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Letter to the Editor

A case of selective IgG subclass deficiency with *STAT3* mutation

Dear Editor,

Human immunoglobulin G (IgG) consists of four IgG subclasses (IgG1, IgG2, IgG3, and IgG4), and selective IgG subclass deficiency is one of the well-known primary antibody deficiency syndromes.[1] Recently, class-switch recombination deficiency with mutations in the postmeiotic segregation 2 gene (*PMS2*) or the mutS homolog 6 gene (*MSH6*) has been suggested as the etiology of a part of the selective IgG subclass and IgA deficiency,[2] although the etiology and the disease severity of selective IgG subclass deficiency varies. More recently, a patient reported with an abnormality in the phosphatidylinositol 3-kinase/v-akt murine thymoma viral oncogene homolog (PI3K/AKT) signaling pathway, specifically a mutation in the phosphatidylinositol 3-kinase catalytic delta polypeptide gene (*PIK3CD*), also showed signs of IgG subclass deficiency.[3] In contrast, hyperimmunoglobulin E (hyper-IgE) syndrome (HIES), defined as extremely high serum levels of IgE, confers immunodeficiency against specific pathogens, including pyogenic bacteria, and chronic mucocutaneous candidiasis, and also includes features such as facial dysmorphism, impaired shedding of deciduous teeth, osteopenia, craniosynostosis, and hyperextensibility.[4] The etiology of HIES is attributed to mutations in five genes, *STAT3*, tyrosine kinase 2 (*TYK2*), dedicator of cytokinesis 8 (*DOCK8*), serine peptidase inhibitor, Kazal type 5 (*SPINK5*), and phosphoglucomutase 3 (*PGM3*).[1] In general, patients with HIES show high serum IgE levels, but not reduced serum IgG levels. In this letter, we describe a patient with a pathogenic *STAT3* mutation, who presented with selective IgG subclass deficiency.

The patient is a girl, now 12 years old, whose immunodeficiency was apparent at 3 years of age, when she suffered oral candidiasis. At the age of four, she was frequently admitted to hospital with episodes of bronchial pneumonia and measles. At the age of five, she suffered a pulmonary abscess, and received immunoglobulin replacement therapy. She was admitted with a prolonged varicella infection at the age of eight. Recently, she has suffered from sinusitis about once every 3 months. There has been no life-threatening or severe infection. She has suffered moderate atopic dermatitis and acne like eczema (Supplementary Fig. 1). However, there is no hyperextensibility, high palate, retained primary teeth, scoliosis, or midline anomaly. Until now, she has suffered a bone fracture with minor trauma twice. Her clinical diagnostic score for HIES, previously defined by the National Institutes of Health (NIH) and 40 points or greater of this score have a high probability for a STAT3 mutation, is 33 points.[5] Her immunological parameters are shown in Table 1, Supplementary Table 1 and Figure 1. She showed relatively lower serum IgE levels than typical HIES patients. Her total serum IgG level was appropriate or mildly increased for her age, but her IgG2 level was low, and her IgG3 and IgA levels were also slightly low (Table 1). Her proportions of $CD19^+$, $CD3^+$, $CD4^+$, and $CD8^+$

Table 1
Immunological findings of the patient at the age of 12 years.

	Patient	Normal values
Blood cells (/μl)		
Leukocytes	4000	3400–9200
Lymphocytes	1916	19.0–45.4 (%Leukocytes)
Neutrophils	1460	45.6–73.2 (%Leukocytes)
Monocytes	192	2.0–7.5 (%Leukocytes)
Eosinophils	412	0.6–8.4 (%Leukocytes)
Lymphocytes subsets (%)		
CD3	82.4	56.0–84.0
CD4	47.6	31.0–52.0
CD8	26.3	18.0–35.0
CD19	7.4	6.0–23.0
NK ($CD3^-$, $CD56^+$, $CD16^+$)	19.9	3.0–22.0
Serum immunoglobulin levels		
IgG (mg/dl)	1934	770–1700
IgA (mg/dl)	27	67–363
IgM (mg/dl)	257	86–343
IgE (U/ml)	740	0–170
IgG subclass (mg/dl)		
IgG1	1450	438.3–1284.3
IgG2	28	190.7–587.1
IgG3	5	13.6–106.4
IgG4	4	3.0–122.4
Specific antibodies		
EBV-VCA-IgG (FA)	ND	<10 folds
EBV-EBNA (FA)	ND	<10 folds
VZV-IgG (EIA)	0.6	<2.0
Rubella-IgG (EIA)	114	<2.0
Measles-IgG (EIA)	7.7	<2.0
Streptococcus pneumonia specific IgG2 (μg/ml)	0.4	<0.35
T cell function		
Lymphocyte proliferation assay		
No stimulus (cpm)	175	
PHA (cpm)	147793	
PHA (stimulation index)	844.5	101.6–2643.8
Con A (cpm)	72570	
Con A (stimulation index)	414.7	74.7–1793.2
Complement factors		
C3 (mg/dl)	111.5	65–135
C4 (mg/dl)	10.9	13–35
50% hemolytic complement activity (U/ml)	39.0	30.0–45.0
Neutrophil function		
Neutrophil sterilizing function (%)	99.5	70–100

Con A, concanavalin A; ND, not detected.

