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CASE REPORT

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# Four diseases, PLAID, APLAID, FCAS3 and CVID and one gene (PHOSPHOLIPASE C, GAMMA-2; *PLCG2*): Striking clinical phenotypic overlap and difference

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**Abstract**

We suggest PLAID, APLAID, and FCAS3 have to be considered as different aspects of the same underlying condition, because of our long-term clinical and genetical experiences. Some CVID patients have the same disease-causing mutations in *PLCG2* gene, so it may be better to define all of them as "*PLCG2*deficiency."

**KEYWORDS**

APLAID, CVID, FCAS3, PLAID, PLCG2

## 1 | INTRODUCTION

The *PLCG2* gene which is located on the 16th chromosome (16q23.3) encodes phospholipase Cγ2 (PLCG2), a transmembrane signaling enzyme that catalyzes the production of second messenger molecules utilizing calcium as a cofactor and propagates downstream signals in several hematopoietic cells.[1] Recently, heterozygous germline mutations in human *PLCG2* were linked to some clinical phenotypes with some overlapping features—PLCγ2-associated antibody deficiency and immune dysregulation syndrome (PLAID) (OMIM 614878) and autoinflammation, antibody deficiency, and immune dysregulation syndrome (APLAID) (OMIM 614878)[2-4] and familial cold autoinflammatory syndrome (FCAS3) (OMIM 614468).[5] All of them are autosomal dominant inherited diseases. Common variable immunodeficiency (CVID) is the most prevalent symptomatic heterogeneous group of primary immunodeficiency (PID) with low serum immunoglobulins and recurrent sinopulmonary infections mostly observed in the first decade of life.[6] Recently, PLCG2 gene was found to be mutated in some of the CVID patients.[1,6]

Antibody deficiency, and immune dysregulation syndrome was characterized by recurrent blistering skin lesions with a dense inflammatory infiltrate and variable involvement of other tissues, including joints, eyes, and gastrointestinal tract. The patients had a mild humoral immune deficiency associated with recurrent sinopulmonary infections, but no evidence of circulating autoantibodies. Zhou et al[3] noted that APLAID was a distinct disorder from PLAID, which they had described earlier,[2] although both disorders shared impaired humoral immune function.

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Familial cold autoinflammatory syndrome is an autosomal dominant immune disorder and autoinflammatory disease characterized by the development of cutaneous urticaria, erythema, and pruritus in response to cold exposure. It is also characterized by the dysfunction of the inflammasome.[5] From this point of view, FCAS3 patients usually display fever and inflammation at different organs, including the skin, joints, central nervous system, and gastrointestinal tract.[5] Affected individuals may have additional immunological defects, including antibody deficiency, decreased number of B cells, defective B cells, increased susceptibility to infection, and increased risk of autoimmune disorders.[2]

In addition to infectious complications in CVID patients, at least one third of the patients experience autoimmune, autoinflammatory, granulomatous, and/or malignant complications.[7] The very heterogenous presentation of CVID strongly suggests a collection of different disease entities with somewhat different pathogenesis and most likely diverse genetic etiologies.[7] Massive gene sequencing technologies have favored the description of mutations in several genes, but only in 10% of CVID patients.[8] These monogenetic defects are as follows: *ICOS, TNFRSF13B (TACI), TNFRS13C (BAFFR), TNRFSF12 (TWEAK), CD19, CD81, CR2 (CD21), MS4A1 (CD20), (CD27), LRBA, CTLA4, PRKCD, NFKB1, NFKB2, PIK3CD, PIK3R, VAV1, RAC1, BLK, IKZF1 (IKAROS, IRF2BP2,* and finally *PLCG2*.[8]

By means of our clinical experiences and recently obtained genetic results in five patients presented below, we suggest that PLAID, APLAID, and FCAS3 are different aspects of the same underlying condition. In addition, a very small proportion of CVID patients are also PLAID/APLAID/FCAS3 patients and all these cases have a disease-causing mutation in *PLCG2* gene, so maybe it may be better to define all of them as "PLCG2 deficiency" patients.

