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Genetic markers of human evolution are enriched in schizophrenia

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Abstract

Background—Why schizophrenia has accompanied us throughout our history despite its negative effect on fitness remains an evolutionary enigma. It is proposed that schizophrenia is a by-product of the complex evolution of the human brain and a compromise for our language, creative thinking and cognitive abilities.

Method—We analyze recent large genome-wide association studies of schizophrenia and a range of other human phenotypes (anthropometric measures, cardiovascular disease risk factors, immune-mediated diseases) using a statistical framework that draws on polygenic architecture and ancillary information on genetic variants. We used information from the evolutionary proxy measure called Neanderthal selective sweep (NSS) score.

Results—We show that gene loci associated with schizophrenia are significantly ($p = 7.30\times10^{-9}$) more prevalent in genomic regions that are likely to have undergone recent positive selection in humans, i.e. with low NSS score. Variants in brain-related genes with low NSS score confer significantly higher susceptibility than variants in other brain-related genes. The enrichment is strongest for schizophrenia, but we cannot rule out enrichment for other phenotypes. The false discovery rate conditional on the evolutionary proxy, points to 27 candidate schizophrenia susceptibility loci, twelve of which are associated with schizophrenia and other psychiatric disorders, or linked to brain development.

Conclusion—The results suggest that there is a polygenic overlap between schizophrenia and NSS score, a marker of human evolution, which is in line with the hypothesis that the persistence of schizophrenia is related to the evolutionary process of becoming human.

Keywords

schizophrenia; GWAS; evolution; human; Neanderthal; polygenic

Introduction

Schizophrenia affects approximately 1% of the world's population and has accompanied us through much of our recorded history (1–6). This seemingly human-specific disorder is characterized by hallucinations and delusions (often involving language), thought disorders and higher order cognitive dysfunctions. The mechanisms of schizophrenia are not well understood, but its heritability is high, between 60% and 80% (7), and the fecundity of affected people is reduced (8). Nevertheless, the prevalence of the disease seems to remain stable across generations giving rise to the yet unresolved "evolutionary enigma" of schizophrenia (3, 4, 9, 10). Large variations in incidence across populations argue for environmental causes. However, by using standard, precisely drawn diagnostic criteria the variation in incidence can be reduced (11). Classical explanations include a single, partially dominant gene with low penetrance giving slight physiological advantages (12), balanced selection, where the gene variants conferring risk of the disease provide an advantage in particular environments, and hitchhiking, where disease variants are passed along with advantageous neighboring gene variants. Newer studies have focused on the polygenic nature of schizophrenia and have attributed the disease's prevalence to the sporadic nature of complex disorders (13).

Archaeological and paleontological evidence points to the appearance of various hominin forms like Homo *habilis*, Homo *erectus*, Homo *neanderthalensis* (Neanderthals) and modern Homo *sapiens* (Humans) over 2.5 million years from the Lower Paleolithic to the Neolithic. It is debated whether the emergence of the 'modern human' was a morphological or a behavioral process, a one-time event or a continuous process of adaptation and assimilation of different forms. Even as morphological changes stopped, behavioral changes continued, rapidly leading to the ultimate success of humans (14).

Over the Pleistocene period, we see the appearance of specialized tools, the introduction of decorative arts, burial practices (15) and possibly the development of language (16). Research suggests that language acquisition played an important role in shaping the brain, helping us to think abstractly and be more creative, but also made us vulnerable to psychiatric disorders like schizophrenia (17). Changes that contributed to our ability to think more creatively and to improve executive function (18) could have also harbored susceptibility to this pathology (19). However, while archeological evidence provides clues about other aspects of human evolution, it cannot offer insights into the origin of psychiatric disorders.

Recent developments in human genetics have provided unprecedented opportunities to investigate evolutionary aspects of schizophrenia. Genome-wide association studies (GWAS) have identified over 100 schizophrenia risk loci and highlighted the polygenic architecture of the disease (20). The genome sequence of Neanderthals (21, 22), close relatives of early modern humans, can help pinpoint the genomic regions affected by positive selection since the two species diverged. The genomic differences between the two *homo* species may help explain specific human features, and thus the relation between human evolution and schizophrenia.

Several lines of evidence indicate that schizophrenia is a polygenic disorder (23, 24) with a large number of risk loci, each with a small effect (20). We have recently developed statistical tools, building on an Empirical Bayesian framework (25), that are specifically designed for polygenic architectures. These tools have successfully been applied to investigate several complex human phenotypes (26–32) but have not yet been used to study the evolutionary features thereof. We hypothesize that schizophrenia is the result of human polygenic adaptation (24) and investigate if regions of the human genome, which may have undergone recent positive selection, are enriched of association with schizophrenia.

