Dissecting the genetic overlap between severe mental disorders and markers of cellular aging: identification of pleiotropic genes and druggable targets

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Abstract

Patients with severe mental disorders such as bipolar disorder (BD), schizophrenia (SCZ) and major depressive disorder (MDD) show a substantial reduction in life expectancy, increased incidence of comorbid medical conditions commonly observed with advanced age and alterations of aging hallmarks. While severe mental disorders are heritable, the extent to which genetic predisposition might contribute to accelerated cellular aging is not known. We used bivariate causal mixture models to quantify the trait-specific and shared architecture of mental disorders and 2 aging hallmarks (leukocyte telomere length [LTL] and mitochondrial DNA copy number), and the conjunctional false discovery rate to detect shared genetic loci. We integrated gene expression data from brain regions from GTEx and used different tools to functionally annotate identified loci and investigate their druggability. Aging hallmarks showed low polygenicity compared with severe mental disorders. We observed a significant negative global genetic correlation between MDD and LTL (r_g = -0.14, p = 6.5E-10), and no significant results for other severe mental disorders or for mtDNA-cn. However, conditional QQ plots and bivariate causal mixture models pointed to significant pleiotropy among all severe mental disorders and aging hallmarks. We identified genetic variants significantly shared between LTL and BD (n = 17), SCZ (n = 55) or MDD (n = 19), or mtDNA-cn and BD (n = 4), SCZ (n = 12) or MDD (n = 1), with mixed direction of effects. The exonic rs7909129 variant in the *SORCS3* gene, encoding a member of the retromer complex involved in protein trafficking and intracellular/intercellular signaling, was associated with shorter LTL and increased predisposition to all severe mental disorders. Genetic variants underlying risk of SCZ or MDD and shorter LTL modulate expression of several druggable genes in different brain regions. Genistein, a phytoestrogen with anti-inflammatory and antioxidant effects, was an upstream regulator of 2 genes modulated by variants associated with risk of MDD and shorter LTL. While our results suggest that shared heritability might play a limited role in contributing to accelerated cellular aging in severe mental disorders, we identified shared genetic determinants and prioritized different druggable targets and compounds.

Introduction

Patients with severe mental disorders such as bipolar disorder (BD), schizophrenia (SCZ) and major depressive disorder (MDD) show premature mortality and decreased life expectancy, up to 10-20 years compared with the general population, mainly due to increased incidence of aging-related conditions such as cardiovascular and metabolic disorders [1]. In addition, severe mental disorders have also been associated with a steeper age-related declined in executive function, as well as with changes in brain structure commonly associated with aging, such as ventricular enlargement, loss of grey matter in the cerebellum and hippocampus, and decreased volume of the prefrontal cortex [2-4] These findings led to hypothesize that severe mental disorders might be characterized by accelerated biological aging, a condition in which the rate of biological aging is increased as compared to chronological aging. Accordingly, a large number of studies reported alterations of markers of accelerated cellular aging, such as leukocyte telomere length (LTL) and mitochondrial DNA copy number (mtDNA-cn) in patients with severe mental disorders [5]. Telomeres are specialized and highly-conserved DNA-protein structures consisting in multiple (TTAGGG)n repeats and associated proteins called shelterins. These specialized structures prevent chromosome shortening and chromosome end fusion, ensuring chromosome stability. While telomeres shorten after each cell division in most somatic tissues, with this progressive decline leading to cell senescence, this physiological shortening can be accelerated by different stressors such as inflammation or oxidative stress [6]. Most studies to date investigated LTL, a practical measure that correlates with telomere length in different tissues [7]. Mitochondrial dysfunction, which results in alteration in energy production and increased levels of reactive oxygen species, is another widely investigated hallmark of cellular aging [8,9]. mtDNA-cn is a biomarker of mitochondrial function which has been repeatedly associated with overall mortality and age-related diseases. This double-stranded DNA molecule is strongly affected by aging-associated mutations due to its high replicative index, oxidative environment with reactive oxygen species generated by mitochondria during ATP synthesis, and limited DNA repair capacity due to its lack of protective histones [8]. While under physiological conditions the mtDNA-cn remains relatively stable, a decrease in mtDNA-cn has been described in different disorders characterized by oxidative stress and dysfunctions of the respiratory chain in mitochondria [9]. However, an increase in mtDNA-cn in these conditions has also been described, possibly due to a compensative upregulation aimed at overcoming the bioenergetic defects caused by some mtDNA mutations [10].

While a growing number of studies suggested that patients with severe mental disorders show biological features suggestive of accelerated cellular aging such as shorter LTL or altered mtDNA-cn, contrasting results have also been reported and there is scarce knowledge on the factors that might accelerate or rather counteract accelerated cellular aging in these patients. For instance, some studies showed longer LTL in patients with BD compared with non-psychiatric controls, with this finding potentially explained by a putative protective effect of the mood stabilizer lithium against accelerated cellular aging [11-13]. In the case of mtDNA-cn, while some studies reported a reduction in patients with severe mental disorders compared with controls [14], other studies reported results in the opposite direction or no significant difference [15,16].

Both mental disorders and hallmarks of aging have a genetic component. The largest GWAS of LTL was conducted in 472,174 well-characterized participants in the UK Biobank [7]. This study identified 197 variants associated with LTL at 138 genomic loci (108 of which were novel). In addition, genetically determined LTL was associated with multiple biological traits (e.g. bone marrow function) as well as a number of diseases spanning neoplastic, vascular and inflammatory disorders [7]. A recent study that derived mtDNA_cn in 383,476 UK Biobank participants of European ancestry using the AutoMitoC pipeline, which leverages single nucleotide polymorphisms (SNP) array probe intensities, identified 71 loci significant at a genome-wide threshold [17]. Few studies have tried to assess whether the putative relationship between mental disorders and hallmarks of aging might be affected by genetic determinants. In a previous study, we used two-sample mendelian randomization analysis to evaluate the bidirectional association between genetically determined LTL (using summary statistics from a GWAS including genetic data for 37,684 individuals [18]) and predisposition to BD (using data from PGC BD freeze 2, including 20,352 cases and 31,358 controls [19]) and reported negative results [12]. Consistently, another study did not find any significant association between polygenic risk for BD, MDD or SCZ and LTL in a sample including 351 participants characterized for depression using self-reported measures [20]. However, a recent study conducted in the larger UK Biobank cohort for which LTL measurements are now available, reported a polygenic risk score (PRS) for depression to be associated with shorter telomeres (β = -0.006, adjusted p = 0.001) [21], suggesting the existence of a possible link between mental disorders and genetically predicted LTL. To our knowledge, no study explored shared genetic bases between severe mental disorders and mtDNA-cn.

Thanks to the development of analytical methods based on pleiotropy, novel genetic variants associated with severe mental disorders as well as genetic determinants shared with related traits, have been identified [22-26]. However, to date this approach has never been applied to LTL or mtDNA-cn. In this study, we used state-of-the-art approaches to quantify the genetic overlap between severe mental disorders and LTL or mtDNA-cn and identify shared genetic determinants and their direction of effect (i.e. whether they predispose patients to accelerated cellular aging or rather play a counteractive role). We used MiXeR to quantify the trait-specific and shared architecture of mental disorders and hallmarks of aging and the conditional / conjunctional false discovery rate (condFDR/conjFDR) method to detect shared genetic loci. Finally, we integrated gene expression data from brain regions and used different tools to functionally annotate and prioritize identified loci and investigate their druggability. Our results elucidate genetic markers shared between severe mental disorders and markers of cellular aging.

Materials and Methods

GWAS samples

We conducted a cross-trait analysis using the largest publicly available releases of GWAS summary statistics from PGC for BD and SCZ, or PGC and iPSYCH for MDD [27-29] and for two markers of biological aging (LTL and mtDNA-cn) from UK Biobank [7,17]. For BD and MDD, to avoid sample overlap, we used the GWAS summary statistics excluding participants from UK Biobank. The BD sample included 40,463 cases from 56 cohorts collected in Europe, North America and Australia and 313,436 controls of European origin [30]. The SCZ sample included 53,386 cases and 77,258 controls of European origin [28], while the MDD sample 166,773 cases and 507,679 controls of European origin [29]. GWAS summary statistics for genetically determined LTL [7] and for mtDNA-cn (ascertained using the AutoMitoC pipeline, which leverages SNP array probe intensities) [17] were obtained for 472,174 and 383,476 UK Biobank participants, respectively. For all GWAS datasets, ethical approval was obtained by the original GWAS studies and quality control procedures, including adjustment for population stratification, were performed by the original studies. Analyses were conducted on autosomal variants common to GWAS on mental disorders and LTL or mtDNA-cn, after exclusion of ambiguous variants (A/T and C/G) or variants located in regions characterized by strong LD such

as the MHC region (chr6:25119106-33854733), chromosome 8p23.1 (chr8:7200000–12500000) and the *MAPT* gene (chr17:40000000–47000000).

Global genetic correlation analysis

Global genetic correlation analysis was conducted using LDSC [31]. To this aim, summary statistics were converted into the LDSC format, while linkage disequilibrium scores were computed using 1000 Genomes European data [31,32]. The cross-trait LDSC method represents an extension of single-trait LDSC to estimate heritability and genetic correlation from GWAS summary statistics. This method allows to study the genetic correlation globally, considering the average of the shared signals across the genome, including the contribution of SNPs that do not reach genome-wide significance [32], taking into account possible sample overlap and population stratification.

Bivariate causal mixture model (MiXeR)

We used bivariate causal mixture model (MiXeR, v. 1.3) to study shared genetic bases between severe mental disorders and LTL or mtDNA-cn beyond genetic correlation. This method quantifies the genetic overlap between two traits estimating the total number of shared and trait-specific genetic variants [33]. We first constructed conditional QQ plots, which represent modified versions of the standard QQ plots that allow to visualize the cross-trait polygenic enrichment. These plots are constructed by creating subsets of SNPs based on the level of association with the secondary phenotype (using three thresholds $p \leq 0.10$, $p \leq 0.01$ and $p \leq 0.001$). Under the null hypothesis, nominal p-values follow the straight line, while under cross-trait polygenic enrichment they show progressive leftward deflections. Next, we applied causal mixture models to quantify the genetic overlap between mental disorders and markers of biological aging. We first computed univariate estimates to quantify trait-influencing loci for each trait of interest. Next, we computed bivariate estimates of genetic overlap between each mental disorder and markers of biological aging. Detailed information on the modelling of genetic effects is available in the original MiXeR article [33]. Briefly, additive genetic effects are modeled as a mixture of components that are plotted in Venn diagrams and that represent SNPs not associated with any of the two traits, SNPs associated with only one trait or with both. In addition, we computed the Dice

coefficient (DC), which represents the proportion of SNPs shared between two traits out of the total number of SNPs estimated to be associated with both traits.

Conditional and conjunctional false discovery rate analysis

To identify shared loci between mental disorders and markers of biological aging, we used the condFDR/conjFDR method implemented in pleioFDR [34,35]. This method represents a complementary approach compared with MiXeR as the first offers information about the total amount the genetic overlap between pairs of traits, while the condFDR/conjFDR method allows to identify the specific shared genetic variants. Specifically, this method allows to re-adjust the GWAS statistics in a primary phenotype (e.g. BD) by leveraging pleiotropic enrichment with a GWAS in a secondary phenotype (e.g. LTL). For each p-value in the primary phenotype, condFDR estimates are obtained by calculating the stratified empirical cumulative distribution function of the p-values [36]. The strata are obtained by the enrichment of SNP associations depending on increased p-values in a secondary phenotype [36]. The conjFDR method is an extension of condFDR aimed at discovering SNPs associated with two phenotypes simultaneously. After inverting the roles of the primary and secondary phenotypes, the conjFDR is defined as the maximum of the two condFDR values. A conjFDR < 0.05 was considered to be significant, as in previous studies [36-39].

