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LETTER TO THE EDITOR

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Three different faces of TACI mutations

Dear Editor,

Transmembrane activator and CAML interactor (TACI) protein, also known as tumour necrosis factor receptor superfamily member 13B (TNFRSF13B), is a member of the tumour necrosis factor (TNF)-like receptor family, a group of receptors that regulate both survival and apoptosis of immune cells. TACI controls T cell-independent B cell antibody responses, isotype switching and homoeostasis and mediates immunoglobulins production. Common variable immunodeficiency (CVID) is a heterogeneous group of diseases characterized by a hypogammaglobulinemia with loss of antibody production and susceptibility to bacterial infections. The frequency of TNFRSF13B mutations in Turkish patients with CVID was found at 7.1%.[1] Symptomatic individuals with normal immunoglobulin levels who have TACI mutation are also reported in the current literature. A few cases with homozygous TACI mutations have been reported to date.

Here, we aimed to disclose the different clinical presentations of our patients having TACI gene mutations. While two of them had the homozygous c.310T > C and c.204 dupA mutations, one had a novel heterozygous c.842_857del mutation.

1 | CASE REPORTS

1.1 | Case 1

A 33-year-old female patient admitted to our clinic with the complaint of recurrent pneumonia, otitis media, malnutrition and intermittent swelling of bilateral parotid glands since the age of 28. There was second-degree consanguinity between her parents. Her older brother had Behçet's disease, and he died because of lymphoma. Physical examination revealed massive hepatosplenomegaly, lymphadenomegaly, crepitation in the lungs and abdominal distention. The laboratory investigation revealed pancytopenia, low serum IgG, M, and A levels and a positive direct Coombs test. Immunologic findings of the patients are given in Table 1. Computerized tomography (CT) of the chest revealed pulmonary nodules with ground-glass opacity, atelectasis and interstitial lung disease. She had massive splenomegaly associated with portal hypertension. Fine-needle aspiration of the parotid gland revealed benign salivary glandular lesions. Her bone marrow biopsy was normal. Besides IVIG therapy for every three weeks, she was treated with rituximab 600 mg for four weeks and methylprednisolone. A homozygous mutation (c.310T > C/p.Cys104Arg) in the TNFRSF13B gene was provided kindly by G. Uzel's laboratory. Although she received IVIG regularly since her diagnosis, the patient died due to interstitial lung disease and *Cytomegalovirus* (CMV) pneumonia (viral load of CMV in bronchoalveolar lavage was 9499 copies/mL) at 42 years old.

1.2 | Case 2

A 14-year-old male patient had recurrent respiratory infections since the age of three. There was third-degree consanguinity between his parents. Physical examination revealed microcephaly (the head circumference was 49.5 cm, <3 P), growth retardation, the weight: 33 kg (<3P, - 3.5 SDS) and the height: 134.5 cm (<3 P, - 5.8 SDS), and hepatosplenomegaly. Testicular volumes were 2 cc, the stretched penis length: 5.6 cm; the axillary and pubic hair had not yet developed. Pancytopenia, low serum immunoglobulins were found in his blood tests Table 1. Serum levels of TSH were 5.037mU/L (0.35-4.94), total testosterone: <0.14 μg/L (1.5-8) and somatomedin C (IGF-1): 31.8 μg/L (237-996). Free T4, ACTH, LH, prolactin and basal cortisol were normal. GH levels after administered glucagon 0.03 mg/kg subcutaneously were 0.36 μg/L at baseline, 0.31 μg/L at 60th minute and 2.56 μg/L at 120th minute; and its peak level was 9.7 μg/L after administering clonidine 150 mg per orally. He had a delayed bone age and a small pituitary gland (the height of the pituitary gland is 6.6 mm), which was confirmed by the cranial magnetic resonance imaging (MRI). Enlarged mediastinal, hilar, retroperitoneal lymphadenopathies and granulomas in both lungs were found on his chest and abdomen CT besides hepatosplenomegaly. Liver biopsy showed only mild lymphocytic inflammation, and his bone marrow biopsy was normal. The patient was commenced on IVIG therapy because of hypogammaglobulinemia and recurrent infections. GH and testosterone treatments were started due to the GH deficiency and the primary hypogonadism. A homozygous c.204insA/p.Leu69Thrfs*12 mutation in the TNFRSF13B gene was detected by next-generation sequencing analysis. The variation was confirmed by Sanger sequencing. There was no mutation in the NFKB2 gene.

