

Diffuse Large B Cell Lymphoma in Hyper-IgE Syndrome Due To *STAT3* Mutation

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Abstract The Job or hyper-immunoglobulinemia E syndrome is a primary immunodeficiency that is usually inherited in an autosomal dominant fashion. With the discovery of mutations in the *STAT3* gene in the majority of autosomal dominant cases, it is now possible to make a molecular diagnosis of hyper-IgE syndrome. Both primary and secondary immunodeficiencies, including hyper-IgE syndrome, may predispose for malignancies, especially lymphomas, mainly mature B cell lymphomas, and classical Hodgkin lymphoma. Here, we report of a 48-year-old male with hyper-IgE syndrome who developed a primary parotid gland diffuse large B cell lymphoma. Analysis for *STAT3* mutations demonstrated that the causal mutation of hyper-IgE syndrome, R382Q, arose de novo in the patient and it was transmitted to three of his five children, all three of whom are

clinically affected. We review the literature regarding lymphoma in hyper-IgE syndrome and the possible etiologic relationship with *STAT3* mutations.

Keywords Immunodeficiency · hyper-IgE syndrome · Job syndrome · lymphoma · *STAT3* · melting analysis

Introduction

Hyper-IgE syndrome is characterized by both somatic features and immunodeficiency [1–3]. The immunological features include severe eczema, elevated serum IgE, skin and lung infections, chronic cutaneous candidiasis, cold staphylococcal abscesses, and pneumonias with cyst formation (pneumatocoles). The skin abscesses are described as being cold for their lack of warmth, redness, tenderness, and fever, indicating an altered inflammatory response, and are the reason the clinical syndrome was originally named after the biblical character Job [4]. Some of the most common non-immunological features are the characteristic facial features, recurrent pathologic fractures after minor trauma, retained primary teeth, and hyperextensible joints. Classical hyper-IgE syndrome patients usually present as sporadic cases; if inherited, it is autosomal dominant. Recent discovery of dominant negative mutations in the *STAT3* (signal transducer and activator of transcription 3) gene in over 90% of patients with classical hyper-IgE syndrome provides a possible explanation for most of the features, as *STAT3* is a critical component of the intracellular signaling of a large number of cytokines and hormones, including IL2, IL6, and IL10 family of cytokines, $\alpha/\beta/\gamma$ interferons, M-CSF, GM-CSF, leptin, and growth hormone, among others [5–7]. However, direct connections between the various clinical manifestations of

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hyper-IgE syndrome and STAT3 mutations have not yet been clearly established. It has been reported that STAT3 deficiency leads to the lack of Th17 cells [7–9]. Th17 cells are critical for protection against extracellular bacteria, thus suggesting a mechanism for the skin infections and pneumonia. There is, however, no experimentally supported explanation of the altered inflammation (e.g., “cold abscess”) or the non-immunological features (e.g., coarse facies). All defects causing hyper-IgE syndrome described to date are heterozygous mutations that are thought to act in a dominant negative fashion due to the dimerization of STAT3 proteins [5–7]. The location of the mutations is not random, and almost all of them are found either in the DNA-binding domain or SH2 domain-encoding exons [3]. The codon of R382 in the DNA-binding domain is the most common mutational hotspot described previously in hyper-IgE syndrome [3, 5, 7, 10–12], and mutations in R382 codon represent ~50% of all hyper-IgE syndrome patients described to date.

In addition to the classical autosomal dominant form of hyper-IgE syndrome, there are similar hyper-IgE syndromes that are autosomal recessive and not linked to mutations in *STAT3*. These recessive forms lack the characteristic non-immunological features, but are also characterized by eczema, elevated IgE, and skin and lung infections [13, 14]. In addition, these patients suffer from chronic viral infections, such as herpes simplex, zoster, and molluscum contagiosum, and often have neurological problems. A recent study found mutations in the *DOCK8* gene in 21 out of 27 autosomal-recessive hyper-IgE syndrome patients [15, 16]. Another reported case of autosomal-recessive hyper-IgE-like case was associated with a homozygous mutation in *TYK2* (tyrosin kinase 2 [17, 18]).

