Shared genetic background between children and adults with attention deficit/hyperactivity disorder

Paula Rovira [1,2,&], Ditte Demontis [3,4,5,&], Cristina Sánchez-Mora [1,2,6], Tetyana Zayats [7,8,9], Marieke Klein [10,11], Nina Roth Mota [10,12,13], Heike Weber [14,15], Iris Garcia-Martínez [1,2,16,17], Mireia Pagerols [1,2], Laura Vilar [1,2], Lorena Arribas [1,2], Vanesa Richarte [2,6,18], Montserrat Corrales [2,6,18], Christian Fadeuilhe [2,6,18], Rosa Bosch [2,6,18], Gemma Español Martin [2,19,18], Peter Almos [20], Alysa E. Doyle [21,22], Eugenio Horacio Grevet [23,12], Oliver Grimm [15], Anne Halmøy [7,24], Martine Hoogman [10], Mara Hutz [25], Christian P. Jacob [20], Sarah Kittel-Schneider [15], Per M. Knappskog [26,27], Astri J. Lundervold [28], Olga Rivero [20], Diego Luiz Rovaris [25,12], Angelica Salatino-Oliveira [25], Bruna Santos da Silva [25,12], Evgenij Svirin [20,29], Emma Sprooten [30], Tatyana Strekalova [31,20,29], ADHD Working Group of the Psychiatric Genomics Consortium [32], 23andMe Research team [32], Alejandro Arias-Vasquez [13,10], Edmund J.S. Sonuga-Barke [33,34], Philip Asherson [35], Claiton Henrique Dotto Bau [25,12], Jan K. Buitelaar [30,36], Bru Cormand [37,38,39,40], Stephen V. Faraone [41], Jan Haavik [7,24], Stefan E. Johansson [27,26], Jonna Kuntsi [33], Henrik Larsson [42,43], Klaus-Peter Lesch [20,31,29], Andreas Reif [15], Luis Augusto Rohde [44], Miquel Casas [1,2,6,18], Anders D. Børglum [3,4,5,&], Barbara Franke [10,13,&], Josep Antoni Ramos-Quiroga [2,1,6,&], María Soler Artigas [1,2,6,&,*], Marta Ribasés [1,2,6,&,*]

[&] These authors contributed equally to this work.

* Correspondence and requests for materials should be addressed to M.R. (email: marta.ribases@vhir.org, Phone number: 0034934894162) or M.S.A (email: maria.soler@vhir.org, Phone number: 0034934894162)

Affiliations

1 Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain

2 Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain

3 Department of Biomedicine (Human Genetics) and Centre for Integrative Sequencing, iSEQ, Aarhus University, Aarhus, Denmark

4 The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark

5 Center for Genomics and Personalized Medicine, Aarhus, Denmark

6 Biomedical Network Research Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

7 Department of Biomedicine, University of Bergen, Bergen, Norway

8 Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

9 Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA

10 Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, The Netherlands

11 University Medical Center Utrecht, UMC Utrecht Brain Center, Department of Psychiatry, Utrecht, the Netherlands

12 ADHD Outpatient Program, Adult Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

13 Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

14 Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

15 Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany

16 Banc de Sang i Teixits (BST), Barcelona, Spain

17 Grup de Medicina Transfusional, Vall d'Hebron Institut de Recerca, Universitat Autònoma de Barcelona (VHIR-UAB), Barcelona, Spain

18 Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain

19 Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron Research Institute (VHIR), Barcelona, Catalonia, Spain

20 Division of Molecular Psychiatry, Center of Mental Health, University of Würzburg, Würzburg, Germany

21 Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA

22 Department of Psychiatry, Harvard Medical School, Boston, MA, USA

23 Department of Psychiatry, Faculty of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

24 Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

25 Department of Genetics, Institute of Biosciences, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

26 Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway

27 Department of Clinical Science, University of Bergen, Bergen, Norway

28 Department of Biological and Medical Psychology, University of Bergen, Norway

29 Laboratory of Psychiatric Neurobiology, Institute of Molecular Medicine, IM Sechenov First Moscow State Medical University, Moscow, Russia

30 Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, the Netherlands

31 Department of Neuroscience, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, The Netherlands

32 A list of members and affiliations appears at the end of the paper

33 Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

34 Department of Child and Adolescent Psychiatry, Aarhus University, Aarhus, Denmark

35 Social Genetic and Developmental Psychiatry, Institute of Psychiatry Psychology and Neuroscience, King's College London, UK

36 Karakter Child and Adolescent Psychiatry, Nijmegen, The Netherlands

37 Department of Genetics, Microbiology and Statistics, Faculty of Biology, University of Barcelona, Catalonia, Spain

38 Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Catalonia, Spain

39 Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Spain

40 Institut de Recerca Sant Joan de Déu (IRSJD), Esplugues de Llobregat, Catalonia, Spain

41 Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA

42 School of medical sciences, Örebro University, Örebro, Sweden

43 Department of Medical epidemiology and biostatistics, Karolinska Institutet, Stockholm, Sweden

44 Division of Child Psychiatry, Hospital de Clinicas de Porto Alegre, Federal University of Rio Grande do Sul, Brazil

Abstract

Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by age-inappropriate symptoms of inattention, impulsivity and hyperactivity that persist into adulthood in the majority of the diagnosed children. Despite several risk factors during childhood predicting the persistence of ADHD symptoms into adulthood, the genetic architecture underlying the trajectory of ADHD over time is still unclear. We set out to study the contribution of common genetic variants to the risk for ADHD across the lifespan by conducting meta-analyses of genome-wide association studies on persistent ADHD in adults and ADHD in childhood separately and comparing the genetic background between them in a total sample of 17,149 cases and 32,411 controls. Our results show nine new independent genome-wide significant loci and support a shared contribution of common genetic variants to ADHD in children and adults. No subgroup heterogeneity was observed among children, while this group consists of future remitting and persistent individuals. We report similar patterns of genetic correlation of ADHD with other ADHD-related datasets and different traits and disorders among adults, children and when combining both groups. These findings confirm that persistent ADHD in adults is a neurodevelopmental disorder and extend the existing hypothesis of a shared genetic architecture underlying ADHD and different traits to a lifespan perspective.

Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that severely impairs the daily functioning of patients due to age-inappropriate levels of impulsivity and hyperactivity, and/or difficulties in focusing attention. ADHD has a prevalence of 3.4% in childhood, and impairing symptoms persist into adulthood in around two-thirds of children with ADHD diagnosis, with an estimated adult prevalence around 3%[1,2].

ADHD is a multifactorial disorder with heritability averaging 76% throughout the lifespan[3-5]. There is consistent evidence that both common and rare variants make an important contribution to the risk for the disorder[6-11]. Several genome-wide association studies (GWAS) and meta-analyses across those have been conducted[7], but only the largest GWAS meta-analysis (GWAS-MA) performed to date, including 20,183 ADHD patients and 35,191 controls, reported genome-wide significant loci (N=12)[6]. This study concluded that common genetic variants (minor allele frequency, MAF, >0.01) account for 22% of the heritability of the disorder[6] and supported substantial genetic overlap between ADHD and other brain disorders and behavioral/cognitive traits[12].

The presentation of ADHD symptoms changes from childhood to adulthood, with lower levels of hyperactivity in adulthood but a high risk for ongoing attention problems, disorganization, and emotional dysregulation[13,14]. As in the general population, the pattern of psychiatric and somatic comorbid conditions in ADHD also changes substantially over time, with learning disabilities, oppositional defiant disorder, enuresis and conduct disorder being more prevalent in children, and substance use disorders, social phobia, insomnia, obesity, and mood disorders becoming more pronounced in adulthood[1,15-18]. In addition, persistent ADHD in adults is, compared to the general population (and to cases with remitting ADHD), associated with higher risk for a wide range of

functional and social impairments, including unemployment, accidents and criminal behavior[7,19-23].

Several risk factors measured in childhood predict the persistence of ADHD symptoms into adulthood, such as the presence of comorbid disorders, the severity of ADHD symptoms, being exposed to psychosocial adversity as well as having a high polygenic risk score for childhood ADHD[24-28]. Twin studies suggest that both stable and dynamic genetic influences affect the persistence of ADHD symptoms[4,5,29,30]. However, specific genetic factors differentiating childhood and persistent ADHD into adulthood are not well understood due to the lack of longitudinal studies. Since molecular gene-finding studies, including the most recent GWAS-MA of ADHD, have been performed in children and adults either separately or jointly[6,31-40], large-scale analyses comparing the genetic basis of children and adults with persistent ADHD are yet to be conducted.

Given this background, we set out to study the contribution of common genetic variants to the risk for ADHD from a lifespan perspective. We report, for the first time, a GWAS-MA on persistent ADHD in adults (according to DSM-IV/ICD-10 criteria), a GWAS-MA on ADHD in childhood (that may include remittent and persistent forms of the disorder), and the comparison of the genetic background of the two.

