1 **Title:**

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3 **Analysis of differentially methylated regions in primates and non-primates**

4 **provides support for the evolutionary hypothesis of schizophrenia**

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33 **Abstract**

34

35 Introduction: The persistence of schizophrenia in human populations separated by
 36 geography and time led to the evolutionary hypothesis that proposes schizophrenia as
 37 a by-product of the higher cognitive abilities of modern humans. To explore this
 38 hypothesis, we used here an evolutionary epigenetics approach building on
 39 differentially methylated regions (DMRs) of the genome.

40 Methods: We implemented a polygenic enrichment testing pipeline using the
 41 summary statistics of genome-wide association studies (GWAS) of schizophrenia and
 42 12 other phenotypes. We investigated the enrichment of association of these traits
 43 across genomic regions with variable methylation between modern humans and great
 44 apes (orangutans, chimpanzees and gorillas; primate DMRs) and between modern
 45 humans and recently extinct hominids (Neanderthals and Denisovans; non-primate
 46 DMRs).

47 Results: Regions that are hypo-methylated in humans compared to great apes show
 48 enrichment of association with schizophrenia only if the major histocompatibility
 49 complex (MHC) region is included. With the MHC region removed from the analysis,
 50 only a modest enrichment for SNPs of low effect persists. The INRICH pipeline
 51 confirms this finding after rigorous permutation and bootstrapping procedures.

52

53 Conclusion: The analyses of regions with differential methylation changes in humans
 54 and great apes do not provide compelling evidence of enrichment of association with
 55 schizophrenia, in contrast to our previous findings on more recent methylation
 56 differences between modern humans, Neanderthals and Denisovans. Our results

57 further support the evolutionary hypothesis of schizophrenia and indicate that the
58 origin of some of the genetic susceptibility factors of schizophrenia may lie in recent
59 human evolution.

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62 **Key Words:** schizophrenia; evolutionary hypothesis; epigenetics; differentially
63 methylated regions; primates; Neanderthals.

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1. Introduction

Schizophrenia is a psychiatric disorder with a prevalence rate of 2.7-8.3/1,000 persons (Messias et al., 2007) and heritability estimated between 60-90% (Cardno et al., 1999; Lichtenstein et al., 2009; Skre et al., 1993; Sullivan et al., 2003). It occurs at quite similar rates across populations worldwide (Ayuso-Mateos, 2002; Brüne, 2004; WHO, 1973) and written records describing its symptoms exist dating back 5,000 years (Jeste et al., 1985). This consistent persistence of the disease despite reduced fecundity (Brüne, 2004; Nichols, 2009) and increased mortality is a paradox (Bassett et al., 1996; Brown, 1997; Larson and Nyman, 1973), since the reduced fecundity of patients afflicted with schizophrenia does not appear to eliminate the disease from the population (Power et al., 2013) Part of the reason may be due to afflicted individuals reproducing prior to the onset of the disease (Markow, 2012). Another contributing factor could be that schizophrenia risk variants may have provided an advantage to the kin of the affected by conferring superior creative and intellectual abilities upon them (Kyaga et al., 2011; Nichols, 2009). To explain the constant occurrence of the disease, TJ Crow (Crow, 1997, 1995) proposed the so-called evolutionary hypothesis of schizophrenia, which suggests that the disease is a consequence of human evolution: the higher cognitive abilities of modern-day humans, including language, may predispose to psychiatric illnesses such as schizophrenia (Crow, 2008, 2000, 1997).

In the post-genomic era (Lander et al., 2001; Venter et al., 2001), emerging lines of evidence are lending support to this hypothesis. Crespi et al. (Crespi et al., 2007) were amongst the first to show that genes with evidence of recent positive selection in

97 humans are also implicated more frequently in schizophrenia. More evidence has
 98 been provided by studies based on comparative genomics (Pollard et al., 2006;
 99 Srinivasan et al., 2015; Xu et al., 2015), a field in which genomes of progressively
 100 older species are compared to identify substitutions and mutations that help estimate
 101 divergence between the species. For instance, a group of regions defined by negative
 102 Neanderthal selective sweep (NSS) scores describe the selective evolution of genomic
 103 regions in modern-day humans over Neanderthals (Burbano et al., 2010; Green et al.,
 104 2010). These regions were shown by Srinivasan et al. (2015) to be enriched for
 105 schizophrenia risk markers, in line with the evolutionary hypothesis of schizophrenia.
 106 Other regions known as human accelerated regions (HARs) (Gittelman et al., 2015;
 107 Pollard et al., 2006; Xu et al., 2015), first described by Pollard et al. (2006), show
 108 accelerated evolution in humans compared to primates or mammals. HARs have also
 109 provided some evidence of enrichment of association with schizophrenia (Xu et al.,
 110 2015), but these findings may have been driven by a few genes since they were not
 111 replicated using a polygenic approach (Srinivasan et al., 2017, 2015) .

