

EXPERT
REVIEWS

Novel mutation of the activation-induced cytidine deaminase gene in a Tajik family: special review on hyper-immunoglobulin M syndrome

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The hyper-immunoglobulin M (HIGM) syndrome comprises a group of primary immunodeficiency disorders characterized by normal or elevated serum levels of IgM and low levels of other immunoglobulin classes. Patients with HIGM usually suffer from a variety of recurrent infections. Herein, we report two siblings of a Tajik family with a HIGM phenotype in which a novel missense mutation in the activation-induced cytidine deaminase (*AICDA*) gene was detected. Mutations in this gene are responsible for an autosomal recessive form of HIGM. We have also reviewed and summarized all published cases with HIGM due to defects in *AICDA*.

KEYWORDS: activation-induced cytidine deaminase • hyper-immunoglobulin M • mutation

The hyper-immunoglobulin M (HIGM) syndrome comprises a heterogeneous group of rare primary immunodeficiency disorders characterized by normal or elevated serum levels of IgM and low serum levels of IgG, IgA and IgE [1,2]. Patients with HIGM usually suffer from a variety of recurrent infections and, in some cases, lymphoid hyperplasia, autoimmune and inflammatory disorders and selected malignancies [1–8]. Using immunoglobulin (Ig) replacement therapy and antibiotic prophylaxis, the clinical picture of the disease dramatically improves in the majority of cases [1,9,10].

The immunological phenotype in HIGM results from failure of the Ig class switch recombination (CSR) process, which involves a number of different gene products [1,2]. A number of gene defects in these factors resulting in X-linked and autosomal recessive types of the disease have been identified. Although the X-linked form of the disease, caused by mutations in the CD40 ligand encoding gene (*CD40L*), seems to be the most common form of the disease, mutations in the activation-induced cytidine deaminase (*AICDA*) gene is the most

frequent aberration among patients with autosomal recessive forms [1,2]. This gene encodes a protein; activation-induced cytidine deaminase (AID), where defects cause severe impairment of both CSR and generation of somatic hypermutation (SHM) [1,2,11–13].

The underlying genetic defect can be identified in approximately 75–80% of patients with HIGM, although the diagnosis of CD40L deficiency may be challenging [14]. More than 40 different mutations in AID have been identified in patients with HIGM. As the prognosis and treatment options varies between different forms of HIGM, the molecular basis should be identified for each patient [15]. Stem cell transplantation can be recommended for patients with defects in CD40L [16] and studies on the clinical effects of *AICDA* mutations may contribute to a better knowledge of the role of AID in antibody diversification events [17,18].

Case presentation

A 5-year-old girl (proband), born from consanguineous parents, was referred to Tehran from

Tajikistan with a history of sinusitis, otitis media and pneumonia since childhood and purulent cough since 1 year ago. She suffered ear discharge when she was 9 months old and underwent adenoidectomy due to adenoid hyperplasia. Her chest CT scan revealed collapsed consolidation, atelectasis and paratracheal adenopathy at the time of admission.

Her 20-year-old brother also had a history of recurrent episodes of sinusitis and otitis media since childhood leading to frequent hospitalizations. He developed chronic cough 3 years ago. His chest CT scan showed tubular bronchiectasis in medial lobe of the right lung. Ecstatic bronchioles with cystic pattern in the lower lobe of the left lung were also noted. However, there was no history of enteroviral infections, autoimmunity or inflammatory disorders.

Immunologic evaluation of the patients was performed, showing near normal numbers of white blood cells, neutrophils, lymphocytes, monocytes and eosinophils in both patients. B- and T-cell subsets were also within the normal range in the proband. However, serum IgG, IgE and IgA levels were all below the normal range, while the serum IgM level in both patients were markedly higher than normal (TABLE 1). Both patients were diagnosed as HIGM and intravenous Ig treatment was initiated.

To identify the genetic defect, DNA from both patients and their parents was analyzed. Polymerase chain reaction (PCR) amplification and sequencing of the *AICDA* and uracil N-glycosylase encoding (*UNG*) genes were performed as previously described [8].