Results

GWAS meta-analysis of persistent ADHD in adults

The GWAS-MA of persistent ADHD in adults included six datasets from the International Multi-centre persistent ADHD CollaboraTion (IMpACT) consortium, two datasets from the Psychiatric Genomics Consortium (PGC) and the subset of adults from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) cohort included in Demontis and Walters et al.[6] (detailed information can be found in Supplementary Table 12 and in the Supplementary Material). In total, 22,406 individuals (6,532 adult ADHD cases and 15,874 controls) were included. The overall lambda (λ) value was 1.09 (λ_{1000}= 1.01) and the linkage disequilibrium (LD) score regression ratio was 0.13, suggesting minimal population stratification or other systematic biases (Supplementary Figure 1A). The proportion of heritability of persistent ADHD attributable to common single nucleotide polymorphisms (SNP-h^2) was 0.21 (SE=0.026), with a nominally significant enrichment in the heritability of variants located in conserved genomic regions (P=5.18E-03) and in the cell-specific histone mark H3K4me1 (P=3.17E-02) (Supplementary Figure 2A). The gene-based analysis revealed six genes significantly associated with persistent ADHD, with *ST3GAL3* being the most significant one (P=8.72E-07) (Supplementary Table 1A). The single-marker analysis showed no variants exceeding genome-wide significance (P<5.00E-08), with the most significant signal being rs3923931 (P=1.69E-07) (Figure 1A and Supplementary Table 2A). Similarly, no significant gene sets were identified in the pathway analysis after correction for multiple comparisons (Supplementary Table 3A [in excel]).

GWAS meta-analysis of ADHD in childhood

To compare the genetic background between persistent ADHD in adults and ADHD in childhood (that may include future remittent and persistent forms of the disorder), we conducted a GWAS-MA on children with ADHD in a total of 27,154 individuals (10,617 ADHD cases and 16,537

controls). The sample consisted of two datasets from Brazil and Spain, seven datasets from the PGC and the subset of children from the iPSYCH cohort included in Demontis and Walters et al.[6] (detailed information can be found in Supplementary Table 12 and in the Supplementary Material). We found no evidence of genomic inflation and minimal population stratification (λ=1.12 and λ_{1000}=1.01, LD score regression ratio=0.13) (Supplementary Figure 1B). The SNP-h^2 for ADHD in childhood was 0.20 (SE=0.023), with a significant enrichment in the heritability of variants located in conserved genomic regions after Bonferroni correction (P=1.21E-06) (Supplementary Figure 2B). The gene-based analysis highlighted a significant association between *FEZF1* and ADHD in childhood (P=5.42E-07) (Supplementary Table 1B). No single genetic variant exceeded genome-wide significance (P<5.00E-08), with the top signal being in rs55686778 (P=1.67E-07) (Figure 1B and Supplementary Table 2B), and no significant gene sets were identified in the pathway analysis after correction for multiple comparisons (Supplementary Table 3B [in excel]).

Comparison of the genetic background of persistent ADHD in adults and ADHD in childhood

We found a strong and significant genetic correlation between persistent ADHD in adults and ADHD in childhood (rg=0.81, SE=0.09, P=2.13E-21). Sign test results provided evidence of a consistent direction of effect of genetic variants associated with ADHD in children in persistent ADHD and vice-versa (P=6.60E-04 and P=4.47E-03, respectively for variants with P<5.00E-05 in either dataset) (Supplementary Table 4). In addition, Polygenic Risk Score (PRS) analyses showed that childhood ADHD PRSs were associated with persistent ADHD at different predefined P-value thresholds, with the P=0.40 threshold explaining the most variance (P=1.20E-27 and R^2=0.0041) (Figure 2A). The quintiles of the PRS built using this threshold showed the expected trend of higher ADHD risk for individuals in higher quintiles (Figure 2B, Supplementary Table 5).

We tested whether the genetic correlation between persistent ADHD and ADHD in childhood was driven by a subset of children enriched for persistent ADHD-associated alleles using the Breaking Up Heterogeneous Mixture Based On Cross-locus correlations (BUHMBOX) analysis. We found no evidence of genetic heterogeneity in children, supporting that the sharing of persistent ADHD-associated alleles between children and adults was driven by the whole group of children, with a statistical power >98% and assuming 65% persistence (Supplementary Table 6).

Meta-analysis of GWAS on ADHD across the lifespan

Given the strong genetic correlation between persistent ADHD in adults and ADHD in children, we performed a GWAS-MA of ADHD across the lifespan including all datasets available (nine GWAS of persistent ADHD in adults and 10 GWAS of ADHD in childhood). In total, we included 49,560 individuals (17,149 ADHD cases and 32,411 controls), and no evidence of genomic inflation nor population stratification was found (λ=1.18 and λ_{1000}=1.01, LD score regression ratio=0.14) (Supplementary Figure 1C). The SNP-h^2 for ADHD across the lifespan was 0.19 (SE=0.01), and a significant enrichment in the heritability of findings in conserved genomic regions after Bonferroni correction (P=1.53E-06) was observed (Supplementary Figure 2C). We identified four genome-wide significant variants (Figure 1C, Figure 3, Table 1A and Supplementary Figure 3) and nine genes (*FEZF1, DUSP6, ST3GAL3, SEMA6D, KDM4A, C2orf82, GIGYF2, AMN* and *FBXL17*) significantly associated with ADHD across the lifespan (Table 1B). The most significantly associated locus was on chromosome 6 (index variant rs183882582-T, OR=1.43 (95% CI 1.26-1.60), P=1.57E-08), followed by loci on chromosome 7 (index variant rs3958046), chromosome 4 (index variant rs200721207) and chromosome 3 (index variant rs1920644) (Table 1A, Figure 3). The gene- set analysis showed a significant association of the “ribonucleoprotein complex” GO term with ADHD across the lifespan (P.adj=0.021) (Supplementary Table 3C [in excel]).

The four loci identified in the single variant analysis had also reached genome-wide significance in the previous GWAS-MA on ADHD by Demontis and Walters et al.[6], and showed consistent direction of the effect between the two studies (Supplementary Table 7A). Genome-wide significant hits reported by Demontis and Walters et al.[6] also showed the same direction of the effect in our data (Supplementary Table 7B and 7C).

Analyses conditioning on the index variant for the four ADHD-associated loci did not reveal new independent markers associated with ADHD. For each variant within the Bayesian credible sets obtained for these four loci, we searched for expression quantitative trait loci (eQTL) using data from blood[41] and from a meta-analysis across different brain regions[42]. After integrating this information, credible sets for three of the four loci contained at least one eQTL within 1Mb of the index variant. The credible set on chromosome 6 included the index variant (rs183882582) and rs12197454. This variant, in LD with the index variant (r^2=0.56), was associated with the expression of *RSPH3* in blood and brain (P.adj<1.65E-05 and P.adj=2.36E-07, respectively) and with the expression of *VIL2* in blood (P.adj=3.21E-03). The credible set for the second most associated locus on chromosome 7 included 24 variants. The index variant, rs3958046, as well as additional variants in this credible set, were eQTLs for *CADPS2* in brain (maximum P.adj=2.91E-03). The credible set for the locus on chromosome 4 contained 50 variants, most of them located in or near *PCDH7*, but no eQTLs were identified. In the credible set for the locus on chromosome 3, which included 98 variants, the index variant, rs1920644, was associated with the expression of *KPNA4*, *IFT80,* and *KRT8P12* in brain (P.adj=1.16E-04, P.adj=1.40E-03, and P.adj=1.77E-03, respectively). Many other variants in this credible set were eQTLs for these genes and also for *TRIM59*, *OTOL1,* and/or *C3orf80* in brain (P.adj<0.05) (Supplementary Table 8 [in excel]).

In a summary-data-based Mendelian Randomization (SMR) analysis, we used summary data from the GWAS-MA of ADHD across the lifespan and the eQTL data in blood and brain from

Westra et al.[41] and Qi et al.[42] to identify gene expression levels associated with ADHD. We found a significant association between ADHD across the lifespan and *RMI1* expression in blood after Bonferroni correction (P_{SMR}=5.36E-06) (Supplementary Table 9 [in excel]). Results from the HEIDI test indicated that this finding was not an artifact due to linkage disequilibrium between eQTL and other ADHD associated variants (P_{HEIDI}=0.60).

