Supplementary Online Content

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eTable. Pathogenic Variants Reported in the Cohort Including 132 for Which the Findings Were Explanatory of the Child's Condition and 10 for Which the Gene Was Associated With Autosomal Recessive in Heritance and Could Not Alone Explain the Child's Condition

eFigure. Sagittal and Axial Images in a Patient With Heterozygous Frameshift Mutation in *RELN* (c.329 dup; p. Gly111Argfs*7)

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. Pathogenic Variants Reported in the Cohort Including 132 for Which the Findings Were Explanatory of the Child's Condition and 10 for Which the Gene Was Associated With Autosomal Recessive in Heritance and Could Not Alone Explain the Child's Condition

PATHOGENIC VARIANTS PROVIDING EXPLANATION OF THE CHILD'S CLINICAL CONDITION							
Obs	**Initial clinical diagnosis**	**Specific Initial Finding**	**Gene(s) affected**	**Type of variant**	**Coordinates or CDNA**	**Size or Protein change**	**Type of error**
246	Brain malformation or structural anomaly	Agenesis of the corpus callosum	DRD3, ZNF80, TIGIT, ZBTB20	CNV	chr3:113,823,720-115,284,540	1.46Mb	deletion
31	Brain malformation or structural anomaly	Agenesis of the corpus callosum	Mulitple	CNV	2p26.3-2p21	46 Mb	deletion
523	Brain malformation or structural anomaly	Agenesis of the corpus callosum	Mulitple	CNV	chr8:176475-6925888; chr8:176475-6925888	6.749Mb loss, 28.581Mb gain	complex
627	Brain malformation or structural anomaly	Cerebellar and Callosal abnormalities	Mulitple	CNV	chr1:835601-9810107	8.7Mb	deletion
430	Brain malformation or structural anomaly	Lissencephaly	LIS1	CNV	chr17:1859374-282608	96Kb	deletion
525*	Brain malformation or structural anomaly	Lissencephaly	LIS1	CNV			deletion
168	Brain malformation or structural anomaly	Microcephaly	DOCK8, KANK1	CNV	chr9:46587-1603814; 16p13.3 (88,165-11,065,307	1.6Mb; 11Mb	complex
62	Brain malformation or structural anomaly	Ventriculomegaly	Mulitple	CNV	chr11:79,448,655-114,375,717	34.93 Mb	deletion
578	Dysmorphic Syndrome	Clinically Dysmorphic	Mulitple	CNV	13q11q14.2.	28.21Mb	gain
722*	Dysmorphic Syndrome	Clinically Dysmorphic	Mulitple	CNV	5q deletion		deletion
490	Dysmorphic Syndrome	Clinically Dysmorphic	Multiple	CNV	11q14.3-q25	43.3Mb	gain
391	Dysmorphic Syndrome	DeGeorge Syndrome	Mulitple	CNV	chr2:165,684,853-166,668,958	not reported	gain
230	Dysmorphic Syndrome	Noonan Syndrome	SHOC2, SMC3, CNNM3	CNV	chr10:104491930-115884864	11.4Mb	deletion
293	Dysmorphic Syndrome	Williams Syndrome	Mulitple	CNV	chr7:72700127-74141603	1.44Mb	deletion

