TITLE PAGE

Evaluation of shared genetic susceptibility loci between autoimmune diseases and schizophrenia based on genome-wide association studies

Louise K. Hoeffding[1,2], Anders Rosengren[1,2], Johan H. Thygesen[1], Henriette Schmock[1,2], Thomas Werge[1,2,3], Thomas Hansen[1,2]

[1]Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services Copenhagen, DK-4000, Denmark.

[2]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark.

[3]Department of Clinical Medicine, University of Copenhagen, DK-2200, Denmark.

Corresponding author:

Louise K. Hoeffding

Address: Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services Copenhagen, Boserupvej 2, DK-4000 Roskilde, Denmark.

Telephone: +45 38642285

Fax: +45 46334367

Email: Louise.K.Enggaard.Hoeffding@regionh.dk

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ABSTRACT

Background: Epidemiological studies have documented higher than expected comorbidity (or in some cases, inverse comorbidity) between schizophrenia and several autoimmune disorders. It remains unknown whether this comorbidity reflect shared genetic susceptibility loci.

Aims: In the present study, we aimed to investigate whether verified genome wide significant variants of autoimmune disorders confer risk of schizophrenia which could suggest a common genetic basis.

Methods*:* 714 genome wide significant risk variants of 25 autoimmune disorders were extracted from the NHGRI GWAS catalogue and examined for association to schizophrenia in the Psychiatric Genomics Consortium schizophrenia GWAS samples (36,989 cases and 113,075 controls).

Results*:* Two independent loci at 4q24 and 6p21.32–33 originally identified from GWAS of autoimmune diseases were found genome wide associated with schizophrenia ($1.7x10^{-8} \geq P \geq 4.0x10^{-21}$). While these observations confirm the existence of shared genetic susceptibility loci between schizophrenia and autoimmune diseases, our findings did not show a significant enrichment.

Conclusion: Our findings do not support a genetic overlap in common SNPs between autoimmune diseases and schizophrenia that in part could explain the observed comorbidity from epidemiological studies.

KEYWORDS: GWAS, schizophrenia, autoimmune diseases, comorbidity

BACKGROUND

Both schizophrenia and autoimmune diseases are complex disorders caused by multiple genetic and non-genetic risk factors. Schizophrenia is a severe mental disorder while autoimmune diseases are a clinical heterogeneous group of diseases with common underlying mechanisms related to an immune response against self. Recently, genome-wide association studies (GWAS) of large case-control samples have identified genome-wide significant SNPs implicating several candidate regions and genes for both autoimmune diseases and schizophrenia (1,2). Here, the most solid genetic finding for both disorders is that common variants in the major histocompatibility complex (MHC) on chromosome 6 confer risk of disease but with very different effect sizes (1,3). The MHC region contains multiple genes and extensive linkage disequilibrium (LD) which have made it difficult to identify the causal variants but the findings do, however, support the notion that similarly to autoimmune diseases, inflammatory processes might be involved in the pathogenesis of schizophrenia (4–8,1). The role of the immune system in the aetiology of schizophrenia is supported by prenatal infections particular during the second trimester increasing the risk of the disease in the offspring as well as insult of infectious agents during childhood (9,10).

There is mounting evidence for higher than expected comorbidity (or in some cases, inverse comorbidity) between schizophrenia and a number of autoimmune disorders both at the individual and familial level when compared to the general population (11–14) which could reflect a common genetic basis. Several GWAS have with great success been carried out for both disorders thus; it seems evident to test for shared genetic susceptibility loci of common SNPs that might contribute to the observed comorbidity between autoimmune diseases and schizophrenia and point towards shared molecular pathways and mechanisms.

AIM

In this study, we examine whether verified genome wide significant variants of autoimmune disorders confer risk of schizophrenia thereby supporting a common genetic basis.

MATERIALS AND METHODS

All SNPs showing genome wide association ($P \leq 5.0 \times 10^{-8}$) to an autoimmune disease were extracted from the National Human Genome Research Institute (NHGRI) GWAS catalogue (15) (http://www.genome.gov/gwastudies/, March, 2015). SNPs from GWAS based on subgroups of patients, case only studies, response to treatment, haplotype-based associations, or shared risk alleles between diseases were excluded from the analysis. Thus, a total of 714 unique SNPs (Supplementary Table 1) of 25 autoimmune disorders from GWAS of European, East Asian, and North India ancestry were included in the study (Table 1).

We used summary statistics from the Psychiatric Genomics Consortium schizophrenia (PGC-SCZ) GWAS samples, a large collection of 36,989 cases with schizophrenia and 113,075 controls of European and East Asian descent (1) (available at http://www.med.unc.edu/pgc/down-loads) to examine whether these 714 SNPs were genome wide associated with schizophrenia. A more in depth description of the PGC-SCZ GWAS samples can be obtained from the original publication (1).

Of the initial 714 SNPs, 706 were present in the PGC-SCZ GWAS samples either by its original refSNP ID reported in the NHGRI GWAS catalogue (N=629), by its current refSNP ID (N=62, retrieved from the file RsMergeArch downloaded at http://www.ncbi.nlm.nih.gov) or by a proxy SNP (N=15, using SNAP (16), 1000 Genomes Pilot 1, CEU reference panel, $r^2=0.1$). The remaining 8 SNPs were not found in the 1000 Genomes/CEU reference panel.

The 706 aforementioned SNPs present in the PGC-SCZ GWAS samples were spread across nearly all chromosomes (except chromosome 13 and the Y chromosome) and 90 SNPs were found in the

MHC region (the extended MHC region was defined as chr6:29,570,005–33,377,699, hg19(17)). By applying the same LD criteria as in (1), 388 of the 706 analysed SNPs remained (1000 Genomes Pilot 1, CEU reference panel, r^2=0.1 and a 500kb window).

In order to evaluate the robustness of our findings regarding the observed number of shared susceptibility loci between autoimmune diseases and schizophrenia, we first used the PGC-SCZ GWAS samples and randomly selected 706 SNPs 1000 times to estimate the expected number of SNPs that would be associated with schizophrenia by chance.