Genetic correlation with other ADHD datasets and phenotypes

We found significant genetic correlations of ADHD in children and adults from the previous GWAS-MA[6] (N=53,296) with persistent ADHD (rg=0.85, SE=0.04, P=5.49E-99), ADHD in childhood (rg=0.99, SE=0.03, P=5.02E-273), and ADHD across the lifespan (rg=0.98, SE=0.01, P<2.23E-308) (Supplementary Table 10). When we excluded sample overlap and considered the subset of new samples in our GWAS-MA on ADHD across the lifespan that were not included in the previous GWAS-MA by Demontis and Walters et al.[6] (N=7,086), a significant genetic correlation was also obtained (rg=0.91, SE=0.35, P=8.70E-03).

We also observed significant genetic correlations between childhood ADHD symptom scores from a GWAS-MA in a population of children reported by the EAGLE consortium[43] (N=17,666) and persistent ADHD (rg=0.65, SE=0.20, P=1.10E-03), ADHD in childhood (rg=0.98, SE=0.21, P=2.76E-06), and ADHD across the lifespan (rg=0.87, SE=0.19, P=4.80E-06). Similarly, significant genetic correlations between GWAS of self-reported ADHD status from 23andMe (N=952,652) and persistent ADHD (rg=0.75, SE=0.05, P=2.49E-45), ADHD in childhood (rg=0.63, SE=0.05, P=1.39E-42), and ADHD across the lifespan (rg=0.72, SE=0.04, P=4.86E-88) were observed (Supplementary Table 10).

We estimated the genetic correlation of persistent ADHD in adults, ADHD in childhood, and ADHD across the lifespan with all available phenotypes in LD-hub[44], including ADHD-related traits and other psychiatric and neurological disorders. In total, results for 139 phenotypes passed

the quality control parameters (h^2>0.1 and z-score>4) and 41 genetic correlations were significant after Bonferroni correction in both children and adults with persistent ADHD (Supplementary Table 11 [in excel]). The genetic correlations with ADHD were consistent across the lifespan, with similar patterns found in adulthood and childhood (Pearson's r=0.89) (Figure 4A, Supplementary Table 11 [in excel]). The phenotypes showing the strongest genetic correlations with ADHD were traits related to academic performance, intelligence and risk-taking behaviors, including smoking and early pregnancy (Figure 4B).

Discussion

In the current study, we set out to explore the contribution of common genetic variants to the risk of ADHD across the lifespan. Using the largest GWAS datasets available from the Psychiatric Genomics Consortium (PGC), the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), and the International Multi-centre persistent ADHD CollaboraTion (IMpACT) consortia, we found evidence for a common genetic basis for ADHD in childhood and ADHD in adults that meet DSM-IV/ICD-10 criteria. We report a high genetic correlation between childhood and persistent ADHD in adulthood, and identified nine novel genome-wide significant loci associated with the disorder in single-variant and/or gene-based analyses.

We found a highly similar proportion of the heritability of ADHD explained by common variants in children (SNP-h^2=0.21) and in adults (SNP-h^2=0.20). This is consistent with the ADHD SNP-h^2 estimate reported in the recent GWAS-MA (SNP-h^2=0.22)[6], which mainly (but not exclusively) included children with ADHD. Our finding is in line with multiple studies supporting the stability of ADHD's heritability from childhood to adulthood[3-5]. The heritability results, together with the 0.81 genetic correlation found between children and adults with ADHD reinforce the hypothesis of the neurodevelopmental nature of persistent ADHD in adults. Consistently, the sign test and the PRS analysis confirmed the extensive overlap of common genetic risk variants for ADHD in childhood and adulthood. In addition, the result of the BUHMBOX analysis supported genetic similarities in ADHD across the lifespan with no evidence of a subset of patients enriched for persistent ADHD-associated alleles within the group of children.

Despite not having identified specific genetic contributions for ADHD in children or persistent ADHD, our results are not inconsistent with evidence suggesting changes in the genetic contribution to ADHD symptoms from childhood into adulthood, as described in previous twin studies in the general population[4,5,29,30]. Our study design and the still limited statistical power of the GWAS-MAs on ADHD may have facilitated the identification of the shared genetic basis

rather than specific genetic factors for persistence. In addition, differences between such twin studies and the present study in the origin of the samples (population-based versus clinical) and/or discrepancies between self- and medical reports could also explain the reason for not identifying genetic variants associated specifically with childhood and/or persistent ADHD in our study. In addition, given that Chen et al.[45] and Biederman et al.[46] reported that persistence of ADHD into adulthood indexed stronger familial aggregation of ADHD, we cannot yet discard other types of genetic variation, such as rare mutations or copy number variation, playing a role in the different ADHD trajectories across the lifespan.

We also found strong and significant positive genetic correlations of ADHD ascertained in clinical populations of adults, children or both with other ADHD-related measures from general population samples, including the largest GWAS of self-reported ADHD status from 23andMe participants (N=952,652) and the GWAS-MA of childhood rating scales of ADHD symptoms in the general population[43]. In agreement with previous reports, these data suggest that a clinical diagnosis of ADHD in adults is an extreme expression of continuous heritable traits[6] and that a single question about ever having received an ADHD diagnosis, as in the 23andMe sample, may be informative for molecular genetics studies.

Similar patterns of genetic correlation of ADHD with different somatic disorders and anthropometric, cognitive and educational traits were identified for children and adults with ADHD. These findings were highly similar to those observed in the recent GWAS-MA[6] and further extend the existing hypothesis of a shared genetic architecture underlying ADHD and these traits to a lifespan perspective.

We report 13 gene- and SNP-based associations for childhood and adult ADHD as well as ADHD across the lifespan. Four ADHD-associated loci were previously identified by Demontis and Walters et al.[6], which was expected due to the sample overlap between the two datasets (42,609

individuals shared out of the 49,560 in our study). The new loci identified in the present study mainly included genes involved in brain formation and function, such as *FEZF1*, a candidate for autism spectrum disorder implicated in the formation of the diencephalon[47,48], *RSPH3*, which participates in neuronal migration in embryonic brain[49], *CADPS2*, which has been associated with many psychiatric conditions due to its role in monoamine and neurotrophin neurotransmission[50-53], *AMN,* which is involved in the uptake of vitamin B12[54,55], essential for brain development, neural myelination, and cognitive function[56], and *FBXL17,* which has previously been related to intelligence[57].

In summary, the present cross-sectional analyses identify new genetic loci associated with ADHD and, more importantly, confirm that persistent ADHD in adults is a neurodevelopmental disorder that shows a high and significant genetic overlap with ADHD in children.

Online methods

Sample Description

A total of 19 GWAS of ADHD comprising 49,560 individuals (17,149 cases and 32,411 controls), provided by the Psychiatric Genomics Consortium (PGC), the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), and the International Multi-centre persistent ADHD CollaboraTion (IMpACT), were analyzed in the present study. All participants were of European ancestry and provided informed consent and all sites had documented permission from local ethics committees. The meta-analysis on persistent ADHD included 22,406 individuals (6,532 ADHD adult cases and 15,874 controls) from nine datasets. The sample consisted of six datasets from the IMpACT consortium, two datasets from the PGC and the subset of adults from the iPSYCH cohort included in Demontis and Walters et al[6]. The meta-analysis on ADHD in childhood included 27,154 individuals (10,617 cases and 16,537 controls) from 10 datasets. The sample consisted of two new datasets from Brazil and Spain, seven datasets from the PGC and the subset of children from the iPSYCH cohort included in Demontis and Walters et al[6]. A total of 9,187 samples (4,281 cases and 4,906 controls) included in the iPSYCH cohort in Demontis and Walters et al.[6] were not included in our GWAS-MA due to the distribution of children and adults across the different genotyping waves. Detailed information on each dataset is provided in Supplementary Table 12 and in the Supplementary Material.

Genotyping, imputation, and quality control

Genotyping platforms and quality control (QC) filters for each of the 19 ADHD datasets are shown in Supplementary Table 12. Pre-imputation QC at individual and SNP level, principal component analyses for ancestry genetic outlier detection, and identification of related and/or duplicated individuals and gender discrepancies were performed using the Rapid Imputation and COmputational PIpeLIne (Ricopili) with the default settings

(https://sites.google.com/a/broadinstitute.org/ricopili/). Non-European ancestry samples, related and duplicated individuals, and subjects with sex discrepancies were excluded. Phasing of genotype data was performed using SHAPEIT2 algorithm, and imputation for unrelated samples and trios was performed with MaCH, IMPUTE2, or MINIMAC3 (http://genome.sph.umich.edu/wiki/Minimac3) depending on software availability at the time of imputation[58-60] (Supplementary Table 12). The European ancestry panels of the 1000 Genomes Project Phase 1 version 3 (v3) (April 2012) and Phase 3 version 5 (v5) (October 2014) using genome build hg19 were considered as references for the imputation of adult and children samples, respectively (ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/).

