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Case Report

Novel RAG2 Mutation in a Patient with Leaky Severe Combined Immunodeficiency

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Abstract

T and B lymphocytes development and function are highly dependent on Recombination Activating Genes (RAG) 1 and 2. RAG mutations result in different degrees of T and B cell impaired function, broad clinical manifestations, and immunological manifestations. Pathogenic mutations cause severe combined immunodeficiency (SCID) phenotype, while hypomorphic mutations are responsible for leaky or partial SCID.

Here, we described a 4-year-old girl who had a persistent diarrhea, recurrent infection, and vomiting. Although physicians were suspicious about autoimmune enteropathy, her molecular report showed a homozygous and novel RAG2 mutation in its core domain. The number of CD4 T cells and IgA level were lower than normal ranges. Lack of IgA brought about different GI complications. Our patient died finally because of liver and gallbladder failure.

Keywords: RAG2; Combined Immunodeficiency; Severe Combined Immunodeficiency; Primary Immunodeficiency; IgA Deficiency

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Introduction

Severe combined immunodeficiency (SCID) is the prototype of primary immunodeficiency disease (PID) (1), and its prevalence rate is roughly estimated at 1:50,000 to 1:100,000 in a worldwide live births population (2). Iran and other countries with a higher rate of consanguinity, the precise number of SCID cases seem to be higher than it has been reported earlier (3). SCID patients have severe T-cell dysregulation and impaired B-cell function, which makes them prone to opportunistic infections, persistent diarrhea, skin rashes, pneumonitis, and failure to thrive (FTT) with early childhood onset (4).

SCID patients are subclassified into four different groups based on their defects; (i) functional dysregulation in the pre-T-cell antigen receptor complex (CD3ε/γ/ζ and CD45); (ii) signaling defects in common γ-chain dependent cytokine receptors, including Interleukin 2 (IL-2) receptor γ-chain, IL-7 receptor α-chain, and Janus kinase 3; (iii) impaired in V(D)J recombination (Artemis, *RAG1, RAG2*); (iv) early death of lymphocytes caused by purine metabolic dysfunction *ADA* deficiency) (5).

The recombination-activating gene 1 and 2 (RAG1/2) play a significant role in variable (V), diversity (D), joining (J) segments recombination of T and B cell receptors (TCR, BCR) (6). RAG1 and RAG2 are not only necessary for TCR and BCR diversity but also for their survival and development. RAG1 and RAG2 mutations are correlated with several types of immunodeficiencies, such as $T^-B^-NK^+$ SCID, Omenn syndrome (OS), leaky SCID (LS) with γς T cell expansion, and combined immunodeficiency with granulomas and/or autoimmunity (CID/AI) (7-10). In the present study, we reported a patient with RAG2 deficiency who had been initially diagnosed with selective immunoglobulin A deficiency (SIgAD).

Case presentation

Our patient was a 4-year-old girl and the first child of consanguineous parents. No significant findings were found in her family history. Between the ages 3-month to 36-month, she was admitted several times due to persistent dry coughs, persistent and chronic diarrhea, pneumonia, and failure to thrive (FTT). At age 3.5 years, she was referred to Tehran Children's Medical Center and hospitalized there because of cough, diarrhea, and hypoalbuminemia. IgA deficiency, along with CD4 deficiency, was revealed in her Immunological evaluations. Based on her lab findings and biopsy and endoscopy of the intestine, physicians were suspected about Intestinal lymphangiectasia, autoimmune enteropathy, and common variable immunodeficiency. Cotrimoxazole, Salbutamol, Montelukast, and monthly Intravenous Immunoglobulin (IVIG) were prescribed for her complications. Although most of her internal organs were found normal in CT scan, hyperaeration, diffuse bronchiectasis, pre-bronchial thickening, atelectasis, and consolidation in RML medical segments were reported in axial spiral High-resolution computed tomography (HRCT) of the chest without contrast media.

One month later, she was admitted to our center again because of chronic diarrhea, jaundice, vomiting, cough and crackles. Gastric antrum and esophageal mucosa biopsy showed moderate chronic gastritis with focal activity in addition to mild esophagitis. Spiral abdominal CT scan with contrast media showed centrilobular nodule with tree in bud appearance which seen in both lungs. Moreover, the colon is severely dilated and fluid filled down to the rectum. Gallbladder sonography showed sludge and cholesterol deposition. Cholestatic liver disease with significant ductopenia was observed in her liver biopsy. Furthermore, her bone marrow aspiration was normal but hyper eosinophilia. Respiratory distress, opportunistic pulmonary infections, persistent lymphopenia, and oral candidiasis were also reported this time-course hospitalization.

