factors, we recently characterized the induction of gene expression networks during long-term potentiation (LTP) of synaptic strength in the hippocampus of live rats (17), because LTP is considered one of the major cellular mechanisms of learning and memory (18,19). We

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found that the complement cascade and antigen-presentation were the two top-ranked gene sets of differential expression during LTP, including increased expression of complement component C3 and members of the polymorphic group of major histocompatibility complex (MHC) class I and class II genes (17). This adds to the growing evidence that implicates the activity of the classical complement cascade and MHC class I in the development and plasticity of the central nervous system (20–22).

Based on our findings, strengthened by the confirmed link between genetic markers within the HLA complex and schizophrenia (10–12), we here investigate a subset of the complement and MHC gene sets for genetic association to schizophrenia in three independent case–control samples of German, Danish, and Norwegian origin.

Methods and Materials

Patient Samples

The German case–control discovery sample consisted of patients with schizophrenia recruited from consecutive admissions to the inpatient units of the Central Institute of Mental Health in Mannheim, and the Department of Psychiatry at the University of Bonn. A description of this sample is given elsewhere (M.R., M.M., *et al.*, unpublished data) (23). In brief, the sample includes genotypes from 466 patients and 1273 controls. Diagnoses were made according to DSM-IV criteria based on an Structured Clinical Interview for DSM (SCID)-I interview, medical records, and the family history method, and the OPCRIT14 system. Average age of onset was 22.9 $\pm$ 10.1 years.

The two replication samples of Norwegian and Danish patients with schizophrenia and control subjects were obtained from the Scandinavian Collaboration on Psychiatric Etiology. A detailed description of the samples has been given previously (24,25). Briefly, we successfully genotyped 667 patients and 1171 controls (506 patients and 896 controls from the Danish sample and 161 patients and 275 controls from the Norwegian sample). Danish patients were diagnosed according to an ICD-10 interview and had a mean age of onset of illness of 27.7 $\pm$ 12.0 years. Norwegian patients were diagnosed according to DSM-IV criteria based on an SCID-I interview and had mean age of onset of illness of 27.5 $\pm$ 8.6 years. Control individuals were matched to patients on sex, age, and ethnicity. Danish control subjects were recruited among 15,000 blood donors from the Danish Blood Donor Corps in the Copenhagen area. Norwegian control subjects were randomly selected from statistical records from the same catchment area as the patient group. Apparent abnormal behaviors were exclusion criteria, and subjects were screened by interview and with the Primary Care Evaluation of Mental Disorder. The Norwegian Scientific-Ethical Committees, the Norwegian Data Protection Agency, the Danish Scientific Committees, and the Danish Data Protection Agency approved the study.

Candidate Genes, Tag Single Nucleotide Polymorphism Selection, and Illumina GoldenGate Assay Design

Our recent microarray-based Gene Set Enrichment Analysis of hippocampal High-Frequency Stimulated (HFS) Long-Term Potentiation (LTP) in live rats disclosed significant responses from immunity-linked biological processes, and in particular from gene sets categorized for complement and MHC class I and MHC class II (MHCI/II)-mediated immunity (17). Real-time polymerase chain reaction assays confirmed activity-induced expression of 1) complement component C3, 2) the nonclassical MHCI genes (the *rt1-a* and *rt1-ce* families), and 3) the MHCII invariant chain (*CD74*) and specific MHCII genes (*rt1-Ba* and *rt1-Da*) that are encoded by the MHCII region of the HLA complex (17). In Phase I of the study, a German genome-wide association study (GWAS) of 466 patients with schizophrenia cases and 1273 control subjects was examined using data mining for nominal association to corresponding human MHC genes and regulators of complement activity (gene list in Table S1 in Supplement 1). The search covered 2726 and 1677 single nucleotide polymorphisms (SNPs) linked to complement and MHC activity, respectively. The German schizophrenia GWAS was also mined for the MHC class I–related genes *MICA*, *MICB,* and *MR1*, but these genes were not included for genotyping in Norwegian and Danish samples (discussed subsequently).

