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1 **Gene expression imputation across multiple brain regions reveals schizophrenia risk**
2 **throughout development.**
3
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39 **Abstract**

40 Transcriptomic imputation approaches offer an opportunity to test associations between disease
41 and gene expression in otherwise inaccessible tissues, such as brain, by combining eQTL
42 reference panels with large-scale genotype data. These genic associations could elucidate signals
43 in complex GWAS loci and may disentangle the role of different tissues in disease development.
44 Here, we use the largest eQTL reference panel for the dorso-lateral pre-frontal cortex (DLPFC),
45 collected by the CommonMind Consortium, to create a set of gene expression predictors and
46 demonstrate their utility. We applied these predictors to 40,299 schizophrenia cases and 65,264
47 matched controls, constituting the largest transcriptomic imputation study of schizophrenia to
48 date. We also computed predicted gene expression levels for 12 additional brain regions, using
49 publicly available predictor models from GTEx. We identified 413 genic associations across 13
50 brain regions. Stepwise conditioning across the genes and tissues identified 71 associated genes
51 (67 outside the MHC), with the majority of associations found in the DLPFC, and of which
52 14/67 genes did not fall within previously genome-wide significant loci. We identified 36
53 significantly enriched pathways, including hexosaminidase-A deficiency, and multiple pathways
54 associated with porphyric disorders. We investigated developmental expression patterns for all
55 67 non-MHC associated genes using BRAINSPAN, and identified groups of genes expressed
56 specifically pre-natally or post-natally.

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58 **Introduction**

59 Genome-wide association studies (GWAS) have yielded large lists of disease-associated loci.
60 Despite this, progress in identifying the causal variants driving these associations, particularly for
61 complex psychiatric disorders such as schizophrenia, has lagged much further behind.
62 Interpreting associated variants and loci is therefore vital to understanding how genetic variation
63 contributes to disease pathology. Expression Quantitative Trait Loci (eQTLs), which are
64 responsible for a substantial proportion of gene expression variance, have been posited as a
65 potential link between associated loci and disease susceptibility[1–5], and indeed have yielded
66 results for a host of complex traits[6–9]. Consequently, numerous methods to identify and interpret
67 co-localisation of eQTLs and GWAS loci have been developed[10–13]. However, these methods
68 require simplifying assumptions about genetic architecture (i.e., one causal variant per GWAS
69 locus) and/or linkage disequilibrium, may be underpowered or overly conservative, especially in
70 the presence of allelic heterogeneity, and have not yet yielded substantial insights into existing or
71 novel loci.

72

73 Biologically relevant information can be extracted by transcriptomic investigations, as recently
74 described by the CommonMind Consortium[14] (CMC), thanks to detailed RNA-sequencing in a
75 large cohort of genotyped individuals with schizophrenia and bipolar disorder[14]. These analyses
76 however are underpowered to detect with statistical confidence differential expression of genes
77 mapping at schizophrenia (SCZ) risk loci, due to the small effects predicted by GWAS combined
78 with the difficulty of obtaining adequate sample sizes of neurological tissues[14]. Still, such
79 methods do not necessarily identify all risk variation in GWAS loci. Transcriptomic imputation
80 is an alternative approach that leverages large eQTL reference panels to bridge the gap between
81 large-scale genotyping studies and biologically useful transcriptome studies[15,16]. This approach
82 seeks to identify and codify the relationships between genotype and gene expression in matched
83 panels of individuals, then impute the genetic component of the transcriptome into large-scale
84 genotype-only datasets, such as case-control GWAS cohorts, which enables investigation of
85 disease-associated gene expression changes. This will allow us to study genes with modest effect
86 sizes, likely representing a large proportion of genomic risk for psychiatric disorders[14,17].

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88 The access to the large collection of dorso-lateral pre-frontal cortex (DLPFC) gene expression
89 data collected by the CommonMind Consortium[14] affords us a unique opportunity to study and
90 codify relationships between genotype and gene expression. Here, we present a novel set of gene
91 expression predictor models, built using CommonMind Consortium DLPFC data[14]. We compare
92 different regression approaches to building these models (including elastic net[15], Bayesian sparse
93 linear mixed models and ridge regression[16], and using max eQTLs), and benchmark performance
94 of these predictors against existing GTEx prediction models. We applied our CMC DLPFC
95 predictors and 12 GTEx-derived neurological prediction models to predict gene expression in
96 schizophrenia GWAS data, obtained through collaboration with the Psychiatric Genomics
97 Consortium (PGC) schizophrenia working group, the "CLOZUK2" cohort, and the iPSYCH-
98 GEMS schizophrenia working group. We identified 413 genome-wide significant genic
99 associations with schizophrenia in our PGC+CLOZUK2 sample, constituting 67 independent
100 associations outside the MHC region. We demonstrate the relevance of these associations to
101 schizophrenia aetiopathology using gene set enrichment analysis, and by examining the effects
102 of manipulation of these genes in mouse models. Finally, we investigated spatio-temporal
103 expression of these genes using a developmental transcriptome dataset, and identified distinct
104 spatio-temporal patterns of expression across our associated genes.
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113 **Results**

114 **Prediction Models based on CommonMind Consortium DLPFC expression**

115 Using matched genotype and gene expression data from the CommonMind Consortium Project,
116 we developed DLPFC genetically regulated gene expression (GREX) prediction models. We
117 systematically compared four approaches to building predictors[15,16] within a cross-validation
118 framework. Elastic net regression had a higher distribution of cross-validation R^2 (R_{CV}^2) and
119 higher mean R_{CV}^2 values (Supplementary Figures 1, 2A) than all other methods. We therefore
120 used elastic net regression to build our prediction models. We compared prediction models
121 created using elastic net regression on SVA-corrected and uncorrected data[14]. The distribution of
122 R_{cv}^2 values for the SVA-based models was significantly higher than for the un-corrected data[14,18]
123 (ks-test; p<2.2e-16; Supplementary figure 1B-C). In total, 10,929 genes were predicted with
124 elastic net cross-validation $R_{cv}^2 > 0.01$ in the SVA-corrected data and were included in the final
125 predictor database (mean $R_{cv}^2 = 0.076$).

126

127 To test the predictive accuracy of the CMC-derived DLPFC models, and to benchmark this
128 against existing GTEx-derived prediction models, genetically-regulated gene expression (GREX)
129 was calculated in an independent DLPFC RNA-sequencing dataset (the Religious Orders Study
130 Memory and Ageing Project, ROSMAP[19]). We compared predicted GREX to measured
131 ROSMAP gene expression for each gene (Replication $R^{2,}$ or R_R^2) for the CMC-derived DLPFC
132 models and twelve GTEx-derived brain tissue models[15,20,21] (Figure 1, Supplementary Figure
133 2B). CMC-derived DLPFC models had higher average R_R^2 values (Mean $R_R^2 = 0.056$), more
134 genes with $R_R^2 > 0.01$, and significantly higher overall distributions of R_R^2 values than any of the
135 twelve GTEx models (ks-test, $p<2.2\times10^{-16}$ across all analyses; Figure 1). Median R_R^2 values were
136 significantly correlated with sample size of the original tissue set (rho=0.92, $p=7.2\times10^{-6}$), the
137 number of genes in the prediction model (rho=0.9, $p=2.6\times10^{-5}$), and the number of significant
138 'eGenes' in each tissue type (rho=0.95, $p=5.^{5x10-7}$; Figure 1C). Notably, these correlations persist
139 after removing obvious outliers (Figure 1C).

140

141 To estimate trans-ancestral prediction accuracy, genetically regulated gene expression was
142 calculated for 162 African-American individuals and 280 European individuals from the NIMH
143 Human Brain Collection Core (HBCC) dataset (supplementary figure 2B). R_R^2 values were

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144 higher on average in Europeans than African-Americans (average $R_{R_EUR}^2$ = 0.048, $R_{R_AA}^2$ =
145 0.040), but were significantly correlated between African-Americans and Europeans (rho=0.78,
146 p<2.2 x10^{-16}, Pearson test; supplementary figure 3).
147
148 **Application of Transcriptomic Imputation to Schizophrenia**
149 We used CMC DLPFC and the 12 GTEx–derived brain tissue prediction models to impute
150 genetically regulated expression levels (GREX) of 19,661 unique genes in cases and controls
151 from the PGC-SCZ GWAS study[22]. Predicted expression levels were tested for association with
152 schizophrenia. Additionally, we applied CMC and GTEx-derived prediction models to summary
153 statistics from 11 PGC cohorts (for which raw genotypes were unavailable) and the CLOZUK2
154 cohort. Meta-analysis was carried out across all PGC-SCZ and CLOZUK2 cohorts using an
155 odds-ratio based approach in METAL. Our final analysis included 40,299 cases and 65,264
156 controls (Figure 2A).
157
158 We identified 413 genome-wide significant associations, representing 256 genes in 13 tissues
159 (Figure 3A). The largest number of associations were detected in the CMC DLPFC GREX data
160 (Figure 3C; 49 genes outside the MHC, 69 genes overall). We sought replication of our CMC
161 DLPFC SCZ-associations in an independent dataset of 4,133 cases and 24,788 controls in
162 collaboration with the iPSYCH-GEMS SCZ working group (Figure 2B). We found significant
163 correlation of effect sizes (p=1.784 x10^{-04}; rho=0.036) and –log10 p-values (p=1.073 x10^{-05};
164 rho=0.043) between our discovery (PGC+CLOZUK2) and replication (iPSYCH-GEMS)
165 samples. Non-MHC Genes reaching genome-wide significance in our discovery sample (49
166 genes) were significantly more likely to reach nominal significance in the replication sample, and
167 had significantly more consistent directions of effect than might be expected by chance
168 (binomial test, p=2.42 x10^{-05}, p=0.044). (Suppl. info).
169
170 To identify the top independent associations within genomic regions, which include multiple
171 associations for a single gene across tissues, or multiple nearby genes, we partitioned genic
172 associations into 58 groups defined based on genomic proximity and applied stepwise forward
173 conditional analysis within each group (Supplementary Table 1). In total, 67 genes remained
174 genome-wide significant after conditioning (Table 1; Figure 3A-B). The largest signal was