She was admitted again in her late three years old and complaining about respiratory distress, bile duct paucity, vomiting, and persistent diarrhea. Interstitial lung disease (ILD), along with bronchiectasis were reported in the chest X-ray (CXR) report. She received several corticosteroids for lessening pulmonary complications along with nebulizer ventilation, meropenem, and amphotericin. Paromomycin was also prescribed for her diarrhea. Regarding the probability of combined immunodeficiency, whole-exome sequencing (WES) was requested, and *RAG2* deficiency was identified. Her detailed WES report is summarized in **Table 1.**

At age four, she was hospitalized at E-ICU due to respiratory distress, and other clinical manifestations including fever, cough, jaundice, persistent diarrhea, pulmonary bronchiectasis, weight loss, and appetite loss were also observed. The patient underwent magnetic resonance cholangiopancreatography (MRCP), which showed primary sclerosing cholangitis (PSC). She was also a candidate for endoscopic retrograde cholangiopancreatography (ERCP), which was not conducted

due to the patient's age. Although the physicians believed that the medication must be continued, her parents discharged her from the hospital with their consent. Unfortunately, the patient died a few weeks later due to liver and gallbladder failure.

Table 1. Detailed WES Report

Gene	*RAG2*
Zygosity	Homozygous
Genomic Coordinates	Chr11:36614985
Amino Acid Change	p.Pro245Leu
SIFT	Damaging

Some clinical presentation of our patient was in accordance with previously reported *RAG2* deficient patient in **Table2,** including FTT, chronic diarrhea, recurrent infection. Although our patient exhibited a normal percentage of B cells and most of the immunoglobulin levels were normal, the IgA level was undetectable, and it may reveal that our patient had SIgAD along with *RAG2* deficiency. Some typical *RAG2* deficiency manifestations were not present in our patient, including erythroderma, hepatomegaly, splenomegaly, and lymphadenopathy. Lack of mucosal immunity due to undetectable IgA level, our patient, had faced additional complications in her GI system.

As provided in **Table 3**, most of the SCID cases, had early disease onset, but our patient's clinical manifestations were started when she was 1.5 years old. This delay of onset may correlate with the disease phenotype. Regarding that, most of the SCID cases have a lower number of T and/or B lymphocyte along with hypogammaglobulinemia; clinical presentations occur in the first days or months of the newborns. In our patient's case, due to the leaky phenotype of the disease, just CD4 T cells, and B cell numbers, and IgA serum levels were lower normal ranges. This leaky SCID form may defer the disease onset.

Table 2. Immunological Data

Test	Result 3 y/o	4 y/o	Units	Reference Range
WBC	11190	15690	10^3/µl	4000-10000
Lymph	3710	4300	10^3/µl	1500-3500
PMN	6200	9400	10^3/µl	
Hb	12.2	9	g/dl	13-17
PLT	271000		µl	170000-450000
IgG	933	579	md/dl	700-1600
IgA	<8	Undetectable	mg/dl	48-345
IgM	140	85	mg/dl	55-210
IgE	10	9	IU/ml	up to 52
CD3	46.4	63	%	30-78
CD4	16	18	%	22-58
CD8	47	41	%	10-37
CD19	5	8	%	9-38
CD20	5	8	%	9-38
CD16/56	29	25	%	5-19
NBT	100		%	97
Anti-Tetanus	0.04		IU/ml	> 0.1
Anti-Diphtheria	0.01		IU/ml	> 0.1

Discussion

RAG1 and *RAG2* genes located on chromosome 11p13 are essential for Ig recombination and T-cell receptor (TCR) loci. A homozygous mutation in these two critical genes results in T and B lymphocytes development arrest and cause SCID. On the other hand, the hypomorphic mutation in *RAG1* and *RAG2* genes, halt all types of lymphocytes development but oligoclonal and activated T cells and cause Omenn syndrome, leaky SICD and other types of immunodeficiencies (2).

Table 3. Clinical and Genetic Information of RAG2 deficient patients.