Second, we used the LD pruned version of the PGC-SCZ GWAS samples where SNPs within 500kb of, and in $r^2 \geq 0.1$ with, another (more significant) SNP were discarded as described in (1). From this LD pruned dataset, we randomly extracted 388 SNPs 1000 times where the 388 SNPs correspond to the number of independent autoimmune loci tested for genome wide association to schizophrenia (as described above). The observed number of shared susceptibility loci between autoimmune diseases and schizophrenia found in this study were considered statistical significant if less than 5% of the number of randomly chosen loci were found with $P \leq 5.0 \times 10^{-8}$.

Third, we extracted and evaluated all SNPs within 50kb up- and downstream of the non-MHC gene *BANK1* (chr4:102,711,764–102,995,969, hg19) that had previously been reported in GWAS of autoimmune diseases ($P \leq 5.0 \times 10^{-6}$) (rs4522865 and rs13126505 both associated with systemic lupus erythematosus (SLE)) from the NHGRI catalogue. Regional association plot was generated using LocusZoom (18) and all analyses related to the study were carried out using the statistical program R ver3.1.3 (http://www.r-project.org/).

(TABLE 1 HERE PLEASE)

RESULTS

A total of 714 risk variants were selected from GWAS of 25 autoimmune disorders (Table 1 and supplementary Table 1) and evaluated for genome wide association to schizophrenia in the latest PGC-SCZ GWAS sample in order to identify shared genetic susceptibility loci (see Materials and Methods for details regarding the SNP selection). Here, 706 SNPs were present in the PGC-SCZ GWAS sample (corresponding to 388 independent genomic regions) and of these 16 variants were found genome wide associated with schizophrenia ($P \leq 3.1 \times 10^{-8}$, Figure 1-2 and Table 2). Of the 16 identified genome wide associated variants 15 were present in the MHC region on chromosome 6p21.32–33 (strongest $P=4.0 \times 10^{-21}$) while the last SNP was located in the non-MHC gene *BANK1* at chromosome 4q24 ($P=1.2 \times 10^{-8}$) (Table 2).

Six SNPs originating from celiac disease (rs424232), crohn's disease (rs13126505), systemic sclerosis (rs3129763 and rs443198) and rheumatoid arthritis (rs805297 and rs9272219) had the same direction of effect in the PGC-SCZ GWAS sample while the remaining 10 variants had opposite effects (N=8) or unavailable at-risk alleles (N=2) despite contact to the corresponding author of the original GWAS.

To determine whether the 16 observed loci shared between autoimmune diseases and schizophrenia occurred more often than expected, we first sampled 706 SNPs from the PGC-SCZ GWAS dataset 1000 times (see methods). Here, we did not sample more than 8 loci showing genome wide association to schizophrenia from the 1000 permutations. However, as 15 of the 16 shared variants between schizophrenia and autoimmune diseases were situated in the MHC region with strong LD structures, we in addition found that the two shared independent loci at 6p21.32–33 and 4q24

showed a considerable trend toward significance since 5.5% of the 388 randomly drawn SNPs from the LD pruned PGC-SCZ GWAS sample had $P \leq 5 \times 10^{-8}$ (Figure 3).

None of the neighbouring SNPs that had previously been associated with an autoimmune disease (SLE) positioned in the non-MHC gene *BANK1* showed additional association to schizophrenia in the PGC-SCZ GWAS samples (rs4522865, $P=5.3 \times 10^{-2}$ and rs10516487, $P=1.7 \times 10^{-2}$, Figure 4 and Supplementary Table 2).

(TABLE 2 AND FIGURE 1-4 HERE PLEASE)

CONCLUSSION

Several epidemiological studies have shown that autoimmune diseases occur more frequently in patients suffering from schizophrenia than in the general population (11–14), however, no studies have addressed whether this could reflect shared genetic susceptibility loci between the diseases. This study aimed to make a comprehensive assessment of the genetic overlap of common SNPs between the two epidemiologically related diseases by investigating whether genome wide associated variants originally identified from GWAS of autoimmune diseases were genome wide associated with schizophrenia using the largest GWAS samples of schizophrenia to date (1). Several aspects of our work merit further discussion.

First, we identified two independent susceptibility loci at 6p21.32–33 and 4q24 shared by specific autoimmune diseases and schizophrenia (Table 2); however, when compared to randomly selected SNPs the number of shared loci were only marginally significant (P=0.055) (Figure 3). Thus, common SNPs captured as significant in current GWAS only contribute with little effect to the autoimmune comorbidity among patients with schizophrenia that could instead be explained by non-significant or rare variants interacting with non-genetic factors which have so far not been addressed in the literature. However, as the GWAS sample size continue to grow it is likely that more shared susceptibility loci of common SNPs between schizophrenia and autoimmune diseases will be discovered.

Second, the MHC region on chromosome 6 is a universal genetic susceptibility region for all autoimmune diseases studied in addition to schizophrenia and the number of shared MHC loci found in this study, ensured the reliability of our findings. However, the magnitude of effect for each shared risk variants in the MHC region was markedly different between autoimmune disease

and schizophrenia (Table 2) which may suggests that specific loci in the MHC region have key phenotype-determining role for autoimmune diseases when compared to schizophrenia where only weak effects are present.

Third, the single shared loci outside the MHC region implicating the immune related gene *BANK1* could imply an important role for B cell immune response pathways in the pathogenesis of both autoimmune diseases and schizophrenia. Despite this shared loci being a good candidate pointing directly towards shared immunological components outside the MHC region, neighbouring SNPs previous associated with SLE were not genome wide associated with schizophrenia suggesting that this may not be a true shared locus of association. Similarly, Pouget et al. (19) recently analysed whether common variation in immune gene outside the MHC region contributed to schizophrenia and found no enrichment of immune loci which were in contrast to five autoimmune diseases of known immune origin. Further analysis including the *BANK1* locus is necessary in order to clarify whether this could represent shared pathways involved in both schizophrenia and autoimmune diseases.

