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ORIGINAL ARTICLE

Increased burden of rare protein-truncating variants in constrained, brain-specific and synaptic genes in extremely impulsively violent males with antisocial personality disorder

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Abstract

The genetic correlates of extreme impulsive violence are poorly understood, and there have been few studies that have characterized a large group of affected individuals both clinically and genetically. We performed whole exome sequencing (WES) in 290 males with the life-course-persistent, extremely impulsively violent form of antisocial personality disorder (APD) and analyzed the spectrum of rare protein-truncating variants (rPTVs). Comparisons were made with 314 male controls and publicly available genotype data. Functional annotation tools were used for biological interpretation. Participants were significantly more likely to harbor rPTVs in genes that are intolerant to loss-of-function variants (odds ratio [OR] 2.06; $p < 0.001$), specifically expressed in brain (OR 2.80; $p = 0.036$) and enriched for those involved in neurotransmitter transport and synaptic processes. In 60 individuals (20%), we identified rPTVs that we classified as clinically relevant based on their clinical associations, biological function and gene expression patterns. Of these, 37 individuals harbored rPTVs in 23 genes that are associated with a monogenic neurological disorder, and

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23 individuals harbored rPTVs in 20 genes reportedly intolerant to loss-of-function variants. The analysis presents evidence in support of a model where presence of either one or several private, functionally relevant mutations contribute significantly to individual risk of life-course-persistent APD and reveals multiple individuals who could be affected by clinically unrecognized neuropsychiatric Mendelian disease. Thus, Mendelian diseases and increased rPTV burden may represent important factors for the development of extremely impulsive violent life-course-persistent forms of APD irrespective of their clinical presentation.

KEYWORDS

aggressive behavior, antisocial personality disorder, brain, copy number variation, dissocial personality disorder, genetics, impulsive violence, neuropsychiatric disease, rare variants, whole-exome sequencing

1 | INTRODUCTION

Antisocial personality disorder (APD), or its equivalent dissocial personality disorder, is a mental condition of adults characterized by impulsive, irresponsible and often criminal behavior. The prevalence of APD is estimated to be 1%–3% in the general population, with males being diagnosed with this condition three to five times more frequently than females.[1] The prevalence of APD reaches up to 18% across a variety of psychiatric settings[2] and 40%–70% among prisoners.[3] In most individuals, symptoms of APD abate in adulthood. However, in some individuals APD persists throughout life without remission[4,5] and can present with aggressive or nonaggressive behavior, with the former being a more stably heritable trait.[6]

Life-course-persistent APD is often associated with abnormalities in brain structure and function. There is clinical overlap with cognitive impairment and neurodevelopmental, neuropsychiatric and neurodegenerative diseases. APD has a significant genetic component,[1,7,8] and meets criteria for a neurodevelopmental disorder; for review see reference 9.

Individuals with life-course-persistent aggressive APD likely have a heterogeneous group of neurodevelopmental or neurodegenerative diseases that may be genetic, acquired, or a combination. Identification of the genetic architecture and neurobiological correlates of life-course-persistent APD is therefore required to identify, treat specifically and further research the causes in affected individuals. Like many other neurologic and neuropsychiatric conditions, understanding the genetic basis of these conditions will provide pathophysiologic insight and allow for more precise definitions of clinical syndromes. In addition, understanding the genetic underpinnings of disease will decrease the inherent bias against antisocial behavior.

Characterization of the genetic architecture of APD requires consideration of various genetic models and multiple genetic approaches. Association studies, linkage studies, candidate gene-based research and genomic rearrangement analyses have revealed several potential candidate genomic loci and genes relevant to APD (for review see reference 10). However, with the exception of monoamine oxidase A,[11,12] no specific genes or genetic variants robustly associated with APD have been identified.

In our recent work,[13] we used the strategy of extreme phenotype sampling and performed a genome-wide rare copy-number variation (CNV) analysis in 281 males who met strict criteria for the life-course-persistent and extremely impulsively violent form of APD, and found that 123 (44%) of 281 cases harbored one to several rare CNVs that impacted genes associated with autosomal dominant or X-linked Mendelian disorders affecting adult behavior, cognition, learning and intelligence. CNVs also occurred in genes of as yet undetermined function that are specifically expressed in the brain, and in genes relevant to synapses, neurodevelopment, neurodegeneration, obesity and neuropsychiatric phenotypes.

In this work, we performed whole exome sequencing (WES) on the same cohort and analyzed the spectrum of rare genetic variants predicted to disrupt corresponding protein synthesis and function by introducing either a premature stop codon, a frameshift, or altered splice site. We hypothesized that, as in similar conditions,[14] these rare, likely protein truncating variants (rPTVs) might contribute to individual APD liability and that a proportion of investigated individuals may be affected by currently undiagnosed Mendelian diseases, as was the case for 31 cases with clinically relevant CNVs identified in our previous study.[13]

2 | MATERIALS AND METHODS

2.1 | Subjects

The Ethical Committee of the First Psychiatric Clinic, Prague and General University Hospital in Prague approved this study. Subjects were recruited from four high-security male prisons with a specialized program for prisoners with personality disorders. In total, 313 participants ≥18 years, with an ICD 10 diagnosis of Antisocial Personality Disorder F60.2, the absence of an organic brain disorder (F00–F09 and F70–F79), no evidence of intellectual disability (all participants completed at least elementary school), and with a proven history of repetitive

violent assaults and at least two convictions for violent attacks (robbery, murder or attempted murder) were included in this study. They originated from 488 participants who were characterized as extremely violent by prison psychologists from 6390 ascertained individuals. Details on subject recruitment, psychiatric assessment, clinical characterization and ancestry determination are described elsewhere.[13]

2.2 | Exome sequencing

Genomic DNA of all available individuals was extracted from whole blood samples in a standard manner. Sequencing libraries were constructed and sequenced on an Illumina HiSeq 2500 system and data analysis was performed as described previously.[15] Briefly, the resulting FASTQ files were aligned to the human reference genome (hg19) using Novoalign v.2.08.03 (Novocraft Technologies, Selangor, Malaysia). After genome alignment, conversion of SAM format to BAM and duplicate removal were performed with Picard Tools v.1.129. The Genome Analysis Toolkit (GATK v.3.5) was used for local realignment around indels, base recalibration and variant recalibration and genotyping. All processed BAM files (cases and controls) were jointly genotyped using GATK Unified Genotyper. Variants were annotated with SnpEff 3.6 using Ensemble gene annotation version 75. Samples with average coverage <40× and with <90% of targets covered at least 10×, with kinship relations and ethnic outliers were excluded from the analysis.

2.3 | Controls and rPTV detection

Comparisons were made with exomes from Czech and Slovak-matched males available from the database of genomic variants maintained by the Czech National Center for Medical Genomics (http://ncmg.cz/en); ($n = 1260$). The control group ($n = 314$) that was used for all comparisons was composed of randomly selected healthy males who presented with conditions unrelated to mental health (cardiomyopathy [58%], statin-induced myopathy [7%]), and fathers of patients investigated for a broad spectrum of recessive Mendelian phenotypes (35%). Other comparisons were made with publicly available genotype data from The Genome Aggregation Database (gnomAD).[16] We defined rPTVs as being absent in Czech and Slovak matched control samples and having a frequency ≤0.1% among subjects reported in gnomAD datasets.

2.4 | Gene-set and gene network analyses of rPTVs and prioritization of candidate genes

Gene set analysis was performed and candidate genes were prioritized through functional annotation tools available in FUMA,[17] g:Profiler (g:GOSt),[18] and by individual expert evaluation. Only significantly enriched terms were listed (false discovery rate adjusted p-value <0.05). Genes with specific expression in brain were identified in The Genotype-Tissue Expression Project Portal (GTEx V7 release) when their maximum expression levels (transcripts per million values) in any brain region were at least five times higher than the average in other tissues. Tissue-specific enriched expression of gene sets was tested using Tissue-Specific Expression Analysis (TSEA) tool.[19] Background gene set in GENE2FUNC analysis in FUMA was set to "protein coding."

Genes that are intolerant to rPTVs have substantial and consistent impact across neurodevelopmental and psychiatric disorders.[20] To identify such genes among group-specific genes we used the criterion of the probability of loss-of-function intolerance (pLI) value ≥0.90[21] that is reported in the ExAC v1.0 dataset, which excludes psychiatric cohorts. Clinically relevant rPTVs were defined as those that affect genes with reported autosomal dominant and X-linked inheritance patterns or de novo mutations and neurological phenotypes in the Online Mendelian Inheritance in Man (OMIM) database. Potentially clinically relevant rPTVs were defined as those that affect genes with reported autosomal dominant and X-linked inheritance patterns or de novo mutations and a phenotypic description potentially related to the phenotype.

2.5 | Statistical analysis

Odds ratios (ORs) and p-values from Fisher's exact test were obtained using the epitools package implemented in R (version 4.0.0).

3 | RESULTS

3.1 | Distribution of individual rPTV categories is similar in cases and control subjects

Of 313 case samples, 290 passed stringent quality control and were successfully genotyped. From these samples, we identified 2418 rPTVs fulfilling the selected criteria (Table S1). Of these, 978 were frameshift mutations, 814 were stop-gain mutations, 508 affected either donor or acceptor splice sites, 79 affected initiation codons (start lost) and 39 affected termination codons (stop-loss; Figure 1A). The distribution of rPTV counts per case is shown in Figure 1B. Identified rPTVs impacted 2128 genes, with 249 genes impacted with more than two (2–5) different rPTVs (Figure 1C). The majority of rPTVs (2165) occurred only once in the population; 253 rPTVs were found in more than one case (2–15 times; Figure 1D).

The most frequent case-specific variant was a stop-gain variant in *BAHD1* (rs139014605; p.Arg20Ter), which was identified in a heterozygous state in 15 individuals of Roma ancestry. BAHD1 is a component of a multi-protein complex associated with histone deacetylases.[22,23] BAHD1 haploinsufficiency results in an anxiety-like phenotype in male mice,[24] and a disruption of *BAHD1* was described in a single case of teenage onset of progressive intellectual deterioration.[25] Using a PCR-RFLP-based genotyping assay we found a similar frequency (6 out of 98 males) in Roma controls. Thus, this variant probably represents a Roma population-specific polymorphism.

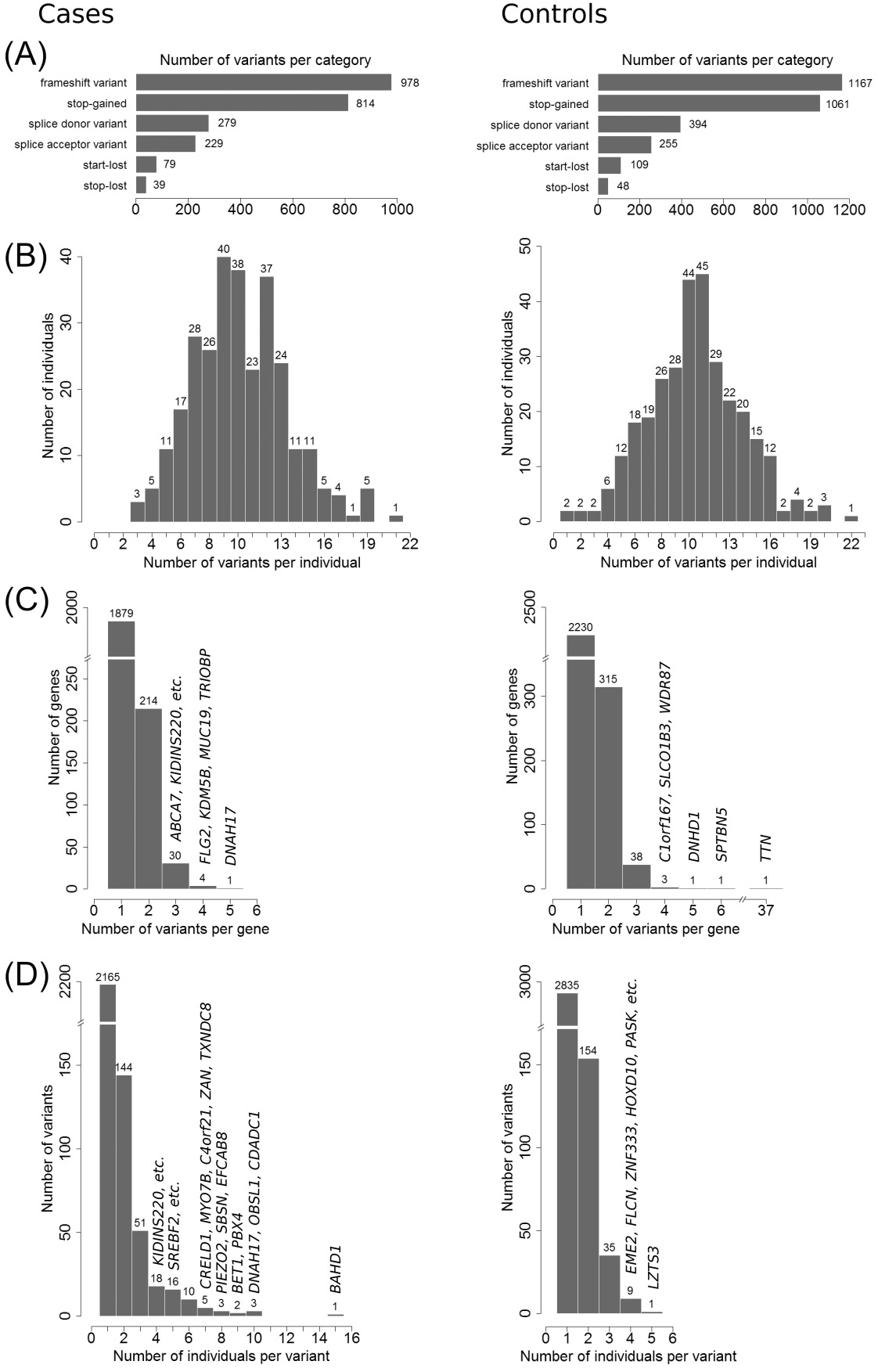


FIGURE 1 Legend on next page.