There was no mutation in *UNG* in the proband. However, two gene alterations in *AICDA* (OMIM*605257) were found in

the index patient: one novel homozygous missense mutation (7603 G>T) in exon 3, the other aberration being a homozygous silent mutation in exon 4 which has previously been reported as a benign SNP (544T>C as rs2028373 [19]). The former mutation results in the replacement of glycine by valine at codon 133 (G133V) and is predicted to be probably damaging [101]. The same homozygous mutation (G133V, G>T) was also found in the affected sibling, while their parents carried the mutation in a heterozygous form (FIGURE 1).

Discussion

The *AICDA* gene, located on 12p13.31, encodes a 198 amino-acid protein, known as AID. The role of AID in SHM and CSR has not yet been completely understood but two models have been proposed for its molecular mechanism: the RNA-editing hypothesis and the DNA deamination hypothesis [20–23]. In the RNA-editing hypothesis, AID changes mRNA precursors of endonucleases responsible for DNA cleavage to novel ones [13]. In the DNA deamination hypothesis, AID is directly responsible for cytidine deamination to uracil in the targeted DNA. In the SHM and CSR processes, AID can induce DNA lesions in targeted sequences in S and V regions required for DNA cleavage [23,24]. However, it has recently been shown that the CSR and SHM activities of various AID mutants do not always correlate with their DNA deamination activity [20,22].

AID contains four regions, a nuclear localization signal (NLS) (aa 8–26), a cytidine deaminase region (aa 55–94), an apolipoprotein B editing complex (APOBEC)-like domain (aa 119–183) and a nuclear export signal (NES; aa 183–198) [17,25,26]. The reported mutation is a substitution of glycine by valine – a more

hydrophobic amino acid – in the APOBEC-like region. This domain shares homology with the APOBEC, which deaminates a cytidine in the intestinal apolipoprotein B RNA [13,27]. To date, eight mutations, including five missense and three nonsense mutations, have been reported in this domain in a total of 13 patients.

Single gene defects of the immune system usually cause severe and/or frequent infections in early childhood, raising suspicion of an immunodeficiency disorder [9,10,28,29]. Therefore, these patients are usually diagnosed in early childhood. However, a diagnosis of HIGM may be delayed to the second or even third decade of life in patients with AID deficiency [28], similar to the affected brother of the proband in this study. In these patients, the high levels of IgM antibodies apparently provide an effective means of defense, at least against some infectious agents [6,30]. Thus, infections in these patients are not severe or frequent enough to elicit a suspicion of immunodeficiency disease [28].

Table 1. Immunologic findings of the patients.

	Patient 1	Patient 2	Normal range
<i>Complete blood cell count</i>			
White blood cells	11,100	7100	4.5–11.010 ³ /μl
Neutrophils (%)	63	74	45–74
Lymphocytes (%)	30	24	25–45
Monocytes (%)	5	–	4–7
Eosinophils (%)	2	2	0–3
<i>Immunoglobulins</i>			
IgG (mg/dl)	<5	<5	635–1775
IgA (mg/dl)	5	<5	71–237
IgM (mg/dl)	1975	1026	70–486
IgE (IU/ml)	1	14	0–200
<i>Lymphocyte subsets</i>			
CD3 ⁺ T cells (%)	56	ND	49–76
CD3 ⁺ CD4 ⁺ T cells (%)	30	ND	31–63
CD3 ⁺ CD8 ⁺ T cells (%)	23	ND	17.4–34.2
CD19 ⁺ B cells	15	ND	14–37

ND: Not done.

Review of the literature

The authors searched PubMed and ISI Web of Science for articles published, with no time and language limitations up to March 2012. We used free text and MESH terms to search the Medline electronic bibliographical Database (accessing via PubMed) combining terms for study patients/population, problem and intervention. HIGM and/or *AICDA* were searched through the literature and articles were selected for their relevance to the analysis. The authors have also used the AICDabase [31,102] and the Resource of Asian Primary Immunodeficiency Diseases [32,103]. A review of the world literature revealed 110 cases of HIGM with mutations in *AICDA*. At the time of writing, 41 unique mutations have been reported in 12 studies (TABLE 2). Most of these mutations were missense mutations, followed by nonsense mutations and frameshift deletions/insertions in

a homozygous or compound heterozygous state. The majority affected exon 3 and the cytidine deaminase catalytic region of the protein. In some case series, selected mutations in *AICDA* have been reported as hot spots in some populations where R112H and C87R were frequently found in the Japanese and Hungarian populations, respectively, while R112C was more common in French–Canadians [19,28,33,34].

