The American Journal of Human Genetics

Supplemental Data

De Novo Mutations in *CHAMP1* Cause Intellectual Disability with Severe Speech Impairment

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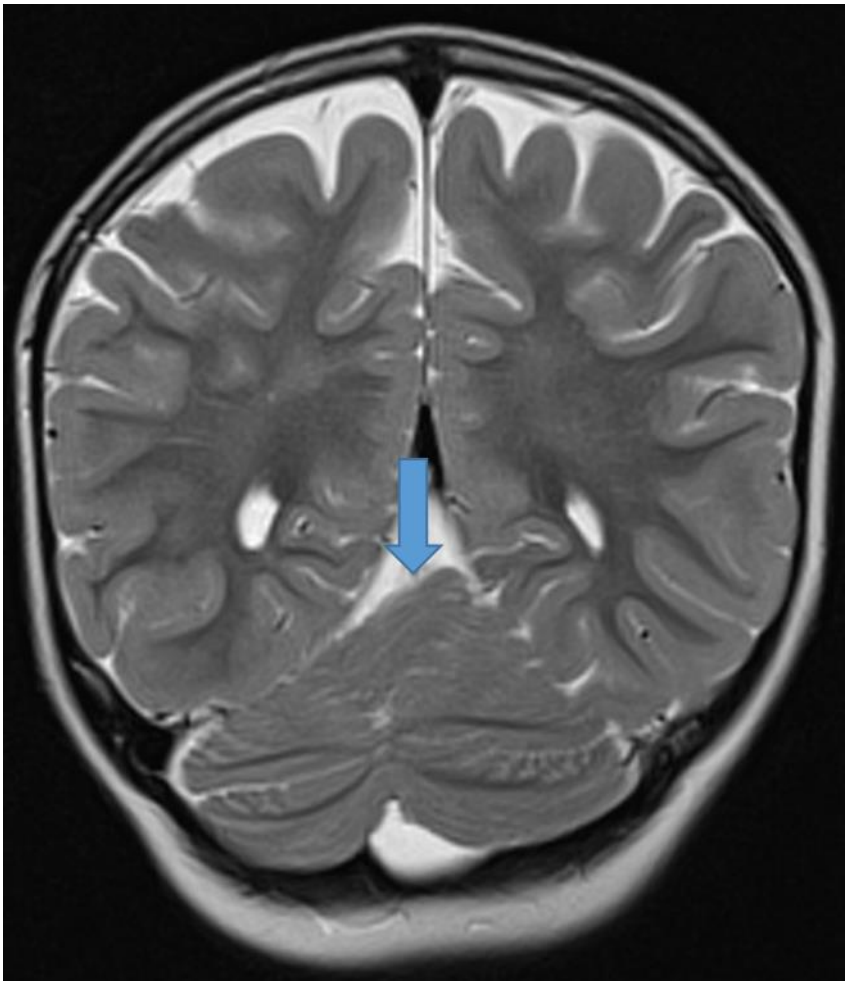

Figure S1 Coronal section from a brain MRI of individual A:II-1. Note a partial rhombencephalosynapsis of the superior posterior cerebellar hemispheres (blue arrow) while the inferior and anterior parts of the cerebellar hemispheres are separated and the vermis is regular.