Immunodeficiencies, including both inherited primary immunodeficiencies and immunodeficiencies secondary to HIV infection or drug treatments, increase the risk of lymphoma development. Increased risk of lymphomas is reported in hyper-IgE syndrome patients, but these studies, with two exception [19, 20], were conducted before the discovery of the role of *STAT3* in hyper-IgE syndrome and *DOCK8* in autosomal-recessive hyper-IgE syndrome [21–23]. Assessment of the risk of lymphomas in hyper-IgE syndrome is important for patient care. A recurring theme in these patients is a neoplastic growth that is initially often deemed to be an infection (cold abscess) but does not respond to antibiotic treatment, and only the eventual histological examination leads to a correct diagnosis. In addition, investigation of STAT3-deficient patients might yield important discoveries about the role of STAT3 in the pathogenesis of lymphomas and other malignancies. STAT3 may be considered a therapeutic target in these lymphomas, but hyper-IgE syndrome patients may be at increased risk of infections caused by therapeutic targeting of STAT3.

Materials and Methods

DNA isolation and molecular testing were performed as described in Kumánovics et al. [12]. Immunohistochemical stains for CD3, CD20, CD30, and MIB-1 were performed at the Intermountain Healthcare Central Laboratories, Murray, UT, USA, and EBER in situ hybridization was performed at ARUP Laboratories, Salt Lake City, UT, USA, with standard methods and appropriately reactive controls. Literature searches were performed using PubMed at www.ncbi.nlm.nih.gov, last accessed on June 15, 2010. References not accessible to us or published in languages in other than English or German (see Table 1) were also used as reported by Leonard et al. [23].

Results

The patient was diagnosed with hyper-IgE syndrome at 15 years of age after a lifetime history of recurrent infections, coarse facies, multiple bone fractures (arm, leg, clavicular, and hand fractures), poor dentition with dental infections, and thoracic and lumbar scoliosis. The infections were mainly staphylococcal and candidal skin and nail infections. He has also had a number of lower respiratory tract infections and recurrent otitis media. The recurrent otitis media left him with perforated tympanic membranes and 80% decreased hearing in both ears. He suffers from severe eczema and has IgE levels around 4,000 IU/mL. The patient has five children (Fig. 1) of which three are similarly affected. The mutation (R382Q) arose de novo in the patient, as his parents did not carry the mutation. The same R382Q mutation was detected in three of his five tested children. The three daughters who had the *STAT3* mutation are symptomatic and have been diagnosed with hyper-IgE syndrome.

Approximately 8 months prior to the lymphoma diagnosis, the patient noticed a lump developing along the left side of his face. He thought that it was related to his chronic ear infection or was one of the boils he suffered throughout his life. This lump caused no pain, nor was it associated with fever, chills, or night sweats. At one point, he tried antibiotics, but the lump continued to grow; therefore, he visited his primary care physician for further antibiotic treatment. The primary care physician referred him to ultrasound-guided fine-needle biopsy for suspicion of malignancy. On ultrasound, the hypoechoic, minimally vascular mass was measured as $2.8 \times 5.2 \times 2.5$ cm. The fine-needle biopsy showed large atypical cells concerning for lymphoma but it was not diagnostic. Fine-needle biopsy was followed up with an open biopsy that was diagnostic and demonstrated a diffuse large B cell lymphoma, not otherwise specified (DLBCL-NOS). Microscopic examination of the specimen showed several fragments