Fourth, several autoimmune disorders have in nation-wide population based register studies been associated with schizophrenia including the majority of the autoimmune diseases that were found to share risk variants with schizophrenia in this study (12,13). In addition, we identified shared loci with opposite directions for schizophrenia contradicting the epidemiological observations (e.g. autoimmune hepatitis and celiac disease) (12,13) and we did not exclusively find that the at-risk variants of rheumatoid arthritis are protective of schizophrenia as would be expected based on both epidemiological and genetic studies (12,13,20,21). These conflicting observations could suggest that the effect of the underlying causal variant vary among cell types and tissues emphasizing the

functional importance of the implicated genes and their biological impact and translation into phenotypes. Discordant associations are a common observation across autoimmune diseases (as reviewed by Parkes et al. (22)) which highlight the complexity of SNP or haplotype sharing. It has recently been explained how population-level phenomena (including genetic drift, natural selection, mutation or migration) are the likely reason behind this complexity of gene effects in different autoimmune diseases (2) which might also account for the observations in this study.

In summary, by merging GWAS data from multiple autoimmune diseases and schizophrenia we were not able to show that common SNPs significantly contribute to the observed comorbidity between the two epidemiologically related diseases.

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DISCLOSURE OF INTEREST

Dr. Werge has served as a lecturer for and consultant to H. Lundbeck A/S.

LEGENDS OF FIGURES AND TABLES

FIGURE 1. Quantile-quantile plots of the 706 autoimmune SNPs included in the analysis of the PGC-SCZ GWAS samples.

Fig. 1: A quantile-quantile plot of the 706 SNPs extracted from the NHGRI catalogue of 25 autoimmune diseases. Association testing was performed in the PGC-SCZ GWAS samples of 36,989 schizophrenia cases and 113,075 controls.

FIGURE 2. Risk variants from autoimmune disorders associated with schizophrenia

Fig. 2: Genome wide significant SNPs from autoimmune diseases replicated in the PGC-SCZ GWAS samples. The negative logarithm of the *P*-value is plotted against each chromosome. The vertical red line represents $P = 5 \times 10^{-8}$.

FIGURE 3. Analysis of the number of shared genetic susceptibility loci between autoimmune diseases and schizophrenia.

Fig. 3: The distribution of P-values ($P \leq 5 \times 10^{-8}$) of associated loci for the 388 SNPs drawn randomly 1000 times from the LD pruned version of the PGC-SCZ GWAS samples. The frequency of randomly drawn loci (SNPs) showing either two or three genome wide associated SNPs per 388 SNPs randomly drawn are 5.1% and 0.4%, respectively being only marginally significant (P=0.055). The y-axis represents the frequency while the x-axis shows the number of independent loci with P-values less than 5×10^{-8} from each extraction of 388 SNPs from the LD pruned version of the PGC-SCZ GWAS samples.

FIGURE 4. Regional association plot of the chromosomal region of the non-MHC gene *BANK1*.

Fig. 4: A regional plot showing the chromosomal position of the SNP rs13126505 in the gene *BANK1* against $-\log_{10}$(P-value) in the PGC-SCZ GWAS samples. The SNP (rs13126505) that was found genome wide associated with both an autoimmune disease and schizophrenia are represented by a purple diamond. The SNPs rs10516487 ($P_{SCZ}=1.7\times10^{-2}$) and rs4522865 ($P_{SCZ}=5.3\times10^{-2}$) that has previously been associated with and autoimmune disease (red arrows) were not genome wide associated with schizophrenia. Other SNPs in the region are coloured according to their LD patterns (generated using LocusZoom).

TABLE 1. The 25 autoimmune diseases included in the study and their respective number of genome wide associated SNPs

TABLE 2. Association results for verified risk variants for autoimmune diseases in the PGC-SCZ GWAS samples

SUPPLEMENTARY INFORMATION

Supplementary TABLE 1. The 714 genome wide associated SNPs from autoimmune diseases included in the study

Supplementary TABLE 2. SNPs previously associated with an autoimmune disease in the non-MHC gene *BANK1*

Table 1. The 25 autoimmune diseases included in the study and their respective number of genome wide associated SNPs

Autoimmune Diseases	No. of GWA SNPs[a]	References (PMID)[b]	Ethnic origin[c]
Alopecia areata	6	20596022	European
Ankylosing spondylitis	15	22138694;20062062;21743469	European and East Asian
Arthritis (juvenile idiopathic)	1	18576341	European
Autoimmune hepatitis type-1	1	24768677	European
Behcet's disease	13	20622878;23001997;23291587;20622879	European and East Asian
Celiac disease	33	24999842;23936387;20190752;18311140;17558408	European
Crohn's disease	157	22936669;17554261;17554300;22293688;18587394;23266558;17804789;17684544;23850713; 17447842;21102463;22412388;20570966;17435756;23128233	European and East Asian
Dermatomyositis	0	NA	NA
Graves' disease	22	21900946;236129;21841780	East Asian
Kawasaki disease	9	22081228;22446962;22446961	European and East Asian
Multiple sclerosis	74	19525955;2245734;21244703;22570697;19525953;18941528;23412934;18997785;22190364; 20598377;20159113;20453840;21833088;17660530	European
Myasthenia gravis	3	23055271	European
Primary biliary cirrhosis	27	21399635;20639880;23000144;19458352	European and East Asian
Primary sclerosing cholangitis	2	21151127	European
Psoriasis	27	19169255;19169254;20953190;18369459;18364390;20953188;20953189	European and East Asian
Psoriatic arthritis	4	22170493;20953186	European
Rheumatoid arthritis	137	21156761;2150507;17804836;17554300;21653640;21844665;20453841;23028356;19503088; 24449572;18794853;17982456;22446963;18668548;24782177;20453842;23918589;21452313; 24390342;24532677	European, East Asian, and North India
Sarcoidosis	2	22837380;229367	European
Sjögren's syndrome	5	24097066	East Asian
Systemic lupus erythematosus	58	19838193;1820409;23053960;23273568;18204447;20169177;19165918;21044949;18204446; 24871463;21408207;22291604	European and East Asian
Systemic sclerosis	14	20383147;21779181;21750679	European
Type 1 diabetes	53	17554300;22293688;17554260;18978792;17632545;18198356;18840781;19430480;19966805; 21980299	European
Ulcerative colitis	91	19122664;20228798;18836448;19915572;20228799;20848476;19915573;21297633;23511034; 24837172;23128233	European, East Asian, and North India
Vitiligo	29	20526339;22951725;21326295;20410501;22561518	European and East Asian
Wegener's granulomatosis	2	23740775	European