Methods and Materials

Samples

We obtained summary statistics for ~1.0–2.5 million single nucleotide polymorphisms (SNPs) from GWASs of schizophrenia (conducted by the Psychiatric Genomics Consortium (PGC)) and other phenotypes, including anthropometric measures (body mass index (BMI), height, waist-hip ratio (WHR)), cardiovascular disease risk factors (systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG)), immune-mediated diseases (celiac disease (CeD), Crohn's disease (CD), rheumatoid arthritis (RA), ulcerative colitis (UC)) as well as other psychiatric and central nervous system disorders (attention deficit, hyperactivity

disorder (ADHD), Alzheimer's disease (AD), bipolar disorder (BD), and multiple sclerosis (MS)) (Table S1). In total, these studies included approximately 1.3 million phenotypical observations although overlap between samples makes the number of unique subjects lower.

Neanderthal selective sweep score

The Neanderthal selective sweep (NSS) score is obtained through alignment of human, Neanderthal and primate consensus sequences (21, 33) and is downloadable from the UCSC genome browser (http://genome.ucsc.edu, ntSssZScorePMVar track (S-scores)). This track consists of two entries per SNP, (z-score + sd) and (z-score − sd). The NSS score provides a likelihood index of positive selection in humans sometime after the divergence of humans and Neanderthals (21, 33) by measuring the relative abundance of ancestral/non-ancestral (i.e. aligned/non-aligned with primate consensus) alleles in these two lineages. A negative NSS score indicates scarcity of non-ancestral alleles in Neanderthal compared to modern humans and therefore possible positive selection in the latter. The (z-score + sd) entries in the genome track represent an upper bound on the statistic and are therefore conservative measures of positive selection likelihood. These were extracted for all SNPs in the GWASs of interest (Table S1 in Supplement 1) and follow the distribution illustrated in Fig. S1 in Supplement 1. The (z-score + sd) entries, termed NSS scores, were used as ancillary information or covariates in the enrichment analyses. Using the NSS scores, the authors of the two articles on Neanderthal genome identified regions of the human genome that are significantly likely to have undergone recent positive selection. The same analyses performed directly using the NSS scores were also performed using linkage disequilibrium (LD) weighted scores (see Analytical approach below) measuring affiliation to these regions.

Brain genes

In order to control the enrichment analyses for affiliation to brain genes, we identified genes with a known function in the brain using information from the NCBI (http://www.ncbi.nlm.nih.gov/gene). The query "human brain" in Homo sapiens revealed 2494 genes (March 2015). For comparison, we also used the list of brain genes from Kang *et al.* (34), which includes 1415 genes selected based on expression in various neural cells. The LD weighted procedure (see Analytical approach) applied to the NSS regions mentioned above was applied to these genes, yielding brain genes LD weighted affiliation scores.

Analytical approach

We employed a genetic enrichment method recently developed to dissect the genetic architecture of complex traits (26, 28, 29) (32, 35). Specifically, we investigated the enrichment of associations concurrent with the NSS score selection index in a covariate-modulated statistical approach (32). We investigated whether SNPs with low NSS score and therefore in regions possibly subjected to positive selection in humans, are more likely associated with schizophrenia or other phenotypes. All statistical analyses were carried out with a covariate-modulated enrichment analysis package developed on R (www.r-project.org) and MATLAB (www.mathworks.se/products/matlab/) programming platforms.

Quantile-Quantile (Q-Q) and Fold enrichment (36) plots—Q-Q plots are designed to compare two distributions; here we compared the nominal p-value distribution to the

empirical distribution. In the presence of null relationships only, the nominal p-values form a straight line on a Q-Q plot when plotted against the empirical distribution. We plotted $-\log_{10}$ nominal p-values against $-\log_{10}$ empirical p-values for the two SNP strata determined by the NSS score (conditional Q-Q plots) as well as for all SNPs. Leftward deflections of the observed distribution from the null line reflect increased tail probabilities in the distribution of test statistics (z-scores) and consequently an over-abundance of low p-values compared to that expected under the null hypothesis.

To graphically assess genetic enrichment, we used conditional fold enrichment plots. Here, a direct measure of the enrichment is given by the degree of deflection from the expected null. The fold enrichment is derived as follows: first the empirical cumulative distribution of −log10(p)-values for SNP association is computed for a given phenotype for all SNPs, and for the two dichotomous SNPs strata determined by the NSS score. Each stratum's fold enrichment is then calculated as the ratio $CDF_{stratum}/CDF_{all}$ between the −log10(p) cumulative distribution for that stratum and the cumulative distribution for all SNPs. The nominal −log10(p) values are plotted on the x-axis, the fold enrichment in the y-axis. To assess polygenic effects below the standard GWAS significance threshold, we focused the fold enrichment plots on SNPs with nominal $-\log10(p) < 7.3$ (corresponding to $p > 5\times10^{-8}$).