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175 identified in the CMC DLPFC predicted expression data (24 genes; Figure 3C), followed by the
176 Putamen (7 genes). 19/67 genes did not lie within 1Mb of a previously genome-wide significant
177 GWAS locus[22] (shown in bold, Table 1); of these, 5/19 genes were within 1Mb of a locus which
178 approached genome-wide significance ($p<5x10^{-07}$). The remaining 14 genes all fall within
179 nominally significant PGC-SCZ GWAS loci ($p<8x10^{-04}$), but did not reach genome-wide
180 significance.
181

182 **Implicated genes highlight SCZ-associated molecular pathways and gene set analyses**

183 We tested for overlap between our non-MHC SCZ-associated genes and 8,657 genesets
184 comprised of 1) hypothesis-driven pathways and 2) general molecular database pathways. We
185 corrected for multiple testing using the Benjamin-Hochberg false discovery rate (FDR)
186 correction[23].
187

188 We identified three significantly associated pathways in our hypothesis-driven analysis (Table
189 2). Targets of the fragile-X mental retardation protein formed the most enriched pathway
190 (FMRP; $p=1.96x10^{-8}$). Loss of FMRP inhibits synaptic function, is comorbid with autism
191 spectrum disorder, and causes intellectual disability, as well as psychiatric symptoms including
192 anxiety, hyperactivity and social deficits[24]. Enrichment of this large group of genes has been
193 observed frequently, in the original CommonMind analysis[14], by colleagues investigating the
194 same PGC and CLOZUK2 samples[26] as well as by investigators studying autism[24,27]. There was
195 a significant enrichment among our SCZ associated genes and genes that have been shown to be
196 intolerant to loss-of-function mutations[28] ($p=5.86x10^{-5}$) as well as with CNVs associated with
197 bipolar disorder[29] ($p=7.92x10^{-8}$), in line with a recent variant-based study of the same
198 individuals[26].
199

200 Next, we performed an agnostic search for overlap between our schizophrenia-associated genes
201 and ~ 8,500 molecular pathways collated from large, publicly available databases. 33 pathways
202 were significantly enriched after FDR correction (Table 2, Suppl. Table 2), including a number
203 of pathways with some prior literature in psychiatric disease. We identified an enrichment with
204 porphyrin metabolism ($p=1.03x10^{-4}$). Deficiencies in porphyrin metabolism lead to “Porphyria”,
205 an adult-onset metabolic disorder with a host of associated psychiatric symptoms, in particular

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206 episodes of violence and psychosis[30–35]. Five pathways potentially related to porphyrin
207 metabolism, regarding abnormal iron level in the spleen, liver and kidney are also significantly
208 enriched, including 2/5 of the most highly enriched pathways ($p<2.0 \times 10^{-04}$). The PANTHER
209 and REACTOME pathways for Heme biosynthesis and the GO pathway for protoporphyrinogen
210 IX metabolic process, which are implicated in the development of porphyric disorders, are also
211 highly enriched ($p=2.2 \times 10^{-04}$, 2.6×10^{-04}, 4.1×10^{-04}), although do not pass FDR-correction.
212
213 Hexosaminidase activity was enriched ($p=3.47 \times 10^{-05}$) in our results; this enrichment is not
214 driven by a single highly-associated gene; rather, every single gene in the HEX-A pathway is
215 nominally significant in the SCZ association analysis (Supplementary Table 2). Deficiency of
216 hexosaminidase A (HEX-A) results in serious neurological and mental problems, most
217 commonly presenting in infants as "Tay-Sachs" disease[36]. Adult-onset HEX-A deficiency
218 presents with neurological and psychiatric symptoms, notably including onset of psychosis and
219 schizophrenia[37]. Five pathways corresponding to Ras- and Rab- signaling, protein regulation and
220 GTPase activity were enriched ($p<6 \times 10^{-05}$). These pathways have a crucial role in neuron cell
221 differentiation[38] and migration[39], and have been implicated in the development of schizophrenia
222 and autism[40–43]. We also find significant enrichment with protein phosphatase type 2A regulator
223 activity ($p=5.24 \times 10^{-05}$), which was associated with MDD and across MDD, BPD and SCZ in the
224 same large integrative analysis[44], and has been implicated in antidepressant response and
225 serotonergic neurotransmission[45].
226

227 **Predicted gene expression changes are consistent with functional validation studies**

228 To test the functional impact of our SCZ-associated predicted gene expression changes (GREX),
229 we performed two in-silico analyses. First, we compared directions of effect in our meta-analysis
230 to those in the CMC analysis of differentially expressed genes between SCZ cases and controls.
231 This analysis highlighted six loci where expression levels of a single gene putatively affected
232 schizophrenia risk. All six of these genes are nominally significant in our DLPFC analysis, and
233 two (*CLCN3* and *FURIN*) reach genome-wide significance. In the conditional analysis across all
234 brain regions, one additional gene (*SNX19*) reaches genome-wide significance. The direction of
235 effect for all six genes matches the direction of gene expression changes observed in the original
236 CMC paper, indicating that gene expression estimated in the imputed transcriptome reflects

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237 measured expression levels in brains of individuals with Schizophrenia. Further, this observation
238 is consistent with a model where the differential expression signature observed in CMC is caused
239 by genetics rather than environment.
240
241 The original CMC analysis identified 21 eSNP genes using SHERLOCK[14,46], of which 17 were
242 present in our CMC DLPFC analysis. 14/17 genes reached nominal significance (significantly
243 more than expected by chance, $p=3.6\times10^{-16}$), and 11 reached genome-wide significance
244 (binomial p-value 6.04×10^{-55}). Additionally, 31 regions contained genes ranked highly by
245 Sherlock in the original CMC analysis (supplementary data file 2 in Fromer, M. *et al.* Gene
246 expression elucidates functional impact of polygenic risk for schizophrenia. *Nat. Neurosci.* 19,
247 1442–1453 (2016)[14]). Of these, 14 regions lay near one of our CMC DLPFC associated genes,
248 and 13/14 regions had common genes between SHERLOCK and PrediXcan analyses. Five loci
249 included multiple SHERLOCK genes; in every instance we are able to specifically identify one
250 or two associated genes from the longer SHERLOCK list.
251
252 To understand the impact of altered expression of our 67 SCZ-associated genes, we performed
253 an in-silico analysis of mouse mutants, by collating large, publicly available mouse databases[47–
254 51]. We identified mutant mouse lines lacking expression of 37/67 of our SCZ-associated genes,
255 and obtained 5,333 phenotypic data points relating to these lines, including 1,170 related to
256 behavioral, neurological or craniofacial phenotypes. 25/37 genes were associated with at least
257 one behavioral, neurological or related phenotype (Supplementary table 3). We repeated this
258 analysis for genes identified in 366 GWAS, including any GWAS for which at least ten mutant
259 mouse lines exist (105 GWAS). SCZ-associated genes were more likely to be associated with
260 behavior, brain development and nervous system phenotypes than genes in these GWAS sets
261 (p=0.057).
262
263 **Spatiotemporal expression of SCZ-associated genes indicated distinct patterns of risk**
264 **throughout development**
265 We assessed expression of our SCZ-associated genes throughout development using
266 BRAINSPAN[52]. Data were partitioned into eight developmental stages (four pre-natal, four post-
267 natal), and four brain regions[29,52] (Figure 4A). We noted that SCZ-associated genes were

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268 significantly co-expressed, in both pre-natal and post-natal development and in all four brain
269 regions, based on local connectedness[53] (Figure 4B), global connectedness[53] (i.e., average path
270 length between genes, supplementary Figure 6), and network density (i.e., number of edges,
271 supplementary Figure 7). Examining pairwise gene expression correlation (suppl. Fig 8) and
272 gene co-expression networks (suppl. Fig 9) for each spatiotemporal point indicated that the same
273 genes do not drive this co-expression pattern throughout development; rather, it appears that
274 separate groups of genes drive early pre-natal, late pre-natal and post-natal clustering.
275
276 To visualize this, we calculated Z scores of gene expression for each SCZ-associated gene,
277 across all 32 time-points (Figure 5). Genes clustered into four groups (supplementary fig 10),
278 with distinct spatio-temporal expression signatures. The largest cluster (Cluster A, Figure 5A; 29
279 genes) spanned early to late-mid pre-natal development (4-24 weeks post conception), either
280 across the whole brain (22 genes) or in regions 1-3 only (7 genes). 12 genes were expressed in
281 late pre-natal development (Figure 5D; 25-38 pcw); 10 genes were expressed in regions 1-3,
282 post-natally and in the late pre-natal period (Figure 5C), and 15 genes were expressed throughout
283 development (Figure 5B), either specifically in region four (nine genes) or throughout the brain
284 (six genes). We used a stratified qq-plot approach[54] to examine whether SNPs in cis-regions of
285 genes in these four clusters are differentially enriched in psychiatric disorders. SNPs in cis-
286 regions of genes in the two pre-natal clusters are more highly enriched than SNPs in cis-regions
287 of genes in post-natal clusters, and compared to all SNPs, in childhood-onset disorders (ASD and
288 ADHD, supplementary figure 13), but not adult-onset disorders (BPD and MDD, data not
289 shown).
290
291 We noticed a relationship between patterns of gene expression and the likelihood of behavioral,
292 neurological or related phenotypes in our mutant mouse model database. Mutant mice lacking
293 genes expressed exclusively pre-natally in humans, or genes expressed pre- and post-natally,
294 were more likely to have any behavioral or neurological phenotypes than mutant mice lacking
295 expression of genes expressed primarily in the third trimester or post-natally ($p=1.7\times10^{-04}$)
296 (supplementary figure 11).
297
298

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299 **Discussion**

300 In this study, we present gene expression prediction models for the dorso-lateral pre-frontal
301 cortex (DLPFC), constructed using CommonMind Consortium genotype and gene expression
302 data. These prediction models may be applied to either raw data or summary statistics, in order to
303 yield gene expression information in large data sets, and across a range of tissues. This has the
304 significant advantage of allowing researchers to access transcriptome data for non-peripheral
305 tissues, at scales currently prohibited by the high cost of RNA sequencing, and circumventing
306 distortions in measures of gene expression stemming from errors of measurement or
307 environmental influences. Since disease status may alter gene expression but not the germline
308 profile, analyzing genetically regulated expression ensures that we identify only the causal
309 direction of effect between gene expression and disease[15]. Large, imputed transcriptomic datasets
310 represent the first opportunity to study the role of subtle gene expression changes (and therefore
311 modest effect sizes) in disease development.