[a]The number of SNPs included in the study that are genome wide associated with an autoimmune disease $P \leq 5.0 \times 10^{-8}$ (extracted from the NHGRI GWAS catalogue).

[b]The PubMed ID of the GWAS included in the analysis.

[c]The ethnic origin of the subjects from the original GWAS.

Table 2. Association results for verified risk variants for autoimmune diseases in schizophrenia

GWAS SNP$_{AD}$[a]	Region	AD(s)	Risk allele$_{AD}$	P_{AD}	OR$_{AD}$	Mapped gene	A1/A2$_{SCZ}$	P_{SCZ}	OR$_{SCZ}$
rs2647044*	6p21.32	T1D	A	$1.0x10^{-16}$	8.3		A/G	$4.0x10^{-21}$	0.84
rs3131379	6p21.33	SLE	A	$2.0x10^{-52}$	2.4	*MSH5*	A/G	$1.9x10^{-18}$	0.85
rs558702*	6p21.33	SLE	A	$8.0x10^{-21}$	2.3	*C2;ZBTB12*	A/G	$3.3x10^{-18}$	0.85
rs3130544*	6p21.33	MG	A	$2.0x10^{-90}$	5.6		A/C	$3.6x10^{-18}$	0.86
rs2596565*	6p21.33	RA	A[b]	$9.0x10^{-9}$	1.4		A/G	$3.8x10^{-18}$	0.85
rs3134792*	6p21.33	PS	-	$1.0x10^{-9}$	-		T/G	$4.8x10^{-18}$	1.17
rs2040406*	6p21.32	MS	G	$1.0x10^{-20}$	2.1		A/G	$3.7x10^{-16}$	1.13
rs2187668*	6p21.32	AH, SLE ,CD	T[b]/T/T	$2.0x10^{-78}$/$1.0x10^{-50}$/$6.0x10^{-28}$	2.9/6.2/2.2	*HLA-DQA1*	T/C	$2.6x10^{-13}$	0.87
rs1150754	6p21.33	SLE	T	$6.0x10^{-29}$	2.2	*TNXB*	T/C	$5.2x10^{-12}$	0.90
rs805297*	6p21.33	RA	A	$3.0x10^{-10}$	1.6	*BAG6;APOM*	A/C	$1.1x10^{-10}$	1.08
rs9272219*	6p21.32	RA	G[b]	$1.0x10^{-45}$	1.9		T/G	$2.4x10^{-10}$	0.92
rs2157337*	6p21.32	RA	-	$9.0x10^{-52}$	-		T/C	$7.7x10^{-10}$	0.92
rs424232*	6p21.32	CD	C	$5.0x10^{-21}$	-		T/C	$7.9x10^{-10}$	0.92
rs443198*	6p21.32	SSc	A	$9.0x10^{-21}$	1.8	*NOTCH4*	A/G	$1.0x10^{-9}$	1.08
rs13126505	4q24	CSD	A	$2.0x10^{-12}$	1.2	*BANK1*	A/G	$1.2x10^{-8}$	1.14
rs3129763*	6p21.32	SSc	G[b]	$1.0x10^{-11}$	1.7		A/G	$1.7x10^{-8}$	0.93

A1 is reference allele for the odds ratio. "-" indicate that the information is unavailable. Unadjusted *P*-values are given.
Abbreviations: OR, odds ratio; *P*, *P*-value; AD; autoimmune disease, SCZ; Schizophrenia, SLE; Systemic lupus erythematosus, RA; Rheumatoid arthritis, AH; Autoimmune hepatitis, SSc; Systemic sclerosis, T1D; Type 1 diabetes, CD; Celiac disease, MG; Myasthenia gravis, PS; Psoriasis, CSD; Crohn's disease.

[a] Genome wide significant SNP for an autoimmune disease extracted from NHGRI GWAS catalogue.

[b] The risk allele are obtained by personal communication with the corresponding author.

[*] SNPs found in the Psychiatric Genomics Consortium schizophrenia GWAS samples by a different refSNP ID than reported in the NHGRI GWAS catalogue.

Supplementary information

Supplementary table 1. The 714 genome wide associated SNPs from autoimmune diseases included in the study

ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP	ID	SNP
1.	rs10036748	52.	rs11089637	103.	rs12191877	154.	rs13330176	205.	rs1738074	256.	rs2150702	307.	rs2413583	358.	rs3091315	409.	rs3814231	460.	rs4795067	511.	rs624988	562.	rs7015630	613.	rs773125	664.	rs9268645
2.	rs1004446	53.	rs11117432	104.	rs1219414	155.	rs13333054	206.	rs17391694	257.	rs2155219	308.	rs2425752	359.	rs3091316	410.	rs3821236	461.	rs479777	512.	rs638893	563.	rs7020673	614.	rs7731626	665.	rs9268839
3.	rs10045431	54.	rs11129295	105.	rs12212193	156.	rs1335532	207.	rs17445836	258.	rs2157337	309.	rs2451258	360.	rs3091338	411.	rs3823355	462.	rs4802307	513.	rs6421571	564.	rs702873	615.	rs77331626	666.	rs9268853
4.	rs10065637	55.	rs11150589	106.	rs12242110	157.	rs13361189	208.	rs17482078	259.	rs2187668	310.	rs2456973	361.	rs3093023	412.	rs3824660	463.	rs4809330	514.	rs6426833	565.	rs703842	616.	rs7743761	667.	rs9268877
5.	rs10168266	56.	rs11154801	107.	rs12251307	158.	rs13385731	209.	rs17582416	260.	rs2188962	311.	rs2469434	362.	rs3093024	413.	rs3825932	464.	rs4810485	515.	rs6441286	566.	rs706778	617.	rs7746082	668.	rs9268923
6.	rs1016883	57.	rs11167764	108.	rs12261843	159.	rs13428812	210.	rs17695092	261.	rs2201841	312.	rs2474619	363.	rs3118470	414.	rs3828309	465.	rs4813003	516.	rs6445975	567.	rs706779	618.	rs7748270	669.	rs9270984
7.	rs10175798	58.	rs11171739	109.	rs12368653	160.	rs1372072	211.	rs17696736	262.	rs2205960	313.	rs2476601	364.	rs3125734	415.	rs3893464	466.	rs4819388	517.	rs6451493	568.	rs7076156	619.	rs7752903	670.	rs9271100
8.	rs10181042	59.	rs11175593	110.	rs12379034	161.	rs1373692	212.	rs17716942	263.	rs2228145	314.	rs2523393	365.	rs3129763	416.	rs3897478	467.	rs4820425	518.	rs6457617	569.	rs7090512	620.	rs7758128	671.	rs9271366
9.	rs10201872	60.	rs11190140	111.	rs12413578	162.	rs1385374	213.	rs17728338	264.	rs2230926	315.	rs2542151	366.	rs3129882	417.	rs4077515	468.	rs4822024	519.	rs6457620	570.	rs7097397	621.	rs7765379	672.	rs9271588
10.	rs10210302	61.	rs11195128	112.	rs12466022	163.	rs1393350	214.	rs17810546	265.	rs2233152	316.	rs254560	367.	rs3129889	418.	rs4085613	469.	rs483905	520.	rs6478106	571.	rs7111341	622.	rs7774434	673.	rs9272219
11.	rs102275	62.	rs11203203	113.	rs1250550	164.	rs140522	215.	rs17824933	266.	rs2233287	317.	rs2546890	368.	rs3129934	419.	rs4112788	470.	rs4852324	521.	rs6479800	572.	rs7134599	623.	rs780093	674.	rs9272346
12.	rs1024161	63.	rs11209026	114.	rs1250552	165.	rs1417210	216.	rs1799964	267.	rs2233424	318.	rs2549794	369.	rs3130544	420.	rs4151657	471.	rs485499	522.	rs6499188	573.	rs713875	624.	rs7804356	675.	rs9275390
13.	rs1043099	64.	rs11221332	115.	rs12521868	166.	rs1456893	217.	rs1800693	268.	rs2233434	319.	rs2561477	370.	rs3130573	421.	rs415890	472.	rs4871611	523.	rs650258	574.	rs71508903	625.	rs7809799	676.	rs9275406
14.	rs10466829	65.	rs11229030	116.	rs12525220	167.	rs1456896	218.	rs1800871	269.	rs2236313	320.	rs2582532	371.	rs3131379	422.	rs4239702	473.	rs4900384	524.	rs653178	575.	rs7197475	626.	rs7812879	677.	rs9275572
15.	rs10484554	66.	rs11235667	117.	rs12529514	168.	rs1456988	219.	rs1801274	270.	rs2240335	321.	rs2596565	372.	rs3132613	423.	rs424232	474.	rs4902642	525.	rs6545946	576.	rs7200786	627.	rs7923837	678.	rs9277554
16.	rs10486483	67.	rs11249215	118.	rs12531711	169.	rs1464510	220.	rs181359	271.	rs224136	322.	rs2617170	373.	rs3134792	424.	rs4246905	475.	rs4902647	526.	rs6556412	577.	rs7202877	628.	rs7927894	679.	rs9282641
17.	rs10488631	68.	rs1126510	119.	rs12537284	170.	rs1465788	221.	rs1819658	272.	rs2241880	323.	rs2618476	374.	rs3135338	425.	rs4248154	476.	rs4908760	527.	rs6556416	578.	rs7210086	629.	rs7927997	680.	rs9286879
18.	rs10492972	69.	rs1128334	120.	rs12586317	171.	rs1487630	222.	rs1847472	273.	rs2242944	324.	rs26232	375.	rs3135388	426.	rs425105	477.	rs4917014	528.	rs6568421	579.	rs7221109	630.	rs793108	681.	rs9292777
19.	rs10495903	70.	rs1129038	121.	rs12617656	172.	rs1495965	223.	rs1854853	274.	rs2248359	325.	rs2647044	376.	rs3180018	427.	rs4263839	478.	rs4938534	529.	rs657075	580.	rs7238078	631.	rs798502	682.	rs9296015
20.	rs10499194	71.	rs11465804	122.	rs1265564	173.	rs151181	224.	rs1858037	275.	rs2254546	326.	rs26595	377.	rs3184504	428.	rs4272	479.	rs4939490	530.	rs6584283	581.	rs726288	632.	rs8005161	683.	rs9303277
21.	rs10509540	72.	rs1150754	123.	rs1265883	174.	rs1516971	225.	rs1877030	276.	rs227163	327.	rs2664035	378.	rs3194051	429.	rs4282438	480.	rs4947296	531.	rs6590330	582.	rs72634030	633.	rs8016947	684.	rs934734
22.	rs10516487	73.	rs11564258	124.	rs12663356	175.	rs1518111	226.	rs1893217	277.	rs2273017	328.	rs2664170	379.	rs3197999	430.	rs4285028	481.	rs4948088	532.	rs660895	583.	rs729302	634.	rs8017161	685.	rs9355610
23.	rs10517086	74.	rs11574637	125.	rs12677663	176.	rs1521	227.	rs1893592	278.	rs2274910	329.	rs2671692	380.	rs3213094	431.	rs4305317	482.	rs4948496	533.	rs6651252	584.	rs73013527	635.	rs8023715	686.	rs9372120
24.	rs1063635	75.	rs11574914	126.	rs12708716	177.	rs1551398	228.	rs1913517	279.	rs2281388	330.	rs267939	381.	rs33980500	432	rs4313034	483.	rs495337	534.	rs6679677	585.	rs73081554	636.	rs8026898	687.	rs9373594
25.	rs10734105	76.	rs11581062	127.	rs12720356	178.	rs1558744	229.	rs1943199	280.	rs2281808	331.	rs2736337	382.	rs340630	433.	rs4349859	484.	rs4957048	535.	rs669607	586.	rs73194058	637.	rs802734	688.	rs9378815
