SUPPLEMENTARY MATERIALS

Supplementary method - Deep sequencing

Regarding R105, a mosaic variant in *MECP2* exon 1 (NM_001110792.1: c.31G>T, p.Gly11*) was confirmed by targeted amplicon sequencing (TAS) using DNA derived from peripheral blood leukocytes, saliva, nails, and hair roots of the affected individuals. TAS libraries were prepared using reagents from the SureSelect XT Human All Exon kit (Agilent Technologies), in accordance with the manufacturer's instructions. The TAS library was run on a MiSeq sequencer (Illumina) with 150-bp paired-end reads. Alignment, recalibration, and variant calling were performed as previously described for WES without PCR deduplication. Allele frequency was calculated based on manual read counts in bam files using the Integrative Genomics Viewer (IGV, http://www.broadinstitute.org/igv/).

ID	Analysis status	Gene	Phenotype group (reason suspected as RTT-like for group 3) 1. typical RTT 2. atypical RTT 3. RTT-like features	A period of regression followed by recovery or stabilization	Main criteria				Exclusion criteria for typical RTT	Supportive criteria for atypical RTT
					1. Partial or complete loss of acquired purposeful hand skills.	2. Partial or complete loss of acquired spoken language	3. Gait abnormalities: Impaired (dyspraxic) or absence of ability.	4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms	1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems 2. Grossly abnormal psychomotor development in first 6 months of life	1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis 7. Growth retardation 8. Small cold hands and feet 9. Inappropriate laughing/screaming spells 10. Diminished response to pain 11. Intense eye communication "eye pointing"
R002	SNV_identified	*CACNA1G*	3, autistic behavor with stereotypic movements and gait abnormalities	No	No	No	Yes	Yes		1,2,4,5,6,7,10,11
R006	SNV_identified	*SHANK3*	1, typical RTT	Yes	Yes	Yes	Yes	Yes		2,3,4,5,6,7,8,10,11
R008	CNV_identified	*STXBP1_deletion*	3, autistic spectrum disorder with hypotonia and intellectual disability	No	No	No	Yes	Yes		1,2,3,4,6,7,8,10
R016	VUS	*TCF4*	3, stereotypic movements	No	No	No	Yes	Yes	Brain injury perinatally	2,3,4,6,7,8
AMU3	SNV_identified	*SCN8A*	2, atypical RTT	Yes	Yes	No	Yes	Yes		2,3,4,6,9,
AMU4	SNV_identified	*PDHA1*	3, clinical atypical RTT without metabolic disease exclusion	Yes	No	No	Yes	Yes		2,4,6,7,8,10
AMU5	SNV_identified	*CDKL5*	2, atypical RTT	Yes	Yes	No	Yes	Yes		2,3,4,7,8,9
SN01	Candidate	*ATP6V0A1*	2, atypical RTT	Yes	Yes	No	Yes	Yes		1,3,4,6,7,9
SN04	SNV_identified	*MAST1*	2, atypical RTT	Yes	No	No	Yes	Yes		2,3,4,7,9,10
SN05	MECP2_CNV	*MECP2*	1, typical RTT	Yes	Yes	Yes	Yes	Yes		3,4,7,9,
SN06	SNV_identified	*PPT1*	2, atypical RTT	Yes	Yes	Yes	Yes	Yes		3,4,9,
SN07	VUS	*UBE3A*	2, atypical RTT	Yes	Yes	No	Yes	No		2,3,4,9,
SN08	SNV_identified	*FOXG1*	2, atypical RTT	Yes	Yes	No	Yes	Yes		3,4,7,9,
SN12	CNV_identified	*MEF2C_deletion*	2, atypical RTT	Yes	Yes	No	Yes	Yes		2,3,4,6,7
SN14	MECP2_CNV	*MECP2*	1, typical RTT	Yes	Yes	Yes	Yes	Yes		1,2,3,4,6
SN15	SNV_identified	*STXBP1*	2, atypical RTT	Yes	Yes	No	Yes	Yes	Pathologically diagnosed atypical Wilson disease (biallelic variants in *ATP7B* were not found.)	2,4,9,11
SN16	VUS	*PCDH19*	2, atypical RTT	Yes	Yes	Yes	Yes	Yes		4,9
R039	SNV_identified	*UBE3A*	3, suspected of RTT and angelman syndrome with epilepsy	No	No	No	Yes	No		3,4,7,9
R040	MECP2_CNV	*MECP2*	1, typical RTT	Yes	Yes	Yes	Yes	Yes		N.D.
R046	SNV_identified	*UBE3A*	3, developmental delay with scoliosis	No	No	No	Yes	No		6
R047	SNV_identified	*HDAC8*	2, atypical RTT	Yes	Yes	Yes	Yes	Yes		1,2,3,4,5,7,8,9,10,11
R048	VUS	*GRIN2B*	1, typical RTT	Yes	Yes	Yes	Yes	Yes		6
R049	SNV_identified	*TCF4*	2, atypical RTT	No	No	Yes	Yes	Yes		6
R050	SNV_identified	*STXBP1*	3, developmental delay with walk disability	No	No	No	Yes	No		N.D.
R053	SNV_identified	*NR2F1*	3, stereotypic movements of hands	Yes	No	No	Yes	Yes		4
R066	SNV_identified	*WDR45*	1, typical RTT	Yes	Yes	Yes	Yes	Yes		1,2,4,5,6,7,8,11
R072	SNV_identified	*SYNGAP1*	3, abnormal sleep pattern	No	No	No	No	No		3
R076	SNV_identified	*GRIN2B*	3, developmental delay with scoliosis, abnormal sleep pattern	No	No	No	No	No		2,6
R078	CNV_identified	*22q13 deletion*	3, walk disability and scoliosis	No	No	No	Yes	No		N.D.
R082	CNV_identified	*2p23 microdeletion*	3, autistic spectrum disorder with hypotonia and intellectual disability	No	No	No	Yes	No		N.D.
R092	SNV_identified	*UBE3A*	3, autistic spectrum disorder with hypotonia and sleep disturbance	No	No	No	Yes	No		N.D.
R093	SNV_identified	*NALCN*	3, female with acquired microcephaly	No	Yes	No	Yes	Yes		1,2,3,4,7,8,
R095	Candidate	*USP8*	2, atypical RTT	Yes	No	No	Yes	Yes		1,2,3,4,6,7,8,9
R096	Candidate	*NCOR2*	3, microcephalus	No	No	No	Yes	No		N.D.
R097	SNV_identified	*SCN2A*	1, typical RTT	Yes	Yes	Yes	Yes	Yes		N.D.
R104	SNV_identified	*IQSEC2*	1, typical RTT	Yes	Yes	Yes	Yes	Yes		N.D.
R105	Mosaic	*mecp2_e1*	2, atypical RTT	Yes	Yes	Yes	Yes	Yes		1,2,5,8,9,11
R106	SNV_identified	*STXBP1*	2, atypical RTT	Yes	Yes	Yes	Yes	Yes		N.D.
R110	SNV_identified	*IRF2BPL*	3, stereotypic movements, autistic feature	No	No	No	No	Yes	Mild psychomotor delay (head control at 5 months, sit alone at 2 years)	4
R112	CNV_identified	*WDR45_deletion*	2, atypical RTT	No	No	No	Yes	Yes		1,2,7,9
R113	SNV_identified	*WDR45*	3, stereotypic movements	No	No	No	Yes	Yes		N.D.
R114	SNV_identified	*STXBP1*	3, stereotypic movements	No	No	No	Yes	Yes		4
R115	SNV_identified	*ITPR1*	3, autistic feature	No	No	Yes	No	No		2,4
R120	SNV_identified	*WDR45*	2, atypical RTT	No	No	No	Yes	Yes	Influenza encephalopathy	N.D.
R122	SNV_identified	*CUX2*	3, stereotypic movements	No	No	No	No	Yes		1,2,3
R123	SNV_identified	*FOXG1*	3, microcephalus	No	No	No	No	No		N.D.
R124	SNV_identified	*SHANK3*	2, atypical RTT	No	No	No	Yes	Yes		N.D.
R127	SNV_identified	*KIF1A*	3, autistic behaivor with gait abnormalities	No	No	No	Yes	Yes	Mild developmental delay at infantile	4,5,6,7,8,9,10
R128	SNV_identified	*WDR45*	3, stereotypic movements, microcephalus	No	No	No	No	Yes		3,4
R129	SNV_identified	*CACNA1D*	3, stereotypic movements with gait abnormalities	No	No	No	Yes	Yes		N.D.
R130	SNV_identified	*CAMK2B*	3, stereotypic movements, microcephalus	No	No	No	No	Yes		3,4,7
R132	Candidate	*MAST3*	3, autistic behavior with gait abnormalities	Yes	No	No	Yes	No		3,4,9,11
R133	SNV_identified	*GABRA1*	3, autistic behavor, stereotypic movements	No	Yes	Yes	Yes	Yes	Infantile spasms at three month-of-age	1,2,3,4,10
R135	SNV_identified	*SHANK3*	3, autistic behavor with gait abnormalities	No	No	No	Yes	No		N.D.
R136	SNV_identified	*COL4A1*	3, autistic feature, stereotypic movements	No	No	No	No	Yes		4

Supplementary table S1. Diagnostic criteria for Rett syndrome (RTT) of 55 patients with variants in known and novel genes

Typical and atypical RTT were evaluated based on the main criteria for RTT in this study [2]. Supportive criteria for atypical RTT were partially available. Abbreviations: N.D., no data; SNV, single nucleotide variant; CNV, copy number variation; VUS, variants of uncertain significance.