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558	Dysmorphic Syndrome	Williams Syndrome	Mulitple	CNV	chr7:72,722,981-74,200,092	1.48Mb	deletion
462	Dysmorphic Syndrome	Wolf-Hirschhorn	FGFR3, LETM1, WHSC1, WHSC2	CNV	chr4:71420-2343851	2.3Mb	deletion
717*	Dysmorphic Syndrome	Wolf-Hirschhorn	Mulitple	CNV	46, XX del(4)(p16)		deletion
504	Dysmorphic Syndrome	Wolf-Hirschon	Mulitple	CNV	ring Chromsome 4,46, XX, r(4)(p.16.3q35.2)	Ring Chr 4	deletion
570	Dysmorphic Syndrome	Wolf-Hirschorn	Mulitple	CNV	chr4:49,450-11,487,322	11.44Mb	deletion
663	Dysmorphic Syndrome	Wolf-Hirschorn	Mulitple	CNV	chr4:68345-12922536	12.9Mb	deletion
509	Unknown	Development normal/mild-equivocal delay	Multiple	CNV	chr16:21839340-22435811	596 kb	deletion
464**	Unknown	Development normal/mild-equivocal delay	Multiple	CNV	1p36.12p36.11 chr1:752,566-22,333,595;x4	4.2Mb	gain
491	Unknown	Developmental delay	CDKL5	CNV	chrX:18460280-18573966	114Kb	loss
135	Unknown	Developmental delay	Mulitple	CNV	chr1:849466-2330338	2.3 Mb	loss
225	Unknown	Developmental delay	Mulitple	CNV	chr1:849466-3324209	2.48Mb	loss
394	Unknown	Developmental delay	Mulitple	CNV	chr4: 4q21.1-q21.3	10.4Mb	loss
703	Unknown	Developmental delay	Mulitple	CNV	1p36.33p36.23 deletion (from 0-7970027)	8Mb	loss
98	Unknown	Developmental delay	multiple	CNV	chr16 29678569-30363689	16p11.2 0.519 Mb loss	loss
482	Unknown	Developmental delay	NDE1, MYH11, ABCC6, XYLT1	CNV	chr16:15493046-18164698	2.7Mb	loss
14	Unknown	Developmental delay	PRRT2	CNV	chr16:29378488-30199186	771Kb	loss
476	Unknown	Developmental delay	UBE3A,SNRPN, OCA2	CNV	chr15:20161372-28544359	8.4Mb	insertion
381	Dysmorphic Syndrome	DiGeorge syndrome	Mulitple	Del	chr21:18,919,528-21,460,595	2.54Mb	loss
319	Neurocutaneous	Tuberous Sclerosis Complex	TSC2	Del	deletion of exon 33		deletion

Obs	Initial clinical diagnosis	Specific Initial Finding	Gene(s) affected	Type of variant	Coordinates or CDNA	Size or Protein change	Type of error
592	Neurocutaneous	Tuberous Sclerosis Complex	TSC2	Del	chr16:2098079-2121566	23.5Kb	loss
566	Other	Atrophy/pseudo atrophy	STXBP1	Del	deletion exon 4 +		deletion
644	Unknown	Development normal/mild-equivocal delay	SCN1A	Del	deletions exons 14-15		deletion
20	Unknown	Developmental delay	KCNQ2	Del	deletions exons 11-13		deletion
548	Unknown	Development normal/mild-equivocal delay	UBEA3	Dup	chr15:20848460-27662530X4		duplication
68	Brain malformation of structural anomaly	Agenesis of the corpus callosum	SETBP1	SNV	c.2608G>A	p.Gly870Ser	missense
414*	Brain malformation of structural anomaly	Cerebellar hypoplasia	CASK	SNV			
173	Brain malformation of structural anomaly	Holoprosencephaly	TGIF1	MNV	c.340_349dupGGGGCCAAGA	p.Ile117Argfs*6	frameshift
183	Brain malformation of structural anomaly	Microcephaly	ASPM(MCPH5)	MNV	c.8711_8712delAA	p.Arg1405Cys	frameshift
189	Brain malformation of structural anomaly	Microcephaly	ATP1A3	SNV	c.2771T>C	p.Leu924Pro	missense
55*	Brain malformation of structural anomaly	Microcephaly	BRAT1	SNV	c.171delG; c.419T>C	p.Glu57Aspfs*7; p,Leu140Pro	missense
155	Brain malformation of structural anomaly	Microcephaly	FOXG1	SNV	c.1402_1405delTCTG	p.Ser468GlyfsX19	missense
498	Brain malformation of structural anomaly	Microcephaly	HNRNPR	SNV	c.1663C>T	p.Gln555X	nonsense
586	Brain malformation of structural anomaly	Walker-Warburg Syndrome	FKTN	SNV	c.642dupT	p.Asp215X	nonsense