Tagging markers (SNPs) were selected using HapMap data (http://www.hapmap.org; Phase II March 8, on NCBI B36 assembly, dbSNP b126) as previously described (23). SNP genotype data from the CEU (Utah residence with ancestry from northern and western Europe) sample were downloaded for the genomic regions listed (Table S1 in Supplement 1). HapMap markers were analyzed with Haploview 3.2 (26) (http://www.broadinstitute.org/haploview/haploview) with the following criteria: Hardy–Weinberg equilibrium p value threshold .001, minimum genotypes 85%, maximum number of Mendelian errors = 1, and minimum minor allele frequency = .01–.10 (Table S1 in Supplement 1). Tagging markers were selected using the Tagger function implemented in Haploview with the following criteria: aggressive tagging, two- and three-marker haplotypes, and r^2 threshold of .8. In addition, explored markers with nominal statistical significance in the German GWAS sample (Phase I) were forced-included during the tagging SNP selection (allelic association test; $p < .05$). We also selected gene-specific tagging SNPs on the basis of optimal predicted performance scores in the multiplex Illumina Custom GoldenGate Oligo Pool Assay. The predicted Oligo Pool Assay performance was analyzed using the Illumina Assay Design Tool and supplier's recommended thresholds for Designability Rank and Error Codes. The 2.06-Mb-long *CSMD1* and 650-kb-long *CSMD2* genes were partially covered in the tagSNP assays based on significant associations in the German GWAS (Methods in Supplement 1).

Genotyping and Analysis

Genotyping was performed at the Bergen node of the Norwegian Microarray Consortium, a national platform for microarray technology and high-throughput genomics (http://www.microarray.no), using the GoldenGate Genotyping Assay implemented in the Illumina Iscan system platform (Illumina; http://www.illumina.com). The genotyping assay was performed following the supplier's instructions (Protocol "GoldenGate Genotyping Assay, Manual Experienced User Card (Universal BeadChip)"; Illumina) with the exception of using 375-ng input DNA in the reactions. Genotype cluster files were assigned using the GenomeStudio Genotyping Software v. 1.0.10 (Illumina). A signal threshold of .25 was used for exclusion of low intensity genotypes. Two CEU DNAs (11992 and 12144) with known genotypes were obtained from Coriell Cell Repositories (http://ccr.coriell.org) and used as positive controls for the genotyping. The markers in this report were part of one multiplexed GoldenGate assay for 1536 SNPs. All genotypes were manually inspected for control of the genotype cluster calls. One hundred thirty-six of the 1536 SNPs (8.9%) were excluded from further analysis because of genotyping failure.

Data Analysis

Genotype data were analyzed using the Golden Helix SNP and Variation Suite 7 (SVS7) software version 7.3.0 (Golden Helix, Bozeman, Montana). Genotypes determined by GoldenGate Assays were quality controlled by using the following exclusion criteria:

Table 1. List of *p* Values, OR, and Allele Frequencies for Markers in *CSMD2* (chr. 1p35.1-34.3) with Significant Association to Schizophrenia

