

A Novel RFXANK Mutation in a Chinese Child With MHC II Deficiency: Case Report and Literature Review

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Major histocompatibility complex (MHC) II deficiency is a rare primary immunodeficiency disorder that is characterized by the deficiency of MHC class II molecules. The disease is caused by transcription factor mutations including class II transactivator (*CIITA*), regulatory factor X-5 (*RFX5*), RFX-associated protein (*RFXAP*), and RFXAP-containing ankyrin repeat (*RFXANK*), respectively. Mutations in the *RFXANK* gene account for >70% of all known patients worldwide. Herein, we reported a 10-month-old boy with MHC II deficiency caused by a novel mutation in the *RFXANK* gene (c.337 + 1G>C). The boy was admitted to the hospital due to pneumonia and diarrhea at 4 months of age. Genetic analysis revealed a novel homozygous mutation in the *RFXANK* gene, which derived from the c.337 + 1G>C heterozygous mutations in the *RFXANK* gene of his parents. The boy died 3 months after diagnosis. More than 200 cases have been reported, and a review of the literature revealed different mutation rates of 4 transcription factors in different countries or regions. This is the first case report of MHC II deficiency from East Asia. We also describe all gene mutations that cause MHC II deficiency and the epidemiology of MHC II deficiency with gene mutations in this paper.

Keywords. gene mutation; immunodeficiency disorder; infection; MHC II deficiency; RFXANK.

Major histocompatibility complex (MHC) II deficiency is a rare primary immunodeficiency disease that is characterized by the deficiency of MHC class II molecules. More than 200 cases have

been reported in the literature. About two-thirds of the patients were reported from North African countries, which have a high prevalence of consanguineous marriages [1]. Although MHC II deficiency is regarded as less severe than severe combined immunodeficiency (SCID) according to the International Union of Immunological Societies classification criteria, patients usually exhibit clinical manifestations of typical combined immunodeficiency (CID) but not SCID [2, 3]. MHC II deficiency is characterized by an early onset of severe and recurrent infections, mainly of the respiratory and gastrointestinal tract, developmental delay, and early death [4]. Protracted diarrhea and recurrent pneumonia can be observed in almost all patients [2]. These patients are susceptible to a broad range of bacterial, viral, fungal, and protozoan infections, while cytomegalovirus (CMV), herpes simplex virus (HPV), *Pneumocystis jirovecii*, *Salmonella*, and *Cryptosporidium* species are the most common pathogens [3].

It is unique that MHC II deficiency exhibits the phenotypic manifestation of loss of molecular MHC II on the surface of specialized cells, while the mutated genes reside outside the MHC II locus [3]. The deficiency of MHC class II molecule, caused by transcription factor mutations, leads to impaired antigen presentation by HLA-DR, HLA-DQ, and HLA-DP molecules on antigen-presenting cells (APCs) such as dendritic cells and macrophages [5]. Moreover, transcription factor mutations could affect both the cell-mediated and humoral immunity due to defective CD4+ T-cell development and a lack of Th-cell-dependent antibody production by B cells [6].

Different from the major histocompatibility complex I (MHC I) molecule expressed on almost all cells, the MHC II molecule is expressed on restricted cells like thymic epithelial cells and professional antigen-presenting cells or other types of cells stimulated by interferon- γ [7]. Besides the different expression loci, the expression of the MHC II gene is regulated by MHC II enhanceosome (a cell-specific multiprotein complex) [7]. Based on the experiment results of the isolation of the gene from the patients with MHC II deficiency, Reith et al. found 2 key regulatory factors that activate transcription of the genes encoding MHC II, class II transactivator (*CIITA*) and multiprotein RFX complex [8]. The RFX complex, which is composed of regulatory factor X-5 (*RFX5*), RFX-associated protein (*RFXAP*), and RFXAP-containing ankyrin repeat (*RFXANK*), binds directly to the promoters of MHC II genes and associates with other pleiotropic factors to form the MHC II enhanceosome [9]. Subsequently, due to the 4 different transcript factors, MHC II deficiency is divided into 4 groups from group A to D, which are *CIITA*, *RFXANK*, *RFX5*, and *RFXAP*, respectively [4].

