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Supplemental information

Genome-wide structural variant analysis identifies risk loci for non-Alzheimer's dementias

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Genome-wide structural variant analysis identifies risk loci for non-Alzheimer dementias

Karri Kaivola, Ruth Chia, Jinhui Ding, et al.

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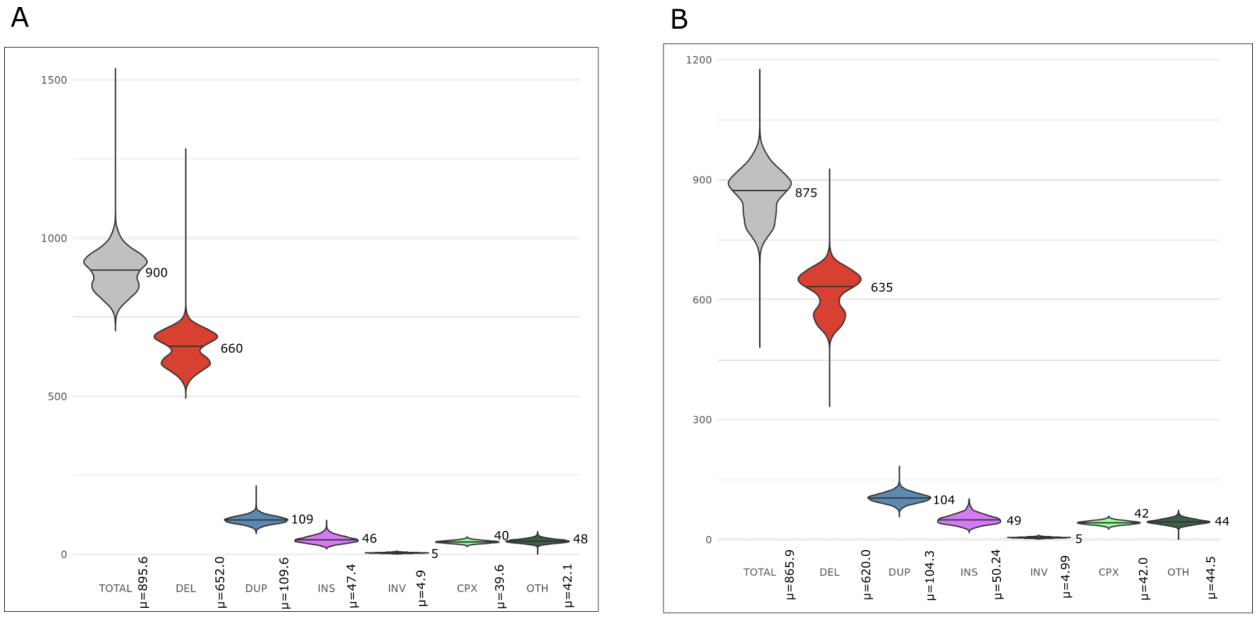
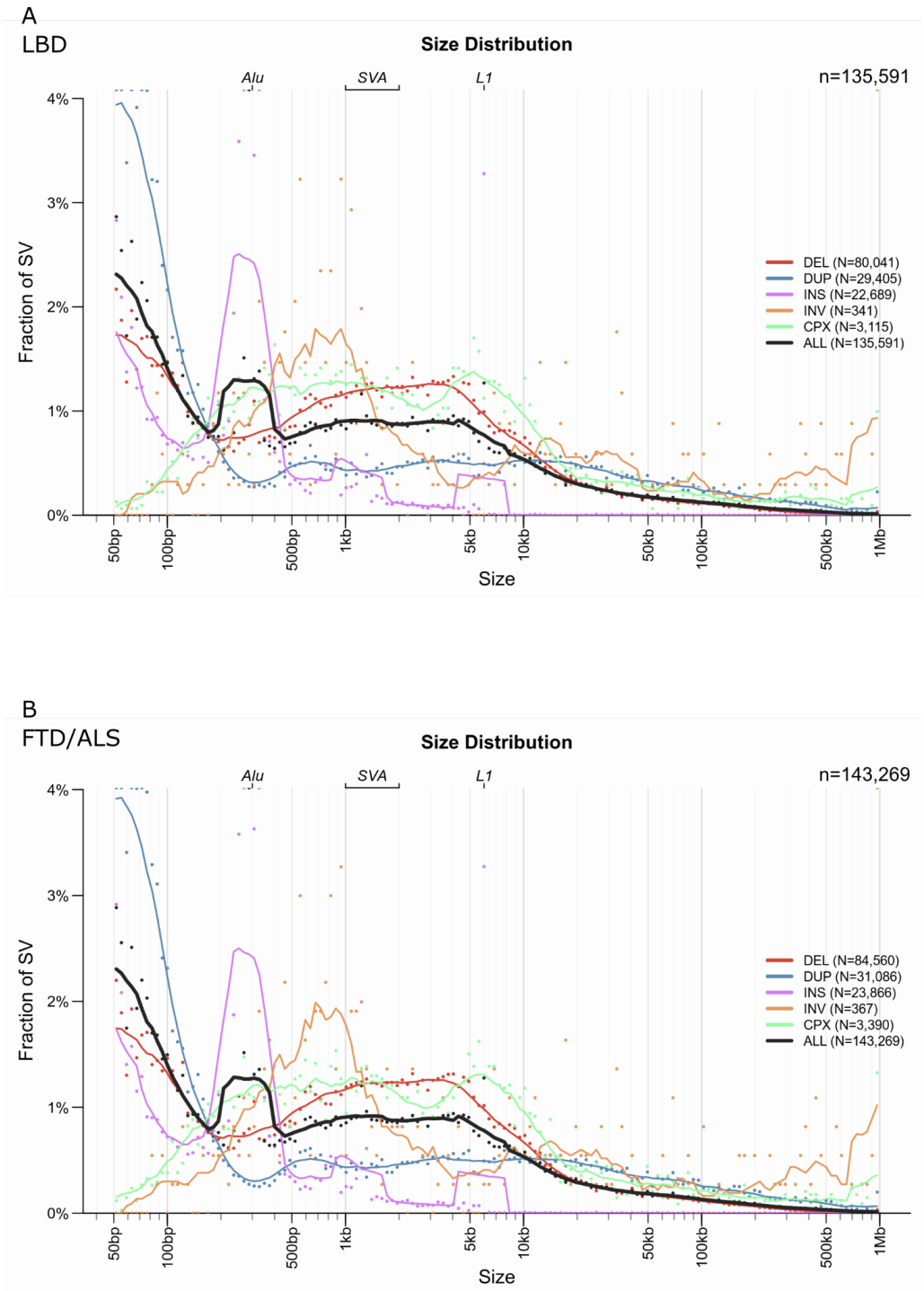
Supplementary Figures