Sample *N* Cases/Controls	GER 466/1273	DEN 506/896	NOR 161/275	All 1133/2444	Perm.	Country Covariate	Conditional Regression
rs1925338 (G)							
Allelic Association	1.54E-03	1.35E-01	4.40E-01	6.24E-04	.002	8.66E-04	7.22E-01
OR (95% CI)	.77 (.65–.91)	.88 (.74–1.04)	.89 (.65–1.20)	.83 (.74–.92)		.82 (.74–.92)	
MAF Cases/Controls	.28/.34	.30/.33	.28/.30	.29/.33			
rs12742027 (G)							
Allelic Association	5.19E-04	1.92E-02	3.88E-01	1.60E-05	.001	4.17E-05	9.54E-01
OR (95% CI)	.73 (.61–.88)	.81 (.67–.97)	.86 (.61–1.21)	.77 (.69–.87)		.78 (.69–.88)	
MAF Cases/Controls	.22/.28	.23/.27	.20/.22	.22/.27			
rs10737374 (G)							
Allelic Association	4.17E-05	6.13E-03	3.25E-01	4.07E-07	.001	1.01E-06	5.01E-01
OR (95% CI)	.71 (.60–.84)	.79 (.66–.93)	.86 (.63–1.17)	.75 (.67–.84)		.75 (.67–.84)	
MAF Cases/Controls	.26/.33	.27/.32	.26/.29	.26/.32			
rs911213 (G)							
Allelic Association	7.29E-05	3.11E-03	6.66E-02	4.04E-08	.001	1.72E-07	Regressor
OR (95% CI)	.72 (.61–.85)	.77 (.64–.91)	.75 (.55–1.02)	.73 (.65–.82)		.74 (.66–.83)	
MAF Cases/Controls	.27/.33	.25/.31	.25/.31	.26/.32			
rs2358516 (A)							
Allelic Association	6.13E-05	2.58E-03	2.15E-01	1.13E-07	.001	3.44E-07	5.62E-01
OR (95% CI)	.71 (.60–.84)	.77 (.65–.91)	.82 (.60–1.12)	.74 (.66–.83)		.74 (.66–.83)	
MAF Cases/Controls	.26/.33	.26/.32	.24/.28	.26/.32			
rs1321623 (G)							
Allelic Association	3.60E-03	2.22E-02	8.32E-01	5.42E-05	.001	2.67E-04	1.71E-02
OR (95% CI)	1.31 (1.09–1.57)	1.23 (1.03–1.46)	1.04 (.75–1.43)	1.27 (1.13–1.43)		1.24 (1.1–1.4)	
MAF Cases/Controls	.23/.19	.28/.24	.25/.24	.26/.22			
rs753893 (A)							
Allelic Association	1.26E-03	1.64E-03	5.69E-01	3.88E-06	.001	9.54E-06	7.87E-01
OR (95% CI)	.74 (.62–.89)	.74 (.61–.89)	.90 (.64–1.28)	.75 (.66–.85)		.75 (.66–.85)	
MAF Cases/Controls	.20/.25	.19/.24	.19/.21	.20/.25			

Values are listed for samples from Germany (GER), Denmark (DEN), and Norway (NOR), plus combined data of all samples (All). Genes with multiple hits and markers with statistically significant association in the merged sample analysis are listed (p value $< .001$, country covariate). Minor alleles are given in parenthesis. Regression p values for an additive genotypic model are listed, using country as covariate. Conditional regression is listed for the additive genotypic model using rs911213 as regressor. A study-wise Bonferroni correction with p value threshold of .05/number of markers, demonstrated that all markers for *CSMD2* remain significant.

MAF, minor allele frequency; OR, odds ratios with 95% confidence interval (95% CI) for the minor allele; Perm., 1000 permutation-test on allelic association in the merged sample set, on the whole set of markers examined in this study.

genotype call rate ($< .85$) and Hardy–Weinberg Equilibrium (p value $< .001$). For each gene, the number of assays designed and retained after quality control are listed in Table S1 in Supplement 1. The SNPs that passed quality control were analyzed as single markers by logistic regression in which the case versus control status was the outcome predicted by the genotype. Allelic associations were calculated with chi-square, regression, and analysis of deviance (ANODEV) raw p values as implemented in SVS7. ANODEV p values are reported in Tables 1 and 2 (Tables S2–S4 in Supplement 1). The genotypes were also compared with an F test in which bins of one genotype versus the two others were compared with a split-analysis (as implemented in SVS7) to test for dominant, codominant, and recessive mode of transmission. Test for significant markers were also performed using permutation with 1000 shuffles (Tables 1 and 2) and Bonferroni correction (Table 1; SVS7).

Results

Phase I: Mining of German Case–Control GWAS Data

Candidate genes were selected on the basis of our Gene Set Enrichment analysis of rat hippocampal HFS-LTP (17), as described in Methods and Materials. A knowledge-based selection was performed for genes that encode 1) complement-regulatory proteins acting from the step of initiation of the classical complement cascade (the C1Q complex) to the activation of C3, and 2) key regulators of antigen loading and presentation by MHC class I and MHC class II genes (Table S1 in Supplement 1). We examined 23 regulators of the complement pathway, nine genes linked to antigen presentation, and the full HLA complex (Table S1 in Supplement 1). The search covered 2726 and 1677 SNPs linked to complement and MHC activity, respectively. The focused data mining suggested genetic associations within the classical complement cascade and MHC class II molecules (> 11 gene regions supported by a significance level of $p < .05$) (Table S1 in Supplement 1). In addition, markers of the *CSMD1*, *CSMD2*, and *CD82* genes were represented among the top-ranked markers in the German GWAS.