PATIENT NO.	AGE (M)	SEX	MUTATION	STATUS	LYMPHOCYTE (CELL/ML)	CD3	CD4	CD8	CD19	CD16/56	IGM (MG/DL)	IGG (MG/DL)	IGA (MG/DL)	IGE (IU/ML)	CLINICAL MANIFESTATIONS	REF.
1	24	F	a. T77N b. G451A	Hetero-zygous	769-1554 L	538-1057 L	328-668 L	177-326 L	54-202 L	131-355	11.3 L	146 L	< 6 L	< 5	Recurrent pneumonia, severe varicella infection, acute respiratory distress syndrome, profound hypogammaglobulinemia, low number of B and T cells, splenomegaly, granulomatous disease	(9)
2	4	F	a-b. M459L	Homozy-gous	869 L	149 L	85 L	61 L	4 L	279	54.9	193 L	UD L	NA	Erythroderma, Pseudomonas aeruginosa pneumonia, Coombs' positive hemolytic anemia, Recurrent pulmonary infection, onychomycosis, lymphopenia	(11)
3	4	M	a-b. M459L	Homozy-gous	NA	691 L	311 L	173 L	173 L	657	171 H	< 152 L	UD L	NA	Recurrent skin abscesses, recurrent pneumonias, Pseudomonas aeruginosa sepsis, colitis, CMV, oral candidiasis, hepatosplenomegaly, AIHA	(11)
4	0	F	G2567A	Homozy-gous	45000 H	41850 H	28458 H	11718 H	0 L	NA	NL	NL	NL	30 H	Erythroderma, loss of hair, hepatosplenomegaly, inguinal and axillary lymph nodes enlargement, epiderma; acanthosis, papillomatosis, spongiosis	(12)
5	0	-	a. Q278X b. R73H	Hetero-zygous	8339	7071	4009	1909	0 L	NA	< 4 L	461	< 4 L	7	Eczema, diarrhea, FTT, hepatosplenomegaly, lymph nodes enlargement	(13)
6	1	M	a-b. M443I	Homozy-gous	5700	2355	390	890	11.4	NA	< 2 L	220	< 1 L	< 2 L	Generalized Erythroderma, hepatosplenomegaly, Pseudomonas aeruginosa sepsis	(13)
7	0	-	a-b. R229W	Homozy-gous	280	149	67	23	17	53	20	385	34	8500	Erythroderma, skin rash	(14)
8	4 m	-	a-b. R229W	Homozy-gous	NA	77 (%)	74	4	4	2	NA	NA	NA	NA	Erythroderma, lymphadenopathy, hepatomegaly, splenomegaly,	(14)
9	4 m	-	a-b. R229W	Homozy-gous	NA	61 (%)	59	8	2	19	NA	NA	NA	NA	Erythroderma, lymphadenopathy, hepatomegaly, splenomegaly,	(14)
10	1 w	-	a. C41W b. M285R	Hetero-zygous	5880	2646	317	926	< 59	2470	6	101	< 6	316	FTT, erythroderma, skin rash, lymphadenopathy, hepatomegaly, splenomegaly, protracted diarrhea	(14)
11	4	-	a-b. W307X	Homozy-gous	720 L	< 7 L	< 1 L	< 1 L	<7 L	533	< 1 L	< 100 L	< 1 L	NA	FTT. Protracted diarrhea	(14)
12	1 w	-	a-b. N474S	Homozy-gous	1120	22	<1	<1	< 11.2	784	8	670*	7	NA	FTT. Protracted diarrhea	(14)
13	2.5	-	a. R229Q b. locus deletion	Hetero-zygous	322	113	30	13	16	161	< 8	208	11	21	Erythroderma, protracted diarrhea, hepatomegaly	(4, 14)
14	2 w	-	a-b. R229Q	Homozy-gous	8600	3698	444	592	< 86	3956	87	205	8	9100	FTT, erythroderma, skin rash, pneumonia, hepatomegaly, protracted diarrhea	(4, 14)
15	0	-	a-b. C478Y	Homozy-gous	2000	80	< 1 L	< 1 L	<20	820	< 10 L	460	< 10	< 2		(14)
16	2 w	-	a-b. C478Y	Homozy-gous	5000	3500	1610	735	< 50	2050	< 5	90	< 5	3	FTT, erythroderma, skin rash, pneumonia, lymphadenopathy, hepatomegaly, splenomegaly	(4, 14)
17	2	-	Frameshift	Homozy-gous	66	< 1	< 1	< 1	< 1	46	< 10	200	< 10	138	FTT	(14)
18	1	-	F206C R148X	Hetero-zygous	71	41	8	15	< 1	25	< 5	< 100	< 5	5	FTT, erythroderma, skin rash, pneumonia, lymphadenopathy, hepatomegaly, splenomegaly	(14)
19	-	-	a-b. T215I		600	240	58	36	0	198	25	0	< 6	NA		(15)
20	-	-	a-b. R229W		287	46	7	6	6	184	23	448	10	NA		(15)
21	-	-	a-b. R229W		1972	1045	470	156	40	375	20	385	34	14551 mg		(15)
22	-	-	a. R229W b. G95R		1953	1074	440	150	78	19	9	0	0	NA		(15)
23			a-b. G35V		1850	537	107	37	130	370	12	120	7	NA		(15)
24			a-b. R229W		110	40	6	3	0	45	145	1200	7	NA		(15)

