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Clinical and Molecular Characters of a Yemeni Child with Wiskott-Aldrich Syndrome

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Abstract

Wiskott-Aldrich Syndrome is an x-linked immunodeficiency condition characterized by microthrombocytopenia, eczema and recurrent infections. It is caused by mutations in the Wiskott Aldrich Protein (WASP) gene. Hereby we report a 13-month-old Yemeni male infant with mutation in WASP Gene, who presented with congenital microthrombocytopenia, eczema, bleeding tendency and recurrent infections. The variant found in this case creates a shift in the reading frame located in the exon 10 of WAS gene. These variants were also detected in the child's mother in heterozygous state.

Subject Areas

Internal Medicine

Keywords

Wiskott-Aldrich, Microthrombocytopenia, Eczema, Yemen

1. Introduction

Wiskott-Aldrich Syndrome is an x-linked immunodeficiency condition characterized by microthrombocytopenia, eczema and recurrent infection [1]. Wiskott-Aldrich Syndrome is due to a mutation in the Wiskott-Aldrich syndrome protein (WASP) Gene [2]. The WASP Gene was discovered in 1994. It comprises 12 exons that encode 502 amino acids [3]. WASP plays an important role in actin cytoskeletal rearrangement widely expressed in hematologic lineage. Absence or

defective WASP leads to disturbance in cellular and humoral immunity, as well as impaired platelets formation [4]. Mutations in WASP are now known to result in a clinical spectrum which encompasses three clinical forms; classical WAS with the triad of thrombocytopenia, eczema and recurrent infection, X-linked Thrombocytopenia (XLT) which is the milder form and X-linked neutropenia (XLN) without features of classical WAS or XLT [5]. Classical WAS carries the poorest prognosis and currently the only curative therapy is Hematopoietic Stem Cell Transplantation (H.S.C.T) [6] [7]. In Asia various mutations have been discovered in several countries [8] [9]. Herein we describe a Yemeni male infant with a classical Wiskott-Aldrich Syndrome and a variant mutation of WAS gene.

2. Case Presentation

A 13-month-old infant was referred to us with a chief complaint of fever, purpuric skin rash, recurrent eczema since infancy. He was the product of full term normal vaginal delivery of an unconsanguineous marriage. He was apparently well until 6 months of age when he has developed eczema over the face, neck, back and trunk, skin purpuric rash, and bleeding from gums and nose. He visited several doctors in Ibb and Sana'a Cities, where different medications were given but no improvement was noted and no diagnosis was reached. Clinical examination revealed a feverish and anemic infant with upper respiratory tract infection, eczema with scratching marks over his face, purpuric rash spread over legs, and there was mild splenomegaly. The laboratory investigations during 2017 are presented in (**Table 1**) and showed no significant improvement in hemoglobin level and platelet counts despite transfusions of packed RBC'S and platelets concentrates. Blood film study showed thrombocytopenia with small sized platelets (**Figure 1**). Bone marrow aspiration showed normal cellularity with presence of megakaryocytes forming small platelets. According to the described clinical manifestations and laboratory data with anemia and thrombocytopenia with small platelets, the diagnosis of Wiskott-Aldrich Syndrome was considered with a recommendations of undergoing genetic analysis for confirmation of the diagnosis. The patient was treated with corticosteroid, intravenous immunoglobulin, broad spectrum antibiotics, and blood transfusion as needed and his parents was advised to go with their child outside our country for further investigations including gene analysis and hematopoietic stem cell transplantation which are not available in Yemen. They went to Saudia Arabia and blood samples from the patient and his mother were sent to Germany (CENTOGEN Gold Laboratory) for genetic analysis. The results confirmed the initial diagnosis of WAS syndrome were a whole exon sequencing showed a variant mutation of WASP Gene; WAS c.1250del p.(Pro417Leuf*28) was located in exon 10 and creates a shift in reading frame starting at code 417 (**Figure 2** and **Figure 3**). The new frame ends in a stop codon 27 positions downstream (**Figure 3**). The mutation analysis of the mother was the same mutation variant found in her child but

in a heterozygous state (Figure 4). At present the baby still in Saudi Arabia waiting in the list for bone marrow transplantation.

Table 1. Results of hematological parameters of our patient during 2017.

