Detection of Six Novel Mutations in WASP Gene in Fifteen Iranian Wiskott-Aldrich Patients

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Received: 27 December 2011; Received in revised form: 11 January 2012; Accepted: 24 January 2012

ABSTRACT

Wiskott-Aldrich syndrome (WAS) is a life-threatening X-linked recessive immunodeficiency disease described as a clinical triad of thrombocytopenia, eczema, and recurrent infections, caused by mutations of the WAS protein (WASP) gene. The milder form of this disease is X-Linked thrombocytopenia (XLT) that presents only as platelet abnormalities. Mutation analysis for 15 boys with Wiskott-Aldrich syndrome was performed. Five previously reported mutations and six novel mutations including G8X, R41X, D283E, P412fsX446, E464X, and AfsX358 were detected.

Keywords: Mutations; Thrombocytopenia; Wiskott-Aldrich syndrome

INTRODUCTION

Wiskott-Aldrich syndrome (WAS) was first described by Wiskott in 1937 and was further characterized by Aldrich in 1954. It is an X-linked recessive immunodeficiency syndrome characterized by recurrent bacterial, eczema, and bleeding diathesis caused by thrombocytopenia and decreased platelet volume. However, only a third of patients with the syndrome have the classic triad symptoms.1 The gene for the Wiskott-Aldrich syndrome protein (Wasp) is localized to Xp11.22-23 and consists of 12 exons that has 502 amino acid (53 kD) protein. Wasp is a cytosolic protein that is expressed on all hematopoietic cell lineages and is essential factor for normal antibody function, T-cell responses and platelet production.2

It also regulates transcription, actin polymerization and a selective post-transcriptional role in Th2 effector
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cDNA and genomic DNA. Based on searching the literature and the human gene mutation database, we hereby report six novel WASP gene mutations identified in Iranian Wiskott Aldrich cases, i.e., G8X, R41X, D283E, P412fsX446, E464X, and AfsX358 (Figure 1).

A mutation was found predominantly in exon 1, which leads to changing of Arginine at position 13 to stop codon. The 2 other new mutations in exon 1; R41X, and G8X point mutation lead to a premature stop codon in the WH1 domain. G70R mutation in exon 2 located in WASP homology I (WHI) domain, interacts with PIP2 and WASP interacting protein (WIP) resulting in missense substitution which was described previously.16 Point mutation detected in exon 2 (A56V) which leads to an amino acid change in the WH1 domain, had been previously reported.17 Considering the existence of this unique mutation in two unrelated patients in a few number of cases involved in this study, it may be possible to claim that this mutation is one of the hotspot sites, in WAS gene.

**Figure 1.** Diagrams of WASP mutations identified by sequencing method in patients. WASP gene mutations in WAS patients are identified by arrow: 1) Exon 1 have a substitution of cytosine for thymine 37 (R13X). 2) The mutation in exon 1, resulting in substitution of cytosine 121 to thymine (R41X). 3) The mutation in exon 1, resulting in substitution of guanine 22 to thymine (G8X). 4) The mutation in exon 2, resulting in substitution of guanine 208 to adenine (G70R). 5) The mutation in exon 2, resulting in substitution of cytosine 167 to thymine (A56V). 6) The mutation in exon 4, resulting in substitution of cytosine 381 to guanine (N127K). 7) The mutation in exon 9, resulting in substitution of cytosine 849 to guanine (D283E). 8) The mutation in exon 10, resulting in deletion of cytosine 1281 (P412fsX445). 9) The mutation in exon 10, resulting in insertion of adenine (AfsX358). 10) The mutation in exon 11, resulting in substitution of guanine 1390 to thymine (E464X).
A new mutation was observed in exon 9, that leads to changing of Aspartic acid at position 283 to Glutamic acid. Two new mutations in exon 10 were also identified, which generate frame shift, bringing stop codon including a deletion and an insertion mutation. A new E464X mutation was found in exon 11. The control group was negative for these mutations.

A more direct method for diagnosis of new mutations should always be coupled with direct mutation analysis, such as WASP expression to suggest a correlation between the level of WASP expression and variation in expressed phenotypes of clinically affected patients. The data presented here suggests the diagnostic approaches in patients suspected of to WAS disease and also provide further information concerning the spectrum of WASP mutations responsible for Wiskott-Aldrich. Our data are similar to those of previous reports and support the importance of the N-terminal of WASP in its function due to the clustering of WAS mutations within the 2 exons of the gene (WH1 domain).

REFERENCES