Figure S1 | Structural variant counts per structural variant type.



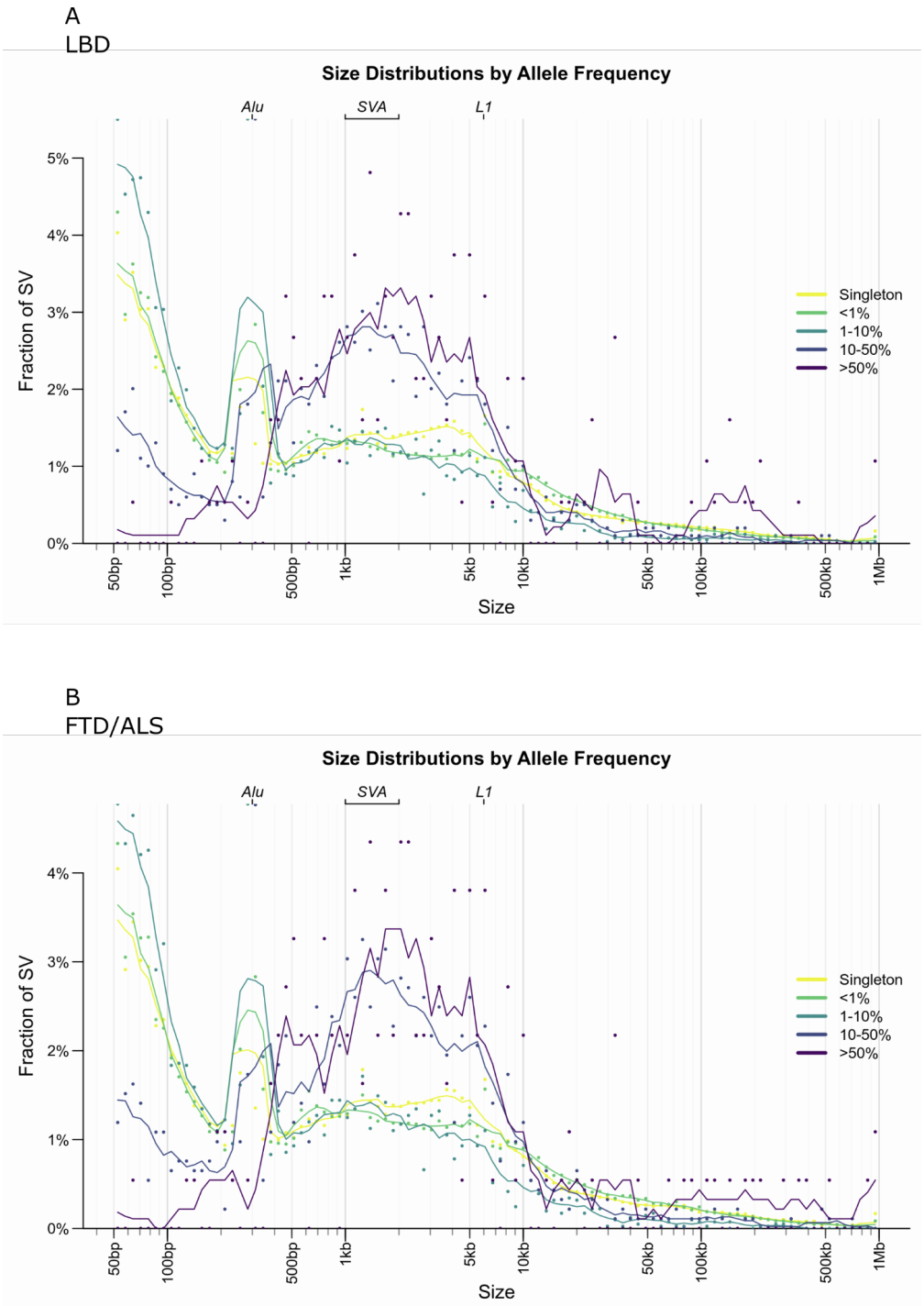
This figure shows the structural variant counts per variant type in the final filtered data used in the analyses. **(A)** shows the results for the LBD case-control cohort, and **(B)** illustrates the FTD/ALS case-control cohort counts. The horizontal line in each violin plot represents the median value and μ refers to the mean. Abbreviations: DEL, deletions; DUP, duplications; INS, insertions; INV, inversions; CPX, complex structural variants; OTH, other structural variants. Related to Figure 2.

Figure S2 | Structural variant size per structural variant type.



