Triple Diagnosis established by Whole Exome Sequencing

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Whole exome sequencing (WES) was requested to determine the possible genetic cause of symptoms (table 1, figure 1) for a 37-year-old Lebanese patient. WES performed on Illumina Platform only for the index (Nextera Rapid Capture Exome Kit, ~95% of target bases were covered at ≥10x). All disease-causing variants reported in HGMD®, in ClinVar or in CentoMD® (class 1), as well as all variants with minor allele frequency (MAF) of less than 1% in ExAC/gnomAD were considered. Using WES as a diagnostic tool, three different molecular diagnoses (table 2) have been discovered for this patient with a complex phenotype (table 3).

	FEATURES
DYSMORPHIC FEATURES	Hypertelorism
	Microphthalmia
	Blepharphimosis
	Epicanthus
	Short palpebral fissures
	Broad nasal root
	Long nose
	Hypoplastic alae nasi
	Thick vermilion of upper and lower lips
	Mild mandibular prognathism
DENTAL	Caries
	Hypodontia
	Microdontia
NEUROLOGIC	Developmental delay
	Intellectual Disability
	Hydrocephaly
	Seizures (clonic)
SKIN	Smooth, thin, dry skin
	Hypotrichosis (scalp)
SKELETAL	Hypoplastic ribs first ribs from both side
	Brachydactyly
	Radio cubital synostosis
	Delayed bone age
GENITAL	Micropenis
	Ectopic testis

Table 1: Clinical Findings

GENE (TRANSCRIPT)	NUCLEOTIDE [PROTEIN]	ZYGOSITY	CLASSIFICATION[1]	DISORDER (OMIM[2], INHERITANCE)
THOC6 (NM_024339.3)	c.893del [p.(Pro298Glnfs*20)]	Hom.	Likely pathogenic	Beaulieu-Boycott-Innes Syndrome (613680, AR)
PTCH2 (NM_003738.4)	c.528del [p.(Met176Ilefs*9)]	Het.	Likely pahtogenic	Basal cell nevus syndrome (109400, AD)
EDAR (NM_022336.3)	c.486del [p.(Ser163Argfs*26)]	Het.	Pathogenic	Ectodermal dysplasia type 10A (129490, AD/AR)

Table 2: WES Results

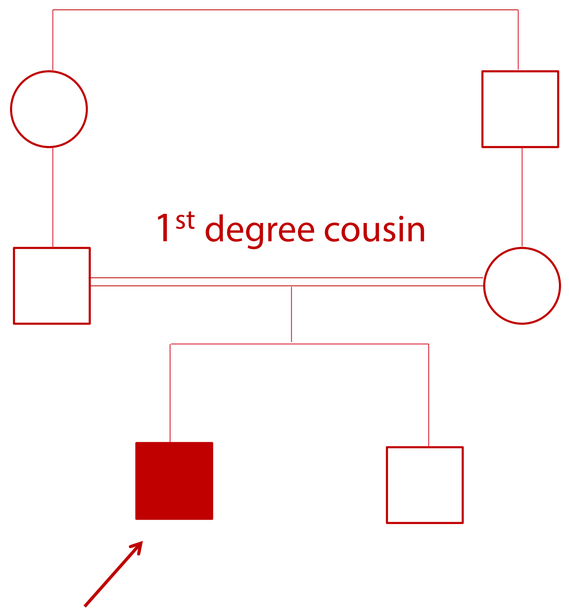

Figure 1: Pedigree

SYSTEMS	FEATURES	THOC6	EDAR	PTCH2
Dysmorphism	Short palpebral fissures	+		
	Broad nasal root			+
	Long nose	+		
	Thick vermilion of upper and lower lips	+		
	Mild mandibular prognathism			+
Dental	Caries	+		
	Hypodontia		+	
	Microdontia		+	
Neurologic	Developmental delay	+		
	Intellectual Disability	+		+
Skin	Smooth, thin, dry skin		+	
	Hypotrichosis (scalp)		+	
Skeletal	Hypoplastic ribs first ribs from both side			+
	Brachydactyly			+

Table 3: Features explained by WES Results

References

1. Richards S. *et al.* 2015
2. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), {20.01.2017}. World Wide Web URL: https://omim.org/

Disclosures

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