## 2 | PATIENTS

### 2.1 | Patient 1

A 12-year-old girl presented with a history of recurrent respiratory tract infections for a few years and with decreased immunoglobulin levels. Her parents were consanguineous and her mother had recurrent otitis media in childhood. In her physical examination, purulent postnasal discharge, splenomegaly, and fine crackels in lower lobes of both lungs (bilateral bronchopneumonia) were observed.

Routine blood tests showed low serum immunoglobulins and lymphocyte counts compared to age-related healthy normals[9,10]; IgG: 616 mg/dL, (normal: 1075 ± 228 mg/dL); IgA:17 mg/dL, (normal: 125 ± 43 mg/dL); IgM:33 mg/dL, (normal: 110 ± 38 mg/dL) and absolute lymphocyte

**TABLE 1** Demographic, remarkable clinical, and laboratory finding of the study group

| Patient no | Gender | Consanguinity | Age (year) | Age at admission (year) | Remarkable clinical findings | Laboratory findings | Therapy |
|---|---|---|---|---|---|---|---|
| 1 | Female | 2nd degree | 17 | 12 | • Recurrent respiratory tract infections<br>• Splenomegaly | • Hypogammaglobulinemia<br>• Lymphopenia<br>• Decreased memory B cell | • IVIG replacement<br>• Itraconazole/TMP-SMX prophylaxis |
| 2 | Male | (-) | 10 | 3 | • Recurrent eczematous rash and sinopulmonary infections<br>• Chronic bronchitis and bronchiolitis | • Hypogammaglobulinemia<br>• B cell lymphocytopenia<br>• Urticaria and erythema | • IVIG replacement |
| 3 | Male | (-) | 4 | 1st month | • Maculopapular rash | Hypogammaglobulinemia<br>• B cell lymphocytopenia<br>• Urticaria and erythema | • IVIG replacement |
| 4 | Female | (-) | 7 | 5 | • Recurrent severe abdominal pain, prolonged high fever, joint pain and swelling of the face | High acute phase reactants during attacks | • Canakinumab |
| 5 | Male | (-) | 11 | 9 | • Recurrent fronculus and respiratory infections | • Specific antibody deficiency | • Prophylactic antibiotics |

**TABLE 2** Phospholipase Cγ2 mutations and early diagnosis of the patients

| Patient no | Patient PLCG2 mutation | Mother PLCG2 mutation | Father PLCG2 mutation | PolyPhen-2 | INFEVERS | CLINVAR | Early diagnosis | Diagnosis: PID due to |
|---|---|---|---|---|---|---|---|---|
| 1 | p.S718R Heterozygous mutation | p.S718R Heterozygous mutation | No mutation *No mutation in healthy brother | BENIGN Score: 0.171 | VUS | VUS | CVID | PLCG2 defect |
| 2 | p.T168A Heterozygous mutation | p.T168A Heterozygous mutation | No mutation | BENIGN Score: 0.00 | BENIGN | VUS | $CVID^{+}$ APLAID | PLCG2 defect |
| 3 *Patients 2 and 3 are siblings | p.T168A Heterozygous mutation | p.T168A Heterozygous mutation | No mutation | BENIGN Score: 0.00 | BENIGN | VUS | $CVID^{+}$ APLAID | PLCG2 defect |
| 4 | p.Y482H/p.N571S Compound heterozygous mutation | No mutation | p.Y482H/p.N571S Compound heterozygous mutation | PROBABLY DAMAGING score: 0.974/ BENIGN Score: 0.001 | BENIGN | BENIGN | FCAS3 | PLCG2 defect |
| 5 | p. P139S Heterozygous mutation | p. P139S Heterozygous mutation | No mutation | PROBABLY DAMAGING Score: 0.977 | VUS | VUS | PLAID | PLCG2 defect |

count:1320/μL, (normal >1500/μL) (Table 3). Lymphocyte subsets by flow cytometry were in the normal range and also specific antibody levels against vaccines were also in protective levels (Table 3). There was a decreased percentage of $CD19^+$ $CD27^+$ B cells (0.5%, normal: 1.5-6.2%). Screening tests for autoimmunity were all negative. *Streptococcus pneumoniae* and *Moraxella catarrhalis* were detected in sputum culture.

