Supplementary Table 1. Criteria for Classifying Pathogenic Variants according to ACMG guidelines*.

Evidence of pathogenicity	Category
Very strong	**PVS1** Null variant (nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease
Strong	**PS1** Same amino acid change as a previously established pathogenic variant regardless of nucleotide change
	PS2 De novo (both maternity and paternity confirmed) in a patient with the disease and no family history
	PS3 Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product
	PS4 The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls
Moderate	**PM1** Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation
	PM2 Absent from controls (or at extremely low frequency if recessive) in general population databases #
	PM3 For recessive disorders, detected in trans with a pathogenic variant. This requires testing of parents (or offspring) to determine phase
	PM4 Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants
	PM5 Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before
	PM6 Assumed de novo, but without confirmation of paternity and maternity
Supporting	**PP1** Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease
	PP2 Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease
	PP3 Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc)
	PP4 Patient's phenotype or family history is highly specific for a disease with a single genetic etiology
	PP5 Reputable source recently reports variant as pathogenic but the evidence is not available to the laboratory to perform an independent evaluation

The criteria selected to classify the variant c.900dup, p.(Glu301Argfs*56) as pathogenic are shown in green. * Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–424.). # the variant c.900dup, p.(Glu301Argfs*56) has not been described in gnomAD database (https://gnomad.broadinstitute.org/).