Herein, we report on a Chinese patient with MHC II deficiency caused by a novel homozygous mutation in the *RFXANK*

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that the patient may have had CID because of MHC II deficiency [10]. So, we performed exome sequencing and flow cytometric evaluation of the MHC II molecule. As a result, we found a homozygous c.337 + 1G>C mutation in *RFXANK* in this patient, whose parents were carriers of a heterozygous mutation. The patient died 3 months after diagnosis. Our experience from the diagnosis and treatment of this patient suggests that if a patient is diagnosed with primary immunodeficiency (PID) and with several opportunistic infections, especially *Pneumocystis jirovecii*, it is best to undertake whole-exome sequencing and flow cytometric evaluation of the MHC II molecule to determine whether the PID is caused by the MHC II deficiency. Moreover, we found a novel *RFXANK* mutation that results in MHC II deficiency. At the same time, the homozygous mutations of the *RFXANK* gene were derived from the heterozygous mutation of his parents, who were not close relatives, which may imply that the rate of this kind of heterozygous mutation carrier is not low in Chinese people, even in East Asians.

LITERATURE REVIEW

MHC II deficiency is classified into 4 complementation groups, named by the order of their discovery according to MHC II molecule expression after pairwise fusion of different patient cell lines [3]. MHC II deficiency is divided into 4 groups, groups A to D, which are *CIITA*, *RFXANK*, *RFX5*, and *RFXAP*, respectively [4]. Group B MHC II deficiency is the most common, with more than half of the patients [11]. Besides the *RFXANK* gene mutation, most MHC II deficiency patients present with the context of consanguinity or ethnically similar communities, the majority in North Africa [12]. Nevertheless, it is interesting and unique that our patient had a homozygous c.337 + 1G>C mutation in the *RFXANK* gene given the parents' ethnicity—Chinese. The parents of our patient are not closely related, which means that the heterozygous mutation in the *RFXANK* gene may be more widespread in the East Asian population than previously thought, considering that MHC II deficiency is a kind of autosomal recessive inheritance disease [7]. Ultimately, the mutation found in our patient leads to a splicing defect and nonfunctional *RFXANK* protein and prevents the transcription of the MHC II molecule, resulting in a severe immunodeficiency phenotype. Moreover, we carried out a systematic literature review on all reported patients with MHC II deficiency in PubMed with the keywords “MHC II deficiency” and “bare lymphocyte syndrome,” which is the former name of MHC II deficiency, up to April 2020. The data were extracted from those studies with gene mutation or ethnicity information for patients. Here, clinical data for each of the 4 different groups are presented in Tables 1–4, each containing information about the gene mutations and ethnicities of the patients.

Epidemiology

Our systematic literature review (Supplementary Table 1) revealed 238 patients with MHC II deficiency. With our present knowledge of MHC II deficiency disease and with the development of gene sequencing technology, patients who used to be diagnosed with PID would be further diagnosed as having MHC II deficiency. The geographical distribution of MHC II defects is mainly limited to areas with a high incidence of consanguineous marriages [13]. MHC II deficiency is more prevalent in North African countries or Mediterranean countries. Of the 178 patients with MHC II deficiency whose ethnicity is known, 117 (65.7%) come from North Africa and 152 (85.4%) from Mediterranean countries. Consanguineous marriages, which increase the incidence of autosomal recessive disorders due to the limited gene pool, are quite prevalent in these regions [14]. However, Group B MHC II deficiency is more concentrated in North African areas, while Group A seems to be more prevalent in European countries, and Group D is more prevalent in Asian countries (Supplementary Table 1). Such differences may be caused by the gene differences of the different races. More studies are needed to investigate the difference.

