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Inherited human ZNF341 deficiency

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Abstract

Typical hyper-IgE syndromes (HIES) are caused by autosomal-dominant-negative (DN) variants of *STAT3* (Signal Transducer And Activator Of Transcription 3) or *IL6ST* (Interleukin 6 Cytokine Family Signal Transducer), biallelic partial loss-of-function (LOF) variants of *IL6ST*, or biallelic complete LOF variants of *ZNF341* (Zinc Finger Protein 341). Including the two new cases described in this review, only 20 patients with autosomal-recessive (AR) ZNF341 deficiency have ever been reported. Patients with AR ZNF341 deficiency have clinical and immunological phenotypes resembling those of patients with autosomal-dominant STAT3 deficiency, but with a usually milder clinical presentation and lower NK (Natural Killer) cell counts. ZNF341-deficient cells have 50% the normal level of STAT3 in the resting state. However, as there is no clear evidence that STAT3 haploinsufficiency causes HIES, this decrease alone is probably insufficient to explain the HIES phenotype observed in the ZNF341-deficient patients. The combination of decreased basal expression level and impaired autoinduction of STAT3 observed in ZNF341-deficient lymphocytes is considered a more likely pathophysiological mechanism. We review here what is currently known about the *ZNF341* gene and ZNF341 deficiency, and briefly discuss possible roles for this protein in addition to its control of STAT3 activity.

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Conflict of interest statement

Nothing to declare.

Introduction

Patients with Job's syndrome or hyper-IgE syndrome (HIES) classically display severe bacterial infections of the skin and lungs, chronic mucocutaneous candidiasis (CMC), eczema, high-serum IgE (Immunoglobulin E) levels, poor or delayed clinical and biological inflammation, and skeletal, connective tissue and vascular abnormalities [1–4]. In 2007, more than 40 years after the first description of this syndrome, Minegishi and coworkers reported that dominant-negative (DN) monoallelic variants of the *STAT3* gene, encoding signal transducer and activator of transcription 3, were responsible for most cases of autosomal-dominant (AD) HIES [5]. More than 140 heterozygous variants of *STAT3* have since been reported [6]. A DN disease- causing mechanism has recently been confirmed for most (at least 95% of the 150 alleles tested) *STAT3* variants [6]. The complexity of signaling via STAT3, a ubiquitously expressed transcription factor that acts downstream from a large number of cytokine or growth factor receptors, has made it difficult to understand the mechanism underlying HIES [7]. The discovery of biallelic partial loss-of-function (LOF) and monoallelic DN variants of *IL6ST* encoding GP130 (Glycoprotein 130), the common chain of the receptors of the IL-6 (interleukin 6) cytokine family, in patients with autosomal recessive (AR) and AD HIES, respectively, has highlighted the key role of this family of cytokines in the pathophysiology of this disease [8–10]. These variants strongly impair IL-6 and IL-11 signaling, but have a lesser effect on signaling by other IL-6 family cytokines (e.g. Leukemia Inhibitory Factor (LIF), Oncostatin-M (OSM), and IL-27). Unsurprisingly, AR IL-6R (Interleukin 6 Receptor) and AR IL-11RA (Interleukin-11 Receptor Subunit Alpha) deficiencies reproduce most of the immunological and extrahematopoietic phenotypes of HIES, respectively [11–13]. Other inborn errors of cytokines or their receptors that signal through STAT3 present with only partially overlapping or even different clinical phenotypes. Patients with AR IL-21R (Interleukin 21 Receptor) or IL-21 deficiency share some of the features of HIES, with recurrent respiratory infections, impaired humoral immune responses, and high- serum IgE levels [14–17]. However, in contrast to HIES patients, they also display severe cryptosporidiosis. In 2018, two studies reported a new inborn error of immunity underlying AR HIES: biallelic LOF variants of the zinc finger 341 (*ZNF341*) gene encoding a protein of previously unknown function [18,19]. These two studies demonstrated that ZNF341 is a transcription factor controlling basal and inducible *STAT3* expression. This review summarizes what is currently known about the function of ZNF341. It also reports two new patients with complete ZNF341 deficiency and AR HIES.

