**METHODS S1**

***Ethics Statements***

The study was approved by the CEIs (Comités de Ética en Investigación) from all participating centers:  
Comité de Ética de la Investigación del Hospital Universitario Virgen del Rocío  
Comité Ético de Investigación Clínica del Hospital Universitario Fundación Alcorcón  
Comité de Ética de la Investigación del Hospital Universitario Ramón y Cajal  
Comité Ético de Investigación Clínica del Hospital Clínico San Carlos  
Comité de Ética de la Investigación Clínica de la Fundación Jiménez Díaz  
Comité Ético de Investigación Clínica del Hospital Universitario 12 de Octubre  
Comité Ético de Investigación Clínica del Hospital Universitario de la Princesa  
Comité de Ética de la Investigación del Hospital Universitario Príncipe de Asturias  
In addition, the study was conducted according to the principles expressed in the Helsinki Declaration. Each individual who participated in the study signed a written informed consent form prior to blood withdrawal

**Prediction of the significance of variants**

For the prediction of the significance of variants we followed the combination of several criteria:

1) Type of the variation: whether variation results in a null variant: that is nonsense, frameshift or affecting to canonical splice sites that result in frameshift of the coding sequence, mutations affecting the initiation codon, and those leading to exon(s) deletion.

2) In-silico prediction: We used multiple bioinformatics tools and the impact was interpreted with respect to all known isoforms of each gene. For missense variants, a total of thirteen tools were examined. Therefore, we used 6 functional prediction scores (SIFT, Polyphen-2, MutationTaster, MutationAssesor, LRT, and FATHMM), 4 conservation scores (GERP++, PhyloP, PhastCons, and Grantham Score), and three ensemble-based prediction scores (CADD, LR, and RadialSVM). A threshold was set for each tool above in which the variant was classified as damaging (Table S1). In addition, all variants were analyzed using GWAVA, CADD, and the splicing predictions from the Batch version of the annotation software package Alamut (Interactive Biosoftware, Rouen, France), that integrates 5 sources: Splice Site Finder, MaxEntScan, NNSplice, GeneSplicer and Human Splicing Finder (Table S1). We also considered the dbscsnv11 database for predicting the splicing impact by Ada Boost and Random Forest (Table S1). Moreover, non-coding variants were prioritized when ReMM-score >0.8 and IW-score with an associated *P*-value<0.05.

3) Score from Regulome-DB of 1.

4) Co-occurrence with pathogenic variants.