Phase II: Replication in Norwegian and Danish Case–Control Samples

A tagSNP-based genotyping study was performed in Danish and Norwegian case–control samples on all the complement- and MHC-related gene sets examined in Phase I, apart from three genes distantly related to the MHC family (see Methods and Materials). For the custom-made genotyping approach, we also included the genes not reaching statistical significance in the German GWAS to allow a more complete pathway analysis in the larger sample sets.

In summary, genes that were investigated in both Phase I and Phase II included regulators of the classical complement cascade leading to the activation of C3 (*C1QA, C1QB, C1QC, C1S, CFH, CFI, C1, C1RL, CR2, C3, CR1, CR1L, CD46/MCP, C1QL1, and C1QBP*) and a set of

Table 2. List of *p* Values, Odds Ratios and Allele Frequencies for Markers in *CSMD1* (chr. 8p23.2) with Significant Association to Schizophrenia

Sample *N* Cases/Controls	GER 466/1273	DEN 506/896	NOR 161/275	All 1133/2444	Perm.	Country Covariate	Conditional Regression
rs664600 (C)							
Allelic Association	1.40E-02	5.10E-03	8.45E-01	8.24E-04	.002	4.77E-04	1.06E-03
OR (95% CI)	1.33 (1.06–1.67)	1.41 (1.11–1.78)	.95 (.60–1.52)	1.30 (1.12–1.52)		1.32 (1.13–1.54)	
MAF Cases/Controls	.14/.11	.14/.10	.10/.10	.13/.10			
rs4876061 (A)							
Allelic Association	4.29E-03	1.06E-01	3.04E-01	1.74E-03	.003	6.18E-04	1.85E-03
OR (95% CI)	1.50 (1.14–1.97)	1.29 (.95–1.76)	1.41 (.73–2.72)	1.37 (1.13–1.66)		1.41 (1.16–1.72)	
MAF Cases/Controls	.09/.06	.07/.06	.05/.04	.08/.06			
rs7017888 (C)							
Allelic Association	2.57E-03	1.06E-01	1.00E-01	5.53E-04	.001	1.77E-04	regressor
OR (95% CI)	1.32 (1.10–1.58)	1.17 (.97–1.42)	1.37 (.94–1.98)	1.24 (1.10–1.41)		1.27 (1.12–1.44)	
MAF Cases/Controls	.24/.19	.21/.19	.19/.14	.22/.19			
rs7011965 (A)							
Allelic Association	3.98E-03	6.76E-02	6.18E-01	1.39E-03	.001	4.38E-04	4.65E-01
OR (95% CI)	1.36 (1.11–1.68)	1.23 (.99–1.53)	1.13 (.71–1.80)	1.27 (1.10–1.46)		1.3 (1.12–1.5)	
MAF Cases/Controls	.17/.13	.16/.13	.10/.09	.15/.13			

Values are listed for samples from Germany (GER), Denmark (DEN), and Norway (NOR), plus combined data of all samples (All). Genes with multiple hits and markers with statistically significant association in merged samples analysis are listed (p value $< .001$, country covariate). Minor alleles are given in parenthesis. Regression p values for an additive genotypic model are listed, using country as covariate. Conditional regression is listed for the additive genotypic model using rs7017888 as regressor.

MAF, minor allele frequency; OR, odds ratios with 95% confidence interval (95% CI) for the minor allele; Perm., 1000 permutation-test on allelic association in the merged sample set, on the whole set of markers examined in this study.

brain-expressed regulators of complement activity (RCA; *CSMD1, CSMD2, SEZ6*, *SPARC,* and *SPARCL1*). For antigen-presenting molecules, we investigated genes encoding key regulators of loading, transport, and presentation of endogenous and exogenous antigens, including the MHCII region of the HLA complex (encoding at least 11 MHCI/II related genes), *CD74, CD82*, *HLA-E,* and the MHCI receptors *KLRC1*, *KLRC2*, *LAIR2,* and *LILRB4*.