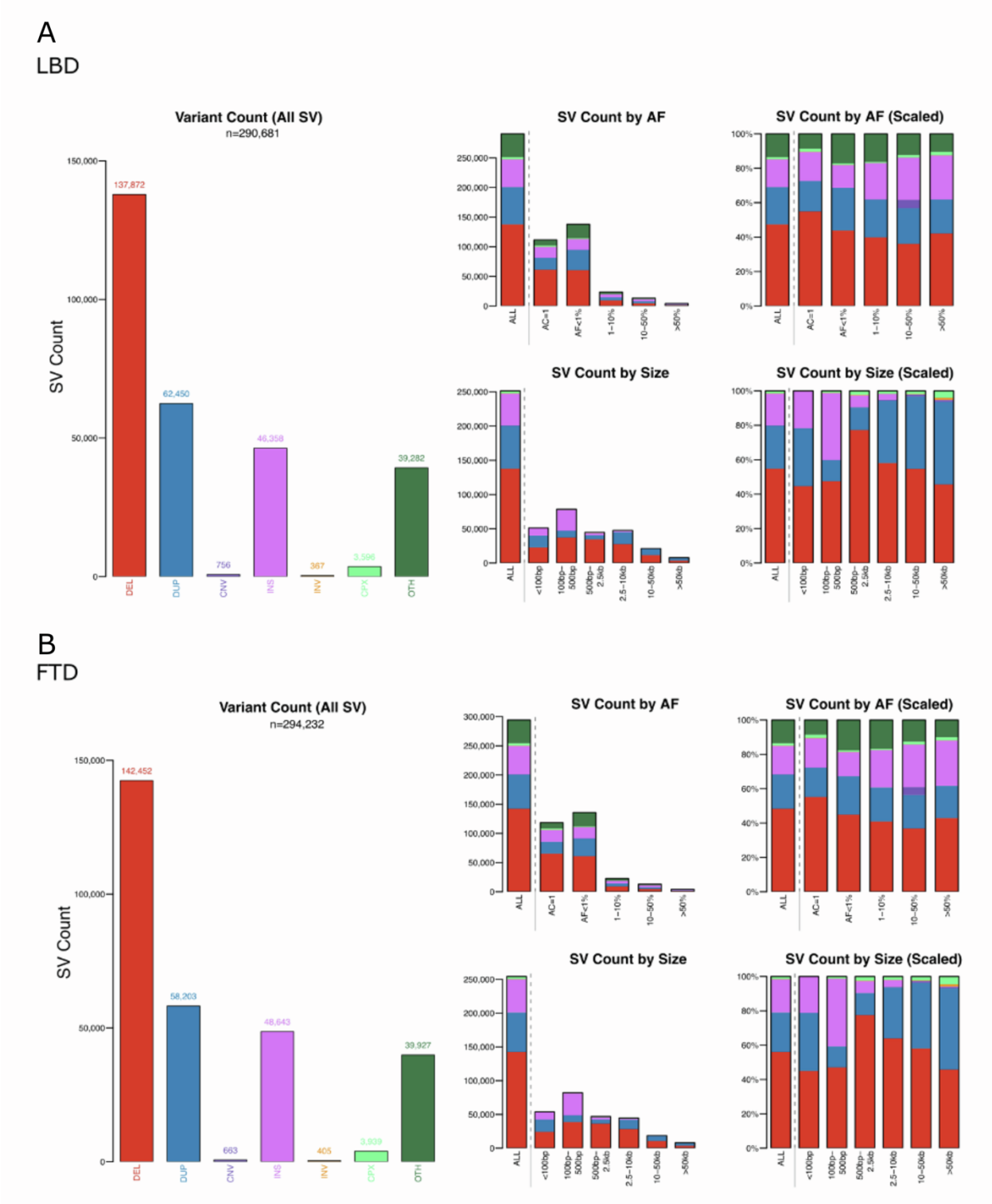
This figure shows the structural variant size for each variant type in the final filtered data used in the analyses. **(A)** shows the results for the LBD case-control cohort, and **(B)** illustrates the FTD/ALS case-control results. Abbreviations: DEL, deletions; DUP, duplications; INS, insertions; INV, inversions; CPX, complex structural variants; OTH, other structural variants. Related to Figure 2.

Figure S3 | Structural variant size and structural variant allele frequency.



This figure shows the structural variant size per the structural variant allele frequency in the final filtered data used in the analyses. **(A)** shows the results for the LBD case-control cohort, and **(B)** illustrates the FTD/ALS case-control results. Increased frequencies are observed at ~300 bp, 1.2 kb, and 6kb, corresponding to abundant mobile elements in the human genome (Alu, SVA, L1). Related to Figure 2.

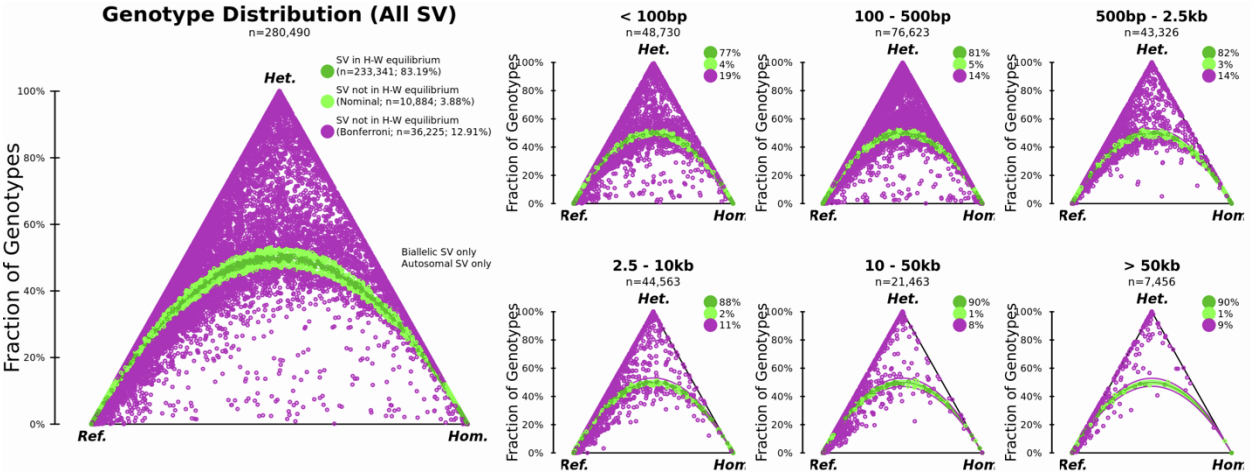
Figure S4 | Descriptive statistics of unfiltered structural variants mapped by the GATK-SV pipeline in the study cohorts.