Date	Hb mg/dl	WBC (cell/mm^3)	Platelets count (cell/mm^3)	ESR (%)
16/03/2017	5.9	11,600	32,000	-
10/04/2017	6.1	6600	6000	110
10/04/2017	9	6680	18,000	-
17/04/2017	8.5	12,000	18,000	65
24/04/2017	7.4	4700	35,000	69
01/05/2017	6.5	12,900	4000	-
08/05/2017	9.6	7100	4000	-
15/05/2017	9	9500	9000	-
22/05/2017	8	4200	10,000	126
28/05/2017	7.7	4100	9000	-
05/06/2017	7.5	9500	17,000	140
12/06/2017	7	13,600	15,000	70
03/07/2017	6.7	7800	11,000	121
13/07/2017	7.5	5700	27,000	59
20/07/2017	8.3	6400	13,000	98
07/08/2017	9.6	10,400	12,000	103
23/10/2017	8.2	7500	10,000	81
26/10/2017	8	6100	12,000	79
30/10/2017	8.7	5800	10,000	120
23/11/2017	8	11,400	12,000	129
30/11/2017	7.6	9000	8000	-

Hb = hemoglobin, WBCs = White blood cells, ESR = erythrocyte sedimentation rate.

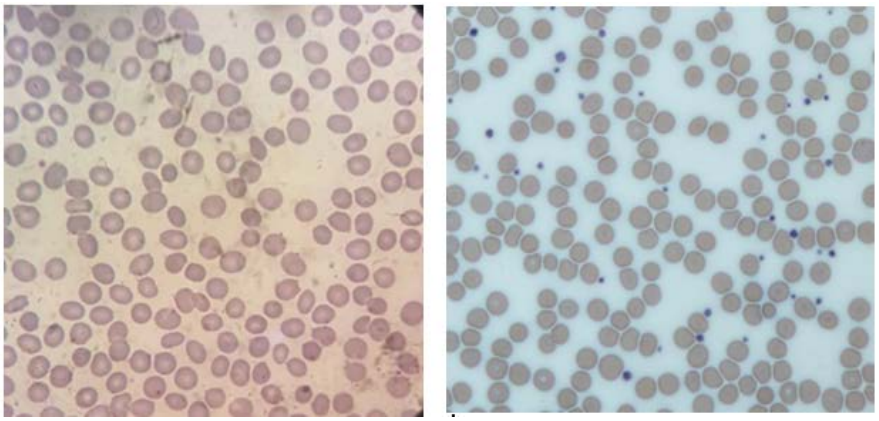
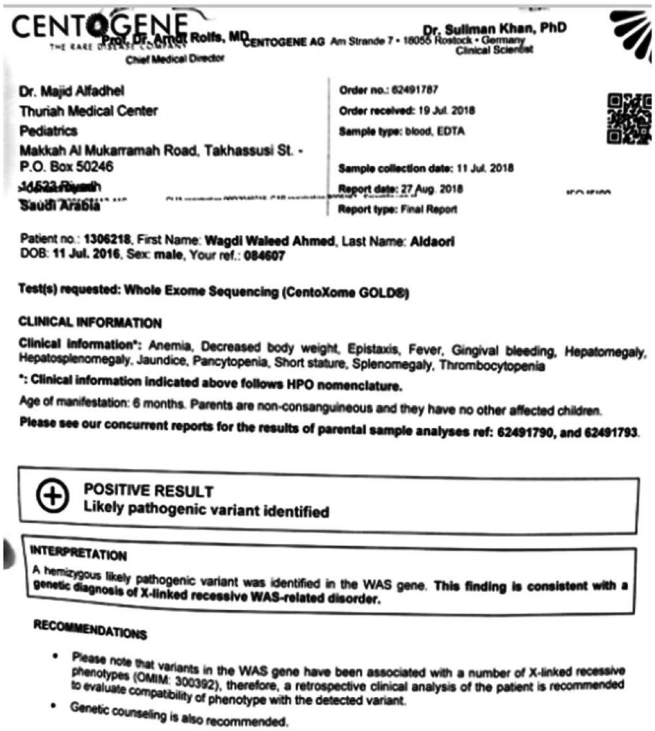


Figure 1. Blood film of our patient in the Left in comparison with normal blood film in the right.