A total of 1034 tagSNPs covering complement-related ($n = 717$ markers) and antigen presenting ($n = 317$ markers) genes were designed and applied for genotyping in 667 cases with schizophrenia and 1171 control subjects from two samples of Norwegian and Danish origin. One hundred fifty markers were removed during quality control (85 for poor genotyping and 65 for Hardy–Weinberg disequilibrium). The remaining SNPs were included in the allelic association tests of the Norwegian and Danish samples, with subsequent comparison and merged analysis with the German sample. A summary of the regions, genes, assay numbers, and number of markers investigated and nominally significantly associated are listed in Table S1 in Supplement 1.

Genetic Associations in Genes Encoding RCAs

As shown in Figure 1 and Table 1, the strongest finding was obtained for the *CSMD2* (*CUB and SUSHI Multiple Domains two*) gene, where eight markers showed statistically significant p values, with odds ratios in the same direction in all three samples, leading to strong allelic association in the merged data, for which rs911213 had the strongest associated p value (raw regression $p = 4.0 \times 10^{-8}$; odds ratio [OR] = .73, 95% confidence interval [CI] .65–.82; MAF case/controls = .26/.32). These *CSMD2* markers remained associated with schizophrenia using country as covariate, although with a slight reduction in regression p values (Table 1) (rs911213 as best marker: covariate additive model regression $p = 1.72 \times 10^{-7}$; OR = .74, 95% CI .66–.83). In a genotypic test, rs911213 remained the most significant marker in a recessive model, with a protective effect linked to the minor G allele (covariate recessive model $p = 6.35 \times 10^{-7}$; OR = .51, 95% CI .39–.68).

The signal of genetic association in *CSMD2* was linked to a block of seven markers, as shown by conditional regression with rs911213 (the most significant marker) as regressor (Figure 2 and Table 1). When searching for linkage equilibrium to published HapMap SNPs, none of the SNPs affected protein-coding sequences (http://www.broadinstitute.org/mpg/snap/ldsearch.php).

Intriguingly, the second most significant p values were observed for the homologous *CSMD1* gene with several SNPs being associated to schizophrenia, both in the separate samples as well as in the joint analysis of the three populations (Figure 1). Four markers were observed with p values $< .001$ (Table 2). The most significant allelic

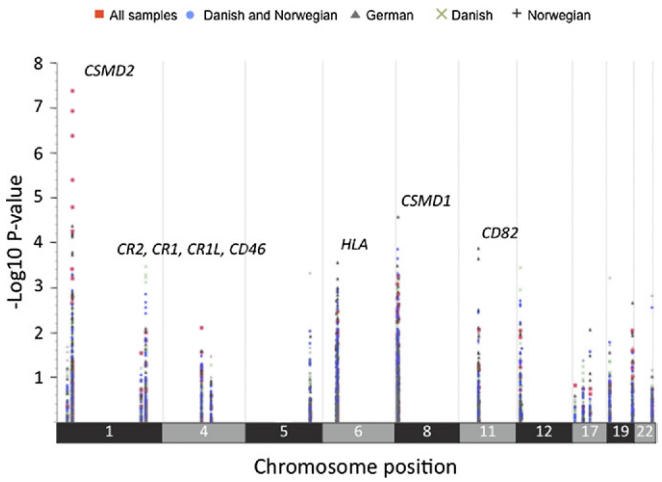

Figure 1. p values and chromosomal positions of allelic associations of tag single nucleotide polymorphisms in 30 immunity-related genes and in the major histocompatibility complex class II region of the human leukocyte antigen (HLA) complex. Allelic association is illustrated for Norwegian (+), Danish (X), and German (Δ) samples, Norwegian and Danish samples merged (blue circles), and all samples (red boxes). Gene coordinates are listed in Table S1 in Supplement 1.