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113 While several studies have looked at the evolution of the genome (Bird et al., 2007;
 114 Bush and Lahn, 2008; Gittelman et al., 2015; Paaby and Rockman, 2014; Pollard et
 115 al., 2006), there are reports that the epigenome is evolving as well (Gokhman et al.,
 116 2014; Hernando-Herraez et al., 2015, 2013; Mendizabal et al., 2014; Molaro et al.,
 117 2011). This provides new insights into events leading to the speciation and divergence
 118 of modern humans. The epigenome refers to the layer of chemical modifications, such
 119 as methylation and histone modifications, to the genome that regulate gene expression
 120 (Bernstein et al., 2007; Kundaje et al., 2015; Rivera and Ren, 2013). For instance,
 121 Gokhman et al. (2014) compared the methylomes of humans with Neanderthals and

122 Denisovans. They reported that while 97% of the methylome was comparable
 123 between humans, Neanderthals and Denisovans, some regions showed differential
 124 methylation between the three hominids. Previously (Banerjee et al., 2017), we
 125 analysed the differentially methylated regions (DMRs) identified for Neanderthals,
 126 Denisovans and modern humans by Gokhman et al. (2014), and found evidence that
 127 the regions of the genome with human-specific DMRs harbour relatively more genetic
 128 variants associated with schizophrenia than the rest of the genome, i.e. the DMRs
 129 were enriched for SCZ markers both at the single-nucleotide polymorphism (SNP)
 130 level and at the gene level. These human-specific DMRs thus provide evidence of
 131 enrichment of methylation changes in regions harbouring genetic variants associated
 132 with schizophrenia, at least since the divergence from Neanderthals and Denisovans
 133 (Banerjee et al., 2017).

134

135 Here, we sought to determine if evolutionarily older methylation differences can
 136 provide a further timeframe for the origin of schizophrenia risk markers in the human
 137 lineage. We asked whether we can find epigenetic evidence that the origin of
 138 schizophrenia risk markers predates the origins of the Homo genus, i.e. before the
 139 divergence of chimpanzees and humans around 6-8 million years ago (MYA) (Glazko
 140 and Nei, 2003; Langergraber et al., 2012). We tested this hypothesis by analysing
 141 primate DMRs that trace an evolutionary history of at least 13 million years (Glazko
 142 and Nei, 2003; Hasegawa et al., 1985; Rannala and Yang, 2003). We used the same
 143 statistical analyses as described by Lee et al. (2012), Schork et al. (2013), and
 144 Srinivasan et al. (2015) to test for polygenic enrichment of a set of markers from
 145 genome-wide association studies (GWAS). We interrogated regions of the human
 146 genome which are hypo- or hyper-methylated in comparison to the corresponding

147 ones in chimpanzees, gorillas and orangutans for enrichment of genetic variants

148 associated with schizophrenia or other human traits.

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150 2. Materials and methods

151

152 2.1. GWAS data

153 Summary statistics for thirteen different phenotypes were obtained from their
 154 respective published GWAS studies: schizophrenia (SCZ) (Ripke et al., 2014), bipolar
 155 disorder (BPD) (Sklar et al., 2011), attention deficit hyperactivity disorder (ADHD)
 156 (Demontis et al., 2017), rheumatoid arthritis (RA) (Stahl et al., 2010), blood lipid
 157 markers (high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides
 158 (TG), total cholesterol (TC)) (Teslovich et al., 2010), blood pressure (systolic blood
 159 pressure (SBP), diastolic blood pressure (DBP)) (Ehret et al., 2011), body mass index
 160 (BMI) (Locke et al., 2015), height (Wood et al., 2014) and intelligence (Sniekers et
 161 al., 2017). For studies published with hg18 coordinates (BPD, SBP, DBP, HDL, LDL,
 162 TG, TC, RA), conversion to hg19 was performed using the command line version of
 163 the liftOver tool from the UCSC Genome Browser (Karolchik et al., 2014)
 164 (http://hgdownload.cse.ucsc.edu/downloads.html#utilities_downloads). For BMI and
 165 height SNPs, the genomic coordinates were obtained by mapping them to the
 166 assembly of 1,000 Genomes Project (1KGP) Phase 1 reference panel SNPs (Durbin et
 167 al., 2012).