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Order no.: 62491787
Order received: 19 Jul. 2018
Sample type: blood, EDTA
Sample collection date: 11 Jul. 2018
Report date: 27 Aug. 2018
Report type: Final Report

Patient no.: **1306218**, First Name: **Wagdi Waleed Ahmed**, Last Name: **Aldaori**
DOB: **11 Jul. 2016**, Sex: **male**, Your ref.: **084607**

Test(s) requested: Whole Exome Sequencing (CentoXome GOLD®)

CLINICAL INFORMATION

Clinical information*: Anemia, Decreased body weight, Epistaxis, Fever, Gingival bleeding, Hepatomegaly, Hepatosplenomegaly, Jaundice, Pancytopenia, Short stature, Splenomegaly, Thrombocytopenia

***: Clinical information indicated above follows HPO nomenclature.**

Age of manifestation: 6 months. Parents are non-consanguineous and they have no other affected children.

Please see our concurrent reports for the results of parental sample analyses ref: 62491790, and 62491793.

POSITIVE RESULT
Likely pathogenic variant identified

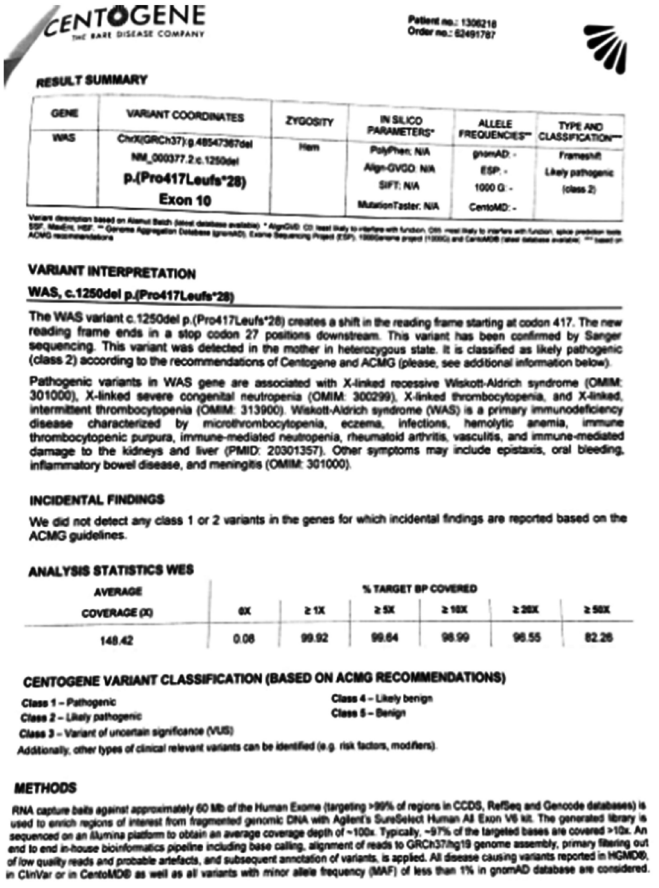
INTERPRETATION

A hemizygous likely pathogenic variant was identified in the WAS gene. **This finding is consistent with a genetic diagnosis of X-linked recessive WAS-related disorder.**

RECOMMENDATIONS

- Please note that variants in the WAS gene have been associated with a number of X-linked recessive phenotypes (OMIM: 300392), therefore, a retrospective clinical analysis of the patient is recommended to evaluate compatibility of phenotype with the detected variant.
- Genetic counseling is also recommended.

Figure 2. Genetic analysis of the studied infant.



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Patient no.: 1306218
Order no.: 62491787

RESULT SUMMARY

GENE	VARIANT COORDINATES	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
WAS	ChrX(GRCh37):g.48547367del NM_000377.2:c.1250del **p.(Pro417Leufs*28)** **Exon 10**	Hem	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A	gnomAD: - ESP: - 1000 G: - CentoMD: -	Frameshift Likely pathogenic (class 2)

Variant detection based on Alamut Batch (latest database available). * AlignGVGD: C0 least likely to interfere with function, C65 most likely to interfere with function, splice prediction tools: ESF, MaxEnt, HSF. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations

VARIANT INTERPRETATION

WAS, c.1250del p.(Pro417Leufs*28)

The WAS variant c.1250del p.(Pro417Leufs*28) creates a shift in the reading frame starting at codon 417. The new reading frame ends in a stop codon 27 positions downstream. This variant has been confirmed by Sanger sequencing. This variant was detected in the mother in heterozygous state. It is classified as likely pathogenic (class 2) according to the recommendations of Centogene and ACMG (please, see additional information below).