In a control group of 314 males, we identified 3034 rPTVs. The distribution of variants according to their impact is shown in Figure 1A. The distribution of rPTV counts per control individual is shown in Figure 1B. Identified rPTVs impacted 2589 genes, with 359 genes impacted by more than two (2–6) different rPTVs. The *TTN* gene was affected 37 times, reflecting the presence of multiple individuals with cardiomyopathy in the control group (Figure 1C). A majority of rPTVs (2835) occurred one time in the population; 199 rPTVs were found more than once (2–5 times; Figure 1D).

3.2 | Cases are significantly more likely to harbor multiple rPTVs in brain-specific and synaptic genes that are intolerant to loss of function mutations

To characterize the genetic architecture of impulsive violence, we adapted the approach that was used to study schizophrenia in South African Xhosa patients.[26] The workflow of this approach is shown in Figure 2.

We first selected genes harboring rPTVs only in the group of cases or in the group of controls. In cases we identified 2100 rPTVs, representing 1753 unique variants in 1597 genes (case-specific events). In controls we identified 2536 rPTVs, representing 2346 unique variants in 2058 genes (control-specific events; Table S1).

Occurrence of rPTVs in the "high pLI" genes in individual cases is shown in Figure 3. At least one rPTV in any of the "high pLI" genes was identified in 156 (53%) cases and 161 (51%) controls (OR 1.11; 95% confidence interval [CI] = 0.80–1.52; $p = 0.54$). When we used the threshold of at least two rPTVs per "high pLI" gene, we identified 70 (24%) cases and 42 (13%) controls (OR 2.06; 95% CI 1.35–3.14; $p < 0.001$). With the threshold of three or more rPTVs per gene, we identified 49 (17%) cases and 14 (4.5%) controls (OR 4.36; 95% CI 2.34–8.08; $p < 0.0001$). In contrast, there was no difference in the rPTV distribution for genes that are tolerant to loss-of-function (pLI values <0.90; Figure 3A).

Similarly, in a subgroup of 69 "high pLI" genes that have been identified in The Genotype-Tissue Expression Project Portal as specifically expressed in the brain, cases are more likely than controls to harbor rPTVs in genes that are affected at least twice; (OR 2.80; 95% CI 1.07–7.32; $p = 0.036$). In contrast, there was no difference in the distribution of rPTVs identified in the "brain-specific" genes with pLI values <0.90 (Figure 3B). In addition, 19 (58%) of 33 brain-specific "high pLI" genes affected in cases (*RET*, *NRXN2*, *GRIA4*, *PPFIA2*, *ANKS1B*, *KSR2*, *PCDH9*, *NOVA1*, *TRIM9*, *RASGRP1*, *RAP1GAP2*, *GNAL*, *UNC13A*, *PTPRT*, *COL11A2*, *KIAA1244*, *LIMK1*, *GPRASP1* and *TENM1*) did not harbor any rPTVs in 1260 Czech and Slovak matched males.

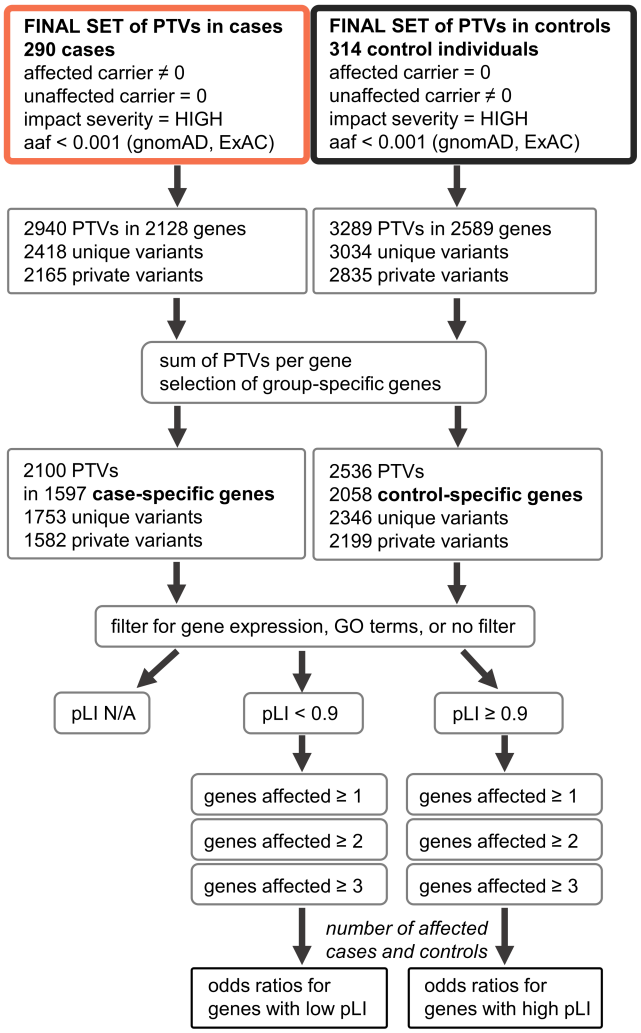
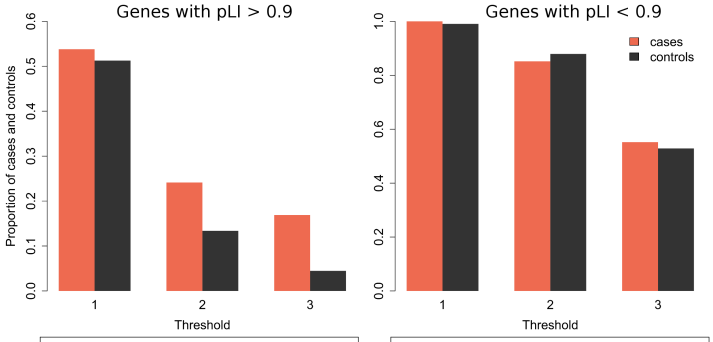


FIGURE 2 Work flow diagram and summary of results. pLI, probability of loss-of-function intolerance; PTVs, protein-truncating variants.

We also compared and found differences in the occurrence of rPTVs in 61 "synaptic" rPTV intolerant genes that have been defined by the SynGO Consortium[27] (Figure 3C). The rPTVs in these synaptic genes were in cases enriched for those that are specifically expressed in brain and pituitary glands (Benjamini–Hochberg corrected *p*-values 1.4×10^{-5} and 0.02 at the specificity index (pSI) threshold <0.01, respectively). In contrast, expression of "synaptic" genes identified in

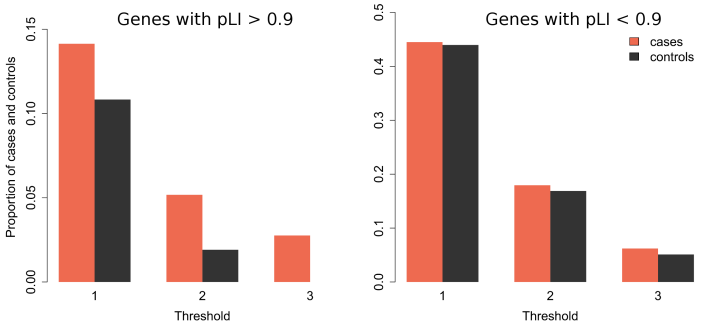
FIGURE 1 Distribution of protein truncating variants identified in 290 impulsively violent individuals with an ICD 10 Diagnosis of Antisocial Personality Disorder and 314 control subject. (A) Distribution of rare protein-truncating variants (rPTVs) into individual impact categories; (B) Distribution of rPTVs per individual in cases; (range 3–21, average 10, median 10) and controls (range 1 to 22, average 10, median 10). (C) Distribution of rPTVs per gene. In cases, rPTVs impacted 2128 genes with 249 genes impacted with 2–5 different rPTVs. In controls, rPTVs impacted 2589 genes with 359 genes impacted with 2–37 different rPTVs. Functionally relevant genes and genes with recurrently observed rPTVs are indicated. (D) Distribution of individuals per rPTV; 253 rPTVs were found in more than one individual (2–15 individuals); 199 rPTVs were found in more than one control (2–5 individuals). Genes with the most frequently observed rPTV and functionally relevant genes with recurrently observed rPTV are indicated.

(A)



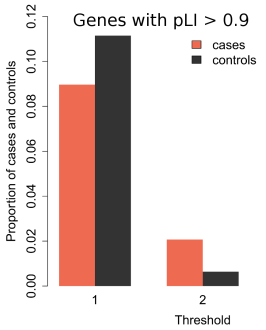
	Genes with pLI > 0.9			Genes with pLI < 0.9		
Cases	156	70	49	290	247	160
Controls	161	42	14	311	276	166
OR	1.11	2.06	4.36		0.79	1.10
(95% CI)	(0.80–1.52)	(1.35–3.14)	(2.34–8.08)		(0.49–1.26)	(0.80–1.51)
p-value	0.54	**0.0008**	**<0.0001**		0.33	0.57
Genes:						
Cases	186	26	11	1318	242	78
Controls	209	20	4	1721	325	73
PTVs:						
Cases	246	86	56	1734	658	330
Controls	235	46	14	2140	744	240

(B)



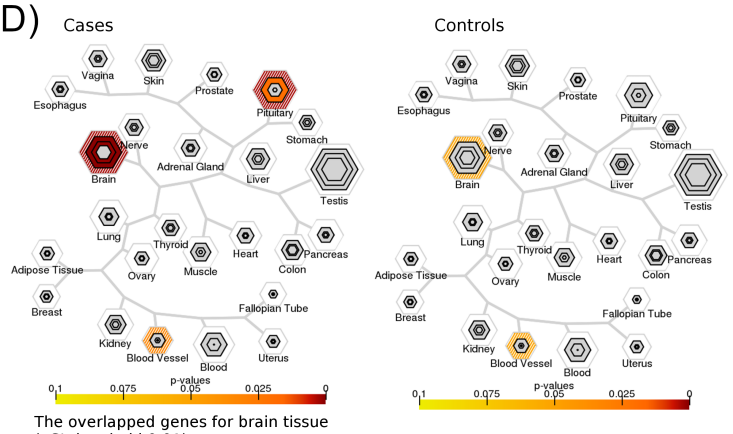
	Genes with pLI > 0.9			Genes with pLI < 0.9		
Cases	41	15	8	129	52	18
Controls	34	6	0	138	53	16
OR	1.36	2.80	18.28	1.02	1.08	1.23
(95% CI)	(0.83–2.20)	(1.07–7.32)	(1.05–318)	(0.74–1.41)	(0.71–1.64)	(0.62–2.47)
p-value	0.22	**0.036**	**0.046**	0.90	0.73	0.55
Genes:						
Cases	33	5	1	136	24	5
Controls	36	3	0	157	27	5
PTVs:						
Cases	44	16	8	168	56	18
Controls	39	6	0	191	61	17

(C)



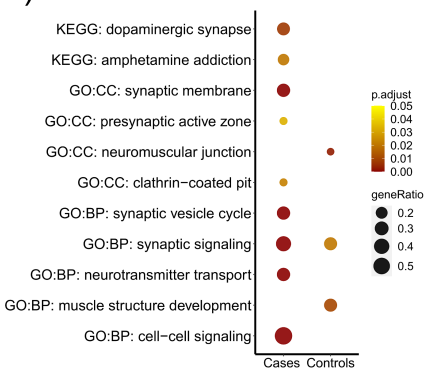
	Genes with pLI > 0.9	
Cases	26	6
Controls	35	2
OR	0.79	3.30
(95% CI)	(0.46–1.34)	(0.66–16.46)
p-value	0.38	0.15
Genes:		
Cases	26	3
Controls	35	1
PTVs:		
Cases	29	6
Controls	36	2

(D)



The overlapped genes for brain tissue (pSI threshold 0.01):
ANKS1B, PTPRT, GRIA4, APC2, CACNA1B, UNC13A, PPFIA2, TRIM9, NRXN3, RIMS2

(E)



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controls was not enriched in any tissue (Figure 3D). We also subjected the list of "synaptic" genes affected by rPTVs to parallel functional profiling and found specific enrichment of case-specific "synaptic" genes in neurotransmitter transport (adjusted p-value $= 1.6 \times 10^{-4}$; *PPFIA2*, *TRIM9*, *UNC13A*, *NRXN3*, *SLC29A1*, *RIMS2*, *CACNA1B*), dopaminergic synapses (adjusted p-value $= 0.007$; *GRIA4*, *CACNA1C*, *PPP1CC*, *CACNA1B*) and synaptic vesicle cycle (adjusted p-value $= 1.8 \times 10^{-5}$; *PICALM*, *PPFIA2*, *TRIM9*, *NRXN3*, *UNC13A*, *AP2M1*, *RIMS2*, *CACNA1B*; Figure 3E). Control-specific "synaptic" genes were specifically enriched for muscle structure development (adjusted p-value $= 0.01$; *MTOR*, *BDNF*, *CACNA1H*, *MYH10*, *LAMA5*, *FXR1*, *CDK5*, *TSC1*, *DMD*) and neuromuscular junction (adjusted p-value $= 2.8 \times 10–3$; *DLG2*, *MYH10*, *LAMA5*, *CDK5*), reflecting the inclusion of patients with genetic cardiomyopathies in the control group (Figure 3E). In addition, 13 (50%) of 26 "synaptic" genes identified in cases (*PICALM*, *GRIA4*, *CACNA1C*, *PPFIA2*, *ANKS1B*, *TRIM9*, *USP8*, *ERBB2*, *UNC13A*, *ACTR2*, *PTPRT*, *SLC29A1* and *TENM1*) did not harbor any rPTV in 1260 Czech and Slovak matched males.