Definition of genetic loci and functional enrichment

Independent significant genetic loci were defined according to the FUMA protocol [40]. Lead SNPs were defined by double clumping (a clumping of SNPs significant and independent at $r^2 < 0.6$, and a secondary clumping of these SNPs at $r^2 < 0.1$). Loci separated by a distance lower than 250 kb were merged. 1000 genome phase 3 was used as a reference panel to compute linkage disequilibrium in FUMA. The direction of allelic effects for significant variants was evaluated by comparing betas reported in the original GWAS. Positional and functional annotation of lead SNPs was performed using different tools. The CADD score, which predicts how deleterious a variant is on protein structure/function by contrasting variants that survived natural selection with simulated mutations, was computed in FUMA [41]. RegulomeDB rank (from 1 to 7, with 1 being associated with highest evidence of functional effects) was calculated using RegulomeDB in FUMA [42] based on known and predicted regulatory elements including regions of DNase hypersensitivity, binding sites of

transcription factors and promoter regions. Next, we searched whether SNPs acted as eQTLs based on genotyping and gene expression data (obtained from a range of 114 - 209 samples) from Genotype-Tissue Expression (GTEx) v.8 in brain regions. While aging is multifactorial process associated with changes at a multiple-organ level, we chose to specifically focus on genes predicted to be modulated in brain regions in order to select targets with the highest probability of playing a relevant role for both phenotypes under study (aging and severe mental disorders), also based on the fact that this list of genes was used as input to investigate druggability. In the GTEx project, gene expression was measured with Illumina TrueSeq RNA sequencing or Affymetrix Human Gene 1.1 ST Expression Array, while genotyping data were obtained with whole genome sequencing, whole exome sequencing, Illumina OMNI 5M, 2.5M or Exome SNP arrays [43]. We reported cis eQTLs in a +/- 1Mb cis window around the transcription start site (TSS) and significant based on FDR. For genes for which expression levels are modulated by SNPs associated with increased risk of mental disorders and shorter LTL or lower mtDNA-cn, we tested the functional enrichment for gene ontology (GO) terms using enrichR [44], adjusting results based on FDR. In addition, we investigated whether proteins encoded by the identified genes showed significant PPI enrichment using STRING [45]. A significant PPI indicates that the identified proteins have more interactions among themselves than would be expected for a random set of proteins of the same size and degree distribution drawn from the genome. Genes modulated by SNPs associated with increased predisposition to mental disorders and shorter LTL or lower mtDNA-cn were searched in DGIdb [46] to assess whether they are known targets of existing drugs (drug-gene interactions) or 'potentially druggable' based on their involvement in selected pathways, molecular functions or gene families [46]. The DGIdb database classifies genes in categories based on information retrieved from different drug target repositories (DrugBank, PharmGKB, Chembl, Drug Target Commons, Therapeutic Target Database and others). In addition, we searched for upstream regulators of prioritized genes using IPA (Ingenuity System Inc, USA). Upstream regulators are defined as genes, microRNAs, transcription factors or chemical compounds that affect the genes of interest through effects on expression, transcription, activation, molecular modification, transport or binding events according to the Ingenuity Knowledge Base, a large collection of observations in various experimental contexts. P-values of overlap for each upstream regulator based on Fisher's exact test calculated by IPA were adjusted for multiple testing with FDR (a q-value < 0.05 was considered to be significant).

Results

Pleiotropic enrichment and quantification of genetic overlap

Among mental disorders, only MDD showed a significant negative global genetic correlation with LTL (r_g = -0.14, p = 6.5E-10). Conversely, global genetic correlation between LTL and BD (r_g = -0.03, p = 0.18) or SCZ (r_g = 0.00, p = 0.98) was not significant. LTL and mtDNA-cn were significantly positively correlated (r_g = 0.12, p = 9.4E-04), while mtDNA-cn was not significantly correlated with any mental disorder (BD: r_g = -0.005, p = 0.88; SCZ: r_g = 0.02, p = 0.82, MDD: r_g = 0.01, p = 0.74).

On the other hand, conditional QQ plots suggested cross-phenotype polygenic enrichment between all severe mental disorders and genetically determined LTL (Supplementary Figure 1). As shown in Supplementary Figure 2, analyses conducted with MiXeR showed a much larger polygenicity for severe mental disorders than for markers of aging. Nonetheless, based on the positive AIC reported in Table 1, for both LTL and mtDNA-cn, the model fitted by MiXeR was found to explain the GWAS signal better than a model considering the maximum possible polygenic overlap given a trait's architecture (i.e. a model in which the causal variants of the least polygenic trait form a subset of the causal variants of the most polygenic trait, best vs max AIC) or a model with the minimal possible polygenic overlap (i.e. a model constrained to a specific value of the genetic correlation, best vs min AIC), supporting the existence of a polygenic overlap.

A large proportion of variants estimated to be associated with markers of biological aging were also associated with severe mental disorders (Table 1). Namely, of variants associated with LTL, 66%, 40% and 91% were also shared with BD, SCZ and MDD, respectively. A lower but still substantial proportion of variants associated with mtDNA-cn was shared with severe mental disorders (from 27% for SCZ and MDD to 30% for BD. Conversely, when considering variants associated with severe mental disorders, only a limited proportion (from 1% to 3%) was also shared with markers of biological aging (Table 1).

Table 1. Proportion of overlapping genetic variants on the total polygenicity of each trait

Trait 1	Trait 2	Dice, mean (se)	% of variants associated with mental disorders and shared with aging markers	% of variants associated with aging markers and shared with mental disorders	best vs min AIC	best vs max AIC
BD	LTL	0.05 (0.02)	3%	66%	12.91	10.03
BD	mtDNA-cn	0.02 (0.01)	1%	30%	1.87	3.45
SCZ	LTL	0.03 (0.01)	2%	40%	6.03	9.08
SCZ	mtDNA-cn	0.01 (0.01)	1%	27%	2.44	6.91
MDD	LTL	0.07 (0.01)	3%	91%	2.09	3.45
MDD	mtDNA-cn	0.01 (0.01)	1%	27%	2.06	5.33

best vs max AIC: comparison of the best model fitted by MiXeR vs the model with maximum possible polygenic overlap given trait's genetic architecture. A positive value means that best model explains the observed GWAS signal better than the max model, despite its additional complexity (due to the fact that MiXeR has to find the value of the polygenic overlap). best vs min AIC: best model vs the model with the minimal possible polygenic overlap. Abbreviations: AIC, Akaike Information Criterion; BD, bipolar disorder; LTL, leukocyte telomere length; MDD, major depressive disorder; mtDNA-cn, mitochondrial DNA copy number; se, standard error; SCZ, schizophrenia

Genetic loci shared between severe mental disorders and markers of aging

Fifteen genetic loci including 17 lead SNPs were shared between BD and LTL at a conjFDR < 0.05 (Supplementary Table 1). Of the 17 lead SNPs, 6 were associated with increased risk of BD and shorter LTL (while 11 with increased risk of BD and increased LTL). Six of the 17 lead SNPs were found to act as expression quantitative trait loci (eQTL) for different genes in at least one brain region (Supplementary Table 1). However, only the intergenic SNP rs10822056, suggested to act as an eQTL for the *ADO* gene in the caudate brain region, was associated with increased predisposition to BD and shorter LTL, while all the other SNPs acting as eQTLs were associated with BD and longer LTL. Four genetic loci including 4 lead SNPs were shared between BD and mtDNA-cn at a conjFDR < 0.05 (Supplementary Table 1). The allele associated with increased predisposition to BD was associated with lower mtDNA-cn for 2 SNPs and with higher mtDNA-cn for the other 2 SNPs. Only one SNP (rs3208937) was found to act as an eQTL for different genes in different brain regions (Supplementary Table 1).

A total of 52 loci were shared between SCZ and LTL at a conjFDR < 0.05 (Supplementary Table 2). Of the 55 lead SNPs, 33 were associated with increased risk of SCZ and shorter LTL. Twenty-eight of the 55 lead SNPs were found to act as eQTLs for different genes in at least one brain region (Supplementary Table 2). Of these, 16 SNPs were associated with increased predisposition to SCZ and shorter LTL, while the other SNPs acting as eQTLs with increased predisposition to SCZ and longer LTL. Genes modulated by SNPs associated with increased predisposition to SCZ and shorter LTL were enriched for 2 cellular component and 9 molecular GO terms (Supplementary Table 3). Proteins encoded by the identified genes also showed a significant protein-protein interaction (PPI) enrichment (PPI enrichment p-value: 1.0E-05, Supplementary Figure 3). Twelve genetic loci were shared between SCZ and mtDNA-cn at a conjFDR < 0.05 (Supplementary Table 2). Of these, 3 SNPs were associated with increased risk of SCZ and shorter mtDNA-cn and all acted as eQTLs for different genes in at least one brain region (Supplementary Table 2). Genes modulated by these SNPs were

enriched for 4 biological processes GO terms: Negative Regulation Of Cell Population Proliferation (GO:0008285, p = 7.3E-04, FDR = 0.04, OR = 22.4, genes: *EIF2AK2, CDK10, GAS8*); Negative Regulation Of Cellular Process (GO:0048523, p = 0.002, FDR = 0.04, OR = 15.6, genes: *EIF2AK2, CDK10, GAS8*); Regulation Of Cell Population Proliferation (GO:0042127, p = 0.006, FDR = 0.04, OR = 10.8, genes: *EIF2AK2, CDK10, GAS8*); Cellular Component Assembly (GO:0022607, p = 0.007, FDR = 0.04, OR = 19.1, genes: *FANCA, GAS8*).

Finally, 19 loci were shared between MDD and LTL at a conjFDR < 0.05 (Supplementary Table 4). Of the 19 lead SNPs, 13 were associated with increased risk of MDD and shorter LTL and 6 were significant eQTLs for different genes in at least one brain region (Supplementary Table 4). Four of the 6 eQTLs were associated with increased predisposition to MDD and shorter LTL. Genes modulated by these SNPs were significantly enriched for 5 biological process different GO terms (Supplementary Table 5). Only 1 locus with rs4955411 as the lead SNP was shared between MDD and mtDNA-cn. This SNP was found to be a significant eQTL for several genes in different brain regions (Supplementary Table 4).

Druggable genes and upstream regulators

The *ADO* gene, which was modulated by SNPs associated with BD and increased biological aging, is not part of the druggable genome based on the Drug Gene Interaction Database (DGIdb). Conversely, 14 and 7 genes modulated by SNPs associated with shorter LTL and SCZ (Table 2) or MDD (Table 3), respectively, were druggable.

Table 2. Druggable genes modulated by SNPs associated with SCZ and shorter LTL or lower mtDNA-cn

Chr	Lead SNP	Location	EA / OA	beta SCZ	beta LTL	eQTL in brain regions (GTEx v. 8)	Druggable genes
1	rs4844621	*C1orf132*	A/G	**0.05**	**-0.01**	*CD46* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hyppocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra)	*CD46*
10	rs17883150	*GSTO1*	G/A	**0.04**	**-0.01**	*RP11-127L20.3* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *GSTO2* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, frontal cortex, hippocampus,	*GSTO2*

						hypothalamus, nucleus accumbens, putamen); *ITPRIP* (cortex)	
11	rs10838843	Intergenic	G/T	**-0.07**	**0.01**	*FOLH1* (caudate, cerebellum, nucleus accumbens, putamen)	*FOLH1*
12	rs73230058	*PITPNM2*	C/T	**0.06**	**-0.01**	*ABCB9* (cerebellum); *KMT5A* (cerebellum)	*ABCB9*
15	rs16969894	*IREB2*	C/T	**0.07**	**-0.01**	*CHRNA3* (caudate, nucleus accumbens); *CHRNA5* (nucleus accumbens)	*CHRNA3, CHRNA5*
15	rs4702	*FURIN*	G/A	**0.08**	**-0.01**	*FURIN* (frontal cortex)	*FURIN*
20	rs310653	*SRMS*	T/C	**-0.04**	**0.01**	*PTK6* (caudate)	*PTK6*
22	rs4822000	*RP11-12M9.4*	T/C	**-0.04**	**0.01**	*MCHR1* (cerebellum); *RP11-12M9.4* (cerebellum); *SLC25A17* (cerebellum, nucleus accumbens); *ZC3H7B* (cerebellum)	*MCHR1, SLC25A17*
22	rs138832	*BRD1*	A/G	**-0.05**	**0.01**	*ALG12* (hippocampus, nucleus accumbens); *CRELD2* (hypothalamus); *RP3-522J7.6* (cerebellum); *ZBED4* (cerebellum)	*CRELD2*
Chr	**Lead SNP**	**Location**	**EA / OA**	**beta SCZ**	**beta mtDNA-cn**	**eQTL in brain regions (GTEx v. 8)**	
2	rs11899117	*EIF2AK2*	G/A	**0.04**	**-0.01**	*NDUFAF7* (cerebellum); *EIF2AK2* (cerebellum)	*EIF2AK2*
16	rs164749	Intergenic	T/G	**-0.04**	**0.01**	*SPATA33* (anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus); *LINC02166* (anterior cingulate cortex, caudate, cortex, nucleus accumbens); *GAS8* (anterior cingulate cortex, cerebellum, cortex, nucleus accumbens, putamen); *CDK10* (cerebellum); *FANCA* (cerebellum); *VPS9D1* (cortex)	*CDK10*
22	rs41297816	*TBX1*	A/G	**-0.05**	**0.01**	*DGCR12* (amygdala); *TXNRD2* (caudate)	*TXNRD2*

Table 3. Druggable genes modulated by SNPs associated with MDD and shorter LTL

Chr	Lead SNP	Gene	EA / OA	beta MDD	beta LTL	eQTL in brain regions (GTEx v. 8)	Druggable genome
1	rs4653448	Intergenic	A/G	**0.02**	**-0.03**	*PARP1* (cerebellum)	*PARP1*
3	rs34614773	*RNF123*	T/G	**0.03**	**-0.01**	*FAM212A* (cerebellum); *GMPPB* (cerebellum, cortex, hyppocampus, putamen); *HYAL3* (cerebellum), *MST1R* (caudate, cerebellum, cortex); *RBM6* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra); *RNF123* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hypothalamus, nucleus accumbens)	*HYAL3, MST1R, RNF123*
11	rs112181005	*C11orf49*	G/A	**0.03**	**-0.01**	*LPR4* (caudate, nucleus accumbens, putamen); *MADD*	*NR1H3*

22	rs7290458	Intergenic	T/C	**-0.02**	**0.01**	(cerebellum); *NR1H3* (caudate, nucleus accumbens) *ZC3H7B* (cerebellum); *MCHR1* (cerebellum); *RP11-12M9.4* (cerebellum); *SLC25A17* (nucleus accumbens)	*MCHR1, SLC25A17*

After multiple testing correction, significant upstream regulator of genes modulated by SNPs associated with SCZ and shorter LTL included 1 drug, 1 microRNA and 5 other genes 1(Supplementary Table 6). A network of these regulators and the 6 modulated genes is shown in Figure 1.