312

313 There are some inherent limitations to this approach. The accuracy of transcriptomic imputation
314 (TI) is reliant on access to large eQTL reference panels, and it is therefore vital that efforts to
315 collect and analyze these samples continue. TI has exciting advantages for gene discovery as
316 well as downstream applications[15,55,56]; however, the relative merits of existing methodologies
317 are as yet under-explored. Our analysis suggests that, overall, sparser elastic net models better
318 capture gene expression regulation than BSLMM; at the same time, the improved performance of
319 elastic net over max-eQTL models suggests that a single eQTL model is over-simplified[2,15].
320 Fundamentally, transcriptomic imputation methods model only the genetically regulated portion
321 of gene expression, and so cannot capture or interpret variance of expression induced by
322 environment or lifestyle factors, which may be of particular importance in psychiatric disorders.
323 Given the right study design, analyzing genetic components of expression together with observed
324 expression could open doors to better study the role of gene expression in disease.

325

326 Sample size and tissue matching contribute to accuracy of TI results. Our CMC-derived DLPFC
327 prediction models had higher average validation R^2 values in external DLPFC data than GTEx-
328 derived brain tissue models. Notably, the model with the second highest percent of genes passing
329 the R^2 threshold is the Thyroid, which has the largest sample size among the GTEx brain

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330 prediction models. When looking at mean R^2 values, the second highest value comes from the
331 GTEx Frontal Cortex, despite the associated small sample size, implying at least some degree of
332 tissue specificity of eQTLs architecture.
333
334 We were able to compare TI accuracy in European and African-American individuals, and found
335 that our models were applicable to either ethnicity with only a small decrease in accuracy.
336 Common SNPs shared across ethnicities have important effects on gene expression, and as such
337 we expect GREX to have consistency across populations. There is a well-documented dearth of
338 exploration of genetic associations in non-European cohorts[57,58] We believe that these analyses
339 should be carried out in non-European cohorts.
340
341 We applied the CMC DLPFC prediction models, along with 12 GTEx-derived brain expression
342 prediction models, to schizophrenia cases and controls from the PGC2 and CLOZUK2
343 collections, constituting the largest transcriptomic analysis of schizophrenia to date. Predicted
344 gene expression levels were calculated for 19,661 unique genes across brain regions (Figure 1C)
345 and tested for association with SCZ case-control status. We identified 413 significant
346 associations, constituting 67 independent associations. We found significant replication of our
347 CMC DLPFC associations in a large independent replication cohort, in collaboration with the
348 iPSYCH-GEMS consortium. A recent TWAS study of 30 GWAS summary statistic traits[55]
349 identified 38 non-MHC genes associated at tissue-level significance with SCZ in CMC- and
350 GTEx-derived brain tissues (ie, matching those used in our study). Of these, 26 also reach
351 genome-wide significance in our study, although in many instances these genes are not identified
352 as the lead independent associated gene following our conditional analysis. Among our 67 SCZ-
353 associated genes, 19 were novel, i.e. did not fall within 1Mb of a previous GWAS locus
354 (including 5/7 of the novel brain genes identified in the recent TWAS analysis).
355
356 We used conditional analyses to identify independent associations within loci. These analyses
357 clarify the most strongly associated genes and tissues (Table 1), while we note that nearly
358 collinear gene-tissue pairs could also represent causal associations. The tissues highlighted
359 allowed us to tabulate apparently independent contributions to SCZ risk from different brain

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360 regions, even though their transcriptomes are highly correlated generally. We find DLPFC and
361 Cerebellum effects, as well as from Putamen, Caudate and Nucleus Accumbens Basal Ganglia.
362
363 We used these genic associations to search for enrichments with molecular pathways and gene
364 sets, and identified 36 significant enriched pathways. Among novel pathways, we identified a
365 significant association with HEX-A deficiency. Despite the well-studied and documented
366 symptomatic overlap between adult-onset HEX-A deficiency and schizophrenia, we believe that
367 this is the first demonstration of shared genetics between the disorders. Notably, this overlap is
368 not driven by a single highly-associated gene which is shared by both disorders; rather, every
369 single gene in the HEX-A pathway is nominally significant in the SCZ association analysis, and
370 five genes have $p < 1x10^{-03}$, indicating that there may be substantial shared genetic aetiology
371 between the two disorders that warrants further investigation. Additionally, we identified a
372 significant overlap between our SCZ-associated genes and a number of pathways associated with
373 porphyrin metabolism. Porphyric disorders have been well characterized and are among early
374 descriptions of "schizophrenic" and psychotic presentations of schizophrenia, as described in the
375 likely eponymous mid-19th century poem "Porphyria's Lover", by Robert Browning[59], and have
376 been cited as a likely diagnosis for the various psychiatric and metabolic ailments of Vincent van
377 Gogh[60–65] and King George III[66].
378
379 Finally, we assessed patterns of expression for the 67 SCZ-associated genes throughout
380 development using spatio-temporal transcriptomic data obtained from BRAINSPAN. We
381 identified four clusters of genes, with expression in four distinct spatiotemporal regions, ranging
382 from early pre-natal to strictly post-natal expression. There are plausible hypotheses and genetic
383 evidence for SCZ disease development in adolescence, given the correlation with age of onset, as
384 well as prenatally, supported by genetic overlap with neurodevelopmental disorders[67–69] as well
385 as the earlier onset of cognitive impairments[70–73]. Understanding the temporal expression
386 patterns of SCZ-associated genes can help to elucidate gene development and trajectory, and
387 inform research and analysis design. Identification of SCZ-associated genes primarily expressed
388 prenatally is striking given our adult eQTL reference panels, and may reflect common eQTL
389 architecture across development, which is known to be partial[74–76]; therefore, our results should
390 spur interest in extending TI data and/or methods to early development[74]. Identification of SCZ-

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391 associated genes primarily expressed in adolescence and adult-hood is of particular interest for
392 direct analysis of the brain transcriptome in adult psychiatric cases.
393
394 eQTL data have been recognized for nearly a decade as potentially important for understanding
395 complex genetic variation. Nicolae et al[1] showed that common variant-common disease
396 associations are strongly enriched for genetic regulation of gene expression. Therefore,
397 integrative approaches combining transcriptomic and genetic association data have great
398 potential. Current TI association analyses increase power for genetic discovery, even while many
399 open areas of TI remain to be developed, such as leveraging additional data types such as
400 chromatin modifications[77] (e.g. methylation, histone modification), imputing different tissues or
401 different exposures (e.g. age, smoking, trauma) and modeling trans/coexpression effects. It
402 remains critical to leverage TI associations to provide insights into specific disease mechanisms.
403 Here, the accelerated identification of disease associated genes allows the detection of novel
404 pathways and distinct spatiotemporal patterns of expression in schizophrenia risk.
405
406

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407 **Online Methods (Limit 3,000 words, at end of manuscript, currently 2,064)**

408

409 **Creating gene expression predictors for the dorso-lateral pre-frontal cortex**

410 **eQTL Data**

411 Genotype and RNAseq data were obtained for 538 European individuals through the
412 CommonMind Project[14]. RNA-seq data were generated from post-mortem human dorsolateral
413 prefrontal cortex (DLPFC). The gene expression matrix was normalized to log(counts per
414 million) using voom. Adjustments were made for known covariates (including sample
415 ascertainment, quality, experimental parameters, ancestry) and surrogate variables, using linear
416 modelling with voom-derived regression weights. Details on genotyping, imputation and RNA-
417 seq generation may be found in the CommonMind Consortium flagship paper[14].

418

419 A 1% MAF cut-off was applied. Variants were filtered to remove any SNPs in high LD (r^2>0.9),
420 indels, and all variants with ambiguous ref/alt alleles. All protein coding genes on chromosomes
421 1-22 with at least one cis-SNP after these QC steps were included in this analysis. SNPs in trans
422 have been shown not to provide a substantial improvement in prediction accuracy[15] and were not
423 included here.

424

425 **Building gene expression prediction databases**

426 Gene expression prediction models were created following the "PrediXcan" method[15]. Matched
427 genotype and gene expression data were used to identify a set of variants that influence gene
428 expression (Supplementary Figure 2A). Weights for these variants are calculated using
429 regression in a ten-fold cross-validation framework. All cross-validation folds were balanced for
430 diagnoses, ethnicity, and other clinical variables.

431

432 All SNPs within the cis-region (+/- 1mb) of each gene were included in the regression analysis.
433 Accuracy of prediction was estimated by comparing predicted expression to measured
434 expression, across all 10 cross-validation folds; this correlation was termed cross-validation R^2 or
435 R_{cv}^2. Genes with $R_{cv}^2 > 0.01$ (~$p<0.05$) were included in our final predictor database.

436

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437 Prediction models were compared across four different regression methods; elastic net
438 (prediXcan), ridge regression (using the TWAS method[16]), Bayesian sparse linear mixed
439 modelling (BSLMM; TWAS), and linear regression using the best eQTL for each gene
440 (Supplementary Figure 1A). Mean R_{cv}^2 values were significantly higher for elastic net regression
441 (mean R_{cv}^2=0.056) than for eQTL-based prediction (mean R_{cv}^2=0.025), BSLMM (mean
442 R_{cv}^2=0.021) or Ridge Regression (mean R_{cv}^2=0.020). The distribution of R_{cv}^2 values was also
443 significantly higher for elastic net regression than for any other method (ks-test, $p<2.2\times10^{-16}$).
444

445 **Replication of gene expression prediction models in independent data**

446 Predictive accuracy of CMC DLPFC models were tested in two independent datasets.
447 First, we used data from the Religious Orders Study and Memory and Aging Project
448 (ROSMAP[19]). This study included genotype data and DLPFC RNA-seq data[78] for 451
449 individuals of European descent (Supplementary Figure 2B).
450

451 DLPFC genetically-regulated expression (GREX) was calculated using the CMC DLPFC
452 predictor models. Correlation between RNA-seq expression and CMC DLPFC GREX
453 ("Replication R^2 values" or R_R^2) was used as a measure of predictive accuracy. R_R^2 was
454 calculated including correction for ten ancestry components, as follows:

455 *Equation 1: R_R^2 calculation.*

456 $$R_{R1}^2 = (M \sim GREX + PC_1 + PC_2 + \cdots + PC_{10})$$
457 $$R_{R2}^2 = (M \sim PC_1 + PC_2 + \cdots + PC_{10})$$
458 $$R_R^2 = R_{R1}^2 - R_{R2}^2$$
459

460 Where:

M	Measured expression (RNA-seq)
$GREX$	GREX imputed expression
PC_n	n^{th} Principal Component

461

462 A small number of genes (158) had very low predictive accuracy and were removed from further
463 analyses. Cross-validation R^2 (R_{cv}^2) values and R_R^2 values were highly correlated (rho=0.62,
464 p<2.2e-16; Supplementary Figure 3A). 55.7% of CMC DLPFC genes had R_R^2 values > 0.01.