3.3 | Clinical and biological interpretation identified 114 clinically relevant rPTVs in 102 genes in 110 cases

To assess the clinical relevance of individual genes impacted by rPTVs in cases, we considered their clinical associations, biological function, patterns of gene expression obtained from the Genotype-Tissue Expression Project Portal (GTEx),[28] and genic intolerance to deletions and duplications[29] and loss of function mutations.[21] This analysis identified 114 rPTVs in 102 genes in 110 cases. Ninety-one cases had 1, 17 cases had 2 and 2 cases had 3 clinically relevant rPTVs (Tables 1–5).

3.4 | Thirty-seven cases harbored rPTVs in 23 genes that are associated with neurological phenotypes in the OMIM database

To identify cases potentially affected by monogenic disease, we downloaded the OMIM database and restricted the original set of 2128 genes impacted by rPTVs to genes reported with autosomal dominant and X-linked inheritance patterns or de novo mutations and a phenotypic description. This analysis identified 165 cases that had 200 rPTVs in 175 genes (Table S1). Functional annotation identified over-representation of genes impacted by these rPTVs in gene sets related to ion channel complexes, cell junction and adhesion, neuron projection and maturation, synaptic transmission, regulation of membrane potential, synapses, calcium signaling, and NCAM signaling. Twenty-three genes were associated with neurodegeneration in the UniProt Keywords database (Figure S1).

From these 165 cases, further evaluation identified 37 (13%) cases with 29 clinically significant rPTVs in 23 genes that are associated with neurological phenotypes (Table 1)[30–65] compared with 16 (5%) individuals identified in controls (OR 2.72; 95% CI 1.48–5.01; $p = 0.001$). One case (7587) had two clinically significant rPTVs. Four (544G, 499G, 1090G and 1217G) had a combination of one clinically significant rPTV with one of the 20 potentially clinically significant rPTVs that were found in additional 19 cases (Table 2). There were 7 cases with three different mutations in *KIDINS220*, four cases with three different mutations in *ABCA7*, four cases with premature stop codons or frame-shift mutations in *RTN4R* and three cases with premature stop codons in *TGM6*. Two cases had different mutations in *CACNA1B*. The other 18 mutations affected *RELN*, *GRIA4*, *GNAL*, *RTN2*, *SOX11*, *SAMD9L*, *SHROOM4*, *PHIP*, *DPP6*, *NOTCH3*, *C9orf72*, *PUF60*, *NOL3*, *CHRNA4*, *FAT2*, AFG3L2, *SEMA3E* and *CDON* and were found in 17 cases and each occurred once in the population of cases.

3.5 | Fifty-two cases harbored rPTVs in genes intolerant to loss of function mutations

Using the criterion of a pLI value ≥0.90 to define the intolerance of a gene to truncating mutations, we identified 169 "high pLI" rPTVs in 162 genes in 143 cases, with 10 cases having 3 and 44 cases having 2 of these rPTVs. Two different mutations were found in seven genes (*ACTR2*, *AKAP13*, *C16orf70*, *PCDH9*, *PSIP1*, *RIMS2* and *USP47*); 155 genes were affected once. Thirteen rPTVs were observed more

FIGURE 3 Distributions of rare protein truncating variants in genes intolerant to loss-of-function mutations. Histograms indicate the proportions and occurrence of rare protein truncating variants (rPTVs) identified exclusively in cases (red bars) and controls (black bars). Genes considered to be intolerant to loss of function mutations have the probability of loss-of-function intolerance (pLI) value ≥0.90. Thresholds indicate the minimum number of rPTV variants in a case or a control gene. (A) A higher proportion of cases than controls harbor rPTVs in "high pLI" genes. OR, odds ratio; 95% CI, 95% confidence interval; p-value, Fisher's exact test. There is no difference for genes with pLI values <0.90. (B) A higher proportion of cases than controls harbor rPTVs in "high pLI" genes specifically expressed in brain. There is no difference for genes with pLI values <0.90. (C) Cases and controls have similar distribution in "high pLi" "synaptic" genes that have been defined by the SynGO Consortium. (D) Tissue Specific Expression Analysis (TSEA) tool analysis showing that rPTVs in these synaptic genes were enriched in cases for those that are specifically expressed in brain and pituitary glands. Benjamini–Hochberg corrected p-values at different levels of the specificity index thresholds (pSI) are depicted by color corresponding to the look-up tables. In contrast, expression of "synaptic" genes identified in controls was not enriched in any tissue. (E) Parallel functional profiling with g:Profiler found enrichment of case-specific "synaptic" genes involved in neurotransmitter transport, dopaminergic synapses and synaptic vesicle cycle. Control-specific "synaptic" genes were enriched for genes involved in muscle structure development and formation of neuromuscular junction, pointing to the inclusion of patients with genetic cardiomyopathies in the control group. The color corresponds to the adjusted p-values and the size of the dot corresponds to the ratio of the genes associated with the term.

TABLE 1 Rare clinically significant PTVs with reported autosomal dominant and X-linked inheritance patterns or de novo mutations and a phenotypic description in OMIM identified in 37 males with an ICD 10 Diagnosis of Antisocial Personality Disorder and their frequencies in controls.

NAF	ID	Position	aa	aa_length	Impact	Gene	MIM number	Phenotypes	aaf_gnomad
4	7560 1219G 2507G 3488G	chr2:8887273–8887274; C\T	-	1771	SDV	*KIDINS220*	615,759	Spastic paraplegia, intellectual disability, nystagmus and obesity, AD[30] KIDINS220 plays a role in regulation of neuronal activity, synaptic transmission and plasticity, neuronal activity and control of neuronal excitability. Various neuropsychiatric pathologies have been associated with mutations of the KIDINS220 or alterations of KIDINS220 protein levels[31]	8.13E-06
2	7567 476G	chr2:8938430–8938435; CTAGA\C	-	1031	SAV	*KIDINS220*	615,759		0.000206
1	544G	chr2:8867043–8867048; GCTAT\G	−1050	1057	fs	*KIDINS220*	615,759		0.000154
2	526G 2703G	chr19:1063827–1063829; CG\C	−1835	2008	fs	*ABCA7*	605,414	Alzheimer disease 9, susceptibility to, AD[32–34]	−1
1	2291G	chr19:1046867–1046868; C\CT	L426L?	2008	fs	*ABCA7*	605,414		−1
1	1058G	chr19:1054254–1054255; G\A	W1076*	2008	Stop	*ABCA7*	605,414		0.000611
3	7456 7455 2298G	chr22:20231165–20231166; G\A	R14*	558	Stop	*RTN4R*	605,566	Schizophrenia, susceptibility to, AD *RTNR4* encodes a receptor for reticulon 4 (alias NOGO Receptor), essential protein for the regulation of axonal regeneration and plasticity of the central nervous system.[35] *RTN4R* is one of the major candidate genes of the 22q11.2 Deletion Syndrome associated with impaired social cognition and neuropsychiatric symptoms[36,37]	0.000242
1	499G	chr22:20231147–20231155; CAGGGCTT\C	−17	558	fs	*RTN4R*	605,566		8E-05
3	545G 1213G 2698G	chr20:2380368–2380369; G\T	G279*	625	Stop	*TGM6*	613,900	Spinocerebellar ataxia, 35 AD[38] *TGM6* encodes Transglutaminase 6 that catalyzes the cross-linking of proteins and the conjugation of polyamines to proteins	2.04E-05
1	1090G	chr9:140995622–140995623; A\T	K128*	162	Stop	*CACNA1B*	601,012	Dystonia 23, AD[39]	−1
1	1062G	chr9:140952703–140952704; T\C		1533	SDV	*CACNA1B*	601,012	*CACNA1B* encodes the CaV2.2 channels regulating transmitter release at inhibitory and excitatory synapses	−1
1	2296G	chr7:103155713–103155716; TAC\T	−2679	3458	fs	*RELN*	600,514	Epilepsy, familial temporal lobe, 7, AD *RELN* encodes a neuronal glycoprotein with a potential role in the development of inhibitory synapses[40] and in the pathogenesis of neurological diseases such as schizophrenia, autism and Alzheimer's disease[41]	−1
1	2662G	chr11:105804529–105804541; AGGGAGTAGCTC\A	−710	884	fs	*GRIA4*	138,246	Neurodevelopmental disorder with or without seizures and gait abnormalities, AD[42] *GRIA4* encodes an AMPA receptor subuni	−1

TABLE 1 (Continued)

NAF	ID	Position	aa	aa_length	Impact	Gene	MIM number	Phenotypes	aaf_gnomad
1	1101G	chr18:11864564–11864566; AT\A	−133	178	fs	*GNAL*	139,312	Dystonia 25, AD[43] *GNAL* encodes G Protein Subunit Alpha L that plays a role in dopamine signaling	−1
1	1217G	chr19:45992621–45992623; TC\T	−134	271	fs	*RTN2*	603,183	Spastic paraplegia 12, AD[44] *RTN2* encodes the endoplasmic reticulum shaping protein reticulon 2	1.71E-05
1	1060G	chr6:79692715–79692716; C\A	E886*	1821	Stop	*PHIP*	612,870	Developmental delay, intellectual disability, aggressive behavior, obesity and dysmorphic features, AD[45] Behavioral problems include ADHD, problems with impulse control, and aggressive behavior.[46] *PHIP* encodes pleckstrin homology domain-interacting protein	−1
1	3475G	chr7:154172025–154172026; G\T	E121*	353	Stop	*DPP6*	616,311	Mental retardation 33, AD DPP6 is a single pass type II transmembrane protein that plays a role in neuronal excitability *DPP* mutations are associated with AD neurodegenerative dementia,[47] neurodevelopmental disorders,[48] autism[49] and Gilles de la Tourette syndrome[50]	−1
1	1605G	chr19:15276273–15276274; G\T	S1907*	2321	Stop	*NOTCH3*	600,276	Cerebral arteriopathy with subcortical infarcts and Leukoencephalopathy 1, AD (CADASIL1); Lateral meningocele syndrome, AD CADASIL1 is characterized by mid-adult onset of recurrent ischemic stroke, cognitive decline progressing to dementia, and mood disturbances[51]	−1
1	3472G	chr8:144906570–144906571; T\C	-	227	SAV	*PUF60*	604,819	Verheij syndrome, AD PUF60 is a component of multimeric complexes regulating RNA splicing and transcription, mutations of which cause a neurodevelopmental syndrome with intellectual disability[52] and CHARGE syndrome[53]	2.08E-05
1	7587	chr18:12360044–12360045; G\C	Y211*	797	Stop	*AFG3L2*	604,581	Spinocerebellar ataxia 28 (SCA28), AD SCA28 is known to be accompanied in some cases with intellectual disability, cognitive difficulties, and/or behavior problems[54]	4.06E-06

(Continues)

TABLE 1 (Continued)

NAF	ID	Position	aa	aa_length	Impact	Gene	MIM number	Phenotypes	aaf_gnomad
1	7587	chr7:83021940–83021941; G\A	R473*	715	Stop	*SEMA3E*	608,166	CHARGE syndrome, AD *SEMA3E* encodes a secreted class 3 semaphorin that modulates axonal growth and synaptic connectivity, and mutations of which cause hypogonadotropic hypogonadism combined with anosmia (Kallmann syndrome)[55]	−1
1	7488	chr2:5833224–5833225; C\CA	K125K?	441	fs	*SOX11*	600,898	Mental retardation 27, AD Coffin-Siris syndrome, AD, characterized by intellectual disability and developmental or cognitive delay[56]	−1
1	7704	chr20:61987293–61987312; CTGTAGAGGACTCACTTGT\C	-	None	SDV	*CHRNA4*	118,504	Nicotine addiction, susceptibility to Epilepsy, nocturnal frontal lobe 1, AD, in some individuals is accompanied by reduced intellect, cognitive deficits, or psychiatric comorbidity.[57] *CHRNA4*, encodes the neuronal acetylcholine receptor subunit alpha-4	0.000274
1	1594G	chr9:27556577–27556578; C\A	E358*	481	Stop	*C9orf72*	614,260	Frontotemporal dementia and/or amyotrophic lateral sclerosis 1, AD[58]	4.07E-06
1	7411	chr16:67208847–67208848; G\A	-	130	SDV	*NOL3*	605,235	Myoclonus, familial cortical, AD[59,60]	0.000645
1	1602G	chr5:150930433–150930434; T\C	-	4349	SAV	*FAT2*	604,269	Spinocerebellar ataxia 45, AD[61]	−1
1	1056G	chr7:92762077–92762078; C\CT	K1069K?	1584	fs	*SAMD9L*	611,170	Ataxia-pancytopenia (ATXPC) syndrome, AD, which is associated with neurological symptoms including ADHD[62]	−1
1	7578	chr11:125873952–125873953; T\C	M1V	641	start_lost	*CDON*	608,707	Holoprosencephaly 11, AD, Isolated cases[63] *CDON* encodes a cell adhesion protein that promotes neuronal differentiation[64]	4.07E-06
1	7462	chrX:50556962–50556963; G\GC	A19G?	1493	fs	*SHROOM4*	300,579	Stocco dos Santos X-linked mental retardation syndrome, characterized by cognitive disabilities, including ADHD[65]	−1

Abbreviations: aa, affected amino acid residue; aa_length, affected protein length; aaf_gnomad, minor allele frequencies in gnomAD database; AD, autosomal dominant; ADHD, attention deficit hyperactivity disorder; fs, frame shift; ID, id number; NAF, number of affected individuals per variant; position according to hg19 coordinates; SAV, splice acceptor variant; SDV, splice donor variant; start_lost, mutation of initiation codon; Stop/*, premature stop codon; ?, unknown sequence.