Revy *et al.* were the first to establish a link between phenotype of HIGM patients and mutations in *AICDA* [12]. They found ten different mutations in their survey of 18 patients [12]. Most of the patients had missense mutations in the cytidine deaminase catalytic region of the protein and the APOBEC region. Lymphoid hyperplasia has been reported as a common feature in almost all patients with AID deficiency. This is in sharp contrast to the lack of germinal centers in HIGM patients with defects in CD40L [35]. Fiorini *et al.* hypothesized that recurrent infections caused the lymphoid hyperplasia, as resolution has been seen after initiation of Ig replacement therapy [11]. The most probable explanation is that continuous induction of B-cell proliferation through the B-cell receptor by antigens in the absence of functional AID results in this phenomenon [6,12].

In contrast to patients with defects in CD40L, patients with mutations in *AICDA* do not suffer from opportunistic infections. This is probably explained by the nature of disease as a pure B-cell deficiency [2,6,12]. Minegishi *et al.* reported three novel mutations in *AICDA* in 18 patients and suggested an association between a history of meningitis and a mutation in codon 112 of *AICDA* (R112C) [28]. Revy *et al.* and Minegishi *et al.* both found a milder phenotype in patients with amino acid substitution than in patients with nonsense mutations. Thus, it seems that mutant AID proteins with amino acid changes may not be completely nonfunctional [12,28]. Quartier *et al.* reported AID deficiency with 15 distinct genetic alterations in 29 cases (from missense

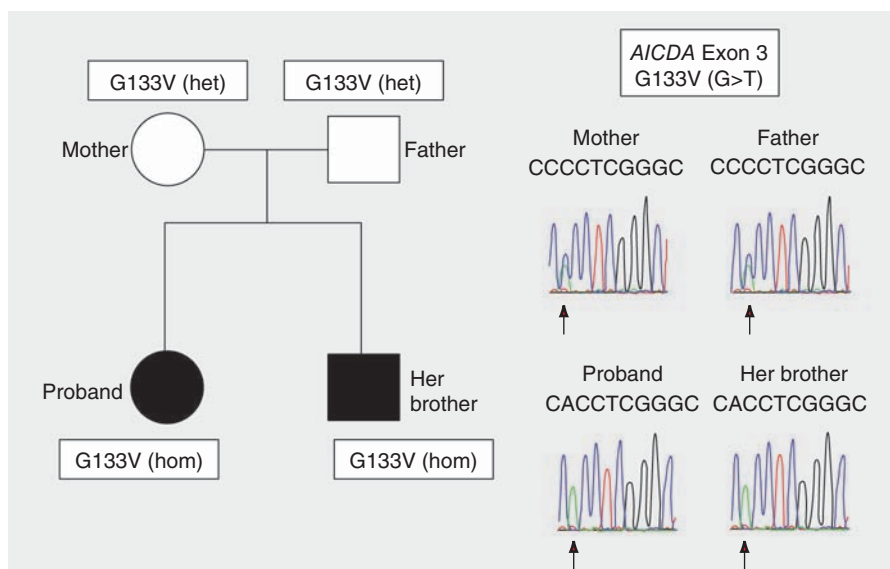


Figure 1. Novel mutation at the exon 3 of the *AICDA* gene. The patient codon 133 has changed from GGG to GTG in the patients and their parents. Mutation analysis showed homozygous mutation in patients and heterozygous mutation in the parents.

mutations to complete deletion of the *AID* gene) [6]. They were the first to report autoimmune manifestations in HIGM patients with mutations in *AICDA* with frequency of about 20% [6]. Surprisingly, a survey of children with atopic asthma revealed 4 new mutations in *AICDA* and an association between a silent mutation and development of asthma and markedly elevated total serum IgE levels in adults [36].