Gene Mutation Analysis

Due to the lack of unique clinical manifestations between MHC II deficiency and other immunodeficiency diseases, it is difficult for doctors to distinguish these 2 kinds of disease [13]. However, with gene sequencing technology, the list of mutations underlying MHC II deficiency is increasing. MHC II deficiency can be distinguished from PID by examination of the MHC II molecule on immune cells, or gene sequencing [3]. Gene sequencing can not only find the main deficiency-causing mutation, but also other mutations that may pose potential disease risk [15]. There were only 5 kinds of mutations in the *CIITA* gene reported before 2000, while the number reached 12 in 2018 [16]. Herein, we find a novel homozygous mutation in the *RFXANK* gene. Interestingly, the patient is a homozygous carrier of the c.337 + 1G>C mutation (Figure 1), with both parents showing a heterozygous configuration. This mutated allele may be widespread within the Chinese population considering the autosomal recessive inheritance of the MHC II deficiency. It is of great value to identify the genetic defects underlying MHC II deficiency for targeted gene therapy, which is a potential treatment.

The first discovered MHC II deficiency mutated gene was *CIITA* localized on chromosome 16 [17]. The N-terminal region of the *CIITA* acts as a transcriptional activator, while the C-terminal region provides MHC II promoter specificity [18]. The *CIITA* possesses 3 isoforms, all of which contain a leucine-rich region (LRR) participating in a protein–protein interaction. The LRR domain plays an important role in *CIITA* movement into the nucleus and in regulating its transactivation function [19]. Hanna and Etzioni reported in 2014 that there

Table 1. The Mutations of the CIITA of the Patients With MHC II Deficiency

Mutation of CIITA	Result	Case Number	Ethnicity	Author	Year of Publication	Reference
Homozygous c.2436C>A	p. Cys812Ter	1	Indian	Aluri et al.	2018	[32]
Homozygous c.929delA p. Asp310fs	P/S/T domain was impaired	1	Egyptian	El Hawary et al.	2018	[1]
Homozygous c.3317 + 1G>A	-	1	Mexican-Iranian	Dimitrova et al.	2014	[33]
Homozygous p. Glu381X	Nonsense mutation in exon 11, leading to loss of the C-terminal nuclear localization domain/ impaired binding of CIITA to enhanceosome	1	Austrian	Schmetterer et al.	2010	[34]
Homozygous c.1256G>T (p. Glu381X)	Premature stop	1	Australian	Schmetterer et al.	2010	[34–36]
		1	Austrian	Bontron et al.	1997	
		1	North African	Mannhalter et al.	1991	
Heterozygous c.G2178A (p. Trp to X)Paternal allele: only silent mutations	Premature stop	1	NC	Dziembowska et al.	2002	[37]
Allele 1: del3003-3084 Allele 2: CATdel3193-5	Allele 1: exon skipping between Leu964 and Asp991 (27 aa)	1	NC	Dziembowska et al.	2002	[37]
No mutations in coding or noncoding regions	Probably mutated stabilizing region or regulatory sequence	1	NC	Dziembowska et al.	2002	[37]
Homozygous c.1524T>C (p. L469P)	Missense mutation in N-terminal end of LRR motif, which is essential for CIITA activity	3	Greek	Wiszniewski et al.	2001	[38]
Homozygous c. 84bp del 3265–3348	Splice donor site mutation results in 28-aa truncated protein	1	Turkish	Peijnenburg et al.	2000	[39]
Homozygous p. F961S	Missense mutation leading to an inactive protein	1	NC	Quan et al.	1999	[40]
Homozygous c. 72bp del2932-3003	Exon skipping -24-aa truncated protein	1	NC	Steimle et al.	1993	[17]

Abbreviations: aa, amino acid; CIITA, class II transactivator; LRR, leucine-rich region; NC, no comment.

were 9 mutations of the CIITA that induce MHC II deficiency disease [9]. Most of the mutations of the CIITA result in a premature stop codon, leading to a truncated protein or missense mutations, making for inactive proteins (Table 1). Nevertheless, we find that 13 mutations of the CIITA could account for Group A related to MHC II deficiency. Most defective CIITA proteins lose the ability to bind to the enhanceosome complex in the promoter of the MHC II gene due to a defective LRR region. Here, we study 16 (16/177) patients diagnosed with MHC II deficiency because of the CIITA gene mutation. There are 3 patients with the homozygous c.1256G>T (p. Glu381X) mutation and 3 with the homozygous c.1524T>C (p. L469P) mutation. The first mutation is found not only in European patients, but also in North African patients, while the other mutations were only found in Greek patients. Given the autosomal recessive inheritance of this disease, the CIITA mutation may be more prevalent in the European population, which is consistent with previous reports [8].