Binomial proportion test (BPT) (37)—Upon randomly subdividing a set of SNPs into two disjoint subsets, one would expect these to present similar p-values distributions. In particular, the proportion of SNPs with a p-value below a certain threshold should be the same in the two subsets. BPT measures deviations from this null hypothesis below a threshold of interest. We compared the proportions of SNPs in the top −log10(p) percentile within the two NSS strata. The BPT assumes independence of the data. Because of LD between SNPs, this independence requirement does not hold. We therefore subdivided the whole SNP set into blocks defined by 1Mb windows and an LD r^2 threshold of 0.2 and randomly selected ten sets of SNP representatives from all blocks. Ten sets of BPTs were carried out on the approximately independent randomly chosen SNPs and the final p-value was calculated from the median of the BPT statistics.

LD weighted SNP annotation score—The use of GWAS SNPs in DNA regions of interest may underestimate the extent to which those regions are represented in the analysis. We used an LD weighted scoring algorithm developed in(26) order to identify SNPs that tag specific DNA regions even if they are not situated within them.

For each GWAS SNP a pairwise correlation coefficient approximation to LD (r^2) was calculated for all 1KGP SNPs within a 1,000,000 base pairs (1Mb). All r^2 values < 0.2 were set to 0 and each SNP was assigned an r^2 value of 1.0 with itself. LD weighted region annotation scores for all DNA regions of interest were computed as the sum of LD r^2 between the tag SNP and all 1KGP SNPs in those regions. Given SNP_i, its LD weighted region annotation score was computed as LD $score_i = \Sigma_j \delta_j r_{ij}^2$, where r_{ij}^2 is the LD r-squared between SNP_i and SNP_j and δ_j takes values of 1 or 0 depending on whether the 1KGP SNP_j is within the region of interest or not.

Intergenic SNPs—Intergenic SNPs are defined as having LD weighted annotation scores for each of the genomic categories analyzed by Schork *et al.* (26) equal to zero and being in LD with no SNPs in the 1KGP reference panel located within 100,000 base pairs of a protein coding gene, within a non-coding RNA, within a transcription factor binding site or within a miRNA binding site. Those singled out in this way are expected to form a collection of non-genic SNPs not belonging to any (annotated) functional elements within the genome (including through LD) and therefore represent a collection of SNPs more likely to be null.

Intergenic correction—Intergenic SNPs were used to estimate the inflation of GWAS summary statistics due to cryptic relatedness. We used intergenic SNPs because their relative depletion of associations (26) suggests they provide a set of SNPs whose statistics are less inflated by polygenic associations. The inflation factor, λ_{GC}, was estimated as the median squared z-score of independent (LD $r^2 < 0.2$) sets of intergenic SNPs across one hundred LD-pruning iterations, divided by the expected median of a chi-square distribution with one degree of freedom.

Squared z-score regression—The hypothesis here is that there is some proportionality between a continuous covariate of interest and the incidence of SNP association with a phenotype. A viable proxy for the latter is the extent of the association z-scores. We therefore regressed the squared z-scores against the NSS scores. Other covariates were included in the regression as well to account for possible confounding factors. These were exonic, intronic, 5′UTR, 3′UTR annotation scores (26, 38), brain gene affiliation scores, genotypic variance and total LD. As done for the BPT, regression analyses were performed on the ten sets of SNP representatives and the regression coefficient p-values were calculated from the median of the ten regression coefficient estimates.

Replication—The procedure used to compute the conditional rate of replication (for details see supplement 1) follows the one of Schork *et al.* (26). The 52 sub-studies were subdivided into two groups of 26 in 50 different ways, the first group, D_k, $k = 1\ldots50$, serving as discovery group, the second, R_k, $k = 1\ldots50$, as replication group. Cumulative replication rates were calculated over each of 1,000 equally-spaced bins spanning the range of negative $\log_{10}$(p-values) observed in the discovery group and for each of the 50 subdivisions. Every cumulative replication rate was calculated as the fraction of SNPs with a discovery negative $\log_{10}$(p-value) greater than the lower bound of the bin, that had a replication p-value smaller than 0.05. Average cumulative replication rates were subsequently computed across the 50 subdivisions.

Results

We first assessed the influence exerted on schizophrenia association propensity by the Neanderthal “character” of the SNP’s DNA region, as measured by the NSS score selection index (21) (Fig. S1). Using data from the recently published schizophrenia GWAS (20), we conditioned schizophrenia association p-values on the NSS score. The conditional Q-Q (Fig. 1A) and fold enrichment (Fig. 1B) plots show that SNPs with negative NSS scores are enriched for associations with schizophrenia compared to SNPs with positive NSS score. These results are nominally confirmed by the binomial proportion test (BPT), (p =

2.40×10^{-2}) and more robustly by the squared z-score regression against the NSS score ($\beta = -0.067$, $p = 7.30\times10^{-9}$) (Table 1).

To control for the known effect of immune-related genes, all analyses were repeated after exclusion of SNPs in the MHC regions. These do not appear to affect the fold-enrichment to any measurable extent (Table S2, Fig. S2 in Supplement 1). Thus, it appears that the SNPs in human DNA regions that diverge from their Neanderthal counterparts have a higher propensity to be associated with schizophrenia. Similar analyses were repeated using affiliation to NSS regions that were deemed *significantly* likely (top 5%) to have undergone positive selection upon alignment with the Neanderthal genome. In this case, we investigated the original (21) as well as the more recently sequenced Neanderthal genome (22) and confirmed the initial results (Table S3, Fig. S3 in Supplement 1).

