MAIN FINDINGS

SEQUENCE VARIANTS							
GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES **	TYPE AND CLASSIFICATION ***
UBA1	NM_003334.3:c.121A>G	p.(Met41Val)	N/A	Heterozygous	PolyPhen: Benign Align-GVDG: C15 SIFT: Tolerated MutationTaster: Disease causing Conservation_nt: high Conservation_aa: high	gnomAD: - ESP: - 1000 G: - CentoMD: -	Missense Likely pathogenic (class 2)

Variant annotation based on OTFA (using VEP v94). * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

VARIANT INTERPRETATION

UBA1, c.121A>G p.(Met41Val)

The *UBA1* variant c.121A>G p.(Met41Val) causes an amino acid change from Met to Val at position 41. This variant has been confirmed by Sanger sequencing. ClinVar lists this variant (Interpretation: Conflicting interpretations of pathogenicity; Pathogenic (4)|Likely pathogenic(1)|Uncertain significance(1); Variation ID: 836983). It is classified as likely pathogenic (class 2) according to the recommendations of CENTOGENE and ACMG (please, see additional information below).

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome (VEXAS) is an adult-onset inflammatory disease that affects only males and is caused by somatic, not germline, mutations. The disorder is characterized by adult onset of rheumatologic symptoms at a mean age of 64 years. Features include recurrent fevers, pulmonary and dermatologic inflammatory manifestations, vasculitis, deep vein thrombosis, arthralgias, and ear and nose chondritis. Laboratory studies indicate hematologic abnormalities, including macrocytic anemia, as well as increased levels of acute-phase reactants; about half of patients have positive autoantibodies. Bone marrow biopsy shows degenerative vacuolization restricted to myeloid and erythroid precursor cells, as well as variable hematopoietic dyspoiesis and dysplasias. Mode of Inheritance: somatic (OMIM®: 301054).
A recent study (Huang et al., 2021, PMID: 33741056) indicated that patients with myelodysplastic syndromes (MDS) and autoimmune disorders (AD) who have characteristic vacuoles in myeloid and erythroid precursor cells should be screened for UBA1 mutation. These patients are likely to have VEXAS syndrome and unlikely to improve with immunosuppressive drugs and should be considered for other alternative therapies. Pathogenic variants in the *UBA1* gene are also associated with X-linked spinal muscular atrophy-2 (SMAX2). Mode of Inheritance: X-linked recessive (OMIM®: 301830).

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