Patient ID	Capture kit (SureSelect Human All Exon kit version)	Sequenced base (bp)	Mean depth	Covered regions (%)		
				> 5 reads	> 10 reads	> 20 reads
R002	50Mb	3704090949	110.66	97.2	96.4	94
R004_Patient1	v6	2738293353	81.81	98.1	97.6	95.7
R004_Patient2	v6	2837108719	84.76	98	97.5	95.8
R006	50Mb	4204356545	125.61	97.3	96.6	94.7
R008	v6	2670429622	79.78	98	97.5	95.6
R010_Patient1	v4	3786038604	113.11	95.9	94.5	90.4
R010_Patient2	v4	3695649497	110.41	95.8	94.4	90.4
R0014	v4	4069973828	121.59	96	94.6	91
R0015	v4	3911072574	116.85	95.8	94.4	90.5
R0016	v4	4851694116	144.95	96.1	94.9	91.9
AMU1	v4	2952284454	88.2	95.3	93.1	87
AMU3	v4	2626688060	78.42	94.9	92.2	84.7
AMU4	v4	3817383658	114.05	95.8	94.4	90.3
AMU5	v4	3630014086	108.38	95.5	93.8	89.1
SN01	v4	3933550662	117.52	95.9	94.4	90.6
SN02	v4	4070290908	121.6	95.9	94.5	90.9
SN03	v4	3908355894	116.76	95.9	94.5	90.7
SN04	v4	3813528681	113.93	95.8	94.3	90.3
SN05	v4	3757856048	112.27	95.9	94.4	90.5
SN06	v4	3856444464	115.21	95.9	94.5	90.6
SN07	v4	3174765631	94.85	95.6	93.8	88.7
SN08	v4	3617335584	108.07	95.8	94.2	89.9
SN09	v4	3904330157	116.64	95.9	94.4	90.6
SN11	v4	4031302359	120.44	95.9	94.6	91
SN12	v4	3392802503	101.36	95.7	94	89.3
SN13	v4	4032949334	120.49	95.9	94.6	90.9
SN14	v4	3857364294	115.24	95.9	94.5	90.6
SN15	v4	3629653169	108.44	95.8	94.2	90
SN16	v4	4305871744	128.64	96	94.7	91.3
SN17	v4	3658458674	109.3	95.7	94	89.7
R039_Patient1	v4	4605782320	137.6	96.3	95.3	92.4
R039_Patient2	v4	5736829917	171.39	96.4	95.6	93.5
R040_Patient1	v4	5647781103	168.73	96.5	95.7	93.8
R040_Patient2	v4	6019721174	179.84	96.4	95.6	93.6
R046	v5	4955181217	148.04	96.2	95.1	92.4
R047	v5	4135150133	123.54	96	94.7	91.2
R048	v5	4855006629	145.05	96.1	95	92.2
R049	v5	4336345033	129.55	96	94.7	91.3
R050	v5	4439183407	132.62	96	94.6	91.2
R053	v5	4394326408	131.28	96	94.6	91.2
R066	v5	4717077393	140.93	96.1	95	92
R072	v5	4632252763	138.39	96.2	95.3	93.4
R076	v5	4487942762	134.08	97.4	96.8	95.1
R078	v5	3051793184	91.17	94.2	89.4	79.7
R082	v5	2943981593	87.95	97	95.8	92.3
R091	v5	2630348641	78.58	97.2	96	91.9
R092	v5	2965753471	88.6	97.2	96.3	92.2
R093	v5	2655606406	79.34	97.1	96	93.2
R095	v5	2786061084	83.24	97.3	96.2	92.5
R096	v5	2757762704	82.39	97.1	96	92.3
R097	v5	3352003219	100.14	97.2	96.3	93.5
R104	v6	1952649879	58.34	97.5	96.2	91.8
R105	v6	2820397535	84.26	98	97.4	95.3
R106	v6	2094689063	62.58	97.9	97	93.5
R107	v6	2771793878	82.81	98.1	97.6	95.9
R108	v6	2451296100	73.23	98	97.3	94.7
R110	v6	1955631055	58.43	97.9	97	92.5
R111	v6	1889237643	56.44	97.8	96.6	91.1
R112	v6	1793048562	53.57	97.9	96.8	91.3
R113	v6	2030759768	60.67	98	97.2	93.4
R114	v6	1831118244	54.71	97.8	96.8	91.4
R115	v6	2203366131	65.83	97.9	97.2	93.8
R116	v6	2104317474	62.87	97.9	97.2	93.7
R119_Patient1	v6	1731199747	51.72	97.7	96.5	90.2
R119_Patient2	v6	2365016567	70.66	98.1	97.5	94.8
R120	v6	1796915145	53.68	97.8	96.5	90.4
R121	v6	1732903030	51.77	97.8	96.6	90
R122	v6	2285605866	68.28	98.1	97.4	94.4
R123	v6	1904331498	56.89	97.8	96.8	92
R124	v6	2319651802	69.3	97.9	97.2	94.1
R125	v6	2164559283	64.67	98	97.3	93.8
R126	v6	2080061871	62.14	97.9	97.1	93.4
R127	v6	2226328824	66.51	97.9	97.2	94.1
R128	v6	2178011691	65.07	98	97.2	94
R129	v6	2650340010	79.18	98.1	97.6	95.5
R130	v6	2265139274	67.67	98	97.3	94.3
R132	v6	2121454909	63.38	97.9	97.2	93.7
R133	v6	2143254952	64.03	97.9	97.1	93.4
R134	v6	2019811191	60.34	97.9	97.1	93.3
R135	v6	2494965949	74.54	98	97.4	95.1
R136	v6	2555166459	76.34	98	97.5	95.4
R137	v6	2184724184	65.27	98	97.2	94
Average		3215409467	96.06060976	96.88536585	95.75	92.09634146

Supplementary table S2. Whole exome sequencing (WES) performance

WES was performed in 77 families (82 affected patients and their parents). R002 and R006 were sequenced on a Genome Analyzer IIx sequencer (Illumina) with 108-bp paired-end reads. WES of the other families was performed on a HiSeq 2000 or 2500 platform with 101-bp paired-end reads.

Chr	Gene	Chr	Gene	Chr	Gene	Chr	Gene	Chr	Gene
1	*GABRD*	4	*SLC34A2*	9	*APTX*	13	*COL4A1*	19	*MCOLN1*
1	*PEX10*	4	*PHOX2B*	9	*GALT*	13	*COL4A2*	19	*CACNA1A*
1	*ATP13A2*	4	*SCARB2*	9	*PIGO*	13	*CHAMP1*	19	*C19orf12*
1	*PIGV*	4	*COQ2*	9	*EXOSC3*	14	*FOXG1*	19	*SCN1B*
1	*PPT1*	4	*MTTP*	9	*FXN*	14	*L2HGDH*	19	*ATP1A3*
1	*SLC2A1*	4	*TBCK*	9	*VPS13A*	14	*GCH1*	19	*PNKP*
1	*EIF2B3*	4	*MFSD8*	9	*AUH*	14	*KIAA0586*	19	*MYH14*
1	*ALG6*	5	*SDHA*	9	*GABBR2*	14	*SMOC1*	19	*PRKCG*
1	*NTNG1*	5	*SLC6A19*	9	*STXBP1*	14	*EIF2B2*	20	*PDYN*
1	*KCNA2*	5	*SLC6A3*	9	*SPTAN1*	14	*GALC*	20	*TGM6*
1	*AP4B1*	5	*TRIO*	9	*SETX*	14	*VRK1*	20	*PANK2*
1	*POGZ*	5	*C5orf42*	9	*TSC1*	14	*DYNC1H1*	20	*ABHD12*
1	*CHRNB2*	5	*HCN1*	9	*SURF1*	15	*UBE3A*	20	*SLC12A5*
1	*KCNJ10*	5	*NDUFS4*	9	*KCNT1*	15	*GABRB3*	20	*KCNB1*
1	*KCNH1*	5	*ERCC8*	9	*INPP5E*	15	*SPG11*	20	*ADNP*
1	*FLVCR1*	5	*NDUFAF2*	9	*GRIN1*	15	*CLN6*	20	*DPM1*
1	*RAB3GAP2*	5	*HEXB*	10	*PHYH*	15	*HEXA*	20	*CHRNA4*
1	*ADCK3*	5	*ANKRD31*	10	*ZEB1*	15	*CHRNA5*	20	*KCNQ2*
2	*EIF2B4*	5	*MEF2C*	10	*JMJD1C*	15	*WDR73*	20	*EEF1A2*
2	*NRXN1*	5	*ALDH7A1*	10	*POLR3A*	15	*POLG*	21	*SON*
2	*BCL11A*	5	*SIL1*	10	*LGI1*	15	*KIF7*	21	*DYRK1A*
2	*PEX13*	5	*PURA*	10	*TCTN3*	15	*CHD2*	21	*SIK1*
2	*SPR*	5	*GABRA1*	10	*C10orf2*	16	*TSC2*	21	*CSTB*
2	*STAMBP*	5	*GABRG2*	11	*CTSD*	16	*TBC1D24*	21	*PCNT*
2	*NPHP1*	5	*PDLIM7*	11	*TH*	16	*MGRN1*	22	*PEX26*
2	*PTPN4*	6	*NHLRC1*	11	*PGAP2*	16	*PMM2*	22	*PLA2G6*
2	*RAB3GAP1*	6	*SYNGAP1*	11	*TPP1*	16	*GRIN2A*	22	*CACNA1I*
2	*ZEB2*	6	*BTBD9*	11	*BDNF*	16	*CLN3*	22	*ADSL*
2	*NEB*	6	*PEX6*	11	*PEX16*	16	*RPGRIP1L*	22	*ACO2*
2	*SCN2A*	6	*PPP2R5D*	11	*TMEM138*	16	*GNAO1*	22	*ARSA*
2	*TTC21B*	6	*EFHC1*	11	*TMEM216*	16	*GPR56*	22	*SHANK3*
2	*SCN1A*	6	*SLC17A5*	11	*SPTBN2*	16	*FA2H*	X	*OFD1*
2	*PGAP1*	6	*RARS2*	11	*NDUFS8*	16	*TMEM231*	X	*PIGA*
2	*SATB2*	6	*AHI1*	11	*FOLR1*	16	*TUBB3*	X	*CDKL5*
2	*TMEM237*	6	*PEX3*	11	*MRE11A*	17	*PAFAH1B1*	X	*PDHA1*
2	*BCS1L*	6	*EPM2A*	11	*ATM*	17	*PIGL*	X	*ARX*
2	*CYP27A1*	6	*GRM1*	11	*PTS*	17	*B9D1*	X	*XK*
2	*KIF1A*	6	*SYNE1*	11	*FOXRED1*	17	*PEX12*	X	*DDX3X*
3	*ITPR1*	7	*DDC*	12	*CACNA1C*	17	*PGAP3*	X	*CASK*
3	*SETD5*	7	*KCTD7*	12	*KCNA1*	17	*GRN*	X	*SLC35A2*
3	*SLC6A1*	7	*PEX1*	12	*PEX5*	17	*EFTUD2*	X	*WDR45*
3	*ZNF620*	7	*ASNS*	12	*GRIN2B*	17	*GFAP*	X	*IQSEC2*
3	*ANO10*	7	*AP4M1*	12	*DNM1L*	17	*KANSL1*	X	*ARHGEF9*
3	*QARS*	7	*RELN*	12	*PRICKLE1*	17	*PNPO*	X	*OPHN1*
3	*ARL13B*	7	*DLD*	12	*TUBA1A*	17	*TSEN54*	X	*MED12*
3	*CP*	7	*CEP41*	12	*SCN8A*	17	*SGSH*	X	*ATP7A*
3	*TBL1XR1*	7	*CNTNAP2*	12	*CEP290*	17	*TBCD*	X	*PGK1*
3	*EIF2B5*	8	*CLN8*	12	*POLR3B*	18	*PIEZO2*	X	*PCDH19*
3	*ALG3*	8	*RHOBTB2*	12	*MVK*	18	*AFG3L2*	X	*PLP1*
3	*EIF4G1*	8	*KAT6A*	12	*TCTN1*	18	*NPC1*	X	*SMARCA1*
3	*CLCN2*	8	*TTPA*	12	*ACADS*	18	*EPG5*	X	*SLC9A6*
3	*OPA1*	8	*CSPP1*	12	*EIF2B1*	18	*TCF4*	X	*FMR1*
4	*HTT*	8	*CPA6*	12	*TCTN2*	18	*PIGN*	X	*ABCD1*
4	*WFS1*	8	*PEX2*	13	*SACS*	19	*NDUFS7*	X	*MECP2*
4	*CC2D2A*	8	*TMEM67*	13	*ATP7B*	19	*SEMA6B*	X	*FLNA*
4	*QDPR*	8	*KCNQ3*	13	*CLN5*	19	*LONP1*		
4	*SEPSECS*	9	*VLDLR*	13	*NALCN*	19	*TUBB4A*		