We carried out the same analyses on other phenotypes in order to assess the specificity of the evolutionary enrichment. As shown in Q-Q plots and fold enrichment plots (Fig. 2), other phenotypes show mostly modest or scarce enrichment as a function of NSS compared to schizophrenia. The only other significant excesses of low p-values were detected by the BPTs and the regression analyses for height and to some extent for BMI. (Table 1). Height in particular has effect size comparable to that of schizophrenia, and possibly larger still, but its standard error is somewhat larger. Targeted analyses of other psychiatric (ADHD, BD, MDD) and neurological (AD, Migraine, MS) disorders, revealed no measurable enrichment effect (Fig. S4–S5 in Supplement 1). Schizophrenia has by far the largest NSS effect size among the psychiatric and neurological GWASs, all of which have similar standard errors (Fig. S8). To test the extent to which the effect on schizophrenia depends on the power of the GWAS from 2014 (20), we performed the same analyses on the smaller schizophrenia GWAS from 2013(39), which is comparable in size to several of the other GWASs. The enrichment was somewhat diminished (Fig. S6 in Supplement 1) but remained nominally significant according to the regression analysis ($\beta = -0.038$, $p = 7.93\times10^{-3}$). We also tested the censored (methods in Supplement1) schizophrenia GWAS summary statistics and still found a significant (regression coefficient $p=2.87\times10^{-6}$) residual enrichment.

The effect of brain genes affiliation on enrichment was further investigated by testing whether brain genes with negative NSS scores are more enriched of associations with schizophrenia than any brain genes. The enrichment plots (Fig. 3) for brain genes with negative NSS show a wider deflection from baseline and the BPT shows a significant difference in the proportion of association p-values in the lowest percentile ($p = 5.5\times10^{-3}$).

We used the conditional FDR (condFDR) analysis (see methods in Supplement 1) to identify possible genomic loci associated with schizophrenia subject to the condition of having a negative NSS score. A total of 27 genomic loci were identified (condFDR<0.01). They are listed in Table S4 (Supplement 1) together with the annotated genes. A closer inspection of Table S4 (Supplement 1) reveals no preferential direction of effect (Fig. S7 in Supplement 1), i.e. positive and negative z-scores were equally represented. This lack of directionality is confirmed upon regressing the SNPs z-scores against their NSS score (regression data not shown), i.e. no significant association between the two could be detected. None of the loci are identified by the analyses involving NSS region affiliation scores. This is probably due to

the dichotomous origin of this measure which is less well suited to the FDR lookup table smoothing procedure.

To assess the reliability of the genomic loci identified via condFDR, we investigated the association replication rates in independent schizophrenia sub-studies, defined as the proportion of SNPs declared significant in training samples with p-values below 0.05 in the replication sample and with z-scores with the same sign in both discovery and replication samples. We found that SNPs with NSS < 0 replicate at a higher rate than other SNPs (Fig. 4). This confirms that the observed enrichment is due to associations and not to population stratification or other potential sources of spurious effects. Replication rates were extrapolated for the 27 NSS candidate loci and reported in Table S4 as well.

Discussion

Applying a polygenic statistical approach, we leveraged recent large GWAS data and showed that schizophrenia associations have a higher propensity to be found in genomic regions that diverge from their Neanderthal counterparts (negative NSS score). Such polygenic overlap between schizophrenia and a marker of human evolution is in accordance with the hypothesis of Crow *et al.* (19), suggesting that a number of schizophrenia susceptibility factors might have arisen as a "side effect" of human achievements like language and creative thinking (17). The current findings support the view that this evolutionary process also made us vulnerable to schizophrenia.

Previous studies of evolutionary factors of schizophrenia have focused on small sets of genes (40, 41). Bigdeli *et al.*'s analysis (42) was more systematic but applied human accelerated regions (HAR) as evolutionary proxy. Xu *et al.* (43), using special HARs, showed that genes next to HARs in primates were under greater selection pressure compared to other genes and are more likely to be associated with schizophrenia susceptibility loci. Green *et al.* (21), who reported the first Neanderthal draft sequence, introduced the selective sweep score and investigated its relationship with the disease association but only for the most significant genes singled out by their analysis. Here, we use the information from Green *et al.*'s original publication (21), as well as the more recent report by Prüfer *et al.* on the complete Neanderthal genome sequence (22), to identify evolutionary enrichment patterns with a polygenic approach. Another asset for our study was the availability of a large schizophrenia GWAS of more than 80,000 participants (20), which makes it feasible to investigate evolutionary factors in schizophrenia with adequate power.

