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The Phenomenon of Spontaneous Genetic Reversions in the Wiskott-Aldrich Syndrome: A Report of the Workshop of the ESID Genetics Working Party at the XIIth Meeting of the European Society for Immunodeficiencies (ESID). Budapest, Hungary October 4–7, 2006

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Abstract The Wiskott-Aldrich syndrome (WAS) is a primary immunodeficiency disease caused by mutations in the Wiskott-Aldrich Protein (WASP) gene, which typically leads to absent WASP protein expression in WAS leukocytes. However, some patients have been found with small populations of WASP-expressing cells caused by reverse or second-site mutations that allow protein expression. An international consortium was established to further investigate these phenomena. This paper summarizes data collected by this consortium that was presented at a workshop held during the XIIth Meeting of the European Society for Immunodeficiencies (ESID), October, 2006. WASP reversions were noted in approximately 11% of 272 patients tested. Many different cell lineages showed reversions. These data form the foundation for further investigation into this phenomenon, which has implications for therapy of this disease.

Keywords Wiskott-Aldrich syndrome · mutation · reversion · flow cytometry

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Introduction

The Wiskott-Aldrich syndrome (WAS, OMIM #301000) is an X-linked primary immunodeficiency disease characterized by thrombocytopenia with small platelets, humoral and cell-mediated immune dysfunction, autoimmunity, increased risk of malignancy, and eczema. It is caused by mutations in the gene for the Wiskott-Aldrich syndrome protein (WASP). "Spontaneous genetic reversion" in this syndrome refers to the observation of a population of WASP-positive cells in the peripheral blood of a patient in whom the majority of the cells are WASP-negative, that is, whose original mutation had resulted in the absence of WASP expression [1, 2]. These patients thus demonstrate somatic mosaicism with respect to the presence of WASP in peripheral blood cells. Genetic mechanisms causing revertant cells to appear include true back-mutations in which the original DNA sequence has been restored, fully compensating same-site mutations, in which the original mutation is not perfectly corrected, but the coding sequence is reverted to normal, or second-site mutations that allow the synthesis of either a normal or partially defective protein.

The initial reports of spontaneous genetic reversions in the Wiskott-Aldrich syndrome led to the establishment of an international consortium to study mosaicism (chimerism) in WAS patients in July, 2004. Drs. Tadashi Ariga and Masafumi Yamada of Hokkaido Medical School in Sapporo, Japan and Drs. Fabio Candotti, Donn M. Stewart, and David L. Nelson of the NIH in Bethesda, Maryland, USA, organized this consortium. Participants in the consortium were provided a monoclonal antibody, 3F3A5, recognizing the WAS gene product, WASP, and were encouraged to

examine nontransplanted patients for somatic mosaicism in peripheral blood cells by flow cytometry [1, 2]. The technique [3] is highly suited for this purpose, as it allows for the detection of protein at the single-cell level, and is rapid, sensitive, and specific. Data returned to the consortium organizers was collected and discussed at a workshop held during the XIIth Meeting of the European Society for Immunodeficiencies (ESID), in Budapest, Hungary from October 4 to 7, 2006. This workshop was held under the auspices of the ESID Genetics Working Party to consider the phenomenon of "Spontaneous Genetic Reversions in the Wiskott-Aldrich syndrome." This brief report summarizes the content of this workshop. The groups and individuals submitting data to the workshop, including members of the ESID Genetics Working Party, are listed in the Acknowledgements section of this paper.

Results and Discussion

The XIIth Meeting of ESID was viewed as an opportune venue to collect and collate the available data about spontaneous genetic reversions in the WAS as most participating investigators were likely to be in attendance. In the summer of 2006, a questionnaire regarding reversions in WAS was sent to those groups/laboratories who had agreed to participate in the consortium and was also sent to members of the ESID. All responses were received at the NIH. In brief, respondents were asked how many WAS patients they had followed or were following, whether they had looked for reversions and by what methods, and if reversions had been found or not. If reversions had been observed, the respondents were asked for data on the patient's age, disease severity, and the following, if known: 1) the cell lineages in which revertant cells were observed, 2) the clonality of the revertant cells, and 3) the mutant WASP sequence and the sequence resulting in reversion to somatic mosaicism (chimerism).

