

**Supplementary Table 1:** Additional SIM2 (NM\_005069.6) gene variants found by clinical exome sequencing assayed in this study.

Sex	Age (years)	Phenotype	Variants thought to explain phenotypes	Nucleotide (Amino Acid) Polyphen-2	Reads	gnomAD Database (allele frequency)
F	5.8	Acute renal and liver dysfunction, enteropathy, heart disease, global developmental delay, mild hypotonia, dysmorphic features, short stature, failure to thrive, mild structural brain abnormality, and an abnormal N-glycan and transferrin test. Unusual movements possibly related to seizures associated with Streptococcus pneumonia bacteremia	c.280G>A (p.V94M) <i>probably damaging</i>	31/72	Not present	
F	20.7	Postural orthostatic tachycardia syndrome (POTS), possible seizures, abnormal movements (random flinching), gastrointestinal symptoms, slight scoliosis and skin anomalies.	c.322G>A (p.A108T) <i>probably damaging</i>	46/85	0.00001063	
M	66.0	Bilateral hearing loss, multifactorial gait difficulty, balance issues, weakness, peripheral neuropathy, cerebellar atrophy, short term memory loss, vitamin B12 deficiency and history of concussion.	Heterozygous c.35delG (p.G12fs) variant in the <i>GJB2</i> gene, a common pathogenic variant associated with autosomal recessive deafness (1). A novel hemizygous c.197C>A (p.A66D) variant of unknown significance (VUS) in the <i>BCAP31</i> gene. <i>BCAP31</i> variants cause deafness, dystonia, and cerebral hypomyelination (DDCH), an X-linked recessive disorder with phenotypes including lack of psychomotor development, dysmorphic facial features, deafness, dystonia and cerebral hypomyelination(2).	c.515A>T (p.N172I) <i>probably damaging</i>	21/53	0.000003977
F	7.9	Prematurity, delayed speech, refractory epilepsy, structural brain abnormalities (right frontal developmental venous anomaly), chronic otitis media, and persistent asthma.	c.1146A>C (p.R382S) <i>probably damaging</i>	83/184	0.000007964	

## **Supplementary References**

1. Kenneson A, Van Naarden Braun K, Boyle C. GJB2 (connexin 26) variants and nonsyndromic sensorineural hearing loss: A HuGE review. *Genetics in Medicine*. 2002;4(4):258-74.
2. Cacciagli P, Sutera-Sardo J, Borges-Correia A, Roux J-C, Dorboz I, Desvignes J-P, et al. Mutations in BCAP31 Cause a Severe X-Linked Phenotype with Deafness, Dystonia, and Central Hypomyelination and Disorganize the Golgi Apparatus. *The American Journal of Human Genetics*. 2013;93(3):579-86.