PATIENT NO.	AGE (M)	SEX	MUTATION	STATUS	LYMPHOCYTE (CELL/ML)	CD3	CD4	CD8	CD19	CD16/56	IGM (MG/DL)	IGG (MG/DL)	IGA (MG/DL)	IGE (IU/ML)	CLINICAL MANIFESTATIONS	REF.
25			a-b. G35V		576	110	21	2	0	433	12	380	7	NA		(15)
26			a-b. G35V		290	9	< 1	< 1	0	159	U	U	U	NA		(15)
27	3		a. R229Q b. R229Q		8600	3698	946	1462	U	3956	U	U	U	U	Erythroderma, chronic diarrhea, FTT, myocarditis, interstitial pneumonia	(16)
28	3		g.4593delT 4953delT		900	0	9	1	2	280	U	U	U	U		(16)
29	-	-	a-b. E480X		10686	2779	611	222	0	3740	110	UD	UD	UD	Erythroderma, lymphadenopathy, skin infections, pneumonia	(17)
30	-	-	a-b. G157V		5600	4592	2342	1423	56	504	UD	433	79	UD	Erythroderma, prolonged rotavirus infection, PCP	(17)
31	-	-	a-b. D65Y		400	16	< 1	< 1	8	228	18	70	43	15	Erythroderma, pneumonia, diarrhea, oral thrush	(17)
32	7	-	a. K440N b. P253R	Hetero-zygous	792	103	8	2	8	657	NA	NA	NA	NA	Pneumonia	(18)
33	3 w	-	a. S106L b. M502V	Hetero-zygous	9064	725	543	72	UD	1360	UD	73	UD	200	FTT, Erythroderma, skin rash, lymphadenopathy, pneumonia	(18)
34	15 d	-	a-b. R229W	Homozy-gous	889	595	357	130	4	231	56	721	72	> 2000	Erythroderma, skin rash, recurrent URTI, hepatomegaly, generalized edema	(18)
35	3 m	-	a-b. W416L	Homozy-gous	34000	31647	25317	5063	UD	1347	< 7	< 7	< 7	124	FTT, Erythroderma, skin rash, lymphadenopathy, splenomegaly, protracted diarrhea	(18)
36	3 m	-	a-b. G35V	Homozy-gous	NA	UD	UD	UD	UD	NA	16	244	6	NA	FTT, Pneumonia	(18)
37	1 m	-	a-b. V120fs	Homozy-gous	6230	5046	3027	1311	UD	758	4	705	310	79	Erythroderma, skin rash, pneumonia, protracted diarrhea	(18)
38	-	-	a-b. R229w	Homozy-gous	-	-	-	-	-	-	-	-	-	-	-	(19)
39	-	-	a-b. R229w	Homozy-gous	-	-	-	--	-	-	-	-	-	-	-	(19)
40	-	-	a-b. ΔT251	Homozy-gous	-	-	-	-	-	-	-	--	-	-	-	(19)
41	<5 m	M	a. G95R b. W453R	Hetero-zygous	10200	5202	2548	1456	204	NA	16	146	UD	3	Seborrhea-like dermatitis, Staphylococcus aureus skin infection, lymphadenopathy, splenomegaly, interstitial pneumonitis	(20)
42	2 m	M	a. R39G b. R229Q	Hetero-zygous	10000	7400	NA	NA	0	NA	NA	NA	NA	NA	Diffuse erythroderma, protracted diarrhea, eosinophilia, FTT.	(21)
43	3 m		a. G59R b. E480X	Hetero-zygous	10686	2871	2351	855	0	3800	110	UD	UD	UD	Erythroderma, alopecia, lymphadenopathy, liver and spleen enlargement	(22)
44	4 m		a-b. G35V	Homozy-gous	1320	488	244	244	0	500	UD	UD	UD	UD	Erythroderma, alopecia, lymphadenopathy, liver and spleen enlargement	(22)
45	5 m		a-b. G156V	Homozy-gous	5600	4612	2855	1757	1	504	UD	433	79	UD	Skin diffuse eruption	(22)
46	-	-	a-b. Q16X	Homozy-gous	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		(23)
44	-	-	a-b. w453R	Homozy-gous	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		(23)
45	3 m	-	a-b. I444M	Homozy-gous	620	67	56	25	< 1	29	< 250	1200	< 180	3.1 k/l	Recurrent chest infection, chronic diarrhea, FTT, eczema, BCGosis, CMV infection, dies of sepsis	(24)
46	5 m	-	a-b. K127X	Homozy-gous	810	< 1	< 1	< 1	< 1	95	70	1800	40	< 5 K/L	Chronic diarrhea, oral thrush	(24)
47	1 m	-	a-b. K127X	Homozy-gous	978	< 1	< 1	< 1	< 1	93	-	-	-	-	Chronic diarrhea	(24)
48	-	-	a-b. S18X	Homozy-gous	489	< 1	< 1	< 1	< 1	94	< 250	1300	< 170	< 2 KL	Chronic diarrhea, FTT, disseminated BCGosis	(24)
49	-	-	a-b. Q4X	Homozy-gous	167	1	< 1	< 1	1	99	< 250	4200	< 180	< 2 KL	Chronic diarrhea, FTT, recurrent chest infection, CMV infection	(24)
50	-	-	a-b. C478Y	Homozy-gous	U	0	0	U	U	U	U	U	U	U		(4)
51	-	-	a-b. R39G b. R229Q	Hetero-zygous	U	0	U	U	0	U	U	U	U	U		(25)
52	12 d	M	a-b. I215I & R229Q	Homozy-gous	684	34.2	0	0	7	382	9	340	< 17	NA	Oral ulcers, pneumonia, CMV	(26)