TABLE 2 Rare PTVs of potential clinical significance with reported autosomal dominant and X-linked inheritance patterns or de novo mutations and a phenotypic description identified in 19 males with an ICD 10 Diagnosis of Antisocial Personality Disorder and their frequencies in controls.

ID	Position	aa	aa_length	Impact	Gene	MIM number	Phenotypes	aaf_gnomad
1217G	chr11:78482175–78482177; GC\G	−104	149	fs	*TENM4*	610,084	Essential tremor, hereditary, 5, AD	−1
3476G	chr6:100868720–100868722; GC\G	−371	766	fs	*SIM1*	603,128	Obesity, severe, AR, AD, Multifactorial	−1
7535	chr3:63985123–63985124; A\C	-	114	SAV	*ATXN7*	607,640	Spinocerebellar ataxia 7, AD	−1
7583	chr3:179137253–179137254; G\A	R46*	340	Stop	*GNB4*	610,863	Charcot–Marie–Tooth disease, dominant intermediate F, AD	4.06E-06
7671	chr3:87325468–87325469; A\G	-	169	SDV	*POU1F1*	173,110	Pituitary hormone deficiency, combined, 1, AR, AD	−1
1090G	chr20:57227126–57227127; A\G	-	119	SAV	*STX16*	603,666	Pseudohypoparathyroidism, type IB, AD	−1
7020	chr1:40778124–40778125; T\TA	-	224	SDV	*COL9A2*	120,260	Epiphyseal dysplasia, multiple, 2, AD; Stickler syndrome, type V, AR	4.08E-06
7021	chr15:50905911–50905912; G\A	R125*	535	Stop	*TRPM7*	605,692	Amyotrophic lateral sclerosis-parkinsonism/dementia complex, susceptibility to, AD	−1
7538	chr2:25384137–25384138; C\A	E206*	245	Stop	*POMC*	176,830	Obesity, adrenal insufficiency and red hair due to POMC deficiency, AR; Obesity, early-onset, susceptibility to, AR, AD, Multifactorial	0.000415
2325G	chr20:5294956–5294958; TG\T	−20	384	fs	*PROKR2*	607,123	Hypogonadotropic hypogonadism 3 with or without anosmia, AD	9.34E-05
544G	chr17:62474100–62474101; C\A	*152 L	151	stop_lost	*POLG2*	604,983	Progressive external ophthalmoplegia with mitochondrial DNA deletions, AD	−1
7487	chr2:238243532–238243533; C\G	-	2570	SAV	*COL6A3*	120,250	Bethlem myopathy 1, AR, AD; Dystonia 27, AR; Ullrich congenital muscular dystrophy 1, AR, AD	1.63E-05
1233G	chr6:70942284–70942285; C\T	-	678	SDV	*COL9A1*	120,210	Epiphyseal dysplasia, multiple, 6, AD; Stickler syndrome, type IV	−1
2505G	chr12:57892219–57892230; AGTGGAACACC\A chr12:57892232–57892234; CT\C	−134 −139	231	fs	*MARS*	156,560	Charcot–Marie–Tooth disease, axonal, type 2 U, AD	4.06E-06 4.06E-06
7595	chr16:776366–776367; T\C	M1V	438	start_lost	*CCDC78*	614,666	Centronuclear myopathy 4, AD	3.11E-05
1068G	chr6:152539538–152539539; C\CT	-	1654	SAV	*SYNE1*	608,441	Emery-Dreifuss muscular dystrophy 4, AD, Spinocerebellar ataxia, 8, AR	9.37E-05
1063G	chr2:178936545–178936546; C\A	E207*	933	Stop	*PDE11A*	604,961	Pigmented nodular adrenocortical disease, primary, 2, AD	−1

(Continues)

TABLE 2 (Continued)

ID	Position	aa	aa_length	Impact	Gene	MIM number	Phenotypes	aaf_gnomad
499G	chrX:120181949–120181950; C\T	Q138*	558	Stop	*GLUD2*	300,144	Parkinson disease, age of onset, modifier	0.000263128
7540	chr17:15134149–15134151; CT/C	−129	161	fs	*PMP22*	601,097	Charcot–Marie–Tooth disease, type 1A and 1E, AD; Dejerine-Sottas disease, AR, AD; Neuropathy, inflammatory demyelinating, AD; Neuropathy, recurrent, with pressure palsies, AD; Roussy-Levy syndrome, AD	8.47E-06
7021	chr2:167133698–167133699; T/TA	G878G?	1977	fs	*SCN9A*	603,415	Dravet syndrome, modifier, AD; Epilepsy, generalized, with febrile seizures plus, type 7, AD; Erythermalgia, primary, AD; Febrile seizures, familial, 3B, AD; HSAN2D, AR; Insensitivity to pain, congenital, AR; Paroxysmal extreme pain disorder, AD; Small fiber neuropathy, AD	−1

Abbreviations: aa, affected amino acid residue; aa_length, affected protein length; aaf_gnomad, minor allele frequencies in gnomAD database; AD, autosomal dominant; fs, frame shift; ID, id number—position according to hg19 coordinates; NAF, number of affected individuals per variant; SAV, splice acceptor variant; SDV, splice donor variant; start_lost, mutation of initiation codon; Stop/*, premature stop codon; ?, unknown sequence.

than once: *BAHD1* 15 times, *GTPBP1*, *PKN1* and *SREBF2* 5 times; *LRRC16A*, *SPATS2L* and *ZNF195* 3 times; and *DDX21*, *GTPBP4*, *KSR2*, *PSIP1*, *PTPRU* and *TKTL1* twice. Functional annotation identified over-representation of genes impacted by these rPTVs in several categories related to nervous system development. In the category of cellular components, these included gene sets related to nucleoplasm, coated vesicle, neuron part, retromer complex and presynaptic active zone. In the category of biological processes and pathways, these were gene sets related to RNA processing, vesicle-mediated transport, guanyl-nucleotide exchange factor activity, actin filament formation, synapse organization, neurotransmitter transport, regulation of axonogenesis and EPH-Ephrin signaling (Figure 2).

Individual expert evaluation identified 10 cases with 10 clinically significant rPTVs in 10 "high pLI" genes (*KATNAL1*, *PTPRT*, *BAIAP2*, *OTUD7A*, *PLXND1*, *NRXN2*, *NRXN3*, *UNC13A*, *CIZ1* and *PTPN4*; Table 3).[66–78]

There were an additional 46 cases with rare, potentially clinically relevant rPTVs in 39 "high pLI" genes. Forty-two cases had one and 4 cases that had two of these rPTVs (Table 4).[79–94]

3.6 | Thirteen cases harbored rPTVs in 10 genes reportedly intolerant to loss of function mutations in the nonpsychiatric version of ExAC database

The ExAC database reports variants that were identified in adult control subjects from population genetic studies and in patients with various adult-onset diseases.[16] The nonpsychiatric version of ExAC does not report variants identified in psychiatric cohorts.[20] To identify genes that may also contribute to impulsive violence we selected and considered the clinical relevance of rPTVs that are mutated more frequently in psychiatric patients, for example, variants in genes that had different loss-of-function intolerance (pLI) values in the nonpsychiatric and the psychiatric versions of the database. We therefore restricted the search to genes that had neither OMIM link nor high pLI as defined above, but fulfilled the criterion of pLI nonpsych – pLI ExAC >0.4. Potentially clinically significant rPTVs were identified in 13 cases with each one having one of these rPTVs (Table 5).[95–110]

3.7 | Integrated analysis of rPTVs and CNVs and the course of imprisonment

As a final analysis we integrated rPTVs identified in this study with rare CNVs identified in this cohort earlier[13] and correlated their occurrence with the participant's course of imprisonment (Figure 4). Altogether, clinically significant rPTV and CNV variants were identified in 63 (22%) cases. In an additional 129 (44%) cases we identified likely clinically relevant variants that impacted highly phenotypically relevant genes whose contributions to psychiatric illness require further investigation. There was only one gene (*DPP6*) that was affected by both rPTVs and CNVs. Clinically relevant rPTVs or CNVs were not identified in 98 (34%) of cases.

TABLE 3 Rare PTVs of clinical significance in genes that are intolerant to loss of function mutations identified in 10 males with an ICD 10 Diagnosis of Antisocial Personality Disorder and their frequencies in controls.

NAF	ID	Position	Gene	aa	aa_length	impact	Phenotypic correlation	aaf_gnomad
1	7677	chr13:30784475–30784477; AC\A	*KATNAL1*	−417	490	fs	*KATNAL1* is a candidate gene for AD intellectual disability associated with the 13q12.2q13.1 microdeletion syndrome.[66,67] Behavioral, neurological and ciliary anomalies were also observed in mice with missense mutations in *Katnal1*[68]	4.22E-06
1	379G	chr20:40739001–40739002; C\CG	*PTPRT*	P1065P?	1431	fs	*PTPRT* encodes Protein Tyrosine Phosphatase Receptor Type T, a regulator of synaptic formation.[69] *PTPRT* mutations have been repeatedly found in small families with intellectually disabled siblings[70]	−1
1	2503G	chr17:79090045–79090047; CA\C	*BAIAP2*	−534	552	fs	Mutations in *BAIAP2* are implicated in autism spectrum disorders, schizophrenia and ADHD; impaired social interaction and communication in −/− and +/− mouse[71]	0.000102
1	7592	chr15:31776309–31776310; G\T	*OTUD7A*	Y656*	926	Stop	*OTUD7A* is a major regulatory gene for 15q13.3 microdeletion syndrome[72,73]	−1
1	7591	chr3:129276039–129276040; G\T	*PLXND1*	Y167*	229	Stop	De novo mutations in *PLXND1* cause Möbius syndrome[74]	−1
1	7019	chr11:64374859–64374860; G\T	*NRXN2*	C1579*	1642	Stop	Genomic alterations in *NRXN* genes have been identified in autism spectrum disorders, schizophrenia, intellectual disability and addiction[75]	−1
1	2291G	chr14:80320559–80320560; T\TGTAA	*NRXN3*	-	None	SDV		−1
1	1103G	chr19:17734349–17734350; C\G	*UNC13A*	-	1703	SDV	A de novo missense variant of *UNC13A* results in deficits in social and communicative domains, repetitive behaviors, a notable short attention span, a high level of distractibility, and hyperactive and impulsive behaviors in affected individual[76]	−1
1	1610G	chr9:130953086–130953111; AGCTGCTGCTGCTGTTGCTGGAGCT\A	*CIZ1*	-	None	SDV	Mutation in *CIZ1* is associated with AD adult-onset primary cervical dystonia[77]	0.000519
1	7539	chr2:120690030–120690031; A\G	*PTPN4*	M1V	559	start_lost	Haplo-insufficiency of *PTPN4* found in Rett syndrome-like phenotype[78]	−1

Abbreviations: aa, affected amino acid residue; aa_length, affected protein length; aaf_gnomad, minor allele frequencies in gnomAD database; AD, autosomal dominant; fs, frame shift; ADHD, attention deficit hyperactivity disorder; ID, id number—position according to hg19 coordinates; NAF, number of affected individuals per variant; SAV, splice acceptor variant; SDV, splice donor variant; start_lost, mutation of initiation codon; Stop/*, premature stop codon; ?, unknown sequence.

TABLE 4 Rare PTVs of potential clinical significance in genes that are intolerant to loss of function mutations identified in 46 males with an ICD 10 Diagnosis of Antisocial Personality Disorder and their frequencies in controls.

