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Genetics of suicide attempts in individuals with and without mental disorders: a population-based genome-wide association study

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Abstract

Family studies have shown an aggregation of suicidal behavior in families. Yet, molecular studies are needed to identify loci accounting for genetic heritability. We conducted a genome-wide association study and estimated single nucleotide polymorphisms (SNP) heritability for a suicide attempt. In a case-cohort study, national data on all individuals born in Denmark after 1981 and diagnosed with severe mental disorders prior to 2013 ($n = 57,377$) and individuals from the general population ($n = 30,000$) were obtained. After quality control, the sample consisted of 6024 cases with an incidence of suicide attempt and 44,240 controls with no record of a suicide attempt. Suggestive associations between SNPs, rs6880062 (p-value: 5.4×10^{-8}) and rs6880461 (p-value: 9.5×10^{-8}), and suicide attempt were identified when adjusting for socio-demographics. Adjusting for mental disorders, three significant associations, all on chromosome 20, were identified: rs4809706 (p-value: 2.8×10^{-8}), rs4810824 (p-value: 3.5×10^{-8}), and rs6019297 (p-value: 4.7×10^8). Sub-group analysis of cases with affective disorders revealed SNPs associated with suicide attempts when compared to the general population for gene PDE4B. All SNPs explained 4.6% [CI-95: 2.9–6.3%] of the variation in suicide attempt. Controlling for mental disorders reduced the heritability to 1.9% [CI-95: 0.3–3.5%]. Affective and autism spectrum disorders exhibited a SNP heritability of 5.6% [CI-95: 1.9–9.3%] and 9.6% [CI-95: 1.1–18.1%], respectively. Using the largest sample to date, we identified significant SNP associations with suicide attempts and support for a genetic transmission of suicide attempt, which might not solely be explained by mental disorders.

Introduction

The lifetime prevalence of suicide attempts is estimated to be 2.7% [1, 2]. Family studies using clinical and epidemiological data have consistently shown an aggregation of suicidal behavior in families [3–7]. Both twin and adoption studies have indicated that genes account for as

much as 30–50% of the observed familial aggregation [8–10]. Hence, molecular studies have attempted to identify specific genes that contribute to suicide risk [11].

The advantage of molecular genetic studies lies in the estimation of genetics effects via single nucleotide polymorphisms (SNPs) rather than through familial relationships. Candidate gene and genome-wide association study (GWAS) designs have identified numerous loci associated with suicide attempts, including *5HTR2A* (rs1885884) [12]; a locus on 2p25 (rs300774) [11, 13]; and *ABI3BP* (rs2576377) [14] among others [15]. Still, to date most molecular genetic studies, even combined ones, have been conducted on small sample sizes (sample < 8900; cases < 2810) [11, 16], implying that they potentially were underpowered and subject to false positives as well as false negatives. Additionally, studies have rarely adjusted for mental disorders or included a non-psychiatric, population-representative sample.

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Mental disorders are strongly linked to suicidal behavior [17–19]. Indeed, often mental disorders and suicidality are seen as clinically related, e.g., suicidal ideation is considered as a qualifying symptom for the diagnosis of depression. Given that liability for a wide range of mental disorders is associated with a common set of genetic factors [20, 21], it is plausible that the effect of genes on suicidal behavior could be mediated through their impact on mental disorders [11, 22, 23]. Although family studies have indicated support for a generic transmission of suicidal behavior independent of mental disorders [3, 4, 6, 10, 22, 23], this remains to be confirmed using molecular genetic data.

The aim of this study was to examine whether specific genetic variants are associated with suicide attempt in a population-based sample of individuals with and without severe mental disorders using a GWAS approach while controlling for mental disorders. In addition, we aimed to estimate the heritability explained by common genetic variation while taking mental disorders into account.

Material and methods

Design and data source

We used a nested case-cohort study design [24]. In Denmark, a unique personal id-number is assigned to all persons born or migrating into the country [25]. This id-number was introduced in 1968 and is listed in the Danish Civil Registration System along with data on gender, birth date, and parents' id number [26]. Since 1981, blood samples from all newborns in Denmark have been archived in the Danish Newborn Screening Biobank at the Danish Statens Serum Institut [27, 28]. Likewise, individual records of all hospital contacts for mental and somatic disorders have been recorded in the Danish Psychiatric Central Research Register since 1968 and the National Registry of Patients since 1977, respectively [29, 30].

Sample

The iPSYCH dataset was constructed from complete and consecutive birth cohorts of all singletons born in Denmark between May 1, 1981 and December 31, 2005 [31]. Among individuals who were residents on their first birthday ($N = 1,472,762$ persons), those who later were diagnosed with one or more severe mental disorders prior to 31st December 2012 ($n = 57,377$) were selected. Severe mental disorders were identified as the following diagnoses recorded according to the 10th revision of International Classification of Diseases (ICD-10) [32]: schizophrenia (F20), bipolar disorders (F30, F31), affective disorders (F30–39), autism spectrum disorders (F84.0, F84.1, F84.5, F84.8, or

F84.9), anorexia (F50), and ADHD (F90.0). In addition, a population-based random sample of individuals ($n = 30,000$) was included in iPSYCH [31].