Conversely, significant upstream regulators of genes modulated by SNPs associated with MDD and shorter LTL included 20 drugs, 20enzymes, 5 transcription regulators, 30 chemical compounds and 37 other genes (Supplementary Table 7). Among upstream regulators drugs, genistein has been suggested to exert anti-inflammatory and antioxidant effects, as well as to be a promising therapeutic compound in different age-related disorders. A subset of the network including this drug, the 2 genes of our list suggested to be modulated by this drug (*HYAL3* and *CTSF*) as well as other significant modulators or transcription regulators of these 2 genes are shown in Figure 2.

Discussion

In this study, we explored pleiotropy between severe mental disorders and two hallmarks of aging. Using global genetic correlation, we found only MDD to be significantly associated with shorter LTL (r_g = -0.14, p = 6.5E-10). This result is in line with a recent study suggesting shorter LTL in individuals with depression in UK Biobank as well as a significant association between a PRS for depression and shorter LTL [21]. However, using a method able to identify specific genetic loci between two traits, rather than just investigating genetic correlation at a global level, we identified significant cross-trait enrichment between all the investigated severe mental disorders and genetically determined LTL or mtDNA-cn. Interestingly, a high percentage of identified loci showed lead SNPs with a direction of effect unexpected based on the hypothesis that severe mental disorders are characterized by accelerated cellular aging. Specifically, only 35%, (6/17), 60% (33/55) and 68% (13/19) of lead SNPs were associated with increased risk of BD, SCZ or MDD, respectively, and shorter LTL. BD showed the highest percentage of loci with an unexpected direction of effect. Interestingly, among mental disorders, BD is the one for which the most conflicting results have been reported as regards to shorter LTL

compared with individual without mental illness. Indeed, a number of studies has observed longer LTL in patients with BD compared with controls [12,47]. While treatment with the mood stabilizer lithium might exert a potential counteractive effect on telomere shortening [11,48], it might also be the case that some genetic variants associated with increased risk of BD might protect patients from accelerated telomere shortening. Among lead SNPs associated with shorter LTL but reduced risk of BD, we found the rs12919664 SNP, located in the *TERF2* gene. This gene encodes a telomere specific protein which is a component of the telomere nucleoprotein complex, plays a key role in the protective activity of telomeres and is a negative regulator of telomere length. The C allele, that we found to be associated with increased risk of BD and longer LTL, reduces levels of the *TERF2* gene in the cerebellum and in the cortex (Supplementary Table 1).

Among SNPs with a functional effect associated with higher risk of BD and cellular aging, the rs11556924 SNP in the *ZC3HC1* gene and the rs7909129 SNP in the *SORCS3* gene, were predicted to exert a detrimental effect on proteins based on the Combined Annotation Dependent Depletion (CADD) score. In particular, the rs11556924 in the *ZC3HC1* gene is an exonic non-synonymous variant with a CADD score of 30 (variants with scores above 20 are predicted to be among the 1.0% most deleterious substitutions in the human genome) [41,49]. In our data, the rs11556924 C allele was associated with reduced risk of BD and reduced LTL. The latter observation is in accordance with results from a recent study linking the in *ZC3HC1* rs56179563 SNP (which is in linkage disequilibrium with rs11556924, D' = 0.95, R^2 = 0.87) with overall survival. Namely, the rs56179563 A allele, which is correlated with the rs11556924 T allele, was associated with increased lifespan in a mortality risk-factor-informed GWAS [50]. The other SNP with a potential detrimental effect, located in the *SORCS3* gene, was associated with shorter LTL and increased predisposition to all three mental disorders (Supplementary Tables 1-3). This gene has been previously implicated in different mental disorders [51-53] as well as in Alzheimer's disease [53,54]. The protein encoded by this gene is a member of the vacuolar protein sorting 10 (Vps10) family of receptors, which represent cargos of the retromer complex and are involved in protein trafficking and intracellular/intercellular signaling in neuronal and non-neuronal cells [55,56]. The retromer is a complex of proteins that control the reverse transport of molecules from the endosomes trans-Golgi network or to the cell surface, thus potentially playing a relevant role in different neurodegenerative diseases. Besides their roles as cargo proteins of the retromer complex, members of the Vps10 receptor family such as SORCS3 have been shown to modulate neurotrophic signaling pathways [56]. Based on this evidence,

SORCS3 represents an interesting target that might be involved in the molecular mechanisms underlying accelerated cellular aging in severe mental disorders. In addition, four loci with rs11588837, rs11638445, rs12629701 and rs2345964 as lead SNPs, were associated with longer LTL and predisposition to both BD and SCZ. Three of these variants are significant eQTLs for a variety of genes in different brain regions. Among genes modulated by these variants, rs11588837 can affect the expression of *VPS45* (a gene encoding another protein involved in trafficking through the endosomal system [57]) in the frontal cortex.

SCZ was the severe mental disorder for which we identified the highest number of genetic loci shared with LTL (52 loci with 55 lead SNPs) or mtDNA-cn (12 loci with 12 lead SNPs), with around half of these SNPs found to act as significant eQTLs for a variety of genes in at least one brain region (Supplementary Table 2). Genes modulated by SNPs associated with increased predisposition to SCZ and shorter LTL were enriched for GO terms related to Acetylcholine Receptor Activity and S-adenosylmethionine-dependent Methyltransferase Activity. Genes included in this GO term encoded two subunits of the cholinergic receptor (*CHRNA3* and *CHRNA5*) that we found to be modulated by the rs16969894 SNP in brain regions. Specifically, the rs16969894 C allele, that we found to be associated with increased risk of SCZ and reduced LTL, increases expression of *CHRNA3* in the caudate and of both genes in the nucleus accumbens. Analyses conducted with IPA showed proteins included in the neuregulin (NRG) family to be significant upstream regulators of both *CHRNA3* and *CHRNA5* (Supplementary Table 6). Genetic variation at the *CHRNA3/5* locus has been previously associated with lifespan [58,59]. However, it is unclear whether this effect might be entirely or only partially mediated by nicotine dependence, by an increased vulnerability to smoking effects [58], or also by other factors.

MDD was the disorder for which most SNPs showed the expected direction of effect (the allele associated with increased predisposition to MDD was also associated with shorter LTL). This observation is in line with the finding of a significant negative global genetic correlation between MDD and LTL. Using the list of 7 genes modulated by SNPs associated with MDD and shorter LTL as input, we found genistein (4',5,7-trihydroxyisoflavone) as a common upstream regulator of *HYAL3* and *NR1H3*, two genes for which the MDD risk allele induced lower expression in either cerebellum (*HYAL3*) or caudate and nucleus accumbens (*NR1H3*) (Table 5). Genistein is a plant-derived phytoestrogen part of the flavonoid family. Due to its chemical structure similar to that of the mammalian estrogens, this compound can modulate endogenous estrogens via binding to

the estrogen receptors [60,61]. Genistein is gaining high interest due to its suggested antiproliferative [62,63], anti-inflammatory [60] and antioxidant [64] effects in *in-vitro* models and in preclinical studies, leading to explore its potential pharmacological effects in a range of disorders characterized by a state of chronic inflammation or microinflammation, such as metabolic [65], cardiovascular [66] and neurodegenerative diseases [67]. Indeed, a chronic state of low-grade inflammation and oxidative stress have been hypothesized to play a role in the pathogenesis of severe mental disorders as well as of age-related disorders. A recent study using a system biology approach based on the analysis of metabolomic and gut microbiota data, suggested genistein to be among the most potentially promising novel compounds to treat MDD [68], supporting previous observation of antidepressants effects in rats [69]. While randomized human clinical trials will be needed to establish potential clinical utility and safety of genistein, it might be speculated that this molecule with anti-inflammatory properties might be especially useful for patients with MDD with high genetic load for accelerated cellular aging.

We conducted a large cross-trait analysis between severe mental disorders and markers of cellular aging using state-of-the-art methods. Some limitations have to be taken into consideration when interpreting our results. Firstly, our analyses were restricted to participants of European origin. It is therefore possible that these results might not be directly transferable to participants with a different origin. Secondly, aging is a multifactorial process driven by genetic and environmental factors, including lifestyle factors that have not been the focus of this study. Future expansions of this work might include taking into account environmental exposure to factors previously shown to be associated with accelerated aging, as well as testing the association between severe mental disorders and epigenetic measures of aging. Finally, while we evaluated the functional effect of the identified genetic variants on gene expression in brain regions, our analyses were restricted to peripheral markers of biological aging. Future expansions of this work might focus on other aging hallmarks with brain relevance, such as brain age. Our study leveraged the largest publicly available GWAS summary statistics for BD, SCZ and MDD to gain insights on the genetic determinants specifically shared between each of these severe mental disorders and markers of aging. However, genetic determinants of psychiatric disorders have been shown to transcend diagnostic boundaries, thus supporting the utility of cross-disorder analyses to enable the discovery of novel variants [70] and dissect molecular mechanisms underlying different disorders. A recent cross-disorder study reported that genes shared between different mental disorders are disproportionately

associated with biological pathways related to neurodevelopment and show distinctive gene expression patterns [71]. Since similar differences might also be observed in the association between mental disorders and accelerated cellular aging, future expansions of our study will include evaluating the association between cross-disorder genes and markers of aging, in order to discover novel genetic determinants potentially underlying accelerated cellular aging in mental disorders as well as better dissect differences between cross-disorder and disorder-specific mechanisms.

While the present study has leveraged large GWAS summary statistics, future studies to be conducted in datasets with individual genotype data might allow to explore additional relevant aspects related to cellular aging in severe mental disorders such as the role of gene-gene interactions as well as the aggregated effects of sets of genetic variants. In addition, while we conducted in-silico analyses to identify genetic variants acting as eQTLs, future studies might assess whether genes predicted to be modulated by these variants show differences in gene expression, either in peripheral or brain tissues, in patients with severe mental disorders compared with non-psychiatric controls. Finally, the increased availability of cellular models such as neurons and neural precursors cells derived from induced-pluripotent stem lines might allow to gain insights on the potential brain relevance of identified targets. Our results support the existence of shared genetic loci between severe mental disorders and markers of biological aging and prioritize functional loci and druggable targets for further investigation. Based on the direction of effect of identified variants, shorter LTL in patients with SCZ or BD could be at least partly counteracted by genetic factors. In addition, our data point to the retromer complex and intracellular protein trafficking as interesting cross-disorder molecular mechanisms potentially underlying the shared genetic bases between severe mental disorders and markers of biological aging.

Authors' contributions

CP, conceptualization, data curation, data analysis, visualization, writing and review; DC, writing – review & editing; AM, writing – review & editing; PP, visualization, writing – review & editing; GPP, writing – review & editing; GS, writing – review & editing; RA, writing – review & editing; CC, writing – review & editing; MM, visualization, writing – review & editing; AS, conceptualization, writing – review & editing. All authors read and approved the final manuscript.