Table 1 Review of literature

Age	Sex	Diagnosis	Site	Stage	EBV	Outcome ^a	Citation
10	Female	Histiocytic NHL	Brain	IV	nr	Died	Bale et al. 1977 [21]
19	Male	Hodgkin lymphoma	nr	nr	nr	nr	Buckley et al. 1981 ^a
7	Male	Burkitt	Retroperitoneal	IV	–	Died	Gorin et al. 1989 [50]
23	Female	Centroblastic NHL	Cervical LN	Ia	–	Alive	Einsle et al. 1990 [51]
24	Male	Hodgkin lymphoma	Mediastinal LN	I	nr	nr	Kowalchuk et al. 1996 [52]
69	Female	Mantle cell lymphoma	Generalized LN	IV	nr	Alive	Takimoto et al. 1996 ^b
46	Male	DLBCL	Cervical LN	Ila	+	Died	Nester et al. 1998 [22]
10	Male	Hodgkin lymphoma	Cervical LN	III	+	Died ^c	Lin et al. 1998 [53]
14	Female	Large anaplastic NHL	nr	nr	nr	Died	Sinclair et al. 1999 ^b
20	Male	DLBCL	Groin LN	III	–	Alive	Huber et al. 2000 [54]
18	Female	Cutaneous TCL	Multiple skin	nr	–	Died	Lei et al. 2000 [16]
54	Female	PTCL	nr	nr	nr	Died	Chang et al. 2002 ^b
13	Female	Large T cell NHL	Neck, axilla, inguinal LN	IV	– ^d	Died	Mosseri et al. 2002 [55]
57	Female	ALCL	Cervical LN	IIIb	nr	nr	Lee et al 2003 [56]
22	Male	DLBCL	L2 vertebra, spleen	IV	– ^e	Alive	Leonard et al. 2004 [23]
4	Female	Hodgkin lymphoma	Cervical LN	II	nr	Died	Kashef et al. 2006 [57]
19	Female	PTCL	Frontal, cervical parotid	IV	nr	Alive	Onal et al. 2006 [42]
17	Male	DLBCL	Inguinal LN	nr	– ^f	Alive	Wallet et al. 2007 [58]
nr	Female	Burkitt	nr	nr	nr	nr	Engelhardt et al. 2009 [15]
nr	Female	Burkitt	nr	nr	nr	nr	Engelhardt et al. 2009 [15]
44	Male	DLBCL	Inguinal LN	IIIa	nr	Alive	Beleda et al. 2010 [19]
18	Female	Extranodal NK/T	Temporal skin	IE	+	Alive	Chang et al. 2010 [20]
48	Male	DLBCL	Parotid	Ila	–	Alive	This report

DLBCL diffuse large B cell lymphoma, *PTCL* peripheral T cell lymphoma, *Cutaneous TCL* cutaneous T cell lymphoma, *ALCL* anaplastic large cell lymphoma, *Extranodal NK/T* extranodal NK/T cell lymphoma of the skin, *nr* not reported

^a Reported in Leonard et al. [23]

^b As reported at the time of publication

^c Died due to infection

^d EBV viral capsid antigen serology positive, but biopsy specimen is EBV negative

^e EBER was not definitive due to poor RNA preservation, but EBV PCR was negative

^f EBV serology: previous exposure, EBV viral load PCR pos., EBER neg., LMP-1 neg.

of fibrocollagenous and glandular tissue infiltrated by large cells (Fig. 2). Immunohistochemical stains showed that the large cells were CD20 positive and CD30 negative. Scattered cells stained positive with CD3. MIB-1, a proliferation marker, was positive in about 60% of the large atypical cells. In-situ hybridization for EBV (EBER) was negative.

Initial staging PET scan showed lymphoma involving the entire left parotid gland. A right-sided supraclavicular node was involved in the process, whereas the other nodes visualized were likely reactive, perhaps related to the frequent infections due to the underlying hyper-IgE syndrome. No other obvious sites of disease were seen on the PET/CT scan. The peripheral blood and the bone marrow biopsy and aspirate showed no evidence of the malignant process. He was, therefore, diagnosed with DLBCL-NOS, stage IIA.

The patient received three courses of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone)

treatment followed by one time rituximab treatment. The patient received 5 days of prednisone treatment just prior to the first cycle and tolerated the treatment without severe infection (he was on prophylactic antibiotic treatment with Septra and Diflucan) or other adverse reactions. After the second cycle of chemotherapy, the parotid mass largely disappeared. The patient continued to work full time during therapy.

The patient had a complete response to chemotherapy as determined by PET scan and no longer had enlarged submandibular, jugulodigastric, cervical, supraclavicular, or axillary lymphadenopathy by palpation or using PET criteria. At this point, the patient was referred for radiation therapy. The patient received a total dose of 3,600 cGy radiation in 20 daily treatments (180 cGy per fractions, 20 fractions). There was an initial concern about the sensitivity of skin of a patient with severe eczema, but he tolerated the

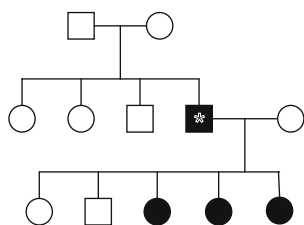


Fig. 1 Family tree of the patient. Individuals represented with *circles* are females and *squares* are males. *Filled squares* and *circles* are the affected family members. All family members were genotyped. R382Q mutation arose de novo in the proband (labeled with *asterisk*) and was inherited by three of his five children

treatment well. The patient remains in remission at 6 months following completion of therapy.