Cases

Individuals in the iPSYCH sample who at some point prior to December 31, 2012 had been recorded with one or more incidents of non-fatal suicide attempts were considered as cases. Suicide attempts were identified by screening the Danish Psychiatric Central Research Register and the National Registry of Patients for diagnoses of suicide attempts (ICD-10: X60–X84). In addition, contacts where the "reasons for contact"-variable indicated suicide attempt were included, as well as combinations of diagnoses where the main diagnosis had been recorded as a mental disorder (ICD-10: F chapter) together with a diagnosis of poisoning by drugs or other substances (ICD-10: T36–T50, T52–T60) or injuries to hand, wrist, and forearm (ICD-10: S51, S55, S59, S61, S65, S69). This is a well-established proxy for suicide attempt [33, 34].

Controls

All persons who had not been recorded with one or more suicide attempts were included in the control group. The control group consisted of persons with mental disorders as well as persons with no mental disorders.

Extraction and genotyping

The Danish Newborn Screening Biobank consists of blood spot samples from almost 100% of all newborns in Denmark, which are collected 4–7 days after birth through heel prick and stored at $-20\,^{\circ}\mathrm{C}$ [27, 28, 35]. Two 3.2 mm disks were punched from blood spots for each individual. Genomic DNA was extracted and whole genome amplified (WGA) with the use of Extract-N-Amp Blood PCR Kit (Sigma-Aldrich, Seelze, Germany) and RepliG kit (Qiagen, Venlo, The Netherlands) [35, 36]. Genotyping was carried out using Infinium PsychChip v1.0 array (Illumina, San Diego, CA, USA) according to the manufacturer's instructions and handled by the Broad Institute (Boston, MA, USA) over 23 waves. The extraction and genotyping procedures have previously been tested by comparing call and conflict rates of WGA DNA from >20-year-old stored blood spots with those of high quality, recent genomic DNA from the same individuals; concluding a high quality of the WGA DNA [35, 37].

Genotype quality control and imputation

After initial genotyping and quality control at the Broad Institute, a total of 77,639 subjects and 554,360 SNPs were

obtained. A subset of 246,369 high-quality SNPs was identified by excluding SNPs showing deviations from the Hardy–Weinberg equilibrium (p-value $< 1 \times 10^{-6}$) in controls, minor allele frequencies <1%, multi-allelic SNPs, and SNPs in non-autosomal loci within a subset of individuals with a homogenous European ancestry. This set of high-quality SNPs were pre-phased using SHAPEIT3 [38] and the resulting haplotypes were imputed in 10 batches using IMPUTE2 [39] and the 1000 genomes phase3 reference haplotypes, which yielded a total of 80.7 million variants.

The post-imputation quality control excluded SNPs for the following, non-exclusive reasons: variants with minor allele frequencies < 0.001 ($n \approx 67$ million); variants with imputation INFO scores < 0.2 ($n \approx 17$ million); SNPs missing in more than 10% of the imputed samples ($n \approx 1.8$ million); SNPs showing strong associations to genotyping wave ($n \approx 291,937$) or imputation batch ($p < 5 \times 10^{-8}$) ($n = 33$); SNPs showing differential imputation quality between psychiatric cases and controls ($p < 1 \times 10^{-6}$) ($n \approx 527,912$); and SNPs violating Hardy–Weinberg equilibrium in controls. Finally, a total of 11,601,089 markers were retained.

Population stratification and kinship

Principal components of genetic ancestry were generated using Eigensoft smartPCA [40]. Using a subset of 47,856 individuals whose parents and grandparents were born in Denmark as our reference, we censored individuals deviating from the multivariate mean of the joint distribution of first 10 principal components. Principal components were re-generated using the remaining samples and the second round of censoring was performed. KING was used to generate kinship coefficients to ensure that no two samples were related beyond the second degree [41]. The imputation and quality control process has previously been documented [42].

Statistical analysis

The GWAS was conducted by comparing the imputed additive genotype dosages between cases with one or more suicide attempts to controls with no recorded suicide attempt. Logistic regressions were applied to calculate log odds ratios and 95% confidence intervals using PLINK2 [43] and the R package qqman [44] to generate Manhattan plots. The level of significance and suggestive significance was set to $p < 5 \times 10^{-8}$ and $p < 5 \times 10^{-6}$, respectively. Two different GWAS models were employed; Model 1 contained covariates on gender, years under follow-up where the participant was 15 years of age or older, and the first 10 principal components of genetic ancestry. Model 2: In addition to the covariates used in Model 1, binary covariates for diagnosis of schizophrenia, bipolar disorders, affective

disorders, autism spectrum disorders, anorexia, and any other disorder (ICD-10: F chapter) were included. In a third association study, we compared 4302 individuals with affective disorder and at least one recorded suicide attempt to 14,938 controls with affective disorders and no suicide attempt. However, a lack of association was attributed to low statistical power and the model was modified by using only population-based sample of healthy controls ($n = 13,294$) while adjusting for socio-demographic conditions.