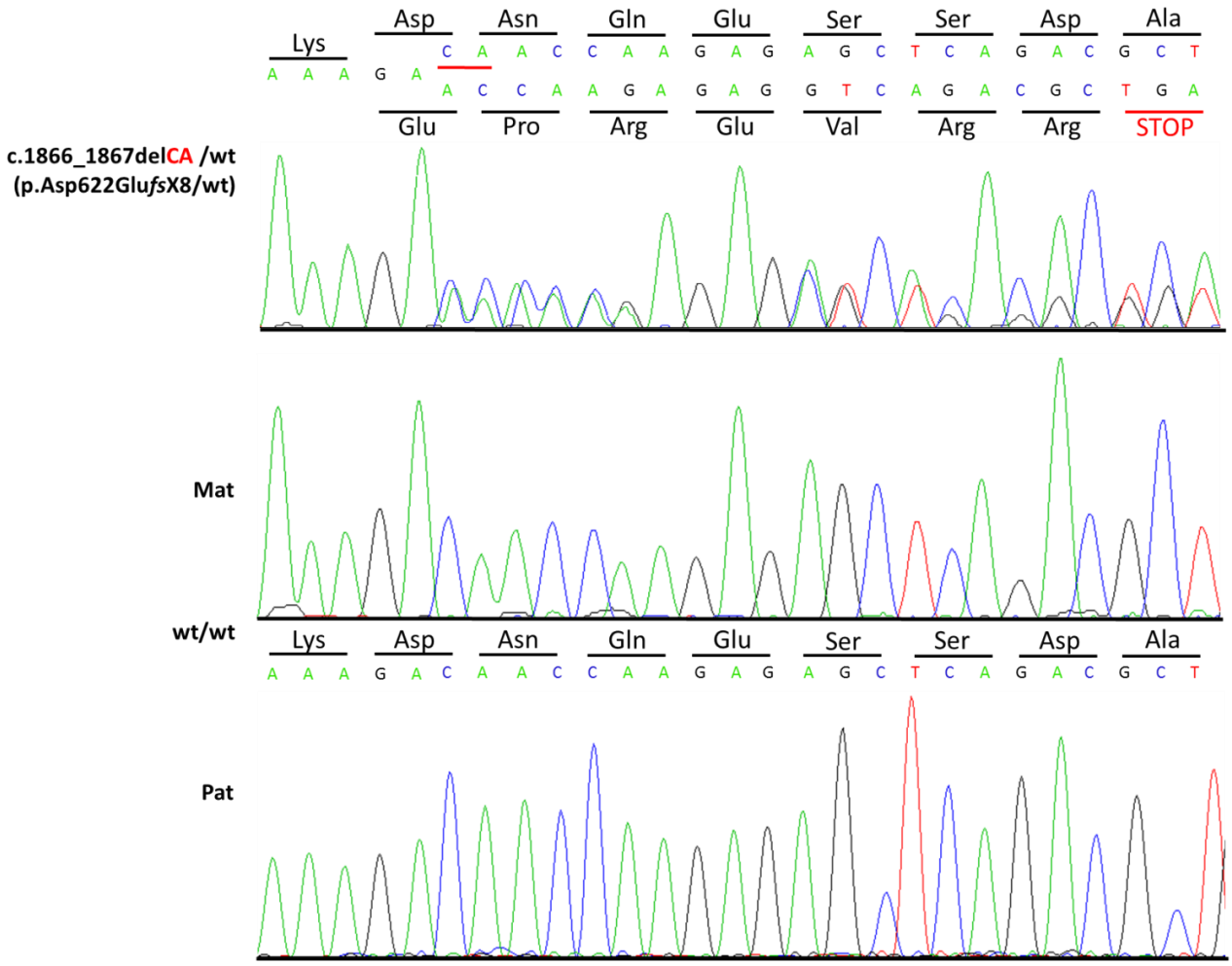

Figure S2 Sanger sequencing chromatograms of parts of *CHAMP1* after PCR amplification of genomic DNA. Sequencing results for A:II-1 bearing a heterozygous c.1866_1867delCA (p.Asp622Glu*fs**8) and his mother (Mat) and father (Pat) homozygous for the reference sequence (WT/WT). The amino acid translation is shown in the three letter code above the chromatograms. Nucleotide numbering uses +1 as the A of the ATG translation initiation codon in the reference sequence, with the initiation codon as codon 1.