Discussion

The previous reports of hyper-IgE syndrome patients with lymphomas are summarized in Table I. The median age of hyper-IgE syndrome patients at presentation of lymphoma is 19 years, ranging from as young as 4 to 69 years old. Six of the 23 reported lymphomas were T cell in origin. The remaining lymphomas included 13 B cell lymphomas and four classical Hodgkin lymphomas. Of the B cell lymphomas, six were diagnosed as DLBCL (three as Burkitt lymphomas),

whereas the other subtypes of lymphomas were each represented by single cases. Eleven out of the 21 reported lymphoma cases were nodal (52%). Of the 11 lymphomas tested for EBV, only three were unequivocally positive (27%).

Classical Hodgkin lymphomas present in the general population in a bimodal distribution pattern with one peak at 15–35 years of age and a second peak late in life. Hyper-IgE syndrome patients presented with Hodgkin lymphoma at a median of 14.5 years of age (range 4–24 year old). The outcome was not reported in the literature for most of the Hodgkin lymphoma patients. The gender distribution of Hodgkin lymphomas in hyper-IgE syndrome is similar to that of the general population (three males and one female).

DLBCL-NOS constitutes 25–30% of non-Hodgkin lymphomas in the general population of western countries and 26% in hyper-IgE syndrome patients with lymphoma. The median age is in the seventh decade in the general population, whereas it is 33 years in hyper-IgE syndrome (range, 17–48 year old). All six reported patients with hyper-IgE syndrome and DLBCL were male. Five out of the six reported DLBCL cases were alive at the time of report.

We reported the first case of lymphoma in hyper-IgE syndrome, a diffuse large cell non-Hodgkin lymphoma of the brain in a 10-year-old female [21]. We reported another case in 1998: The patient presented with DLBCL, stage IIa

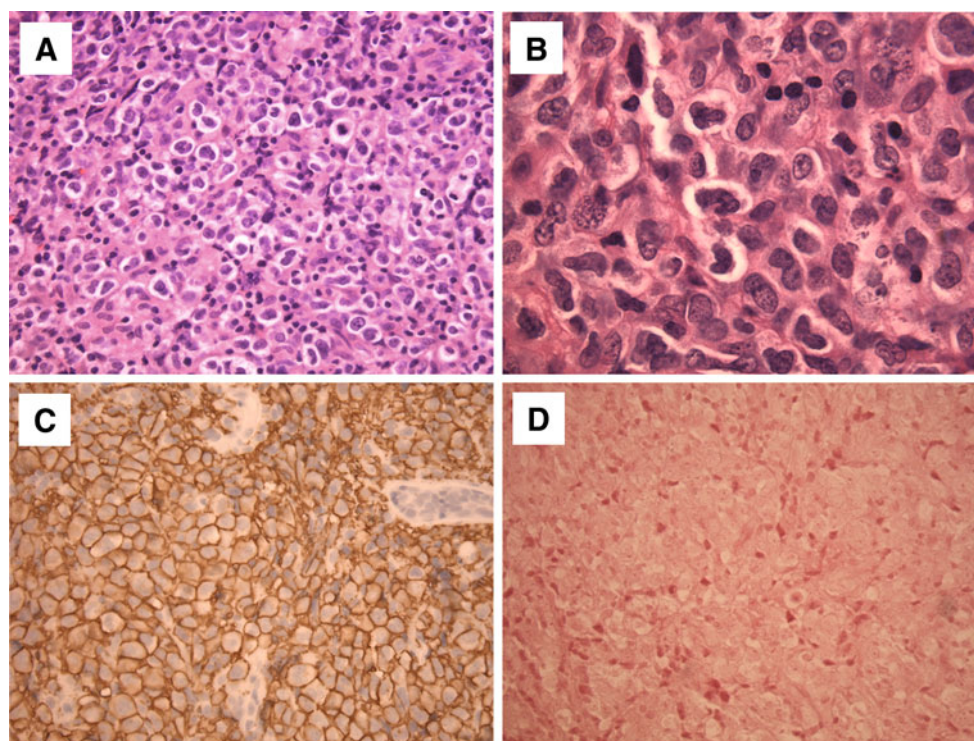


Fig. 2 Microscopic examination of the parotid mass. The large cells contain moderate amounts of eosinophilic cytoplasm, nuclei with irregular nuclear contours, marginated chromatin, and two to three indistinct nucleoli. Some of the cells are binucleate. H&E staining was

taken at $\times 200$ (a) or $\times 400$ (b) magnification. The large cells are strongly positive for CD20 (c, $\times 200$) and negative by EBER in situ hybridization (d, $\times 200$)