The GREML approach implemented in the genome-wide complex trait analysis (GCTA) software package was utilized to estimate the SNP variation [45]. A genetic relatedness cutoff of 0.034 was applied to account for cryptic relatedness between samples. The analysis was adjusted for the same covariates as Model 1.

Enhancer annotations

Enhancer annotations were taken from the GeneHancer database [46], and enhancer IDs corresponded to those in GeneCards (v4.6.0 Build 15). SNP positions were converted to genome build hg38 using the UCSC liftOver [47] and were subsequently mapped onto enhancers using BEDTools [48].

Ethical permission

Anonymized data were stored in the Computerome database at the Technical University of Denmark with restricted access. The project has been approved by the Danish Scientific Ethics Committee, the Danish Health Data Authority, the Danish Data Protection Agency, and Danish Newborn Screening Biobank Steering Committee.

Results

In all, 77,639 individuals born in Denmark between May 1, 1981 and December 31, 2005 were genotyped. Of these, 12,128 participants were excluded during the quality control and 15,247 did not reach the age of 15 during follow-up (Supplementary Figure 1).

The sample consisted of 50,264 individuals over the age of 15 years on December 31, 2012. Of these, 6024 (12.0%) persons had been recorded with a suicide attempt while the remaining 44,240 (88.0%) were considered as controls (Supplementary Table 1).

The results of the GWAS for Model 1 (genomic inflation factor, $\lambda_{gc} = 1.04$) showed suggestive associations on chromosomes 1, 19, and 20. Furthermore, associations for SNPs rs6880062 (NC_000005.9:g.153298025A>G; p-value: 5.4×10^{-8}) and rs6880461 (NC_000005.9: g.153298024G>A; p-value: 9.5×10^{-8}) on chromosome 5
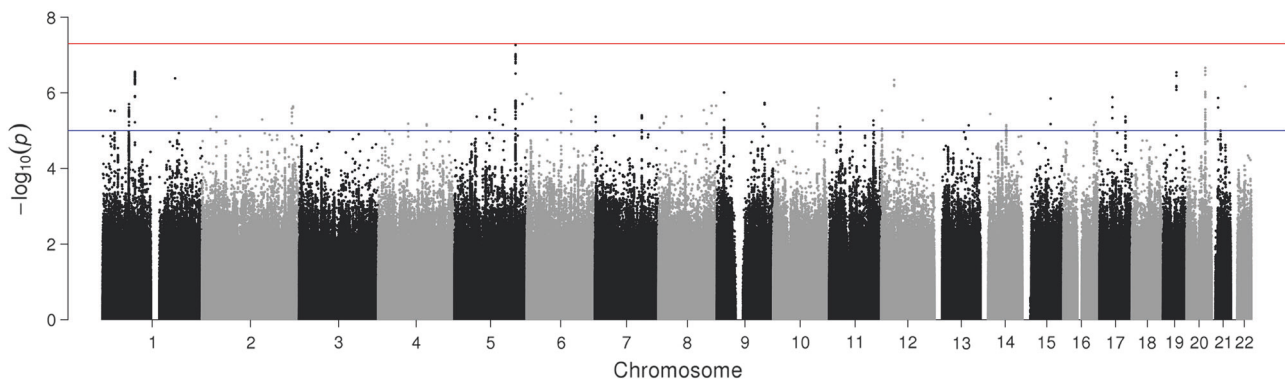
Fig. 1 Manhattan plot of genome-wide association study (GWAS) of suicide attempt adjusted for: gender, number of years under follow-up being (aged ≥15 years), first 10 principal components of genetic ancestry (Model 1). *Note*: The red line marks the threshold of $p = 5 \times 10^{-8}$ for significant associations while the blue line marks the threshold of $p = 5 \times 10^{-6}$ for suggestive associations

fell short of genome-wide significance, as seen in Fig. 1 and Table 1.

GWAS Model 2 (genomic inflation factor, $\lambda_{gc} = 1.02$), revealed three genome-wide significant SNPs; rs4809706 (NC_000020.10:g.47193719A>G; *p*-value: 2.8×10^{-8}), rs4810824 (NC_000020.10:47193708G>C; *p*-value: 3.5×10^{-8}), and rs6019297 (NC_000020.10:g.47197230C>T; *p*-value: 4.7×10^{-8}) on chromosome 20 (Fig. 2). In addition, suggestive associations were noted on chromosomes 6, 8, and 9. The three significant SNPs showed suggestive associations in Model 1.

The third association study comparing individuals with depressive disorder and a suicide attempt to healthy controls (genomic inflation factor $\lambda_{gc} = 1.08$) revealed a genome-wide significant locus on chromosome 1 with the lead SNP rs4554696 (NC_000001.10:g.66408011C>T; *p*-value: 5.63×10^{-9} OR = 0.85 ± 0.05 95% CI) and suggestive associations on chromosomes 2, 5, and 9 (Fig. 3). The Manhattan plot for the GWAS and a GTEX expression plot [49] for PDE4B are presented in Supplementary Figure 2–3 and Supplementary Table 2.