A total of 40 groups/laboratories from 16 countries responded to the questionnaire and 612 WAS patients had been or were currently under observation. Of the 40 groups/laboratories reporting, 14 had looked for reversions in a total of 272 patients and 11 laboratories had found them. A total of 30 patients with revertant somatic mosaicism were identified.

The submitted data are summarized in Table I. As can be seen, spontaneous genetic reversions in the WAS have been observed in many parts of the world. These reversion events have been observed in patients from <1 year of age to patients >40 years of age. A clinical scoring system has been proposed for the WAS [4], which allows a general description of disease severity (score 1–5, from mild to severe disease). Genetic reversions were found at all clinical scores from 1 through 5. No correlation appeared between the occurrence of a reversion and the severity of the disease. This might be caused by the broad nature of the scoring classification and the possibility that this system might not accurately reflect disease severity as it relates to this particular event. It should be pointed out that no data were collected for the clinical scores of WAS patients not undergoing reversions, so this comparison was not possible. Moreover, once a genetic reversion was observed there appeared to be little clinical score change with time, but the data to support this is limited. This again could reflect the broad nature of the scoring system and/or the lack of sufficient time for the reversion to become clinically significant. In this regard, it should be pointed out that very little data exist regarding the amount of chimerism necessary after bone marrow transplantation to achieve clinical improvement in the WAS (L. Filipovich, personal communication). For durability of the reversion process, once a reversion was observed in a particular patient it was always observed subsequently when testing was performed. That is to say, these reversion events were not transient and once established the revertant cells tended to persist or expand, rather than disappear. Studies of the cells affected by the reversion process revealed that multiple lineages of hematopoietic cells could be involved. The usual cellular frequencies observed were T cells > B cells > NK cells. Some patients had reversions limited to T cells. Reversions in T cells were found in both CD4+ and CD8+ cells [1, 5] and in both memory (CD45RO+) and naïve (CD45RA+) cells [1, 5]. Investigations of cellular clonality by T-cell receptor type using monoclonal antibodies or by immunoscope revealed both polyclonality and oligoclonal populations of the revertant cells in several lineages.

In most of the reported cases, the sequence of the original mutation and the revertant was determined. Figure 1 shows the locations in the WASP cDNA of the mutations that reverted, along with a large group of mutations in WASP previously reported for comparison [6]. Mutations that reverted include missense and nonsense substitutions in exons, insertions and deletions, and splice-site mutations. There seemed to be no favored location for mutations that reverted; however, it should be noted that 30% of the reversions occurred in exon 10.

Several of the groups reporting reversions to the consortium have published the sequence data (Table II). In the discussion that follows, sequence data are referred to the WASP mRNA sequence HS12707. (For readers interested in the sequence data of unpublished reversions, please contact the individual laboratories).

In some cases, the initial mutation was truly reversed. The substitution mutation seen in Sapporo patient 1 was reversed by another substitution event at the same base [1], and the A insertion seen by the Boston group was reversed

Table I Revertant Patients

Laboratory	Patient #	Age at discovery	Clin. Score before/after	T-cells**	B-cells**	NK-cells**	Monocytes**	Other cells†	Clonality
Buenos Aires	1	2 years	4/4	Y (9%)	N	N	N		Polyclonal
	2	<1 year	5/5					1	
Hannover	1	1 year		Y(35%)	N	N	N	2	NT
	2	3 years		Y(45%)	N	Y(30%) CD56	N	2	NT
	3	4 years		Y(64%)		Y(30%)			NT
Brescia	1	8 months*	2 to 3/2	Y(40%)	Y (100%) CD20	Y(80%) CD56	N		
	2	10 months*							
	3	10 months*	/3						
	4	3 years	/2 to 3						
Milano	1	20 years	5/5	Y	N	N	N		
Sendai	1	15 years	/5	Y(16%)	N	N(4.4%) CD56	N		NT
	2	18 years	/2	Y(7%)	N	N(0.7%)	N		NT
	3	10 years	5/5	Y(61%)	N	Y(25%) CD56	N		Oligoclonal T
Sapporo	1	32 years	5/5	Y(55%, CD4 10%, CD8 60%)	N	N	N	2	Polyclonal
	2	4 years	?/?						NT
	3	8 years	?/?	Y(CD4 6%, CD8 54%)	Y(1.5%) CD20	Y(88.4%) CD56	N		NT
Moscow	1	12 years	5					3	NT
	2	2 years	2 to 3					4	NT
	3	3 months	2	Y(5%)	N	N	N		NT
London	1		/4	Y(10%)					
Bethesda (Candotti lab)	1	22 years	5/	Y(80%)	NT	NT	NT		NT
	2	43 years	?/5	Y(80%)	N	N	N		Oligoclonal T
	3	12 years	?/5	Y(38%)	N	N	N		NT
	4	8 years	?/5	Y(25%)	Y(mol. evid.)	N	N		Oligoclonal
	5	41 years	5/5	Y(10%)	Y (20%)	N	N		NT
	6	16 years	3/3	Y(28%)	N	N	N		NT
Boston	1	9 years	/1 to 2	N	N	Y(>40%) CD56+ CD3-	NT		NT
	2	not specified							
	3	not specified							
Seattle	1	not specified	5/5	Y(36-53%)	Y(5-10%) CD19	Y(2%) CD56			No