Supplementary table S3. Gene list for analysis using Nord's method

A total of 283 genes (259 autosomal and 24 X-chromosomal) are causative and/or candidates for neurodevelopmental disorders, including intellectual disability, developmental delay, Rett syndrome, epilepsy, and metabolic disorders. We selected 262 genes from among those registered in Human Gene Mutation Database and added 21 candidate genes through a review of the literature on Rett syndrome.

Family ID	Phenotype group	*Gene*	Accession number	Variants	Affected proteins	Inheritance	Allele frequency		Prediction scores				NGS analysis
							ExAC	gnomAD	SIFT	PolyPhen2 (HVAR)	Mutation Taster	CADD	
SN07	2	*UBE3A*	NM_130838.1	c.845_863delinsT	p.Ala282_Lys288 delinsVal	Unknown	0	0	ND	ND	ND	ND	Case only
SN16	2	*PCDH19*	NM_001105243	c.617T>G	p.Phe206Cys	Unknown	0.00002303	0.000005709	0.002	0.819	1	24.1	Case only
R016	3	*TCF4*	NM_001243234.1	c.1291C>T	p.Leu431Phe	Not maternal	0	0	0.001	1	1	30	Case only
R048	1	*GRIN2B*	NM_000834.3	c.3296G>A	p.Arg1099His	Not maternal	0	0	ND	0.98	1	25.5	Case only

Supplementary table S4. Variants of uncertain significance in known genes

In SN07, SN16, R016, and R048, four variants of uncertain significance were found, a status that was partly due to familial samples being unavailable. In the phenotype group column, 1, 2, and 3 indicate typical RTT, atypical RTT, and RTT-like phenotypes, respectively. *PCDH19* is X-linked and *UBE3A*, *TCF4*, and *GRIN2B* are autosomal.

ID		SN01	R095	R096	R132
Gene		*ATP6V0A1*	*USP8*	*NCOR2*	*MAST3*
Gender		Female	Male	Female	Female
Diagnosis		Atypical RTT	Atypical RTT Optic atrophy	Microcephaly	Epilepsy (Dravet syndrome-like)
Current (or last follow up) age		8y3m	7y9m	8y	7y8m
Peak of skills	Age	6y3m	7y9m (current age)	8y (current age)	7y8m (current age)
	DQ	DQ: 12, profound	DQ <20, profound	Severe ID (no DQ data)	DQ <20, profound
	Motor skills	Moter DQ: 9	Roll over	Unsteady gait	Run at a trot, pinch and scrabble
	Language	Language DQ: 9	Unacquired	Unacquired	Unacquired
Autistic regression		Yes	No	No	Yes
Physical growth	Height	118.1 cm (-1.4 S.D.)	109.4 cm (-2.6 S.D)	93.5 cm (-2.7 S.D.)	121.0 cm (-0.2 S.D.)
	Weight	21 kg (-1.0 S.D.)	17.9 kg (-1.5 S.D.)	14.3 kg (-1.2 S.D.)	21.0 kg (-0.7 S.D.)
	Head circumference	48 cm (-2.7 S.D.)	48.4 cm (-2.4 S.D.)	46.0 cm (-2.7 S.D.)	50.0 cm (-1.1 S.D.)
	Age	8y2m	7y6m	5y	7y6m
Development	Head control	Delayed	Delayed	5m	4m
	Sitting	11m	No	10m	8m
	Walking	1y10m	No	6y (unstable)	2y7m
	Meaningful words	3y6m	No	No	No
Facial or somatic dysmorphisms		No	No	No	Yes, saddle nose, wide mouse
Seizures	Age of onset	7m	4y8m	No	12m
	Types of seizures	Severe, partial seizure, generalized seizure	Partial seizure	No	Tonic-clonic, atonic, and tonic, often in clusters with fever. Non-convlusive status epilepticus.
Involuntary movements		Yes, stereotypy	Choreic movements	No	No
Behavioral abnormality (ASD, ADHD etc.)		Yes, hyperactivity autistic feature	Screaming	No	ASD
Dysautonomia	arrhythmia	EKG unexamined	No	No	No
	gastrointestinal problems	Unkown	Constipation	No	No
	breath holding	Yes with epileptic seizure	Yes	No	No
	peripheral coldness	Unkown	Yes	No	No
MRI findings	Findings	No data	Corpus callosum hypoplasia, delay of myelination	Enlargesd lateral ventricle, low white matter volumee, cortical dysplasia (pachygyria)	No abnormal findings
	Age	11m	6y6m	3y	2y

Supplementary table S5. Clinical features of patients with variants in novel four genes

In SN01, R095, R096 and R132, candidate variants in novel four genes (*ATP6V0A1, USP8, NCOR2* and *MAST3*) were found. Developmental quotient (DQ) were evaluated using Kyoto scale of psychological development test. Abbreviations: S.D.; standard deviation; y, years; m, months; ASD, autism spectrum disorder; ID, intellectual disability.