The results presented here are in line with the idea of polygenic adaptation which is believed to play a role in the development of many complex human diseases, as it likely happened in our adaptation to pathogens and in the variation of morphological traits like height (44–46). Classic selective sweeps, originating from strong selective pressure, are relatively rare in modern humans (47) and natural selection is not the only factor shaping human variation. Instead, polygenic selection involving subtle shifts of allele frequencies at many loci simultaneously has been suggested to be common for complex traits in humans (47). Thus, selection acting simultaneously on many of standing variants could be an efficient mechanism for phenotypic adaptation (48, 49). Given these premises, it becomes desirable

to employ analytical tools designed to capture polygenicity. The methods applied in our analyses have been useful in studying polygenic factors in schizophrenia before (28, 29, 50, 51). Our results indicate that many schizophrenia susceptibility factors in modern humans may have emerged after their divergence from Neanderthals.

Several of the genes found to likely have undergone positive selection in modern humans (21) are involved in cognitive functions. The enrichment of SNPs associations observed for schizophrenia may therefore be due to an overlap between swept genomic regions and brain and other CNS genes and the regulatory regions thereof. This question is addressed by the regression analysis in which protein coding annotations are accounted for (Table 1). Even the inclusion of brain genes annotation scores in the regression did not reduce the enrichment for schizophrenia. Interestingly however, among the brain genes themselves, the ones with a negative NSS score were more enriched of associations with schizophrenia compared to other brain genes, let alone just any genes (Fig. 3).

The loci identified by the conditional FDR analysis harbor many genes that could plausibly play a role in the etiology of schizophrenia. Genes like *DPYD*, *ZNF804A, NRXN1, NRG3* and *VRK2*, which were previously known to be associated with the disease, confirm its potentially evolutionary nature (52–54). Other interesting patterns emerge from genes like *AGBL4, CEP170*, *IFT81*, and *SDCCAG8*, related to ciliogenesis and ciliary disorders (55–57), and *DPP10* and *FOXP1*, related to autism (58, 59). The functional implications of the current associations based on tag SNPs need to be explored in experimental studies. It will be of interest at a later stage to investigate whether the current polygenic evolutionary signal in schizophrenia is associated with human specific brain structure variance. GWAS for relevant brain structures, however, are not yet adequately powered (n~15,000 – 21,000 participants) (60). Further, the interplay of the polygenic effects and *de novo* mutations, such as schizophrenia risk CNVs, should also be examined, even if the latter appear to explain a very small proportion of schizophrenia cases (61).

Notably, the enrichment found here seems to be related to schizophrenia, and some anthropomorphic human traits. However, we cannot rule out that there may be enrichment also in other disorders or diseases. The sample sizes available to some of the CNS GWAS might have limited the power to detect any enrichment. At any rate, the analysis of the smaller schizophrenia GWAS from 2013(39) also revealed a nominally significant enrichment effect, further supporting the notion of a specific association between schizophrenia and positive selection.

In conclusion, the present findings of a prevalence of schizophrenia risk loci overlapping with some genetic signatures of human evolution support the argument that both the emergence and the persistence of schizophrenia are connected to the human *sapientia.* This may help to explain the “evolutionary enigma” of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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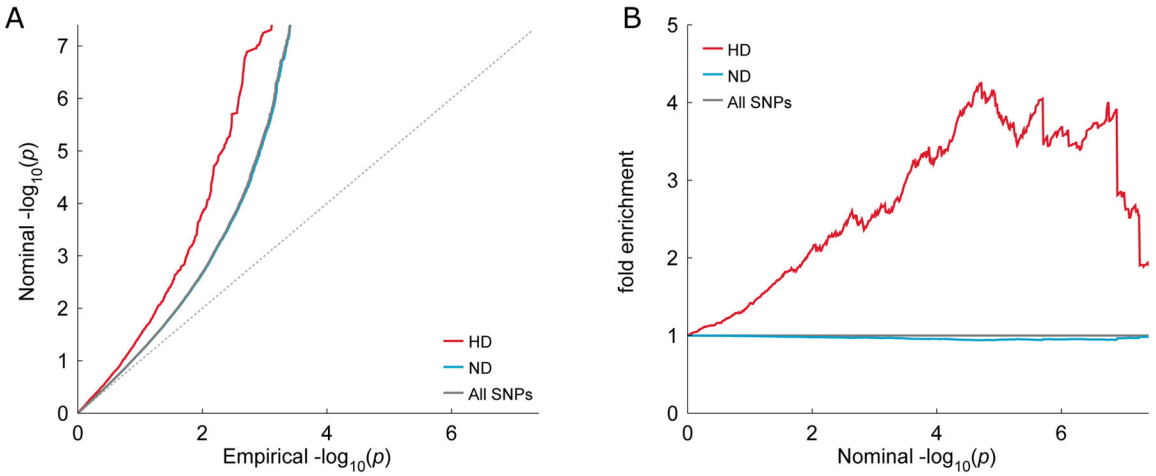

Fig. 1. Q-Q and fold enrichment plots of schizophrenia stratified according to Neanderthal selective sweep score

Shown are A) quantile-quantile (Q-Q) and B) fold enrichment plots of GWAS summary statistics *p*-values for schizophrenia (SCZ), stratified based on Neanderthal selective sweep (NSS) score. The human divergent (HD) stratum comprises single nucleotide polymorphisms (SNPs) with negative NSS scores. The regions around these SNPs present fewer derived alleles in Neanderthal than expected given the frequency of derived alleles in humans, and may therefore have undergone recent positive selection in the latter. The non-divergent (ND) stratum comprises all SNPs with positive NSS scores. HD SNPs show a marked leftward (A) and upward (B) deflection from the lines corresponding to All SNPs. This signifies a comparatively higher proportion of low *p*-values among HD SNPs.