*Found by sequencing PBMC

**Y = yes, N = no, NT = not tested, % positive if yes

† 1 = lymphocytes 50% (not specified), 2 = No, 3 = 10% not specified, 4 = 14% not specified

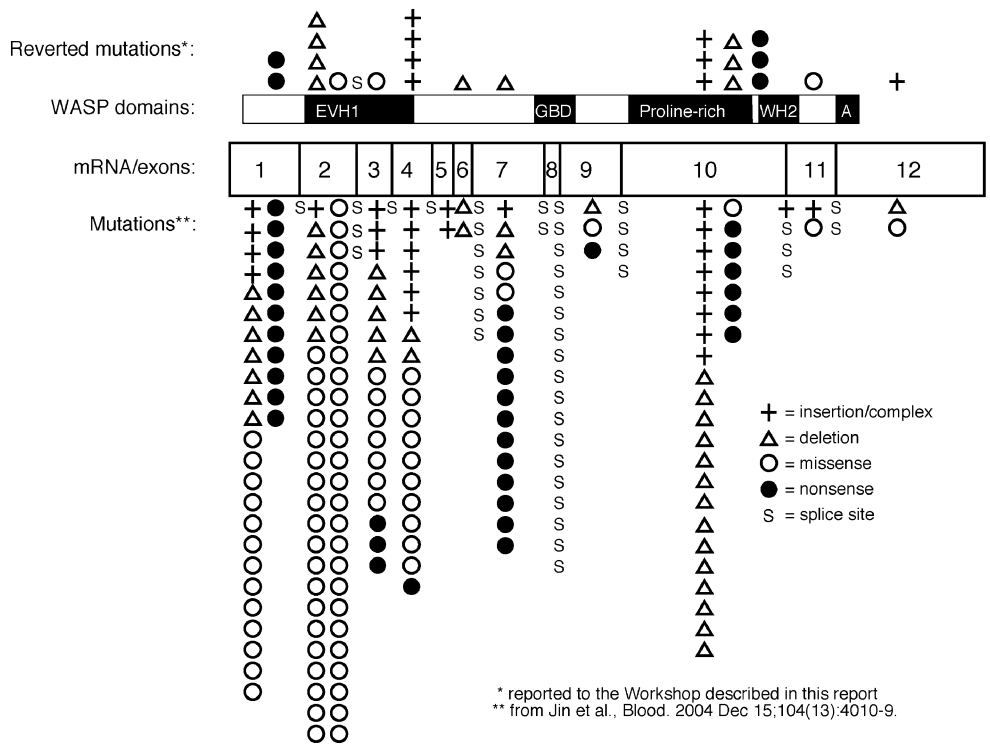

Fig. 1 cDNA sites of mutations that reverted. Shown above the schematic depiction of WASP cDNA are the locations and types of mutations that were reported as having reverted. The sites are those of the original mutations, localized to exons or splice sites. In several cases, a compensating second-site mutation occurred at some distance away from the original mutation, but this is not shown in the figure.

by a deletion of the same base, or another of the string of seven A's in the mutant [7]. Similarly, a 6-bp insertion seen in the Bethesda group's patient 1 was exactly reversed by a deletion of the same bases [5]. In this case, the 6-bp element was one of three tandem repeats, and a DNA polymerase slippage mechanism may have accounted for both the mutation and its reversion. This patient's affected siblings had the identical reversion [8]. In all these cases, a wild-type protein is predicted to be present and functional in the revertant cells.