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Competing interests

The authors have nothing to disclose

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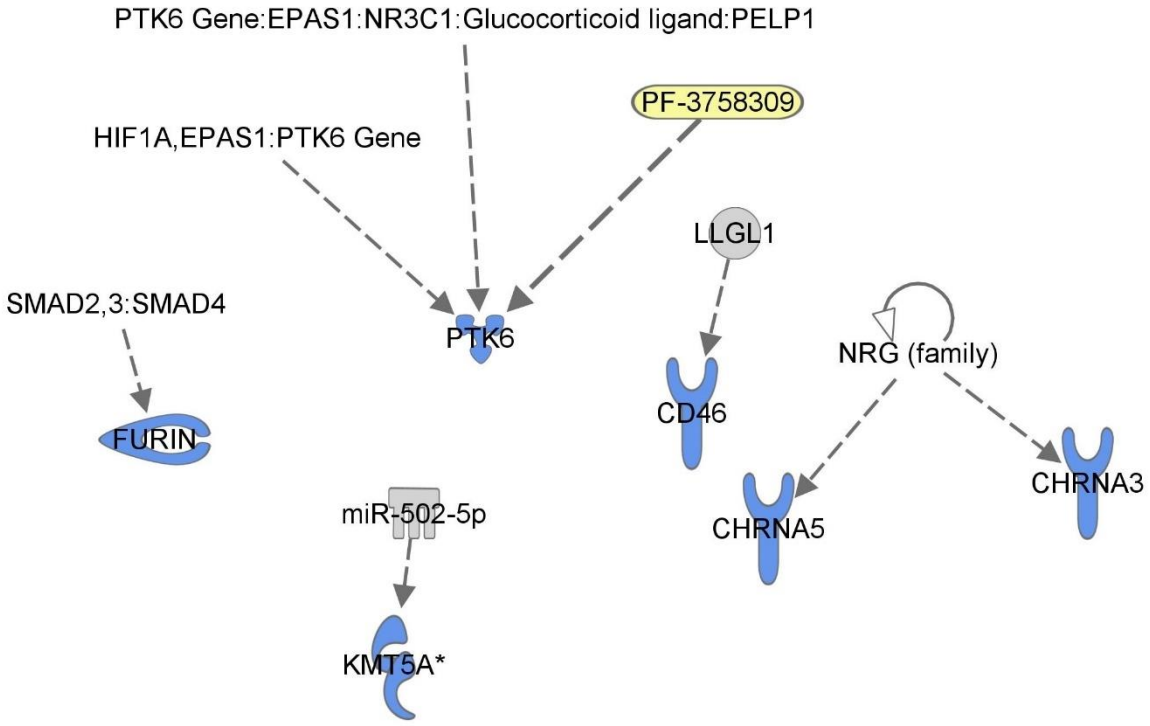
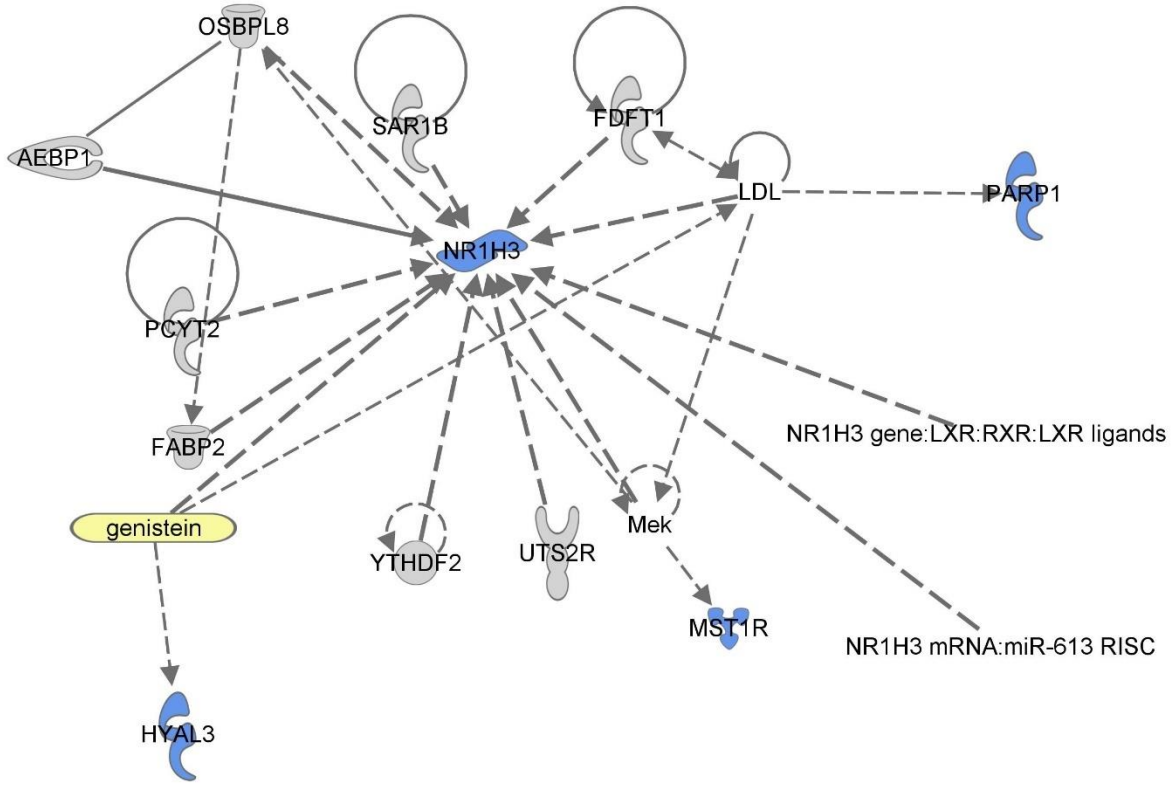
Figure legends

Figure 1. Network of upstream regulators of genes modulated by SNPs associated with increased risk of SCZ and shorter LTL



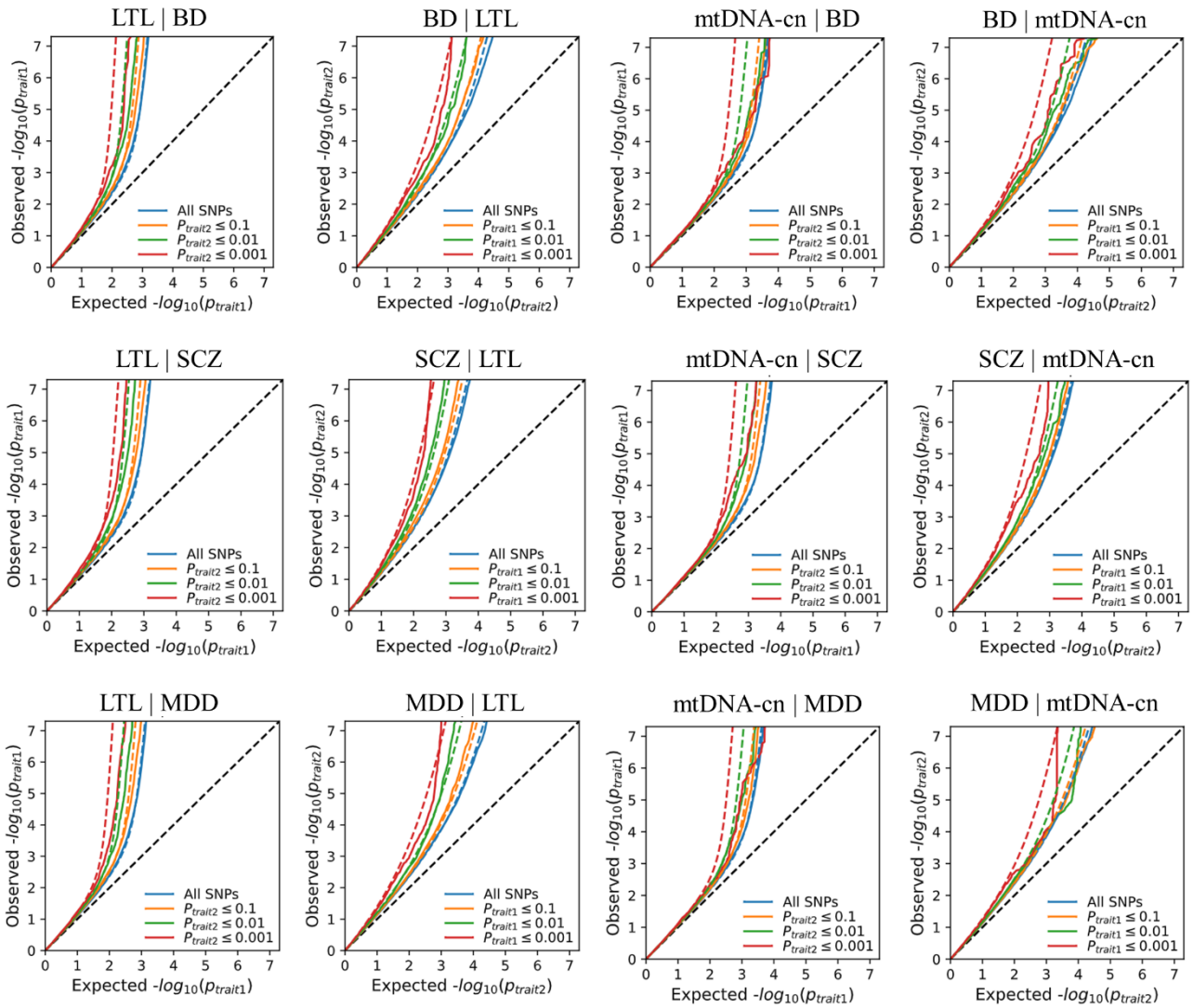
The figure shows a network constructed based on significant upstream regulators of genes modulated by SNPs associated with increased risk of SCZ and shorter LTL (shown in blue). Among upstream regulators, drugs are shown in yellow while other regulators in grey.

Figure 2. Network of upstream regulators of genes modulated by SNPs associated with increased risk of MDD and shorter LTL



The figure shows a network constructed based on the drug genistein, the 2 genes in our dataset (shown in blue) predicted to be modulated by this compound as well as other upstream regulators of these genes. Among upstream regulators, drugs are shown in yellow while genes in grey.

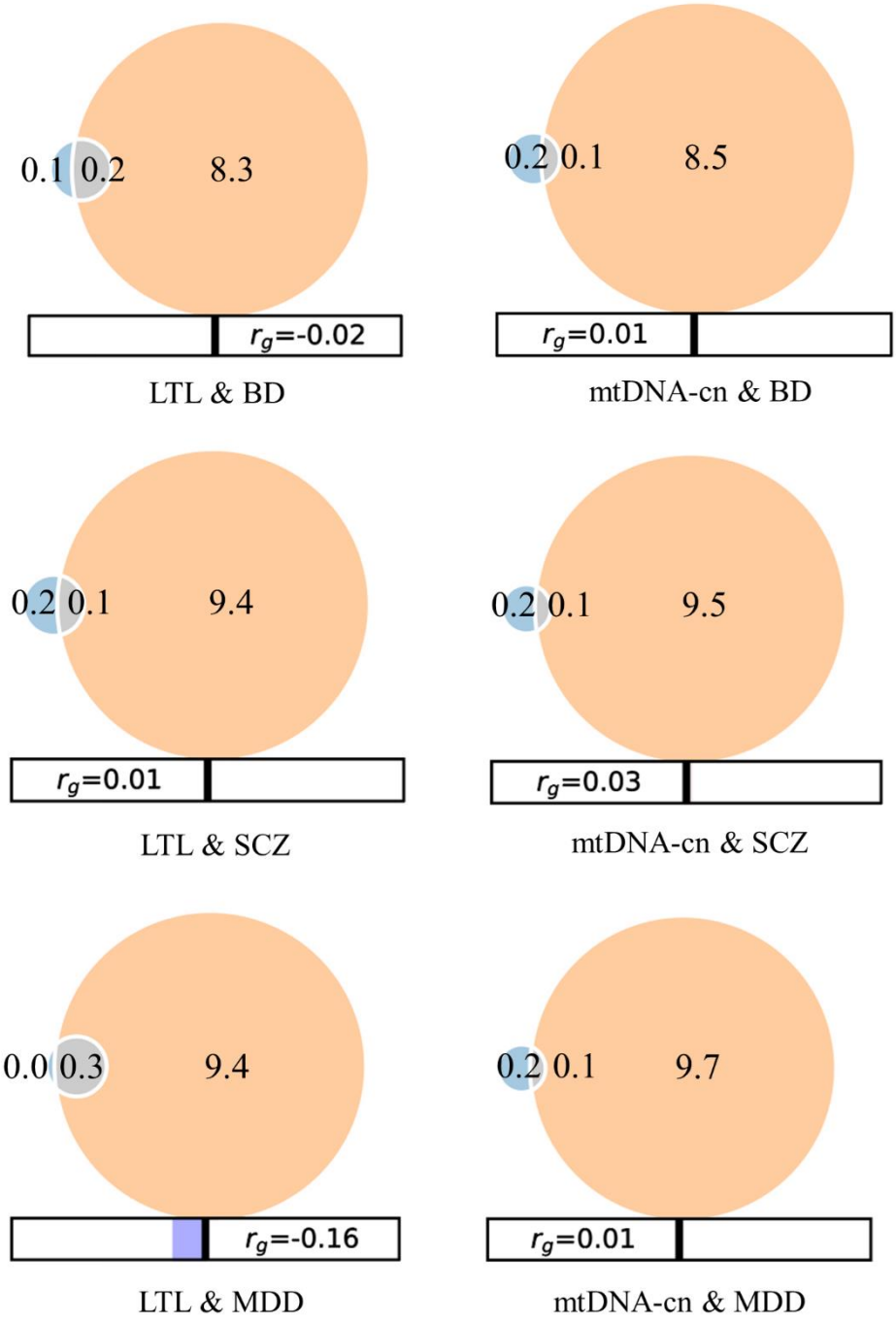
Supplementary Figure 1. Conditional QQ plots suggesting cross-phenotype polygenic enrichment between mental disorders and markers of biological aging



The figure shows conditional QQ plots of observed versus expected −log10 p-values in the primary trait (e.g. LTL) based on significance of association with a secondary trait (e.g. BD) at $p \leq 0.1$ (orange solid line), $p \leq 0.01$ (green solid line), or $p \leq 0.001$ (red solid line). The blue line indicates all SNPs. Dashed lines indicate model prediction at each p level. The black dotted line indicates the expected QQ plot under the null hypothesis (no SNP associated with the phenotype).