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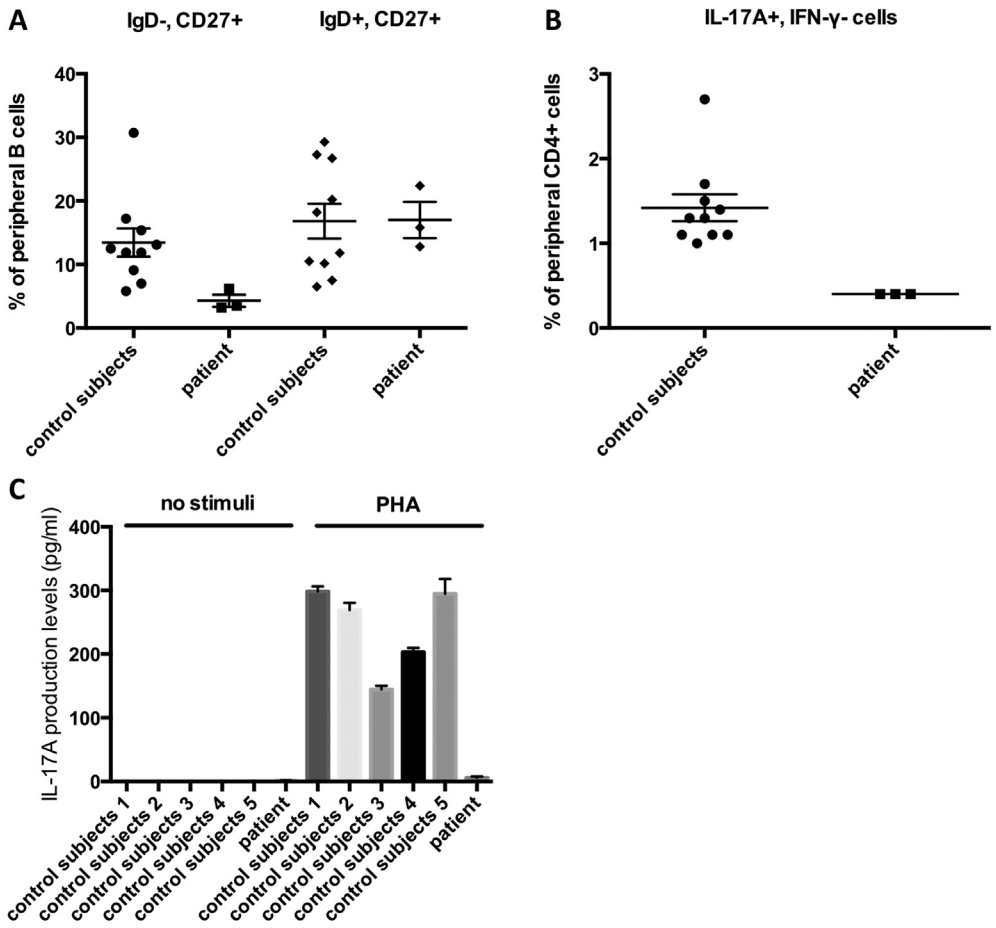

Fig. 1. Lymphocyte subsets of the patient and age-matched control subjects. **(A)** Flow-cytometric analysis of memory B cells. The proportion of isotype-class-switched memory B cells ($CD20^+$,$CD27^+$,IgD^-) was lower in the patient than in the control subjects ($n = 10$; aged 10–17 years; mean ± SD = 13.5 ± 7.0%). **(B)** Flow-cytometric analysis of Th17 cells. The proportion of $CD4^+$,$IL\text{-}17A^+$,$IFN\text{-}\gamma^-$ T-helper type 17 (Th17) cells, which were incubated with 25 ng/mL phorbol myristate acetate and 1 μg/mL ionomycin for 4 h, was lower in the patient than in the control subjects ($n = 10$; aged 10–17 years; mean ± SD = 1.42 ± 0.50%). **(C)** IL-17A production levels in the patient and control subjects evaluated with enzyme-linked immunosorbent assay. The production of IL-17A by the phytohemagglutinin-stimulated for 24 h PBMCs from the patient (5.87 ± 2.05 pg/mL) was significantly lower than that from cells of the control subjects (242.04 ± 62.56 pg/mL) ($n = 5$; aged 10–16 years). The statistical significance of differences between the patient and the control subjects was analyzed with the Mann–Whitney *U* test. *P* values < 0.05 were considered statistically significant.