Pathogenic variants in WAS gene are associated with X-linked recessive Wiskott-Aldrich syndrome (OMIM: 301000), X-linked severe congenital neutropenia (OMIM: 300299), X-linked thrombocytopenia, and X-linked, intermittent thrombocytopenia (OMIM: 313900). Wiskott-Aldrich syndrome (WAS) is a primary immunodeficiency disease characterized by microthrombocytopenia, eczema, infections, hemolytic anemia, immune thrombocytopenic purpura, immune-mediated neutropenia, rheumatoid arthritis, vasculitis, and immune-mediated damage to the kidneys and liver (PMID: 20301357). Other symptoms may include epistaxis, oral bleeding, inflammatory bowel disease, and meningitis (OMIM: 301000).

INCIDENTAL FINDINGS

We did not detect any class 1 or 2 variants in the genes for which incidental findings are reported based on the ACMG guidelines.

ANALYSIS STATISTICS WES

AVERAGE COVERAGE (X)	% TARGET BP COVERED					
	0X	≥ 1X	≥ 5X	≥ 10X	≥ 20X	≥ 50X
148.42	0.08	99.92	99.64	98.99	96.55	82.26

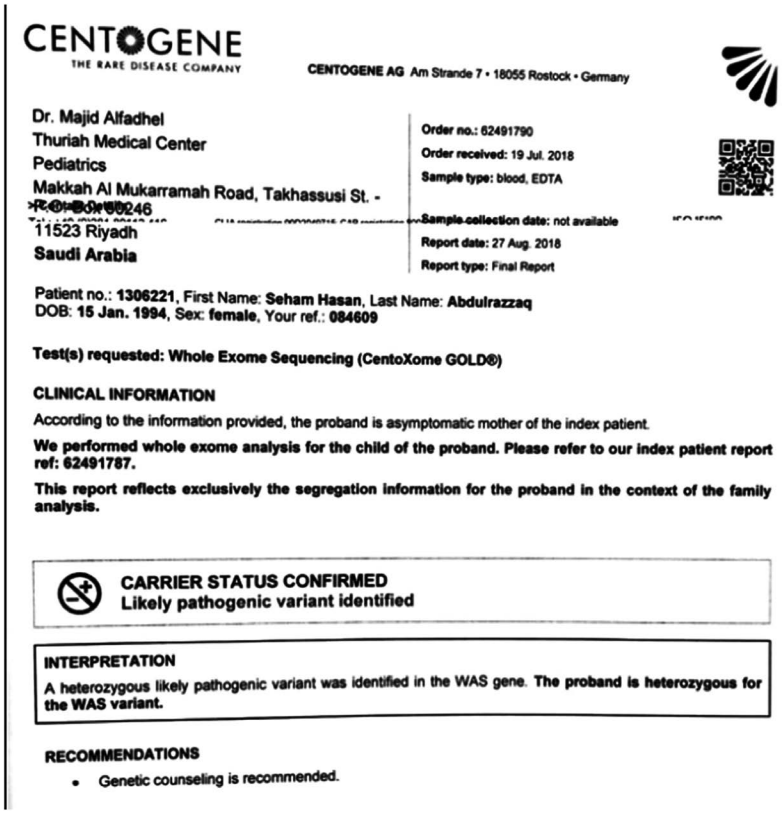
CENTOGENE VARIANT CLASSIFICATION (BASED ON ACMG RECOMMENDATIONS)

Class 1 – Pathogenic
Class 2 – Likely pathogenic
Class 3 – Variant of uncertain significance (VUS)
Class 4 – Likely benign
Class 5 – Benign
Additionally, other types of clinical relevant variants can be identified (e.g. risk factors, modifiers).