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465
466 Prediction accuracy was also assessed for 11 publicly available GTEx neurological predictor
467 databases, and R_R^2 values used to compare to CMC DLPFC performance. CMC DLPFC models
468 had higher average R_R^2 values, more genes with $R_R^2 > 0.01$, and significantly higher overall
469 distributions of R_R^2values than any of the twelve GTEx brain tissue models (ks-test, p<2.2e-16;
470 Figure 1A,B).
471
472 To estimate trans-ancestral prediction accuracy, genetically regulated gene expression was
473 calculated for 162 African-American individuals and 280 European individuals from the NIMH
474 Human Brain Collection Core (HBCC) dataset[79] (Supplementary Figure 2C). Predicted gene
475 expression levels were compared to DLPFC expression levels measured using microarray. There
476 was a significant correlation between the European and African-American samples for R_{CV}^2
477 values and R_R^2 values (rho=0.66, 0.56; Supplementary figure 3B-C). R_R^2 values were higher on
478 average in Europeans, but were significantly correlated between African-Americans and
479 Europeans (rho=0.78, p<2.2e-16, Pearson test; supplementary figure 3D).
480

481 **Extension to Summary Statistics**

482 Transcriptomic Imputation may be applied to summary statistics instead of raw dosages, in
483 instances where raw data is unavailable. However, this method suffers from slightly reduced
484 accuracy, requires covariance matrices calculated in an ancestrally-matched reference
485 population[80] (usually only possible for European cohorts), and precludes testing of
486 endophenotypes within the data, and so should not be applied when raw data is available.
487
488 We assessed concordance between CMC DLPFC transcriptomic imputation results using
489 summary-statistics (MetaXcan[80]) and raw genotypes (PrediXcan[15]) using nine European and
490 three Asian PGC-SCZ cohorts[22] for which both data types were available. Cohorts were chosen
491 to encompass a range of case : control ratios, to test previous suggestions that accuracy is
492 reduced in unbalanced cohorts[80]. Covariances for all variants included in the DLPFC predictor
493 models were computed using MetaXcan[80]. For all European cohorts, Pearson correlation of log-
494 10 p-values and effect sizes was above 0.95. The mean correlation was 0.963 (Supplementary
495 Figure 4). There was no correlation between total sample size, case-control ratio, p-value or

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496 effect-size. Seven genes were removed due to discordant p-values. For the three Asian cohorts
497 tested, the mean correlation was 0.91 (Supplementary Figure 5).
498
499 Concordance was also tested for the same nine European PGC-SCZ cohorts, across 12
500 neurological GTEx prediction databases. All correlations were significant (rho>0.95, p<2.2e-16).
501 There was a significant correlation between p-value concordance and case-control ratio
502 (rho=0.37, p=7.606 x10^{-15}). 114 genes had discordant p-values between the two methods and
503 were excluded from future analyses.
504

505 **Application to Schizophrenia**

506 **Dataset Collection**

507 We obtained 53 discovery cohorts for this study, including 40,299 SCZ cases and 65,264
508 controls (Figure 2). 52/53 cohorts (35,079 cases, 46,441 controls) were obtained through
509 collaboration with the Psychiatric Genomics Consortium, and are described in the 2014 PGC
510 Schizophrenia GWAS[22]. The remaining cohort, referred to as CLOZUK2, constitutes the largest
511 single cohort of individuals with Schizophrenia (5,220 cases and 18,823 controls), collected as
512 part of an effort to investigate treatment-resistant Schizophrenia[26].
513
514 50/53 datasets included individuals of European ancestry, while three datasets include
515 individuals of Asian ancestry (1,836 cases, 3,383 controls). All individuals were ancestrally
516 matched to controls. Information on genotyping, quality control and other data management
517 issues may be found in the original papers describing these collections[22,26]. All sample
518 collections complied with ethical regulations. Details regarding ethical compliance and consent
519 procedures may be found in the original manuscripts describing these collections[22,26].
520
521 Access to dosage data was available for 44/52 PGC-SCZ cohorts. The remaining PGC cohorts,
522 and the CLOZUK2 cohort provided summary statistics. Three European PGC cohorts were trio-
523 based, rather than case-control.
524
525 Additionally, we tested for replication of our CMC DLPFC associations in an independent
526 dataset of 4,133 cases and 24,788 controls obtained through collaboration with the iPSYCH-

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527 GEMS schizophrenia working group (effective sample size 14,169.5; Figure 2B, supplementary
528 information).
529

530 **Transcriptomic Imputation and association testing**

531 Transcriptomic Imputation was carried out individually for each case-control PGC-SCZ cohort
532 with available dosage data (44/52 cohorts). Predicted gene expression levels were computed
533 using the DLPFC predictors described in this manuscript, as well as for 11 other brain tissues
534 prediction databases created using GTEx tissues[15,20,21,81] (Figure 1C). Associations between
535 predicted gene expression values and case-control status were calculated using a linear
536 regression test in R. Ten ancestry principal components were included as covariates. Association
537 tests were carried out independently for each cohort, across 12 brain tissues.
538

539 For the 8 PGC cohorts with no available dosage data, the three PGC trio-based analyses, and the
540 CLOZUK2 cohort, a summary-statistic based transcriptomic imputation approach was used
541 ("MetaXcan"), as described previously.
542

543 **Meta-analysis**

544 Meta-analysis was carried out across all 53 cohorts using METAL[82]. Cochran's Q test for
545 heterogeneity was implemented in METAL[82,83], and a heterogeneity p-value threshold of $p >$
546 $1x10^{-3}$ applied to results. A conservative significance threshold was applied to these data,
547 correcting for the total number of genes tested across all tissues (121,611 gene-region tests in
548 total). This resulted in a genome-wide significance threshold of $4.1x10^{-7}$.
549

550 Effect sizes and direction of effect quoted in this manuscript refer to changes in predicted
551 expression in cases compared to controls i.e., genes with negative effect sizes have decreased
552 predicted expression in cases compared to controls.
553

554 **Identifying independent associations**

555 We identified a number of genomic regions which contained multiple gene associations and/or
556 genes associated across multiple tissues. We identified 58 of these regions, excluding the MHC,
557 based on distance between associated genes, and verified them using visual inspection. In order

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558 to identify independent genic associations within these regions, we carried out a stepwise
559 forward conditional analysis following "GCTA-COJO" theory[84] using "CoCo"
560 (https://github.com/theboocock/coco/), an R implementation of GCTA-COJO. CoCo allows the
561 specification of custom correlation matrices by the user (for example, ancestrally specific LD
562 matrices). For each region, we generated a predicted gene expression correlation matrix for all
563 significant genes ($p \leq 1x10^{-6}$), as the root-effective sample size (N_{eff}, eqn 2) weighted average
564 correlation across all cohorts where we had access to dosage data.

565 *Equation 2: Effective Sample Size, N_{eff}*

566
$$N_{eff} = \frac{4}{(\frac{1}{N_{cases}} + \frac{1}{N_{controls}})}$$

567

568 Forward stepwise conditional analysis of all significant genes was carried out using joint linear
569 regression modeling. First, the top-ranked gene was added to the model, then the next most
570 significant gene in a joint model is added if significant at a given p-value threshold, and so on
571 until either all genes are added to the model, or no joint statistic reaches the significance
572 threshold.

573

574 We calculated effect sizes and odds ratios for SCZ-associated genes by adjusting "CoCo" betas
575 to have unit variance (Table 1, eqn. 3).

576 *Equation 3: GREX Beta adjustment*

577
$$\beta = \beta_{CoCo}\, x \sqrt{GVAR}$$

578

579 Where GVAR is the variance of the GREX predictor for each gene.

580

581 **Gene set Analyses**

582 Pathway analyses were carried out using an extension to MAGMA[85]. P-values were assigned to
583 genes using the most significant p-value achieved by each gene in the meta-analysis. We then
584 carried out a competitive gene-set analysis test using these p-values, using two gene sets:

585

586 1. 159 gene sets with prior hypotheses for involvement in SCZ development, including loss-
587 of-function intolerant genes, CNV-intolerant genes, targets of the fragile-X mental

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588 retardation protein, CNS related gene sets, and 104 behavioural and neurological
589 pathways from the Mouse Genome Informatics database[14,26,67,86].
590 2. An agnostic analysis, including ~8,500 gene sets collated from publicly available
591 databases including GO[87,88], KEGG[89], REACTOME[90], PANTHER[91,92], BIOCARTA[93]
592 and MGI[48]. Sets were filtered to include only gene sets with at least ten genes.
593
594 Significance levels were adjusted across all pathways included in either test using the
595 Benjamini-Hochberg "FDR" correction in R[23].
596
597 **Coexpression of SCZ genes throughout development**
598 We investigate spatiotemporal expression of our associated genes using publicly available
599 developmental transcriptome data, obtained from the BRAINSPAN consortium[94]. We partitioned
600 these data into biologically relevant spatio-temporal data sets[95], corresponding to four general
601 brain regions; the frontal cortex, temporal and parietal regions, sensory-motor regions, and
602 subcortical regions (Figure 4A[96]), and eight developmental time-points (four pre-natal, four post-
603 natal)[95].
604
605 First, we tested for correlation of gene expression for all SCZ-associated genes at each
606 spatiotemporal time-point. Genes with pearson correlation coefficients >= 0.8 or <=-0.8 were
607 considered co-expressed. 100,000 iterations of this analysis were carried out using random gene
608 sets with equivalent expression level distributions to the SCZ-associated genes. For each gene
609 set, a gene co-expression network was created, with edges connecting all co-expressed genes.
610 Networks were assessed using three criteria; first, the number of edges within the network, as a
611 crude measured of connectedness; second, the Watts-Strogatz average path length between
612 nodes, as a global measure of connectedness across all genes in the network[53]; third, the Watts-
613 Strogatz clustering coefficient, to measure tightness of the clusters within the network[53]. For
614 each spatio-temporal time point, we plotted gene-pair expression correlation (suppl. Fig 8) and
615 co-expression networks (suppl. Fig 9).
616
617 For each of the 67 SCZ-associated genes, we calculated average expression at each
618 spatiotemporal point. We then calculated Z-Score of expression specificity using these values,