Gene Ontology term	Target genes (50 genes)		Reference genes (19663 genes)		Corrected P-value	False discovery rate	Genes annotated to the term
	Cluster genes	frequency	Cluster genes	frequency			
regulation of membrane potential	19	38.0%	420	2.1%	2.24E-16	0.00%	*MEF2C, CACNA1D, GABRA1, CACNA1G, NALCN, CUX2, HCN1, KCNJ10, GRIA3, SHANK3, GABRB2, KCNA2, GRIN2B, GABRD, SCN2A, MECP2, SCN8A, SCN1A, GRIN2A*
ion transport	25	50.0%	1600	8.1%	9.17E-12	0.00%	*MEF2C, ATP6V0A1, CACNA1D, GABRA1, CACNA1G, NALCN, CLTC, HCN1, STXBP1, KCNJ10, GRIA3, SHANK3, GABRB2, CTNNB1, KCNA2, CAMK2B, GRIN2B, SLC35A2, GABRD, SCN2A, ITPR1, SCN8A, SLC6A1, SCN1A, GRIN2A*
chemical synaptic transmission	18	36.0%	644	3.3%	1.11E-11	0.00%	*MEF2C, GABRA1, CACNA1G, PPT1, CUX2, STXBP1, KCNJ10, GRIA3, SHANK3, GABRB2, CTNNB1, CAMK2B, GRIN2B, GABRD, MECP2, SYNGAP1, SLC6A1, GRIN2A*
anterograde trans-synaptic signaling	18	36.0%	644	3.3%	1.11E-11	0.00%	*MEF2C, GABRA1, CACNA1G, PPT1, CUX2, STXBP1, KCNJ10, GRIA3, SHANK3, GABRB2, CTNNB1, CAMK2B, GRIN2B, GABRD, MECP2, SYNGAP1, SLC6A1, GRIN2A*
trans-synaptic signaling	18	36.0%	648	3.3%	1.24E-11	0.00%	*MEF2C, GABRA1, CACNA1G, PPT1, CUX2, STXBP1, KCNJ10, GRIA3, SHANK3, GABRB2, CTNNB1, CAMK2B, GRIN2B, GABRD, MECP2, SYNGAP1, SLC6A1, GRIN2A*
synaptic signaling	18	36.0%	649	3.3%	1.27E-11	0.00%	*MEF2C, GABRA1, CACNA1G, PPT1, CUX2, STXBP1, KCNJ10, GRIA3, SHANK3, GABRB2, CTNNB1, CAMK2B, GRIN2B, GABRD, MECP2, SYNGAP1, SLC6A1, GRIN2A*
ion transmembrane transport	21	42.0%	1114	5.7%	8.43E-11	0.00%	*MEF2C, ATP6V0A1, CACNA1D, GABRA1, CACNA1G, NALCN, HCN1, KCNJ10, GRIA3, SHANK3, GABRB2, KCNA2, GRIN2B, SLC35A2, GABRD, SCN2A, ITPR1, SCN8A, SLC6A1, SCN1A, GRIN2A*
nervous system development	26	52.0%	2237	11.4%	2.16E-09	0.00%	*TCF4, MEF2C, COL4A1, EIF2B2, PPT1, FOXG1, DNMT3A, CUX2, HCN1, STXBP1, KCNJ10, SHANK3, KIF1A, GABRB2, CTNNB1, KCNA2, CDKL5, CAMK2B, GRIN2B, UBE3A, SCN2A, MECP2, SCN8A, SATB2, SYNGAP1, GRIN2A*
cell-cell signaling	22	44.0%	1585	8.1%	8.19E-09	0.00%	*MEF2C, CACNA1D, GABRA1, CACNA1G, PPT1, CLTC, CUX2, STXBP1, KCNJ10, GRIA3, SHANK3, GABRB2, CTNNB1, CAMK2B, GRIN2B, GABRD, ITPR1, MECP2, SYNGAP1, SLC6A1, USP8, GRIN2A*
cation transport	19	38.0%	1109	5.6%	1.02E-08	0.00%	*MEF2C, ATP6V0A1, CACNA1D, CACNA1G, NALCN, CLTC, HCN1, KCNJ10, SHANK3, CTNNB1, KCNA2, CAMK2B, GRIN2B, SCN2A, ITPR1, SCN8A, SCN1A, SLC6A1, GRIN2A*
inorganic ion transmembrane transport	17	34.0%	829	4.2%	1.05E-08	0.00%	*ATP6V0A1, CACNA1D, GABRA1, CACNA1G, NALCN, HCN1, KCNJ10, GABRB2, KCNA2, GRIN2B, GABRD, ITPR1, SCN2A, SCN8A, SCN1A, SLC6A1, GRIN2A*
metal ion transport	17	34.0%	870	4.4%	2.25E-08	0.00%	*ATP6V0A1, CACNA1D, CACNA1G, NALCN, CLTC, HCN1, KCNJ10, CTNNB1, KCNA2, CAMK2B, GRIN2B, ITPR1, SCN2A, SCN8A, SCN1A, SLC6A1, GRIN2A*
transmembrane transport	21	42.0%	1505	7.7%	2.73E-08	0.00%	*MEF2C, ATP6V0A1, CACNA1D, GABRA1, CACNA1G, NALCN, HCN1, KCNJ10, GRIA3, SHANK3, GABRB2, KCNA2, GRIN2B, SLC35A2, GABRD, SCN2A, ITPR1, SCN8A, SLC6A1, SCN1A, GRIN2A*
cation transmembrane transport	16	32.0%	832	4.2%	1.29E-07	0.00%	*MEF2C, ATP6V0A1, CACNA1D, CACNA1G, NALCN, HCN1, KCNJ10, SHANK3, KCNA2, GRIN2B, ITPR1, SCN2A, SCN8A, SCN1A, SLC6A1, GRIN2A*
regulation of ion transport	14	28.0%	621	3.2%	3.09E-07	0.00%	*CTNNB1, KCNA2, MEF2C, CACNA1D, CACNA1G, CAMK2B, NALCN, SCN2A, HCN1, SCN8A, STXBP1, KCNJ10, SCN1A, SHANK3*
regulation of synaptic plasticity	9	18.0%	174	0.9%	5.49E-07	0.00%	*MEF2C, CAMK2B, GRIN2B, MECP2, STXBP1, KCNJ10, SYNGAP1, SHANK3, GRIN2A*
regulation of biological quality	29	58.0%	3694	18.8%	9.22E-07	0.00%	*HDAC8, MEF2C, ATP6V0A1, CACNA1D, GABRA1, CACNA1G, PPT1, NALCN, CUX2, HCN1, STXBP1, KCNJ10, GRIA3, SHANK3, GABRB2, CTNNB1, KCNA2, CDKL5, CAMK2B, RHOBTB2, GRIN2B, GABRD, SCN2A, ITPR1, MECP2, SCN8A, SYNGAP1, SCN1A, GRIN2A*
regulation of postsynaptic membrane potential	8	16.0%	130	0.7%	1.38E-06	0.00%	*CUX2, MECP2, MEF2C, GABRA1, GRIA3, SHANK3, GRIN2B, GRIN2A*
neurogenesis	19	38.0%	1524	7.8%	2.31E-06	0.00%	*TCF4, MEF2C, EIF2B2, PPT1, FOXG1, DNMT3A, CUX2, HCN1, STXBP1, KCNJ10, SHANK3, GABRB2, CTNNB1, CDKL5, CAMK2B, MECP2, SATB2, SYNGAP1, GRIN2A*
localization	37	74.0%	6468	32.9%	3.41E-06	0.00%	*PPT1, HCN1, GRIA3, GABRB2, CDKL5, CAMK2B, GRIN2B, GABRD, ITPR1, GRIN2A, HDAC8, CACNA1D, ATP6V0A1, MEF2C, CACNA1G, GABRA1, NALCN, FOXG1, CLTC, CUX2, STXBP1, KCNJ10, WDR45, SHANK3, KIF1A, CTNNB1, KCNA2, RHOBTB2, SLC35A2, UBE3A, SCN2A, MECP2, SCN8A, SATB2, SYNGAP1, SCN1A, SLC6A1*
inorganic cation transmembrane transport	14	28.0%	748	3.8%	3.43E-06	0.00%	*KCNA2, ATP6V0A1, CACNA1D, CACNA1G, GRIN2B, NALCN, SCN2A, ITPR1, HCN1, SCN8A, KCNJ10, SLC6A1, SCN1A, GRIN2A*
nervous system process	18	36.0%	1385	7.0%	3.72E-06	0.00%	*MEF2C, CACNA1D, GABRA1, PPT1, CUX2, KCNJ10, GRIA3, SHANK3, GABRB2, KCNA2, GRIN2B, GABRD, SCN2A, MECP2, SCN8A, SYNGAP1, SCN1A, GRIN2A*
system process	21	42.0%	2087	10.6%	1.11E-05	0.00%	*MEF2C, CACNA1D, GABRA1, CACNA1G, PPT1, CUX2, KCNJ10, GRIA3, SHANK3, GABRB2, KCNA2, CAMK2B, GRIN2B, GABRD, SCN2A, ITPR1, MECP2, SCN8A, SYNGAP1, SCN1A, GRIN2A*
regulation of ion transmembrane transport	11	22.0%	438	2.2%	1.11E-05	0.00%	*KCNA2, MEF2C, CACNA1D, CACNA1G, NALCN, SCN2A, SCN8A, HCN1, KCNJ10, SHANK3, SCN1A*
excitatory postsynaptic potential	7	14.0%	109	0.6%	1.20E-05	0.00%	*CUX2, MECP2, MEF2C, GRIA3, SHANK3, GRIN2B, GRIN2A*
regulation of synapse structure or activity	8	16.0%	175	0.9%	1.45E-05	0.00%	*CUX2, MECP2, MEF2C, SYNGAP1, PPT1, SHANK3, CAMK2B, GRIN2B*
chemical synaptic transmission, postsynaptic	7	14.0%	115	0.6%	1.75E-05	0.00%	*CUX2, MECP2, MEF2C, GRIA3, SHANK3, GRIN2B, GRIN2A*
modulation of chemical synaptic transmission	10	20.0%	353	1.8%	1.84E-05	0.00%	*MEF2C, CAMK2B, GRIN2B, CUX2, MECP2, STXBP1, KCNJ10, SYNGAP1, SHANK3, GRIN2A*
regulation of trans-synaptic signaling	10	20.0%	354	1.8%	1.89E-05	0.00%	*MEF2C, CAMK2B, GRIN2B, CUX2, MECP2, STXBP1, KCNJ10, SYNGAP1, SHANK3, GRIN2A*
membrane depolarization during action potential	5	10.0%	36	0.2%	3.40E-05	0.00%	*SCN2A, SCN8A, CACNA1D, CACNA1G, SCN1A*
neuron differentiation	16	32.0%	1291	6.6%	7.04E-05	0.00%	*TCF4, GABRB2, CTNNB1, MEF2C, CDKL5, PPT1, CAMK2B, FOXG1, DNMT3A, CUX2, MECP2, HCN1, SATB2, STXBP1, SYNGAP1, SHANK3*
neuron apoptotic process	8	16.0%	215	1.1%	7.19E-05	0.00%	*SCN2A, GABRB2, CTNNB1, MECP2, MEF2C, STXBP1, SYNGAP1, PPT1*
transport	31	62.0%	5059	25.7%	7.50E-05	0.00%	*MEF2C, ATP6V0A1, CACNA1D, GABRA1, CACNA1G, PPT1, NALCN, CLTC, CUX2, HCN1, STXBP1, KCNJ10, GRIA3, SHANK3, KIF1A, GABRB2, CTNNB1, KCNA2, CAMK2B, RHOBTB2, GRIN2B, SLC35A2, GABRD, UBE3A, SCN2A, ITPR1, MECP2, SCN8A, SLC6A1, SCN1A, GRIN2A*
regulation of transmembrane transport	11	22.0%	530	2.7%	7.86E-05	0.00%	*KCNA2, MEF2C, CACNA1D, CACNA1G, NALCN, SCN2A, SCN8A, HCN1, KCNJ10, SHANK3, SCN1A*
monovalent inorganic cation transport	11	22.0%	536	2.7%	8.81E-05	0.00%	*KCNA2, ATP6V0A1, CACNA1D, CACNA1G, NALCN, SCN2A, SCN8A, HCN1, KCNJ10, SLC6A1, SCN1A*
neuron death	9	18.0%	316	1.6%	9.93E-05	0.00%	*GABRB2, CTNNB1, MEF2C, PPT1, GRIN2B, SCN2A, MECP2, STXBP1, SYNGAP1*

Supplementary table S6. Gene Ontology (GO) term analysis for 50 genes related to RTT-like phenotypes