Here, we described a 4-year-old girl with primary immunodeficiency who was hospitalized several times for her recurrent respiratory infection, diarrhea, and vomiting. Her initial diagnosis was CD4 deficiency along with IgAD, WES was also requested for the exact diagnosis. Her WES report showed a C734T missense mutation in the *RAG2* gene. This probably damaging mutation is novel and has not been reported so far. The detected homozygous mutation reflects the consanguinity of her parents. The mentioned mutation was in the core domain of the *RAG2* mutation, which is crucial for *RAG2* catalytic activity. Although this mutation was in the core domain of the *RAG2* gene and a more severe phenotype was expected, it seems that this type of mutation resulted in hypomorphic mutation and leaky form of the disease.

The genetic defect underlying SCID is not always reported; our patient had a novel mutation in the RAG2 gene, all patients with SCID are susceptible to life-threatening opportunistic infections (27). The analysis of phenotypes of B and T lymphocytes of our patient showed low number of T and B cells, but elevated NK cell counts. The phenotype of B, T and NK cells of the patient in the study of Shen et al. was similar to our patient (28). The low numbers of T and B cells frequently caused severe infections at a young age (29,30). Children with SCID reveal monoclonal TCR peaks associated with T cell dysfunction. This, along with B cell dysplasia, causes cellular and humoral immune system abnormalities (31). The cause of death of our patient was the liver and gallbladder failure. In Sadeghi-shabestari et al.'s study, the patient with RAG 2 mutation died due to disseminated BCG disease (27).

Hematopoietic stem cell transplantation (HSCT) can be an effective and permanent treatment for children with RAG2-SCID (32, 33). Although HSCT is a life-saving treatment in these patients, it can be limited by factors such as high rates of graft-versus-host disease (GVHD), transplant-related mortality, lack of suitable donors, and high costs (34).

Consanguineous marriage and family history of early death due to frequent infections should also be cautioned to underlying immunodeficiency diseases. In Iran, due to the high rate of consanguineous marriage, genetic counseling should be provided.

Conclusion

RAG deficiency should be a consideration in older patients with evidence of combined humoral and cellular immunodeficiency.

Conflict of interest

The authors declare that they have no conflicts of interest.

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