The SNP heritability of suicide attempt was found to be 4.6% [CI-95: 2.9–6.3%] when adjusting for socio-demographic characteristics (Table 2). When introducing diagnosed mental disorders as binary covariates in the GCTA model, SNP heritability was reduced to 1.9% [CI-95: 0.3–3.5%]. Calculation of SNP heritability among people with no mental disorders did not render a significant estimate [OR = 3.3%; CI-95: −0.1 to 7.6%], while a significant h^2 estimate of 2.8% [0.7–4.9%] was noted within subjects with mental disorders. The SNP heritability was further estimated within each subgroup of mental disorders while adjusting for socio-demographic covariates. Individuals with affective disorders were estimated to carry a significant SNP heritability of 5.6% [1.9–9.3%] while those with autism spectrum disorders had 9.6% [1.1–18.1%]. The SNP heritability for individuals with schizophrenia and ADHD were 0% [−27.5 to 27.5%] and 0.4% [−6.6 to 7.4%], respectively.

Discussion

To our knowledge, this is the largest molecular genetic study to examine suicide attempt. By including a population-based sample, it was possible to adjust for the presence of mental disorders, hereby, addressing the possible mediating role of mental disorders. Albeit significant associations were identified by this study, the heritability estimates suggest that diagnosed mental disorders do not fully explain the genetic transmission of a suicide attempt.

GWAS

The lead SNP, rs6880062 on chromosome 5, of Model 1 is intergenic, with the closest gene being *FAM114A2* (distance = 71.6 kb) and has not previously been associated with suicidal behavior [15]. When intersected with Gene-Hancer database of enhancer regions (version: 4.6.0 build 15) [46], one of the suggestive SNPs on chromosome 22, rs150801052 (*p*-value: 6.78×10^{-7}) was found to be within an enhancer (Enhancer ID: GH22H035858) for the protein-coding gene myoglobin, elevated levels of which has previously been suggested for monitoring in two previous cases involving an adolescent female with suicide attempt and an older adult with depression and psychosis [50, 51].

The enhancer was also connected to the *RBFOX2* gene, which encodes an RNA-binding protein that is thought to be involved in exon splicing in the nervous system. Recently,

Table 1 SNP showing significant or suggestive association with a suicide attempt in adjusted GWAS