The key DNA binding component of the MHC II enhanceosome regulating the expression of MHC II genes is the RFX complex, which comprised of 3 proteins: RFXANP, RFX5, and RFXAP. The RFXANK gene consisting of 10 exons

is located on the 19p12 locus [12]. The isoforms of RFXANK proteins depend on the number of ankyrin repeats, which are the crucial protein–protein interaction sites for the formation of the RFX complex [20]. Each repeat, composed of 2 antiparallel helices and a beta-hairpin, is stacked in a superhelical arrangement coupled with other repeats [21]. In addition, the RFXANK β -hairpin loops 1–3 are responsible for the binding of RFXANK to RFXAP. Mutations in the RFXANK gene in MHC II deficiency belong to group B, the largest group of the MHC II deficiency patients; 75.3% (131/174) of all known MHC II deficiencies with gene mutation information are defects in the RFXANK (Table 2). There are 19 different mutations that have been identified in patients with RFXANK mutations. The most frequent mutation is 752delG26, which originated from an ancestor from the Maghreb (North Africa), leading to the formation of an mRNA lacking exons 5 and 6 [18]. The rest of the mutations are clustered in exons 5 to 9, a region that encodes ankyrin repeats, and are found in patients from different countries (Italy, Saudi Arabia, Iran, Kuwait, and Turkey). Most of the mutations result in protein lacking either some or all of the ankyrin repeats, causing truncated or inactive proteins. It is interesting that the 752delG-25 and IVS4 defects (IVS4 + 1G>C,

Table 2. The Mutations of the FRANK of the Patients with MHC Deficiency

Mutation of FRANK	Result	Case Number	Ethnicity	Author	Year of Publication	Reference
Homozygous c.495G>A p. Trp165*	Premature stop	1	Iranian	Abolnezhadian et al.	2018	[11]
G>A in TGG codon for W188	A premature stop codon in exon 3	1	Iranian	Farrokhi et al.	2018	[16]
c.431T>C p. Leu144Pro	Ankyrin repeat 1-containing domain was impaired	2	Egyptian	El Hawary et al.	2018	[1]
c.247_250delTCAG	Frameshift deletion	1	Egyptian	El Hawary et al.	2018	[1]
c.600delG	Frameshift deletion	1	Egyptian	El Hawary et al.	2018	[1]
Homozygous c.469C>T	p. R157X	1	Mexican	Clarridge et al.	2017	[27]
Homozygous c.362A>T	Asp121Val	1	Saudi Arabian	Abu-Arja.	2014	[41]
		4	Kuwaiti	Al-Herz et al.	2012	[9]
insTCAC.IVS4 + 1	An aberrant splicing with a frameshift mutation and premature termination	4	Kuwaiti	Al-Herz et al.	2012	[9]
AW188x	Premature truncated RFXNAK protein	2	Kuwaiti	Al-Herz et al.	2012	[9]
Homozygous p.L195P	Break the inner helix in the third ankyrin repeat	1	NC	Nekrep et al.	2003	[7]
Homozygous IVS4 + 5G>A	Splicing mutation	1	Jewish/Egyptian	Alcaide-Loridan et al.	2003	[22]
Homozygous p. R212X	Nonsense mutation in exon 9–48 residue truncation	1	Saudi Arabian	Wojciech et al.	2003	[42]
Homozygous p. D121V	Missense mutation in exon 6	1	Turkish	Wojciech et al.	2003	[42]
Homozygous c. IVS4 + 1G>C	p. del28aa	1	North African	Lennon-Duménil et al.	2001	[21]
Homozygous p. E101X	Premature stop codon in exon 5–158 residue truncation	1	Turkish	Wiszniewski et al.	2000	[43]
Homozygous p. R156X	Premature stop codon in exon 7–105 residue truncation	1	Italian	Wiszniewski et al.	2000	[43]
Homozygous p. L195P	Missense mutation in exon 8 in the third ankyrin repeat	1	NC	Nagarajan et al.	2000	[44]
Homozygous p. Q103X	Nonsense mutation in exon 5-truncated protein	1	NC	Nagarajan et al.	2000	[44]
Homozygous c.752delG26bp	The same mutation leading to the same results, excision of exons 5 and 6, premature stop codon in exon 9	25	Tunisian	Ben-Mustapha et al.	2013	[10]
		9	Algerian	Djidjik et al.	2012	[18]
		2	Tunisian	Guirat-Dhouib et al.	2012	[45]
		35	Algeria (25) Moroccan (4) Tunisian (6)	Ouederni et al.	2011	[46]
		10	Moroccan	Naamane et al.	2010	[12]
		1	NC	Nagarajan et al.	2000	[44]
		17	Algerian (12) Tunisian (3) Moroccan (1) Algerian/ French (1)	Wiszniewski et al.	2000	[43]
		2	NC	Nagarajan et al.	1999	[47]
		3	NC	Masternak et al.	1998	[48]