26.	rs10758669	77.	rs11584383	128.	rs12722489	179.	rs1569723	230.	rs1950897	281.	rs2283792	332.	rs2736340	383.	rs34330	434.	rs4380874	485.	rs4958881	536.	rs6705628	587.	rs7329174	638.	rs8032939	689.	rs9388489
27.	rs10761659	78.	rs11616188	129.	rs12822507	180.	rs1571878	231.	rs1980422	282.	rs2284553	333.	rs27434	384.	rs34536443	435.	rs4409764	486.	rs4959053	537.	rs6715284	588.	rs734999	639.	rs805297	690.	rs9394159
28.	rs10768122	79.	rs11642873	130.	rs12924729	181.	rs1610677	232.	rs1990760	283.	rs2290400	334.	rs27524	385.	rs34695944	436.	rs4409785	487.	rs4963128	538.	rs6716753	589.	rs736289	640.	rs8070463	691.	rs941576
29.	rs10774624	80.	rs11676348	131.	rs12928822	182.	rs16872571	233.	rs1998598	284.	rs2292239	335.	rs2797685	386.	rs354033	437.	rs4410871	488.	rs4979462	539.	rs6718520	590.	rs740495	641.	rs8083786	692.	rs941823
30.	rs1077667	81.	rs11676922	132.	rs1297265	183.	rs16940186	234.	rs2019960	285.	rs2293152	336.	rs280519	387.	rs35675666	438.	rs443198	489.	rs5029939	540.	rs6720394	591.	rs7423615	642.	rs8133843	693.	rs943072
31.	rs10781499	82.	rs1167796	133.	rs12994997	184.	rs16940202	235.	rs2024092	286.	rs2293370	337.	rs2812378	388.	rs359457	439.	rs4452313	490.	rs504963	541.	rs67250450	592.	rs744166	643.	rs8192917	694.	rs9468925
32.	rs10782001	83.	rs11697848	134.	rs13003464	185.	rs16967103	236.	rs2040406	287.	rs2294025	338.	rs281379	389.	rs3734266	440.	rs4505848	491.	rs505922	542.	rs6732565	593.	rs751728	644.	rs853308	695.	rs947474
33.	rs10790268	84.	rs117026326	135.	rs13010713	186.	rs17006292	237.	rs2051549	288.	rs229527	339.	rs2816316	390.	rs3745516	441.	rs4510766	492.	rs516246	543.	rs6738825	594.	rs7517810	645.	rs860413	696.	rs9479482
34.	rs10797432	85.	rs11712165	136.	rs13015714	187.	rs1701704	238.	rs20541	289.	rs229541	340.	rs2816958	391.	rs3748816	442.	rs4552569	493.	rs533259	544.	rs678170	595.	rs7517847	646.	rs864745	697.	rs9491697
35.	rs10800309	86.	rs11739663	137.	rs13017599	188.	rs17035378	239.	rs2056626	290.	rs2297441	341.	rs2836878	392.	rs3749946	443.	rs458017	494.	rs538147	545.	rs678347	596.	rs7522462	647.	rs874040	698.	rs951005
36.	rs10801047	87.	rs11742570	138.	rs13073817	189.	rs17066096	240.	rs2058660	291.	rs2297909	342.	rs28374715	393.	rs3757247	444.	rs4613763	495.	rs539514	546	rs6804441	597.	rs7524102	648.	rs874628	699.	rs9603616
37.	rs10806425	88.	rs11747270	139.	rs13096142	190.	rs17085007	241.	rs2062305	292.	rs2300603	343.	rs2838519	394.	rs3761847	445.	rs4622329	496.	rs548234	547.	rs6822844	598.	rs7554511	649.	rs877819	700.	rs9653442
38.	rs10821944	89.	rs11755527	140.	rs13098911	191.	rs170934	242.	rs2066808	293.	rs2300747	344.	rs28411352	395.	rs3761959	446	rs4639966	497.	rs549182	548.	rs6832151	599.	rs7574070	650.	rs881375	701.	rs9657904
39.	rs10845606	90.	rs11805303	141.	rs13126505	192.	rs17095830	243.	rs2066847	294.	rs2301271	345.	rs2841277	396.	rs3763309	447.	rs4648356	498.	rs558702	549.	rs6837335	600.	rs7574865	651.	rs886774	702.	rs968451
40.	rs10865331	91.	rs11810217	142.	rs13142500	193.	rs17129789	244.	rs2072438	295.	rs2301436	346.	rs2847297	397.	rs3764021	448.	rs4654903	499.	rs561722	550.	rs6856616	601.	rs7595037	652.	rs897200	703.	rs968567
41.	rs10876864	92.	rs11871801	143.	rs13151961	194.	rs17174870	245.	rs2075876	296.	rs2301888	347.	rs28493229	398.	rs3764147	449.	rs4654925	500.	rs5743289	551.	rs6859219	602.	rs7608910	653.	rs907611	704.	rs9792269
42.	rs10883365	93.	rs11889341	144.	rs131654	195.	rs17207986	246.	rs2076530	297.	rs2303759	348.	rs2857151	399.	rs3774959	450.	rs4675374	501.	rs5753037	552.	rs6871626	603.	rs7616215	654.	rs909685	705.	rs9822268
43.	rs10889677	94.	rs11894081	145.	rs1317209	196.	rs17221417	247.	rs2076756	298.	rs2304256	349.	rs2867461	400.	rs378108	451.	rs4676406	502.	rs5771069	553.	rs6890853	604.	rs762421	655.	rs911263	706.	rs9826828
44.	rs10903122	95.	rs11900673	146.	rs13191343	197.	rs17229285	248.	rs2082412	299.	rs2305480	350.	rs2872507	401.	rs3781913	452.	rs4713693	503.	rs5912838	554.	rs6897932	605.	rs763361	656.	rs917997	707.	rs9847710
45.	rs10911628	96.	rs11933540	147.	rs13192471	198.	rs17234657	249.	rs2105325	300.	rs2310173	351.	rs2903692	402.	rs3783782	453.	rs4722672	504.	rs59374417	555.	rs6908425	606.	rs76418789	657.	rs924043	708.	rs9858542
46.	rs10931468	97.	rs11966200	148.	rs13192841	199.	rs1728785	250.	rs2111485	301.	rs231735	352.	rs2945412	403.	rs3790567	454.	rs4728142	505.	rs5987194	556.	rs6910071	607.	rs7665090	658.	rs924080	709.	rs987870
47.	rs10946940	98.	rs12048904	149.	rs13204742	200.	rs1728918	251.	rs2119704	302.	rs2327832	353.	rs296547	404.	rs3792109	455.	rs4763879	506.	rs6017342	557.	rs6911490	608.	rs7682241	659.	rs9258260	710.	rs9888739
48.	rs10947261	99.	rs12101261	150.	rs1323292	201.	rs17293632	252.	rs212388	303.	rs2395029	354.	rs30187	405.	rs3806156	456.	rs4766578	507.	rs6088765	558.	rs6920220	609.	rs7702331	660.	rs9260489	711.	rs9891119
49.	rs10985070	100.	rs12134279	151.	rs13277113	202.	rs17309827	253.	rs212402	304.	rs2395148	355.	rs3024493	406.	rs3806308	457.	rs4780401	508.	rs610604	559.	rs6927022	610.	rs7705924	661.	rs9263739	712.	rs9926296
50.	rs10995271	101.	rs12140275	152.	rs13314993	203.	rs1736020	254.	rs2130392	305.	rs2395185	356.	rs3024505	407.	rs3806624	458.	rs478222	509.	rs615672	560.	rs694739	611.	rs7714584	662.	rs9264942	713.	rs9976767
51.	rs11073328	102.	rs12188300	153.	rs13315591	204.	rs1736135	255.	rs2149085	306.	rs240993	357.	rs3087243	408.	rs3810936	459.	rs4788084	510.	rs61839660	561.	rs6974491	612.	rs771767	663.	rs9266406	714.	rs998731