[22], similar to the present case. This patient was resistant to CHOP chemotherapy and received a peripheral stem cell transplant at another institution. It appeared that the stem cell transplant alleviated the signs of hyper-IgE syndrome (e.g., normalized IgE levels and neutrophil migration defects), but the patient died secondary to pulmonary fibrosis and diffuse alveolar damage. Interestingly, the family history was notable for non-Hodgkin's lymphoma in the patient's father. The *STAT3* mutation was later determined in this patient and his family, as an in-frame deletion in exon 21 (c.2069del30bp, p.E690_P699del; reference sequence NM_139276.2), the first report of *STAT3* mutation in hyper-IgE syndrome patient with malignancy [12].

As hyper-IgE syndrome is a rare disorder, the increased risk of malignancy was not fully recognized until 2004, when the relative risk was calculated as 259 (95% confidence interval 102, 416; [23]). Malignancies other than lymphomas are occasionally reported, but these appear to be rare events [24]. Primary immunodeficiency patients have an estimated average of ~200-fold increased risk of developing lymphomas over the general population, which is similar to the risk estimated for hyper-IgE syndrome patients [23]. Lymphomas developing in primary immunodeficiency patients do not differ in their morphology from lymphomas in immunocompetent patients, but are more likely to be extranodal presentations. DLBCL is the most common type of lymphoma in primary immunodeficiencies, and it is also the most common lymphoma in the general population. T cell lymphomas represent the minority in both groups. Review of the literature demonstrated that these findings also hold true for hyper-IgE syndrome. DLBCL occurring in immunodeficiency patients is more often EBV positive than in the immunocompetent patients (~10%). In our review of literature, 27% (three out of 11) of the tested lymphomas in hyper-IgE syndrome were EBV positive. The survival rate in lymphomas was first suspected to be lower in hyper-IgE syndrome than in the general population, but hyper-IgE syndrome patients were often treated less aggressively than those that were immunocompetent due to concern that the underlying immunodeficiency might impact outcome [23]. The patient presented here responded well to a short R-CHOP chemotherapy combined with involved-field radiation therapy. Similarly, Belada et al. reported durable remission in one DLBCL patient with a modified short R-CHOP treatment [19].

The increased risk of malignancy in immunosuppressed patients can be the consequence of the decreased immune surveillance of tumor cells or persistence or recurrence of infectious agents and episodes leading to chronic inflammation and stimulation. The malignancy can also be another manifestation of the underlying process that also leads to immunodeficiency, such as in ataxia teleangiectasia, where there is an abnormal DNA repair due to mutations in the *ATM* gene that leads to both immunodeficiency and increased risk of

malignancy. The reason for increased risk of lymphomas in hyper-IgE syndrome may be due to the immunodeficiency and decreased immune surveillance or, like perhaps the non-immunological features, may reflect an independent consequence of the altered function of the mutant *STAT3* protein.

STAT3 has long been known to contribute to malignant processes [25–27]. In addition to evasion of immune surveillance, cancer cells are characterized by uncontrolled proliferation, resistance to apoptosis, and promotion of neovascularization, and *STAT3* is known to participate in all these processes. *STAT3* activation is normally transient. A constitutively activated *STAT3* promotes tumorigenesis by enhancing cell proliferation and survival. Such aberrant *STAT3* activation has been described in Hodgkin lymphomas, CD30-positive anaplastic large T cell lymphomas, multiple myelomas, and DLBCL as well as in non-hematological malignancies [28–32]. *STAT* proteins can become persistently activated when upstream tyrosine kinases, which are frequently activated oncogenic proteins in cancer cells, become activated. Some tumor cells, for example DLBCL cells, can produce cytokines such as IL6 and IL10 that activate *STAT3* in an autocrine fashion [33]. Persistent activation of *STAT3* by an oncoprotein was first shown for *Src* [34]. Alternatively, *STAT3* itself can become persistently activated by mutations resulting in an intrinsic oncogenic potential [35]. In turn, the activated *STAT3* can directly or indirectly upregulate the expression of genes that are required for uncontrolled proliferation and survival. *STAT3* signaling contributes to malignancy at least in part by preventing apoptosis. For example, *STAT3* increases the expression of the anti-apoptotic BCL-2-family gene BCL-X_L [36], and *STAT3* negatively regulates the expression of p53, which is perhaps one of the most important inhibitors of cell proliferation and inducer of apoptosis [37]. *STAT3* was shown to control the expression of vascular endothelial growth factor, a critical mediator of angiogenesis important for tumor survival [38]. The critical role of *STAT3* in malignant cell survival, including in T and B cell lymphomas, has also been shown using small molecule inhibitors of *STAT3* signaling, *STAT3* ablation by RNA interference, and *STAT3* deletion in mouse model systems [31–33, 39–41].