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619 and plotted Z-Scores to visually examine patterns of gene expression throughout development
620 and across brain regions. Clusters were formally identified using a dendrogram cut at height 10
621 (Suppl. Fig 10).
622

623 **In-silico replication of SCZ-associated genes in mouse models**

624 We downloaded genotype, knock-out allele information and phenotyping data for ~10,000
625 mouse mutant models from five large mouse phenotyping and genotyping projects; Mouse
626 Genome Informatics (MGI[48]), EuroPhenome[47,97], Mouse Genome Project (MGP[47,49]),
627 International Mouse Phenotyping Consortium (IMPC[50]), and Infection and Immunity
628 Immunophenotyping (3I[98]). Where possible, we also downloaded raw phenotyping data
629 regarding specific assays. In total, we obtained 175,012 phenotypic measurements, across 10,288
630 mutant mouse models. We searched for any mouse lines with phenotypes related to behavior
631 (natural, observed, stereotypic or assay-induced); cognition or working memory; brain, head or
632 craniofacial dysmorphology; retinal or eye morphology, and/or vision or visual dysfunction or
633 impairment; ear morphology or hearing dysfunction or impairment; neural tube defects; brain
634 and/or nervous system development; abnormal nociception.
635

636 We compared the prevalence of psychiatric phenotypes in mutant mice for our SCZ-associated
637 genes to the prevalence among other disease-associated gene sets. We selected 366 GWAS gene
638 sets, and removed any for which fewer than ten mutant mouse models were included in our
639 databases, leaving 105 gene sets. We compared the prevalence of 13 different categories of
640 psychiatric phenotypes, relating to adrenal gland, behavior, brain development, craniofacial
641 dysmorphology, ear/auditory phenotypes, eye dysmorphology, head dysmorphology, nervous
642 system development, abnormal nociception, seizures, thyroid gland, vision phenotypes. For each
643 GWAS gene set, we counted the number of categories with at least one phenotype, and
644 compared to the number in our SCZ-associated gene set to obtain an empirical p-value.
645

646 **Data Availability**

647 Our CMC-derived DLPFC prediction models will be made publicly available.
648

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649 **Acknowledgements**

650 Data were generated as part of the CommonMind Consortium supported by funding from Takeda
651 Pharmaceuticals Company Limited, F. Hoffman-La Roche Ltd and NIH grants R01MH085542,
652 R01MH093725, P50MH066392, P50MH080405, R01MH097276, RO1-MH-075916,
653 P50M096891, P50MH084053S1, R37MH057881 and R37MH057881S1,
654 HHSN271201300031C, AG02219, AG05138 and MH06692.
655
656 Brain tissue for the study was obtained from the following brain bank collections: the Mount
657 Sinai NIH Brain and Tissue Repository, the University of Pennsylvania Alzheimer's Disease
658 Core Center, the University of Pittsburgh NeuroBioBank and Brain and Tissue Repositories and
659 the NIMH Human Brain Collection Core. CMC Leadership: Pamela Sklar, Joseph Buxbaum
660 (Icahn School of Medicine at Mount Sinai), Bernie Devlin, David Lewis (University of
661 Pittsburgh), Raquel Gur, Chang-Gyu Hahn (University of Pennsylvania), Keisuke Hirai,
662 Hiroyoshi Toyoshiba (Takeda Pharmaceuticals Company Limited), Enrico Domenici, Laurent
663 Essioux (F. Hoffman-La Roche Ltd), Lara Mangravite, Mette Peters (Sage Bionetworks),
664 Thomas Lehner, Barbara Lipska (NIMH).
665
666 ROSMAP study data were provided by the Rush Alzheimer's Disease Center, Rush University
667 Medical Center, Chicago. Data collection was supported through funding by NIA grants
668 P30AG10161, R01AG15819, R01AG17917, R01AG30146, R01AG36836, U01AG32984,
669 U01AG46152, the Illinois Department of Public Health, and the Translational Genomics
670 Research Institute.
671
672 The iPSYCH-GEMS team would like to acknowledge funding from the Lundbeck Foundation
673 (grant no R102-A9118 and R155-2014-1724), the Stanley Medical Research Institute, an
674 Advanced Grant from the European Research Council (project no: 294838), the Danish Strategic
675 Research Council the Novo Nordisk Foundation for supporting the Danish National Biobank
676 resource, and grants from Aarhus and Copenhagen Universities and University Hospitals,
677 including support to the iSEQ Center, the GenomeDK HPC facility, and the CIRRAU Center.
678
679

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680 The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the
681 Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA,
682 NIMH, and NINDS. The data used for the analyses described in this manuscript were obtained
683 from the GTEx Portal on 09/05/16. BrainSpan: Atlas of the Developing Human Brain [Internet].
684 Funded by ARRA Awards 1RC2MH089921-01, 1RC2MH090047-01, and 1RC2MH089929-01.
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757 Potential Conflicts of Interest: TW has acted as advisor and lecturer to H. Lundbeck A/S

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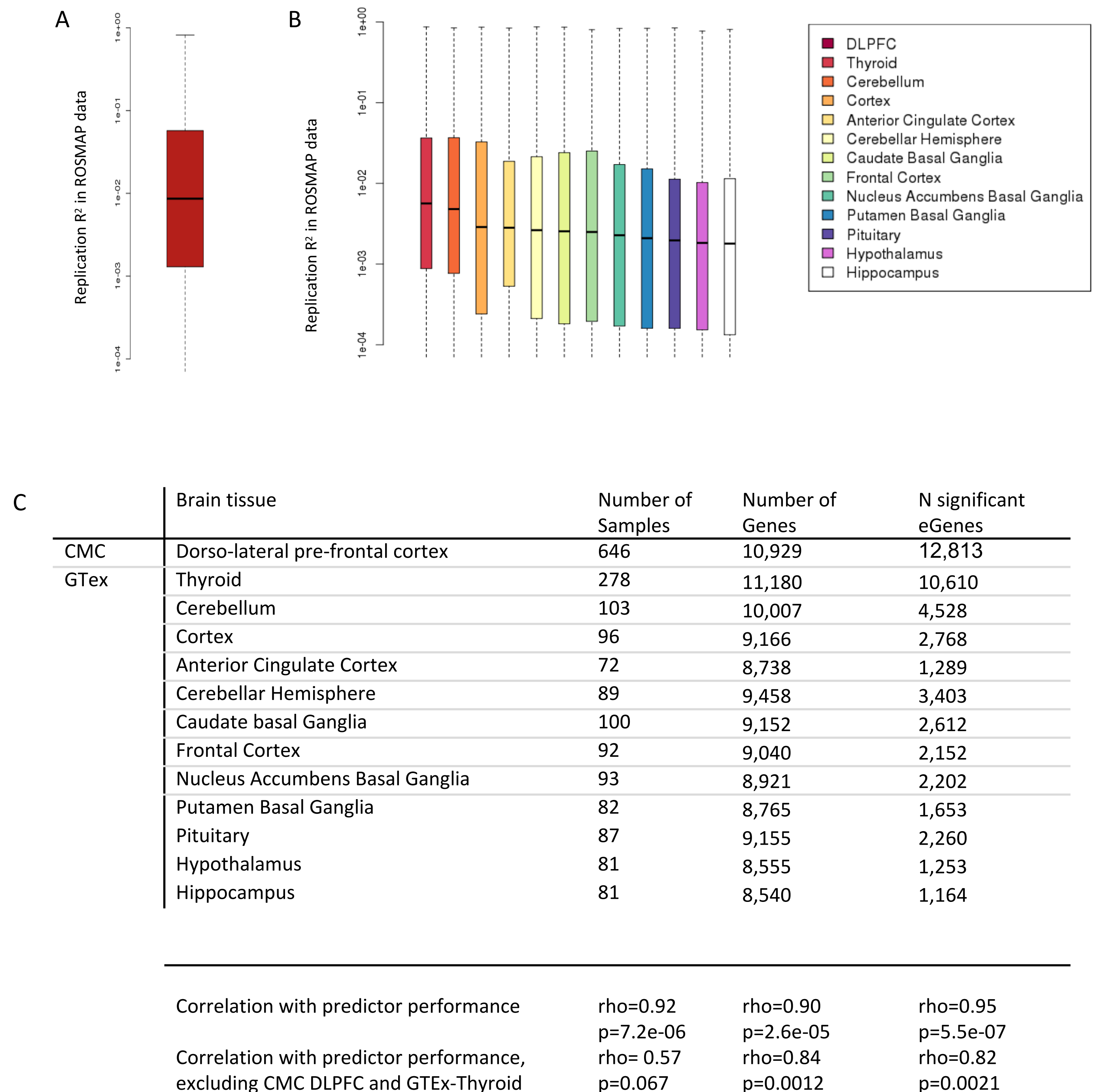

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	Brain tissue	Number of Samples	Number of Genes	N significant eGenes
CMC	Dorso-lateral pre-frontal cortex	646	10,929	12,813
GTex	Thyroid	278	11,180	10,610
	Cerebellum	103	10,007	4,528
	Cortex	96	9,166	2,768
	Anterior Cingulate Cortex	72	8,738	1,289
	Cerebellar Hemisphere	89	9,458	3,403
	Caudate basal Ganglia	100	9,152	2,612
	Frontal Cortex	92	9,040	2,152
	Nucleus Accumbens Basal Ganglia	93	8,921	2,202
	Putamen Basal Ganglia	82	8,765	1,653
	Pituitary	87	9,155	2,260
	Hypothalamus	81	8,555	1,253
	Hippocampus	81	8,540	1,164
	Correlation with predictor performance	rho=0.92 p=7.2e-06	rho=0.90 p=2.6e-05	rho=0.95 p=5.5e-07
	Correlation with predictor performance, excluding CMC DLPFC and GTEx-Thyroid	rho= 0.57 p=0.067	rho=0.84 p=0.0012	rho=0.82 p=0.0021

Figure 1: Replication of DLPFC prediction models in independent data.
Measured gene expression (ROSMAP RNA-seq) was compared to predicted genetically-regulated gene expression for CMC DLPFC and 12 GTeX predictor databases. Replication R^2 values are significantly higher for the DLPFC than for the 12 GTEX brain expression models.