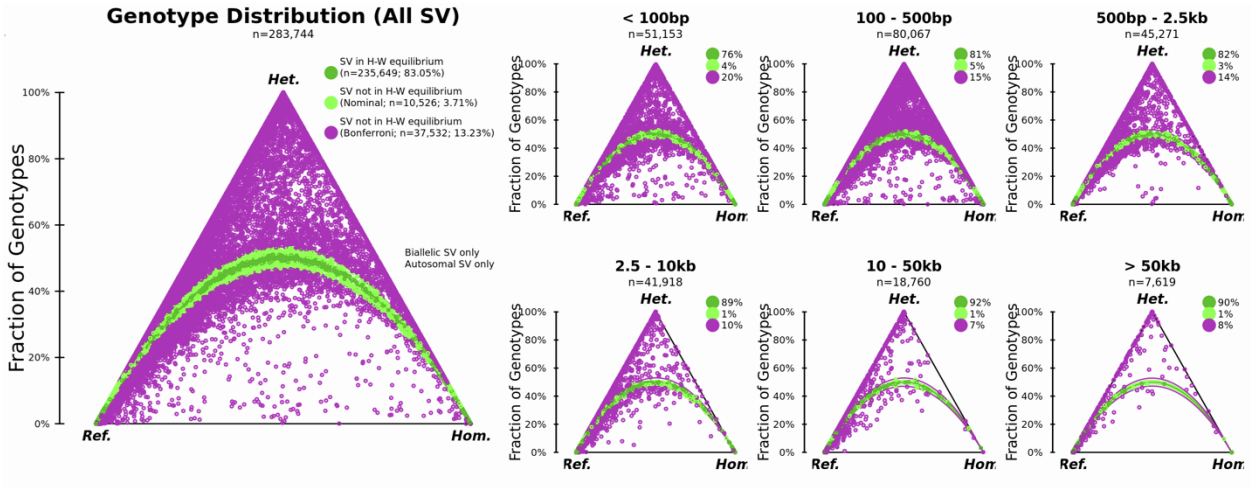
This figure shows the descriptive statistics of unfiltered structural variant calls in the LBD case-control cohort and the FTD-ALS case-control cohort. Related to Figure 2.

Figure S5 | Hardy-Weinberg equilibrium in the study cohorts.