cells were normal for her age, but the proportions of isotype-class-switched memory B cells in the patient were lower than those of the age-matched control subjects (Fig. 1A). The proportions of T helper type 17 (Th17) cells and the production levels of IL-17A were also significantly lower in the patient than in the age-matched control subjects (Fig. 1B, C). Finally, a heterozygous missense mutation c.1145G > A (p. R382Q) was detected in the *STAT3* gene of the patient. This mutation has previously been reported as a pathogenic mutation of HIES and occurs at one of the hot spots in this gene.[6] There was no mutation in the *STAT1, PMS2*, *MSH6* and *PIK3CD* genes.

Thus, we identified a Th17 cell deficiency in this patient with selective IgG subclass deficiency. A deficiency in IL-17 signaling is known to be the etiology of chronic candidiasis, caused by a mutation in the *STAT1*, *STAT3*, *DOCK8*, *AIRE*, *IL17RA*, or *IL17F* gene.[5,7] This patient had suffered mild candidiasis in infancy. However, because her immunodeficiency symptoms were very mild, and she was initially diagnosed with IgG subclass deficiency and relatively low serum IgE levels, her Th17 cell deficiency had not been considered. Interestingly, a recent French survey of HIES with a *STAT3* mutation reported that only one patient had low serum IgG2 levels, although no detailed profile of the patient was provided in that manuscript.[4] Therefore, this seems to suggest that the IgG subclass deficiency is a possible phenotype caused by a *STAT3* mutation.

STAT3 is a signal transducer and a transcription factor for various cytokines and growth factors. It consists of an amino-terminal domain, a coiled-coil domain, a DNA-binding domain (DBD), a linker domain, an SH2 domain, and a transactivation domain. Most of the mutations in *STAT3* causing HIES are located in the DBD and SH2 domain.[6] A recent report showed the various phenotypes of HIES patients with mutations in the DBD like this patient.[8] Although this article by Wolach et al. did not describe the serum IgG subclass values, we consider that patients with low NIH scores and not extremely high serum IgE levels may have an IgG subclass deficiency.

The mechanism underlying the elevated serum IgE levels in STAT3-deficient HIES patients has not been clarified. Avery *et al.* demonstrated impaired IL-21-induced secretion of IgE and enhanced IL-4-induced secretion of IgE from the naïve B cells of STAT3-deficient patients, and showed that their $CD4^+$ T cells produced lower levels of IFN-γ and IL-10 than those of normal subjects.[9] These results may explain the typical phenotype of HIES, but above-mentioned untypical phenotypes cannot yet be explained. On the other hand, it is known that HIES patients have low proportions of memory B cells[4] and the proportion of

isotype-class-switched memory B cells was reduced in this patient. Consequently, this patient suffers a disorder of immunoglobulin class-switching, which might be associated with not only low IgG2 but also low IgA and relatively low IgE in this case. These results may indicate that an aspect of the common variable immune deficiency like feature of STAT3 deficiency.[10] Therefore, we speculate that other genetic factors and environmental factors associated with the cytokine balance, including IL-4, IL-10, IL-21, and IFN-γ, or the differentiation of B cells, may occasionally affect immunoglobulin class-switching in STAT3-deficient patients.

In conclusion, the disease spectrum of HIES, especially STAT3 deficiency, varies greatly, and our findings may provide a clue to the unknown etiology of some patients with selective IgG subclass deficiency.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2016.05.004.

Conflict of interest

The authors have no conflict of interest to declare.

Hidenori Ohnishi [a,*], Norio Kawamoto [a], Hideo Kaneko [b], Kimiko Kasahara [a], Osamu Ohara [c], Zenichiro Kato [a,d], Toshiyuki Fukao [a]

[a] *Department of Pediatrics, Graduate School of Medicine, Gifu University, Gifu, Japan*
[b] *Department of Clinical Research, Nagara Medical Center, Gifu, Japan*
[c] *Department of Technology Development, Kazusa DNA Research Institute, Kisarazu, Japan*
[d] *Structural Medicine, The United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University, Gifu, Japan*

* Corresponding author. Department of Pediatrics, Graduate School of Medicine, Gifu University, 1-1 Yanagido, Gifu 501-1194, Japan.
E-mail address: ohnishih@gifu-u.ac.jp (H. Ohnishi).

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