168

169 2.2. Human hypo- and hyper-methylated regions from primate DMRs

170 These methylated regions were retrieved from the study by Hernando-Herraez et al.
 171 (2015), who identified them by comparing the methylation profile of DNA from
 172 peripheral blood samples of orangutans, chimpanzees and gorillas to that of humans.
 173 Since the DMRs are determined by comparing humans with other primates, we refer
 174 to this set collectively as primate DMRs. Both hypo- and hyper-methylated DMRs

from humans were analysed. As these DMRs are identified in the same tissues in all samples, they are considered to represent species-specific methylation differences, not tissue-specific methylation differences (Gokhman et al., 2014). Altogether, the human hypo- and hyper-methylated DMRs can be used to represent an evolutionary course of history spanning from at least 13 MYA (Glazko and Nei, 2003; Langergraber et al., 2012), when orangutans diverged from the common ancestors, to 6 MYA, when the chimpanzees and humans diverged from each other (Glazko and Nei, 2003; Langergraber et al., 2012). Since our interest was in human-specific enrichment, we focused the analyses on human hypo- and hyper-methylated DMRs.

2.3. Differentially methylated regions (DMRs) from Neanderthals, Denisovans and modern humans

As previously described (Gokhman et al., 2014), these methylated regions have been identified by comparing the methylomes of osteoblasts from modern-day humans with those from Neanderthals and Denisovans. We refer to them in this paper as non-primate DMRs. Gokhman et al. (2014) devised a strategy utilizing information in the form of cytosine (C) to thymine (T) ratios to decipher the ancient methylomes of Neanderthals and Denisovans. Subsequently, they compared the methylomes of Neanderthals, Denisovans and modern humans and inferred the species in which the methylation variation likely took place; this information was used to classify the DMRs as Neanderthal-specific, Denisovan-specific and human-specific. These DMRs represent species-specific methylation (Gokhman et al., 2014).

2.4. Neanderthal selective sweep (NSS) data

199 We obtained NSS marker data from Srinivasan et al. (2015). Negative scores for NSS
200 markers indicate positive selection in humans. Markers with such scores were used in
201 the downstream analyses.

202

203 *2.5. SNP assignment with LDsnpr*

204 The previously published R-based software package LDsnpr (Christoforou et al.,
205 2012) was utilized for assigning SNPs to the respective DMRs using LD (linkage
206 disequilibrium)-based binning at $r^2 \geq 0.8$ in R (R Core Team, 2017). LD-based binning
207 makes it possible to determine whether SNPs from a specific GWAS are in LD with
208 the DMR of interest. Using LD allows the capture of a greater number of relevant
209 SNPs in comparison to an approach where only physically overlapping SNPs are
210 considered. The LD file utilized was in HDF5 format and was constructed from the
211 European reference population of 1KGP and can be publicly downloaded at:
212 <http://services.cbu.uib.no/software/ldsnpr/Download>.

213

214 *2.6. Enrichment analyses based on stratified quantile-quantile (QQ) plots*

215 QQ plots are an essential method used in GWASs to depict the presence of true
216 signals. They help to visually observe the spread of data and deviations from the null
217 distribution. Under the null hypothesis, no difference is expected between the
218 observed and expected distributions of data. As such, a line of no difference or null
219 line is obtained that is equidistant from both X and Y axes. However, if the null
220 hypothesis were to be false, there would be a deviation of the observed data
221 distribution from the expected data distribution. As described in depth by Schork et al.
222 (2013), a leftward deflection of the observed distribution from the null line represents
223 enrichment – the greater the leftward deflection, the stronger the enrichment of true

224 signals. This method has been used recently not only to show how specific genomic
225 annotation affects the distribution of disease SNPs with true signals (Schork et al.,
226 2013), but also to demonstrate that regions of recent evolution are enriched for
227 schizophrenia markers (Banerjee et al., 2017; Srinivasan et al., 2015). We took the
228 SNPs that are in LD with the DMR regions and plotted their p -value distributions
229 from various GWASs. The observed p -value distributions were then determined to be
230 enriched or not using conditional Q-Q plots as described by Schork et al. (2013).
231 Genomic inflation was corrected by λ_{GC} .