Abbreviations: NC, no comment; RFXANK, regulatory factor X-associated protein-containing ankyrin repeat.

IVS4 + 5G>A) can be easily detected through RT-PCR, which might permit simple and early diagnosis for a vast number of RFXANK-mutative patients [22]. The patient described here is the first patient with c.337 + 1G>C destroying the splicing donor site of RFXANK belonging to the pathogenic very strong (PVS1) degree, according to the American College of Medical Genetics and Genomics [23], which may lead to a truncated RFXANK gene product.

All members of this RFX family share a common motif called the RFX DNA-binding domain (DBD) [24]. Previous

experiments have found that RFXAP and RFX5 assemble in the cytoplasm before translocating to the nucleus, in which they constitute the full RFX complex with RFXANK [25]. The RFX5 is in locus 1q21 with 12 exon transcript and contains highly conserved DBDs, which bind the X box MHC II gene before transcription [26]. Moreover, the DBDs of the RFX5 are in the 90–166 residues and 407–614 residues [27]. Eleven mutations have been reported now (Table 3), and more than half of them lead to a premature stop codon before the second DBD region. It has been proven that the 187–265 residues comprise

Table 3. The Mutation of the RFX5 of Patients With MHC II Deficiency

Mutation of RFX5	Result	Case Number	Ethnicity	Author	Year of Publication	Reference
Homozygous c.1154delT	p. Leu385TyrfsTer33	1	Indian	Aluri et al.	2018	[32]
Homozygous c.455G>T (p. Gly152Val)	DNA-binding domain destroyed	1	Egyptian	Rabab et al.	2018	[1]
Homozygous c.1161G>A	Oligomerization domain destroyed	1	Egyptian	Rabab et al.	2018	[1]
Homozygous c.715C>T	Dimerization domain destroyed	1	Egyptian	Rabab et al.	2018	[1]
Homozygous c.445G>A (p. R149Q)	Missense mutation in DBD leading to impaired DNA-binding ability	2	NC	Nekrep et al.	2002	[49]
Homozygous c. 1122 C>T (p. Q321X)	320-aa truncated protein that still contains the DNA-binding domain but is inactive	1	Dutch-Indonesian	Peijnenburg et al.	1999	[50]
Homozygous c. 4ntdel 312–315 (CAAG)fsX403-405	Splice acceptor site mutation leading to 82-aa truncated protein that lacks the DBD	1	Turkish	Peijnenburg et al.	1999	[51]
Homozygous c. 10ntdel259-268fsX334	Mutation in splice donor site	2	NC	Villard et al.	1997	[52]
Allele 1: c. 5Nt del386–390 fsX410 Allele 2: wild-type	Truncated nonfunctional protein	1	NC	Steimle et al.	1995	[53]
Homozygous c. 1032 C>T (p. R>X)	Severely truncated protein	–	NC	Steimle et al.	1995	[53]
Homozygous c. 1378 C>G (p. P>R)	Severely truncated protein	–	NC	Steimle et al.	1995	[53]

Abbreviations: aa, amino acid; DBD, DNA-binding domain; NC, no comment; RFX5, regulatory factor X-5.

the dimerization domain of RFX5 [24]. Except for the mutations destroying the DBD region of RFX5, there is 1 missense mutation in an Egyptian patient leading to the impaired dimerization of RFX5 [1].