The review of the literature on lymphomas in hyper-IgE syndrome is limited by the fact that most of the publications have not determined if the reported patients had classical autosomal dominant hyper-IgE syndrome or one of the autosomal-recessive hyper-IgE syndromes. Although the autosomal-recessive hyper-IgE syndromes are rare in western countries, they may represent a large portion or even the majority of the immunodeficient hyper-IgE syndrome patients in populations with higher rate of consanguineous marriages [13]. At least one patient, from a consanguineous marriage, reported prior to the discovery of the genetic

factors behind hyper-IgE syndrome, raising the possibility of an autosomal-recessive disease [42].

Autosomal-recessive mutations in *DOCK8* (dedicator of cytokinesis 8) are responsible for majority of autosomal-recessive hyper-IgE cases [15, 16]. *DOCK8* is a member of the Rho-Rac family of GTP-exchange factors. *DOCK* family of proteins appears to have a role in regulating cytoskeletal reorganization [43]. In B cells, disturbed actin-cytoskeleton reorganization due to *DOCK8* deficiency leads to a defect in the movement of adhesion molecules into the immunological synapse, where B cells center their antigen receptors and adhesion molecules. Perturbed immunological synapse formation leads to defective germinal center reaction, where cell–cell interaction between B, T, and follicular dendritic cells are critical for humoral immune response [44]. Vulvar, facial, and anal squamous cell carcinomas had been reported in three autosomal-recessive hyper-IgE patients with long-standing HSV, HPV, and molluscum contagiosum infections [16]. One of the patients with squamous cell carcinoma also had a multifocal cutaneous T cell lymphoma [45] (Table I). Another series of 20 autosomal-recessive hyper-IgE cases reported a squamous cell carcinoma in a patient who also had Heck disease (focal epithelial hyperplasia) and two patients with Burkitt lymphomas [15] (Table I). Immunodeficiency and long-standing epithelial viral infections suggest that these cancers in *DOCK8*-deficient patients may be due to impaired tumor surveillance and chronic inflammation and stimulation. However, chromosome 9p24 deletions that included *DOCK8* and reduced the expression of the *DOCK8* gene in gliomas, lung, gastric, and breast cancer suggests that it is also possible that *DOCK8* has tumor-suppressor function [46–48]. There is evidence that the related *DOCK4* also functions as a tumor-suppressor gene [49].

Conclusions

This is one of the first reports of the development of a lymphoma in a molecularly defined hyper-IgE syndrome patient. In two out of the three cases with known *STAT3* mutations, the amino acid changes are in the DNA binding domain (K340T [19]; R382Q, this report) and one in the transactivation domain (p.E690_P699del [12, 22]). It is yet to be determined if there are indeed *STAT3* wild-type classical hyper-IgE syndrome patients [3, 12], and if there are such patients, what is their risk for lymphoma? It is also not known if there are phenotypic differences among patients with various mutations in the *STAT3* gene (e.g., DNA-binding domain vs. SH2 domain mutations), or if increased risk for lymphomas or certain types of lymphomas is associated with a specific genotype, as not all functions of *STAT3* depend on nuclear translocation or DNA binding.

For example, malignant transformation by activated *Ras* requires *STAT3* and *STAT3* mutants that cannot be tyrosine-phosphorylated, or those that cannot bind DNA can still support *Ras*-mediated transformation [26, 27]. The role of *STAT3* is being actively investigated in various malignancies, including lymphomas [25, 31, 32]. Importantly, the *STAT* signaling pathway is being considered as a possible target for therapeutic intervention. Hence, studying the underlying mechanism of lymphomagenesis in hyper-IgE syndrome patients is not only important for the management of these patients but it may also allow a better definition of the role of *STAT3* in the oncologic process.

Disclosure/conflict of interest The authors have no conflicts of interests to declare.

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