In 2003, a heterozygous mutation in the NES domain (R190X), removing the nine C-terminal amino acids of AID, was claimed to be responsible for an autosomal dominant form of HIGM [37]. Imai *et al.* also reported the same mutation in 2005 [38]. These patients had a complete lack of CSR downstream from the DNA cleavage step whereas SHM was intact. Kasahara *et al.* hypothesized that wild-type AID was responsible for the DNA cleavage step, but its function would be inhibited by the dominant negative effect of the mutated form of AID in subsequent steps [37]. Imai *et al.* provided two hypotheses for these phenomena. As most cytidine deaminases act as homodimers or homotetramers, they assumed that a truncated AID would form abnormal AID dimers or tetramers that may exert a dominant negative effect. The second possible explanation is that nuclear accumulation of abnormal AID, lacking the NES domain, could disturb trafficking and function of normal AID [38]. These mutations clearly showed that different domains of AID are involved in SHM and CSR [25,26]. Zhu *et al.* [33] described a patient with a heterozygous mutation in the linker between the cytidine deaminase and APOBEC-like regions (R112H and a heterozygous deletion, (544delC; aa 208 stop) who had a normal rate of SHM compared to age-matched controls but showed a complete lack of CSR. Other authors have also reported this mutation, but the frequency of SHM was not determined in those patients [19,28].

NLS region mutations not only lead to an unstable protein due to a lack of NLS but also cause severe defects in transport of AID into the nucleus [17,26]. Patients with these mutations show severe

Table 2. Reported mutations of the *AICDA* gene in the literature.

Study No.	Nucleotide change	Protein level change	Mutation effects	Domain change	Number of cases	CSR	SHM	Study (year)	Ref.
1	17T>C	M6T	Missense defects	N-terminal	2	–	–	Durandy <i>et al.</i> (2006)	[17]
2	1-597del597	Deletion	No transcript	–	2	–	–	Quartier <i>et al.</i> (2004)	[6]
3	21–39del	R8-Y13del+F15X	Frameshift	NLS	1	–	–	Revy <i>et al.</i> (2000), Durandy <i>et al.</i> (2006)	[12, 17]
4	31T>G	F11V	Missense defects	NLS	1	–	–	Zhu Y <i>et al.</i> (2003)	[33]
5	64A>T	L22X	Nonsense defects	–	2	–	NR	Durandy <i>et al.</i> (2006)	[17]
6	70C>T	R24W	Missense defects	NLS	6	–	–	Revy <i>et al.</i> (2000), Durandy <i>et al.</i> (2006), Zhu <i>et al.</i> (2003)	[12, 17, 33]
7	73C>T	R25C	Missense defects	NLS	– [†]	NA	NA	Noguchi <i>et al.</i> (2001)	[36]
8	93C>A	Y31X	Nonsense defects	–	2	–	NR	Durandy <i>et al.</i> (2006)	[17]
9	127T>C	S43P	Missense defects	Linker between cytidine deaminase and NLS	1	–	–	Zhu <i>et al.</i> (2003)	[33]
10	IVS2+1G>T	–	Splice donor defects	–	2	–	NR	Fiorini <i>et al.</i> (2004)	[11]
11	166C>T	H56Y	Missense defects	Cytidine deaminase	1	–	–	Quartier <i>et al.</i> (2004), Durandy <i>et al.</i> (2006)	[6, 17]
12	172G>A	E58K	Missense defects	Cytidine deaminase	1	–	NR	Erdos <i>et al.</i> (2008)	[34]
13	175–183del	H56-E58delinsV	Amino acid deletion	Cytidine deaminase	2	–	–	Revy <i>et al.</i> (2000), Durandy <i>et al.</i> (2006)	[12, 17]
14	203G>A	W68X	Nonsense defects	Cytidine deaminase	7	–	–	Revy <i>et al.</i> (2000), Quartier <i>et al.</i> (2004), Durandy <i>et al.</i> (2006)	[12, 6, 17]
15	226insT	w76LfsX116	Frameshift	–	1	–	–	Zhu <i>et al.</i> (2003)	[33]
16	235_243del9	W79-F81del	Amino acid deletion	Cytidine deaminase	1	–	–	Zhu <i>et al.</i> (2003)	[33]
17	238T>C	W80R	Missense defects	Cytidine deaminase	1	–	–	Revy <i>et al.</i> (2000), Durandy <i>et al.</i> (2006)	[12, 17]
18	247T>C	S83P	Missense defects	Cytidine deaminase	1	–	NR	Durandy <i>et al.</i> (2006)	[17]
19	252G>A	W84X	Nonsense defects	Cytidine deaminase	2	–	NR	Minegishi <i>et al.</i> (2000)	[28]
20	254G>A	S85N	Missense defects	Cytidine deaminase	1	–	NR	Durandy <i>et al.</i> (2006)	[17]
21	260G>C	C87S	Missense defects	Cytidine deaminase	1	–	NR	Durandy <i>et al.</i> (2006)	[17]
22	259T>C	C87R	Missense defects	Cytidine deaminase	11	–	–	Lee <i>et al.</i> (2005), Erdos <i>et al.</i> (2008), Quartier <i>et al.</i> (2004), Durandy <i>et al.</i> (2006)	[19, 34, 6, 17]
23	292T>G	L98R	Missense defects	Linker between cytidine deaminase and APOBEC-like	1	–	NR	Lee <i>et al.</i> (2005)	[19]