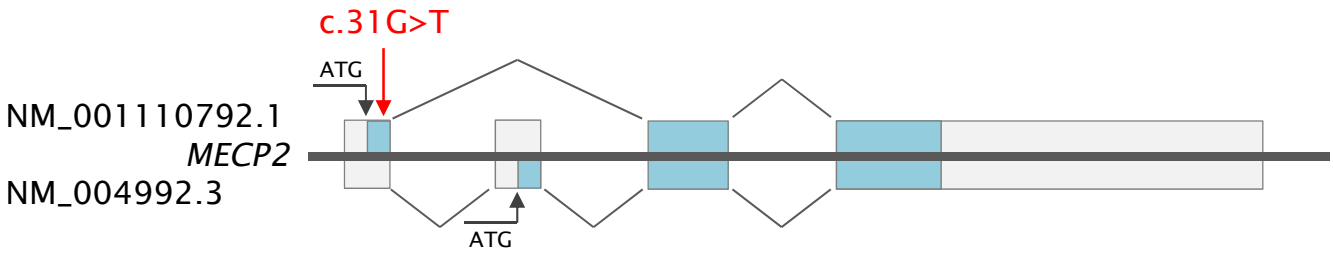
The GO terms of 50 genes that were reported in patients with RTT-like phenotypes in previous or our studies, enriched in ion transport ($9.17E^{-12}$), synaptic signaling ($1.27E^{-11}$), or nervous system development ($2.16E^{-9}$) in the category of molecular function, with comparison to 19,663 reference genes regarding 475,079 codes using GO term finder (https://go.princeton.edu/cgi-bin/GOTermFinder). The p-value was obtained upon Bonferroni correction.

Symbol	Gene	Neurodevelopmental disorders registered in HGMD (2018.2)
IRF2BP2	Interferon regulatory factor 2 binding protein 2	-
EIF2B1	Eukaryotic translation initiation factor 2B subunit alpha	Leukoencephalopathy with vanishing white matter
EIF2B4	Eukaryotic translation initiation factor 2B subunit delta	Leukoencephalopathy with vanishing white matter
TCIRG1	T cell immune regulator 1, ATPase H+ transporting V0 subunit A3	- (osteopetrosis)
ATP6V0A2	ATPase H+ transporting V0 subunit A2	-
MRI1	Methylthioribose-1-phosphate isomerase 1	Infantile epilepsy with severe cystic degeneration of the brain
ATP6V0A4	ATPase H+ transporting V0 subunit A4	- (renal tubular acidosis)
SLC35A3	Solute carrier family 35 member A3	Autism spectrum disorder / epilepsy
SMG5	SMG5, nonsense mediated mRNA decay factor	-
SMC3	Structural maintenance of chromosomes 3	Cornelia de Lange syndrome
CKM	Creatine kinase, M-type	-
GFI1	Growth factor independent 1 transcriptional repressor	-
SLC35A1	Solute carrier family 35 member A1	-
SLC35A5	Solute carrier family 35 member A5	-
DNMT3L	DNA methyltransferase 3 like	-
IRF2BP1	Interferon regulatory factor 2 binding protein 1	-
SCN5A	Sodium voltage-gated channel alpha subunit 5	- (long QT syndrome)
CLTCL1	Clathrin, heavy polypeptide-like	Autism specturm disorder / intellectual disability
SCN9A	Sodium voltage-gated channel alpha subunit 9	Autism spectrum disorder / epilepsy
SCN11A	Sodium voltage-gated channel alpha subunit 11	Autism spectrum disorder

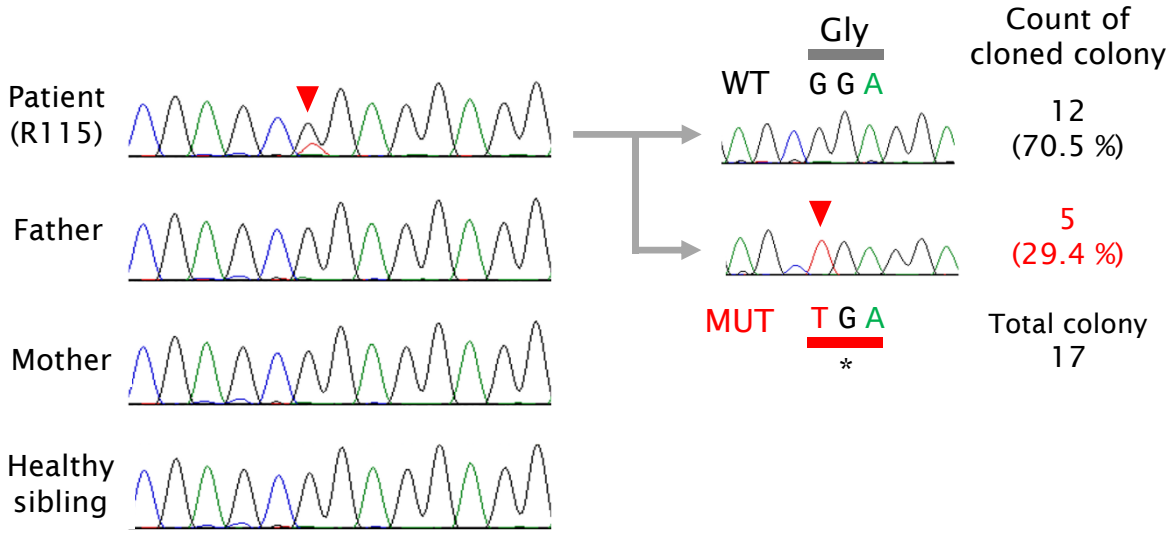
Supplementary table S7. Interactive gene network analysis indicated other related genes

Interactive gene network analysis with GeneMANIA (https://genemania.org/) newly picked up 20 related genes including 11 known genes for neurodevelopmental disorders and non-neurological diseases (in parentheses).

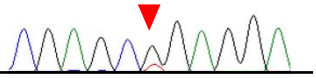
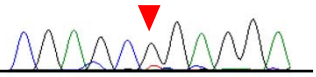
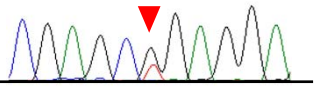
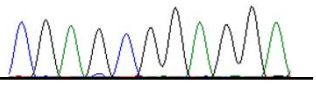
a