NAF	ID	Position	Gene	aa	aa_length	Impact	Phenotypic correlation	aaf_gnomad
5	1103G 7412 7526 3486G 3547G	chr22:42300674–42300675; C\G	*SREBF2*	S199*	255	Stop	Polymorphisms in *SREBF2* are associated with schizophrenia and may play a role in CNS myelination processes.[79] *SREBF2* encodes a transcription factor that controls fatty acid and cholesterol biosynthesis	0.000777
3	7552 3496G 1064G	chr2:201248587–201248588; A\G	*SPATS2L*	-	12	SAV	*SPATS2L* is associated with schizophrenia and hippocampal volume	−1
2	7567 550G	chr12:118112193–118112194; C\T	*KSR2*	M1I	435	start_lost	KSR2 mutations are associated with obesity, insulin resistance and impaired cellular fuel oxidation	−1
2	481G 1219G	chr1:29650141–29650142; G\A	*PTPRU*	-	1433	SAV	*PTPRU* is associated with general cognitive ability	−1
1	2332G	chr15:86283501–86283503; AG\A	*AKAP13*	−2536	2813	fs	CNVs encompassing *AKAP13* were implicated in autism,[80] *AKAP13* is reported to be affected in some patients with cognitive impairment in the DECIPHER database. *Akap13* haploinsufficiency also led to sex-dependent, compulsive-like behavioral changes in a murine model[81]	−1
1	7623	chr15:86077078–86077079; G\A	*AKAP13*	W149*	1744	Stop		4.11E-06
1	7637	chr2:236715954–236715955; C\T	*AGAP1*	R183*	696	Stop	De novo mutations of *AGAP1* were found in cerebral palsy[82]	−1
1	546G	chr12:99139621–99139622; G\A	*ANKS1B*	R458*	460	Stop	*ANKS1B* is involved in synaptic processes.[83] CNVs affecting ANKS1B have been reported in ASD and ID including a de novo deletion in a male with ASD and delayed early language development but average language abilities and IQ[84]	1.24E-05
1	3477G	chr3:183896011–183896012; G\A	*AP2M1*	-	159	SDV	*AP2M1* has been defined as a candidate genes for autism identified in Finnish cohort	7.56E-06
1	7677	chr8:68255572–68255573; T\C	*ARFGEF1*	-	117	SAV	*ARFGEF1* encodes BIG1 which is critical in the survival of deep layer neurons in developing embryonic brain and in the generation of neuronal polarity[85]	−1
1	871G	chr12:125435063–125435066; CCG\C	*DHX37*	−1005	1157	fs	*Dhx37* is required for the biogenesis of glycine receptors and thereby regulates glycinergic synaptic transmission and associated motor behaviors, homozygous missense mutations of DHX37 were found in children with severe microcephaly[86]	−1
1	1226G	chr21:47977658–47977673; TCCTCAGGGTGAGTG\T	*DIP2A*	-	1567	SDV	Recurrent CNVs defined *DIP2A* as a candidate gene for neuropsychiatric disorders[87]	−1

TABLE 4 (Continued)

NAF	ID	Position	Gene	aa	aa_length	Impact	Phenotypic correlation	aaf_gnomad
1	384G	chr3:51297616–51297617; C\T	*DOCK3*	Q739*	2030	Stop	Disruption of *DOCK3* co-segregated in a family with an early onset behavioral/developmental condition, with features of ADHD and intellectual disability. Biallelic DOCK3 mutations cause a neurodevelopmental disorder characterized by unsteady gait, hypotonia and developmental delay	−1
1	7707	chr7:111580246–111580247; G\A	*DOCK4*	R286*	1998	Stop	Exonic deletions of *DOCK4* may act as a risk factor for reading impairment and autism	4.06E-06
1	7526	chr13:99512657–99512658; C\T	*DOCK9*	-	1393	SDV	DOCK9 plays a role in dendrite growth in hippocampal neurons	−1
1	7674	chr3:97467543–97467544; G\C	*EPHA6*	*1131S	1130	stop_lost	Genetic inhibition of the *EphA6* in mice produced behavioral deficits specifically in tests of learning and memory	−1
1	2327G	chrX:101911526–101911528; GA\G	*GPRASP1*	−896	1395	fs	GPRASP1 regulates the cannabinoid 1 receptor CB1R	2.80E-05
1	857G	chr6:138607914–138607915; C\T	*KIAA1244*	R883*	2177	Stop	*KIAA1244* is specifically expressed in brain and associated with suicidal behavior in depression	−1
1	7620	chr7:73497509–73497510; G\T	*LIMK1*	-	677	SDV	De novo deletions of the *LIMK1* are associated with Williams syndrome, a unique neurodevelopmental disorder characterized by severe defects in visuospatial cognition and long-term memory (LTM).[88] *LIMK1*(−/−) mice are selectively defective in a long-lasting synaptic plasticity specifically required for the formation of LTM	0
1	1602G	chr16:14334578–14334589; TTTCACAATTA\T	*MKL2*	−345	378	fs	MKL2 is a synaptic protein. Loss-of-function variants affecting MKL2 are associated with disrupted speech development[89]; missense *MKL2* mutations were found in patients with schizophrenia and autism spectrum disorder; homozygous *MKL2* mutations caused fatal primary human microcephaly	4.41E-06
1	524G	chr9:88631564–88631565; T\TA	*NAA35*	K561K?	725	fs	De novo mutations of *NAA35* were found in cerebral palsy[82]	−1
1	3485G	chr17:15938256–15938257; T\C	*NCOR1*	-	None	SAV	De novo mutations of *NCOR1* were found in autism spectrum disorders	0.000216
1	1603G	chr14:26939678–26939679; C\T	*NOVA1*	W179*	181	Stop	NOVA1 is primarily expressed in neurons and plays an important role by maintaining brain-specific splicing regulation of transcripts encoding synaptic proteins	4.08E-06

(Continues)

TABLE 4 (Continued)

NAF	ID	Position	Gene	aa	aa_length	Impact	Phenotypic correlation	aaf_gnomad
1	6998	chr13:67477634–67477635; C\T	*PCDH9*	-	1237	SDV	*PCDH9* is autism susceptibility gene in humans and *Pcdh9* is implicated in cognitive functions required for long-term social and nonsocial recognition in mice	4.17E-06
1	7515	chr13:67801707–67801709; AC\A	*PCDH9*	−288	1032	fs		−1
1	7507	chr12:54955389–54955390; C\T	*PDE1B*	Q8*	516	Stop	*PDE1B* is specifically expressed in corticostriatal areas of the brain and regulates prefrontal dopamine 1 (D1) receptor signaling that has been linked to cognitive dysfunction in several psychiatric conditions. *Pde1b* confers depression-like behavioral resistance separate from stress-related effects and an exaggerated locomotor response to dopaminergic stimulants such as methamphetamine and amphetamine in mice	0.000797
1	543G	chr11:17126742–17126743; G\T	*PIK3C2A*	Y1218*	1686	Stop	Rare variants in *PIK3C2A* increase the risk in bipolar disorder and schizophrenia[90]	−1
1	7577	chr12:81763080–81763081; T\C	*PPFIA2*	M1V	264	start_lost	*PPFIA2* is a candidate gene for ID	7.01E-06
1	2664G	chr17:2923884–2923885; C\T	*RAP1GAP2*	R564*	711	Stop	SNPs in *RAP1GAP2* were associated in young Finns with hostility in adolescents and adults[91]	8.21E-06
1	3547G	chr5:130762959–130762962; TAG\T	*RAPGEF6*	−1504	1504	fs	De novo deletions in *RAPGEF6* were found in schizophrenia. Deletion of *Rapgef6* disrupts amygdala function in mice[92]	2.05E-05
1	7546	chr15:38795489–38795491; CG\C	*RASGRP1*	−422	749	fs	*RASGRP1* inhibits dopaminergic signaling in the striatum, and deficits in those inhibitory control mechanisms may promote impulsive actions	−1
1	1214G	chr8:104778487–104778488; C\T	*RIMS2*	Q141*	1110	Stop	*RIMS2* encodes regulating synaptic membrane exocytosis protein 2. SNPs in *RIMS2* may contribute to risk for developing heroin addiction	−1
1	543G	chr8:104940117–104940118; G\C	*RIMS2*	-	1110	SDV		4.19E-06
1	7623	chr4:71668700–71668701; G\GT	*RUFY3*	-	567	SDV	Rufy3 is specifically expressed in brain and regulates neuronal polarity and axon growth in mice	−1
1	7021	chr1:151666072–151666077; ATTAG\A	*SNX27*	−435	435	fs	*SNX27* is implicated in adult neurodegenerative diseases and homozygous loss-of-function mutation manifests by infantile myoclonic epilepsy and neurodegeneration. Haploinsufficiency of *SNX27* is associated with defects in synaptic function, learning and memory and a reduction in the ionotropic glutamate receptors in mice[93]	2.03E-05

TABLE 4 (Continued)

NAF	ID	Position	Gene	aa	aa_length	Impact	Phenotypic correlation	aaf_gnomad
1	478G	chr14:35044981–35044986; TTAAG\T	*SNX6*	−183	290	fs	SNX6 is involved in CNS excitatory neurons, *Snx6* knockout mice exhibit deficits in spatial learning and memory and deletion encompassing *SNX6* was found in an adolescent with intellectual disability	−1
1	1610G	chr4:186559270–186559272; AG\A	*SORBS2*	−289	666	fs	Deletions of *SORBS2* have been linked to intellectual disability in humans. Genetic deletion of *SORBS2* alias nArgBP2 in mice leads to manic/bipolar-like behavior including increased activity, compulsive/repetitive risk-taking and hedonistic behaviors. *nArgBP2 controls* excitatory spine-synapse formation and maintenance of the excitatory/impulse balance	2.03E-05
1	2328G	chr11:16633808–16633809; T\G	*SOX6*	-	None	SAV	SOX6 plays a key role in the development of the central nervous system	−1
1	7463	chr11:126137580–126137583; CAG\C	*SRPR*	−48	610	fs	*SRPR* encodes a subunit of the endoplasmic reticulum signal recognition particle receptor that, in conjunction with the signal recognition particle, is involved in the targeting and translocation of signal sequence tagged secretory and membrane proteins across the endoplasmic reticulum. Only 16 individuals with LOF mutation are reported in GnomAD database	1.22E-05
1	7632	chr2:160074141–160074142; G\T	*TANC1*	-	1755	SDV	TANC proteins influence synaptic spines and excitatory synapse strength	−1
1	1069G	chrX:123525898–123525899; T\TA	*TENM1*	-	2725	SDV	De novo mutations of *TENM1* were found in cerebral palsy[82] and congenital general anosmia	−1
1	2662G	chr14:51446091–51446093; GC\G	*TRIM9*	−775	802	fs	Trim9 is specifically expressed in brain and its deletion alters the morphogenesis of developing and adult-born hippocampal neurons and impairs spatial learning and memory in mice.[94] SNP in *TRIM9* was associated with psychosis	1.62E-05

Abbreviations: aa, affected amino acid residue; aa_length, affected protein length; aaf_gnomad, minor allele frequencies in gnomAD database; AD, autosomal dominant; CNVs, rare protein truncating variants; fs, frame shift; ID, id number—position according to hg19 coordinates; NAF, number of affected individuals per variant; SAV, splice acceptor variant; SDV, splice donor variant; start_lost, mutation of initiation codon; Stop, premature stop codon; ?, unknown sequence.

TABLE 5 Rare PTVs of potential clinical significance in genes that are intolerant to loss of function mutations in the nonpsychiatric version of ExAC identified in 13 males with an ICD 10 Diagnosis of Antisocial Personality Disorder and their frequencies in controls.

NAF	ID	Position	Gene	aa	aa_length	Impact	MIM Number	Phenotypic correlation	aaf_gnomad
1	7339	chr1:202718221-202718222;G\A	*KDM5B*	R465*	1274	Stop	605,393	*KDM5B* encodes a histone H3K4 demethylase. Biallelic mutations in *KDM5B* are associated with recessive developmental disorders; de novo and heterozygous PTVs in *KDM5B* were recurrently identified in patients with autism or intelectual disability which suggested that some of these PTVs may be pathogenic with incomplete penetrance[95–97]	−1
1	1093G	chr1:202729541-202729542;C\T	*KDM5B*	-	1274	SDV	605,393		−1
1	7587	chr1:202731849-202731850;G\A	*KDM5B*	R141*	1274	Stop	605,393		−1
1	2563G	chr1:202733256-202733257;A\AT	*KDM5B*	I243N?	1544	fs	605,393		−1
1	483G	chr4:100234976 – 100234977;C\A	*ADH1B*	-	335	SDV	103,720	*ADH1B* encodes alcohol dehydrogenase 1B. Regulatory and missense variants affecting expression and decreasing enzymatic activity of ADH1B are associated with alcohol dependence[98]	−1
1	7473	chr14:6934692-6934693;G\A	*GPR162*	W20*	304	Stop	#	GPR162 is widely expressed in GABAergic as well as other neurons within the hippocampus[99]	-1
1	2507G	chr10:104850365-104850366;A\G	*NT5C2*	-	532	SDV	600,417	*NT5C2 is* associated with psychiatric and psychomotor disorders[100]	4.1E-06
1	7505	chr16:15138244-15138246;CA\C	*NTAN1*	−126	310	fs	615,367	*NTAN1* is a candidate gene for schizophrenia[101]; learning, memory and socially conditioned behavior is altered *in NTAN1*$^{-/-}$ mice[103]	−1
1	2565	chr12:15654990-15654991;C\T	*PTPRO*	R367*	1188	Stop	600,579	PTPRO promotes the formation of excitatory synapses[102]; SNPs in *PTPRO* were associated with learning and memory[104]	4.07E-06
1	7336	chr10:121677927-121677929;CT\C	*SEC23IP*	−382	789	fs	617,852	Rare coding variants of *SEC23IP* were associated with adult ADHD[105] and recessive mutations were found in individuals with neurodevelopmental disorders	−1
1	3483G	chr3:10858051 – 10858052;G \GCCCGCGCGCCA	*SLC6A11*	P35PARH?	208	fs	607,952	*SLC6A11* encodes GAT-3, a postsynaptic GABA transporter that mediates GABA clearance. Haploinsufficiency of *SLC6A11* has been implicated in intellectual and behavioral problems and epilepsy[106] and alcohol dependance[107]	−1
1	7589	chr11:121323238-121323239;A\AG	*SORL1*	R67R?	2214	fs	602,005	*SORL1* encodes the neuronal apolipoprotein E receptor. Rare loss of function mutations in SORL1 have been associated with early onset Alzheimer disease[108]	4.41E-05
1	7617	chr17:20108916-20108921;CTGAA\C	*SPECC1*	−23	533	fs	608,793	*SPECC1* is a candidate gene for harm avoidance learning in humans[109] and mice[110]	4.06E-06

Abbreviations: aa, affected amino acid residue; aa_length, affected protein length; aaf_gnomad, minor allele frequencies in gnomAD databases.; AD, autosomal dominant; fs, frame shift; ID, id number—position according to hg19 coordinates; NAF, number of affected individuals per variant; SAV, splice acceptor variant; SDV, splice donor variant; start_lost, mutation of initiation codon; Stop/*, premature stop codon; ?, unknown sequence.