Supplementary information

Supplementary table 2. SNPs previously associated with an autoimmune disease in the non-MHC gene *BANK1*

GWAS SNP_{AD}[a]	Region	Position(hg19)	AD(s)	Risk $allele_{AD}$	P_{AD}	OR_{AD}	Mapped gene	$A1/A2_{SCZ}$	P_{SCZ}	OR_{SCZ}
rs13126505	4q24	102865304	CSD	A	$2.0x10^{-12}$	1.2	*BANK1*	A/G	$1.2x10^{-8}$	1.14
rs10516487	4q24	102751076	SLE	G	$4.0x10^{-10}$	1.4	*BANK1*	A/G	$1.7x10^{-2}$	1.03
rs4522865	4q24	102715888	SLE	A	$5.0x10^{-6}$	1.4	*BANK1*	A/G	$5.3x10^{-2}$	1.03

A1 is reference allele for the odds ratio. Unadjusted *P*-values are given. Abbreviations: OR, odds ratio; *P*, *P*-value; AD; autoimmune disease, SCZ; Schizophrenia, SLE; Systemic lupus erythematosus, CSD; Crohn's disease.

[a] SNPs associated with an autoimmune disease ($P \leq 5.0x10^{-6}$) extracted from NHGRI GWAS catalogue.

Figure 1.