A LBD



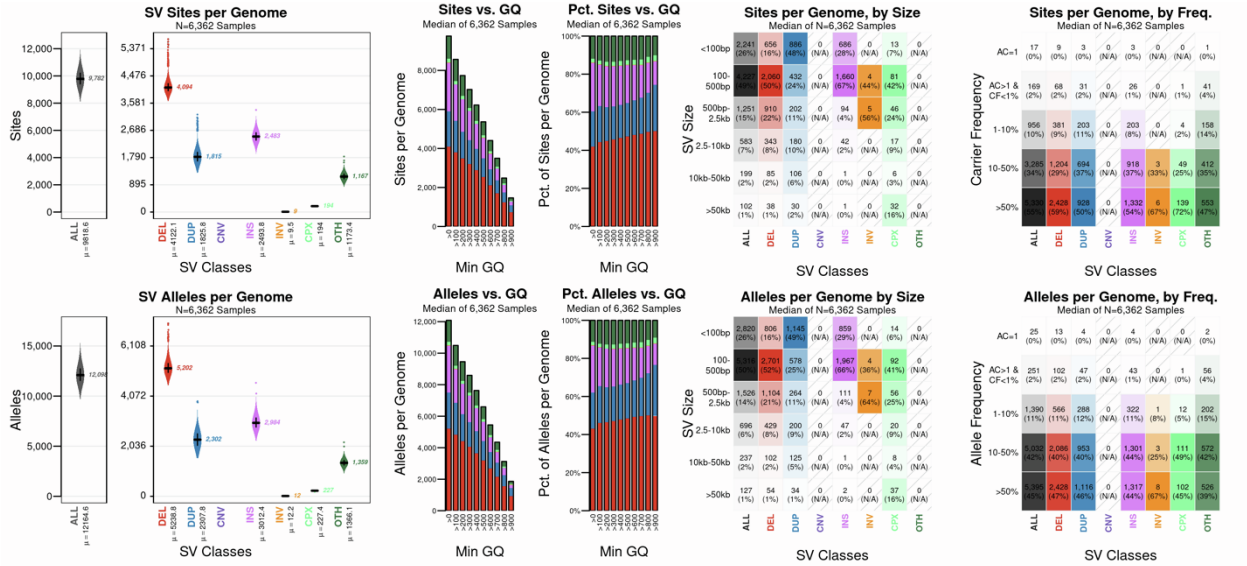
B FTD/ALS



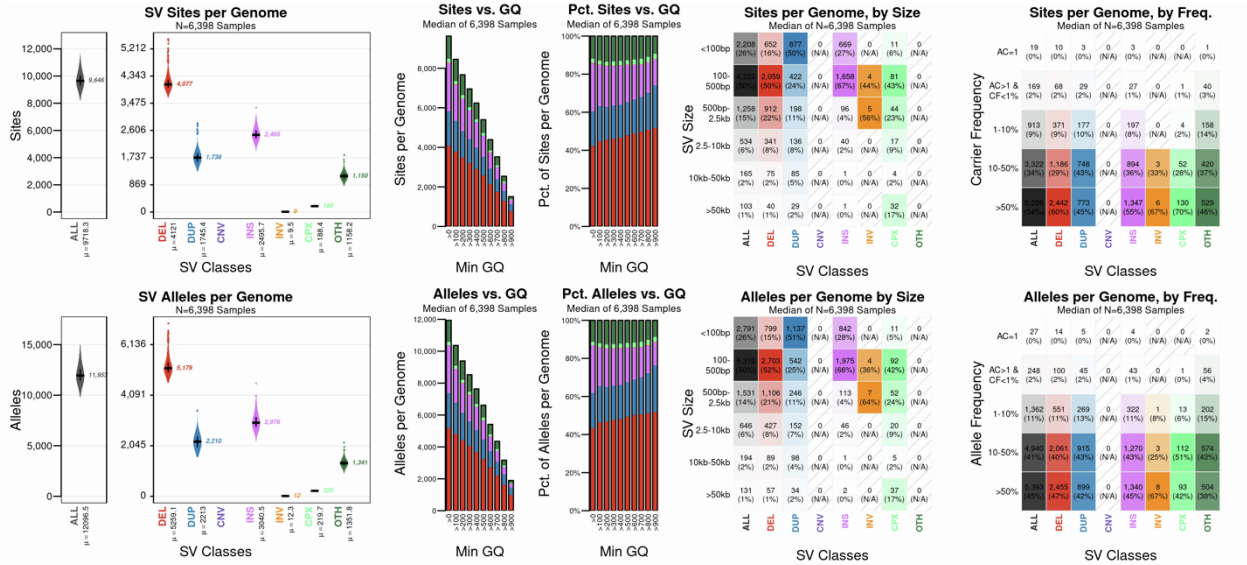
Distribution of the Hardy-Weinberg equilibrium of unfiltered structural variants identified in the LBD case-control cohort **(A)** and FTD/ALS case-control cohort **(B)** using the GATK-SV pipeline. Hardy-Weinberg equilibrium metrics refer to all biallelic structural variants localized to the autosomes. Deviation from Hardy-Weinberg equilibrium was assessed using a chi-square goodness-of-fit test with one degree of freedom. All sites are shaded according to their chi-squared *p*-values. The vertex labels reflect genotypes: Ref. denotes homozygous reference allele; Het. denotes heterozygous for the alternate allele; Hom. denotes homozygous for the alternate allele. Related to Figure 2.

Figure S6 | Characteristics of the unfiltered structural variants.