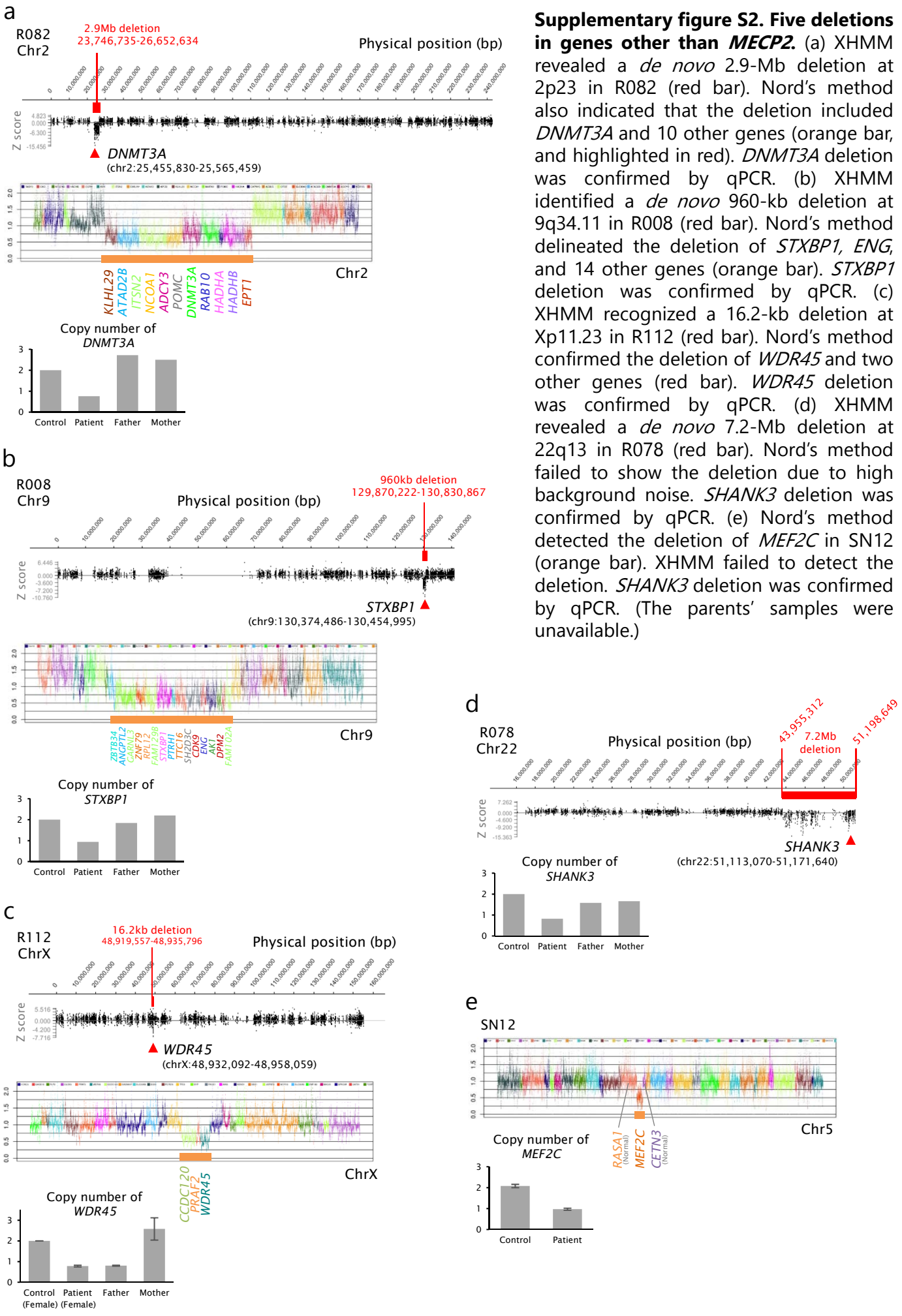
b



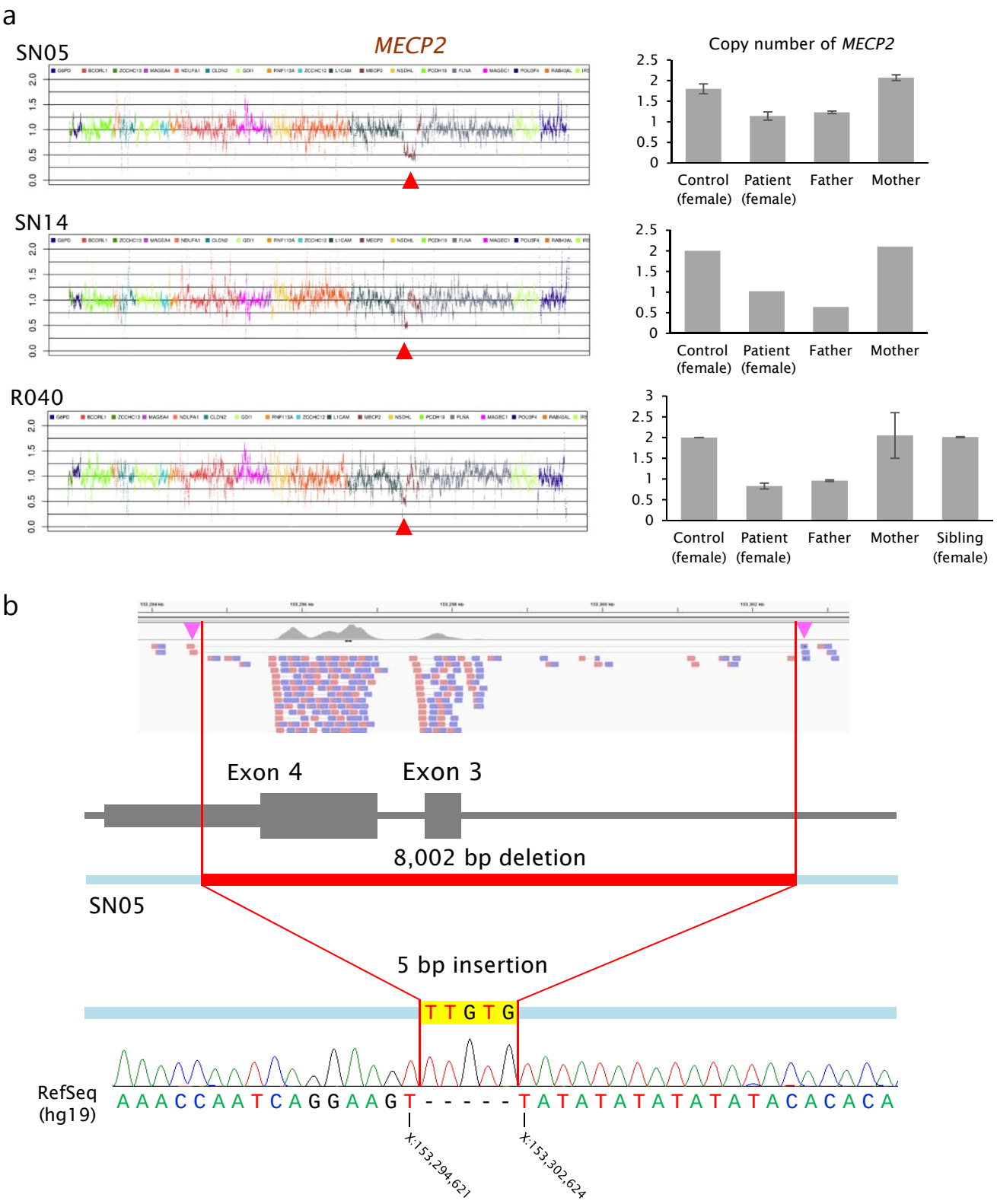
c

Sample origin	Depth	G (WT)	T (MUT)	Other substitutions				Electropherogram
				C	A	del	Ins	
Blood	3092	2179 (70%)	909 (29%)	3	1	0	2	
Saliva	4079	2806 (69%)	1259 (31%)	4	10	0	3	
Nail	13475	8052 (60%)	5374 (40%)	33	16	5	35	
Hair	2574	2514 (98%)	47 (2%)	12	1	1	0	

Supplementary figure S1. Mosaic nonsense *MECP2* mutation at exon 1 (c.31G>T based on NM_001110792.1) in R105 (male) with RTT. (a) *MECP2* consists of four exons; it has two known splicing variations, with (NM_004992.3) and without exon 2 (NM_001110792.1), referred to as human MeCP2 transcript. (b) Sanger sequencing of the male proband shows a heterozygous nonsense mutation at *MECP2* exon 1. Normal copy number of *MECP2* was confirmed using qPCR (data not shown). TA cloning and Sanger sequencing for samples derived from blood showed 29.4% mosaic mutation (5/17 cloned colonies). (c) Deep sequencing of PCR products harboring the variant confirmed variant allele frequency of 2%–40% in four different tissues (blood leukocytes, saliva, nails, and hair roots) of the patient.