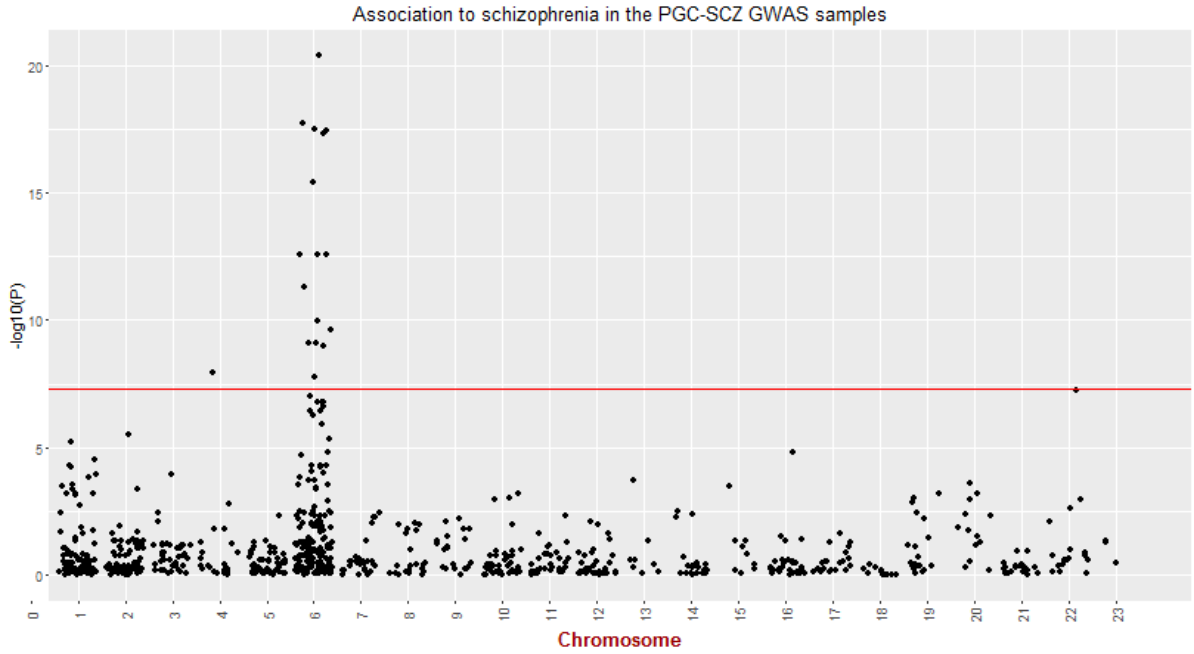

Figure 2

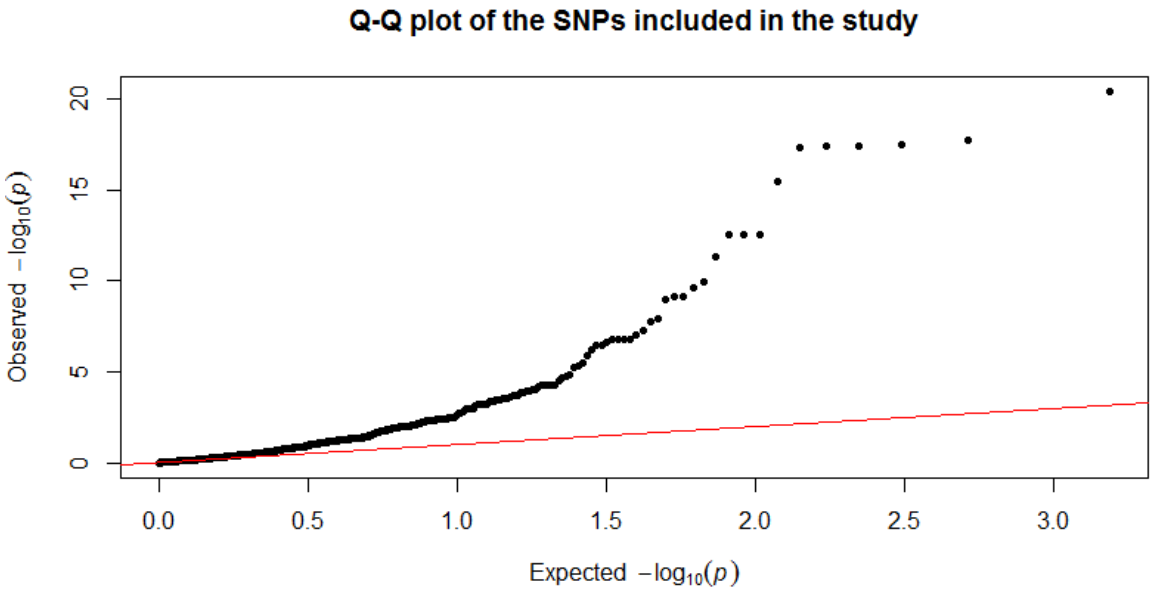

Figure 3

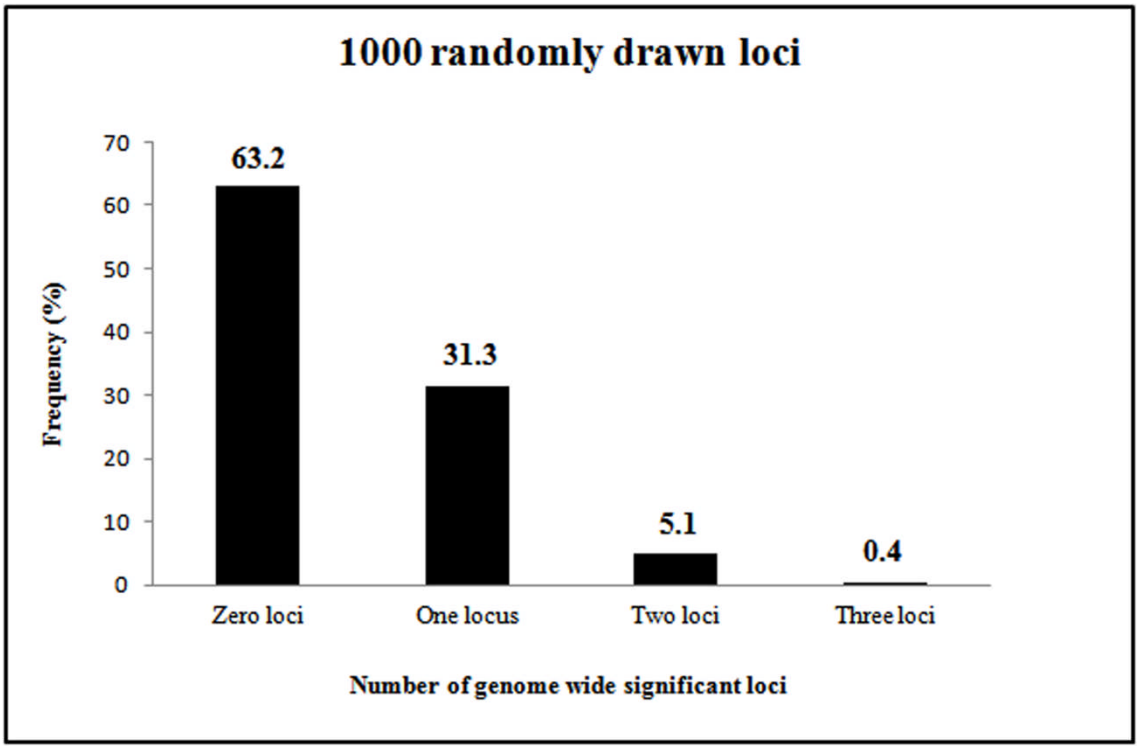

Figure 4