**Supplementary material**

**1. Whole exome sequencing (WES)**

Genomic DNA was extracted from peripheral blood leukocytes (PBLs) using the QIAsymphony DSP DNA Midi kit (QIAGEN, Hilden, Germany), according to the manufacturer's instructions. NGS analysis was performed using the SureSelectQXT Clinical Research Exome V2 kit (Agilent, Santa Clara, CA). Libraries were sequenced by 151 bp paired-end reads on the Illumina NextSeq 550 platform (Illumina, San Diego, CA). The BaseSpace BWA Enrichment v2.1 App (Illumina) was used to align sequences (through BWA-MEM v0.7.7 on GRCh37/hg19 and Picard v1.79) and call variants (through GATK HaplotypeCaller v1.6). Variants were then annotated using ANNOVAR (April 2018) and filtered according to a custom pipeline (guided by GATK Best Practice), which removes reads with bad quality calling score, low coverage (<10), falling in segmental duplication regions (SuperDups>0.9), synonymous and unknown variants and common SNPs (MAF>1%).

Trio analysis was then performed starting from these filtered VCF files, in order to collect autosomal dominant/recessive, X-linked and *de novo* variants. Several *in silico* prediction tools (including SIFT, PolyPhen2, MutationTaster) were used to define the pathogenic score of identified variants and disease-variant/gene databases (e.g. HGMD, ClinVar, OMIM) were used to assess causative associations.

WES identified 72901 variants, with a Q30 sequencing percentage of 91,5% and uniform coverage above 100X. After the filtering steps, the variants left were 1952. Trio analysis was then performed starting from these filtered VCF files, finally retaining 152 variants.

**2. Sanger sequencing**

The presence of the putative *DDX3X* pathogenic variant identified by WES was subsequently confirmed by Sanger sequencing. DNAs from the proband and her parents were sequenced using the BigDye Terminator v3.1 Cycle Sequencing Kit on an ABI PRISM 3130xl Genetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA). Electropherograms were analyzed with the ChromasPro software 1.42 (Technelysium Pty Ltd, Tewantin, QLD, Australia) using the wild-type sequence of the *DDX3X* gene (NM\_001356) as reference.

**3. Supplementary Table 1.** Prediction of pathogenicity of the identified *DDX3X* variant by *in silico* tools.

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| **Predictor** | **Damaging score range** | **Score and functional impact** |
| SIFT | from 0 to 0.05 | 0.008 (damaging) |
| Polyphen-2 HVAR | from 0.447 to 1 | 0.859 (probably damaging) |
| LRT | from 0 to 0.0005 | 0 (damaging) |
| MutationTaster | from 0.5 to 1 | 1 (disease-causing) |
| MutationAssessor | > 0.935 | 0.695 (neutral) |
| FATHMM | < -1.5 | 2.53 (tolerated) |
| PROVEAN | from 14 to -2.5 | -5.79 (damaging) |
| VEST3 | from 0.5 to 1 | 0.699 (damaging) |
| CADD | from 20 to 39 | 26.9 (damaging) |
| DANN | from 0.96 to 1 | 0.993 (damaging) |
| fathmm\_MKL | from 0.5 to 1 | 0.91 (damaging) |
| MetaSVM | from 0.5 to 1 | -0.905 (tolerated) |
| MetaLR | from 0.5 to 1 | 0.140 (tolerated) |