A. Distribution of R_R^2 values of CMC DLPFC predictors in ROSMAP data. Mean $R_R^2 = 0.056$. 47.7% of genes have $R_R^2 >= 0.01$.
B. Distribution of R_R^2 values of 12 GTeX predictors in ROSMAP data.
C. Table of sample sizes and p-val thresholds for CMC DLPFC and GTeX data. Number of samples, number of genes in the prediXcan model and number of eGenes are all significantly correlated with predictor performance in ROSMAP data.

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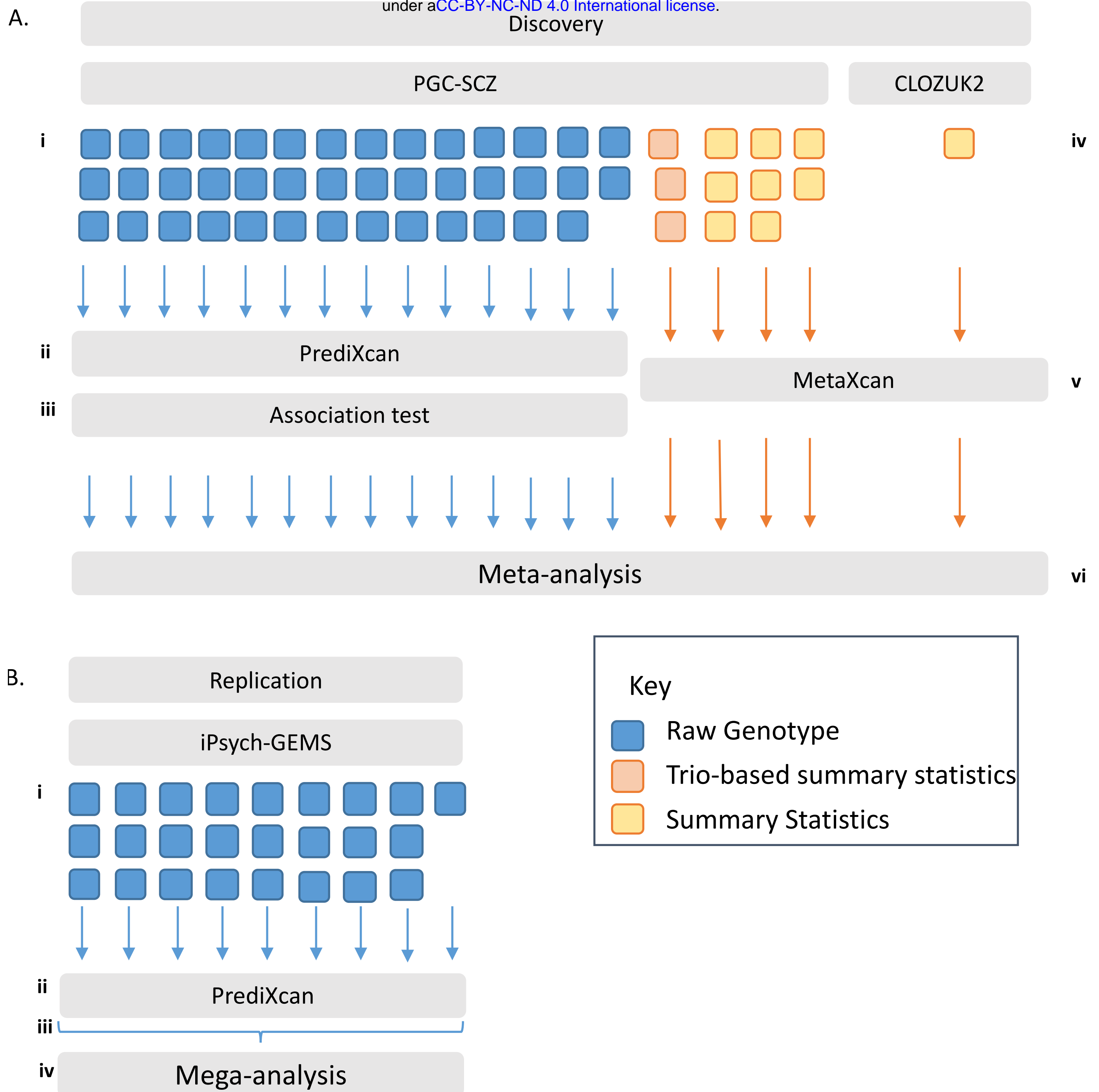

Figure 2: Analysis outline.

A) Discovery Samples. 41 PGC-SCZ cohorts had available raw genotypes (i). Predicted DLPFC gene expression was calculated in each cohort using prediXcan (ii) and tested for association with case-control status (iii). 11 PGC cohorts (3 trio, 8 case-control) and the CLOZUK2 cohort had only summary statistics available (iv). MetaXcan was used to calculate DLPFC associations for each cohort (v). Results were meta-analysed across all 53 cohorts (vi). This procedure was repeated for 12 GTEx prediction models.

B) Replication Samples. iPSYCH-GEMS samples were collected in 25 waves (i). Predicted DLPFC gene expression was calculated in each wave separately using prediXcan (ii) and merged for association testing (iii). A mega-analysis was run across all 25 waves, using wave membership as a covariate in the regression (iv)

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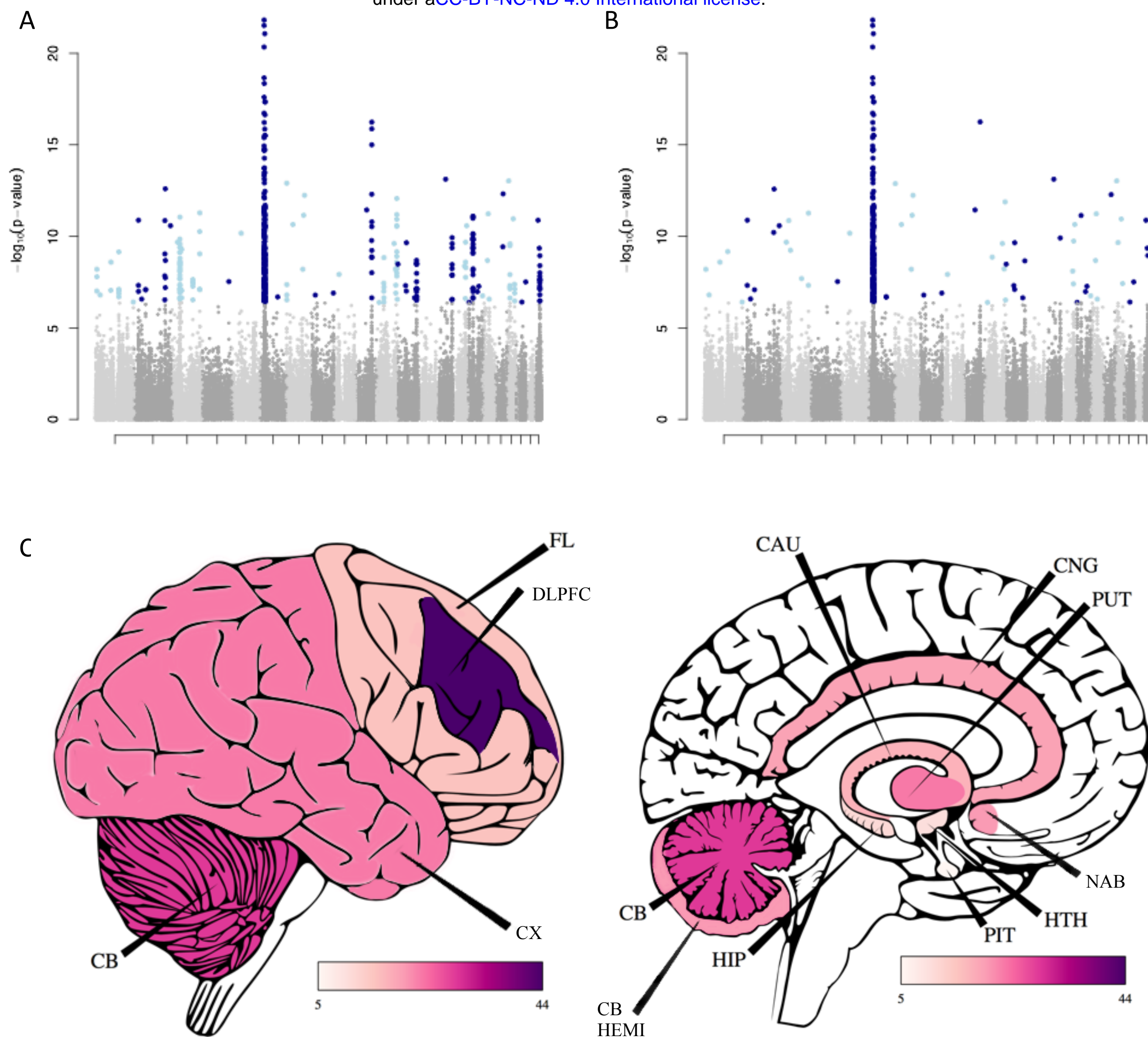

Figure 3: SCZ associations results

A) 413 genes are associated with SCZ across 12 brain tissues

B) 67 genes remain significant outside the MHC after stepwise conditional analysis

C) Number of genome-wide significant loci, outside the MHC region, identified in each brain region. Abbreviations are as follows; CB- Cerebellum; CX- Cortex; FL- Frontal Cortex; DLPFC- Dorso-lateral pre-frontal cortex; CB HEMI- Cerebellar Hemisphere; HIP- Hippocampus; PIT- Pituitary Gland; HTH- Hypothalamus; NAB- Nucleus Accumbens (Basal Ganglia); PUT- Putamen (Basal Ganglia); CAU- Caudate (Basal Ganglia); CNG- Anterior Cingulate Cortex