There were chronic changes secondary to recurrent pulmonary infections on chest X-ray. There was reticular infiltration in the middle and left lung lower lobes, and no bronchiectasis was observed in thorax CT. Abdominal ultrasonography revealed splenomegaly.

The case with lymphopenia, hypogammaglobulinemia, decreased memory B cell, splenomegaly, and recurrent upper/lower respiratory tract infections diagnosed as CVID and intravenous immunoglobulin therapy (IVIG) once a month, prophylactic itraconazole and TMP-SMX treatments were started (Table 1). After 5 years of follow-up, it was observed that the frequency of infections decreased significantly and life quality of the patient was better than before.

Then, we decided to perform "targeted next generation sequencing (TNGS)" in order to understand her molecular pathology. TNGS workflow based on an Ion AmpliSeq™ Primary Immune Deficiency Research Panel was designed for sequencing 264 PID genes on Ion S5™ Sequencer and showed a heterozygous c.2152A>C (p.Ser718Arg) mutation in *PLCG2* gene (Table 2). This mutation was classified as VUS (variant of unknown significance) according to ACMG guidelines in VARSOME.[11] Although it was not listed in INFEVERS, an alternative variant p.Ser718Gly was classified as VUS in CLINVAR database. Having high pathogenicity scores and remarkable clinical and laboratory findings and good response to IVIG treatment, we strongly suggest that it is disease causing. In addition, her mother with recurrent purulent otitis media in childhood had the same mutation and her father and brother without any infectious symptoms during their whole life had no mutation in *PLCG2* gene (Figure 1). Nowadays, the patient is in good general condition, no major infectious episodes, autoimmunity manifestations, and lymphoproliferation occurred. Now, her exact diagnosis is PLCG2 deficiency.