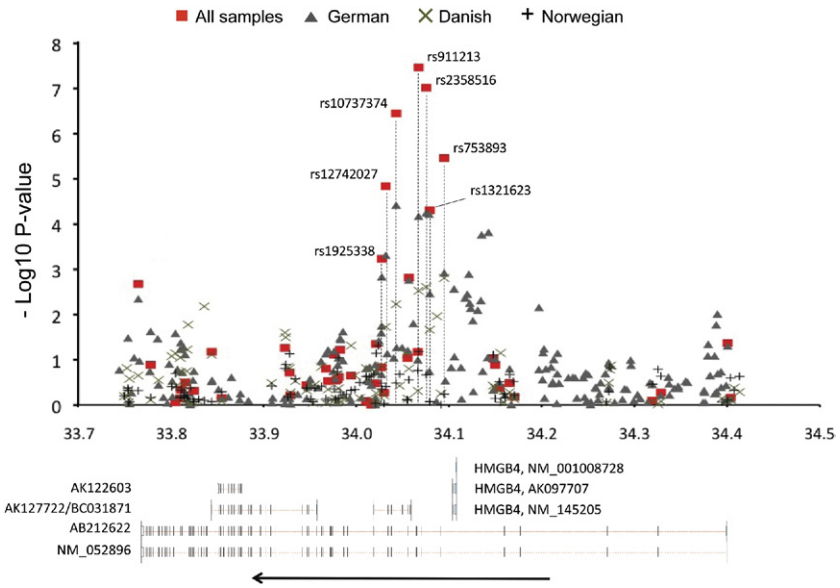

Figure 2. *p* values for allelic association and chromosomal positions for single nucleotide polymorphisms in *CSMD2*. Raw *p* values are plotted for Norwegian (+), Danish (X), and German (Δ) samples, as well as for merged analysis of all samples (red boxes) (single nucleotide polymorphisms with association –log 10 *p* value $< .05$ is not shown). The genotyped region is aligned to Ref.Seq and to University of California Santa Cruz annotated genes (NCBI_36). Direction of transcription is indicated with arrows.

associations were observed for markers rs7017888 ($p = 1.77 \times 10^{-4}$, OR = 1.27) and rs7011965 ($p = 4.38 \times 10^{-4}$, OR 1.30; Table 2), both showing the strongest signals of association in the merged sample when using country as covariate (Table 2). These two markers might also reflect the same signal of association, as shown by a conditional regression analyses (additive genotypic; Table 2). Several other tagSNPs in *CSMD1* displayed marked association to schizophrenia, in addition to markers with a flip-flop effect (27) or missing data (due to failed genotyping assays) in the other sample (Table S2 in Supplement 1). This includes rs10094093 from the German sample ($p = 2.62 \times 10^{-5}$, OR = .65) and rs24886 ($p = 2.23 \times 10^{-4}$, OR = 1.29) and rs13249525 ($p = 5.03 \times 10^{-4}$, OR = .78) from the Danish sample.

Analysis of other receptors of complement C3- and C4-derived ligands that are encoded by the *CR1* locus (*CR2, CR1*, *CR1L,* and *CD46*) showed replicated genotypic association for two markers that represent one signal in the 3′ untranslated region (UTR) of *CD46* (rs7144 and rs10449303; $r^2 = .98$; Table S3 in Supplement 1). In addition, several SNPs in *CR2* and *CR1* showed apparently strong allelic associations, either in the German and the Danish samples, but with flip-flop effects (i.e., disease susceptibility to the opposite alleles; Figure 1, Table S3 in Supplement 1). The strongest association was obtained for rs10494884 in the Danish sample (recessive split *p* value $= 9.1 \times 10^{-6}$; AA frequency case/controls = .41/.24; OR = 1.80, 95% CI 1.39–2.33).

Associations in Genes Encoding MHC Class II Proteins

We also observed several nominally significant allelic associations between markers in the partial HLA complex on chromosome 6 and schizophrenia (Figure 1, Table S4 in Supplement 1). In the merged sample, allelic association was observed for an Ile197Thr Mis-sense polymorphism in *HLA-DMB* (rs1042337; Table S4 in Supplement 1). The MHC class II region of the HLA complex also scored statistically significant with a genotypic association test (recessive model), and the two top-ranked SNPs, rs2071556 (*p* value $= 1.1 \times 10^{-3}$) and rs1042337 (*p* value $= 1.2 \times 10^{-3}$) both locate to the transcript-coding region of *HLA-DMB*. There is some limited LD between these two markers ($r^2 = .46$).