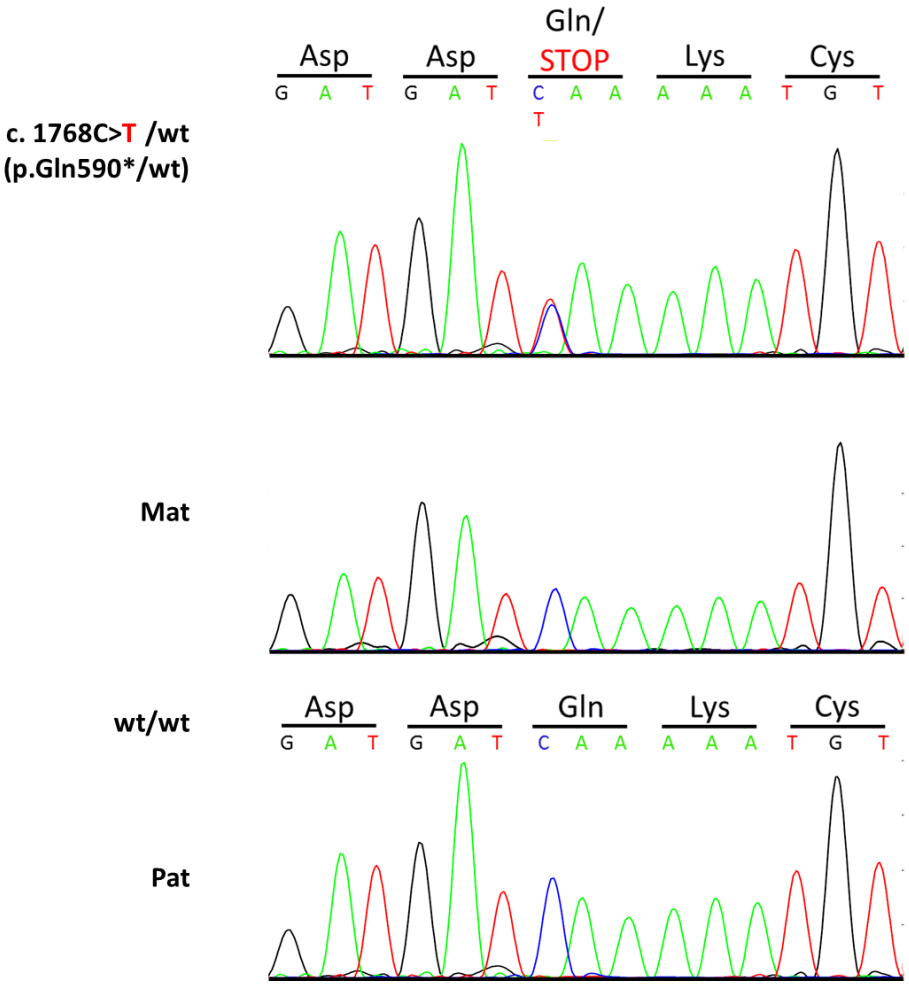

Figure S3 Sanger sequencing chromatograms of parts of *CHAMP1* after PCR amplification of genomic DNA. Sequencing results for B:II-3 bearing a heterozygous c.1768C>T (p.Gln590*) and his mother (Mat) and father (Pat) homozygous for the reference sequence (WT/WT). The amino acid translation is shown in the three letter code above the chromatograms. Nucleotide numbering uses +1 as the A of the ATG translation initiation codon in the reference sequence, with the initiation codon as codon 1.