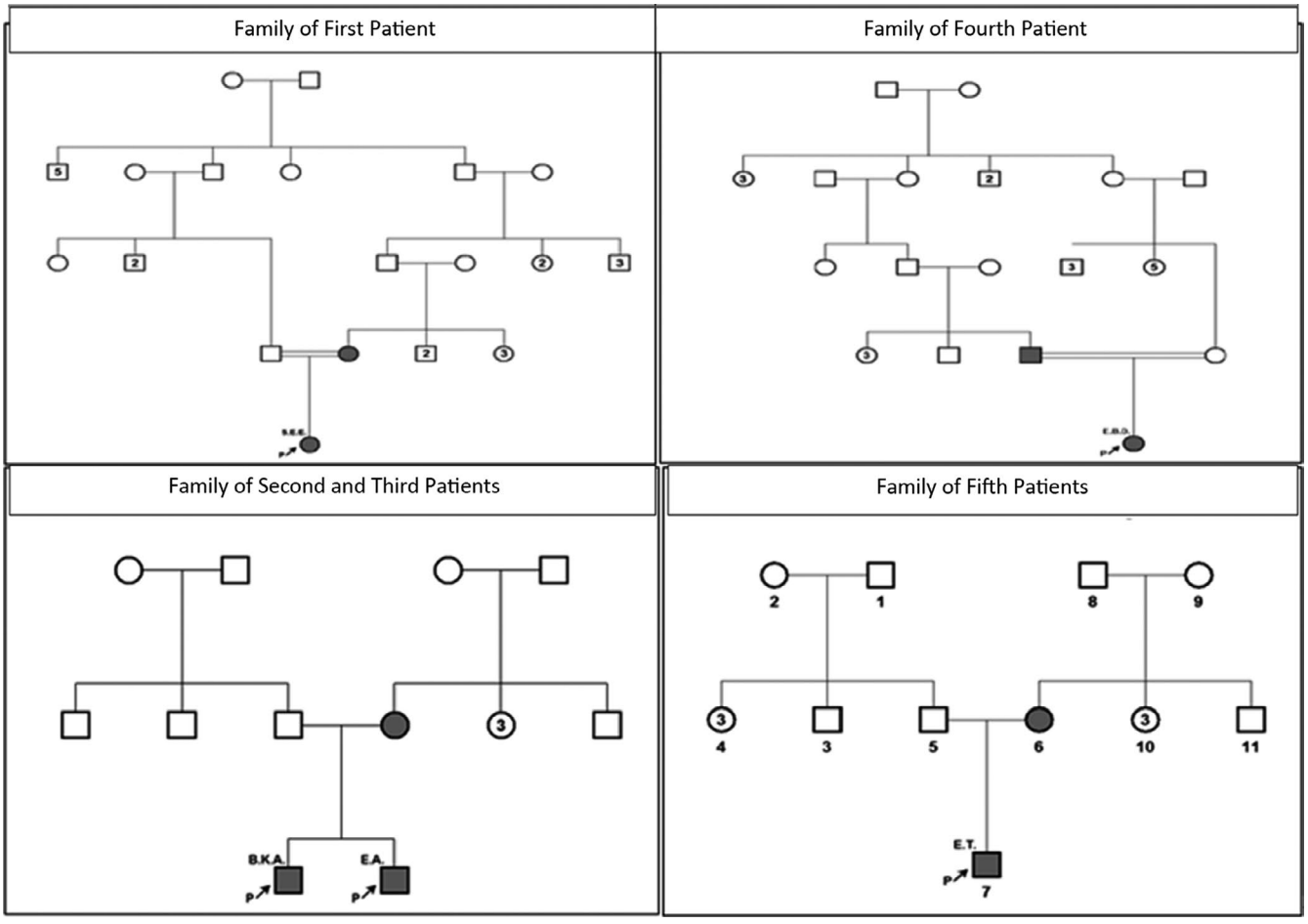


**FIGURE 1** Family pedigrees of all patients

## 2.2 | Patient 2-3 (siblings)

A 3-year-old boy admitted with a history of severe eczematous rash, recurrent bronchiolitis, acute otitis media, and bronchopneumonia. His parents were non-consanguineous and his mother is always ill, because of upper respiratory tract infections, arthritis, and diseases with skin eruptions. His physical examination at admission was normal except for a mild eczematous rash on both hands, arms, and body (Figure 2).

His initial immunologic evaluation revealed low IgG (410 mg/dL, normal: 848 ± 208 mg/dL) and IgM levels (39 mg/dL, 98 ± 33 mg/dL), normal IgA (78 mg/dL, normal: 58 ± 26 mg/dL) (Table 3). In flow cytometric lymphocyte subsets analysis, he had normal numbers of $CD3^+$ T cells (86%) and low $CD19^+$ B cells (1.7%). Specific IgG antibodies against tetanus and hepatitis B vaccines were both undetectable (Table 3). His other laboratory tests including leukocyte, lymphocyte, hemoglobin counts, liver and kidney function tests, serologic investigations for common viruses, autoantibodies such as antinuclear antibody, direct Coombs tests, and abdominal ultrasonography were all normal. In chest CT, he had chronic bronchitis and bronchiolitis.

When he was 5 years old, genetic analyses for *RAG1* and *BTK* were performed and no disease-causing mutations were detected in these genes which were known to be associated with severe combined immune deficiency and X-linked agammaglobulinemia. We began to give him intravenous immunoglobulin (IVIG) replacement therapy (0.5 gm/kg) with 4-week intervals. During follow-up of 7 years under IVIG therapy, he was extremely well and had never severe infections.