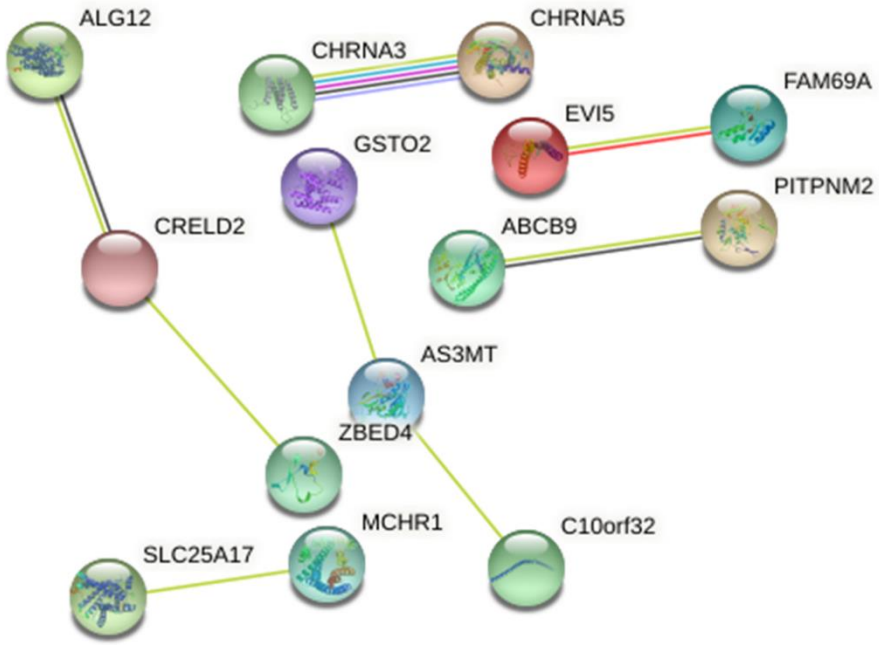
The progressive leftward deflection from the null line as levels of SNP associations with the secondary phenotype increase shows significant cross-trait enrichment between primary and secondary phenotype

Supplementary Figure 2. Venn diagrams showing unique and shared trait-influencing variants associated with markers of biological aging and severe mental disorders



The Venn diagrams show the estimated number of causal variants (in thousands), explaining 90% of heritability for two markers of biological aging (LTL and mtDNA-cn) and for severe mental disorders. Shared variants are colored in gray, variants specific for markers of biological aging in blue, while variants specific for mental disorders in orange. The size of the circles reflects the degree of polygenicity of each trait. The genetic correlation for each pair as estimated by MiXeR (r_g) is indicated in blue (negative correlation) or red (positive correlation).
Abbreviations: BD, bipolar disorder; LTL, leukocyte telomere length; MDD, major depressive disorder; mtDNA-cn, mitochondrial DNA copy number; SCZ, schizophrenia

Supplementary Figure 3. Protein-protein interaction network of genes modulated by SNPs associated with increased predisposition to SCZ and shorter LTL



Nodes represent genes, lines of different colors represent different types of evidence used by STRING to predict the association.

Supplementary Table 1. Genetic loci and lead SNPs associated with risk of BD and LTL or mtDNA-cn

Chr	Start locus	Stop locus	Lead SNP	Nearest gene (Kb)	EA/OA	beta BD	beta LTL	conjFDR	CADD score	RDB rank	eQTL in brain regions (GTEx v. 8)
1	149999764	150514149	rs11588837	*PLEKHO1* (46.9)	A/G	0.06	0.01	0.035	5.25	6	*VPS45* (frontal cortex)
1	163582980	163766672	rs2345964	*RP4-640E24.1* (12)	A/G	0.05	0.01	0.030	1.68	6	-
1	226613126	226702300	rs1299858	*CDKN2AIPNLP1* (15.3)	T/C	**0.05**	**-0.02**	**0.023**	0.03	NA	-
2	210043728	210322212	rs34842775	*MEAF6P1* (102.6)	A/C	0.04	0.01	0.039	1.72	7	-
3	52277445	52838402	rs12629701	*PBRM1*	T/C	0.06	0.01	0.033	0.14	7	*GNL3* (cerebellum, hypothalamus, putamen); *RP5-966M1.7* (cerebellum, cortex, putamen); *PPM1M* (cerebellum); *NEK4* (cerebellum); *GLYCTK* (cerebellum); *ITIH4* (cortex, hypothalamus, putamen); *POC1A* (putamen)
6	11920763	12037477	rs11968174	*RP3-420J14.1* (88.6)	T/C	**-0.07**	**0.01**	**0.032**	6.29	6	-
7	129663496	129685597	rs11556924	*ZC3HC1*	C/T	**0.04**	**-0.01**	**0.049**	28.00	1f	-
10	64451233	64556238	rs10822056	*ALDH7A1P4* (13)	C/T	**-0.05**	**0.01**	**0.010**	1.03	6	*ADO* (caudate)
10	106453550	106560225	rs7909129	*SORCS3*	A/G	**-0.04**	**0.01**	**0.034**	14.63	7	-
15	74099922	74161676	rs4886643	*RP11-8P11.3* (40.5)	C/T	-0.04	-0.01	0.013	1.06	5	-
15	84703470	85344550	rs11638445	*LINC00933* (14.3)	C/A	0.06	0.01	0.009	3.24	5	*GOLGA2P7* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *CSPG4P12* (anterior cingulate cortex, cerebellum, cortex, hippocampus, hypothalamus, putamen); *LINC00933* (anterior cingulate cortex, caudate, cortex); *GOLGA6L5P* (anterior cingulate cortex, caudate, cortex, putamen, substantia nigra); *NMB* (caudate); *DNM1P51* (frontal cortex); *RP11-182J1.14* (cortex), *EFTUD1P1* (hypothalamus)
16	69141138	69432250	rs12919664	*TERF2*	T/C	-0.05	-0.02	0.004	1.45	7	*VPS4A* (anterior cingulate cortex, caudate, cortex, hypothalamus, nucleus accumbens, putamen); *TERF2* (cerebellum, cortex); *SNTB2* (cerebellum), *NIP7* (nucleus accumbens); *UTP4* (nucleus accumbens)
18	52297945	52504252	rs117201218	*RAB27B*	T/G	-0.14	-0.02	0.016	3.01	6	-
18	52297945	52504252	rs56162185	*RAB27B*	C/T	-0.04	-0.01	0.030	1.83	7	-

20	33224174	33360785	rs6059976	*PIGU*	G/A	-0.04	-0.01	0.049	2.62	6	*MAP1LC3A* (anterior cingulate cortex, caudate, cerebellum, cortex, hypothalamus, nucleus accumbens); *MYH7B* (cerebellum); *ACSS2* (cerebellum, cortex); *EDEM2* (cortex); *MMP24-AS1* (cortex)
20	35488246	35503978	rs75438122	*SOGA1* (4.1)	T/C	**0.11**	**-0.02**	**0.019**	2.16	7	-
20	35488246	35503978	rs1291117	*RN7SL156P* (3.4)	A/G	-0.06	-0.02	0.047	5.00	3a	
Chr	**Start locus**	**Stop locus**	**Lead SNP**	**Nearest gene (Kb)**	**EA/OA**	**beta BD**	**beta mtDNA-cn**	**conjFDR**	**CADD score**	**RDB rank**	**eQTL in brain regions (GTEx v. 8)**
1	172371151	172453840	rs4916266	*C1orf105* (12.8)	C/A	**-0.04**	**0.01**	**0.015**	2.61	5	-
2	21216815	21239667	rs62122481	*AC012361.1* (155.4)	C/A	**-0.04**	**0.01**	**0.029**	1.88	7	-
22	31536133	32043630	rs3208937	*RNF185*	A/G	0.04	0.01	0.045	0.56	NA	*LIMK2* (anterior cingulate cortex, caudate, cortex, nucleus accumbens); *SFI1* (caudate, cortex, hippocampus, putamen); *RNF185* (cerebellum, cortex); *LINC01521* (cortex)
22	43186763	43410447	rs7286299	*PACSIN2*	G/A	-0.04	-0.01	0.026	0.88	5	-

Loci reported in bold are concordant with the hypothesis of higher predisposition to BD being associated with shorter LTL or lower mtDNA-cn.
The nearest gene column indicates the nearest gene and the distance in Kb in case for SNPs located in an intergenic region.
Abbreviations: BD, bipolar disorder; CADD, Combined Annotation Dependent Depletion; Chr, chromosome; conjFDR, conjunctional false discovery rate; EA, effect allele; eQTL, expression quantitative trait locus; LTL, leukocyte telomere length; mtDNA-cn, mitochondrial DNA copy number; OA, other allele; RDB, RegulomeDB

Supplementary Table 2. Genetic loci and lead SNPs associated with risk of SCZ and LTL or mtDNA-cn

Chr	Start locus	Stop locus	Lead SNP	Nearest gene (Kb)	EA / OA	beta SCZ	beta LTL	conjFDR	CADD score	RDB rank	eQTL in brain regions (GTEx v. 8)
1	92664966	93035020	rs10874656	GFI1	T/C	**-0.05**	**0.01**	**0.043**	8.13	4	*EVI5* (amygdala, caudate, cortex, hyppocampus, hypothalamus, putamen, substantia nigra); *RP4-621B10.8* (cerebellum, cortex); *FAM69A* (cerebellum); *C1orf146* (cerebellum)
1	146919919	146984386	rs1874422	*OR13Z3P* (10.2)	A/G	-0.05	-0.01	0.035	0.29	5	-
1	149999764	150514149	rs11588837	*PLEKHO1* (46.9)	A/G	0.06	0.01	0.026	5.25	1f	*VPS45* (cortex)
1	153768740	154162493	rs7521047	*NUP210L*	T/C	0.04	0.01	0.038	7.97	3a	*CREB3L4* (caudate); *SLC27A3* (cerebellum)
1	163582980	163766672	rs2345964	*RP4-640E24.1* (12)	A/G	0.05	0.01	0.022	1.68	5	-
1	207917499	208049502	rs4844621	*C1orf132*	A/G	**0.05**	**-0.01**	**0.012**	9.88	4	*CD46* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hyppocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra)
1	226694849	226694849	rs58787117	*CDKN2AIPNLP1* (13.7)	A/G	-0.06	-0.01	0.032	5.53	5	-
2	48178775	48324044	rs11891807	*AC079807.4*	T/G	**0.04**	**-0.01**	**0.036**	15.08	5	*FOXN2* (caudate, cerebellum, frontal cortex, nucleus accumbens, putamen)
2	53864496	54497500	rs7583622	*GPR75-ASB3*	G/A	**0.05**	**-0.01**	**0.015**	0.49	5	-
2	53864496	54497500	rs7567556	*ACYP2*	C/T	**-0.11**	**0.07**	**0.022**	3.26	5	-
2	58872553	58991868	rs7591382	*LINC01122*	T/C	**-0.04**	**0.01**	**0.023**	5.48	7	-
3	48446237	49631585	rs12107252	*CELSR3*	T/C	-0.06	-0.01	0.013	15.51	1f	*NCKIPSD* (anterior cingulate cortex, caudate, cerebellum, cortex, nucleus accumbens, putamen); *WDR6* (caudate, cerebellum, cortex, nucleus accumbens, putamen); *CCDC71* (cerebellum); *PFKFB4* (cerebellum); *TREX1* (cortex, nucleus accumbens)
3	52277445	52838402	rs12629701	*PBRM1*	T/C	0.06	0.01	0.024	0.14	7	*GNL3* (cerebellum, cortex, hypothalamus, putamen); *RP5-966M1.7* (cerebellum, cortex, putamen); *PPM1M* (cerebellum); *NEK4* (cerebellum); *GLYCTK* (cerebellum); *ITIH4* (cortex, hypothalamus, putamen); *POC1A* (putamen)
4	48342682	48697149	rs34386102	*SLAIN2* (56)	T/C	**0.04**	**-0.01**	**0.041**	1.49	4	-
4	102766892	102931290	rs34208976	*BANK1*	G/T	-0.04	-0.01	0.013	5.45	5	-
4	105375274	105443381	rs10034519	*CXXC4*	A/C	**0.04**	**-0.01**	**0.018**	0.09	6	-
4	153018256	153101286	rs35296212	*RP11-18H21.2*	T/G	0.04	0.01	0.025	0.47	5	-