232

233 *2.7. INRICH-based enrichment analysis*

234 The stratified QQ plots provide a visual depiction of data distributions and enrichment
235 of true signals within a stratum of data, but they do not quantify this enrichment.
236 Therefore, we used the INterval EnRICHment (INRICH) analysis tool to statistically
237 quantify the enrichment observed. This pipeline performs permutation and
238 bootstrapping procedures to determine with statistical confidence whether LD-
239 implicated genomic intervals are enriched in specific gene sets (Lee et al., 2012). The
240 INRICH analysis takes into account several potential biases that can otherwise lead to
241 false positives, such as variable gene size, SNP density within genes, LD between and
242 within genes, and overlapping genes in the gene sets. We used the same procedure
243 reported previously (Banerjee et al., 2017; Xu et al., 2015) with SNPs in the extended
244 MHC region and SNPs with MAF <0.05 excluded from the analysis. Additional
245 details can be found in the Supplementary Information.

246

247 **3. Results**

248

249 3.1. Co-localisation of human hypo-methylated regions and genetic variants

250 *associated with schizophrenia in the MHC.*

251 We ascertained whether there is any enrichment of human hypo- and hyper-
252 methylated regions in schizophrenia-associated SNPs. Using previously published
253 methodology (Christoforou et al., 2012), we mapped schizophrenia markers to human
254 hypo-methylated regions (hypo-DMRs) and hyper-methylated regions (hyper-DMRs).
255 Out of a total of ~9.4 million SCZ markers obtained from the GWAS, 10,165 markers
256 tagged hypo-DMRs and 4,503 tagged hyper-DMRs.

257
258 Figure 1A shows the conditional QQ plots for schizophrenia markers (all markers, the
259 hypo-DMR set and the hyper-DMR set) including those in the MHC region. For
260 hypo-DMR markers (Supplementary Dataset 1), we observed a significant enrichment
261 as depicted by the leftward deviation. No enrichment was observed for hyper-DMR
262 markers. Since the MHC region is a region of extended linkage disequilibrium, which
263 can bias the enrichment estimates, and since it is the main region of association with
264 schizophrenia, we also tested the enrichment with the MHC region removed (Figure
265 1B). Under these conditions there is a trend for enrichment of hypo-DMR markers at
266 higher p -value thresholds, but this enrichment is substantially less than when the
267 MHC is included (Figure 1A).

268

269 3.2. Enrichment of markers is not seen for other human traits

270 Next, we tested if the human hypo- and hyper-methylated regions are enriched for
271 other human traits and phenotypes. We tested a total of thirteen different phenotypes,
272 full details of which can be found in section 2.1. Each GWAS had been performed
273 with a different number of genotyped SNPs, and this difference could potentially bias

our results. To circumvent this, we created a list of ~2.4 million common SNPs that were genotyped across all the phenotypes investigated in the present study. Only SNPs on this list were used for enrichment analysis.

As can be seen in Fig. 2, no enrichment was observed in any of the traits, with the possible exception of height at higher p -value threshold markers. The common list of markers did not contain the MHC region and as such no enrichment is observed for schizophrenia either.

3.3. Evidence of enrichment for hypo-methylated regions with SNPs at high p -values

The enrichment plots allowed us to visually ascertain enrichment in the datasets. However, they did not give any indication of the statistical robustness of the enrichment. To ascertain if the human hypo- and hyper-methylated regions are statistically enriched for schizophrenia and height markers, we implemented the INRICH pipeline, which performs 10,000 permutations and 5,000 bootstrapping calculations, to determine with statistical confidence the enrichment observed (Lee et al., 2012).

The INRICH analysis confirmed a significant ($p < 0.05$) enrichment of association for human hypo-DMRs, but not hyper-DMRs, with schizophrenia at SNPs of higher p -value thresholds ($p < 10e-3$ to $p < 10e-4$) (Fig. 3). This enrichment was at the gene level, and complemented the enrichment observed at the SNP level for higher p -value thresholds (Fig. 1B). Importantly, this enrichment persisted upon testing a pruned schizophrenia dataset (Supplementary Fig. 1). The enrichment was however not significant at the genome-wide threshold ($p < 5 \times 10e-8$) and was much weaker than that

observed for non-primate DMRs (Fig. 3). We also observed a similar trend for height where there was enrichment at SNPs of higher but not lower p -value thresholds. This enrichment was similarly less pronounced than for non-primate DMRs (Supplementary Fig. 2).