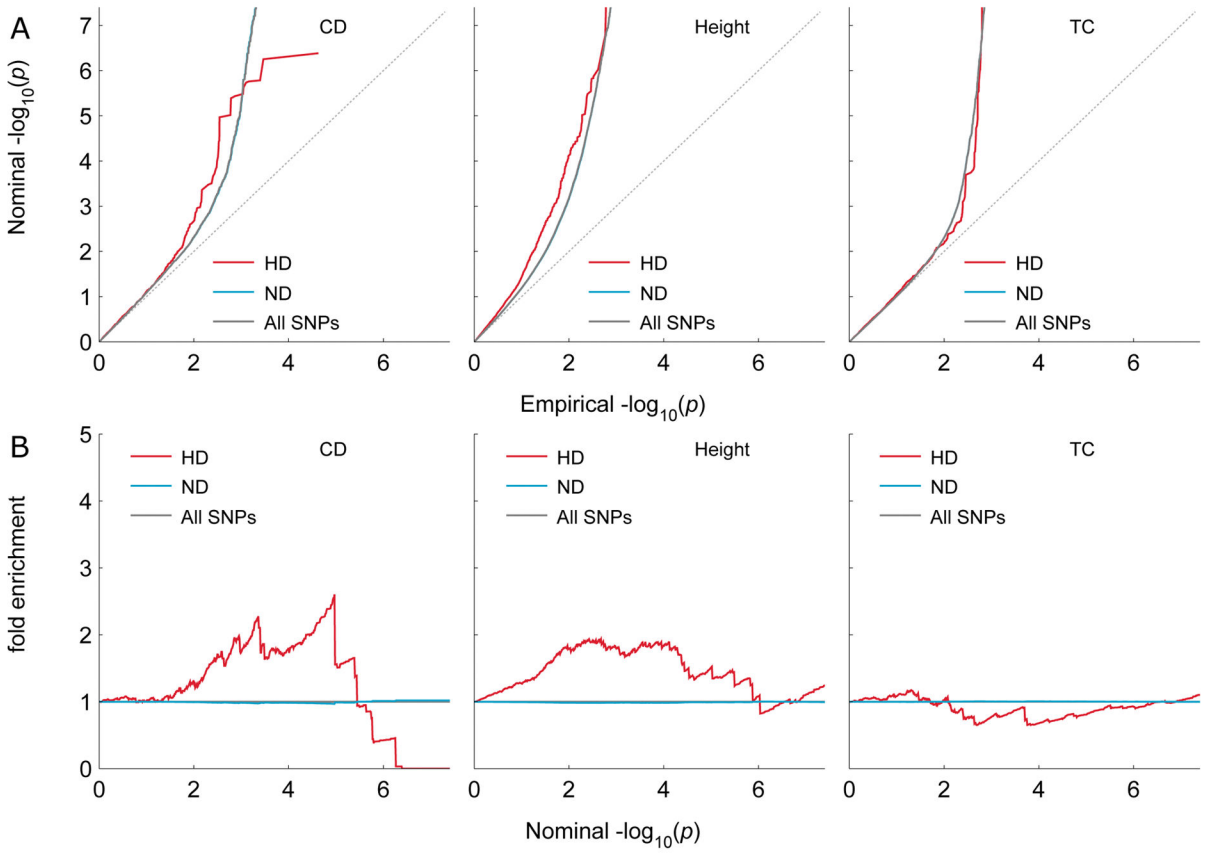

Fig. 2. Q-Q and fold enrichment plots of three non-schizophrenia phenotypes stratified according to Neanderthal selective sweep scores

Phenotypes: Crohn's disease (CD), Height and total cholesterol (TC). A) The quantile-quantile (Q-Q) plots show GWAS summary statistics *p*-values of SNPs tagging human divergent regions (HD), non-divergent (ND) regions as well as All SNPs. There is no indication of enrichment as seen in SCZ in (Fig. 1). B) The fold enrichment counterparts of the Q-Q plots in A) illustrate the lack of enrichment. The regression analysis however shows significant enrichment for Height. (Table 1).