A LBD

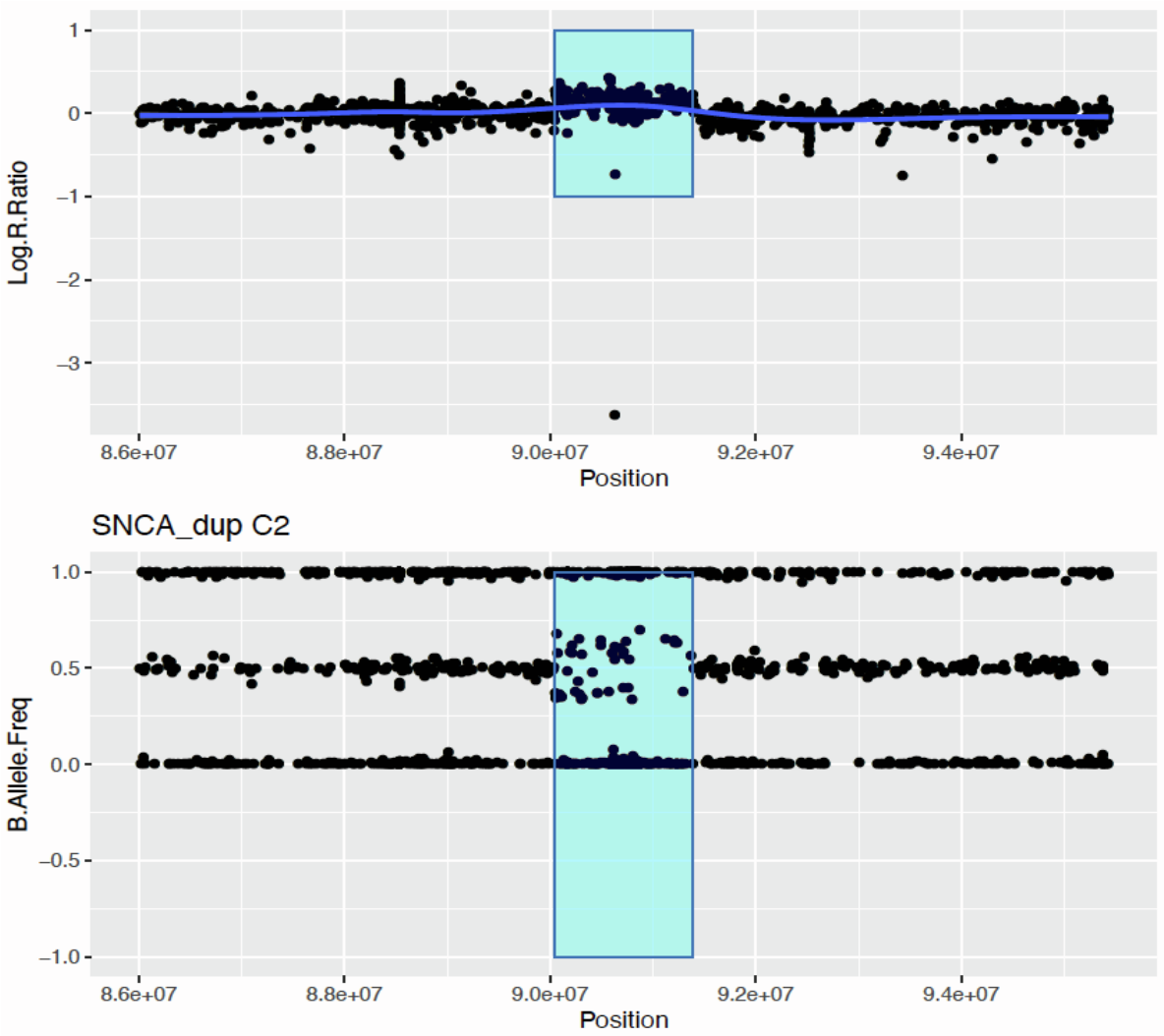


B FTD/ALS



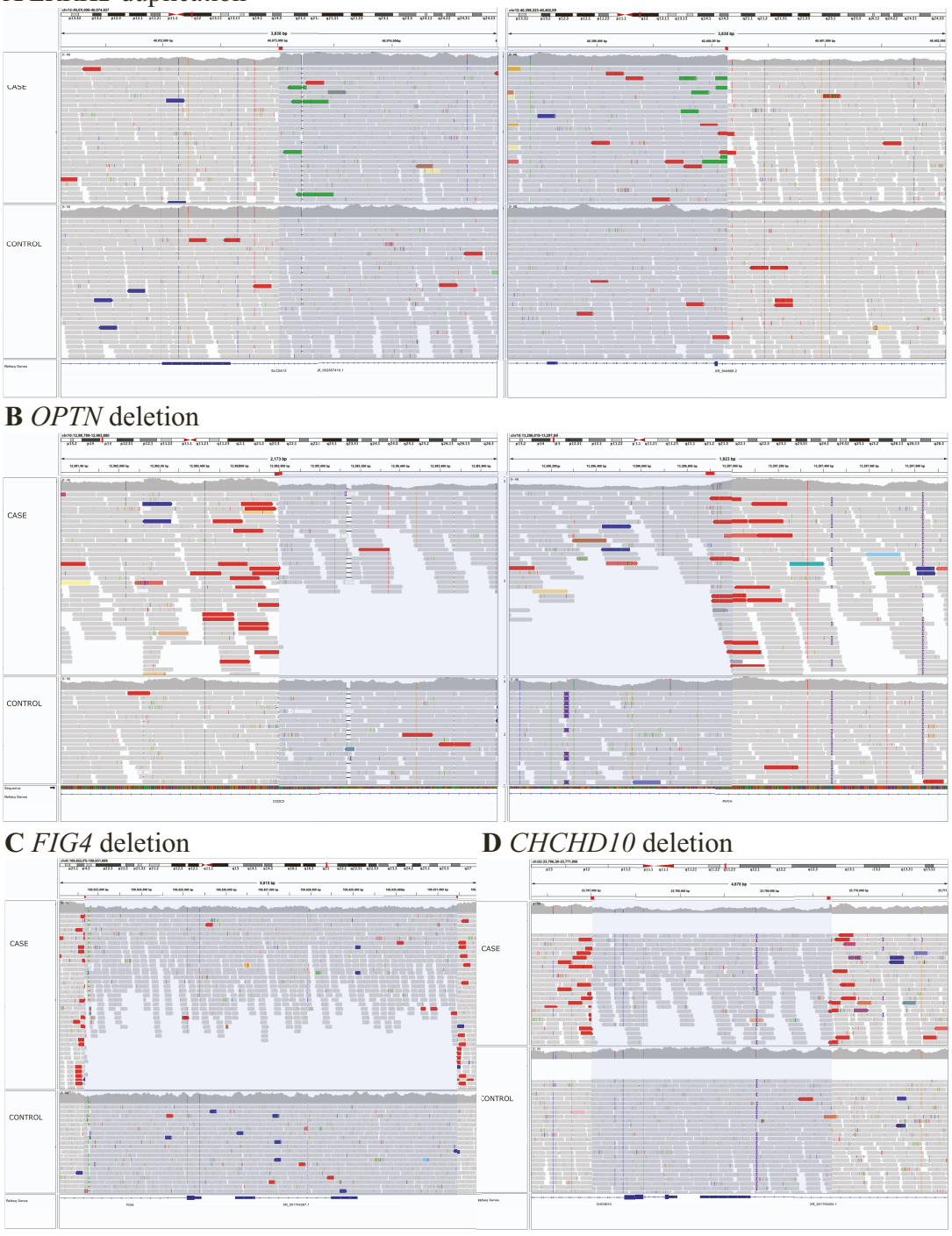
Structural variant site, quality, and allele frequency information of unfiltered structural variants in the LBD case-control cohort **(A)** and FTD/ALS case-control cohort **(B)**. Related to Figure 2.

Figure S7 | Validation of an *SNCA* duplication.



These plots are based on NeuroChip genotyping array data (Illumina). The characteristic double-band pattern of the B-allele frequency plot with a corresponding elevation in the log R ratio at the *SNCA* locus are consistent with a duplication. Related to Table 2.

Figure S8 | Structural variant validation using the IGV-viewer.