Model	SNP	Chromosome	Position	A1/A2	Minor allele frequency	INFO	Odds ratio [CI-95%][a]	p-Value
Model 1: Adjusted for socio-demographic conditions[b]								
rs12130410	1	81359237	C/A	0.0593	0.963265	0.7948 ± 0.089964	5.67E−07
rs12118384	1	81360791	G/A	0.0607	0.963841	0.7935 ± 0.088984	3.55E−07
rs72134670	1	81361781	AGTGT/A	0.0592	0.970028	0.7956 ± 0.089768	5.90E−07
rs114428613	1	81363409	T/A	0.0592	0.971558	0.7945 ± 0.089768	5.05E−07
rs12122457	1	81364694	G/C	0.0592	0.972986	0.7941 ± 0.089768	4.77E−07
rs12119932	1	81364728	T/G	0.0592	0.973008	0.7941 ± 0.089768	4.76E−07
rs12119912	1	81364903	A/G	0.0592	0.973055	0.7941 ± 0.089768	4.74E−07
rs201713449	1	81365218	G/GCA	0.0592	0.973134	0.7940 ± 0.089768	4.72E−07
rs116584414	1	81365419	T/G	0.0592	0.973185	0.7940 ± 0.089768	4.69E−07
rs79479721	1	81365444	T/G	0.0592	0.973191	0.7940 ± 0.089768	4.69E−07
rs115355703	1	81365722	A/C	0.0592	0.973267	0.7939 ± 0.089768	4.66E−07
rs114035422	1	81366040	A/G	0.0592	0.973354	0.7939 ± 0.089768	4.64E−07
rs115194926	1	81366100	G/T	0.0592	0.973373	0.7939 ± 0.089768	4.63E−07
rs115255447	1	81366951	T/A	0.0592	0.97427	0.7935 ± 0.089768	4.38E−07
rs115410239	1	81369030	T/A	0.0592	0.977419	0.7937 ± 0.089572	4.30E−07
rs12132818	1	81371930	C/G	0.0592	0.98065	0.7919 ± 0.089572	3.23E−07
rs72940613	1	81373376	A/G	0.0595	0.976727	0.7927 ± 0.089376	3.55E−07
rs6681193	1	81374082	C/T	0.0592	0.982108	0.7913 ± 0.089572	2.94E−07
rs114462636	1	81375885	C/T	0.0589	0.985097	0.7916 ± 0.089572	3.20E−07
rs12130052	1	81379254	T/A	0.0588	0.989481	0.7932 ± 0.089376	3.80E−07
rs12130531	1	81380084	C/T	0.0588	0.989333	0.7932 ± 0.089376	3.77E−07
rs12121366	1	81381621	T/C	0.0589	0.990004	0.7923 ± 0.089376	3.26E−07
rs112409531	1	81384412	A/G	0.0588	0.990039	0.7933 ± 0.089376	3.80E−07
rs12135658	1	81384847	C/G	0.0594	0.991295	0.7967 ± 0.088592	5.08E−07
rs17105681	1	81385360	C/G	0.0596	0.991544	0.7974 ± 0.088592	5.37E−07
rs12125794	1	81386101	A/C	0.0595	0.991884	0.7974 ± 0.088592	5.49E−07
rs72940624	1	81387664	T/G	0.0595	0.992104	0.7972 ± 0.088592	5.36E−07
rs74092049	1	81387673	T/C	0.0595	0.992106	0.7972 ± 0.088592	5.35E−07
rs74092050	1	81387892	A/G	0.0596	0.99158	0.7971 ± 0.088592	5.12E−07
rs17105699	1	81391541	A/G	0.0589	0.991587	0.7928 ± 0.08918	3.36E−07
rs74092063	1	81393160	G/A	0.059	0.991599	0.7923 ± 0.08918	3.05E−07
rs7548691	1	81396755	G/A	0.0591	0.992042	0.7920 ± 0.08918	2.91E−07
rs17105728	1	81398266	T/C	0.0589	0.992018	0.7917 ± 0.08918	2.89E−07
rs12133801	1	81401114	G/A	0.0589	0.993456	0.7919 ± 0.08918	2.89E−07
rs79780846	1	81419288	G/A	0.0588	0.987839	0.7911 ± 0.089572	2.83E−07
rs12139190	1	81420151	A/C	0.0587	0.987233	0.7913 ± 0.089572	3.05E−07
rs72940689	1	81428767	G/A	0.0586	0.978883	0.7897 ± 0.09016	2.78E−07
rs2560038	5	153272968	G/A	0.3232	0.993039	0.8960 ± 0.04214	3.10E−07
rs1593827	5	153280893	G/A	0.3112	0.995496	0.8914 ± 0.042532	1.17E−07
rs898709	5	153286964	A/G	0.3117	1	0.8929 ± 0.042336	1.66E−07
rs1870738	5	153287549	T/A	0.3126	0.998605	0.8921 ± 0.042336	1.31E−07
rs2085865	5	153290253	G/A	0.3121	0.998881	0.8913 ± 0.042336	1.06E−07
rs2035099	5	153290835	C/A	0.3121	0.998768	0.8914 ± 0.042336	1.07E−07
rs7726518	5	153293565	G/A	0.3123	0.998245	0.8914 ± 0.042336	1.06E−07
rs2126160	5	153294271	C/T	0.3123	0.99833	0.8914 ± 0.042336	1.07E−07
rs7732031	5	153294900	A/G	0.3123	0.998254	0.8914 ± 0.042336	1.08E−07

Table 1 (continued)

Model	SNP	Chromosome	Position	A1/A2	Minor allele frequency	INFO	Odds ratio [CI-95%][a]	p-Value
	rs1599408	5	153296017	C/T	0.3125	0.998001	0.8927 ± 0.042336	1.53E−07
	rs1599409	5	153296064	C/A	0.3123	0.998137	0.8915 ± 0.042336	1.10E−07
	rs1599410	5	153296073	C/T	0.3123	0.998137	0.8915 ± 0.042336	1.10E−07
	rs6880461	5	153298024	G/A	0.3138	0.997715	0.8911 ± 0.042336	9.52E−08
	rs6880062	5	153298025	A/G	0.3107	0.989144	0.8884 ± 0.042728	5.44E−08
	rs2614123	5	153300215	C/T	0.3139	0.996726	0.8914 ± 0.042336	1.06E−07
	rs7862648	9	18290857	A/G	0.2187	0.991736	1.1212 ± 0.045864	9.80E−07
	rs112595860	12	32640591	C/G	0.2172	0.931883	0.8798 ± 0.049784	4.55E−07
	rs113067218	12	32641482	CT/C	0.2174	0.932194	0.8814 ± 0.049784	6.54E−07
	rs10506086	12	32642659	C/T	0.2162	0.930623	0.8808 ± 0.04998	6.17E−07
	rs4810824	20	47193708	G/C	0.6268	0.959962	0.8994 ± 0.040376	2.65E−07
	rs4809706	20	47193719	A/G	0.6273	0.958887	0.8987 ± 0.040376	2.19E−07
	rs6125386	20	47196367	A/G	0.6323	0.971916	0.9042 ± 0.04018	9.42E−07
	rs6019297	20	47197230	C/T	0.625	0.958847	0.9002 ± 0.040376	3.34E−07
	rs150801052	22	36255928	AT/A	0.0167	0.677581	1.5076 ± 0.161896	6.78E−07
Model 2: Adjusted for socio-demographic conditions and mental disorders[c]								
	rs4053798	6	85943189	A/C	0.9945	0.926872	0.5418 ± 0.242844	7.60E−07
	rs76426299	8	58350711	G/A	0.0189	0.556548	1.6189 ± 0.191688	8.40E−07
	rs7862648	9	18290857	A/G	0.2187	0.991736	1.1281 ± 0.047824	7.82E−07
	rs4810824	20	47193708	G/C	0.6268	0.959962	0.8884 ± 0.04214	3.56E−08
	rs4809706	20	47193719	A/G	0.6273	0.958887	0.8875 ± 0.04214	2.80E−08
	rs6019294	20	47194199	G/A	0.5818	0.974655	0.9014 ± 0.04116	7.68E−07
	rs6066764	20	47194229	C/A	0.5759	0.971501	0.8994 ± 0.04116	4.57E−07
	rs6066765	20	47194232	G/C	0.5759	0.971509	0.8994 ± 0.04116	4.57E−07
	rs6019295	20	47194750	G/A	0.5841	0.984819	0.9011 ± 0.040964	6.42E−07
	rs6122700	20	47196231	T/C	0.6901	0.970105	0.8969 ± 0.043512	9.10E−07
	rs6125386	20	47196367	A/G	0.6323	0.971916	0.8947 ± 0.041944	2.03E−07
	rs6012487	20	47196557	G/C	0.6317	0.972012	0.8953 ± 0.041944	2.36E−07
	rs4810826	20	47196647	T/C	0.6311	0.972755	0.8950 ± 0.041944	2.13E−07
	rs4810827	20	47196809	T/C	0.6314	0.971384	0.8951 ± 0.041944	2.29E−07
	rs6019297	20	47197230	C/T	0.625	0.958847	0.8893 ± 0.04214	4.71E−08