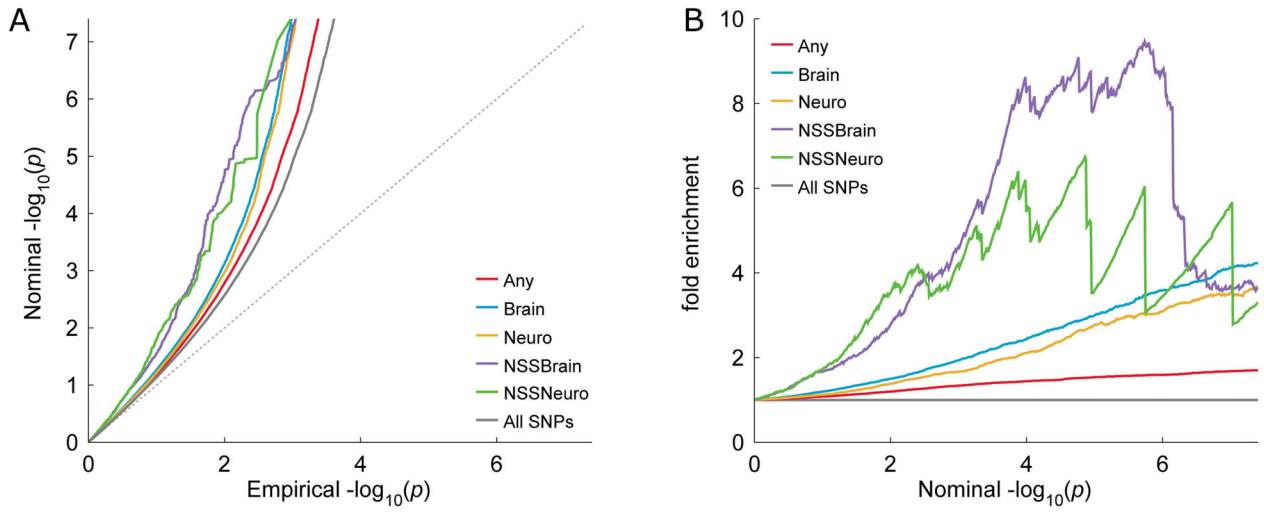

Fig. 3. Q-Q and fold enrichment plots showing schizophrenia association enrichment of brain genes with negative Neanderthal selective sweep (NSS) score

Shown are A) the quantile- quantile (Q-Q) and B) the fold enrichment plots for: SNPs annotated to generic genes (Any); SNPs annotated to genes associated with the brain, as established by an NCBI site search (Brain); SNPs annotated to genes associated with the brain, defined by Kang *et al.* (34) (Neuro); SNPs with negative NSS score and annotated to genes associated with the brain, as established by an NCBI site search (NSSBrain); or to genes defined by Kang *et al.* (34) (NSSNeuro); and all SNPs (All SNPs). The NSS Brain category is enriched (deflected left) compared to the other categories, i.e. presents a higher incidence of associations (lower p-values) with schizophrenia (SCZ). This is confirmed by the Binomial Proportion Test (BPT) comparing Brain and NSS Brain groups ($p = 5.5\times10^{-3}$).

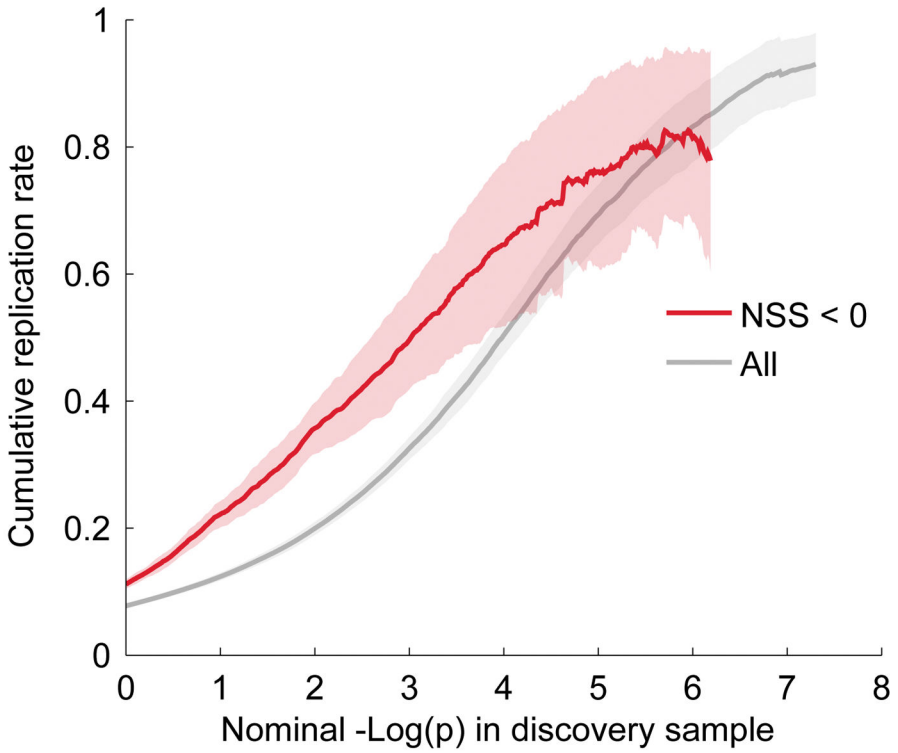

Fig. 4. Replication plot for schizophrenia with and without conditioning on Neanderthal selective sweep score < 0