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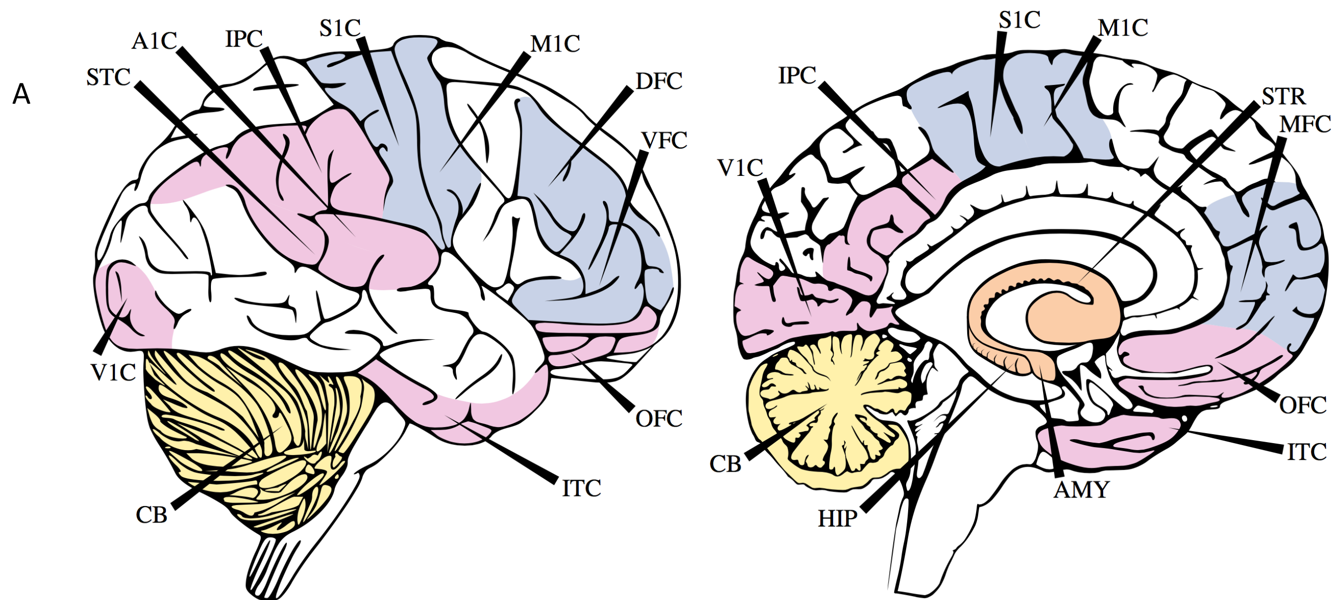

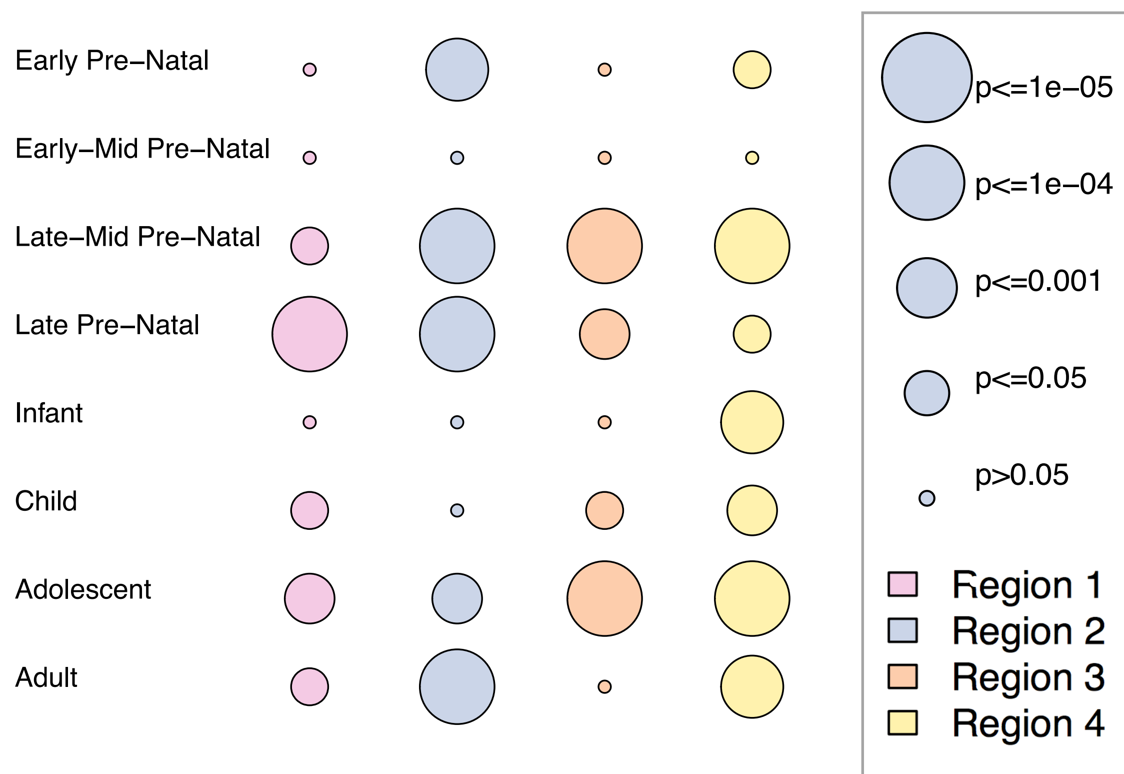

Figure 4: SCZ-associated genes are co-expressed throughout development and across brain regions

A) Brain tissues selected for each of four BRAINSPAN regions. Region 1: IPC, V1C, ITC, OFC, STC, A1C; Region 2:S1C, M1C, DFC, VFC, MFC; Region 3:HIP, AMY, STR; Region 4: CB

B) Average clustering coefficients were calculated for all pairs of SCZ-associated genes, and compared to permuted gene networks to obtain empirical significance levels.

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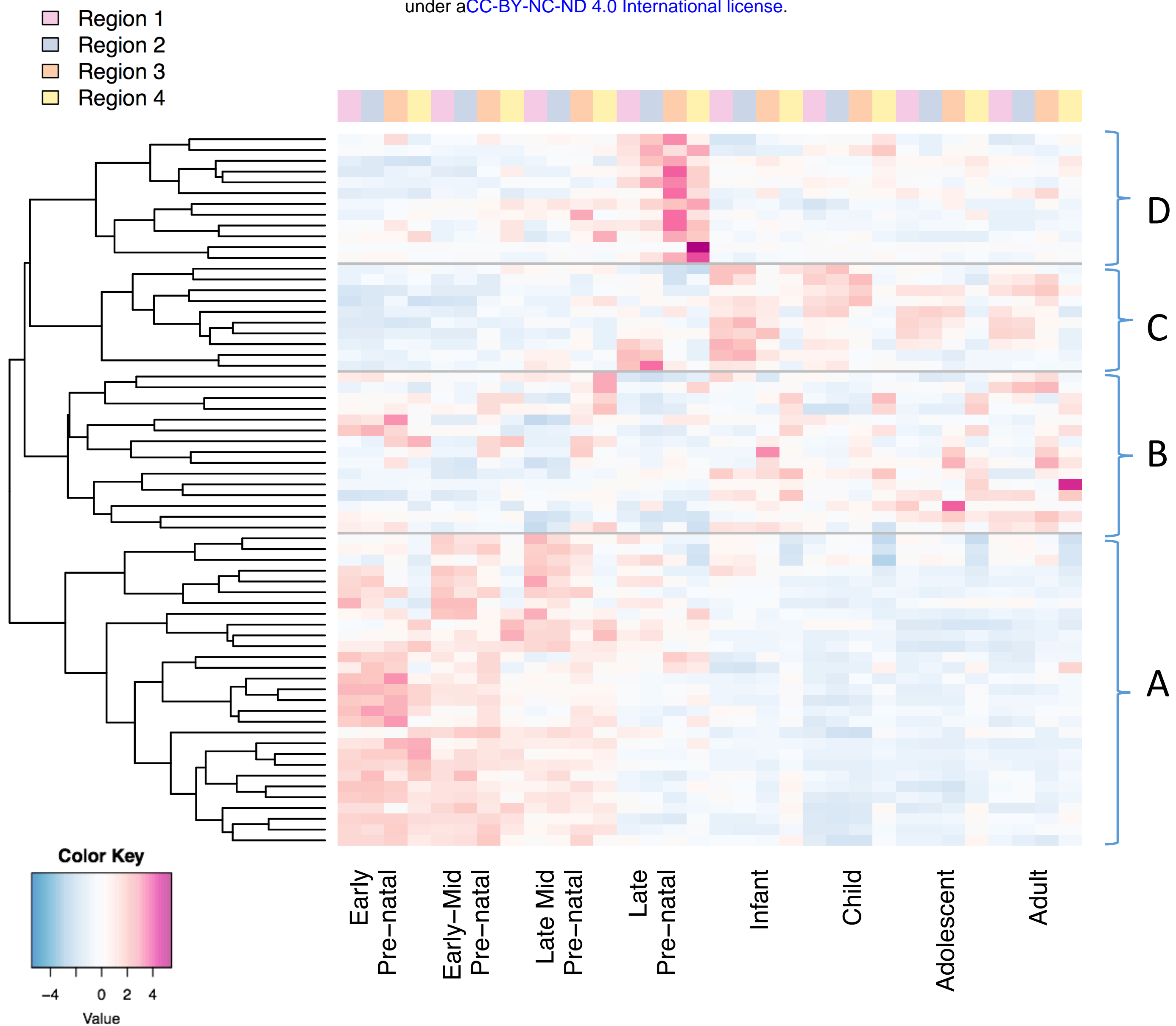

Figure 5: Gene expression patterns for SCZ-associated genes cluster into four groups, relating to distinct spatiotemporal expression.
Brain regions are shown in figure 5a.