4. Discussion

In our study, we investigated if regions of the human genome whose methylation has evolved since the divergence of modern humans from great apes are enriched for markers of schizophrenia. We found evidence that there is enrichment for hypo-methylated DMRs driven by the MHC locus, a known risk region that harbours the most significant schizophrenia GWAS markers (Ripke et al., 2014). When the MHC region was excluded from the analysis, there remained a trend towards enrichment of hypo-DMRs driven by SNPs of higher p -value thresholds. This finding was complemented by the INRICH analyses that indicated significant enrichment among SNPs of higher p -value thresholds. When analysing a global SNP list common to GWAS of several traits, we failed to find evidence of enrichment of any trait with the possible exception of height at higher SNP p -value thresholds. We tested this further with the INRICH pipeline, which revealed gene-level enrichment of LD intervals for height markers below the genome-wide threshold ($p < 5 \times 10^{-8}$). Compared to our previous study, in which we demonstrated enrichment of association with schizophrenia for non-primate DMRs that were derived by comparing human, Neanderthal and Denisovan methylomes (Banerjee et al., 2017), the primate DMRs tested here show far less enrichment. The primate and non-primate DMRs have very

324 little overlap, which suggests that the methylation changes that took place since the
325 divergence of modern humans from Neanderthals and Denisovans occurred in
326 different regions of the genome compared to those that took place since divergence
327 from great apes.
328

329 The central role of the MHC region in the enrichment of human hypo-methylated
330 regions poses interesting questions. The MHC region is known for its complex LD
331 architecture, which renders the interpretation of genetic signals very challenging.
332 Other groups have previously reported that the MHC region is one of the fastest
333 evolving regions of the human genome (Meyer et al., 2017) and have implicated it in
334 mate preference (Bernatchez and Landry, 2003; Kromer et al., 2016; Potts and
335 Wakeland, 1990; Roberts et al., 2008; Winternitz et al., 2017), odour perception
336 (Roberts et al., 2008; Santos et al., 2005) and immune response (Benacerraf, 1981;
337 Horton et al., 2004). Recently it was shown that a large proportion of the association
338 of the region with schizophrenia can be explained by complement C4 haplotypes that
339 include C4 copy number variation (Sekar et al., 2016). Nevertheless, there remains a
340 part of the association in this region that is unexplained (Gejman et al., 2011) and will
341 need further investigation. It is interesting to consider the possibility that the MHC
342 region and the immune system in general play a central role in evolution at the
343 epigenomic as well as at the genomic level (Meyer et al., 2017; Potts and Wakeland,
344 1990; Sommer, 2005; Traherne, 2008). The mechanisms by which hypo-methylation
345 could influence the aforementioned processes are open to speculation since the MHC
346 region has more than 200 genes in close physical proximity and LD with one another
347 (Beck et al., 1999). This makes it hard to interpret the exact biological consequences
348 of our findings.

349

350 Interestingly, the gene-level analysis via INRICH seems to suggest enrichment of
351 SNPs of higher p -value thresholds in primate DMRs for both schizophrenia and
352 height. This enrichment is far lower than what we found for non-primate DMRs for
353 both schizophrenia and height (Banerjee et al., 2017) and which persisted for
354 schizophrenia even with pruned datasets.

355

356 The very small overlap between primate and non-primate DMRs might suggest that
357 the divergence from Neanderthals and Denisovans brought about more significant
358 methylation changes in regions implicated in the aetiology of schizophrenia and
359 height than the divergence from great apes. In other words, our results might suggest
360 that the evolutionary factors that regulate methylation variation acted on different
361 segments of the genome at different time points. So while the methylation variation
362 since the divergence from Neanderthals and Denisovans may mark a genome-wide
363 increase of schizophrenia susceptibility (Banerjee et al., 2017), the methylation
364 variation from the time period between 13 and 6 MYA appears not to have
365 significantly increased the risk for schizophrenia (except possibly for some markers in
366 the MHC region),

367

368 Our results are also in line with the findings of Srinivasan et al. (2017), who failed to
369 find evidence of enrichment of schizophrenia using genomic markers of evolution
370 dating back to 200 MYA. The same authors also reported enrichment of association
371 for regions of more recent evolution in modern humans (Srinivasan et al., 2015).
372 Interestingly, one of the evolutionary proxies used by Srinivasan and colleagues
373 (2017), namely HARs, also showed enrichment for height, similar to our recent study