6	11957303	12038979	rs209809	*RP3-420J14*.1 (101.5)	G/T	**0.05**	**-0.01**	**0.046**	0.92	4	-
6	24905311	24998665	rs77386029	*FAM65B*	C/T	0.12	0.03	0.025	1.83	5	*GPLD1* (cortex)
7	23600173	23881813	rs798641	*AC006026*.9 (17.1)	G/A	**-0.06**	**0.02**	**0.022**	1.28	5	*FAM221A* (caudate, nucleus accumbens)
8	70943083	70990615	rs3750228	*PRDM14*	T/C	-0.05	-0.02	0.037	18.69	5	-
9	34081331	34130435	rs11557154	*DCAF12*	C/T	0.05	0.03	0.043	25.30	5	*UBAP1* (substantia nigra)
9	96181075	96381916	rs564	*FAM120A*	T/C	0.04	0.01	0.028	17.04	2b	-
9	138378856	138378856	rs2078266	*PPP1R26*	A/G	0.07	0.01	0.022	15.10	3a	-
10	78741559	78763297	rs11001965	*KCNMA1*	G/A	**-0.04**	**0.01**	**0.030**	15.27	5	-
10	104697781	104741114	rs12414777	*CNNM2*	C/T	**0.08**	**-0.01**	**0.010**	0.46	7	*AS3MT* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hypothalamus, nucleus accumbens, putamen, substantia nigra); *RPARP-AS1* (caudate, cerebellum, cortex, nucleus accumbens); *BORCS7* (cerebellum, cortex); *RPL22P17* (cerebellum); *RP11-724N1.1* (cerebellum)
10	106003861	106076414	rs17883150	*GSTO1*	G/A	**0.04**	**-0.01**	**0.023**	5.83	4	*RP11-127L20.3* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *GSTO2* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *ITPRIP* (cortex)
10	106453550	106560225	rs7909129	*SORCS3*	A/G	**-0.05**	**0.01**	**0.009**	14.63	5	
11	46330604	47207362	rs61882672	*CREB3L1* (3.2)	C/A	**-0.09**	**0.01**	**0.001**	0.04	4	*C11orf49* (cerebellum)
11	47925962	49248150	rs10838843	*OR4B2P* (10.5)	G/T	**-0.07**	**0.01**	**0.048**	1.51	6	*FOLH1* (caudate, cerebellum, nucleus accumbens, putamen)
12	53730164	54028059	rs34169640	*RP11-793H13.8*	A/G	**-0.12**	**0.02**	**0.032**	3.51	5	-
12	57486647	57492996	rs4559	*STAT6*	C/T	**-0.04**	**0.01**	**0.029**	5.37	2b	-
12	110229434	110229434	rs117145318	*TRPV4*	C/A	**-0.12**	**0.02**	**0.039**	0.23	7	-
12	122804256	123144293	rs7952868	*CLIP1*	A/G	**-0.04**	**0.02**	**0.020**	3.34	5	-
12	123421902	123897177	rs73230058	*PITPNM2*	C/T	**0.06**	**-0.01**	**0.028**	0.06	5	*ABCB9* (cerebellum); *KMT5A* (cerebellum)
12	123421902	123897177	rs1727302	*PITPNM2*	G/A	**0.07**	**-0.02**	**1.0E-07**	4.12	4	*PITPNM2* (cerebellum); *RP11-282O18.3* (cerebellum); *KMT5A* (cerebellum); *ZCCHC8* (cerebellum); *CCDC62* (cerebellum)
13	79855297	80159615	rs3187338	*RBM26*	C/T	0.05	0.01	0.048	12.36	3a	*RBM26* (cerebellum); *LINC01068* (cerebellum)
14	104332759	104363528	rs10139856	*CTD-2134A5.4* (8.1)	T/C	**0.05**	**-0.01**	**0.027**	**2.90**	**5**	*TDRD9* (caudate, cerebellum, cortex)
15	38820606	38869666	rs28582094	*RASGRP1*	A/G	**-0.04**	**0.01**	**0.029**	**7.58**	**6**	-

15	78712119	78858400	rs16969894	*IREB2*	C/T	**0.07**	**-0.01**	**0.001**	**0.53**	**5**	*CHRNA3* (caudate, nucleus accumbens); *CHRNA5* (nucleus accumbens)
15	82827938	83406857	rs783522	*CPEB1*	A/G	-0.05	-0.01	0.019	0.30	5	*GOLGA2P10* (amygdala, caudate, cerebellum); *GOLGA6L9* (anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, nucleus accumbens); *GOLGA6L10* (caudate, cerebellum, cortex, hippocampus, putamen, substantia nigra); *CSPG4P10* (caudate, cerebellum); *ADAMTS7P1* (cerebellum); *RPS17* (cortex, frontal cortex, hippocampus); *CPEB1* (cortex); *AP3B2* (cortex)
15	84703470	85344550	rs11638445	*LINC00933* (14.3)	C/A	0.06	0.01	0.007	3.24	5	*GOLGA2P7* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hypothalamus, nucleus accumbens, putamen); *CSPG4P12* (anterior cingulate cortex, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *DNM1P51* (cortex); *EFTUD1P1* (hypothalamus); *GOLGA6L5P* (anterior cingulate cortex, caudate, cortex, putamen, substantia nigra); *LINC00933* (anterior cingulate cortex, caudate, cortex); *NMB* (caudate); *RP11-182J1.14* (cortex)
15	91416550	91429042	rs4702	*FURIN*	G/A	**0.08**	**-0.01**	**0.040**	**17.36**	**4**	*FURIN* (frontal cortex)
16	68285847	68419298	rs61593058	*PRMT7*	T/C	-0.06	-0.01	0.003	4.89	6	*PRMT7* (caudate, cortex, nucleus accumbens, putamen, substantia nigra)
16	69141138	69432250	rs8049057	*RNU6-22P*	G/T	-0.04	-0.02	0.014	0.82	1d	*COG8* (cortex); *NIP7* (cortex, nucleus accumbens, putamen); *SNTB2* (cerebellum); *TERF2* (cerebellum); *UTP4* (nucleus accumbens); *VPS4A* (anterior cingulate cortex, caudate, cortex, nucleus accumbens, putamen)
16	90109372	90120171	rs3743824	*URAHP*	G/A	**0.05**	**-0.01**	**0.001**	**0.76**	**4**	-
18	4930206	5038613	rs4798275	*RP11-172F10.1*	G/A	**0.04**	**-0.01**	**0.047**	**0.10**	**5**	-
18	9129337	9414607	rs2902839	*RP11-888D10.3*	C/T	-0.08	-0.02	0.034	1.86	1f	-
20	32903904	33294945	rs6059779	*ITCH*	C/T	0.04	0.01	0.015	0.15	4	*ACSS2* (cerebellum); *EDEM2* (cortex); *ITCH* (cortex); *MAP1LC3A* (anterior cingulate cortex, caudate, cerebellum, cortex, hypothalamus, nucleus accumbens, putamen); *MMP24-AS1* (cortex, nucleus accumbens, substantia nigra); *MYH7B* (cerebellum)
20	62127121	62171556	rs1741617	*EEF1A2*	T/C	**-0.05**	**0.02**	**0.006**	2.71	4	-

20	62127121	62171556	rs310653	*SRMS*	T/C	**-0.04**	**0.01**	**0.020**	1.09	4	*PTK6* (caudate)
22	29162506	29358802	rs6005928	*CTA-292E10.6* (11.7)	T/C	-0.04	-0.01	0.019	2.10	5	-
22	41411804	41613303	rs4822000	*RP11-12M9.4*	T/C	**-0.04**	**0.01**	**0.004**	14.31	7	*MCHR1* (cerebellum); *RP11-12M9.4* (cerebellum); *SLC25A17* (cerebellum, nucleus accumbens); *ZC3H7B* (cerebellum)
22	50162136	50321623	rs138832	*BRD1*	A/G	**-0.05**	**0.01**	**0.026**	3.27	1f	*ALG12* (hippocampus, nucleus accumbens); *CRELD2* (hypothalamus); *RP3-522J7.6* (cerebellum); *ZBED4* (cerebellum)
22	50978504	50982272	rs58111256	*CTA-384D8.35*	C/T	**-0.08**	**0.02**	**0.008**	2.79	4	-
Chr	**Start locus**	**Stop locus**	**Lead SNP**	**Nearest gene (Kb)**	**EA / OA**	**beta SCZ**	**beta mtDNA -cn**	**conjFDR**	**CADD score**	**RDB rank**	**eQTL in brain regions (GTEx v. 8)**
1	150246070	150500107	rs6670974	*PRPF3*	G/A	0.05	0.01	0.043	0.34	7.00	*RPRD2* (caudate, cerebellum, cortex, hippocampus, hypothalamus); *ECM1* (cerebellum); *SEMA6C* (cerebellum)
2	37368452	37409499	rs11899117	*EIF2AK2*	G/A	**0.04**	**-0.01**	**0.019**	8.30	4.00	*NDUFAF7* (cerebellum); *EIF2AK2* (cerebellum)
4	102766892	102841949	rs11931658	*BANK1*	T/C	-0.05	-0.01	0.003	10.25	7.00	-
5	60588572	60824235	rs4276369	*CTC-436P18.3* (65.1)	A/G	-0.05	-0.01	0.020	4.28	2b	-
10	53813181	53822301	rs75062856	*PRKG1*	A/C	0.08	0.02	0.041	3.19	7.00	-
10	104318966	104318966	rs7893954	*SUFU*	A/G	0.04	0.01	0.044	0.74	5.00	*MFSD13A* (caudate, cerebellum, cortex, hypothalamus, putamen); *ACTR1A* (caudate, putamen); *RPARP-AS1* (cortex, nucleus accumbens)
12	110501407	111278708	rs7960988	*ATP2A2*	G/A	0.06	0.01	0.045	2.37	3a	*FAM216A* (cerebellum); *VPS29* (hippocampus); *ATP2A2* (substantia nigra)
16	89682006	89771870	rs164749	*DPEP1* (3.4)	T/G	**-0.04**	**0.01**	**0.038**	1.21	NA	*SPATA33* (anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus); *LINC02166* (anterior cingulate cortex, caudate, cortex, nucleus accumbens); *GAS8* (anterior cingulate cortex, cerebellum, cortex, nucleus accumbens, putamen); *CDK10* (cerebellum); *FANCA* (cerebellum); *VPS9D1* (cortex)
17	2022191	2211343	rs216196	*SMG6*	T/C	-0.04	-0.01	0.033	3.68	NA	*SRR* (cerebellum)
17	17747289	18030240	rs4925133	*AC087163.3*	A/G	-0.04	-0.01	0.022	8.70	4.00	*TOM1L2* (cerebellum)
20	1610201	1684221	rs4813190	*RP11-77C3.3*	A/G	0.05	0.01	0.012	0.93	7.00	-
22	19761025	19766782	rs41297816	*TBX1*	A/G	**-0.05**	**0.01**	**0.040**	1.43	4.00	*DGCR12* (amygdala); *TXNRD2* (caudate)

Loci reported in bold are concordant with the hypothesis of higher predisposition to SCZ being associated with shorter LTL or lower mtDNA-cn.
The nearest gene column indicates the nearest gene and the distance in Kb in case for SNPs located in an intergenic region.