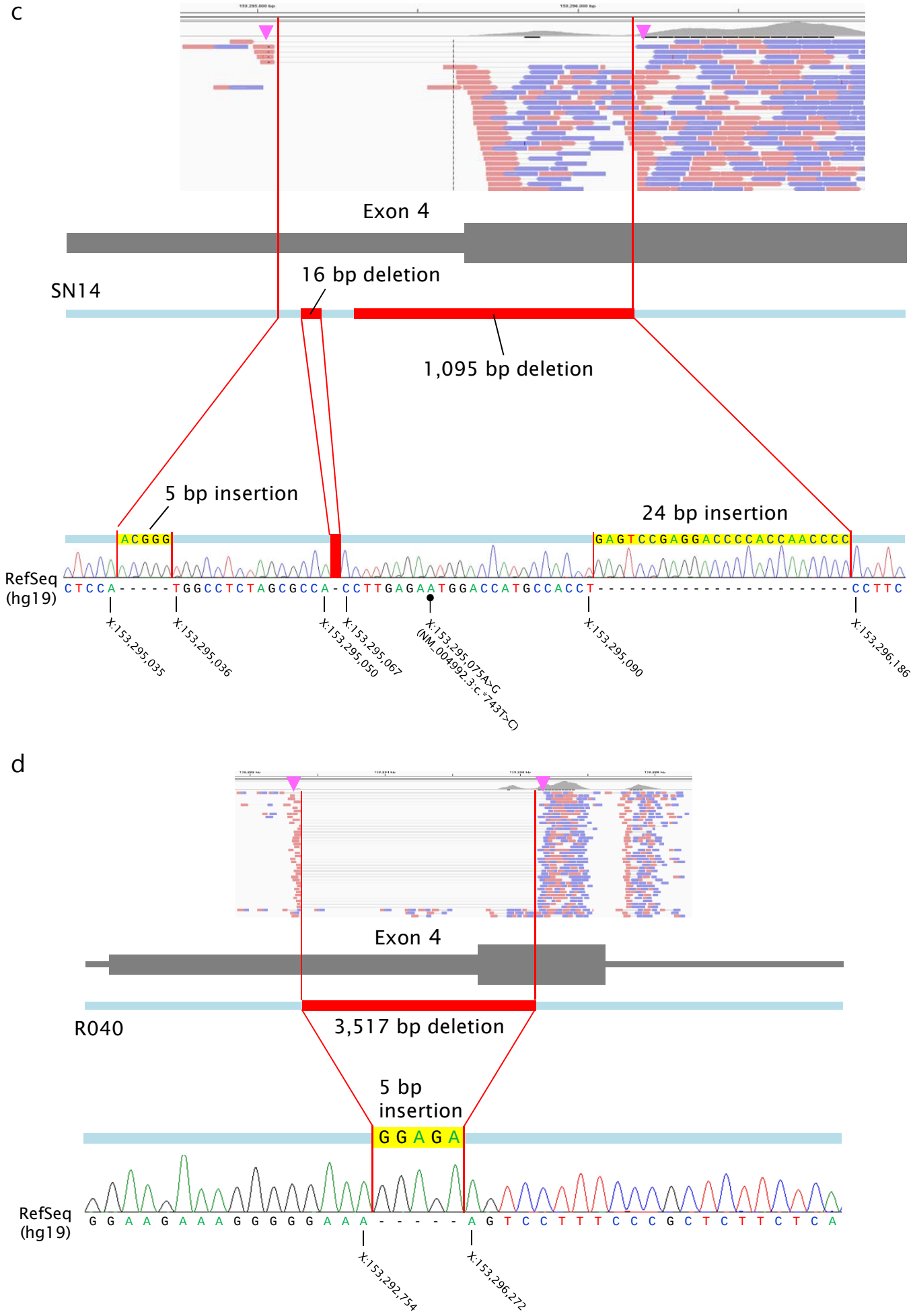


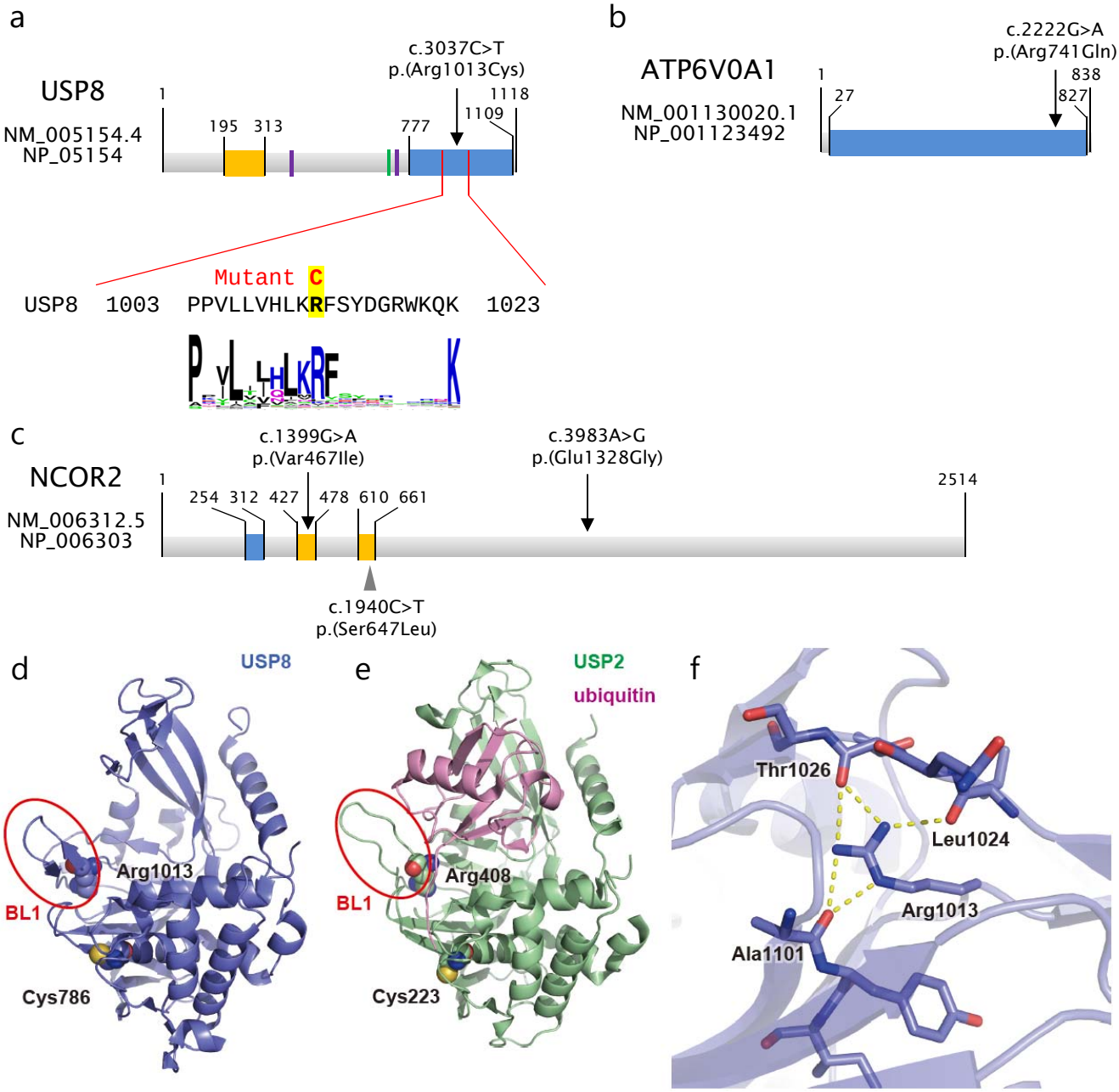
Supplementary figure S2. Five deletions in genes other than *MECP2*. (a) XHMM revealed a *de novo* 2.9-Mb deletion at 2p23 in R082 (red bar). Nord's method also indicated that the deletion included *DNMT3A* and 10 other genes (orange bar, and highlighted in red). *DNMT3A* deletion was confirmed by qPCR. (b) XHMM identified a *de novo* 960-kb deletion at 9q34.11 in R008 (red bar). Nord's method delineated the deletion of *STXBP1, ENG*, and 14 other genes (orange bar). *STXBP1* deletion was confirmed by qPCR. (c) XHMM recognized a 16.2-kb deletion at Xp11.23 in R112 (red bar). Nord's method confirmed the deletion of *WDR45* and two other genes (red bar). *WDR45* deletion was confirmed by qPCR. (d) XHMM revealed a *de novo* 7.2-Mb deletion at 22q13 in R078 (red bar). Nord's method failed to show the deletion due to high background noise. *SHANK3* deletion was confirmed by qPCR. (e) Nord's method detected the deletion of *MEF2C* in SN12 (orange bar). XHMM failed to detect the deletion. *SHANK3* deletion was confirmed by qPCR. (The parents' samples were unavailable.)



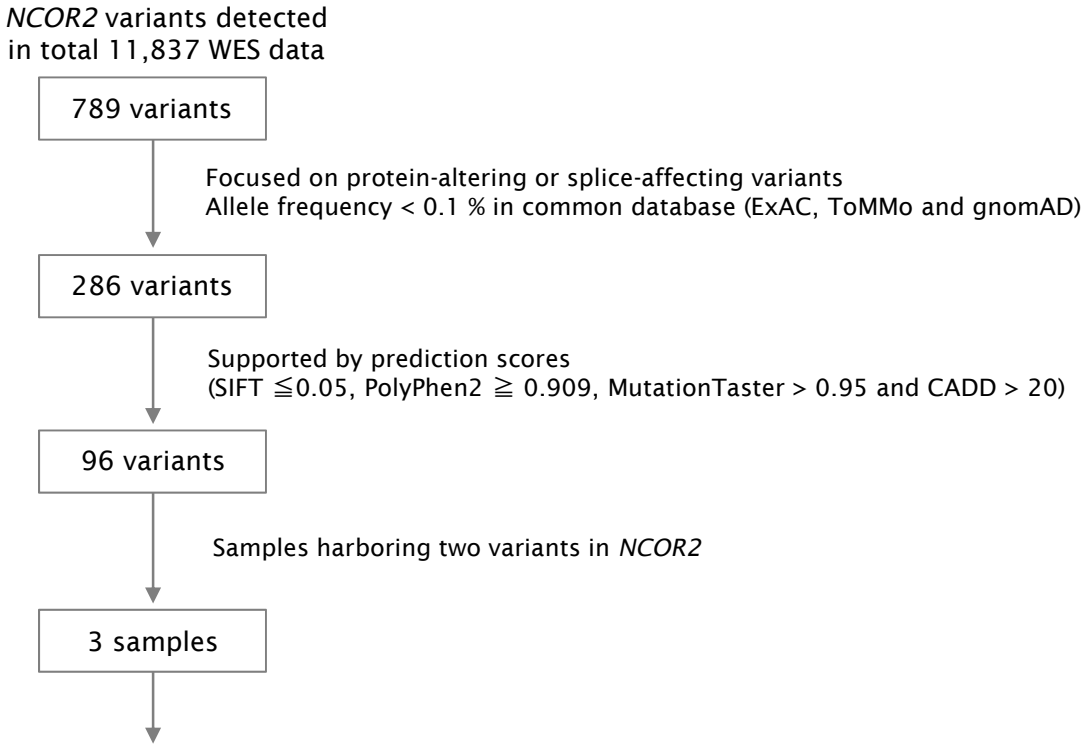
Supplementary figure S3. Partial *MECP2* deletions in SN05, SN14, and R040. (a) Nord's method successfully detected partial *MECP2* deletions in SN05, SN14, and R040 (each XHMM was negative, not shown). The *de novo* deletion was confirmed in each case by qPCR. In R040, the affected sibling carrying a normal *MECP2* copy showed a different phenotype (epilepsy) from the proband. (b) IGV demonstrated two discordant read pairs, indicating a possible deletion (pink arrowhead). Breakpoint PCR and Sanger sequencing confirmed an 8,002-bp deletion (red bar) with a 5-bp insertion (TTGTG, highlighted yellow) involving exon 3 and part of exon 4 of *MECP2*. (c) IGV demonstrated five discordant read pairs, which indicated an abnormal insert size (pink arrowhead). Breakpoint PCR and Sanger sequencing revealed 1,095- and 16-bp deletions (red bar) with 24- and 5-bp insertions (highlighted yellow) including part of exon 4. (d) IGV demonstrated various discordant read pairs, indicating a possible deletion (pink arrowhead). Breakpoint PCR and Sanger sequencing revealed a 3,517-bp deletion (red bar) with a 5-bp insertion (GGAGA, highlighted yellow) involving part of exon 4.

Supplementary figure S3 (continued)