In other cases, the revertant cells were found to have second-site mutations predicted to allow synthesis of an imperfect but detectable protein. The original, disease-causing mutation in the Sendai group's patient 1 was a single-base deletion 10 bases after the start codon. This was predicted to produce a frame shift, and a truncated protein of only 40 amino acids. In the revertant cells, there was a second-site mutation in the start codon that rendered it inactive. This second mutation allowed the protein synthesis machinery to use the sixth codon ATG as a new start codon, resulting in the synthesis of a detectable protein lacking the first five amino acids [9]. The Bethesda group's patients 3 and 4, which were affected brothers, both inherited a single-base insertion. Revertant cells were present in both, in which the reading frame was restored by a 19-bp deletion that included the inserted base [2]. In this case, a hairpin structure at the insertion site may have facilitated the reversions.

Spontaneous chimerism resulting from genetic reversions has previously been described in several immunologic disorders including the primary immunodeficiency diseases adenosine deaminase deficiency (ADA deficiency) [10], X-linked severe combined immune deficiency (XSCID) [11], and leukocyte adhesion deficiency type 1 (LAD) [12]. After our description of reversions in WAS patients [1, 2], a spontaneous genetic reversion has also been described in a patient with hyper-IgM associated with ectodermal dysplasia (XHM-ED) [13] caused by defects in the Nemo gene

Table II Published Mutations with Reversions*

Laboratory	Pt.	Original mutation	Original protein	Revertant sequence	Revertant protein	Exon	Reversion mechanism
Sendai	1	45 del G	fs	35 A>T	aa 1–5 deleted	1	Second start codon used
Sapporo	1	354 A>G	Y107C	wt	wt	3	354 G>A
Bethesda FC	1, 2, 6	434 ins 6 bp	E133 ins DE	wt	wt	4	434 del 6 bp
Bethesda FC	3, 4	1305 ins G	G424 fs	1299-1316 del	aa 422-427 deleted	10	1299–1316 del
Boston	1	476 ins A	K147 fs	wt	wt	4	476 del A

*See text for references.

[14]. Other diseases with spontaneous genetic reversions include epidermolysis bullosa [15, 16], Fanconi anemia [17, 18], and hereditary tyrosinemia type I [19, 20]. These genetic reversions occur in both X-linked disorders (one defective gene copy) as well as autosomal recessive (two defective gene copies) diseases. In all cases, the revertant cells are thought to have a selective advantage over the mutant cells because of enhanced proliferative capacity, extended cell life span, or both. This conclusion in the case of WASP is supported by *in vitro* cell culture studies [1] where the revertant cells have shown a growth advantage over mutant cells, and *in vitro* functional studies [1, 2, 5] in which the revertant cells function normally. These functional studies are supported by morphologic studies on the revertant cells, which demonstrate a wild-type phenotype [1]. Perhaps the best evidence supporting a selective survival advantage for the revertant cells is the reported expansion of revertant T-cell numbers in a WAS patient *in vivo* over time [2]. These observations on the survival advantage of revertant cells were important considerations in the selection of ADA deficiency and XSCID for human gene therapy trials [21, 22], and further suggest that a gene therapy approach might be useful in WAS [23].

The reasons underlying the remarkably high incidence of revertant events in WAS remain unclear. There is no known role of WASP in DNA replication and/or repair that could explain a higher genomic mutation rate in this disease compared to other genetic disorders. It is therefore tempting to speculate that WAS patients represent particularly favorable "biological incubators" where the revertant cells are able to accumulate and reach the detection threshold.

The purpose of this report is to alert the immunology and genetics communities to this phenomenon and to the seemingly high prevalence of spontaneous reversions in the WAS. Newly diagnosed patients and patients being followed under conservative management should be studied for this phenomenon so that the natural history of these reversion events might be defined and their relevance exploited for treatment, particularly in patients for whom bone marrow transplantation is not feasible. If further data are collected in the WAS and other primary immunodeficiency diseases, this might result in additional reports, perhaps at the ESID meeting in 2008.

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