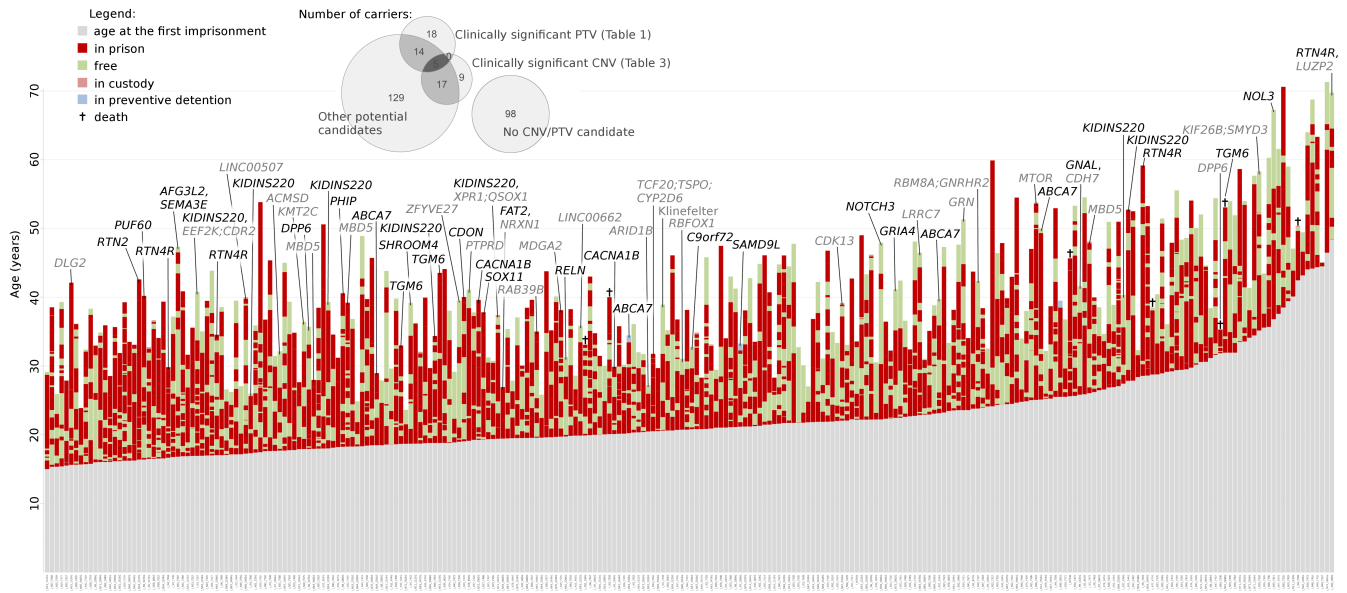

FIGURE 4 Integrated analysis of rare protein truncating variants (rPTVs) and copy-number variations (CNVs) and the course of imprisonment. X-axis reports individual participants who are ranked according to the age of their first imprisonment (gray bar). Individual prison terms and their time course are shown by a red bar. Custody is shown by a pink bar, detention by a blue bar, time on release by a green bar. Clinically significant variants identified in participants are shown in black (rPTVs) or gray (CNVs).

4 | DISCUSSION

Life-course-persistent APD with aggressive behavior is often associated with changes in brain structure and function and overlaps with cognitive impairment and neurodevelopmental, neuropsychiatric and neurodegenerative diseases.[9] An underlying genetic basis for similar neuropsychiatric disorders has been evaluated, with rare inherited and de novo variants in genes involved in brain development, homeostasis and neuronal communication identified as major contributors to individual risk for autism,[111] attention deficit hyperactivity disorder (ADHD),[112] intellectual disability,[113] schizophrenia[114] and bipolar disorder.[115]

PTVs in genes that are intolerant to loss of function mutations are expected to exhibit stronger effects[116] and are well suited to capture the impact of rare to ultra-rPTVs on the cognitive, behavioral, and developmental spectrum.[113] In this investigation, we identified rPTVs in 290 cases classified by strict criteria as having life-course-persistent APD dominated by impulsive violence.[13] Consistent with the results of similar studies in ADHD and cognition-related phenotypes,[112,117,118] we found that cases were significantly more likely to harbor rPTVs in brain-specific and synaptic genes that are intolerant to loss of function mutations and affected by multiple events in the cohort. In 60 (20% of all) cases we identified rPTVs that we classified as clinically relevant. Of these, 37 (13% of all) individuals harbored rPTVs in 23 genes that are associated with a neurological phenotype in the OMIM database, demonstrating either AD and X-linked inheritance patterns or occurrence of de novo mutations. An additional 23 (8% of all) cases harbored clinically significant rPTVs in 20 genes reportedly intolerant to loss of function mutations, either in the general population or in nonpsychiatric cohorts. None of the genes affected by these rPTVs localizes in genome-wide significant loci identified in the largest GWAS meta-analysis of antisocial behavior.[119] Three rPTVs affected 6 of 76 potential risk genes (*HYI*, *VRK1*, *ZNF852*, *XRN2*, *ABHD5* and *MST1R*) that are localized in 27 genome-wide significant loci identified in the largest GWAS meta-analysis study of ADHD.[120] However, none of these three genes and corresponding proteins can be functionally linked to impulsively violent behavior upon current knowledge.

Joint analysis of rPTVs identified in this study with rare CNVs identified in this cohort earlier[13] support the oligogenic model of life-persistent APD with aggressive behavior, in which the disorder can be either directly caused or significantly modulated by rare damaging variants in either one or several genes in an individual. Different genetic and biological pathways implicated in neuron projection and maturation, regulation of neuronal activity, synaptic transmission and plasticity, neuronal activity and control of neuronal excitability are affected, with little individual overlap and recurrence, resulting in a diverse phenotypic population. While GWAS studies have suggested that a multitude of genes are responsible for many continuous traits such as height and weight, in this study, we show the presence of as little as one or just a few rPTVs may significantly contribute to otherwise polygenic genetic liability to life-course-persistent APD.

This study has several limitations, which we have discussed in our previous manuscript.[13] This study is not a standard association study that is testing the statistical significance of differences in allelic frequencies in case and control cohorts. Instead, we performed a case–control study comparing the presence of rare protein-disrupting variants in individuals with APD vs. unaffected controls. We followed the strategy of extreme phenotype sampling.[121] This strategy is based on the selection of individuals at the extreme end of a disease phenotype

distribution and may identify rare genetic variants by sequencing a relatively small sample size. A significant proportion of participants were of Roma ancestry, with little information available on genetic variability of this population, limiting rigorous assessment of variant frequencies. However, we studied variants that are not found in the population and are rarely present in any population. The rarity of the variant is reinforced by the absence in other cases, in the Czech and Slovak matched control samples (including also individuals of Roma ancestry) and among subjects reported in gnomAD datasets (including 25,000 people of East and South Asian ancestry). The nature of the study did not allow for collection, phenotyping and genotyping of parents and siblings of study participants to establish either de novo origin or assess the segregation of identified variants with antisocial violent behavior in families. For most of the variants, we have no functional data, and some may therefore be of low impact or benign. It is important to note that while these mutations may contribute to APD in these individuals, this does not imply that mutations in similar genes in the general population are associated with a higher risk of APD.

Another limitation of this study is the small amount of research that has been performed in APD and specifically in incarcerated populations. This prevented comparison with similar studies. While the protection of prisoners' rights is of high importance, this has led to less research in a group of individuals that are highly in need of further scientific understanding of their disorder. Such research could aid in the treatment of these individuals and hopefully prevent criminal behavior in the future.

Despite these limitations, the important finding of our studies was the identification of 63 (22%) cases who may be affected by clinically unrecognized neuropsychiatric Mendelian disease. This prevalence is similar to other neuropsychiatric conditions. For example, 6%–37% of autistic individuals[122,123] and 40% of individuals with intellectual disability[124] have been diagnosed with an identifiable genetic syndrome. This work thus provides evidence that Mendelian diseases and rare variant burden may represent important causal or dispositional factors for development of APD irrespective of their clinical presentation.

Prisoners have high rates of psychiatric disorders that are frequently underdiagnosed and poorly treated. With the increasing availability of genetic analysis and improvement in clinical interpretation of genomic data, genetic investigations can now be performed in incarcerated individuals with extreme (severe) forms of neuropsychiatric illness. If positive, genomic testing may integrate descriptive psychiatric classification and genetic (biologic) etiology into a specific diagnosis. This information may help identify prognosis and possibly specific interventions.[125] Genetic diagnosis may potentially change some established procedures in penitentiary practice like assessment of criminogenic risks or evaluation of the effectiveness of prison-based rehabilitation programs.

AUTHOR CONTRIBUTIONS

D.M, A.P., M.Z., M.W., B.T., S.W.S., A.J.B and S.K. carried out data analysis, interpreted the data and co-wrote the article. J.V., V.J. and P.B. recruited and clinically assessed cohort of impulsively violent males and collected blood for DNA isolation. H.H. K.H., I.J., H.T. and L.N. were responsible for sample collection, DNA isolation, genotyping and whole exome sequencing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Stanislav Kmoch, upon reasonable request.

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REFERENCES

1. Werner KB, Few LR, Bucholz KK. Epidemiology, comorbidity, and behavioral genetics of antisocial personality disorder and psychopathy. *Psychiatric Annals*. 2015;45(4):195-199. doi:10.3928/00485713-20150401-08
2. Zimmerman M, Chelminski I, Young D. The frequency of personality disorders in psychiatric patients. *Psychiatr Clin North Am*. 2008;31(3):405-420, vi. doi:10.1016/j.psc.2008.03.015
3. Fazel S, Danesh J. Serious mental disorder in 23000 prisoners: a systematic review of 62 surveys. *Lancet*. 2002;359(9306):545-550. doi:10.1016/S0140-6736(02)07740-1
4. Fairchild G, van Goozen SH, Calder AJ, Goodyer IM. Research review: evaluating and reformulating the developmental taxonomic theory of antisocial behaviour. *J Child Psychol Psychiatry*. 2013;54(9):924-940. doi:10.1111/jcpp.12102
5. Moffitt TE. Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychol Rev*. 1993;100(4):674-701.
6. Eley TC, Lichtenstein P, Moffitt TE. A longitudinal behavioral genetic analysis of the etiology of aggressive and nonaggressive antisocial behavior. *Dev psychopathol Spring*. 2003;15(2):383-402.
7. Polderman TJ, Benyamin B, de Leeuw CA, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet*. 2015;47(7):702-709. doi:10.1038/ng.3285
8. Rhee SH, Waldman ID. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. *Psychol Bull*. 2002;128(3):490-529.