374 (Banerjee et al., 2017). This suggests that regions controlling both genomic and
 375 epigenomic variation in height may also be driven by recent evolution. Finally, our
 376 results agree well with the observation by Srinivasan et al. (2017) of some
 377 involvement of the MHC in an early evolutionary context.
 378
 379 Although our results are in line with several findings in the field, the current methods
 380 have some limitations. Highly polygenic traits such as schizophrenia have a large
 381 number of genetic loci contributing to the aetiology of a disease (Bulik-Sullivan et al.,
 382 2015; Schork et al., 2016). The ability to detect these large numbers of genetic loci is
 383 dependent on the sample size and adequate statistical power (Schork et al., 2016).
 384 Consequently, the polygenic enrichment methods may be limited by the statistical
 385 power of the respective GWAS and trait polygenicity. Furthermore, in the INRICH
 386 analysis that uses LD-clumping of SNPs at $p < 10e-3$ to $p < 10e-8$, higher p -value
 387 thresholds (e.g. $p < 10e-3$) still include SNPs of lower p -values, even though they
 388 become progressively smaller minorities. Thus, although higher p -values increase the
 389 number of LD-clumps tested, we do not expect this to increase the Type I error rate
 390 (Lee et al., 2012).
 391
 392 In conclusion, our results suggest that methylation markers tracing an evolutionary
 393 period dating back to 13 MYA (primate DMRs) are not enriched for schizophrenia
 394 markers, unlike methylation markers from a recent timeframe (non-primate DMRs)
 395 (Banerjee et al., 2017). Taken in consideration with previous studies of genomic
 396 markers of evolution dating back 200 MYA (Srinivasan et al., 2017), our results
 397 support the hypothesis that the origins of schizophrenia lie in more recent

398 evolutionary events, possibly after the divergence of modern-day humans from
399 Neanderthals and Denisovans.

400

401

402 **Appendix A. Supplementary data**

403 Supplementary Information: Additional Methods, Figures and Tables

404 Supplementary Dataset 1: Annotation of human hypo-methylated regions with
405 markers of schizophrenia

406

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768 **Figure legends**

769 **Fig. 1: Enrichment plots of hypo-DMR and hyper-DMR SNPs in schizophrenia**

770 Quantile-quantile (QQ) plots of GWAS SNPs for Schizophrenia (SCZ) with the
771 extended MHC region (chr6: 25-35Mb) unmasked (A) and masked (B). Expected -
772 $\log_{10} p$ -values under the null hypothesis are shown on the X-axis. Observed $-\log_{10} p$ -
773 values are on the Y-axis. The values for all GWAS SNPs are plotted in dark green
774 while the values for SNPs in linkage disequilibrium (LD) with hypo-methylated
775 DMRs are plotted in blue and SNPs in LD with hyper-methylated DMRs are plotted
776 in pink. A leftward deflection of the plotted p -values from the line for all GWAS
777 SNPs indicates enrichment of true signals – the greater the leftward deflection, the
778 stronger the enrichment. Genomic correction was performed on all SNPs with global
779 lambda.

780

781 **Fig. 2: Enrichment plots of hypo-DMR and hyper-DMR SNPs across**
782 **multiple traits**

783 Thirteen different GWASs were analysed using a common set of ~2.4 million
784 SNPs. The p -values for the common set of GWAS SNPs are plotted in dark
785 green; p -values for SNPs that tag hypo-methylated DMRs are plotted in blue;
786 and p -values for SNPs that tag hyper-methylated DMRs are plotted in pink.
787 ADHD, attention deficit hyperactivity disorder; BMI, body mass index; BPD,
788 bipolar disorder; DBP, diastolic blood pressure; HDL, high density lipoprotein;
789 LDL, low density lipoprotein; RA, rheumatoid arthritis; SBP, systolic blood
790 pressure; SCZ, schizophrenia; TC, total cholesterol; TG, triglycerides. The
791 MHC region was absent from the common set of SNPs.

792

Fig. 3: INRICH test for enrichment of association of DMR gene sets and NSS genes with SCZ, MHC masked

A visual heatmap depicting *p*-values from bootstrapping with 5,000 iterations. The various evolutionary annotations compared are as follows. HypoDMR – human hypo-methylated DMRs; HyperDMR – human hyper-methylated DMRs. HypoDMR and HyperDMR were taken from the study by Hernando-Herraez et al. (2013). dmrH – human-specific DMRs (Gokhman et al, 2014), which are referred to as non-primate DMRs in this manuscript. NSS - Neanderthal selective sweep. Datasets marked with * have been previously reported by Banerjee et al. (2017) and are presented here for comparison only.

Figure 1

Figure 2

Figure 3