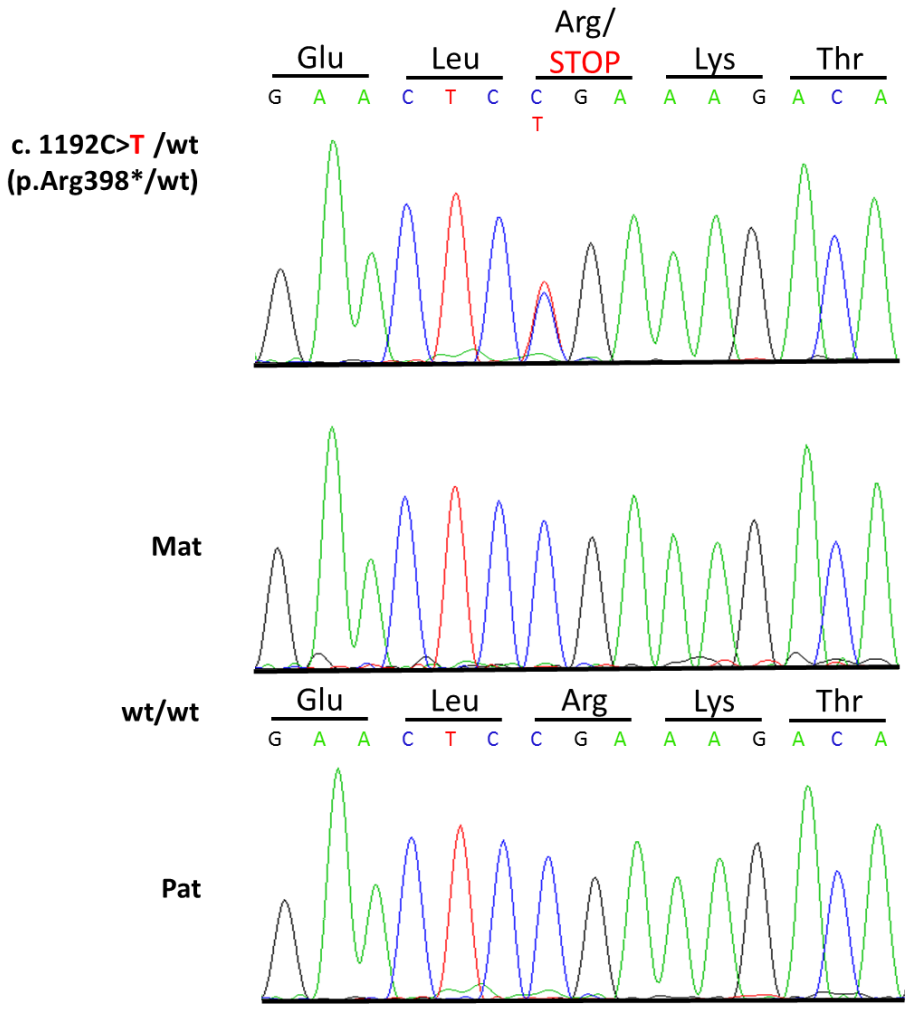

Figure S4 Sanger sequencing chromatograms of parts of *CHAMP1* after PCR amplification of genomic DNA. Sequencing results for E:II-2 bearing a heterozygous c. 1192C>T (p.Arg398*) and her mother (Mat) and father (Pat) homozygous for the reference sequence (WT/WT). The amino acid translation is shown in the three letter code above the chromatograms. Nucleotide numbering uses +1 as the A of the ATG translation initiation codon in the reference sequence, with the initiation codon as codon 1.

TABLE S1A. *De novo* variants identified in individual A:II-1

Gene	Chromosome	Total Depth	Allele Freq.	Nucleotide Change	Protein Change	ExAC
CHAMP1	13	227	49	c.1866_1867delCA	p.Asp622Glu*fs**8	no
BRSK1	19	87	61	c.566C>T	p.Thr189Ile	no
BFSP1	20	410	46	c.1970T>C	p.Lys657Arg	0/1/119638

TABLE S1B. *De novo* variants identified in individual B:II-3

Gene	Chromosome	Total Depth	Allele Freq.	Nucleotide Change	Protein Change	ExAC
PDHA2	4	124	48	c.1049T>C	p.Phe350Ser	no
PEX1	7	52	40	c.3416G>A	p.Gly1139Glu	0/6/121242
PGAP2	11	106	51	c.230G>A	p.Arg77Gln	0/1/121364
CHAMP1	13	226	40	c.1768C>T	p.Gln590*	no

TABLE S1C. *De novo* variants identified in individual C:II-2

Gene	Chromosome	Total Depth	Allele Freq.	Nucleotide change	Protein Change	ExAC
CHAMP1	13	299	54	c.1192C>T	p.Arg398*	no
POLD1	19	20	50	c.1486G>A	p.Asp496Asn	no

TABLE S1D. *De novo* variant identified in individual D:II-2

Gene	Chromosome	Total Depth	Allele Freq.	Nucleotide change	Protein Change	ExAC
CHAMP1	13	218	52	c.635C>T	p.Pro212Leu*fs**7	no

Table S2. Deletion CNVs affecting CHAMP1 listed in the DECIPHER database (July 2015) and literature. Only CNVs affecting *CHAMP1* and not extending into chromosomal band 13q32 and 13q34 are listed (maximum size 13.5 Mb). Probands with terminal deletions caused by ring chromosomes were excluded from the table since ring chromosomes irrespective of the deleted region are discussed as a possible cause of anomalies such as growth retardation.[1]

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# CNV pattern consistent with unbalanced translocation, n.r. not reported, VSD Ventricular septal defect

SUPPLEMENTARY REFERENCES

1. Kosztolanyi, G. (1987). Does "ring syndrome" exist? An analysis of 207 case reports on patients with a ring autosome. Human genetics 75, 174-179.

2. Yang, Y.F., Ai, Q., Huang, C., Chen, J.L., Wang, J., Xie, L., Zhang, W.Z., Yang, J.F., and Tan, Z.P. (2013). A 1.1Mb deletion in distal 13q deletion syndrome region with congenital heart defect and postaxial polydactyly: additional support for a CHD locus at distal 13q34 region. Gene 528, 51-54.

3. Ballarati, L., Rossi, E., Bonati, M.T., Gimelli, S., Maraschio, P., Finelli, P., Giglio, S., Lapi, E., Bedeschi, M.F., Guerneri, S., et al. (2007). 13q Deletion and central nervous system anomalies: further insights from karyotype-phenotype analyses of 14 patients. Journal of medical genetics 44, e60.

4. Quelin, C., Bendavid, C., Dubourg, C., de la Rochebrochard, C., Lucas, J., Henry, C., Jaillard, S., Loget, P., Loeuillet, L., Lacombe, D., et al. (2009). Twelve new patients with 13q deletion syndrome: genotype-phenotype analyses in progress. European journal of medical genetics 52, 41-46.

5. Kirchhoff, M., Bisgaard, A.M., Stoeva, R., Dimitrov, B., Gillessen-Kaesbach, G., Fryns, J.P., Rose, H., Grozdanova, L., Ivanov, I., Keymolen, K., et al. (2009). Phenotype and 244k array-CGH characterization of chromosome 13q deletions: an update of the phenotypic map of 13q21.1-qter. American journal of medical genetics Part A 149A, 894-905.