9. Raine A. Antisocial personality as a neurodevelopmental disorder. *Annu Rev Clin Psychol*. 2018;14:259-289. doi:10.1146/annurev-clinpsy-050817-084819
10. Odintsova VV, Roetman PJ, Ip HF, et al. Genomics of human aggression: current state of genome-wide studies and an automated systematic review tool. *Psychiatr Genet*. 2019;29(5):170-190. doi:10.1097/YPG.0000000000000239
11. Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science*. 1993;262(5133):578-580.
12. Brunner HG, Nelen MR, van Zandvoort P, et al. X-linked borderline mental retardation with prominent behavioral disturbance: phenotype, genetic localization, and evidence for disturbed monoamine metabolism. *Am J Hum Genet*. 1993;52(6):1032-1039.
13. Vevera J, Zarrei M, Hartmannova H, et al. Rare copy number variation in extremely impulsively violent males. *Genes Brain Behav*. 2018;18:e12536. doi:10.1111/gbb.12536
14. Raznahan A, Won H, Glahn DC, Jacquemont S. Convergence and divergence of rare genetic disorders on brain phenotypes: a review. *JAMA Psychiatry*. 2022;79(8):818-828. doi:10.1001/jamapsychiatry.2022.1450
15. Kmoch S, Majewski J, Ramamurthy V, et al. Mutations in PNPLA6 are linked to photoreceptor degeneration and various forms of childhood blindness. *Nat Commun*. 2015;6:5614. doi:10.1038/ncomms6614
16. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016;536(7616):285-291. doi:10.1038/nature19057
17. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun*. 2017;8(1):1826. doi:10.1038/s41467-017-01261-5
18. Raudvere U, Kolberg L, Kuzmin I, et al. G:profiler: a web server for functional enrichment analysis and conversions of gene lists (2019 update). *Nucleic Acids Res*. 2019;47(W1):W191-W198. doi:10.1093/nar/gkz369
19. Wells A, Kopp N, Xu X, et al. The anatomical distribution of genetic associations. *Nucleic Acids Res*. 2015;43(22):10804-10820. doi:10.1093/nar/gkv1262
20. Kosmicki JA, Samocha KE, Howrigan DP, et al. Refining the role of de novo protein-truncating variants in neurodevelopmental disorders by using population reference samples. *Nat Genet*. 2017;49(4):504-510. doi:10.1038/ng.3789
21. Samocha KE, Robinson EB, Sanders SJ, et al. A framework for the interpretation of de novo mutation in human disease. *Nat Genet*. 2014;46(9):944-950. doi:10.1038/ng.3050
22. Bierne H, Tham TN, Batsche E, et al. Human BAHD1 promotes heterochromatic gene silencing. *Proc Natl Acad Sci U S A*. 2009;106(33):13826-13831. doi:10.1073/pnas.0901259106
23. Zhao D, Zhang XJ, Guan HP, et al. The BAH domain of BAHD1 is a histone H3K27me3 reader. *Protein Cell*. 2016;7(3):222-226. doi:10.1007/s13238-016-0243-z
24. Pourpre R, Naudon L, Meziane H, et al. BAHD1 haploinsufficiency results in anxiety-like phenotypes in male mice. *PLoS One*. 2020;15(5):e0232789. doi:10.1371/journal.pone.0232789
25. Pienkowski VM, Kucharczyk M, Mlynek M, et al. Mapping of breakpoints in balanced chromosomal translocations by shallow whole-genome sequencing points to EFNA5, BAHD1 and PPP2R5E as novel candidates for genes causing human Mendelian disorders. *J med Genet*. 2019;56(2):104-112. doi:10.1136/jmedgenet-2018-105527
26. Gulsuner S, Stein DJ, Susser ES, et al. Genetics of schizophrenia in the South African Xhosa. *Science*. 2020;367(6477):569-573. doi:10.1126/science.aay8833
27. Koopmans F, van Nierop P, Andres-Alonso M, et al. SynGO: an evidence-based, expert-curated Knowledge Base for the synapse. *Neuron*. 2019;103(2):217-234 e4. doi:10.1016/j.neuron.2019.05.002
28. Mele M, Ferreira PG, Reverter F, et al. Human genomics. The human transcriptome across tissues and individuals. *Science*. 2015;348(6235):660-665. doi:10.1126/science.aaa0355
29. Ruderfer DM, Hamamsy T, Lek M, et al. Patterns of genic intolerance of rare copy number variation in 59,898 human exomes. *Nat Genet*. 2016;48(10):1107-1111. doi:10.1038/ng.3638
30. Josifova DJ, Monroe GR, Tessadori F, et al. Heterozygous KIDINS220/ARMS nonsense variants cause spastic paraplegia, intellectual disability, nystagmus, and obesity. *Hum Mol Genet*. 2016;25(11):2158-2167. doi:10.1093/hmg/ddw082
31. Scholz-Starke J, Cesca F. Stepping out of the shade: control of neuronal activity by the scaffold protein Kidins220/ARMS. Review. *Front Cell Neurosci*. 2016;10:68. doi:10.3389/fncel.2016.00068
32. Steinberg S, Stefansson H, Jonsson T, et al. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. *Nat Genet*. 2015;47(5):445-447. doi:10.1038/ng.3246
33. Bellenguez C, Charbonnier C, Grenier-Boley B, et al. Contribution to Alzheimer's disease risk of rare variants in TREM2, SORL1, and ABCA7 in 1779 cases and 1273 controls. *Neurobiol Aging*. 2017;59(220.e9):220.e1-220.e9. doi:10.1016/j.neurobiolaging.2017.07.001
34. Cuyvers E, De Roeck A, Van den Bossche T, et al. Mutations in ABCA7 in a Belgian cohort of Alzheimer's disease patients: a targeted resequencing study. *Lancet Neurol*. 2015;14(8):814-822. doi:10.1016/S1474-4422(15)00133-7
35. Fournier AE, GrandPre T, Strittmatter SM. Identification of a receptor mediating Nogo-66 inhibition of axonal regeneration. *Nature*. 2001;409(6818):341-346. doi:10.1038/35053072
36. Lattanzi GM, Buzzanca A, Frascarelli M, Di Fabio F. Genetic and clinical features of social cognition in 22q11.2 deletion syndrome. Review. *J Neurosci Res*. 2018;96(10):1631-1640. doi:10.1002/jnr.24265
37. Kimura H, Fujita Y, Kawabata T, et al. A novel rare variant R292H in RTN4R affects growth cone formation and possibly contributes to schizophrenia susceptibility. *Transl Psychiatry*. 2017;7(8):e1214. doi:10.1038/tp.2017.170
38. Tripathy D, Vignoli B, Ramesh N, et al. Mutations in TGM6 induce the unfolded protein response in SCA35. *Hum Mol Genet*. 2017;26(19):3749-3762. doi:10.1093/hmg/ddx259
39. Groen JL, Andrade A, Ritz K, et al. CACNA1B mutation is linked to unique myoclonus-dystonia syndrome. *Hum Mol Genet*. 2015;24(4):987-993. doi:10.1093/hmg/ddu513
40. Lee SE, Lee GH. Reelin affects signaling pathways of a group of inhibitory neurons and the development of inhibitory synapses in primary neurons. *Int J Mol Sci*. 2021;22(14):7510. doi:10.3390/ijms22147510
41. Armstrong NC, Anderson RC, McDermott KW. Reelin: diverse roles in central nervous system development, health and disease. *Int J Biochem Cell Biol*. 2019;112:72-75. doi:10.1016/j.biocel.2019.04.009
42. Martin S, Chamberlin A, Shinde DN, et al. De novo variants in GRIA4 Lead to intellectual disability with or without seizures and gait abnormalities. *Am J Hum Genet*. 2017;101(6):1013-1020. doi:10.1016/j.ajhg.2017.11.004
43. Deutschlander AB, Wszolek ZK. Dyt-Gnal. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews((R))*. University of Washington; 1993.
44. Montenegro G, Rebelo AP, Connell J, et al. Mutations in the ER-shaping protein reticulon 2 cause the axon-degenerative disorder hereditary spastic paraplegia type 12. *J Clin Invest*. 2012;122(2):538-544. doi:10.1172/JCI60560
45. Webster E, Cho MT, Alexander N, et al. De novo PHIP-predicted deleterious variants are associated with developmental delay,

intellectual disability, obesity, and dysmorphic features. *Cold Spring Harb Mol Case Stud*. 2016;2(6):a001172. doi:10.1101/mcs.a001172
46. Jansen S, Hoischen A, Coe BP, et al. A genotype-first approach identifies an intellectual disability-overweight syndrome caused by PHIP haploinsufficiency. *Eur J Hum Genet*. 2018;26(1):54-63. doi:10.1038/s41431-017-0039-5
47. Cacace R, Heeman B, Van Mossevelde S, et al. Loss of DPP6 in neurodegenerative dementia: a genetic player in the dysfunction of neuronal excitability. *Acta Neuropathol*. 2019;137(6):901-918. doi:10.1007/s00401-019-01976-3
48. Maussion G, Cruceanu C, Rosenfeld JA, et al. Implication of LRRC4C and DPP6 in neurodevelopmental disorders. *Am J med Genet A*. 2017;173(2):395-406. doi:10.1002/ajmg.a.38021
49. Bock I, Nemeth K, Pentelenyi K, et al. Targeted next generation sequencing of a panel of autism-related genes identifies an EHMT1 mutation in a Kleefstra syndrome patient with autism and normal intellectual performance. Case reports. *Gene*. 2016;595(2):131-141. doi:10.1016/j.gene.2016.09.027
50. Prontera P, Napolioni V, Ottaviani V, et al. DPP6 gene disruption in a family with Gilles de la Tourette syndrome. Case reports. *Neurogenetics*. 2014;15(4):237-242. doi:10.1007/s10048-014-0418-9
51. Hack R, Rutten J, Lesnik Oberstein SAJ. Cadasil. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews((R))*. University of Washington; 1993.
52. Low KJ, Ansari M, Abou Jamra R, et al. PUF60 variants cause a syndrome of ID, short stature, microcephaly, coloboma, craniofacial, cardiac, renal and spinal features. *Eur J Hum Genet*. 2017;25(5):552-559. doi:10.1038/ejhg.2017.27
53. Moccia A, Srivastava A, Skidmore JM, et al. Genetic analysis of CHARGE syndrome identifies overlapping molecular biology. *Genet med*. 2018;20(9):1022-1029. doi:10.1038/gim.2017.233
54. Brussino A, Brusco A, Durr A, Mancini C. Spinocerebellar ataxia type 28. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews ((R))*. University of Washington; 1993.
55. Cariboni A, Andre V, Chauvet S, et al. Dysfunctional SEMA3E signaling underlies gonadotropin-releasing hormone neuron deficiency in Kallmann syndrome. *J Clin Invest*. 2015;125(6):2413-2428. doi:10.1172/JCI78448
56. Schrier Vergano S, Santen G, Wieczorek D, Wollnik B, Matsumoto N, Deardorff MA. Coffin-Siris syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews((R))*. University of Washington; 1993.
57. Kurahashi H, Hirose S. Autosomal Dominant Nocturnal Frontal Lobe Epilepsy. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews((R))*. University of Washington; 1993.
58. Shi Y, Lin S, Staats KA, et al. Haploinsufficiency leads to neurodegeneration in C9ORF72 ALS/FTD human induced motor neurons. *Nat med*. 2018;24(3):313-325. doi:10.1038/nm.4490
59. Russell JF, Steckley JL, Coppola G, et al. Familial cortical myoclonus with a mutation in NOL3. *Ann Neurol*. 2012;72(2):175-183. doi:10.1002/ana.23666
60. Macerollo A, Mencacci NE, Erro R, et al. Screening of mutations in NOL3 in a myoclonic syndromes series. Letter. *J Neurol*. 2014;261(9):1830-1831. doi:10.1007/s00415-014-7463-z
61. Nibbeling EAR, Duarri A, Verschuuren-Bemelmans CC, et al. Exome sequencing and network analysis identifies shared mechanisms underlying spinocerebellar ataxia. *Brain*. 2017;140(11):2860-2878. doi:10.1093/brain/awx251
62. Tesi B, Davidsson J, Voss M, et al. Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. *Blood*. 2017;129(16):2266-2279. doi:10.1182/blood-2016-10-743302
63. Bae GU, Domene S, Roessler E, et al. Mutations in CDON, encoding a hedgehog receptor, result in holoprosencephaly and defective interactions with other hedgehog receptors. *Am J Hum Genet*. 2011;89(2):231-240. doi:10.1016/j.ajhg.2011.07.001
64. Jeong MH, Ho SM, Vuong TA, et al. Cdo suppresses canonical Wnt signalling via interaction with Lrp6 thereby promoting neuronal differentiation. *Nat Commun*. 2014;5:5455. doi:10.1038/ncomms6455
65. Nizon M, Andrieux J, Rooryck C, et al. Phenotype-genotype correlations in 17 new patients with an Xp11.23p11.22 microduplication and review of the literature. Review. *Am J Med Genet A*. 2015;167A(1):111-122. doi:10.1002/ajmg.a.36807
66. Bartholdi D, Stray-Pedersen A, Azzarello-Burri S, et al. A newly recognized 13q12.3 microdeletion syndrome characterized by intellectual disability, microcephaly, and eczema/atopic dermatitis encompassing the HMGB1 and KATNAL1 genes. *Am J med Genet A*. 2014;164A(5):1277-1283. doi:10.1002/ajmg.a.36439
67. Mandrile G, Di Gregorio E, Calcia A, et al. A new case of 13q12.2q13.1 microdeletion syndrome contributes to phenotype delineation. *Case Rep Genet*. 2014;2014:470830. doi:10.1155/2014/470830
68. Banks G, Lassi G, Hoerder-Suabedissen A, et al. A missense mutation in Katnal1 underlies behavioural, neurological and ciliary anomalies. *Mol Psychiatry*. 2018;23(3):713-722. doi:10.1038/mp.2017.54
69. Lee JR. Protein tyrosine phosphatase PTPRT as a regulator of synaptic formation and neuronal development. *BMB Rep*. 2015;48(5):249-255.
70. Schuurs-Hoeijmakers JH, Vulto-van Silfhout AT, Vissers LE, et al. Identification of pathogenic gene variants in small families with intellectually disabled siblings by exome sequencing. *J med Genet*. 2013;50(12):802-811. doi:10.1136/jmedgenet-2013-101644
71. Bobsin K, Kreienkamp HJ. Severe learning deficits of IRSp53 mutant mice are caused by altered NMDA receptor-dependent signal transduction. *J Neurochem*. 2016;136(4):752-763. doi:10.1111/jnc.13428
72. Uddin M, Unda BK, Kwan V, et al. OTUD7A regulates neurodevelopmental phenotypes in the 15q13.3 microdeletion syndrome. *Am J Hum Genet*. 2018;102(2):278-295. doi:10.1016/j.ajhg.2018.01.006
73. Yin J, Chen W, Chao ES, et al. Otud7a knockout mice recapitulate many neurological features of 15q13.3 microdeletion syndrome. *Am J Hum Genet*. 2018;102(2):296-308. doi:10.1016/j.ajhg.2018.01.005
74. Tomas-Roca L, Tsaalbi-Shtylik A, Jansen JG, et al. De novo mutations in PLXND1 and REV3L cause Mobius syndrome. *Nat Commun*. 2015;6:7199. doi:10.1038/ncomms8199
75. Kasem E, Kurihara T, Tabuchi K. Neurexins and neuropsychiatric disorders. Review. *Neurosci Res*. 2018;127:53-60. doi:10.1016/j.neures.2017.10.012
76. Lipstein N, Verhoeven-Duif NM, Michelassi FE, et al. Synaptic UNC13A protein variant causes increased neurotransmission and dyskinetic movement disorder. *J Clin Investig*. 2017;127(3):1005-1018. doi:10.1172/JCI90259
77. Xiao J, Uitti RJ, Zhao Y, et al. Mutations in CIZ1 cause adult onset primary cervical dystonia. *Ann Neurol*. 2012;71(4):458-469. doi:10.1002/ana.23547
78. Williamson SL, Ellaway CJ, Peters GB, Pelka GJ, Tam PP, Christodoulou J. Deletion of protein tyrosine phosphatase, non-receptor type 4 (PTPN4) in twins with a Rett syndrome-like phenotype. *Eur J Hum Genet*. 2015;23(9):1171-1175. doi:10.1038/ejhg.2014.249
79. Stokowy T, Polushina T, Sonderby IE, et al. Genetic variation in 117 myelination-related genes in schizophrenia: replication of association to lipid biosynthesis genes. *Sci Rep*. 2018;8(1):6915. doi:10.1038/s41598-018-25280-4
80. Pinto D, Pagnamenta AT, Klei L, et al. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature*. 2010;466(7304):368-372. doi:10.1038/nature09146