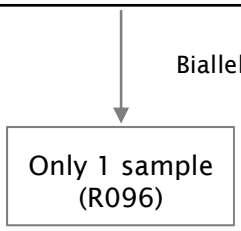




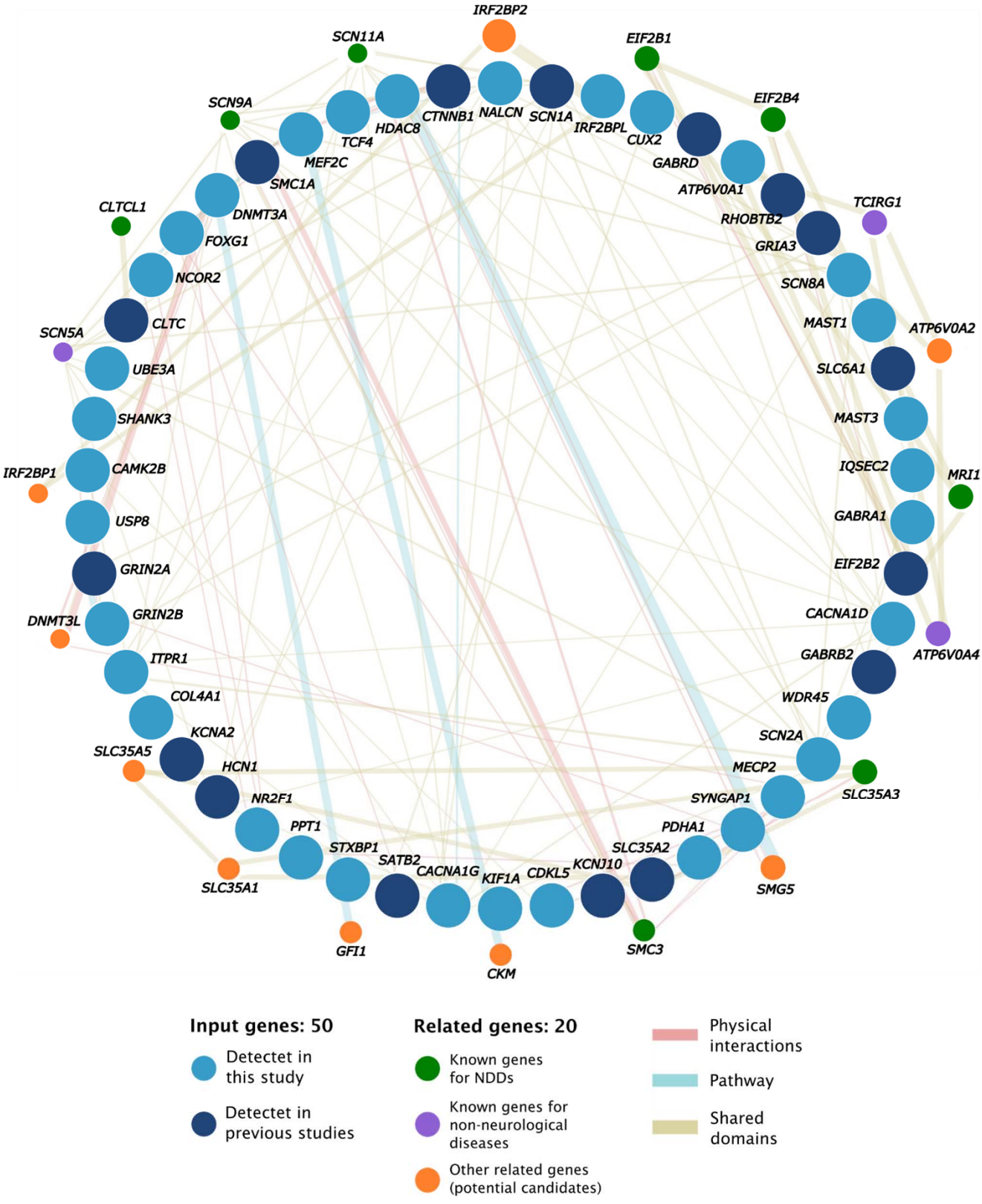
Supplementary figure S4. Schematic presentation of candidate variants in novel genes and structural role of Arg1013 of USP8. (a) Functional domains of novel candidate genes based on UniProtKB (http://www.uniprot.org/) and Prosite (https://prosite.expasy.org/) are shown. Schematic presentation of USP8 protein. Two colored squares indicate Rhodanese domain (orange), SH3-binding motif (residues 405–413 and 738–746, purple), 14-3-3 binding motif (residues 715–720, green), and deubiquitinase catalytic domain (residues 777–1109, blue). p.Arg1013Cys occurred at the conserved amino acid in the deubiquitinase catalytic domain of the USP8 protein (black arrow). Sequence logo that was established from 356 ubiquitin-specific protease domains in Prosite (https://prosite.expasy.org) indicates high conservation of this arginine among several proteins with the same domain. (b) Schematic presentation of ATP6V0A1 shows that the V-type ATPase domain covers the entire protein. (c) NCOR2 protein with three colored squares exhibits a region that interacts with SIN3A/B (residues 254–312, blue) and two SANT domains (residues 427–478 and 610–661, orange). The reported variants (c.1940C>T, gray arrowhead) and novel variants (c.1399G>A and c.3983A>G, black arrow) found in this study are shown. (d) Crystal structure of USP8 (PDB ID 2GFO). Structural figures were prepared with Pymol (http://www.pymol.org). Arg1013 and catalytic Cys786 are shown as van der Waals spheres (nitrogen, oxygen, and sulfur are colored in blue, red, and yellow, respectively). BL1 (see text) is labeled with a red ellipse. (e) Crystal structure of USP2 bound with ubiquitin (PDB ID 2HD5). Arg408 and Cys223 (corresponding to Arg1013 and Cys786 of USP8, respectively) are shown as van der Waals spheres [the color pattern is the same as in (d)]. BL1 is labeled with a red ellipse. (f) Close-up view of the hydrogen bonds involving Arg1013 of USP8.



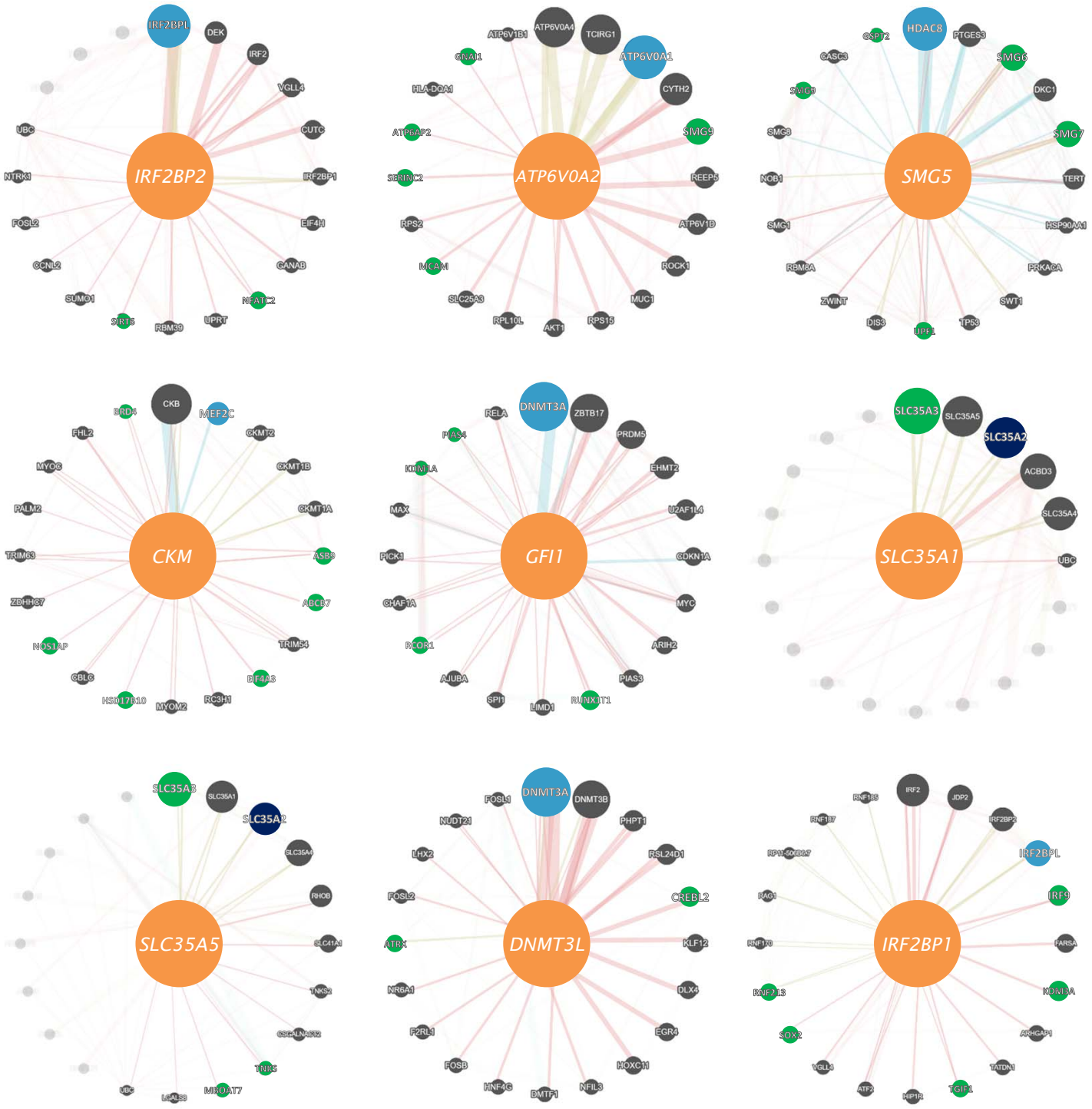
Sample_ID	Status	Variant (NM_006312.5)	Protein	Genotype	Depth count (WT : ALT)
R096	Affected	c.3983A>G	p.E1328G	Het	29:22
		c.1399G>A	p.V467I	Het	33:24
E1089 patient	Affected	c.1024A>C	p.K342Q	Het	61:50
		c.6904A>G	p.N2302D	Het	27:26
E1089 father	Unaffected	c.1024A>C	p.K342Q	Het	84:109
		c.6904A>G	p.N2302D	Het	26:39



Supplementary figure S5. The prevalence of biallelic *NCOR2* variants in our in-house WES data. In a total of 11,837 sets of in-house WES storage data (including both affected and unaffected cases in relation to various rare diseases), 789 variants in *NCOR2* were found. We focused on protein-altering (or splice-affecting) variants with an allele frequency of <0.1% in common databases including ExAC, ToMMo, and gnomAD. Among 96 variants with pathogenic prediction scores [SIFT ≤ 0.05, PolyPhen2 (HVAR) ≥ 0.909, MutationTaster > 0.95, and CADD > 20], only three samples harbored two variants in *NCOR2*. Two of these three samples were a patient (included in an epilepsy cohort) and her father, indicating that their two variants (c.1024A>C and c.6904A>G) are in a paternal allele. Only R096 (in the current study) harbored biallelic variants in *NCOR2* (0.0084%, 1/11,837).



Supplementary figure S6. The chord diagram of interactive gene network analysis (another style of Figure 2c). Fifty genes related to RTT-like phenotypes were selected, including 30 known and 4 novel genes in this study (with blue circles), and 16 genes reported with solid evidence in previous studies (dark blue circles) [1, 3-5, 18, 19]. Interactive gene networks were analyzed using three networks (physical interactions, pathways, and shared protein domains) of GeneMANIA (https://genemania.org/). Genes are arranged in a clockwise manner from the top according to their strength of interaction.



Supplementary figure S7. Interactive gene network analysis of nine potential candidate genes. Each of nine potential candidates indicated strong networks with genes related to RTT-like phenotypes and other neurodevelopmental disorders (NDDs). The genes detected in this study (blue circles) or previous studies (dark blue circles) had higher ranks than other genes. Genes indicated by green circles interact with any of the nine potential candidates and were registered as genes causative of NDDs in Human Genome Mutation Database version 2018.2. Genes are arranged in a clockwise manner from the top according to their strength of interaction.