[a]Odds ratios were calculated with respect to A2

[b]Model 1 was adjusted for gender, number of years under observation over the age of 15, and first 10 principal components of genetic ancestry

[c]Model 2 was adjusted for gender, number of years under follow-up being (aged ≥15 years), first 10 principal components of genetic ancestry, diagnosis of any mental disorder as well as diagnosis of schizophrenia, bipolar disorders, affective disorders, autism spectrum disorders, anorexia, and ADHD

this gene has been highlighted in a GWAS for major depression conducted by the Psychiatric Genomics Consortium, which includes the iPSYCH dataset [52]. Both connections were supported by evidence from C–HiC interactions.

The lead SNP identified on chromosome 20 in Model 2, rs4809706, is also intergenic with the nearest gene being *PREX1* (distance = 47 kb), which has been associated with depression and autism-like behavior [53]. An intersection with GeneHancer database did not reveal any associations with known enhancers or promoters.

By querying the GWAS catalog and PubMed, we attempted to replicate 40 SNPs associated to suicidal ideation or suicide attempt in six previous GWAS studies [13, 14, 54–59], We were unable to replicate either of the genome-wide significant loci identified [13, 58]. Nevertheless, one of the suggestive associations on chromosome 11 [13], rs10437629 showed significance in both models 1 (p = 0.029) and 2 (p = 0.03) in the current data (Supplementary Table 3).

In the association study comparing individuals with major depressive disorders and suicide attempts to healthy
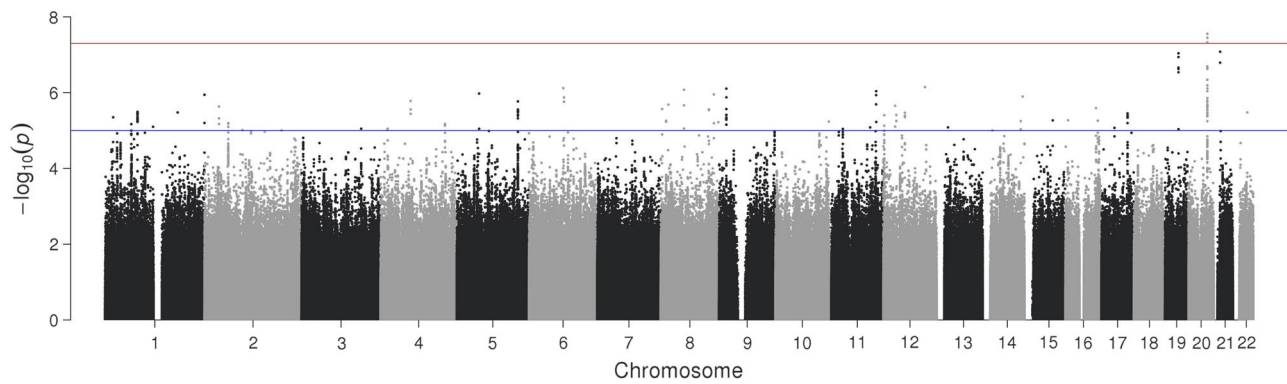
Fig. 2 Manhattan plot of genome-wide association study (GWAS) of suicide attempt adjusted for: gender, number of years under follow-up being (aged ≥15 years), first 10 principal components of genetic ancestry, diagnosis of any mental disorder as well as diagnosis of schizophrenia, bipolar disorders, affective disorders, autism spectrum disorders, anorexia, and ADHD (Model 2). *Note*: The red line marks the threshold of $p = 5 \times 10^{-8}$ for significant associations while the blue line marks the threshold of $p = 5 \times 10^{-6}$ for suggestive associations