SNPs with negative Neanderthal selective sweep score (NSS) score tend to replicate better than baseline SNPs across the 52 schizophrenia (SCZ) meta-analysis sub studies. For example, at a −log(p)-value level of 4 the cumulative replication rate improves from 60% to about 80% when restricting the choice to SNPs with negative NSS score. A negative NSS score seems therefore to be a viable aid to identify non-spurious schizophrenia associations.

Table 1

Neanderthal Selective Sweep Score; z squared logarithm regression and binomial proportion test (BPT).

GWAS	β (Min, Max)	Std. error	p-value	C.I	BPT(p) 1%(Min, Max)
AD	−0.012(−0.029,0.012)	0.016	5.00E-01	−0.041,0.022	2.5E-01(8.0E-04,5.9E-01)
ADHD	0.003(−0.013,0.017)	0.013	8.40E-01	−0.022,0.028	4.5E-01(3.6E-02,6.2E-01)
BD	−0.004(−0.020,0.013)	0.01	7.10E-01	−0.023,0.015	4.8E-01(1.4E-02,9.1E-01)
MDD	−0.018(−0.034,−0.006)	0.012	2.00E-01	−0.042,0.007	5.6E-01(1.1E-01,9.4E-01)
Migraine	−0.006(−0.029,−0.002)	0.013	6.90E-01	−0.032,0.020	7.4E-01(2.3E-01,9.2E-01)
MS	−0.003(−0.034,0.022)	0.02	8.80E-01	−0.042,0.035	5.1E-01(8.7E-03,8.5E-01)
SCZ 1	−0.038(−0.052,−0.026)	0.013	7.90E-03	−0.063,−0.013	1.7E-01(1.8E-02,6.1E-01)
SCZ 2	−0.067(−0.076,−0.056)	0.01	**7.30E-09**	−0.088,−0.047	2.4E-02(5.7E-06,3.7E-01)
BMI	−0.050(−0.061,−0.037)	0.016	4.50E-03	−0.079,−0.023	4.2E-01(6.2E-02,9.2E-01)
Height	−0.074(−0.098,−0.058)	0.015	**8.90E-06**	−0.104,−0.045	1.1E-01(3.9E-04,6.9E-01)
WHR	−0.026(−0.039,−0.019)	0.011	2.50E-02	−0.047,−0.006	2.3E-01(7.1E-03,5.1E-01)
SBP	−0.015(−0.024,−0.003)	0.01	1.80E-01	−0.036,0.005	3.7E-01(9.3E-02,7.3E-01)
TC	−0.001(−0.019,0.023)	0.019	9.80E-01	−0.037,0.039	5.3E-01(3.1E-01,8.6E-01)
TG	−0.017(−0.024,−0.003)	0.015	3.30E-01	−0.048,0.014	4.3E-01(8.2E-03,8.3E-01)
CD	−0.025(−0.049,0.003)	0.019	2.50E-01	−0.062,0.014	5.3E-01(2.6E-01,8.6E-01)
CeD	−0.000(−0.024,0.018)	0.018	9.90E-01	−0.037,0.035	3.7E-01(1.2E-01,8.4E-01)
RA	−0.004(−0.020,0.013)	0.011	7.70E-01	−0.025,0.017	5.7E-01(2.2E-02,8.8E-01)
UC	−0.017(−0.027,0.015)	0.015	3.10E-01	−0.047,0.014	5.3E-01(1.7E-01,9.2E-01)

Phenotypes: psychiatric and other neurological diseases Alzheimer's disease (AD), attention deficit hyperactivity disorder (ADHD), bipolar disorder (BD), major depressive disorder (MDD), migraine, multiple sclerosis (MS), first and second edition of the schizophrenia (SCZ) GWAS by the Psychiatric Genomic Consortium (SCZ1 and SCZ2), anthropometric measures (body mass index (BMI), height, waist-hip ratio (WHR)), cardiovascular risk factors (systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG)), immune-mediated diseases (Crohn's disease (CD), celiac disease (CeD), rheumatoid arthritis (RA), ulcerative colitis (UC)). Squared z-scores logarithm versus Neanderthal selective sweep score (NSS) regression for various phenotypes controlling for other enrichment factors (genic annotation scores, genotypic variance, LD) and top 1% binomial proportion test (BPT) *p*-values.

SCZ is the only phenotype with a significant negative correlation between squared z-scores logarithms and NSS scores while controlling for other covariates. Also, in SCZ2 the top 1% SNPs include a nominally significant excess of SNPs with NSS score < 0 (Human Divergent) compared to any SNPs (BPT).