Supplementary Methods

For the proband and her father in Family 1, whole genome sequencing was performed with the Illumina HiSeq X platform at The Centre for Applied Genomics (TCAG) in Toronto, Canada from DNA extracted from whole blood. Briefly a total of 500ng of DNA was used for library preparation using the Illumina TruSeq Nano DNA Library Prep Kit following the manufacturer's recommended protocol but omitting the PCR amplification step. The final library was sequenced on an Illumina HiSeq X to generate paired-end reads of 150 bases in length. Read alignment and base calling were performed using Illumina HiSeq Analysis Software (HAS) version 2-2.5.55.1311 with resulting variant calls annotated using a custom pipeline developed at TCAG[1,2] based on ANNOVAR.[3] CNVs were called using the read depth method with the programs ERDS v1.1 (estimation by read depth with single-nucleotide variants)[4] and CNVnator v0.3.2 with a window size of 500 bp.[5] Structural variants were detected using MANTA v0.23.1 and Canvas v1.1.0.5. The breakpoints of the inversion/deletion variant were amplified by PCR and confirmed by Sanger sequencing

For patients 2-I, 2-II, 3-I and 4-I, whole exome sequencing was performed. Briefly, total leukocyte derived DNA was enriched using the Agilent SureSelect Human All Exon Capture V4 (Families 2 and 4) or Agilent SureSelect Clinical Research Exome capture kit (Family 3) (Agilent Technologies, Santa Clara, Ca) according to the manufacturer's protocol. Subsequently paired-end sequencing was performed (Illumina Hi-Seq 2500; Illumina, Inc, San Diego, CA). Reads were aligned to the hg19 reference human genome using Burrows-Wheeler Aligner (http://bio-bwa.sourceforge.net). Variant calls were generated using the Genomic Analysis Tool Kit version 2.8.1 (https://software.broadinstitute.org/gatk/). Mutations were confirmed by Sanger sequencing using standard protocols.

In order to determine parental origin of the c.2179_2180del variant, total leukocyte DNA from both affected patients from Family 3 was digested with SmaI according to manufacturer's protocol (https://tools.thermofisher.com/content/sfs/manuals/ MAN0012171_SmaI_10_ UuL_1200U_UG.pdf). DNA from the affected patients was put through the digestion protocol with water in place of enzyme as a control. The digested and undigested DNA was then amplified using long-range PCR primers and sequenced using nested sequencing primers

(Supplementary Methods Table 2.). The PCR product from the long-range primers contains four methylation-sensitive SmaI digestion sites (5′-CCCGGG-3′), therefore the unmethylated paternal copy is not expected to be amplified. As expected the undigested samples were heterozygous for the variant whereas DNA digested with SmaI was homozygous for the reference allele, indicating that the variant was located on the paternal allele (Supplementary Figure 5). This method was adapted from Schaaf et al. 2013 (Schaaf et al. 2013).

For Family 3, family relationships between father, mother and Patient were verified via short tandem repeat analysis of 15 loci using the AmpFISTR® Identifiler® PCR amplification kit.

Table 1. Primer sequences used in sequencing inversion/deletion breakpoints for Family 1

Primer Name	Primer Sequence
MAGEL2-LBPF	TGATCCCCAGTATTTTAACACTC
MAGEL2-LBPR	TCACTGTCATGTTAGCTGCAC
MAGEL2-RBPF	AGCCATTTATTGCTCAACTCA
MAGEL2-RBPR	GGGAGAATCTAAATCTGAGTGACT

Table 2. Primer sequences used in sequencing and phasing variants in MAGEL2 for Family 3.

Primer Name	Primer Sequence	Primer Purpose
MAGEL2x1LRF	GGGAGCCTCTGAACAGCCACGTAG	Long range PCR for sequencing and phase determination.
MAGEL2x1LRR	AGAACAGTAGCCGATTGAAATCAACAC	Long range PCR for sequencing and phase determination.
X1F-H	GACCCCCGGTAGCAG	Nested PCR for sequencing MAGEL2 and phase determination c.2179_2180del
X1R-H	GGCAAAGGGATCCTGCAGA	Nested PCR for sequencing MAGEL2 and phase determination for c.2179_2180del

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