METHODS

RNA capture baits against approximately 60 Mb of the Human Exome (targeting >99% of regions in CCDS, RefSeq and Genocde databases) is used to enrich regions of interest from fragmented genomic DNA with Agilent's SureSelect Human All Exon V6 kit. The generated library is sequenced on an Illumina platform to obtain an average coverage depth of ~100x. Typically, ~97% of the targeted bases are covered >10x. An end to end in-house bioinformatics pipeline including base calling, alignment of reads to GRCh37/hg19 genome assembly, primary filtering out of low quality reads and probable artefacts, and subsequent annotation of variants, is applied. All disease causing variants reported in HGMD®, in ClinVar or in CentoMD® as well as all variants with minor allele frequency (MAF) of less than 1% in gnomAD database are considered.

Figure 3. Genetic analysis of the studied infant.



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Order no.: 62491790
Order received: 19 Jul. 2018
Sample type: blood, EDTA
Sample collection date: not available
Report date: 27 Aug. 2018
Report type: Final Report

Patient no.: **1306221**, First Name: **Seham Hasan**, Last Name: **Abdulrazzaq**
DOB: **15 Jan. 1994**, Sex: **female**, Your ref.: **084609**

Test(s) requested: Whole Exome Sequencing (CentoXome GOLD®)

CLINICAL INFORMATION

According to the information provided, the proband is asymptomatic mother of the index patient.

We performed whole exome analysis for the child of the proband. Please refer to our index patient report ref: 62491787.

This report reflects exclusively the segregation information for the proband in the context of the family analysis.

CARRIER STATUS CONFIRMED
Likely pathogenic variant identified

INTERPRETATION

A heterozygous likely pathogenic variant was identified in the WAS gene. **The proband is heterozygous for the WAS variant.**

RECOMMENDATIONS

- Genetic counseling is recommended.

Figure 4. Genetic analysis of the infant's mother.

3. Discussion

Wiskott-Aldrich Syndrome varies considerably in severity and is usually manifested in the first weeks or months of life with bleeding tendency due to congenital thrombocytopenia, frequently presented with bloody diarrhea, epistaxis, gingival bleeding or petechial rash of the skin and oral mucosa [10] [11] [12]. Subsequently recurrent bacterial infections develop commonly as upper respiratory tract infection, otitis media, pneumonia etc. [12]. There is also depressed cell mediated immunity with increased risk of viral and fungal infections [13]. Eczema is the most common variable feature and is indistinguishable from atopic dermatitis, with scratching [14]. Later in the course of the disease, other manifestations can be noted such as autoimmune hemolytic anemia, arthritis, nephropathy, and increase incidence of malignancy [14] [15]. Our case demonstrated characteristic clinical triad of Wiskott-Aldrich syndrome in the form of intermittent bleeding because of thrombocytopenia, recurrent infections, and intractable eczema since infancy. Low platelets count and small platelets size seen in blood film clinched the diagnosis in favor of Wiskott-Aldrich syndrome, and the diagnosis was confirmed by genetic study. We directed our treatment mainly to control bleeding through transfusions of blood and platelets, and control of infections with antibiotics and Immunoglobulin replacement and we advised our patient's parents to travel for Hamatopoeitic stem cell Transplantation as cure can only be achieved with it [16]. To the best of our knowledge no pre-

vious report about Wiskott-Aldrich Syndrome in Yemeni patient, and few reports were published from Saudi Arabia, Lebanon and Syria (Arab Genomic Center) [17]. More than 300 mutations of the WASP have been reported; mainly of missense/nonsense mutations, among various ethnic groups, these mutations have been reported in all 12 exon with the majority involves the first 3 exon [18] [19]. In our patient the mutation was (WAS exon 10, c.1250del p.(Pro417Leufs*28). This mutation resulting in creating new frame shift starting in codon 417 and ends in codon 27 down stream (WAS Variant) resulting in sever clinical presentations in our patient resembling classical Wiskott-Aldrich Syndrome.

4. Conclusion

We report the clinical manifestations, laboratory investigations and molecular characterization of a Yemeni child with Wiskott-Aldrich Syndrome. Wiskott-Aldrich Syndrome is a rare condition which needs a high index of suspicion for early diagnosis and should be suspected in any male infant with Eczema, recurrent infection and congenital thrombocytopenia.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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