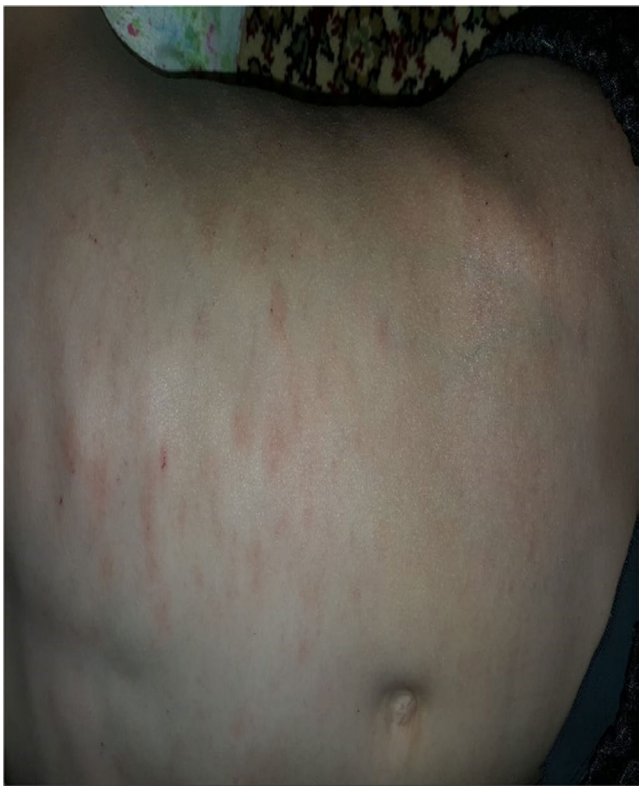

**FIGURE 2** Erythema, eczematous and maculopapular rash of the second patient

When this patient was 6 years old, his brother was born. On the 28th day of his birth, he was admitted to our hospital because of maculopapular rash spreading all over his body especially after bathing. His physical examination was normal except for maculopapular rash. His initial immunologic evaluation revealed normal numbers of $CD3^+$ T cells (88%) and low $CD19^+$ B cells (1.6%) (Table 3). During follow-up, low IgG (228 mg/dL, normal: 507 ± 193 mg/dL), low IgA (10 mg/dL, normal: 28 ± 16 mg/dL), and slightly low IgM levels (37 mg/dL, 67 ± 30 mg/dL) were found (Table 3). He had hypogammaglobulinemia and B cell deficiency, therefore we began to give him IVIG replacement therapy (0.5 gm/kg) with 4-week intervals. After IVIG therapy, his quality of life increased and skin and respiratory system manifestations recovered. He has been followed-up regularly for 4 years in our department.

The elder brother was diagnosed as CVID at the beginning. In addition to recurrent infections, he had skin manifestations such as urticaria, erythema, and recurrent eczematous rash (Figure 2) that we rarely observe in classic CVID patients. Immunoglobulin levels of his sibling were very low when he was 1 year old and did not increase to normal levels as he gets older. Then, we thought that these siblings had a PID associated with dermatologic findings. In TNGS genetic analysis, a heterozygous c.502A>G (p.Thr168Ala) mutation was found in *PLCG2* gene in both them and also in their very ill and symptomatic mother (Figure 1). This mutation was reported as VUS in CLINVAR database, but was reported as likely benign in the VARSOME database and also Polyphen-2 score was 0.00. As a result, their early diagnosis was $CVID^+$ APLAID and now they are called PID due to PLCG2 deficiency (Table 2). We strongly suggest that this mutation is disease causing, not VUS or benign, because of our long-term observations about their disease management.

## 2.3 | Patient 4

A 5-year-old girl had recurrent abdominal pain, fever, joint pain, and swelling of the face. In her investigations, p.Arg202Gln heterozygous mutation had detected in MEFV gene and steroid treatment had been given during the attacks. When she admitted to our center, she had prolonged fever, severe abdominal pain and arthralgia and arthritis at different joints (Table 1). Her parents were nonconsanguineous and her 25 years old father had always severe pain in his joints and abdomen not only in childhood, but also in recent years (Figure 1). She was not thought as familial mediterranean fever (FMF), because the alteration in