GWAS and meta-analyses

Imputed dosages and logistic regression analysis implemented in PLINK 1.9 were used assuming an additive model[61]. In the case-control studies, sex, the first 10 principal components, and other relevant covariates for each study were included (Supplementary Table 12). Summary statistics from each study were filtered prior to meta-analysis, excluding variants with minor allele frequency (MAF) <0.01 and imputation quality scores (INFO) ≤0.8. Inverse-variance weighted fixed-effects meta-analyses were conducted using METAL[62], and results were filtered by effective sample size >70% of the total, defined as $\text{Neff} = \frac{2}{\left(\frac{1}{\text{Nca}}\right)+\left(\frac{1}{\text{Nco}}\right)}$ [63]. After filtering, 7,366,995, 7,465,837 and 7,069,304 SNPs and insertion-deletion variants were included in the GWAS meta-analyses (GWAS-MA) of persistent ADHD, ADHD in childhood, and ADHD across the lifespan, respectively. Genomic inflation factors (λ and λ1000) and the ratio from LD score regression (the proportion of the inflation in the mean chi^2 that the LD Score regression intercept ascribes to causes other than polygenic heritability) were calculated to check population stratification and technical biases. The genome-wide significance threshold was set at P<5.00E-08 to correct for multiple testing. Independent loci for variants exceeding the genome-wide significance threshold

were defined based on clumping using PLINK 1.9. Variants that were ±250 kb away from the index variant (variant with smallest P-value in the region), with P-value<0.001 and with an estimated linkage disequilibrium (LD) of r^2 >0.2 with the index variant were assigned to a clump (p_1=5.00E-08, p_2=0.001, r^2=0.2, kb=250). Manhattan and Forest plots were generated using the 'qqman' and 'forestplot' R packages (3.4.4 version of R), respectively. The LocusZoom software[64] was used to generate regional association plots considering variants located ±500 kb from each index variant. r^2 values between index and secondary variants were estimated based on the European ancestry 1000 Genomes Project Phase 3 reference panel.

Conditional analysis

Conditional analyses for top-signals identified in the GWAS-MA of ADHD across the lifespan (±1,000 kb from each index variant position) were performed using the Genome-wide Complex Trait Analysis (GCTA) software[65] and an in-house cohort of 3,727 individuals of European ancestry, imputed to the 1000 Genomes Project Phase 3 v5 reference panel (October 2014) as a reference for LD calculations.

Bayesian credible set analysis

Credible sets of genetic variants that were 99% likely, based on posterior probability, to contain the causal variant, were defined using the method described by Maller et al.[66] and implemented using a freely available R script (https://github.com/hailianghuang/FM-summary). We included variants located ± 250 kb away from the index variant, with P<1.00E-03 and with r2>0.2. The European ancestry 1000 Genomes Project Phase 3 v5 panel (October 2014) was used as reference for LD calculations.

Functional characterization of genome-wide significant loci

Variant annotation integrator from UCSC (https://genome.ucsc.edu/cgi-bin/hgVai) was used to obtain functional annotation based on the Human hg19 genome build (Feb 2009). Credible causal sets of variants defined above were merged with the summary statistics of expression quantitative trait loci (eQTL) data from peripheral blood[41] and with eQTL data from a meta-analysis across different brain regions (Brain-eMeta data from Qi et al.[42]). In the blood dataset, we used the false discovery rate (FDR) information provided[41], and in the brain dataset we used the 'stats' R package to estimate the FDR (Benjamini & Hochberg) for variants included in any of the four credible sets. The statistical significance for both datasets was set using a threshold of 1.00E-03 for adjusted P-values. Summary data-based Mendelian Randomization (SMR)[67] was used to test for association between gene expression levels and ADHD using summary statistics from the GWAS-MA of ADHD across lifespan and eQTL summary data from blood and brain datasets[41,42]. The heterogeneity in dependent instruments test (HEIDI) was used to assess whether the SMR findings were due to pleiotropy or linkage[67].

SNP-based heritability

The SNP-based heritability (SNP-h^2) was estimated by single-trait LD score regression using summary statistics, HapMap 3 LD-scores, and considering default SNP QC filters (INFO>0.9 and MAF>0.01)[68]. Data of 1,113,287, 1,072,558, and 1,092,418 SNPs from the GWAS-MA of persistent ADHD, ADHD on childhood, and ADHD across the lifespan, respectively, were considered for the calculation of SNP-h^2 estimates. Partitioning and enrichment of the heritability by functional categories was analyzed using the 24 main annotations (no window around the functional categories) described by Finucane et al[69]. Statistical significance was set using Bonferroni correction (P<2.08E-03).

Gene-based and gene-set analyses

MAGMA software was undertaken for gene-based and gene-set association testing using summary data from our GWAS-MAs[70]. Variants were mapped to a gene if they were within 20 kb upstream or downstream from the gene according to dbSNP build 135 and NCBI 37.3 gene definitions. Genes in the MHC region (hg19:chr6:25-35M) were excluded from the analyses. LD patterns were estimated using the European ancestry 1000 Genomes Project Phase 3 v5 (October 2014) reference panel. Gene sets denoting canonical pathways were downloaded from MSigDB (http://www.broadinstitute.org/gsea/msigdb), which integrates Kyoto Encyclopedia of Genes and Genomes (KEGG) (http://www.genome.jp/kegg/), BioCarta (http://www.biocarta.com/), Reactome (https://reactome.org/) and Gene Ontology (GO) (http://www.geneontology.org/) resources. Bonferroni correction (P<2.77E-06 for 18,038 genes in persistent ADHD; P<2.75E-06 for 18,218 genes in childhood ADHD; P<2.79E-06 for 17,948 genes in ADHD across the lifespan) and 10,000 permutations were used for multiple testing correction in the gene-based and gene-set analyses, respectively.

BUHMBOX analysis

The Breaking Up Heterogeneous Mixture Based On cross(X)-locus correlations (BUHMBOX) analysis[71] was used to test whether the genetic correlation between persistent ADHD and ADHD in childhood was driven by subgroup heterogeneity, found when there is a subset of children enriched for persistent ADHD-associated alleles. Subgroup heterogeneity was tested in each childhood dataset considering two different SNP sets from the GWAS-MA of persistent ADHD, with P-value thresholds of P<5.00E-05 (62 LD-independent SNPs) and P<1.00E-03 (710 LD-independent SNPs). LD-independent variants with MAF>0.05 were defined by r^2>0.1 and a distance between them greater than 10,000 kb. BUHMBOX results were meta-analyzed using the standard weighted sum of z-score approach, where z-scores are weighted by the square root of the effective sample size ($\mathrm{Neff} = \frac{2}{\left(\frac{1}{\mathrm{Nca}}\right)+\left(\frac{1}{\mathrm{Nco}}\right)}$)[63]. The statistical power was calculated using

1,000 simulations, considering the ADHD children meta-analysis sample size (10,617 ADHD cases and 16,537 controls), the odds ratios and risk allele frequencies from the GWAS-MA of persistent ADHD and assuming 65% of heterogeneity proportion (π). The analyses of the sets of 62 and 710 variants had 98.4% and 100% of statistical power, respectively.

Sign test

The direction of the effect of variants associated with ADHD in childhood was tested in persistent ADHD and vice versa, using strict clumping (r^2=0.05, kb=500, p_2=0.5) and different P-value thresholds (1.00E-07, 5.00E-07, 1.00E-06, 5.00E-06, 1.00E-05, 5.00E-05, 1.00E-04, and 5.00E-04). The concordant direction of effect was evaluated using a one sample test of the proportion with Yates' continuity correction against a null hypothesis of P=0.50 with the 'stats' R package.

Polygenic risk scoring

Non-ambiguous strand, independent SNPs (p_1=1, p_2=1, r^2=0.1, kb=250) with Neff>70% were selected from the GWAS-MA of ADHD in childhood at different P-value thresholds (P<0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1) to construct polygenic risk scores (PRSs) that were tested for association with persistent ADHD in each of the nine datasets using PRSice-2 (https://choishingwan.github.io/PRSice/). Best guess genotypes from the persistent ADHD datasets were filtered by excluding variants with MAF<0.01, INFO≤0.8 and missing rate >0.02, and only SNPs present in the childhood ADHD GWAS-MA results and in all the persistent ADHD studies were included in the analysis (N=32,584). Each study used the same covariates as included in the GWAS. Results from the nine PRS analyses at each P-value threshold, as well as results for all quintiles, were combined using the inverse-variance weighted meta-analysis.

Genetic correlation

Cross-trait LD score regression with unconstrained intercept was used to calculate genetic correlations (rg) between pairs of traits, considering HapMap3 LD-scores, markers with INFO≥0.90, and excluding the MHC region (hg19:chr6:25-35M)[68]. Other ADHD datasets[6,43] and phenotypes from the LD-hub centralized database[44] (http://ldsc.broadinstitute.org) with heritability z-scores (observed heritability/observed standard error) >4 and with an observed heritability >0.1 were considered (N=139 out of 689 available traits). Statistical significance was set using Bonferroni correction (P<3.60E-04). Pearson's correlation coefficient (Pearson's r) was calculated between the genetic correlations of persistent ADHD with the phenotypes from the LD-hub and the genetic correlations of ADHD in childhood with the phenotypes from the LD-hub.