Abbreviations: CADD, Combined Annotation Dependent Depletion; Chr, chromosome; conjFDR, conjunctional false discovery rate; EA, effect allele; eQTL, expression quantitative trait locus; LTL, leukocyte telomere length; mtDNA-cn, mitochondrial DNA copy number; OA, other allele; RDB, RegulomeDB; SCZ, schizophrenia

Supplementary Table 3. Functional enrichment for genes modulated by SNPs associated with increased predisposition to SCZ and shorter LTL

Term	p	FDR	OR	Genes
Cellular component GO terms				
Acetylcholine-Gated Channel Complex (GO:0005892)	2.43E-04	0.010	106.7	*CHRNA3, CHRNA5*
Monoatomic Ion Channel Complex (GO:0034702)	0.002	0.041	34.5	*CHRNA3, CHRNA5*
Molecular function GO terms				
Ligand-Gated Channel Activity (GO:0022834)	2.1E-04	0.011	117.4	*CHRNA3, CHRNA5*
Acetylcholine-Gated Monoatomic Cation-Selective Channel Activity (GO:0022848)	3.7E-04	0.011	83.8	*CHRNA3, CHRNA5* *CHRNA3, CHRNA5*
Postsynaptic Neurotransmitter Receptor Activity (GO:0098960)	5.3E-04	0.011	69.0	*CHRNA3, CHRNA5*
Acetylcholine Receptor Activity (GO:0015464)	5.9E-04	0.011	65.2	*CHRNA3, CHRNA5*
Ligand-Gated Monoatomic Ion Channel Activity (GO:0015276)	7.8E-04	0.012	55.9	*CHRNA3, CHRNA5*
Excitatory Extracellular Ligand-Gated Monoatomic Ion Channel Activity (GO:0005231)	10.0E-04	0.012	48.9	*CHRNA3, CHRNA5*
Transmitter-Gated Monoatomic Ion Channel Activity Involved In Regulation Of Postsynaptic Membrane Potential (GO:1904315)	0.002	0.018	36.6	*CHRNA3, CHRNA5*
Monoatomic Ion Gated Channel Activity (GO:0022839)	0.002	0.022	30.8	*CHRNA3, CHRNA5*
S-adenosylmethionine-dependent Methyltransferase Activity (GO:0008757)	0.004	0.030	24.4	*AS3MT, KMT5A*

Abbrevations: FDR, false discovery rate; OR, odds ratio

Supplementary Table 4. Genetic loci and lead SNPs associated with risk of MDD and LTL or mtDNA-cn

Chr	Start locus	Stop locus	Lead SNP	Nearest gene (Kb)	EA / OA	Beta MDD	Beta LTL	conjFDR	CADD score	RDB rank	eQTL in brain regions (GTEx v. 8)
1	92661882	93440937	rs6691038	*EVI5*	T/C	0.03	0.01	0.041	0.13	6	*EVI5* (caudate, cortex, putamen)
1	226596686	226700980	rs4653448	*RP11-118H4.3* (13.5)	A/G	**0.02**	**-0.03**	**0.011**	7.363	4	*PARP1* (cerebellum)
2	51503072	51600949	rs7599039	*AC007682.1*	T/C	**0.02**	**-0.01**	**0.038**	1.823	7	-
2	210065783	210223837	rs12470898	*MEAF6P1* (101.2)	A/G	**-0.02**	**0.01**	**0.008**	0.179	6	-
3	18611283	18824298	rs4364183	*AC144521.1*	G/A	**-0.02**	**0.01**	**0.042**	4.316	NA	-
3	49734229	49960388	rs34614773	*RNF123*	T/G	**0.03**	**-0.01**	**0.000**	14.7	3a	*FAM212A* (cerebellum); *GMPPB* (cerebellum, cortex, hyppocampus, putamen); *HYAL3* (cerebellum), *MST1R* (caudate, cerebellum, cortex); *RBM6* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra); *RNF123* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hypothalamus, nucleus accumbens)
3	101297772	101337565	rs10049146	*RNU6-1256P*	C/A	**0.03**	**-0.01**	**0.044**	2.347	5	
6	152201464	152265522	rs4458702	*ESR1*	A/G	**0.03**	**-0.01**	**0.002**	4.062	7	
9	96181075	96381916	rs10992790	*PHF2*	C/T	0.03	0.01	0.001	1.35	5	
10	106453550	106560225	rs7909129	*SORCS3*	A/G	**-0.03**	**0.01**	**0.008**	14.63	7	-
11	46708196	47367371	rs112181005	*C11orf49*	G/A	**0.03**	**-0.01**	**0.008**	7.897	6	*LPR4* (caudate, nucleus accumbens, putamen); *MADD* (cerebellum); *NR1H3* (caudate, nucleus accumbens)
14	64649894	64871010	rs1152577	*ESR2*	T/G	-0.02	-0.01	0.028	1.865	NA	-
15	38820606	38925195	rs56059718	*RASGRP1*	C/A	**-0.02**	**0.01**	**0.025**	0.318	7	-
15	40878474	41053250	rs2263551	*RAD51-AS1*	G/A	-0.02	-0.01	0.029	0.798	7	
15	91416550	91429042	rs4702	*FURIN*	G/A	**0.03**	**-0.01**	**0.039**	17.36	5	...
18	51779019	51958169	rs1657890	*STARD6*	C/T	-0.02	-0.01	0.021	1.552	7	*POLI* (cerebellum)
18	52369516	52470679	rs1833307	*RAB27B*	A/C	-0.02	-0.01	0.001	0.794	5	-
18	74505929	74604088	rs62112159	*RP11-162A12.2*	G/A	**-0.02**	**0.01**	**0.032**	5.891	4	-
22	41411804	41627775	rs7290458	*RP11-12M9.4* (5.1)	T/C	**-0.02**	**0.01**	**0.001**	1.221	1f	*ZC3H7B* (cerebellum); *MCHR1* (cerebellum); *RP11-12M9.4* (cerebellum); *SLC25A17* (nucleus accumbens)

Chr	Start locus	Stop locus	Lead SNP	Nearest gene (Kb)	EA / OA	beta MDD	beta mtDNA-cn	conjFDR	CADD score	RDB rank	eQTL in brain regions (GTEx v. 8)
3	48724599	49604904	rs4955411	*USP19*	A/G	0.03	0.01	0.0007	3.36	NA	*AMT* (anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen, susbtantia nigra); *BSN-AS2* (cortex, putamen); *CCDC71* (caudate, cerebellum, cortex, nucleus accumbens, putamen); *DALRD3* (cerebellum, cortex); *GMPPB* (amygdala, anterior cingulate cortex, cerebellum, hippocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra); *GPX1* (anterior cingulate cortex, caudate, cerebellum, cortex, nucleus accumbens, putamen); *MRPS18AP1* (cerebellum); *MST1* (cerebellum); *NCKIPSD* (amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra); *NICN1* (cerebellum, cortex, nucleus accumbens); *P4HTM* (caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen); *PRKAR2A* (substantia nigra); *QRICH1* (caudate, cerebellum, cortex, nucleus accumbens); *RP11-694I15.7* (cerebellum); *USP4* (cerebellum); *WDR6* (amygdala, cerebellum, hippocampus, nucleus accumbens, putamen, substantia nigra)

Loci reported in bold are concordant with the hypothesis of higher predisposition to MDD being associated with shorter LTL or lower mtDNA-cn.
The nearest gene column indicates the nearest gene and the distance in Kb in case for SNPs located in an intergenic region.
Abbreviations: CADD, Combined Annotation Dependent Depletion; Chr, chromosome; conjFDR, conjunctional false discovery rate; EA, effect allele; eQTL, expression quantitative trait locus; LTL, leukocyte telomere length; MDD, major depressive disorder; mtDNA-cn, mitochondrial DNA copy number; OA, other allele; RDB, RegulomeDB

Supplementary Table 5. Functional enrichment for biological process GO terms for genes modulated by SNPs associated with increased predisposition to MDD and shorter LTL

Term	p	FDR	OR	Genes
Phagocytosis (GO:0006909)	8.9E-4	0.045	54.1	*NR1H3, MST1R*
Negative Regulation Of Defense Response (GO:0031348)	0.002	0.045	32.9	*PARP1. NRH13*
Negative Regulation Of Response To External Stimulus (GO:0032102)	0.004	0.045	25.1	*PARP1. NRH13*
Transcription By RNA Polymerase II (GO:0006366)	0.007	0.045	18.9	*PARP1. NRH13*
Excitatory Extracellular Ligand-Gated Monoatomic Ion Channel Activity (GO:0005231)	0.010	0.045	15.7	*PARP1. NRH13*

Abbrevations: FDR, false discovery rate; OR, odds ratio

Supplementary Table 6. Significant upstream regulators of genes modulated by SNPs associated with increased risk of SCZ and shorter LTL

Upstream regulator	Molecule type	p-value of overlap	q	Target molecules
NRG (family)	group	3.06E-04	3.52E-02	CHRNA3, CHRNA5
HIF1A,EPAS1:PTK6 Gene	complex	1.08E-03	3.52E-02	PTK6
PTK6 Gene:EPAS1:NR3C1:Glucocorticoid ligand:PELP1	complex	1.08E-03	3.52E-02	PTK6
SMAD2,3:SMAD4	group	1.08E-03	3.52E-02	FURIN
PF-3758309	chemical drug	1.08E-03	3.52E-02	PTK6
miR-502-5p (and other miRNAs w/seed UCCUUGC)	mature microRNA	1.08E-03	3.52E-02	KMT5A
LLGL1	other	1.08E-03	3.52E-02	CD46
ARMCX3	other	2.16E-03	5.47E-02	CHRNA3
H4C14	other	2.16E-03	5.47E-02	CHRNA5
ERG	transcription regulator	3.44E-03	7.84E-02	CHRNA3, EVI5, FOLH1
DGKE	kinase	5.39E-03	9.21E-02	CD46
ITSN1	other	5.39E-03	9.21E-02	FOLH1
Meis1	transcription regulator	5.39E-03	9.21E-02	EVI5
Miat	other	6.46E-03	9.21E-02	FURIN
corticotropin	biologic drug	6.46E-03	9.21E-02	FURIN
PHOX2A	transcription regulator	6.46E-03	9.21E-02	CHRNA3
GRK3	kinase	7.53E-03	9.54E-02	CD46
PMCH	other	7.53E-03	9.54E-02	MCHR1
HFE	transmembrane receptor	8.02E-03	9.63E-02	CRELD2, FURIN
HCFC1	transcription regulator	8.60E-03	9.67E-02	KMT5A
KLF11	transcription regulator	8.91E-03	9.67E-02	CHRNA3,CHRNA5
TFR2	transporter	1.07E-02	1.11E-01	FURIN
Histone h4	group	1.15E-02	1.14E-01	CHRNA3, CHRNA5
CD38	enzyme	1.41E-02	1.34E-01	CRELD2, EVI5
dimethyl sulfone	chemical drug	1.61E-02	1.47E-01	PTK6
PAK4	kinase	1.71E-02	1.50E-01	PTK6
estradiol valerate	chemical drug	1.82E-02	1.54E-01	FURIN
FREY1	other	2.03E-02	1.59E-01	CD46
GRK2	kinase	2.03E-02	1.59E-01	CD46
TGFB2	growth factor	2.09E-02	1.59E-01	CD46,FURIN
fluconazole	chemical drug	2.24E-02	1.65E-01	ABCB9
ELF5	transcription regulator	2.35E-02	1.67E-01	FOLH1
TAL1	transcription regulator	2.48E-02	1.69E-01	CHRNA5, EVI5
WDR77	transcription regulator	2.56E-02	1.69E-01	PTK6
HIF1A	transcription regulator	2.66E-02	1.69E-01	FOLH1, FURIN, PTK6
EXOSC3	enzyme	2.67E-02	1.69E-01	ZCCHC8
BCL6	transcription regulator	2.79E-02	1.70E-01	ITPRIP, SLC25A17
nicotine	chemical drug	2.86E-02	1.70E-01	CHRNA3, CHRNA5
ZNF507	transcription regulator	2.98E-02	1.70E-01	FURIN

HSP90AB1	enzyme	2.98E-02	1.70E-01	PTK6
choline fenofibrate	chemical drug	3.09E-02	1.72E-01	FURIN
MAC	complex	3.40E-02	1.85E-01	ITPRIP
imipramine blue	chemical drug	3.50E-02	1.86E-01	GSTO2
NOTCH4	transcription regulator	3.71E-02	1.86E-01	FURIN
THBS4	other	3.71E-02	1.86E-01	CRELD2
miR-24-3p (and other miRNAs w/seed GGCUCAG)	mature microRNA	3.82E-02	1.86E-01	FURIN
PHF6	transcription regulator	3.92E-02	1.86E-01	AS3MT
miR-7a-5p (and other miRNAs w/seed GGAAGAC)	mature microRNA	3.92E-02	1.86E-01	KMT5A
CHRNA7	transmembrane receptor	4.02E-02	1.87E-01	CHRNA3
ELF3	transcription regulator	4.33E-02	1.98E-01	FOLH1
PHACTR1	other	4.54E-02	2.03E-01	ITPRIP
PXR/RXRA/pxr ligand/retinoic acid	complex	4.64E-02	2.04E-01	ABCB9

