**Supplemental Material**

**Bioinformatics Workflow**

(i) Quality control: trimming of adapters and low-quality bases via FASTX-Toolkit [1];

(ii) Short-read alignment: reads were mapped to the latest genome assembly using a number of genome alignment heuristic algorithms, presently Burrows–Wheeler Aligner, allowing the confirmation of read alignments across different aligners and increasing confidence in the accuracy of variant calls;

(iii) Variant calling: single nucleotide polymorphisms (SNPs) were called using samtools pileup [2], and Indels using Dindel [3]. As the field of structural variant (SV) discovery is still undergoing rapid development, we called SVs using established tools such as BreakDancerMax [4] and Pindel [5] while comparing results with newer tools such as inGAP-sv [6] and CREST [7];

(iv) Validation of variants: this was performed against local copies of published variation databases (via EnsEMBL, which collates the Human Gene Mutation Database, the National Center for Biotechnology Information’s (NCBI) dbSNP, and Online Mendelian Inheritance in Man (OMIM).

(v) Quality assurance on data sampling: in addition to basic quality control, we employed KING [8] and EIGENSTRAT [9] principal component analyses in our pipeline to validate population homogeneity of samples.

(vi) Prediction of functional impact of genetic variants: this was performed using SIFT (Sorting Intolerant from Tolerant) [10], PolyPhen2 (Polymorphism Phenotyping v2) [11], Mutation Taster [12], Mutation Assessor [13], phyloP (phylogenetic P-values) [14] and GERP (Genetic Evolutionary Rate Profiling) [15]. All of these strategies enrich for functional sites at which observed variants are more likely to affect phenotype.

**Sanger Sequencing**

Sanger sequencing was performed using the patient’s and the parents’ DNA for the validation of the two sequence variants described in the *LRP2* gene (NM\_004525.2:c.12379C>A; NP\_004516.2:p.Arg4127Ser, and NM\_004525.2:c.10937G>A; NP\_004516.2:p.Arg3646His) by whole-exome sequencing. Briefly, a flanking region around each sequence variant site was amplified by PCR with the following primer pairs: (a) sense primer (5'atgctggggtaagtggaggtagtt-3') and antisense primer (5'-ggagggaggtagagatgtcaataa-3') for Chr2:170009391; and (b) sense primer (5'-gccagagtttgcagggagtg-3') and antisense primer
(5'-caggtcagggtgttcagttcttat-3') for Chr2:170030506. The primers were designed with the PrimerSelect software from the Lasergene genomics suite (DNASTAR, Inc, Madison, WI, USA), and were checked for uniqueness by employing the Basic Local Alignment Search Tool (BLAST) search engine. We used the following PCR conditions for the amplification of both amplicons: (1) initial activation step of 3 min at 94 °C, (2) 40 cycles as follows: 45 s of denaturing at 94 °C, 30 s of annealing at 56 °C, 60 s of extension at 72 °C, and (3) final extension step of 10 min at 72 °C. A 15-µL aliquot of the PCR product was analysed by electrophoresis in a 1.5% agarose gel to confirm the expected size of the two amplicons [457 and 630 bp for (NP\_004516.2:p.Arg4127Ser) and (NP\_004516.2: p.Arg3646His), respectively]. Then, 85µL of each PCR product was purified with the Qiaquick nucleotide removal kit (Qiagen, Valencia, CA, USA) following the manufacturer’s guidelines. Thereafter, the purified PCR products were spectrophotometricallyquantified with a NanoDrop ND-1000 (Wilmington, DE, USA), and sent for Sanger sequencing to the Australian Cancer Research Foundation—Biomolecular Resource Facility (BRF) at the John Curtin School of Medical Research. Bidirectional sequencing of PCR amplicons were carried out by using Big DyeTM chemistry (Big Dye Terminator, Version 3.1; Applied Biosystems, Foster City, CA, USA) with the following internal (nested) primers to ensure specificity: (a) sense (5'-ttcagcaagcccaaccact-3') and antisense (5'-acttcacctgattagacccctgtt-3') for the amplicon containing the (NP\_004516.2:p.Arg4127Ser) sequence variant, and b) sense
(5'-catcccatcagctgaaaaagaaag-3') and antisense (5'-cttccaagctgataaccaaatgtc-3') for the amplicon containing the (NP\_004516.2: p.Arg3646His) sequence variant. The sequencing protocol was followed according to the BRF standard operative procedures.

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