controls, the lead SNP, rs4554696, is in the intronic region of the gene *PDE4B*, which has previously been implicated in schizophrenia and bipolar disorders [60, 61]. Studies in Japanese populations have associated *PDE4B* to panic disorders and major depression [62, 63]. A gene expression analysis from the GTEx portal (release v7) [64] revealed *PDE4B* being highly expressed in brain-related tissues (Supplementary Figure 2). An intersection with the Gene-Hancer database showed that four tag SNPs (LD: $r^2 > 0.8$ with the lead SNP) rs12062815 (*p*-value: 9.22×10^{-9}), rs12062901 (*p*-value: 7.8×10^{-9}), rs1318475 (*p*-value: 7.244×10^{-9}), and rs34482581 (*p*-value: 6.994×10^{-9}) fall within an enhancer for the gene *PDE4B* with the following brain tissue annotations: anterior caudate, cingulate gyrus, inferior temporal lobe, hippocampus middle (Enhancer ID: GH01H065961). The connection to the gene *PDE4B* was further validated by C–HiC interaction. Interestingly, this locus has not been observed to achieve genome-wide significance in previous studies of large-sample GWAS of major depressive disorder [52]; indicating that suicidal behavior could possibly be utilized as a secondary phenotype to explore severity within major depressive disorder. Behavioral and neurochemical characterization of *PDE4B* in an animal model revealed the *PDE4B*-knockout mice to have significantly reduced pre-pulse inhibition, decreased spontaneous locomotor activity, and enhanced response to amphetamine [65]. Additionally, *PDE4B*-deficient mice display anxiogenic-like behavior [66], further supporting the role of the *PDE4B* gene in the etiology of mental disorders.

Various causal pathways have been suggested [26]. While previous studies have identified loci associated with suicidal attempts in clinical or relatively small population samples [11], our findings add significant support to the role of genes in the etiology of suicidal behavior. Liability for mental disorders, such as affective disorders or borderline personality disorders, may be inherited and explain the link to suicidal behavior [20, 26, 27]. Secondly, the relationship between genes and suicidal behavior may be mediated by behavioral traits, such as impulsive and impulsive-aggressive behaviors [67, 68]. Furthermore, environmental factors, such as stressful life events and social constraints, might interact with genetic factors [27].

Heritability

A heritability of 4.6% is substantially lower than reported in the family and twin studies [9]. However, this type of studies cannot fully account for social contamination through social role models, social heritages, such as living conditions, and other shared environmental factors [69]. The GCTA estimates provide a lower bound estimate for genetic heritability, as not all genetic variation can be explained by genotyped SNPs [70]. Still, it is interesting that a heritability of 1.9% was maintained when adjusting for the presence of any and specific mental disorders; this estimate is also lower than the 17.4% noted in observational studies [8, 71]. The reduction from 4.6 to 1.9% indicates that parts of the genetic transmission might be explained through mental disorders.

Schizophrenia has been linked to an absolute suicide risk of 6.5% [19]. Nevertheless, a SNP heritability close to zero might be related to the relatively small number of individuals suffering from schizophrenia with a suicide attempt. Alternative explanations could be that genetic heterogeneity of suicide attempt is explained in part by diagnosed mental

Fig. 3 Region plot of the association evidence in gene *PDE4B* in the chromosome 1p31.3 in a sub-group analysis of cases with affective disorders vs. healthy controls (hg19, LocusZoom viewer) [76].
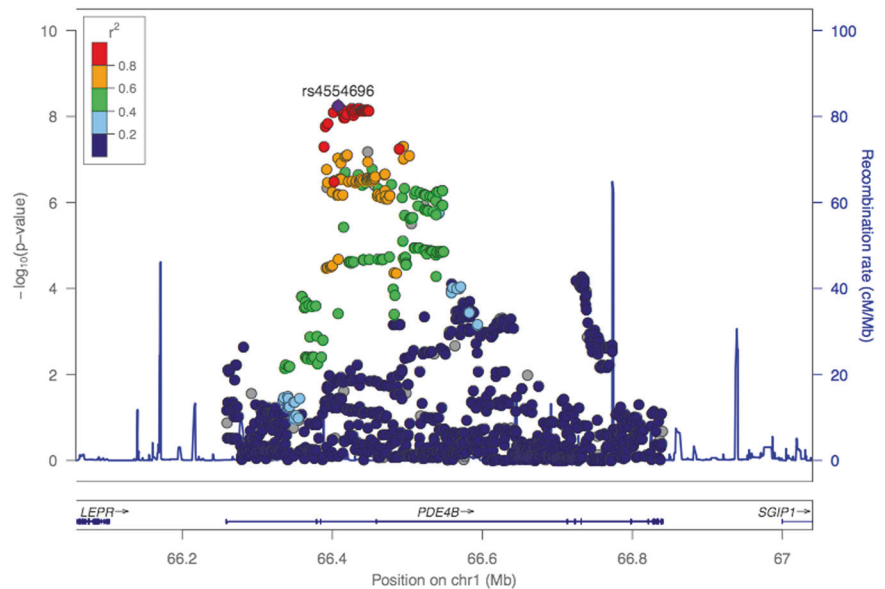
disorders; or in conditions, such as schizophrenia, the genetic factors explaining suicide attempt are not distinct from those genetic factors increasing the risk for the disorder itself. Interestingly, a polygenic overlap between schizoaffective disorders and suicide attempt has previously been suggested [72]. The highest heritability was found for autism spectrum disorders; indicating that SNP heritability accounted for up to 10% of suicide attempts. This has not previously been documented and future studies might gain insights by assessing mental disorders separately.