Obs	Initial clinical diagnosis	Specific Initial Finding	Gene(s) affected	Type of variant	Coordinates or CDNA	Size or Protein change	Type of error
770	Brain malformation of structural anomaly	Walker-Warburg Syndrome	POMT2	SNV	c.1872C>T; c.1006+1G>A	p.Thr588X; IVS8+1G>A	nonsense&frameshift
308	Brain malformation of structural anomaly	Heterotopia (Band)	DCX	SNV	c.574C>T	p.Arg192Trp	missense
10	Brain malformation of structural anomaly	Lissencephaly w/band heterotopia	DCX	SNV	c.176G>A	p.Arg59His	missense
647	Dysmorphic Syndrome	Cornelia de Lange	SMIC1A	MNV	c.1636_1638delATT	p.Ile546del	inframe deletion
40	Metabolic	Alper-Huttenlocher Disease	POLG1	SNV	c.3286C>T;c.2800-2801delAA	p.Arg1096Cys; p.Lys934AspfsX10	missense
673	Metabolic	GM1 gangliosidosis	GLB1	SNV	c.176G>A	p.Arg59His	frameshift
337	Metabolic	Leigh syndrome	mtATP6	SNV	c.8993T>G	p.Leu156Arg	missense
71	Metabolic	Leigh syndrome	mtND5	SNV	G:27.1, a:72.6	p.Asp393Asn	missense
495	Metabolic	Leigh syndrome	ATP6	SNV	c.8993T>G	p.Leu156Arg	missense
554	Metabolic	Mitochondrial disease	FBXL4	SNV	c.64C>T; c.1444C>T	p.Arg22; p.Arg482Trp	nonsense
279	Metabolic	Nonketotic hyperglycinemia	GLDC	SNV	c.1009C>T (HZ)	p.Arg337X	missense
611	Metabolic	Nonketotic hyperglycinemia	GLDC	SNV	c.1054delA	p.Thr352Glnfs*65	frameshift
757	Metabolic	Nonketotic hyperglycinemia	GLDC	SNV	c.499G>T; c.2714T>G	p.Glu167Stop; p.Val905Gly	stop&?
576	Metabolic	Pyruvate dehydrogenas deficiency	PDHA1	SNV	c.707C>A	p.Ala236Glu	missense
197	Metabolic	Zellweger's syndrome	HSD17B4	SNV	c.868+1delG (HZ)	Exon 11 splice donor site	splice site
543	Neurocutaneous	epidermal-nevus + CC abnormality	KRAS	SNV	c.35G>T	p.Thr68Asn(T68N)	missense
309	Neurocutaneous	Linear sebaceous nevus syndrome	KRAS	SNV	c.35G>A	p.Gly12Asp	missense
144	Neurocutaneous	Neurofibromatosis	NF1	SNV	c.3132C>G	p.Tyr1044X	nonsense
527*	Neurocutaneous	Neurofibromatosis	NF1	SNV	c.4537C>T	p.Arg1513*	nonsense
311	Neurocutaneous	Tuberous Sclerosis Complex	TSC1	SNV	c.1797dupG		frameshift
502	Neurocutaneous	Tuberous Sclerosis Complex	TSC1	SNV	c.2272C>T	p.Gln758X	nonsense