Structural variants in neurodegenerative disease genes were visualized in IGV-Viewer. **(A)** shows a duplication of the entire *LRRK2* gene that was present in a patient presenting with non-fluent primary progressive aphasia; **(B)** illustrates a deletion encompassing the entire *OPTN* gene in a patient with pathologically confirmed LBD; **(C)** and **(D)** show partial deletions of *FIG4* and *CHCHD10* in FTD/ALS cases. The upper pane of each panel shows the affected case, and the lower pane of each panel shows a control subject. Related to Table 2.

Supplementary Tables

Table S1. Descriptive statistics of filtered high-quality structural variants in the LBD case-control cohort and FTD/ALS case-control cohort.

A) Descriptive statistics according to structural variant type.

	Deletion	Duplication	Insertion	Inversion	Unresolved variant	Complex variant
LBD cases	0.52*	0.20	0.16	0.0020	0.11*	0.019
LBD controls	0.53	0.20	0.15	0.0023	0.10	0.020
FTD cases	0.52	0.20	0.16	0.0022	0.10	0.021
FTD controls	0.52	0.20	0.16	0.0023	0.10	0.020

The frequency of structural variants was compared between cases and controls for each variant type. * denotes a *p*-value (based on a two-sided Fisher's test) less than 0.0083 (0.05/6 structural variant types). Related to Figure 2.

B) Descriptive statistics according to structural variant length.

	Unresolved	<100bp	100bp-500bp	500bp-2.5kb	2.5kb-10kb	10kb-50kb	>50kb
LBD cases	0.060*	0.20	0.27	0.19	0.16	0.071*	0.049
LBD controls	0.057	0.20	0.27	0.19	0.16	0.077	0.048
FTD cases	0.057	0.20	0.27	0.19	0.16	0.075	0.049
FTD controls	0.057	0.20	0.27	0.19	0.16	0.074	0.050

The frequency of structural variants were compared between cases and controls for each length group. * denotes a *p*-value (based on a two-sided Fisher's test) less than 0.0071 (0.05/7 length groups). Abbreviation: bp = base-pairs. Related to Figure 2.

C) Descriptive statistics according to structural variant allele frequency.

	Singletons	<1%	1-10%	10-50%	>50%
LBD cases	0.57*	0.37*	0.053*	0.013*	0.002*
LBD controls	0.58	0.38	0.039	0.009	0.002
FTD cases	0.59*	0.35*	0.046*	0.011*	0.002
FTD controls	0.57	0.38	0.038	0.009	0.002

The frequency of structural variants was compared between cases and controls per allele frequency group. * denotes a *p*-value (based on a two-sided Fisher's test) less than 0.01 (0.05/5 allele frequency group). Related to Figure 2.

Table S2. Precision (validation rate) and genotype concordance between structural variants called using the GATK-SV pipeline and Nanopore long-read sequencing in 20 samples.

A) Precision and concordance according to the variant call quality.

	All variants		High-quality variants	
	Precision	Genotype concordance	Precision	Genotype concordance
Insertions	69.1 %	61.2 %	60.8 %	94.3 %
Deletions	66.0 %	81.9 %	84.3 %	92.0 %
Duplications	33.8 %	79.3 %	50.2 %	89.2 %
Inversions	32.1 %	86.5 %	52.4 %	87.3 %

Related to STAR Methods.

B) Precision and concordance according to the allele frequency of high-quality variants.

	Minor allele frequency <1%		Minor allele frequency ≥1%	
	Precision	Genotype concordance	Precision	Genotype concordance
Insertions	61.4%	95.4%	61.6%	93.6%
Deletions	79.5%	91.4%	84.7%	92.1%
Duplications	43.3%	89.0%	52.5%	89.3%
Inversions	0 %	0 %	53.2%	87.3%

Related to STAR Methods.

Table S3. Comparison of the study cohort with recent structural variant publications.

Study	Sample N	SV mapping	SVs per genome	SV type distribution (without BNDs)	Median SV length	SVs with MAF < 1%	SVs in HWE	Validation rate against long-read sequencing*
Collins et al., 2020	14,891	GATK-SV	7,439 [1]	DEL ~50% DUP ~15% INS ~30%	331 bp	~90%	~80%	n = 4 DEL 92% DUP 94% INS 97%
Abel et al., 2020	14,623	LUMPY, CNVnator, SVTyper, svtools	4,442[2]	DEL ~ 62 % DUP ~ 16 % INS NA	NA	~90%	NA	n=9 DEL 87% DUP 70% INS NA
Billingsley et al., 2023	7,772	GATK-SV	5,626 [3]	DEL ~53% DUP ~21% INS ~24%	329 bp	NA	NA	n = 8 DEL NA DUP NA INS NA
Byrska-Bishop et al, 2022	3,202	GATK-SV, svtools, Absinthe	9,679	DEL ~50% DUP ~15% INS ~ 30%	NA	~80%	~75%	n = 15 DEL 70% DUP 4 % INS 90%
This study (FTD case/control)	6,398	GATK-SV	9,646	DEL ~ 55% DUP ~ 25 % INS ~ 20 %	322 bp	~90%	~80%	n = 20 DEL 84% DUP 50% INS 61%

* filtering prior to variant validation and validation criteria varied considerably in each study

[1] SV calls in the Collins et al. manuscript excluded uncharacterized breakend variants

[2] SV calls in the Abel et al. manuscript from the public b38 call set

[3] SV calls in the Billingsley et al. manuscript excluded any variant that did not have the "PASS" label, which excludes "MULTIALLELIC" and "UNRESOLVED" variants (including uncharacterized breakend variants)

Related to STAR methods.

Table S4. Expression quantitative trait loci information for the rs6489896 variant located in the chromosome 12q24.13 locus.