Other nominally significant signals within the MHC class II region are from rs3128931, rs6911639, and rs6933546. All three markers are flanking the upstream and downstream regions of the *HLA-DOA* gene for which the two first markers have proxy SNPs (CEU $r^2 >$ .8) in the 3′ UTR of *HLA-DOA*. Similar to the markers in *HLA-DMB*, these also show best statistical association in a recessive genotypic model (Table S4 in Supplement 1). A link between elevated disease risk and the associated markers in *HLA-DMB* and *HLA-DOA* was further supported by a haplotype association test because the haplotype that includes all the minor alleles (CGAGA; Table S4 in Supplement 1) displayed the most significant statistical association to schizophrenia (haplotype regression *p* value $= 2.8 \times 10^{-4}$; frequency case/controls = .061/.043; OR = 1.44, 95% CI 1.16–1.80).

Discussion

Among the human RCAs that we selected for genetic association tests, the two homologous genes encoding the multiple domain proteins *CSMD1* (chr. 8p23.2) and *CSMD2* (chr. 1p35.1-34.3) are strongly associated with schizophrenia, suggesting that variants of RCAs have a significant effect on disease susceptibility. Notably, our candidate gene approach on a small number of markers resulted in genetic associations that in comparison with genome-wide analysis reaches the commonly accepted genome-wide significance threshold of (*p* value) $\sim 5 \times 10^{-8}$ (28). *CSMD1* (MIM * 608397) and *CSMD2* (MIM * 608398) encode large multidomain proteins (about 400 kDa) that contain 14 alternating CUB and Sushi domains, followed by 12 to 15 additional tandem Sushi domains, a single transmembrane domain, and a short cytoplasmic tail with putative phosphorylation sites. Sushi domains are also known as short consensus repeats or complement control protein modules. A repeated pattern of multiple Sushi/SCR/CPP domains is a common feature among regulators of the complement cascade (29), a signaling pathway of the innate immune system that helps, or "complements," the process to clear pathogens or tag them for destruction by other cells. In the peripheral immune system, the cascade can be activated through the classical, alternative, or lectin pathways, all converging on the activation of complement C3 leading to the formation of the membrane attack complex (30).

Functionally, the Sushi repeats of CSMD1 can inhibit the deposition of complement component C3 in vitro similar to that of the complement component C3b/C4b receptor protein CR1L (Crry) (31). The effect of CSMD1 is probably specific to the classical complement pathway, because the protein was reported to have no

effect when the cascade is initiated through the alternative pathway. Notably, genetic variants in complement component C3b/C4b receptors may contribute considerably to the risk of neurodegenerative disorders, as recently exemplified by associations between the *CR1*-locus (homologue of *CR1L*) and Alzheimer's disease (32). Links to neurologic defects are also established for the complement cascade and C3 activity regulator CFH, for which alterations in the protein coding sequence strongly associate to the risk of age-related macular degeneration (33). Our observation of genetic association of CSMD molecules to schizophrenia may reflect a heritable impairment in the regulation of the classical complement cascade. However, complement control–related proteins also have the inherent property of regulating synapse function and excitability, that is, the clustering of postsynaptic receptors and synaptic densities, independent of any known immune function (34,35).

The *CSMD1* and *CSMD2* genes have not previously been widely described in psychiatric genetics, but a few studies have indicated associations between *CSMD1* and *CSMD2* and variation in brain structures or risk of neuropsychiatric disorder. The etiology of complex genetic disorders such as schizophrenia is likely to depend on interactions between risk factors selective to a specific disorder and sets of underlying heritable endophenotypes to which the latter only partially penetrate in disease (36). This is supported by recent data demonstrating partial overlap in the genetic susceptibility for schizophrenia and bipolar disorder (3,10). In the ADNI sample (Alzheimer's Disease Neuroimaging Initiative), GWAS analysis of voxels of the entire brain in healthy subjects, mildly cognitively impaired patients, and Alzheimer's patients identified the *CSMD2* marker rs476463 among the most significantly associated SNPs to brain volume (37). *CSMD2* has also been linked to ADHD and addiction (38,39). For *CSMD1*, strong genetic associations to psychiatric disorders have not previously been fronted, but we have noticed that *CSMD1* SNPs are listed in supplementary data for GWAS reports on major depression, bipolar disorder, and schizophrenia (11,40–43). Most of these reports point at nominal significant associations for a limited number of markers, but in a recent European GWAS-based study on schizophrenia, seven SNPs had p values in the range of 4.45×10^{-5} to 9.26×10^{-4} (11). These observations show that the two RCA-encoding genes that are associated with schizophrenia in our study may have clinical relevance to neuropsychiatric disorders with related endophenotypes or shared susceptibility.

