Supplementary Online Content


eMethods. Molecular Methods
eFigure 1. Growth Chart for Patient 1
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eMethods. Molecular methods

Whole exome sequencing was performed at Personalis, Inc. (Ca, USA) using a solution-phase Agilent SureSelect 38 Mb exome capture (SureSelect Human All Exon Kit; Agilent Technologies Inc., Santa Clara, USA) and the Illumina HiSeq2000 sequencer (Illumina, San Diego, CA). Reads were aligned to the hg19 human reference sequence using Novoalign (Novocraft, Selangor, Malaysia) version 2.05. The ANNOVAR tool (Openbioinformatics.org) was used to annotate SNPs and small insertions/deletions. Variant calls were filtered based on standard quality metrics. A total of 188 shared autosomal variants with a minor allele frequency (MAF) <0.5% in Exome Variant Server (EVS) passed quality filters. Given parental consanguinity and the absence of an affected antecedent, the disease causing variant was likely to be rare and homozygous. We therefore first interrogated the 8 rare (<0.01% MAF in EVS and the UCL-exome cohort) homozygous variants.

Mutation nomenclature was assigned in accordance with GenBank Accession number NM_182916.2 with nucleotide position 1 corresponding to the A of the ATG initiation codon. Variants were identified as novel if not previously reported in the literature and if absent from dbSNP available at http://www.ncbi.nlm.nih.gov/projects/SNP/, NHLBI GO Exome Sequencing Project (ESP), Seattle, WA available at http://evs.gs.washington.edu/EVS/ and 1000 genomes project available at http://www.1000genomes.org/ and the Exome aggregation Consortium (ExAC) Cambridge, MA (http://exac.broadinstitute.org) all accessed 12th November 2015. The likely pathogenicity of novel missense variants was assessed using the predictive algorithms of ‘Sorting Intolerant from Tolerant’ (SIFT) available at http://sift.jcvi.org and Polymorphism Phenotyping v2 (PolyPhen-2) available at http://genetics.bwh.harvard.edu/pph2/.

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eFigure 1. Growth Chart for Patient 1

Height plotted over age 4-15 years with hormone therapy start dates indicated for growth hormone (GH) and oestrogen therapy. Red bar indicates the genetic target for this patient.
**eFigure 2.** Retinal Imaging of the Right Eye for Each Patient

(a) Color fundus photograph (Topcon Great Britain Ltd, Berkshire, UK), (b) Spectralis optical coherence tomography (OCT, Spectralis, Heidelberg Engineering Ltd, Heidelberg, Germany), (c) fundus autofluorescence (Spectralis, Patient 2).

Patient 1, tilted myopic disc with peripapillary atrophy; patients 1, 2 and 3, mild disc pallor. No other abnormalities demonstrated in any patient.