Cell type	Gene	SNP	Beta	*p*-value
Excitatory neurons	*RITA1*	rs6489896	-0.35	**9.8×10^{-8}**
Astrocytes	*TPCN1*	rs6489896	-0.21	0.0011
Excitatory neurons	*TPCN1*	rs6489896	0.18	0.0013
Oligodendrocytes	*DTX1*	rs6489896	-0.40	0.0024
Oligodendroglia precursor cells	*RPH3A*	rs6489896	0.32	0.0034
Inhibitory neurons	*RITA1*	rs6489896	-0.31	0.0035
Excitatory neurons	*PLBD2*	rs6489896	0.15	0.0356
Inhibitory neurons	*PLBD2*	rs6489896	0.21	0.0439
Oligodendrocytes	*SLC8B1*	rs6489896	0.22	0.0536
Endocytes	*PTPN11*	rs6489896	-0.25	0.0615

Data were generated using single-nucleus RNA-sequencing using brain tissue from the ROS/MAP collection. Bolded value denotes a significant *p*-value. Related to Figure 5C.

Table S5. List of fifty genes associated with neurodegenerative diseases that were evaluated for structural variants.

Gene	Chromosome	Start	End
PARK7	1	6,961,711	8,985,505
TARDBP	1	10,012,622	12,025,492
ATP13A2	1	15,985,958	18,011,972
PINK1	1	19,633,458	21,651,511
DNAJC6	1	64,264,694	66,415,869
GBA	1	154,234,448	156,244,862
PSEN2	1	225,870,572	227,896,103
TIA1	2	69,209,444	71,248,641
DCTN1	2	73,361,154	75,374,735
ALS2	2	200,759,458	202,781,172
TUBA4A	2	218,249,711	220,254,608
BSN	3	48,554,477	50,671,549
CHMP2B	3	86,227,263	88,255,548
SNCA	4	88,724,099	90,836,976
MATR3	5	138,273,752	140,331,677
CSF1R	5	149,053,291	151,113,372
SQSTM1	5	178,807,003	180,838,077
FIG4	6	108,691,221	110,825,431
PARK2	6	160,347,417	163,727,766
C9orf72	9	26,560,424	28,573,866
VCP	9	34,056,066	36,072,668
SPTLC1	9	91,031,999	93,115,376
SETX	9	131,261,356	133,354,856
OPTN	10	12,100,082	14,138,276
LRRK2	12	39,224,997	41,369,284
HNRNPA1	12	53,280,690	55,285,246
KIF5A	12	56,549,992	58,586,633
TBK1	12	63,452,120	65,502,113
ATXN2	12	110,452,214	112,599,673
GCH1	14	53,842,006	55902,824
PSEN1	14	72,136,435	74,223,691
SPG11	15	43,562,696	45663,662
VPS13C	15	60,852,391	63,060,465
POLG	15	88,316,305	90,334,795
FUS	16	30,180,110	32,194,871
VPS35	16	45,657,979	47,689,232
PFN1	17	3,945,650	5,949,086
GRN	17	43,345,086	45,353,106
MAPT	17	44,894,382	47,028,333
PANK2	20	2,889,802	4,929,882
VAPB	20	57,389,119	59,451,100
APP	21	24,880,550	27,171,128
SOD1	21	30,659,622	32,668,930
SYNJ1	21	31,628,759	33,727,939
CHCHD10	22	22,765,834	24,767,972
FBXO7	22	31,475,237	33,498,831
PLA2G6	22	37,111,495	39,181,909
UBQLN2	X	55,563,593	57,567,010
TAF1	X	70,366,239	72,466,005
RAB39B	X	154,258,235	156,264,491

Chromosomal positions are shown according to hg38. Related to Table 2.

Table S6. Structural variants in neurodegenerative disease genes.

-> see attached Table_S6.xlsx file

Legend: The table lists the structural variants that were discovered in the study cohorts in fifty genes previously implicated in monogenic forms of neurodegeneration. Abbreviations: BAF, B allele frequency; BND, breakend variant; CPX, complex variant; DEL, deletion; DUP, duplication; INS, insertion; INV, inversion; ME, mobile element (Alu, LINE1, SVA); OTH, other variant; PE, paired-end read; RD, read depth; SR, split read.

Table S7. Filtered structural variants in the study cohorts.

-> see attached Table_S7.xlsx file

Legend: The table lists the structural variants in the study cohorts that were included in the analyses. Abbreviations: BAF, B allele frequency; BND, breakend variant; CPX, complex variant; DEL, deletion; DUP, duplication; INS, insertion; INV, inversion; ME, mobile element (Alu, LINE1, SVA); OTH, other variant; PE, paired-end read; RD, read depth; SR, split read.

Table S8. Unfiltered structural variants identified by the GATK-SV pipeline.

-> see attached Table_S8.xlsx file

Legend: The table lists the unfiltered structural variants in the LBD and FTD/ALS study cohorts. Abbreviations: BAF, B allele frequency; BND, breakend variant; CPX, complex variant; DEL, deletion; DUP, duplication; INS, insertion; INV, inversion; ME, mobile element (Alu, LINE1, SVA); OTH, other variant; PE, paired-end read; RD, read depth; SR, split read.

Table S9. Demographics and clinical features of the LBD case-control cohort, the FTD/ALS case-control cohort and the replication case-control cohort.

	LBD		FTD/ALS		Replication	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Sex, male (%)	1,511 (64.2%)	1,734 (46.9%)	1,234 (53.5 %)	1,720 (46.8 %)	377 (67.9 %)	147 (53.6 %)
Mean age, years	74	72	65	72	75	85
Median age, years	75	79	66	79	75	87

Supplementary Notes

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