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Author contributions

Conception or design of the work: *P.R., D.D., C.S.M, T.Z., C.P.J., O.R., E.Sprooten, A.A.V., P.A., B.C., S.V.F, J.H., S.E.J., K.P.L., M.Casas, A.D.B., B.F., J.A.R.Q., M.S.A., M.R.*

Acquisition, analysis or interpretation of the data: *P.R., D.D., C.S.M, T.Z., M.K., N.R.M, H.W., I.G.M., M.P., L.V., L.A., V.R., M.Corrales, C.F., R.B., G.E.M., P.A., A.E.D., O.G., M.Hoogman, C.P.J, S.K.S., O.R., E.Svirin, T.S.,* ADHD Working Group of the Psychiatric Genomics Consortium, 23andMe Research Team, E.J.S.S.-B., P.A., C.H.D.B., J.K.B., B.C., J.H., S.E.J., H.L., *K.P.L., A.R., L.A.R., M.Casas, A.D.B, B.F., J.A.R.Q., M.S.A., M.R.*

Drafted the work or substantively revised it: *P.R., D.D., C.S.M, P.A., E.H.G., A.H., M.Hutz, P.M.K., A.J.L., O.R., D.L.R., A.S.O., B.S.D.S, E.S., T.S., E.J.S.S-B, P.A., C.H.D.B., B.C., S.V.F., J.K., H.L., A.R., L.A.R., M.Casas, A.D.B., B.F., J.A.R.Q., M.S.A., M.R.*

Competing interests

V.R. has served on the speakers for Eli Lilly, Rubio and Shire in the last 5 years. She has received travel awards from Eli Lilly and Co. and Shire for participating in psychiatric meetings.

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served as a speaker for Evolan Pharma and Shire and has received research grants from Shire; all outside the submitted work. K.P.L. served as a speaker for Eli Lilly and received research support from Medice, and travel support from Shire, all outside the submitted work. L.A.R. reported receiving honoraria, serving on the speakers' bureau/advisory board, and/or acting as a consultant for Eli-Lilly, Janssen-Cilag, Novartis, and Shire in the last 3 years; receiving authorship royalties from Oxford Press and ArtMed; and receiving travel awards from Shire for his participation in the 2015 WFADHD meetings and from Novartis to take part of the 2016 AACAP meeting. The ADHD and juvenile bipolar disorder outpatient programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Janssen-Cilag, Novartis, and Shire. sent by angelica: L.A.R. reported receiving honoraria, serving on the speakers' bureau/advisory board, and/or acting as a consultant for Eli-Lilly, Janssen-Cilag, Novartis, and Shire in the last 3 years; receiving authorship royalties from Oxford Press and ArtMed; and receiving travel awards from Shire for his participation in the 2015 WFADHD meetings and from Novartis to take part of the 2016 AACAP meeting. The ADHD and juvenile bipolar disorder outpatient programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Janssen-Cilag, Novartis, and Shire. M.Casas has received travel grants and research support from Eli Lilly and Co., Janssen-Cilag, Shire and Lundbeck and served as consultant for Eli Lilly and Co., Janssen-Cilag, Shire and Lundbeck. B.F. has received educational speaking fees from Medice and Shire. J.A.R.Q. was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Medice and Eli- Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen- Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious,

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Data availability

The full GWAS-MA summary statistics for the three meta-analyses will be available for download in the https://www.med.unc.edu/pgc/results-and-downloads webpage. The full GWAS summary statistics for the 23andMe ADHD data set will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit research.23andme.com/collaborate/#publication for more information and to apply to access the data.

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Co-authors for the ADHD Working Group of the Psychiatric Genomics Consortium (PGC):

Ole Andreas Andreassen [45,46], Tobias Banaschewski [47], Mark Bellgrove [48], Joseph Biederman [49,22], Christie Burton [50], Jennifer Crosbie [51], Søren Dalsgaard [52,4], Josephine Elia [53,54], Hakon Hakonarson [55,56], Catharina A. Hartman [57], Ziarih Hawi [48], Johannes Hebebrand [58], Anke Hinney [58], Sandra Loo [59], James McGough [59], Benjamin Neale [8,60,9,61], Robert Oades [58], Ted Reichborn-Kjennerud [62], Aribert Rothenberger [63], Russell Schachar [51], Irwin Waldman [64,65].

23andMe Research Team:

Michelle Agee [66], Babak Alipanahi [66], Adam Auton [66], Robert K. Bell [66], Katarzyna Bryc [66], Sarah L. Elson [66], Pierre Fontanillas [66], Nicholas A. Furlotte [66], David A. Hinds [66], Karen E. Huber [66], Aaron Kleinman [66], Nadia K. Litterman [66], Jennifer C. McCreight [66], Matthew H. McIntyre [66], Joanna L. Mountain [66], Elizabeth S. Noblin [66], Carrie A.M. Northover [66], Steven J. Pitts [66], J. Fah Sathirapongsasuti [66], Olga V. Sazonova [66], Janie F. Shelton [66], Suyash Shringarpure [66], Chao Tian [66], Joyce Y. Tung [66], Vladimir Vacic [66], Xin Wang [66], and Catherine H. Wilson [66].

Affiliations

45 NORMENT Centre, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

46 Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

47 Department of Child and Adolescent Psychiatry, Central Institute of Mental Health, Medical Faculty Heidelberg Mannheim, Germany

48 School of Psychological Sciences and Monash Institute for Cognitive and Clinical Neurosciences (MICCN), Monash University, Melbourne, Australia

49 Clinic and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Boston, MA, USA

50 Neurosciences & Mental Health, Hospital for Sick Children, Toronto, Ontario, Canada

51 Psychiatry, Neurosciences and Mental Health, The Hospital for Sick Children, University of Toronto, Toronto, Canada

52 National Centre for Register-based Research, Department of Economics and Business, School of Business and Social Sciences, Aarhus University, Aarhus, Denmark

53 Department of Pediatrics, Alfred I duPont Hospital for Children, USA

54 Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, USA

55 Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

56 Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

57 Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

58 Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

59 Semel Institute for Neuroscience and Behavior, University of California, Los Angeles, USA

60 Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston MA, USA

61 Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, USA

62 Department of Mental Health, Norwegian Institute of Public Health, Norway

63 Clinic for Child and Adolescent Psychiatry and Psychotherapy, University Medical Center, Göttingen, Germany

64 Department of Psychology, Emory University, Atlanta, GA, USA

65 Broad Institute of Harvard and MIT, Cambridge, MA, USA

66 23andMe, Inc, Mountain View, CA, USA.

Figure legends

Figure 1. Manhattan plots of GWAS meta-analyses of (A) Nine cohorts of persistent ADHD in adults, (B) 10 cohorts of ADHD in childhood and (C) GWAS datasets of ADHD across the lifespan (ADHD in childhood + persistent ADHD). Horizontal lines indicate suggestive (P-value=5.00E-06) and genome-wide significant (P=5.00E-08) thresholds in A-B and C, respectively.

Figure 2. Polygenic risk scores for ADHD in childhood tested on persistent ADHD as target sample. (A) Bar plot and (B) Quantile plot of meta-analysis odds ratios (OR meta) with 95% confidence intervals for P-value threshold=0.4 using the third quantile as baseline.

Figure 3. Regional association plots for genome-wide significant loci identified in the GWAS meta-analysis of ADHD across the lifespan. Each plot includes information about the locus, the location and orientation of the genes in the region, the local estimates of recombination rate (in the right corner), and the LD estimates of surrounding SNPs with the index SNP (r^2 values are estimated based on 1000 Genomes phase 3), which is indicated by colour (in the upper left corner).

Figure 4. Genetic correlation of ADHD and several traits. (A) Black and grey dots represent genetic correlations (rg) for all traits considered (with h^2>0.1 and z-score>4) and for those traits which met Bonferroni correction in both children and adult ADHD groups, respectively. r indicates Pearson's correlation coefficient. (B) The 10 strongest genetic correlations (with 95% confidence intervals) surpassing Bonferroni corrections in the children and persistent ADHD analysis are shown for each trait and ADHD.

Table 1. Genome-wide significant loci in the GWAS meta-analysis of ADHD across the lifespan identified through (A) single-variant analysis and (B) gene-based analysis. The location (chromosome (Chr) and base position (BP)), effect allele and its frequency, odds ratio (OR) of the effect allele with 95% confidence interval (CI 95%) and association P-values, along with genes in the locus are shown for each index variant ID (SNP). For the gene-based results, the number of single nucleotide polymorphisms in the genes (*) and the number of relevant parameters used in the model by MAGMA software[70] (**) are given.