A. 29 genes are expressed in the early-mid pre-natal period (4-24 post-conception weeks)
B. 15 genes are expressed throughout development; sub-clusters correspond to either specific expression in region 4, or expression across the brain
C. Ten genes are expressed in the late-prenatal (25-38pcw) and post-natal period
D. 12 genes are expressed in the late pre-natal period (25-39pcw)

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Table 1: SCZ-associated genes

Gene name		Tissue	BETA	P	GVAR	Adjusted BETA	Adjusted OR
GNL3	GTEX	Cerebellum	0.037	1.39E-11	0.115	0.012	1.012
THOC7	GTEX	Cerebellum	-0.113	5.77E-10	0.010	-0.011	0.989
NAGA	GTEX	Cerebellum	0.122	1.12E-09	0.009	0.011	1.011
TAC3	GTEX	Cerebellum	-0.868	8.03E-08	0.000	-0.015	0.985
CHRNA2	GTEX	Cerebellum	-0.016	1.63E-07	0.395	-0.010	0.990
ACTR5	GTEX	Cerebellum	0.208	3.88E-07	0.019	0.029	1.029
INO80E	GTEX	Frontal Cortex	0.130	7.25E-12	0.009	0.012	1.013
PLPPR5	GTEX	Frontal Cortex	-0.672	2.58E-09	0.006	-0.053	0.948
FAM205A	GTEX	Frontal Cortex	0.043	1.21E-08	0.061	0.011	1.011
AC110781.3	GTEX	Thyroid	0.342	1.31E-13	0.002	0.014	1.014
IMMP2L	GTEX	Thyroid	-0.073	7.09E-12	0.046	-0.016	0.984
IGSF9B	GTEX	Thyroid	-0.024	3.05E-07	0.156	-0.010	0.991
NMRAL1	GTEX	Thyroid	0.038	4.03E-07	0.060	0.009	1.009
HIF1A	**CMC**	**DLPFC**	11.130	7.52E-14	0.000	0.148	1.159
TIMM29	CMC	DLPFC	11.207	9.27E-14	0.000	0.168	1.183
ST7-OT4	**CMC**	**DLPFC**	10.170	5.79E-13	0.001	0.318	1.374
H2AFY2	**CMC**	**DLPFC**	10.962	3.60E-12	0.000	0.191	1.211
STARD3	**CMC**	**DLPFC**	10.740	5.90E-12	0.001	0.304	1.355
CTC-471F3.5	**CMC**	**DLPFC**	8.535	1.11E-11	0.000	0.104	1.110
SF3A1	**CMC**	**DLPFC**	8.651	1.32E-11	0.000	0.083	1.086
ZNF512	**CMC**	**DLPFC**	10.312	1.32E-11	0.001	0.261	1.298
FURIN	CMC	DLPFC	-0.084	2.22E-11	0.022	-0.012	0.988
INHBA-AS1	**CMC**	**DLPFC**	8.399	2.24E-11	0.000	0.127	1.135
SF3B1	CMC	DLPFC	0.099	6.14E-11	0.014	0.012	1.012
EFTUD1P1	CMC	DLPFC	-0.092	1.81E-10	0.017	-0.012	0.988
MLH1	CMC	DLPFC	2.840	2.10E-10	0.001	0.069	1.071
GATAD2A	CMC	DLPFC	-0.044	2.18E-10	0.071	-0.012	0.988
METTL1	CMC	DLPFC	9.357	2.23E-10	0.000	0.166	1.181

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DMC1	CMC	DLPFC	7.229	4.48E-10	0.000	0.130	1.139
RAD51D	**CMC**	**DLPFC**	7.612	2.11E-09	0.000	0.111	1.117
RERE	CMC	DLPFC	2.847	6.32E-09	0.000	0.036	1.037
PCCB	CMC	DLPFC	-0.044	2.05E-08	0.054	-0.010	0.990
CLCN3	CMC	DLPFC	0.141	2.96E-08	0.005	0.010	1.010
ATG101	**CMC**	**DLPFC**	8.086	4.90E-08	0.007	0.695	2.005
JRK	CMC	DLPFC	0.032	1.25E-07	0.091	0.010	1.010
PTPRU	CMC	DLPFC	-0.077	1.60E-07	0.016	-0.010	0.990
MARCKS	**CMC**	**DLPFC**	0.398	2.05E-07	0.001	0.015	1.015
TCF4	GTEX	Anterior Cingulate Cortex	-0.059	5.22E-13	0.051	-0.013	0.987
DGKD	GTEX	Anterior Cingulate Cortex	-0.937	2.63E-11	0.001	-0.022	0.979
C1QTNF4	GTEX	Anterior Cingulate Cortex	-0.173	1.37E-09	0.010	-0.017	0.983
PITPNA	GTEX	Anterior Cingulate Cortex	-0.243	1.77E-07	0.002	-0.010	0.990
FXR1	GTEX	Caudate Basal Ganglia	0.439	5.40E-12	0.001	0.017	1.017
ZDHHC1	GTEX	Caudate Basal Ganglia	0.354	5.36E-08	0.001	0.011	1.012
PDE4D	GTEX	Cerebellar Hemisphere	0.365	6.81E-11	0.001	0.013	1.013
DRD2	GTEX	Cerebellar Hemisphere	-0.182	2.47E-10	0.004	-0.012	0.988
PITPNM2	GTEX	Cerebellar Hemisphere	-0.065	2.21E-09	0.028	-0.011	0.989
RINT1	GTEX	Cerebellar Hemisphere	0.086	6.32E-09	0.016	0.011	1.011
SRMS	GTEX	Cerebellar Hemisphere	-0.440	3.08E-08	0.001	-0.011	0.989
SETD6	GTEX	Cerebellar Hemisphere	-0.043	1.05E-07	0.054	-0.010	0.990
APOPT1	GTEX	Cortex	-0.074	1.24E-10	0.026	-0.012	0.988
VSIG2	GTEX	Cortex	-0.092	6.01E-09	0.013	-0.011	0.989
SDCCAG8	GTEX	Cortex	-0.069	3.88E-07	0.002	-0.003	0.997
PIK3C2A	**GTEX**	Cortex	-0.040	4.04E-07	0.365	-0.024	0.976
AS3MT	GTEX	Frontal Cortex	0.594	5.65E-17	0.001	0.017	1.017
FOXN2	**GTEX**	**Hippocampus**	-0.250	2.65E-07	0.021	-0.036	0.964
RASIP1	**GTEX**	**Nucleus Accumbens Basal Ganglia**	0.055	3.80E-08	0.034	0.010	1.010
TCF23	**GTEX**	**Nucleus Accumbens Basal Ganglia**	-0.076	4.83E-08	0.019	-0.010	0.990
TTC14	GTEX	**Nucleus Accumbens Basal Ganglia**	-0.089	4.84E-08	0.013	-0.010	0.990
TYW5	GTEX	Putamen Basal Ganglia	-0.080	2.63E-13	0.035	-0.015	0.985

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SNX19	GTEX	Putamen Basal Ganglia	0.031	1.31E-12	0.179	0.013	1.013
CIART	GTEX	Putamen Basal Ganglia	0.090	6.78E-10	0.017	0.012	1.012
SH2D7	GTEX	Putamen Basal Ganglia	0.096	7.89E-09	0.013	0.011	1.011
DGUOK	**GTEX**	Putamen Basal Ganglia	0.255	8.26E-08	0.002	0.011	1.011
C12orf76	GTEX	Putamen Basal Ganglia	0.031	2.27E-07	0.095	0.010	1.010
LRRC37A	**GTEX**	Putamen Basal Ganglia	-0.035	2.69E-07	0.076	-0.010	0.991
AC005841.1	GTEX	Pituitary	0.162	3.28E-09	0.005	0.011	1.011
RPS17	GTEX	Pituitary	0.035	4.03E-08	0.082	0.010	1.010
MHC Region:							
BTN1A1	GTEX	Caudate Basal Ganglia	-0.2606	1.6666E-22			
VARS2	GTEX	Anterior Cingulate Cortex	0.0747019	7.4821E-15			
HIST1H3H	GTEX	Putamen Basal Ganglia	-1.105982	3.2236E-10			
NUDT3	GTEX	Nucleus Accumbens Basal Ganglia	0.10378753	6.546E-09			

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Table 2: Significantly enriched pathways and gene sets

Analysis	Gene Set	Comp P	FDR P
Hypothesis driven	FMRP-targets	$1.96x10^{-08}$	$3.097x10^{-06}$
	BP denovo CNV	$7.92x10^{-08}$	$6.257x10^{-06}$
	HIGH LOF intolerant	$5.86x10^{-05}$	0.00309
Agnostic	Increased spleen iron level	$2.72x10^{-08}$	0.000245
	Decreased IgM level	$6.80x10^{-07}$	0.00307
	Condensed chromosome	$1.99x10^{-06}$	0.00598
	Chromosome	$2.80x10^{-06}$	0.00632
	Abnormal spleen iron level	$6.79x10^{-06}$	0.00765
	Mitotic Anaphase	$6.39 x10^{-06}$	0.00765
	Mitotic Metaphase and Anaphase	$5.13 x10^{-06}$	0.00765
	Resolution of Sister Chromatid Cohesion	$5.82 x10^{-06}$	0.00765
	Increased liver iron level	$1.03 x10^{-05}$	0.0103
	Separation of Sister Chromatids	$1.28 x10^{-05}$	0.0115
	Regulation of Rab GTPase activity	$1.78 x10^{-05}$	0.0123
	Regulation of Rab protein signal transduction	$1.78 x10^{-05}$	0.0123
	Protein phosphorylated amino acid binding	$1.75x10^{-05}$	0.0123
	Chromosome	$2.57x10^{-05}$	0.0165
	Hexosaminidase activity	$3.47x10^{-05}$	0.0174
	Abnormal learningmemoryconditioning	$3.11x10^{-05}$	0.0174
	Abnormal liver iron level	$3.47x10^{-05}$	0.0174
	Mitotic Prometaphase	$2.99x10^{-05}$	0.0174
	M Phase	$3.70x10^{-05}$	0.0176
	Positive regulation of Rab GTPase activity	$5.93x10^{-05}$	0.0232
	Rab GTPase activator activity	$5.93x10^{-05}$	0.0232
	Protein phosphatase type 2A regulator activity	$5.24x10^{-05}$	0.0232
	Replicative senescence	$5.44x10^{-05}$	0.0232
	Condensed nuclear chromosome	$7.11x10^{-05}$	0.0267
	Ubiquitin-specific protease activity	0.000104	0.0335
	Ras GTPase activator activity	$9.61x10^{-05}$	0.0335
	Metabolism of porphyrins	0.000103	0.0335
	Kinetochore	0.000103	0.0335
	Decreased physiological sensitivity to xenobiotic	0.000127	0.0381
	Antigen Activates B Cell Receptor Leading to Generation of Second Messengers	0.000124	0.0381
	Phosphoprotein binding	0.000146	0.0424
	Abnormal dorsal-ventral axis patterning	0.000152	0.0429