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TABLE 1 The clinical and laboratory findings of the patients

Parameters	P1	P1's son	P1's mother	P1's father
Gender	Female	Male	Female	Male
Clinical symptoms	Recurrent RTI, recurrent parotitis, interstitial lung disease, massive HSM	Epilepsy, neuromotor retardation	No	No
Age of PID diagnosis	33 y	-	-	-
Mutations in the TACI gene	Homozygous c.310T > C	na	Heterozygous c.310T > C	Heterozygous c.310T > C
Outcome	Dead	Alive	Alive	Alive
Laboratory investigations				
White blood cell count (K/μL) (normal range)	1.4 (4.6-10.2)	5.79 (4,5-13.2)	5.68 (4.6-10.2)	4.14 (4.6-10.2)
Absolute Lymphocyte Count (K/μL) (normal range)	0.405 (1.0-2.8)	2.494 (1.0-5.3)	1.553 (1.0-2.8)	1.226 (1.0-2.8)
Absolute Neutrophil Count (K/μL) (normal range)	0.910 (2-6.9)	2.463 (2-6.9)	3.513 (2-6.9)	2.302 (2-6.9)
Haemoglobin (g/dL) (normal range)	9.87 (12.2-18.1)	14.0 (12.4-16.5)	10.5 (12.2-17.8)	11.0 (12.2-17.8)
Thrombocytes (K/μL) (normal range)	43.7 (142-424)	210 (176-452)	261 (128-416)	171.5 (128-416)
Serum Ig G (mg/dL) (normal range)	<152 (913-2100)	943 (913-1884)	1170 (913-2100)	917 (913-2100)
Serum Ig M (mg/dL) (normal range)	<17.6 (88-440)	108 (88-322)	42 (88-440)	42 (88-440)
Serum Ig A (mg/dL) (normal range)	<6.34 (139-440)	52 (139-372)	215 (139-440)	88 (139-440)
Anti Hbs Ab (mIU/mL)	0	77.33	48.64	0.40
Anti tetanus Ab (IU/mL)	-	3.88	<0.01	<0.01
CD3 (%) (K/mcL) (normal range)	90.9 0.36 (0.7-2.1)	61.1 1.5 (0.8-3.5)	78 1.2 (0.7-2.1)	53.1 0.82 (0.7-2.1)
CD4 (%) (K/mcL) (normal range)	65.7 0.26 (0.3-1.4)	41.4 1.0 (0.4-2.1)	38.3 0.59 (0.3-1.4)	27.8 0.43 (0.3-1.4)
CD8 (%) (K/mcL) (normal range)	31.7 0.12 (0.2-0.9)	16.6 0.414 (0.2-1.2)	37.7 0.58 (0.2-0.9)	23.8 0.37 (0.2-0.9)
HLA DR (%)	48.6	30.7	27.5	22.4
CD19 (%) (K/mcL) (normal range)	6 0.02 (0.1-0.5)	20.9 0.18 (0.2-0.6)	5.3 0.82 (0.1-0.5)	8.1 0.12 (0.1-0.5)
CD3-CD16 + CD56 (%) (K/mcL) (normal range)	5 0.02 (0.09-0.6)	17.1 0.426 (0.07-1.2)	14.3 0.22 (0.09-0.6)	36.1 0.56 (0.09-0.6)

Abbreviations: Ab, antibody; HSM, hepatosplenomegaly; Ig, immunoglobulin; na, *not* available; RTI, respiratory tract infections.

1.3 | Case 3

A 4-year-old male patient admitted to our clinic with a fever of unknown origin at 8 months of age. He had delayed milestones (speech and gait) and premature loss of deciduous teeth. There was no consanguinity between her parents. The weight was 8750 g (50p), and the height was 73 cm (75p). Physical examination was revealed low set ears

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P2	P2's mother	P2's father	P3	P3's mother
Male	Female	Male	Male	Female
Recurrent RTI, massive HSM, delayed puberty, short stature, microcephaly	No	No	Fever of unknown origin, delay in milestones, dry skin, early loss of deciduous teeth autoimmune thyroiditis	Vitiligo, autoimmune thyroiditis
15 y	-	-	8 mo	-
Homozygous c.204insA	Heterozygous c.204insA	Heterozygous c.204insA	Heterozygous c.842_857del	Heterozygous c.842_857del
Alive	Alive	Alive	Alive	Alive
3.8 (4,5-13.2)	6.36 (1.0-2.8)	11.0 (4.8-10.4)	8.1 (5.5-15.5)	4.38 (1.0-2.8)
1.410 (1.0-5.3)	1.114 (1.0-2.8)	1.226 (1.0-2.8)	8.1 (1.3-3.8)	1.430 (1.0-2.8)
1.54 (2-6.9)	4.651 (2-6.9)	7.68 (2-6.9)	5.33 (1.5-8.5)	2.53 (2-6.9)
9.67 (12.4-16.5)	8.0 (12.2-18.1)	16.1 (12.2-17.8)	11,2 (11.5-13.5)	16.1 (12.2-18.1)
95 (176-452)	246 (142-424)	232 (128-416)	397 (214-483)	206 (142-424)
285 (876-2100)	1240 (913-1884)	1190 (913-1884)	291 (463-1006)	1250 (913-2100)
134 (77-440)	215 (68-322)	59 (68-322)	<16 (46-159)	103 (88-440)
<6.25 (100-440)	304 (139-372)	172 (139-440)	23.3 (17-69)	186 (139-440)
1.56	0.12	0.00		0.10
-	2.05	0.03	0.5	3.38
80.9 1.1 (0.8-3.5)	86.9 0.92 (0.7-2.1)	72.2 0.88 (0.7-2.1)	67.7 5.5 (1.5-3.7)	64.8 0.92 (0.7-2.1)
32.1 0.456 (0.4-2.1)	50.5 0.56 (0.3-1.4)	51.1 0.62 (0.3-1.4)	40.3 3.2 (0.8-2.1)	39.6 0.56 (0.3-1.4)
34.3 0.483 (0.2-1.2)	33.5 0.32 (0.2-0.9)	19.9 0.24 (0.2-0.9)	22 1.7 (0.4-1.1)	22.5 0.32 (0.2-0.9)
48.6	16.2	11.8	30.4	16.5
13.4 0.18 (0.2-0.6)	3.1 0.15 (0.1-0.5)	6 0.07 (0.1-0.5)	21.2 1.7 (0.4-1.2)	10.7 0.15 (0.1-0.5)
5.4 0.076 (0.07-1.2)	5.8 0.30 (0.09-0.6)	20.5 0.25 (0.09-0.6)	8 0.65 (0.15-0.56)	21 0.30 (0.09-0.6)