81. Maravet Baig K, Su SC, Mumford SL, et al. Mice deficient in AKAP13 (BRX) develop compulsive-like behavior and increased body weight. *Brain Res Bull*. 2018;140:72-79. doi:10.1016/j.brainresbull.2018.04.005
82. McMichael G, Bainbridge MN, Haan E, et al. Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. *Mol Psychiatry*. 2015;20(2):176-182. doi:10.1038/mp.2014.189
83. Enga RM, Rice AC, Weller P, et al. Initial characterization of behavior and ketamine response in a mouse knockout of the post-synaptic effector gene Anks1b. *Neurosci Lett*. 2017;641:26-32. doi:10.1016/j.neulet.2017.01.044
84. Grunblatt E, Oneda B, Ekici AB, et al. High resolution chromosomal microarray analysis in paediatric obsessive-compulsive disorder. *BMC med Genomics*. 2017;10(1):68. doi:10.1186/s12920-017-0299-5
85. Teoh JJ, Iwano T, Kunii M, et al. BIG1 is required for the survival of deep layer neurons, neuronal polarity, and the formation of axonal tracts between the thalamus and neocortex in developing brain. *PLoS One*. 2017;12(4):e0175888. doi:10.1371/journal.pone.0175888
86. Karaca E, Harel T, Pehlivan D, et al. Genes that affect brain structure and function identified by rare variant analyses of Mendelian neurologic disease. Research support, N.I.H., extramural. *Neuron*. 2015;88(3):499-513. doi:10.1016/j.neuron.2015.09.048
87. Egger G, Roetzer KM, Noor A, et al. Identification of risk genes for autism spectrum disorder through copy number variation analysis in Austrian families. *Neurogenetics*. 2014;15(2):117-127. doi:10.1007/s10048-014-0394-0
88. Frangiskakis JM, Ewart AK, Morris CA, et al. LIM-kinase1 hemizygosity implicated in impaired visuospatial constructive cognition. *Cell*. 1996;86(1):59-69.
89. Eising E, Carrion-Castillo A, Vino A, et al. A set of regulatory genes co-expressed in embryonic human brain is implicated in disrupted speech development. *Mol Psychiatry*. 2018;24(7):1065-1078. doi:10.1038/s41380-018-0020-x
90. Lescai F, Als TD, Li Q, et al. Whole-exome sequencing of individuals from an isolated population implicates rare risk variants in bipolar disorder. *Translational Psychiatry*. 2017;7(2):e1034. doi:10.1038/tp.2017.3
91. Merjonen P, Keltikangas-Jarvinen L, Jokela M, et al. Hostility in adolescents and adults: a genome-wide association study of the Young Finns. *Transl Psychiatry*. 2011;1:e11. doi:10.1038/tp.2011.13
92. Maeta K, Hattori S, Ikutomo J, et al. Comprehensive behavioral analysis of mice deficient in Rapgef2 and Rapgef6, a subfamily of guanine nucleotide exchange factors for rap small GTPases possessing the Ras/rap-associating domain. *Mol Brain*. 2018;11(1):27. doi:10.1186/s13041-018-0370-y
93. Wang X, Zhao Y, Zhang X, et al. Loss of sorting nexin 27 contributes to excitatory synaptic dysfunction by modulating glutamate receptor recycling in Down's syndrome. *Nat med*. 2013;19(4):473-480. doi:10.1038/nm.3117
94. Winkle CC, Olsen RH, Kim H, Moy SS, Song J, Gupton SL. Trim9 deletion alters the morphogenesis of developing and adult-born hippocampal neurons and impairs spatial learning and memory. *J Neurosci*. 2016;36(18):4940-4958. doi:10.1523/JNEUROSCI.3876-15.2016
95. Martin HC, Jones WD, McIntyre R, et al. Quantifying the contribution of recessive coding variation to developmental disorders. *Science*. 2018;362(6419):1161-1164. doi:10.1126/science.aar6731
96. Lebrun N, Mehler-Jacob C, Poirier K, et al. Novel KDM5B splice variants identified in patients with developmental disorders: functional consequences. *Gene*. 2018;679:305-313. doi:10.1016/j.gene.2018.09.016
97. Faundes V, Newman WG, Bernardini L, et al. Histone lysine Methylases and demethylases in the landscape of human developmental disorders. *Am J Hum Genet*. 2018;102(1):175-187. doi:10.1016/j.ajhg.2017.11.013
98. Walters RK, Polimanti R, Johnson EC, et al. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci*. 2018;21(12):1656-1669. doi:10.1038/s41593-018-0275-1
99. Caruso V, Hagglund MG, Badiali L, et al. The G protein-coupled receptor GPR162 is widely distributed in the CNS and highly expressed in the hypothalamus and in hedonic feeding areas. *Gene*. 2014;553(1):1-6. doi:10.1016/j.gene.2014.09.042
100. Duarte RRR, Bachtel ND, Cotel MC, et al. The psychiatric risk gene NT5C2 regulates adenosine monophosphate-activated protein kinase signaling and protein translation in human neural progenitor cells. *Biol Psychiatry*. 2019;86(2):120-130. doi:10.1016/j.biopsych.2019.03.977
101. Ingason A, Rujescu D, Cichon S, et al. Copy number variations of chromosome 16p13.1 region associated with schizophrenia. *Mol Psychiatry*. 2011;16(1):17-25. doi:10.1038/mp.2009.101
102. Jiang W, Wei M, Liu M, et al. Identification of protein tyrosine phosphatase receptor type O (PTPRO) as a synaptic adhesion molecule that promotes synapse formation. *J Neurosci*. 2017;37(41):9828-9843. doi:10.1523/JNEUROSCI.0729-17.2017
103. Kwon YT, Balogh SA, Davydov IV, et al. Altered activity, social behavior, and spatial memory in mice lacking the NTAN1p amidase and the asparagine branch of the N-end rule pathway. Research Support, U.S. Gov't, P.H.S. *Mol Cell Biol*. 2000;20(11):4135-4148. doi:10.1128/mcb.20.11.4135-4148.2000
104. LeBlanc M, Kulle B, Sundet K, et al. Genome-wide study identifies PTPRO and WDR72 and FOXQ1-SUMO1P1 interaction associated with neurocognitive function. *J Psychiatr Res*. 2012;46(2):271-278. doi:10.1016/j.jpsychires.2011.11.001
105. Zayats T, Jacobsen KK, Kleppe R, et al. Exome chip analyses in adult attention deficit hyperactivity disorder. *Transl Psychiatry*. 2016;6(10):e923. doi:10.1038/tp.2016.196
106. Dikow N, Maas B, Karch S, et al. 3p25.3 microdeletion of GABA transporters SLC6A1 and SLC6A11 results in intellectual disability, epilepsy and stereotypic behavior. *Am J med Genet A*. 2014;164A(12):3061-3068. doi:10.1002/ajmg.a.36761
107. Augier E, Barbier E, Dulman RS, et al. A molecular mechanism for choosing alcohol over an alternative reward. *Science*. 2018;360(6395):1321-1326. doi:10.1126/science.aao1157
108. Raghavan NS, Brickman AM, Andrews H, et al. Whole-exome sequencing in 20,197 persons for rare variants in Alzheimer's disease. *Ann Clin Transl Neurol*. 2018;5(7):832-842. doi:10.1002/acn3.582
109. Verweij KJ, Zietsch BP, Medland SE, et al. A genome-wide association study of Cloninger's temperament scales: implications for the evolutionary genetics of personality. *Biol Psychol*. 2010;85(2):306-317. doi:10.1016/j.biopsycho.2010.07.018
110. Maroteaux G, Loos M, van der Sluis S, et al. High-throughput phenotyping of avoidance learning in mice discriminates different genotypes and identifies a novel gene. *Genes Brain Behav*. 2012;11(7):772-784. doi:10.1111/j.1601-183X.2012.00820.x
111. Satterstrom FK, Kosmicki JA, Wang JB, et al. Large-scale exome sequencing Study implicates both developmental and functional changes in the neurobiology of autism. *Cell*. 2020;180(3):568-584.e23. doi:10.1016/j.cell.2019.12.036
112. Satterstrom FK, Walters RK, Singh T, et al. Autism spectrum disorder and attention deficit hyperactivity disorder have a similar burden of rare protein-truncating variants. *Nat Neurosci*. 2019;22(12):1961-1965. doi:10.1038/s41593-019-0527-8
113. Ganna A, Satterstrom FK, Zekavat SM, et al. Quantifying the impact of rare and ultra-rare coding variation across the phenotypic Spectrum. *Am J Hum Genet*. 2018;102(6):1204-1211. doi:10.1016/j.ajhg.2018.05.002
114. Singh T, Walters JTR, Johnstone M, et al. The contribution of rare variants to risk of schizophrenia in individuals with and without

intellectual disability. *Nat Genet*. 2017;49(8):1167-1173. doi:10.1038/ng.3903
115. Jia X, Goes FS, Locke AE, et al. Investigating rare pathogenic/likely pathogenic exonic variation in bipolar disorder. *Mol Psychiatry*. 2021;26:5239-5250. doi:10.1038/s41380-020-01006-9
116. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*. 2020;581(7809):434-443. doi:10.1038/s41586-020-2308-7
117. Rajagopal VM, Duan J, Vilar-Ribo L, et al. Differences in the genetic architecture of common and rare variants in childhood, persistent and late-diagnosed attention-deficit hyperactivity disorder. *Nat Genet*. 2022;54(8):1117-1124. doi:10.1038/s41588-022-01143-7
118. Ribases M, Mitjans M, Hartman CA, et al. Genetic architecture of ADHD and overlap with other psychiatric disorders and cognition-related phenotypes. *Neurosci Biobehav Rev*. 2023;153:105313. doi:10.1016/j.neubiorev.2023.105313
119. Tielbeek JJ, Uffelmann E, Williams BS, et al. Uncovering the genetic architecture of broad antisocial behavior through a genome-wide association study meta-analysis. *Mol Psychiatry*. 2022;27(11):4453-4463. doi:10.1038/s41380-022-01793-3
120. Demontis D, Walters GB, Athanasiadis G, et al. Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nat Genet*. 2023;55(4):730. doi:10.1038/s41588-023-01350-w
121. Amanat S, Requena T, Lopez-Escamez JA. A systematic review of extreme phenotype strategies to search for rare variants in genetic studies of complex disorders. *Genes (Basel)*. 2020;11(9):987. doi:10.3390/genes11090987
122. Tammimies K, Marshall CR, Walker S, et al. Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism Spectrum disorder. *JAMA*. 2015;314(9):895-903. doi:10.1001/jama.2015.10078
123. Feliciano P, Zhou X, Astrovskaya I, et al. Exome sequencing of 457 autism families recruited online provides evidence for autism risk genes. *NPJ Genom med*. 2019;4:19. doi:10.1038/s41525-019-0093-8
124. Finucane BM, Ledbetter DH, Vorstman JAS. Diagnostic genetic testing for neurodevelopmental psychiatric disorders: closing the gap between recommendation and clinical implementation. *Curr Opin Genet Dev*. 2021;68:1-8. doi:10.1016/j.gde.2020.12.016
125. Vorstman J, Scherer SW. What a finding of gene copy number variation can add to the diagnosis of developmental neuropsychiatric disorders. *Curr Opin Genet Dev*. 2021;68:18-25. doi:10.1016/j.gde.2020.12.017

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