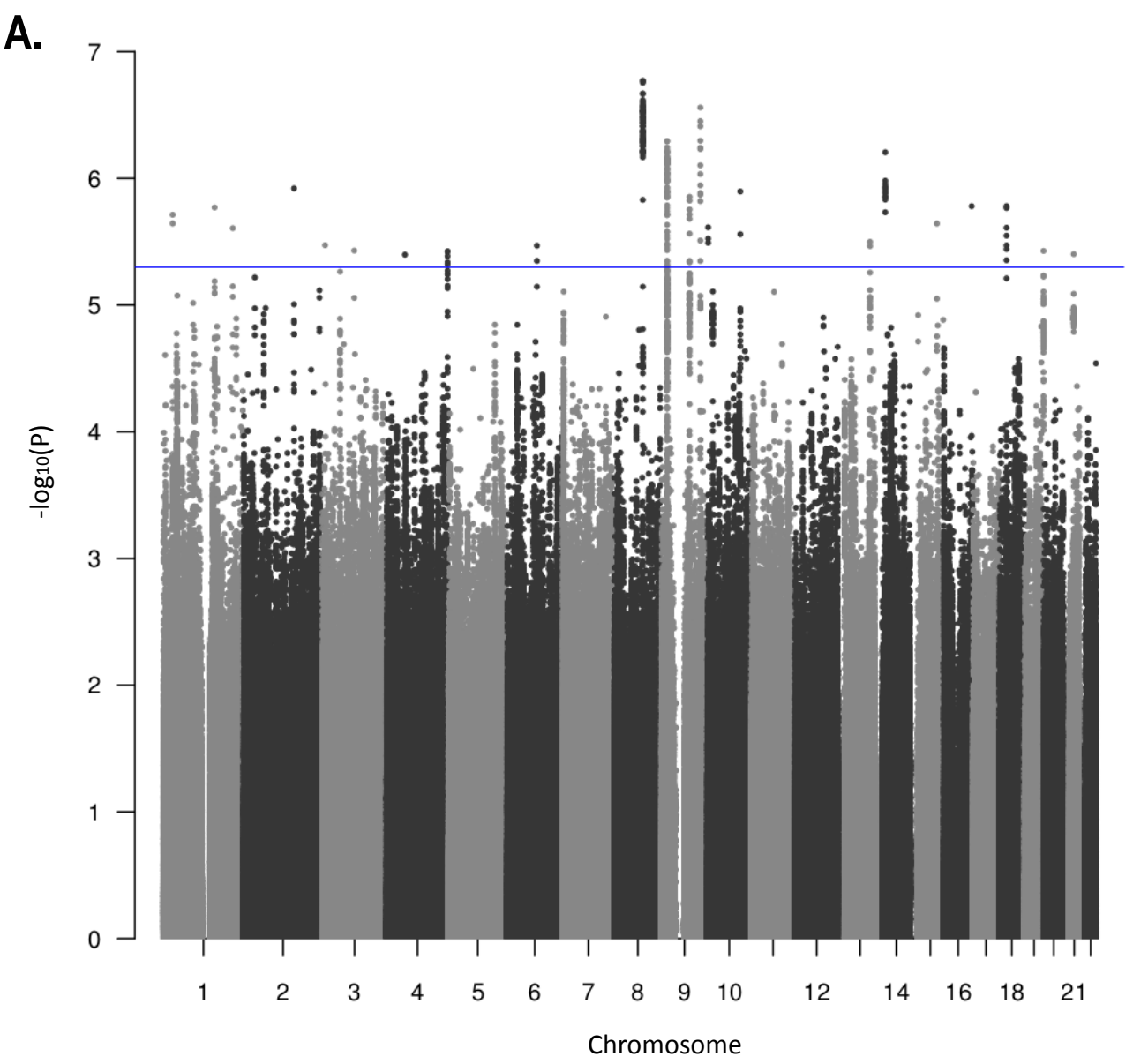
A.

Chr	BP	SNP	Effect allele	Freq Effect allele	OR	CI 95%	P-value	Gene
6	159384224	rs183882582	T	0.98	1.43	1.26-1.60	1.57E-08	*RSPH3* (+14kb)
7	121955328	rs3958046	T	0.40	1.09	1.06-1.10	2.28E-08	*CADPS2* (+3.2kb) / *FEZF1* (-13.9kb) / *FEZF1-AS1* (+5.2kb)
4	31151465	rs200721207	T	0.66	1.10	1.06-1.13	3.56E-08	*PCDH7* (3.0kb)
3	160313354	rs1920644	T	0.52	1.09	1.05-1.12	4.74E-08	*BC125159* (+27.9kb) / *KPNA4* (-30kb) / *ARL14* (-81.6kb)

B.

Gene	Chr	Start	Stop	N SNPs*	N PARAM**	Z-STAT	P-value
FEZF1	7	121921373	121971173	108	18	5.6	9.57E-09
DUSP6	12	89721837	89766296	103	12	5.4	3.51E-08
ST3GAL3	1	44153204	44416837	521	19	5.4	3.58E-08
SEMA6D	15	47456403	48086420	1565	55	5.3	7.24E-08
KDM4A	1	44095797	44191189	169	13	4.9	4.34E-07
C2orf82	2	233713724	233761111	138	17	4.8	7.74E-07
GIGYF2	2	233542015	233745287	511	19	4.8	8.36E-07
AMN	14	103368993	103417179	101	21	4.6	2.56E-06
FBXL17	5	107174734	107738080	1273	35	4.6	2.59E-06

Figure 1.