[†]This mutation was found in a population of asthmatic children.

+: Positive; –: Negative; APOBEC: Apolipoprotein B editing complex; CSR: Class switch recombination; NA: Not applicable; NES: Nuclear export signal; NLS: Nuclear localization signal; NR: Not reported; SHM: Somatic hypermutation.

Table 2. Reported mutations of the *AICDA* gene in the literature (cont.).

Study No.	Nucleotide change	Protein level change	Mutation effects	Domain change	Number of cases	CSR	SHM	Study (year)	Ref.
24	317T>C	L106P	Missense defects	Linker between cytidine deaminase and APOBEC-like	2	–	NR	Revy <i>et al.</i> (2000), Durandy <i>et al.</i> (2006)	[12,17]
25	332C>A	A111E	Missense defects	Linker between cytidine deaminase and APOBEC-like	1	–	–	Durandy <i>et al.</i> (2006)	[17]
26	334C>T	R112C	Missense defects	Linker between cytidine deaminase and APOBEC-like	17	–	+	Minegishi <i>et al.</i> (2000), Lee <i>et al.</i> (2005), Zhu <i>et al.</i> (2003)	[28,19,33]
27	335G>A	R112H	Missense defects	Linker between cytidine deaminase and APOBEC-like	7	–	Variable	Minegishi <i>et al.</i> (2000), Zhu <i>et al.</i> (2003)	[28,33]
28	338T>C	L113P	Missense defects	Linker between cytidine deaminase and APOBEC-like	5	–	NR	Erds <i>et al.</i> (2008), Durandy <i>et al.</i> (2006)	[34,17]
29	364G>T	E122X	Nonsense defects	APOBEC-like	1	–	NR	Aghamohammadi <i>et al.</i> (2009)	[8]
30	407T>A	I136K	Missense defects	APOBEC-like	1	–	NR	Zhu <i>et al.</i> (2003)	[33]
31	416T>C	M139T	Missense defects	APOBEC-like	1	–	NR	Durandy <i>et al.</i> (2006)	[17]
32	415A>G	M139V	Missense defects	APOBEC-like	3	–	–	Revy <i>et al.</i> (2000), Quartier <i>et al.</i> (2004), Durandy <i>et al.</i> (2006)	[12,6,17]
33	441C>A	C147X	Nonsense defects	APOBEC-like	2	–	–	Revy <i>et al.</i> (2000), Durandy <i>et al.</i> (2006)	[12,17]
34	452T>C	F151S	Missense defects	APOBEC-like	2	–	NR	Revy <i>et al.</i> (2000), Durandy <i>et al.</i> (2006)	[12,17]
35	506C>A	S169X	Nonsense defects	APOBEC-like	1	–	NR	Durandy <i>et al.</i> (2006)	[17]
36	522A>C	R174S	Missense defects	APOBEC-like	2	–	–	Quartier <i>et al.</i> (2004), Durandy <i>et al.</i> (2006)	[6,17]
37	543+1delG	D143-L181delinsAfsX184	Amino acid insertion, amino acid deletion, splice donor defects	C-terminal	1	–	+	Durandy <i>et al.</i> (2006)	[17]
38	543+1G>C	L181delinsCfsX196	Exon skipping	C-terminal	2	–	+	Zhu <i>et al.</i> (2003), Durandy <i>et al.</i> (2006)	[33,17]
39	544-2A>G	L181-P182ins31	Amino acid insertion, splice acceptor defects	C-terminal	1	–	+	Quartier <i>et al.</i> (2004), Durandy <i>et al.</i> (2006)	[6,17]
40	544delC	P182fsX208	Frame shift	C-terminal	1	–	+	Zhu <i>et al.</i> (2003)	[33]
41	568C>T	R190X	Nonsense defects	NES	12	–	+	Kasahara <i>et al.</i> (2003), Imai <i>et al.</i> (2005), Durandy <i>et al.</i> (2006)	[37,38,17]