**TABLE 3** Patients' immunological data and specific antibody responses against vaccines

| Patient No/ID | IgG (mg/dL) | IgM (mg/dL) | IgA (mg/dL) | $CD3^+$ (%) | $CD19^+$ (%) | $CD3^+ CD4^+$ (%) | $CD3^+ CD8^+$ (%) | $CD3\text{-}CD16^+ CD56^+$ (%) | Anti-Tetanus UI/mL | Anti-Hib mcg/mL | Anti-Hbs mUI/mL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 616 (N:1075 ± 228) | 33 (N: 110 ± 38) | 17 (N: 125 ± 43) | 70 (N: 58-82) | 17 (N:10-30) | 49 (N: 26-48) | 21 (N: 16-32) | 9 (N: 8-30) | 0.31 (N: >0.1) | 0.46 (N: >0.15) | 275 (N: 10-1000) |
| 2 | 410 (N: 848 ± 208) | 39 (N: 98 ± 33) | 78 (N: 58 ± 26) | 86 (N: 55-79) | 17 (N:11-31) | 53 (N: 26-49) | 28 (N: 9-35) | 20 (N: 5-28) | 0 (N: >0.1) | 0.23 (N: >0.15) | 0 (N: 10-1000) |
| 3 | 228 (N: 507 ± 193) | 37 (N: 67 ± 30) | 10 (N: 28 ± 16) | 88 (N: 51-79) | 16 (N:14-44) | 65 (N: 31-54) | 20 (N: 10-31) | 26 (N: 5-23) | NA | NA | 0 (N: 10-1000) |
| 4 | 896 (N: 1008 ± 209) | 71 (N: 113 ± 40) | 90 (N: 99 ± 37) | 68 (N:55-79) | 22 (N:11-31) | 40 (N:26-49) | 26 (N:9-35) | 8 (N:5-28) | NA | NA | NA |
| 5 | 940 (N: 1088 ± 238) | 28 (N: 104 ± 49) | 134 (N: 124 ± 45) | 82 (N: 58-82) | 96 (N:10-30) | 35 (N: 26-48) | 35 (N: 16-32) | 76 (N: 8-30) | 0.57 (N: >0.1) | 0 (N: >0.15) | 0 (N: 10-1000) |

*Note:* N: mean ± SD of age-related healthy controls (Ref.9 and 10).
Abbreviation: NA, not available.

her *MEFV* gene is a polymorphism and heterozygous and never expected to cause such severe clinical symptoms.

Between the attacks, her laboratory evaluation including leukocyte, lymphocyte, hemoglobin counts, liver and kidney function tests, autoantibodies such as antinuclear antibody, complement levels and rheumatic factor, acute phase reactants such as CRP and ESR were all normal. There was no proteinuria in urine examination. Her eye examination and abdominal ultrasonography were normal. During attack periods, besides clinical findings, we always observed leukocytosis, high erythroid sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA) levels lasting at least 1 week.

The next-generation sequence analysis revealed compound heterozygous c.1444T>C (p.Tyr482His) and c.1712A>G (p.Asn571Ser) mutations in *PLCG2* gene (Table 2). Her father with similar clinical symptoms had the same mutation and her asymptomatic mother did not have any mutation (Table 2). Although these mutations were reported as benign in the INFEVERS, CLINVAR, and VARSOME databases, PolyPhen-2 score was 0.974 (probably damaging) for c.1444T>C (p.Tyr482His) mutation and 0.001 (benign) for c.1712A>G (p.Asn571Ser). Then, the patient was thought to have autoinflammatory periodic fever syndrome and diagnosed as familial cold autoinflammatory syndrome-3 (FCAS3).

Canakinumab was administered monthly for 6 months (initial treatment), bimonthly for 6 months (maintenance treatment), then treatment was discontinued. The patient developed a new attack 1-year after discontinuation of treatment period, canakinumab readministered with 3-month intervals (continuation treatment). Canakinumab was highly effective and the patient was completely recovered and during 2 years of follow-up she had never above clinical symptoms suggesting us that her FCAS3 diagnosis is exactly correct.

## 2.4 | Patient 5

This 11-year-old male patient is the second child of nonconsanguineous parents. He had respiratory infections and recurrent skin infections looking like fronculus when he was 9 years old. The patient, who was given intravenous antibiotic treatment previously, was referred to our department with the diagnosis of PID. His physical examination was normal. Her mother is often having erythematous and urticarial like skin disorders that were disappearing without treatment.