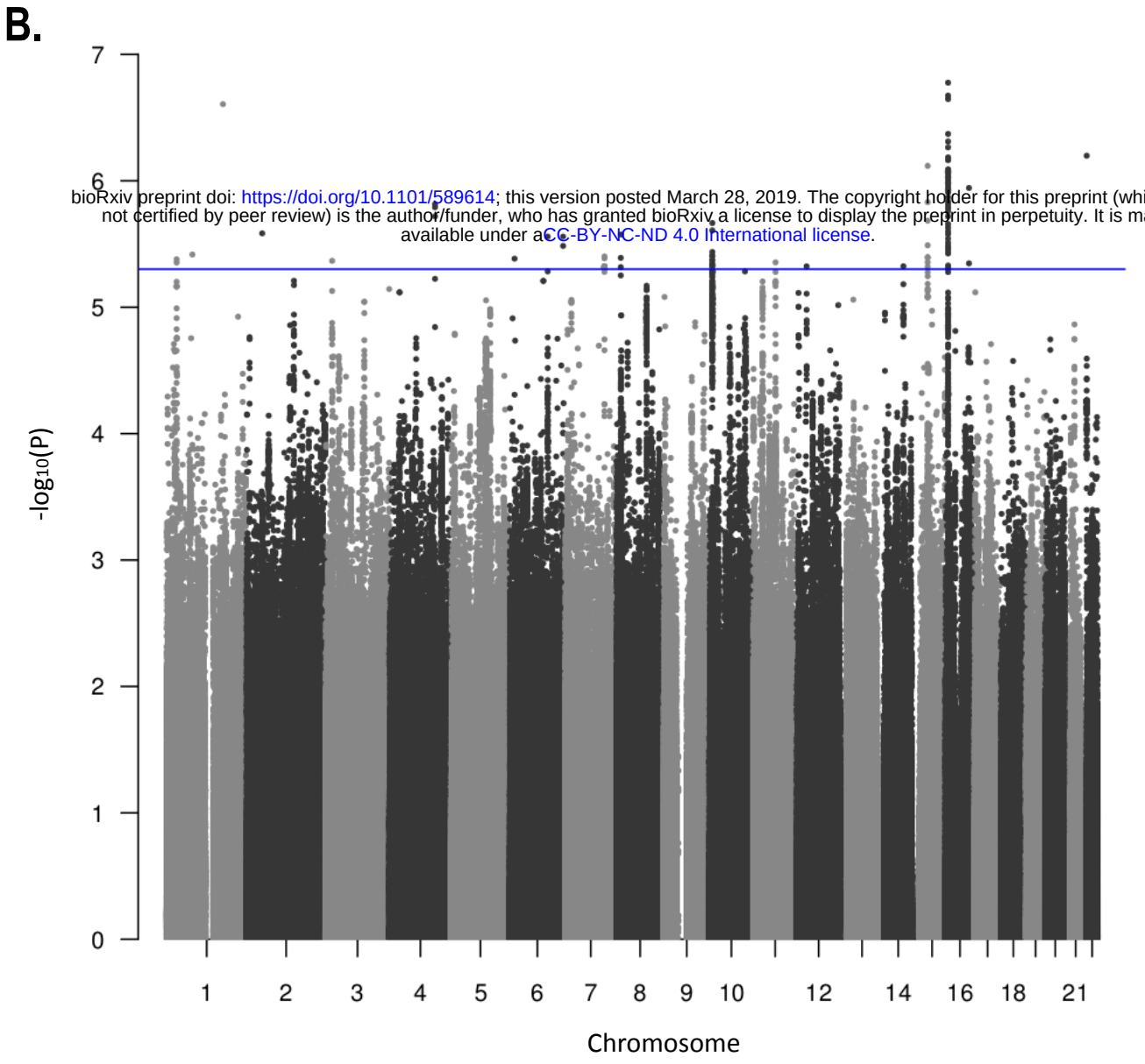
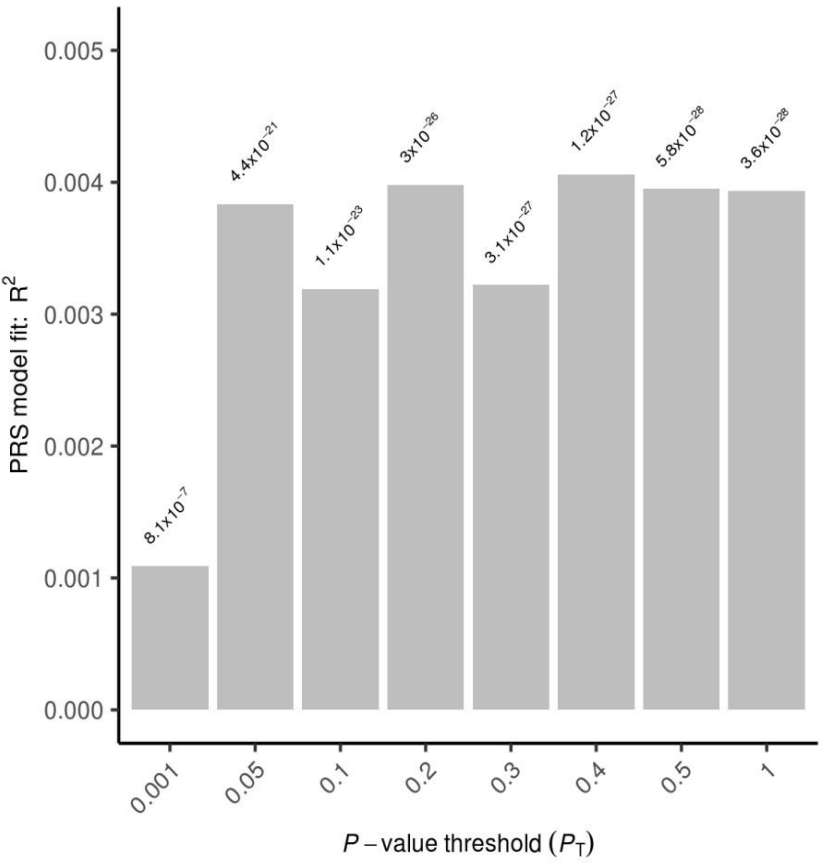


Figure 2.

A.


0.005
0.004
0.003
0.002
0.001
0.000
PRS model fit: R^2
$8.1x10^{-7}$
$4.4x10^{-21}$
$1.1x10^{-23}$
$3x10^{-26}$
$3.1x10^{-27}$
$1.2x10^{-27}$
$5.8x10^{-28}$
$3.6x10^{-28}$
0.001
0.05
0.1
0.2
0.3
0.4
0.5
1
P – value threshold (P_T)

B.

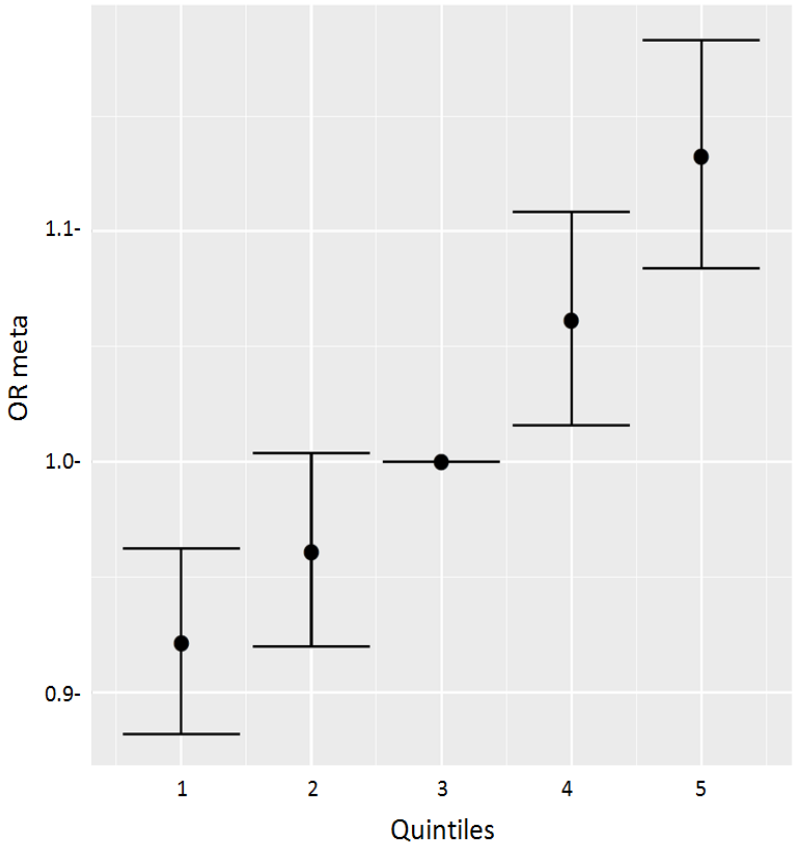
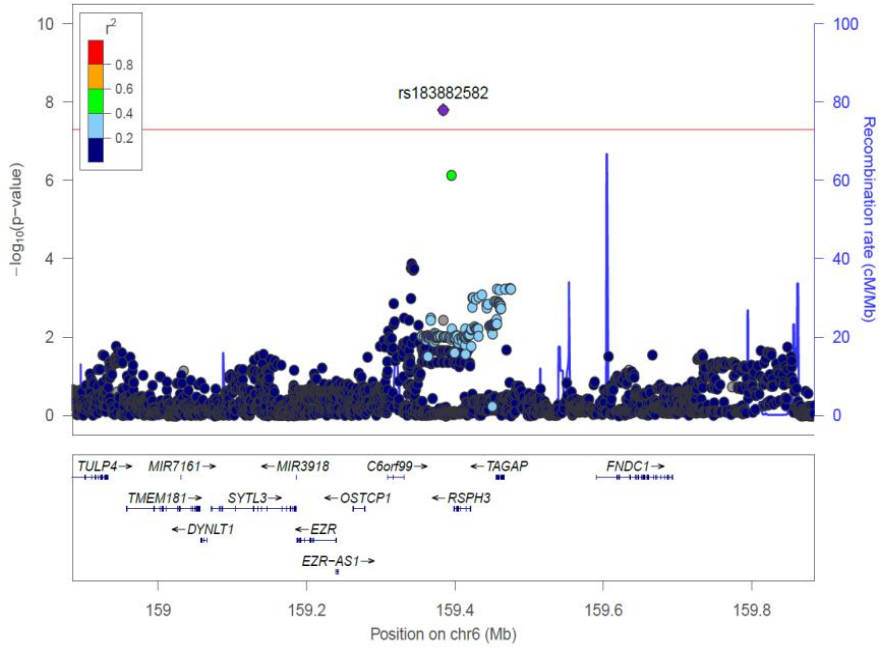
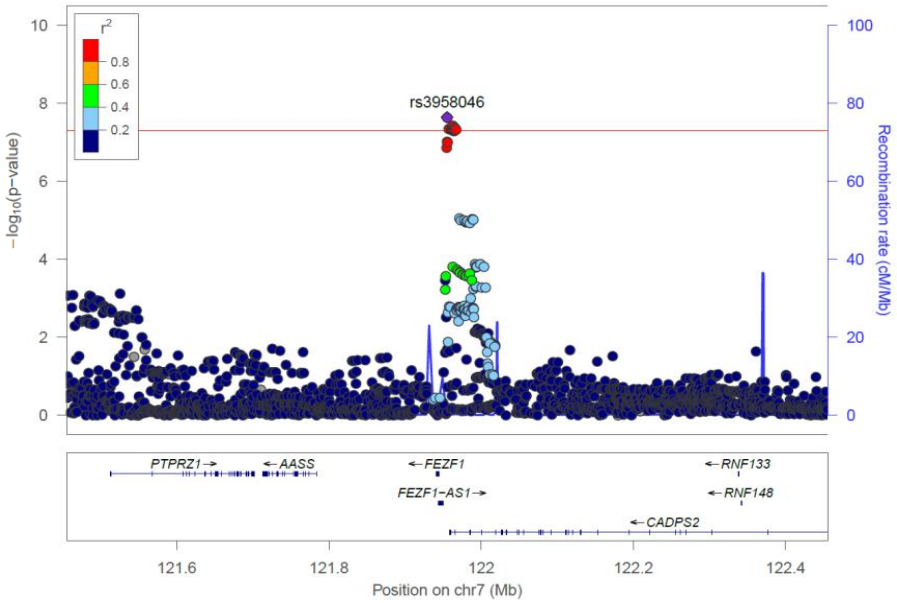
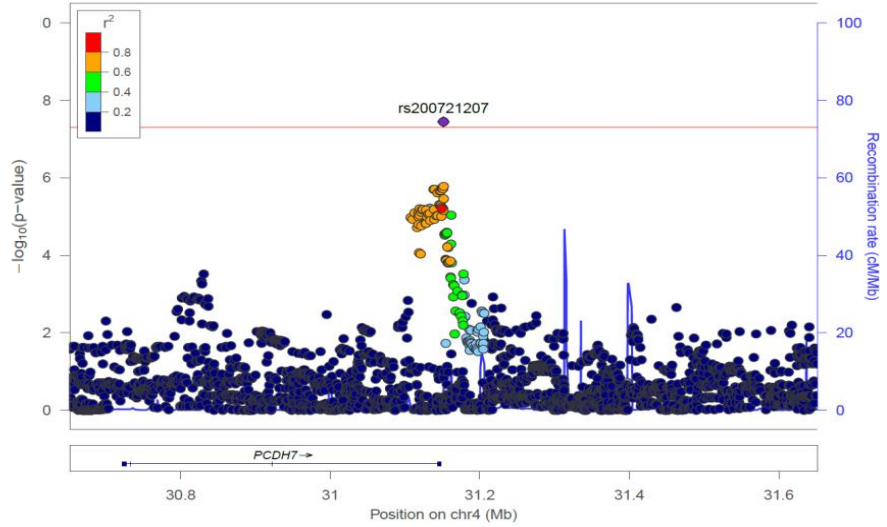
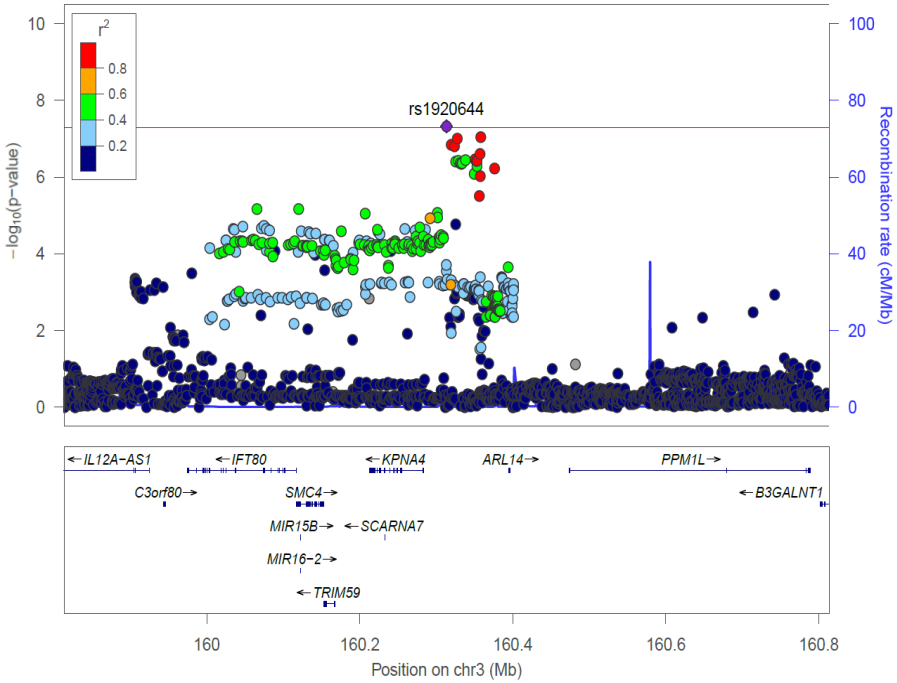