Supplementary Table 7. Significant upstream regulators of genes modulated by SNPs associated with increased risk of MDD and shorter LTL

Upstream regulator	Molecule type	p-value of overlap	q	Target molecules
ARNT/HIF1A	complex	5.40E-04	1.87E-02	MST1R
NR1H3 gene:LXR:RXR:LXR ligands	complex	2.70E-04	1.87E-02	NR1H3
NR1H3 mRNA:miR-613 RISC	complex	2.70E-04	1.87E-02	NR1H3
UBA6-DT	other	2.70E-04	1.87E-02	PARP1
veliparib	chemical drug	5.40E-04	1.87E-02	PARP1
MIR585	microRNA	5.40E-04	1.87E-02	PARP1
RECQL5	enzyme	5.40E-04	1.87E-02	PARP1
MCC	other	8.09E-04	2.46E-02	PARP1
24(S),25-epoxycholesterol	chemical - endogenous mammalian	2.16E-03	2.48E-02	NR1H3
cyanidin 3-O-glucoside	chemical - endogenous non-mammalian	2.16E-03	2.48E-02	NR1H3
Snhg20	other	1.62E-03	2.48E-02	PARP1
TACSTD2	other	2.96E-03	2.48E-02	PARP1
UCHL5	peptidase	2.43E-03	2.48E-02	PARP1
AKR1C3	enzyme	1.62E-03	2.48E-02	PARP1
ZNF365	other	1.08E-03	2.48E-02	PARP1
CHFR	enzyme	1.35E-03	2.48E-02	PARP1
VEGFA	growth factor	2.95E-03	2.48E-02	PARP1, SLC25A17
FUT4	enzyme	1.35E-03	2.48E-02	PARP1
HNRNPUL1	other	1.89E-03	2.48E-02	PARP1
UTS2R	G-protein coupled receptor	2.43E-03	2.48E-02	NR1H3
PMCH	other	1.89E-03	2.48E-02	MCHR1
AEBP1	peptidase	2.70E-03	2.48E-02	NR1H3
CDKN1C	other	2.70E-03	2.48E-02	PARP1
darglitazone	chemical drug	2.96E-03	2.48E-02	NR1H3
lidocaine	chemical drug	2.96E-03	2.48E-02	PARP1
ORIN1001	chemical drug	1.62E-03	2.48E-02	NR1H3
myristic acid	chemical - endogenous mammalian	1.62E-03	2.48E-02	NR1H3
tyrphostin AG 127	chemical drug	2.43E-03	2.48E-02	PARP1
sphingomyelin	chemical - endogenous mammalian	2.96E-03	2.48E-02	NR1H3
LDL	complex	3.21E-03	2.60E-02	NR1H3, PARP1
triciribine	chemical drug	4.04E-03	2.68E-02	PARP1
orotic acid	chemical - endogenous mammalian	4.04E-03	2.68E-02	NR1H3
beta-estradiol	chemical - endogenous mammalian	4.53E-03	2.68E-02	HYAL3, MCHR1,NR1H3, PARP1
echinomycin	chemical drug	4.04E-03	2.68E-02	MST1R
Mek	group	3.56E-03	2.68E-02	MST1R, NR1H3
PX 478	chemical drug	4.58E-03	2.68E-02	PARP1
FABP2	transporter	3.50E-03	2.68E-02	NR1H3
DIRAS3	enzyme	4.31E-03	2.68E-02	PARP1
OSBPL8	transporter	4.31E-03	2.68E-02	NR1H3
Z-LLL-CHO	chemical - protease inhibitor	4.64E-03	2.68E-02	MST1R, PARP1
deguelin	chemical drug	4.04E-03	2.68E-02	PARP1

oxysterol	chemical - endogenous mammalian	4.58E-03	2.68E-02	NR1H3
1-(carboxymethylthio)tetradecane	chemical drug	4.85E-03	2.74E-02	NR1H3
PCYT2	enzyme	5.12E-03	2.78E-02	NR1H3
genistein	chemical drug	5.16E-03	2.78E-02	HYAL3 ,NR1H3
PARG	enzyme	5.65E-03	2.92E-02	PARP1
FDFT1	enzyme	5.65E-03	2.92E-02	NR1H3
miR-218-5p (and other miRNAs w/seed UGUGCUU)	mature microRNA	6.19E-03	3.13E-02	PARP1
SAR1B	enzyme	6.73E-03	3.34E-02	NR1H3
YTHDF2	other	7.53E-03	3.39E-02	NR1H3
MST1	growth factor	7.00E-03	3.39E-02	MST1R
MAFG	transcription regulator	7.26E-03	3.39E-02	PARP1
RELA	transcription regulator	7.53E-03	3.39E-02	MST1R, PARP1
linolenic acid	chemical - endogenous mammalian	7.53E-03	3.39E-02	NR1H3
Ppar	group	8.60E-03	3.48E-02	NR1H3
JINK1/2	group	8.07E-03	3.48E-02	PARP1
FSTL1	other	8.60E-03	3.48E-02	NR1H3
LTB4R	G-protein coupled receptor	8.60E-03	3.48E-02	NR1H3
stearic acid	chemical - endogenous mammalian	8.34E-03	3.48E-02	NR1H3
7-ketocholesterol	chemical - endogenous mammalian	8.60E-03	3.48E-02	NR1H3
NCF1	enzyme	8.87E-03	3.53E-02	HYAL3
C1Q (family)	group	9.41E-03	3.57E-02	PARP1
APOB	transporter	9.41E-03	3.57E-02	NR1H3
L-triiodothyronine	chemical - endogenous mammalian	9.31E-03	3.57E-02	NR1H3, PARP1
asoprisnil	chemical drug	9.68E-03	3.62E-02	PARP1
CRTC2	other	1.02E-02	3.64E-02	NR1H3
HSD11B1	enzyme	1.05E-02	3.64E-02	NR1H3
FABP4	transporter	1.05E-02	3.64E-02	NR1H3
DHX9	enzyme	1.05E-02	3.64E-02	PARP1
22(R)-hydroxycholesterol	chemical - endogenous mammalian	1.05E-02	3.64E-02	NR1H3
arginine	chemical - endogenous mammalian	1.07E-02	3.68E-02	PARP1
SP1	transcription regulator	1.12E-02	3.70E-02	MST1R, PARP1
KEAP1	other	1.13E-02	3.70E-02	MST1R
SN-38	biologic drug	1.13E-02	3.70E-02	PARP1
SRSF2	transcription regulator	1.15E-02	3.74E-02	MST1R
CSF1R	kinase	1.18E-02	3.78E-02	NR1H3
THBS1	other	1.21E-02	3.81E-02	PARP1
benzyl isothiocyanate	chemical - endogenous non-mammalian	1.26E-02	3.93E-02	MST1R
BCAP31	transporter	1.29E-02	3.96E-02	NR1H3
carrageenan	chemical drug	1.39E-02	4.24E-02	PARP1
EIF2AK4	kinase	1.45E-02	4.29E-02	PARP1
nitroprusside	chemical drug	1.45E-02	4.29E-02	PARP1
SFRP1	transmembrane receptor	1.47E-02	4.31E-02	NR1H3
TGFB1	growth factor	1.49E-02	4.31E-02	MST1R, NR1H3, PARP1
KAT2B	enzyme	1.53E-02	4.32E-02	NR1H3
mir-24	microRNA	1.53E-02	4.32E-02	PARP1
pravastatin	chemical drug	1.63E-02	4.57E-02	NR1H3

TNF	cytokine	1.66E-02	4.58E-02	MST1R, NR1H3, PARP1
STAR	transporter	1.71E-02	4.68E-02	NR1H3
panobinostat	chemical drug	1.98E-02	5.06E-02	PARP1
LCK	kinase	1.95E-02	5.06E-02	NR1H3
MMP2	peptidase	1.93E-02	5.06E-02	NR1H3
NDRG1	kinase	1.98E-02	5.06E-02	PARP1
napabucasin	chemical drug	1.93E-02	5.06E-02	PARP1
gemfibrozil	chemical drug	1.98E-02	5.06E-02	NR1H3
NOD2	other	2.03E-02	5.09E-02	NR1H3
KCNIP3	transcription regulator	2.03E-02	5.09E-02	NR1H3
ATM	kinase	2.11E-02	5.24E-02	PARP1
cholic acid	chemical - endogenous mammalian	2.14E-02	5.25E-02	NR1H3
IDH1	enzyme	2.17E-02	5.26E-02	NR1H3
MACROH2A1	other	2.19E-02	5.27E-02	PARP1
olaparib	chemical drug	2.25E-02	5.30E-02	PARP1
SRSF1	other	2.25E-02	5.30E-02	MST1R
FEV	transcription regulator	2.32E-02	5.43E-02	MCHR1
MAP3K14	kinase	2.48E-02	5.75E-02	NR1H3
DMRT1	transcription regulator	2.59E-02	5.84E-02	NR1H3
niacinamide	chemical - endogenous mammalian	2.62E-02	5.84E-02	PARP1
olanzapine	chemical drug	2.64E-02	5.84E-02	MCHR1
romidepsin	biologic drug	2.59E-02	5.84E-02	PARP1
clofibrate	chemical drug	2.64E-02	5.84E-02	NR1H3
bezafibrate	chemical drug	2.69E-02	5.90E-02	NR1H3
NR1H2	ligand-dependent nuclear receptor	2.80E-02	6.07E-02	NR1H3
adavosertib	chemical drug	2.88E-02	6.19E-02	MST1R
miR-3648 (miRNAs w/seed GCCGCGG)	mature microRNA	2.93E-02	6.25E-02	MST1R
trichostatin A	chemical drug	2.96E-02	6.26E-02	NR1H3, PARP1
glutamine	chemical - endogenous mammalian	3.09E-02	6.42E-02	PARP1
Rxr	group	3.06E-02	6.42E-02	NR1H3
plicamycin	chemical drug	3.12E-02	6.42E-02	MST1R
KRAS	enzyme	3.17E-02	6.42E-02	MST1R, PARP1
apigenin	chemical - endogenous non-mammalian	3.17E-02	6.42E-02	PARP1
TGFBR1	kinase	3.27E-02	6.57E-02	MST1R
KAT2A	enzyme	3.33E-02	6.62E-02	NR1H3
ERBB2	kinase	3.37E-02	6.62E-02	MCHR1, NR1H3
fatty acid	chemical - endogenous mammalian	3.38E-02	6.62E-02	NR1H3
uric acid	chemical - endogenous mammalian	3.43E-02	6.67E-02	PARP1
SPOP	other	3.46E-02	6.67E-02	PARP1
FGF1	growth factor	3.51E-02	6.71E-02	NR1H3
MAVS	other	3.61E-02	6.86E-02	MST1R
RIPK2	kinase	3.64E-02	6.86E-02	NR1H3
lysophosphatidylcholine	chemical - other	3.72E-02	6.89E-02	SLC25A17
ciglitazone	chemical drug	3.74E-02	6.89E-02	PARP1
semaxinib	chemical drug	3.69E-02	6.89E-02	PARP1
ADAM10	peptidase	3.80E-02	6.94E-02	MCHR1
ACOX1	enzyme	3.85E-02	6.98E-02	NR1H3
RIGI	enzyme	3.90E-02	7.02E-02	MST1R
ciprofibrate	chemical drug	3.93E-02	7.02E-02	NR1H3

mir-223	microRNA	3.98E-02	7.06E-02	PARP1
MIF	cytokine	4.03E-02	7.10E-02	NR1H3
NLRP3	enzyme	4.08E-02	7.14E-02	PARP1
ERN1	kinase	4.16E-02	7.22E-02	NR1H3
DUSP1	phosphatase	4.29E-02	7.40E-02	PARP1
MSTN	growth factor	4.39E-02	7.47E-02	NR1H3
FGFR1	kinase	4.39E-02	7.47E-02	NR1H3
MAPK9	kinase	4.71E-02	7.94E-02	NR1H3
torkinib	chemical drug	4.84E-02	8.10E-02	PARP1
BRCA1	transcription regulator	4.91E-02	8.12E-02	PARP1
dopamine	chemical - endogenous mammalian	4.91E-02	8.12E-02	MCHR1
STING1	ion channel	4.96E-02	8.15E-02	MST1R