Obs	Initial clinical diagnosis	Specific Initial Finding	Gene(s) affected	Type of variant	Coordinates or CDNA	Size or Protein change	Type of error
200	Neurocutaneous	Tuberous Sclerosis Complex	TSC2	SNV	c.1361G>A	p.Arg454Lys	missense
209	Neurocutaneous	Tuberous Sclerosis Complex	TSC2	SNV	c.1255C>T	p.Pro419Ser	missense
706*	Neurocutaneous	Tuberous Sclerosis Complex	TSC2	SNV	c.1604delG		frameshift
733	Neurocutaneous	Tuberous Sclerosis Complex	TSC2	SNV	c.1832G>A	p.Arg611Gln	missense
750	Neurocutaneous	Tuberous Sclerosis Complex	TSC2	SNV	c.5479T>C	p.Phe1527Leu	missense
181	Other	Dystroglycanopathy	TRAPPC11	SNV	c.851A>C; c.965+5G>T	p.Gln248Pro	framshift&splice site
24*	Other	Tumor(?)	MECP2	SNV	c.316C>T	p.Arg106Trp	missense
163*	Unknown	Development normal/mild-equivocal delay	GABRG2	SNV			
233	Unknown	Development normal/mild-equivocal delay	GABRG2	SNV	c.731G>A	p.Gly244Asp	missense
194	Unknown	Development normal/mild-equivocal delay	PRRT2	SNV	c.649dupC	p.Arg217ProfsX8	frameshift
257	Unknown	Development normal/mild-equivocal delay	PRRT2	SNV	c.215_216delCA	p.Thr72ArgfsX61	frameshift
112	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.141delT	p.Asn47LysfsX45	missense
143	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.2966C>T	p.Ala989Val	missense
153	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.5434T>A	p.Trp1812Arg	missense
175**	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.5273-5277delA	p.Asn1758Ilefsx	frameshift
196	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.1570G>T	p.Glu524X	nonsense

Obs	Initial clinical diagnosis	Specific Initial Finding	Gene(s) affected	Type of variant	Coordinates or CDNA	Size or Protein change	Type of error
450	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	182T>C	p.Leu61Pro	missense
529	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.476delA	p.Tyr159SerfsX13	frameshift
747	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.2585G>C	p.Arg862Pro	missense
758	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.3146_3152dup	p.Asp1052Thrfs*3	frameshift
766	Unknown	Development normal/mild-equivocal delay	SCN1A	SNV	c.739C>G	p.Leu247Val	missense
69	Unknown	Development normal/mild-equivocal delay	SLC2A1	SNV	c.847C>T	p.Gln283*	nonsense
428	Unknown	Development normal/mild-equivocal delay	STXBP1	SNV	c.364C>T	p.Arg122X	missense
760	Unknown	Developmental delay	ALG13	SNV	c.320A>G	p.Asn107Ser	missense
76	Unknown	Developmental delay	ARX	SNV	c.1593_I599dupCATAGCC	p.Ala534HisfsX141	frameshift
418*	Unknown	Developmental delay	ARX	SNV			
550	Unknown	Developmental delay	CDKL5	SNV	c.145+2T>C	p.IVS4+2T>C	splice site
771	Unknown	Developmental delay	CDKL5	SNV	c.1763delC	p.Pro588Leufs*28	frameshift
773	Unknown	Developmental delay	CDKL5	SNV	c.611T>A	p.Leu204His	missense
19*	Unknown	Developmental delay	GRIN2A	SNV	c.1930.A>G	p.Ser644Gly	missense
263	Unknown	Developmental delay	KANSL1	SNV	c.2203+1G>A	IVS6-1G>A	splice site
531	Unknown	Developmental delay	KCNQ2	SNV	c.841G>T	p.Glu281Trp	missense
467	Unknown	Developmental delay	MECP2	SNV	c.808C>T	p.Arg270X	missense

Obs	Initial clinical diagnosis	Specific Initial Finding	Gene(s) affected	Type of variant	Coordinates or CDNA	Size or Protein change	Obs
386	Unknown	Developmental delay	PHF8	SNV	c.1731-2A>G	splice site	splice site
250	Unknown	Developmental delay	PIGN	SNV	c.2340T>A; c.1434+5G>A	p.Tyr780X; intron17 splice site	frameshift
191	Unknown	Developmental delay	PRRT2	SNV	c.649dupC	p.Arg217ProfsX8	frameshift
216	Unknown	Developmental delay	SCN1A	SNV	c.4486C>T	p.Gln1495X	missense
195	Unknown	Developmental delay	ST3GAL5	SNV	c.353delA	p.Lys118Argfs*70	frameshift
7*	Unknown	Developmental delay	STXBP1	SNV	c.703C>T	p.Arg235X	nonsense
92**	Unknown	Developmental delay	STXBP1	SNV	c.416C>T	p.Pro139Leu	missense
226	Dysmorphic Syndrome	Pallister Killian	Tetrasomy	Tertrasomy			
288**	Unknown	Developmental delay	Idic 15	Tetrasomy (partial)			
426	Dysmorphic Syndrome	Partial trisomy chromosome 15	TRI15	Trisomy			
466	Dysmorphic Syndrome	Trisomy 13	TRI13	Trisomy			
762	Dysmorphic Syndrome	Trisomy 15 mosaic+Ring Chr21	TRI15	Trisomy			
125	Dysmorphic Syndrome	Trisomy 18	TRI18	Trisomy			
45	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
57	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
67	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
90	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
159	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
262	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
277	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			