RFXAP, a 3-exon gene localized on chromosome 13q14, contains 3 regions, which are rich in acidic amino acids (DE),

glutamine (Q), and basic amino acids (RK) reminiscent of a nuclear localization signal [28]. Most of the MHC II deficiency patients categorized as group D have defects within the first exon of the RFXAP in a region spanning nucleotides 116–540, which affects the nuclear localization signal or the acidic DE domain [29]. Additionally, the C-terminal end of the associated protein

Table 4. The Mutations of the RFXAP of Patients With MHC II Deficiency

Mutation of RFXAP	Result	Case Number	Ethnicity	Author	Year of Publication	Reference
Homozygous c.460-461insC	p. lys155GlnfsTer21	2	Indian	Aluri et al.	2018	[32]
Homozygous c.709-1G>T	Splicing mutation	1	Indian	Aluri et al.	2018	[32]
Homozygous p. Tyr73X	The introduction of a premature stop codon in the DE region	1	Mexican	Michael et al.	2015	[54]
Homozygous c.323T>A in exon 1	Premature stop codon (p. Leu108x)	1	Mexican	Caroline et al.	2013	[55]
Homozygous c. delG484fsX525	Severely truncated and inactive protein of only 136-aa	1	Austrian	Klaus et al.	2010	[34]
		2	North African	Fondaneche et al.	1998	[56]
		1	Algerian	Villard et al.	1998	[57]
		1	Moroccan	Durand et al.	1997	[28]
Homozygous 75bp insertion in 5-UTR	Transcriptional silence of RFXAP	1	Turkish	Van Eggermond et al.	2008	[31]
Homozygous c. 279C>G (p. Q>X)	52-aa truncated protein	1	Turkish	Fondaneche et al.	1998	[56]
Homozygous c.151ins7 (GCGGGCG) fs329X	136-aa truncated protein	2	Druze	Fondaneche et al.	1998	[56]
Homozygous c. 279 C>G (p. Q>X)	52-aa truncated protein	1	Turkish	Villard et al.	1997	[58]

Abbreviations: aa, amino acid; RFXAP, regulatory factor–associated protein.

(140–243 residues), a conserved sequence of the RFXAP, is substantial for binding to DNA [30]. Nine different mutations are described in Table 4. More than half of the mutations induced a premature stop codon before the C-terminal binding of the RFXAP protein. Five of the 15 patients from North African countries possessed the same c. delG484fsX525 mutation. Thus, it is not unreasonable for us to presume the prevalence of this mutation in the North African region. Interestingly, a homozygous 75-bp insertion in the 5'-UTR mutation in the RFXAP was reported in a Turkish patient [31]. This mutation disrupts the promoter activity of the RFXAP through insertion of a 5-fold 15-bp repeat in the extreme 5' end of the 5'-UTR of RFXAP, which then prohibits RFXAP transcription. This rare mutation, outside the coding region of the RFXAP, reminds us that sometimes whole-exome sequencing is not sufficient to determine the mutation that caused the MHC II deficiency. Whole-genome sequencing would explain more gene mutation information, like the mutations in noncoding regions that affect gene expression.

CONCLUSIONS

Herein, we first describe a case of MHC II deficiency with a novel splicing mutation in the fifth exon of RFXANK in a Chinese patient, whose diagnosis was guided by the finding of *Pneumocystis jirovecii* infection. Through literature review, we found that there have been no cases of MHC II deficiency reported in China, or even in East Asian countries. Moreover, we found that the number of MHC II deficiencies has reached >200, and the mutation rates of the 4 transcription factors were different in different regions. Due to the rareness of the MHC II deficiency, we provided a review of the reported MHC II deficiency cases to help elucidate the spectrum of epidemiological and genetic characteristics of MHC II deficiency disease.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. Consent was obtained from the parents, and the study was approved by the Ethical Committee of the Children's Hospital of Zhejiang University School of Medicine.

Potential conflicts of interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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