Appendix S1

MATERIALS AND METHODS

DNA analysis

Whole exome sequencing was performed at the Institute for Molecular Medicine Finland (FIMM) Technology Centre for case 1. The targeting of the exonic regions was performed using the SureSelect Clinical Research Exome kit (Agilent Technologies, Santa Clara, CA, USA). Sequencing was performed using the Illumina HiSeq1500 sequencer and the data was analysed using an in-house built analysis pipeline called variant calling pipeline (S1). The mean target coverage of the sample was 76.3×. Annotation was performed by use of ANNOVAR (S2) and data was filtered based on population frequencies from the Genome Aggregation Database (http://gnomad.broadinstitute.org/; accessed in 22 March 2019) (S3) and the Sequencing Initiative Suomi project (SISu) (http://sisuproject.fi; accessed in 22 March 2019). Analysis was targeted to coding regions and splice site variants, with an allele frequency <0.01 and performed for all inheritance models. The variant evaluation was based on the predicted consequence on the transcript and protein sequences (conservation, effect, functional protein domains, *in silico* predictions, etc.). Pathogenicity of the candidate variants was evaluated according to the ACMG Standards and Guidelines (S4). Exome sequencing findings were validated by capillary sequencing. Amplification of the 945 bp fragment and sequencing were performed using the primers (SLURP1_F: CAGACCCCATGAGTGAGCTG and SLURP1_R:CACCGAGGTCAGGTGATGAG) covering both the p.(Glu60Lys) and p.(Cys73del) variants. Sequencing chromatograms were analysed using Sequencer 5.1 (Gene Codes Corporation, Ann Arbor, MI, USA).

For case 2, defined candidate gene regions for PPK were amplified from DNA using the TruSeq Custom Amplicon kit v1.5 (Illumina, San Diego, CA, USA). Sample preparation was done according to the TruSeq Custom Amplicon v1.5 Reference Guide (Document #15027983 v02 February 2016). The sequencing was performed on an Illumina MiSeq at the Institute for Molecular Medicine Finland (FIMM) Technology Centre.

For case 3, deep targeted panel sequencing was performed at the Necker Hospital genetics laboratory and Imagine genomic and bioinformatics platform, Paris, France. The targeting of the 317,484 Kb exonic regions was performed using a custom dermatome panel (Agilent Technologies). Sequencing was conducted using the Illumina HiSeq1500 sequencer. Downstream processing was carried out with the Genome Analysis Toolkit, SAMtools, and Freebayes according to documented best practices from the Broad Institute (S5–S7). All variants were annotated based on Ensembl release 71 with an in-house software tool (PolyWeb). They were filtered according to relevant genetic models. We excluded known variants listed in the public databases dbSNP (build 135), the Exome Variant Server (release ESP6500SI-V2), the 1,000 genomes variants (release date 21 May 2011), and variants previously identified in "in-house" exomes. Then we selected variants affecting splice sites or coding regions (non-synonymous substitutions, insertions, or deletions). The mean target coverage of the sample was 563X. All sequencing variants were confirmed by Sanger sequencing. Amplification of the fragments and sequencing were performed with the primers *SLURP1*-2F GTCAGCGAGACTCCTTCAGC/ *SLURP1*-2R-AAGGAGGGAGGCACTTGG and *SLURP1*-3F CAGGTCACAGTCAGAGGAGG/ *SLURP1*-3R GAAGGCCAGTTCTGTAGGGT.

Haplotype analysis was performed on genotyping data. Genotyping was performed at the FIMM Technology Centre, using the Infinium Global Screening Array (Illumina). The haplotypes were phased by use of the SHAPEIT software (S8).

Histology

Sections of formalin-fixed paraffin-embedded (FFPE) and haematoxylin and eosin stained skin samples were analysed by an experienced dermatopathologist.

SUPPLEMENTARY REFERENCES

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