REFERENCE LABORATORY GENETICS

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GENETIC STUDY OF WHOLE GENOME BY MASSIVE SEQUENCING (NGS)

Request No.:	**000**		
Client:	-		
Analysis code:	35032		
Patient Name:	**xxx**		
Date of Birth:	N/A	**Patient Ref.:**	xxx
Gender:	Female	**Sample Type:**	Whole blood
Sample Arrival Date:	DD/MM/AAAA	**Date of Result:**	DD/MM/AAAA

Clinical information: Patient with choroid plexus xanthogranulomas, a peculiar phenotype with suspected bone dysplasia, increased bone density compatible with osteopetrosis and blood leukoerythroblastic reaction.

Results of previous studies: Karyotype study conducted in another laboratory, with result 46XX t(12;20) (q13q;12), apparently balanced translocation. Studies of: comparative genomic hybridization by 60K array (aCGH), clinical exome, trio exome and variant c.1138G> A (p.Gly380Arg) in the FGFR3 gene were negative

RESULT

No variants of interest associated with the patient's clinical condition have been identified.

The presence, in heterozygosis, of the de novo translocation 46XX t(12; 20) (q13; q12) of uncertain clinical significance has been confirmed.

Variant*	Zygosity	Inheritance pattern
t(12;20)(q13q;12)	Heterozygosis	*De novo*

* Nomenclature according to HGVS v15.11

INTERPRETATION

The variant **t(12;20)(q13;q12)** is a structural change due to an apparently balanced translocation between the chromosomal region chr12:49345143 in the long arm of chromosome 12, where intron 1 of the *ARF3* gene is located, and the chromosomal region chr20:38765941 in the long arm of chromosome 20, which corresponds to an intergenic region.

Based on these data, the variant is classified as **Variant of Uncertain Clinical Significance.**
The *ARF3* gene (OMIM: 103190) is not currently associated with any pathology.

RECOMMENDATIONS

Genetic counselling should be offered to the patient by the prescriber physician. If additional information regarding the results or genetic counselling is required, the physician can contact our team at genetics@referencelaboratory.es.

According to the information provided, the origin of the variant is de novo. Therefore, for parents, the risk of recurrence of another affected child in future pregnancies is comparable to that of the general population. However, it is not possible to rule out a possible germinal mosaicism (presence of the variant in the gametes of one of the parents), so it is possible to offer a prenatal diagnosis in future pregnancies.

METHODOLOGY

DNA extraction and quantitative and qualitative evaluation of the DNA obtained.

Capture and enrichment of genomic regions with the Whole Genome Seq™ technology.

Massive sequencing with the NovaSeq™ (Illumina) sequencer.

Identification of the variants of interest in regard to the reference genome (hg19) after filtering, according to specific quality criteria. Annotation of the obtained variants with a specific bioinformatic software: Alamut Visual™ (Interactive Biosoftware), Ingenuity Variant Analysis™ (QIAGEN), Variant interpreter™ (Illumina) and VarAFT™. The used reference databases have been the population databases dbSNP, 1000genomes, EXAC and gnomAD; the clinical databases Human Gene Mutation Database (HGMD version 2019.3), ClinVar and LOVD; the disease specific databases, if applicable, and Reference Laboratory Genetics´own databases. The bioinformatic analysis to evaluate the possible impact of the variants of interest on the structure and functionality of the protein has been carried out with the bioinformatic programs Mutation Taster, SIFT and PolyPhen-2. These analyses are only a predictive tool; they were not experimentally proven.

The nomenclature used to define the variants follows the criteria of the *Human Genome Variation Society (HGVS)* (http://www.HGVS.org/varnomen).

Classification of variants based on the recommendations of the *American College of Medical Genetics and Genomics (ACMG)* (Richards S. *et al*., 2015). Only those variants that, based on current information, are considered pathogenic, likely pathogenic or of uncertain clinical significance, are reported. (The complete list of identified variants is available upon request).

The obtained average reading depth was 32,59x.

The reported INDEL variants are confirmed by Sanger sequencing.

LIMITATIONS: The results obtained do not exclude variants outside the analysed regions of the genome or genetic anomalies not detectable by massive sequencing such as large rearrangements, large deletions/duplications (Copy Number Variant; CNV), insertions / deletions of> = 10 nucleotides, variants in repetitive regions or with a high percentage of GC, and variants in genes with pseudogenes with highly homologous sequences.
It is not possible to rule out the presence of variants in other unanalysed genes.

IMPORTANT NOTE

The information contained in this report is based on current scientific knowledge and the results obtained from the application of the technology in this report, are detailed. Due to continuous advances, the documented information may be modified in the future as a result of the emergence of new scientific evidence.
The genetic/genomic studies carried out by Reference Laboratory S.A. are exclusively intended for qualified health professionals for their interpretation. The results obtained are not, per se, a medical consultation, diagnosis or treatment, nor should they be interpreted as such. Only a specialized professional can correctly interpret the results and offer a diagnosis or prescribe a treatment to a patient based on these. Consequently, no information obtained from our studies can be used to replace the advice and diagnosis of a specialized professional.

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