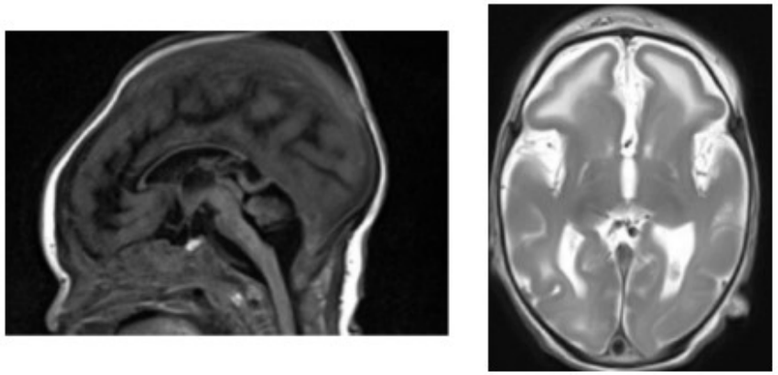
Obs	Initial clinical diagnosis	Specific Initial Finding	Gene(s) affected	Type of variant	Coordinates or CDNA	Size or Protein change	Obs
305	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
327	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
336	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
354	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
537	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
599	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
660	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
678	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
700	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			
767	Dysmorphic Syndrome	Trisomy 21	TRI21	Trisomy			

HETEROZYGOUS PATHOGENIC MUTATIONS FOR AUTOSOMAL RECESSIVE DISORDERS. THESE WERE NOT CONSIDERED FULLY EXPLANATORY OF THE CHILD'S CONDITION

Obs	Initial clinical diagnosis	Specific Initial Finding	Gene(s) affected	Type of variant	Coordinates or CDNA	Size or Protein change	Type of error
47*	Unknown	Development normal/mild-equivocal delay	ALDH7A1	SNV			
127	Unknown	Development normal/mild-equivocal delay	ALDH7A1	SNV	c.1279G>C	p.Glu427Gln	missense
218	Unknown	Developmental delay	ALG3	SNV	c.487C>T	p.Arg163Cys	missense
220	Brain malformation of structural anomaly	microcephaly	C5orf52	SNV	c.8300-1G>C		splice site
342*, ***	Metabolic	Leigh syndrome	NDUFAF5	SNV			
557	Unknown	Developmental delay	FUCA1	SNV	c.1082G>A	p.W361*	nonsense
616	Brain Malformation	Lissencephaly	SAMHD1	MNV	c.155_158insGCTC	p.Ser52fs	frameshift

Obs	Initial clinical diagnosis	Specific Initial Finding	Gene(s) affected	Type of variant	Coordinates or CDNA	Size or Protein change	Type of error
727	Unknown	Development normal/mild-equivocal delay	POLG1	SNV	c.803G>C	p.Gly268Ala	missense
728	Other	infarct/stroke VS metabolic	SCO2	SNV	c.283C>T	p.Arg95Cys	missense
751* **	Brain malformation of structural anomaly	Lissencephaly	RELN	SNV	c.329dup	p.Gly111Argfs*7	frameshift

The actual laboratory report was not available and only partial information was available in the medical record.
**Original interpretation by the clinical lab of Variant of Unknown Significance was reinterpreted as Pathogenic.
***The child's clinical condition was strongly associated with the gene.



eFigure 1. Sagittal and axial images in a patient with heterozygous frameshift mutation in *RELN* (c.329 dup; p. Gly111Argfs*7).