[†]This mutation was found in a population of asthmatic children.

+: Positive; -: Negative; APOBEC: Apolipoprotein B editing complex; CSR: Class switch recombination; NA: Not applicable; NES: Nuclear export signal; NLS: Nuclear localization signal; NR: Not reported; SHM: Somatic hypermutation.

defects in both CSR and SHM [12,17,33]. However, Revy *et al.* reported a residual CSR activity in one of the HIGM patients with a R24W mutation with a complete absence of SHM [12].

The C-terminal part of AID acts as a docking area for CSR-specific cofactors [17,25,26,39]. Therefore, defects result in reduced CSR, whereas a significant residual frequency of SHM has been observed in reported patients [6,17,33]. In addition, it has been shown that nuclear translocation of AID is essential for CSR, but not for SHM [40].

NES domain mutations result in accumulation of abnormal AID in the nucleus, overriding the normal AID function by producing abnormal multimeric complexes [17,38,40,41]. Thus, even heterozygous mutations may result in defective CSR [17,37,38]. Mutations in the linker region between the cytidine deaminase and APOBEC-like region have variable effects in HIGM patients. A111E has been reported to cause a complete lack of CSR and SHM, probably due to a complete change of the structure of the protein with substitution of a nonpolar for a polar aa [17]. A full report indicates that some patients with R112H mutation have low rates of SHM [33]. On the other hand, Zhu *et al.* reported that a patient with a heterozygous mutation of R112C and a concomitant frame shift mutation in the C-terminal region showed a significant frequency of SHM [33].

Expert commentary

Identification of mutations in HIGM patients could not only help clinicians and scientists to understand the nature of the disease and allow genetic counseling of these patients but also further the understanding of events involved in B-cell development and the generation of diverse antibodies of different isotypes.

Five-year view

Our understanding of the role of AID antibody maturation events has entered an evolutionary road since the beginning of the 21st century, but it has not yet reached its destination. It is to be hoped that while the exact pathophysiology of HIGM will be clarified in the future, novel gene defect(s) will be discovered in HIGM patients with intact *CD40L*, *CD40*, *AICDA*, *UNG* and *NEMO* genes.

Financial & competing interests disclosure

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Key issues

- The hyper-immunoglobulin M (HIGM) syndromes constitute a heterogeneous group of rare inherited disorders, characterized by normal or elevated serum levels of IgM and low serum levels of IgG, IgA and IgE.
- Patients with HIGM usually suffer from a variety of recurrent infections as well as lymphoid hyperplasia and autoimmune and inflammatory disorders.
- The immunologic phenotype results from failure of the immunoglobulin class switch recombination process, which involves a number of different gene products.
- Although the X-linked form of disease, caused by mutations in the *CD40L* gene, seems to be the most common form of disease, mutations in the *AICDA* gene constitute the most frequent autosomal recessive form.
- Up to now, more than 40 different mutations of *AICDA* have been identified in patients with HIGM.

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