and dry skin. His laboratory findings were normal except for hypogammaglobulinemia, reduced antibody production, the positivity of anti-thyroid peroxidase (37.3 kU/L, normal range: 0-5.61 kU/L) and anti-thyroglobulin tests (21.8 kU/L, normal range: 0.4-17.7 kU/L). He was treated with thyroid replacement therapy because of autoimmune thyroiditis. Immunologic findings of the patient are given in Table 1. The cranial MRI was normal. His fever attacks

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ended with the administration of regular IVIG infusions. A heterozygous frameshift mutation (c.842_857del/p.ile281Thrfs*37- p.ile281Tfs*37) in TNFRSF13B gene was detected. This mutation has not been reported before. In the presented case, more than 4800 genes were screened with NGS, but there was no other mutation to explain his antibody production defect. According to in silico prediction tools, it is a very likely cause of the disease. The mother had the same mutation. Although she was presented with vitiligo and autoimmune thyroiditis, her serum immunoglobulins were normal.

2 | DISCUSSION

Biallelic *TNFRSF13B* variants are rare causes of CVID and have generally been associated with some degree of antibody deficiency. It has been only a few cases with homozygous mutation of C104R (c.310T > C) of the TACI gene reported so far.[1,2] Our first case is the third case of having a homozygous C104R variant who presented with autoimmunity and lymphoproliferation besides CVID. The presence of autoimmunity was significantly higher in patients having heterozygous for the C104R mutation compare to the other mutations of the TACI gene.[1,3-6] Salzer et al speculated that individuals with heterozygous mutations of the TACI gene had a higher rate of autoimmunity than those with homozygous mutations. The wild-type TACI allele in heterozygotes may be able to promote the survival of autoreactive B cell clones more than any of the 2 mutated TACI alleles.[4] Autoimmune disorders have not been reported in patients with homozygous C104R mutations previously.[3,4] However, our case was suffering from recurrent parotitis episodes that were responsive to short-term steroid treatment.

Primary hypopituitarism may occur due to loss, damage or dysfunction of hormone-secreting cells in the pituitary gland.7 Anterior pituitary dysfunction is thought to be more common in patients with primary antibody deficiency compared to the normal population.[8] The deficit in anterior pituitary function and variable immune deficiency (DAVID) syndrome described by Quentien et al in 2012.[9] They observed the association of ACTH deficiency and CVID in their 4 cases and in 2 cases already published.[9-11] Two of these patients had partial GH deficiency and small pituitary glands, as well as panhypopituitarism and ACTH deficiency, but no LIFE, IKAROS, and EOS gene defects. TACI gene mutation was not investigated in these patients. It has recently been published a case with DAVID syndrome having a heterozygous mutation (c.81G > A variants) in the TACI gene.[12] Our second case with the c.204dupA variant in the TNFRSF13B gene clearly showed the association of DAVID syndrome and TACI mutation. Regarding the association of TACI gene mutation and hypopituitarism, it is not precisely known whether the TACI gene mutation is the cause of hypopituitarism, or it is a coincidence. Further studies may explain this issue.

To date, many variants have been identified in the TACI gene, and the most common ones are the c.310T > C and c.542C > A.[4] To our knowledge, c.842_857del frameshift mutation that was detected in our third case has not been reported in the literature so far. c.842_857del mutation causes a frameshift mutation leading to 24 nucleotide elongation of the deduced amino acid sequence. His mother also had the same mutation, and she presented with vitiligo and autoimmune thyroiditis. Although the mother was only treated with thyroid hormone replacement therapy, her son was treated with IVIG and thyroid replacement therapy.

As a conclusion, we would like to emphasize that homozygous mutations in the TACI gene are rare and can cause severe clinical manifestations, including recurrent infections, autoimmune disorders and lymphoproliferation besides hypogammaglobulinemia. Additionally, not only immunologists but also endocrinologists should be aware that the TACI gene mutation may detect in patients with DAVID syndrome.

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