Schizophrenia is established as a brain developmental disorder. In addition, epidemiologic observations over the past decades have repeatedly correlated the risk of schizophrenia to hyperactivation of the peripheral immune systems (i.e., prenatal infections and autoimmune disorders; (reviewed in Ortega-Hernandez *et al.* [13] and Brown *et al.* [14]). Recent gene network analyses of positional candidate genes also suggest that immunity pathways in general are major risk factors for schizophrenia (44). In support, several studies suggest that the CNS is continuously surveyed by circulating cells and molecules (e.g., leukocytes and cytokines) of the peripheral immune system affecting neuronal plasticity and behaviors (45–49).

However, it is becoming increasingly clear that immune molecules also contribute to brain development and function. Complement components (*C1q, C3*) and MHC class I molecules are localized to developing synapses in normal healthy rodent brains where they play an essential role for synaptic refinement and precise neuronal connectivity (22, 50–52). Mice deficient in MHC class I signaling (*B2m* KO, *TAP* KO, *CD3 zeta* KO), and classical complement cascade (*C1q, C3* KOs) exhibit similar defects in synaptic pruning in the developing visual system, suggesting functional interactions between innate and adaptive immune molecules in the developing brain (20,22,53).

Moreover, a significant upregulation of complement- and MHC-related genes are associated with central nervous system injury and a host of neurodegenerative diseases (reviewed in Alexander *et al.* [54] and Amor *et al.* [55]). Functional mechanisms for how complement factors lead to onset and/or progression of brain diseases are yet to be established but could involve the reactivation of developmental synaptic pruning programs leading to neuronal degeneration (22,56). Thus, complement regulatory proteins may be important in protecting synapses from aberrant elimination during development and disease. Schizophrenia is characterized by brain disconnectivity and progressive loss of gray matter that are proposed to be preceded by an increased rate of synaptic pruning or elimination (57–59). Reduced synaptic and dendritic spine markers are also found in relevant brain regions of patients (60–63). It remains to be explored whether *CSMD1*, *CSMD2,* and the *CR1-locus* are involved in such processes.

In addition to identifying RCA-encoding genes as risk factors in schizophrenia, we also found nominally significant associations to functional variants of the MHC class II molecules *HLA-DMB* and *HLA-DOA*. These genes are encoded by the MHC class II region of the HLA complex. The HLA complex covers more than 200 genes including MHC class I and class II molecules, which in the immune system are specialized for presenting endogenous and exogenous antigens, respectively. This region is infamous for the complexity of its linkage disequilibrium structure. The genomic architecture of this region has been explored in autoimmune disorders in which linkage disequilibrium at the marker level can reach up to several megabases out of the region (64,65). This complex LD architecture renders interpretation of association in this region challenging both at the single marker level as well as at the haplotype level. The recent three meta-analyses on schizophrenia all pointed to significant signals of association in the 6p21.3-22.1 region (10–12), and further work is warranted to pinpoint the original signals. However, it is important to emphasize that from the corresponding rat MHC class II region, we recently detected the expression of *rt1-Ba* and *rt1-Da* (MHC class II genes) in response to HFS-LTP (17). In addition, we show that the expression of the MHC class II invariant chain CD74 was upregulated following LTP (17). These data suggest that MHC class II molecules expressed from this region may modulate neuronal plasticity in the central nervous system.

In conclusion, we have observed highly significant genetic associations to schizophrenia in several immunity-related factors of the innate and adaptive immune systems. The strongest findings were obtained for common SNP variants in the homologous genes *CSMD2* and *CSMD1*. These novel observations implicate a role of complement control-related proteins as risk factors in schizophrenia. Further work is needed to better understand how these molecules may regulate the activation steps of the classical complement cascade, which is a well-known signaling pathway of the innate immune system, with recent evidence that its activity also colocalizes with the patterning of developing neuronal circuits in the brain.

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Supplementary material cited in this article is available online.

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