Strengths and limitations

The Danish Newborn Screening Biobank presents an almost complete coverage and a validated approach for DNA extraction and genotyping was used [27, 35]. Furthermore, complete hospital records of psychiatric inpatients for the entire study period were available while data on emergency department and out-patients were included in 1995 when the oldest birth cohorts were 13 years of age [29], hence, keeping the probability of selection bias low. While previous studies had to rely on self-reported data [73], the phenotype was based on hospital records and measured consistently for all subjects. Using a large population-based sample with limited population heterogeneity adds additional strengths to this study. Furthermore, the inclusion of healthy individuals allowed for stratification by mental disorders [11].

Limitations should be acknowledged. About half of the genotyped SNPs were excluded due to the low-frequency exome SNPs in the iPSYCH array design [31]. Due to the sample acquisition, our findings pertain to suicide attempts among individuals below the age of 32 years; i.e., the age

segment with the highest rates of suicide attempt [74]. Suicide attempt is under-recorded in Danish hospitals [74], and a substantial proportion of individuals do not seek hospital care after a suicide attempt [75]. By including a validated, wider proxy, any bias would likely render our estimates conservative; yet, the possibility of false positives cannot be excluded. For reasons of data availability, it was not feasible to examine different methods separately. Hospital-based diagnoses served as a proxy for severe mental disorders; while it is likely that the severe cases of mental disorders will be seen at the hospital, less severe cases might be missed. Also, we did not account for changes in the status of mental disorders over time. It would have been desirable to account for a range of different covariates, such as physical comorbidity and stressful life events, however, this was not feasible in this study.

Conclusion

This large, population-based GWAS of young adults identified SNPs with novel significant associations to suicide attempt while accounting for diagnoses of mental disorders. An association study comparing individuals with affective disorder and attempted suicide to healthy controls revealed a novel association in the intronic region of the gene PDE4B. Heritability estimates indicated that variation in a suicide attempt is associated with the genetic variation and that this association is, partially but perhaps not entirely, explained through mental disorders.

Table 2 SNP heritability with respect to gender and mental disorders

	Suicide attempt n (%)[a]	Control group n (%)[a]	Model 1[b] h^2 [CI-95%]	p-Value	Model 2[c] h^2 [CI-95%]	p-Value
All	6024 (100.0)	44,240 (100.0)	4.6 [2.9–6.3]	<0.0001	1.9 [0.3–3.5]	0.008
Gender						
Males	1837 (30.5)	22,735 (51.4)	5.3 [2.4–8.2]	0.0001	2.8 [−0.1 to 5.7]	0.026
Females	4187 (69.5)	21,505 (48.6)	4.7 [1.9–7.5]	0.0003	1.9 [−0.7 to 4.5]	0.064
Mental disorders						
No diagnosis	132 (2.2)	13,294 (30.1)	3.3 [−1.0 to 7.6]	0.063		
Any diagnosis	5892 (97.8)	30,946 (70.0)	2.8 [0.7–4.9]	0.0027		
Diagnosis						
Schizophrenia	581 (9.6)	1579 (3.6)	0.0 [−27.5 to 27.5]	0.50		
Bipolar[d]	302 (5.0)	911 (2.1)	16.3 [−32.0 to 64.6]	0.254		
Affective disorders	4302 (71.4)	14,935 (33.8)	5.6 [1.9–9.3]	0.001		
Autism	402 (6.7)	7008 (15.8)	9.6 [1.1–18.1]	0.0115		
Anorexia	1254 (20.8)	7866 (17.8)	10.6 [−10.5 to 31.7]	0.148		
ADHD	350 (5.8)	2389 (5.4)	0.4 [−6.6 to 7.4]	0.45		

[a]Additional cases and controls were excluded from the GCTA analysis due to further adjustment for kinship by accounting for cryptic relatedness

[b]Model 1 was adjusted for gender, number of years under observation over the age of 15, and first 10 principal components of genetic ancestry. The h2 estimates are on the observed scale.

[c]Model 2 was adjusted for gender, number of years under follow-up being (aged ≥15 years), first 10 principal components of genetic ancestry, diagnosis of any mental disorder as well as diagnosis of schizophrenia, bipolar disorders, affective disorders, autism spectrum disorders, anorexia, and ADHD. The h2 estimates are on the observed scale.

[d]Bipolar disorders (ICD: F30–F31) was a subset of affective disorders (ICD: F30–F39)

Compliance with ethical standards

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