1.1-
1.0-
0.9-
OR meta
1
2
3
4
5
Quintiles

Figure 3.


rs183882582
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
TULP4→
MIR7161→
←MIR3918
C6orf99→
←TAGAP
FNDC1→
TMEM181→
SYTL3→
←OSTCP1
←RSPH3
←DYNLT1
←EZR
EZR−AS1→
Position on chr6 (Mb)


rs3958046
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
PTPRZ1→
←AASS
←FEZF1
←RNF133
FEZF1−AS1→
←RNF148
←CADPS2
Position on chr7 (Mb)


rs200721207
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
PCDH7→
Position on chr4 (Mb)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r²
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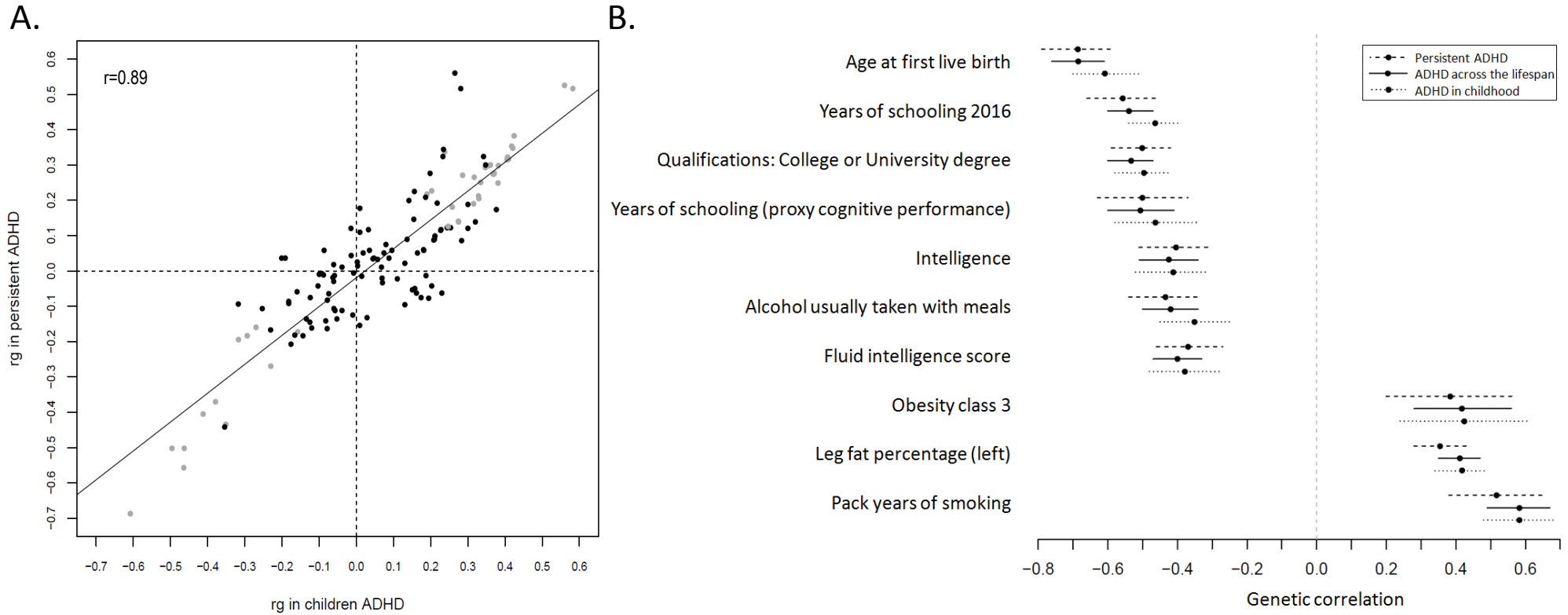
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
←IL12A−AS1
←IFT80
←KPNA4
ARL14→
PPM1L→
C3orf80→
SMC4→
←B3GALNT1
MIR15B→
←SCARNA7
MIR16−2→
←TRIM59
Position on chr3 (Mb)

Figure 4.


A.
r=0.89
rg in persistent ADHD
rg in children ADHD
B.
Age at first live birth
Years of schooling 2016
Qualifications: College or University degree
Years of schooling (proxy cognitive performance)
Intelligence
Alcohol usually taken with meals
Fluid intelligence score
Obesity class 3
Leg fat percentage (left)
Pack years of smoking
Persistent ADHD
ADHD across the lifespan
ADHD in childhood
Genetic correlation