His initial immunologic evaluation revealed normal IgG (940 mg/dL, normal: 1088 ± 238 mg/dL), IgA (134 mg/dL, normal: 124 ± 45 mg/dL), and low IgM levels (28 mg/dL, 104 ± 49 mg/dL) (Table 3). He had normal numbers of $CD3^+$ T cells (82%, 1508/$mm^3$) and $CD19^+$ B cells (9.6%, 176/$mm^3$) and normal numbers and percentages of other lymphocyte phenotypes ($CD3^+$ $CD4^+$ T helper cells 35% and

644/mm$^3$, CD3$^+$ CD8$^+$ T cytotoxic cells 35% and 644/mm$^3$, CD3-CD16$^+$ CD56$^+$ natural killer cells 7.6% and 140/mm$^3$) (Table 3). His other laboratory tests including leukocyte, lymphocyte, hemoglobin counts, liver and kidney function tests, serologic investigations for common viruses were all normal.

Specific IgG antibodies against *Haemophilus influenza type B* (Table 3) and *pneumococcus* vaccines (not included in the Table 3) were undetectable. The patient was diagnosed as "specific antibody deficiency." Specific antibody deficiency (SAD) is a PID characterized by recurrent respiratory system infections, normal immunoglobulin (IG) and IgG subclass levels, and poor response to polysaccharide vaccinations in children older than 2 years of age. We decided to perform "targeted next-generation sequencing (TNGS)" in order to determine the possible genetic causes of this immune deficiency and a heterozygous c.415C>T (p.Pro139Ser) mutation was found in *PLCG2* gene of the patient and his mother (Table 2). This mutation was reported as VUS in the INFEVERS and CLINVAR databases and very high PolyPhen-2 score (0.977) (Table 2). He has been successfully followed-up by using prophylactic antibiotics for 2 years in our clinic and his recent and exact diagnosis is "PLCG2-associated antibody deficiency and immune dysregulation syndrome (PLAID)."

## 3 | DISCUSSION

In 2009; Gandhi et al[12] reported thirty-five subjects who were described as familial atypical cold urticaria (FACU) displaying an autosomal dominant pattern of inheritance. All affected subjects had lifelong symptoms that began in early childhood with pruritus, erythema, and urticaria. A history of atopy was reported in 14% of patients. Most of the patients tested showed immunologic defects, including antibody deficiency (75%), recurrent infections (56%), and autoantibodies or autoimmune disease (56%).[12] Laboratory studies showed decreased serum IgA and IgM, decreased circulating B cells, decreased memory B cells, and decreased natural killer cells.[12] Indeed, some of the initially published patients with PLAID and the ones reported by Gandhi et[12] above fulfilled the diagnostic criteria of CVID. This phenotypical overlap might be explained by aberrant PLCG2 signaling downstream of the B cell receptor and Fcγ receptors on B cells.[6] In addition, it has been reported that defects in PLCG2 gene cause functional disorders in Bruton tyrosine kinase (BTK) enzyme leading to B cell developmental delay and decreased antibody production.[13,14] Szymanski and Ombrello[14] have reported that signaling abnormalities in macrophages and neutrophils caused by PLCG2 gene defects may also contribute to the pathogenesis of granulomatosis in PLAID.

Immune deficiency with increased susceptibility to infection is commonly observed in PLAID, where B lymphocyte abnormalities (patients 2 and 3) and low serum IgG, IgM, and/or IgA levels (patients 1-2-3) are the most common features as they were diagnostic criteria of CVID.[15] CVID is a heterogeneous antibody deficiency syndrome and it is characterized not only by susceptibility to bacterial respiratory tract infections but displays additional signs of immune dysregulation such as autoimmunity, chronic inflammation, and lymphoproliferation in more than 30% of the patients.[16] Overall prevalence of bronchiectasis is 34% in meta-analysis with 8535 CVID patients[17] Evaluations show that the average life expectancy varies from 1 to 49 years and replacement therapy with immunoglobulins increases life expectancy.[18] Our first, second, and third patients had the diagnosis of CVID and successfully treated with IVIG replacement. Qualitatively, many PLAID patients demonstrate reduced antibody responses to specific stimuli, such as pneumococcal antigens.[15] Our 5th patient had specific antibody deficiency (SAD) and PLAID diagnosis. Hajjar et al[19] reported that prophylactic antibiotics and immunoglobulin replacement therapy are equally effective as first line in preventing infections in SAD patients. Our patient responded very well to prophylactic antibiotics and he was prevented from recurrent bacterial infections.

PLCγ2-associated antibody deficiency and immune dysregulation syndrome patients have normal numbers of T cells, but almost all have low numbers of circulating class-switched CD27$^+$ memory B lymphocytes.[15] Our first patient had also decreased CD27$^+$ B cells. Additionally, in Szymanski and Ombrello's study, 3 of 27 PLAID patients had been diagnosed with CVID and had been treated with IVIG for severe, recurrent pneumonia with bronchiectasis.[15] Similarly, our three patients were regularly treated with IVIG. This is important because of the striking phenotypic overlap between PLAID and CVID.

Discovering the genetic causes of monogenic autoinflammatory diseases permitted their recognition as disorders and many of them are mediated by the release of proinflammatory cytokines such as interleukin-1β (IL-1β).[20] In 2005, it has been reported that gain-of-function mutations in *PLCG2* gene lead to severe spontaneous inflammation and autoimmunity.[21] The disease is composed of an autoimmune component mediated by autoantibody immune complexes and B cell– and T cell–independent inflammation.[18] FCAS3 is one of these autoinflammatory diseases and its disease-causing monogene is *PLCG2*. PLCG2 is expressed in lymphocytes as well as innate immune cells and is known to trigger a number of signaling pathways, including protein kinase C.[14] Fever and inflammatory symptoms are predominant in FCAS3 patients and one would expect to have a dramatic response to IL-1 inhibitors such as anakinra and canakinumab.[20] Our fourth patient is exactly diagnosed as FCAS3 by means of her relevant clinical findings and p.P139S heterozygous mutation with extremely high PolyPhen-2 score (0.977). Her very good response to canakinumab therapy also supports our suggestions.

Several striking phenotypes can emerge from PLCG2 disorders, and the pathophysiology leads to a complex mix of loss and gain of function in cellular signaling.[22] These phenotypes may highly overlap or may be somewhat different. For example, unlike in PLAID, the APLAID patients do not have substantial autoantibody formation.[22] Why the point mutations in the same region lead to only minimal or high overlap has yet to be understood. However, we believe that PLAID/APLAID/FCAS3 patients must have the same and unique name as "PLCG2 deficiency" in future studies. The frequency of PLCG2 deficiency in CVID patients needs to be determined and these cases also be mentioned as "PLCG2 deficiency," not CVID.

The other conclusion is although some of these mutations are reported as benign or VUS in INFEVERS and CLINVAR data and have low PolyPhen-2 scores, by means of very important and severe clinical findings and successful response to therapies, we suggest all of them are pathogenic and disease causing. Unfortunately, we are not able to do functional studies about these genetic alterations. We are advising to revise their damaging effects in databases.

Severe and recurrent infections, skin disorders, and inflammatory symptoms such as arthritis, abdominal pain and fever, low serum immunoglobulin levels, low numbers of total or memory B cells, absent specific antibody responses against polysaccharide capsulated antigens are tools for clinicians to detect PLCG2 and initiate treatment.

Patients with PLCG2 deficiency must receive intravenous immunoglobulin therapy if the major finding is immune deficiency and have to be given IL-1 inhibitors if inflammatory symptoms are predominant.

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## CONFLICT OF INTEREST

None of the authors have any conflict of interest to disclose.

## AUTHOR CONTRIBUTIONS

NK: designed the study and wrote the paper. EY: wrote the paper and provided clinical information and the samples. AA, AD, OC, and AB: performed the genetic analysis. NEK, GA, and BGB: performed clinical follow-up of patients.

## ETHICAL APPROVAL

The parents had given written informed consent for the publication.

## DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available in the "PubMed" repository, which is a persistent web link to datasets, https://pubmed.ncbi.nlm.nih.gov/.

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