Genetics of autosomal recessive ZNF341 deficiency

The gene encoding ZNF341 is located on chromosome 20. It contains 15 exons encoding two functional isoforms differing by only seven amino acids at the end of exon 6 [18]. No homozygous predicted loss-of-function (pLOF) variants and only 16 homozygous missense variants are reported in the gnomAD v2.1 and v3.1.2 public databases [20]. Only 18 patients (10 female and 8 male patients) from 10 kindreds with proven AR ZNF341 deficiency have been reported to date [18,19]. These patients were Moroccan, Afro-Caribbean, Iranian, Turkish, Lebanese, or Israeli Arab. All the patients with AR ZNF341 deficiency described to date were homozygous for pLOF variants, consistent with the relatively high consensus-negative selection (CoNeS) score of 0.29 (Figure 1a) [21]. All these variants

induced premature stop codons (p.Gln195*, p.Arg302*, p.Lys355Serfs*28, p.Arg379*, and p.Tyr542*) and were therefore predicted to encode truncated proteins (Figure 1b). The c.904C > T/p.Arg302* variant was identified in 13 patients from six kindreds. A study of three kindreds of three different ethnicities (Iranian, African, and Turkish) showed that the inherited c.904C > T (p.Arg302*) allele belonged to different haplotypes in these patients, suggesting the existence of a mutational hotspot [18]. However, the other three families were from the same Israeli village, in which 5% of the population carried the mutated allele, suggesting a founder effect in this population [19,22]. We report here two additional patients born to consanguineous parents: P19, a 29-year-old man of African descent from the Ivory Coast living in France, and P20, a two-year-old boy from Algeria. P19 is homozygous for an essential splice-site (c.1943+1G > A) variant of *ZNF341*, leading to the skipping of exon 13 and predicted to result in a truncated protein, p.Gly611Glyfs*15 (Figure. 1b, c). P20 is homozygous for the c.191C > A variant of *ZNF341*, with a premature stop codon (p.Ser64*) (Figure 1b). Like the variants previously reported in patients with AR ZNF341 deficiency, the c.1943+1G > A/p.Gly611Glyfs*15 and the c.191C > A/p.Ser64* variants have never been reported in public databases (private variants) and have CADD scores well above the mutation significance cutoff (MSC) (Figure 1d) [23]. Of note, two additional patients with HIES and suspected ZNF341 deficiency were reported but not included in our analysis because the deleterious impact of their mutation (p.Cys352Arg) was not demonstrated [24]. In total, 20 patients with HIES and confirmed biallelic LOF variants of *ZNF341* have now been identified.

Clinical features of patients with autosomal-recessive ZNF341 deficiency

The clinical phenotype of patients with AR ZNF341 deficiency is essentially a phenocopy of AD STAT3 deficiency. However, it has milder consequences, as illustrated by the median HIES NIH (National Institutes of Health) score of 28.5 for these patients, as opposed to 64 for patients with AD STAT3 deficiency (Table 1) [18,19,25–33]. Atopic dermatitis was the most common clinical presentation of patients with ZNF341 deficiency, present in all patients reported, a proportion similar to that for patients with STAT3 deficiency (> 90%). By contrast, newborn rash was rarely reported in patients with ZNF341 deficiency (15%), but was much more frequent (48%) in patients with STAT3 deficiency [25,29]. Both ZNF341-deficient and STAT3-deficient patients were highly prone to recurrent skin infections, with skin abscesses (75% vs. 73%) and CMC (60% vs. 85%). Respiratory phenotype was milder in patients with ZNF341 deficiency than in those with STAT3 deficiency. Recurrent ear, nose, and throat infections were reported in 58% of patients with ZNF341 deficiency, and 90% of those with STAT3 deficiency. Similarly, lung phenotypes were markedly less severe in patients with ZNF341 deficiency than in patients with STAT3 deficiency, with pneumonia, bronchiectasis, and pneumatocele reported in 56%, 35%, and 10%, respectively, of the ZNF341-deficient patients and 90%, 65%, and 52%, respectively of the STAT3-deficient patients. Both ZNF341-deficient and STAT3-deficient patients display skeletal and connective-tissue phenotypes, including facial dysmorphia (53% vs. 95%), high palate (45% vs. 53%), scoliosis (10% vs. 38%), joint hyperextensibility (15% vs. 50%), and the retention of deciduous teeth (25% vs. 65%). However, these extrahematopoietic manifestations were less frequent in ZNF341-deficient patients than in STAT3-deficient patients. Peripheral and brain artery abnormalities were reported in 84% of the STAT3-

deficient patients, and led to vascular complications in some of these patients [34]. None of the ZNF341-deficient patients were reported to have vascular complications (e.g. aneurysm), but more detailed investigations, including full-body magnetic resonance imaging, would be required to exclude such abnormalities definitively. Overall, the clinical description of ZNF341 deficiency resembles a milder form of STAT3 deficiency.

Immunological features of patients with autosomal-recessive ZNF341 deficiency

Patients with ZNF341 deficiency have an immunological phenotype very similar to that of patients with STAT3 deficiency (Table 1). Both defects are associated with high levels of IgE (in 85% vs. 96% of patients, respectively) and eosinophilia (58% vs. 80%, respectively) [25]. However, STAT3-deficient patients may have dampened signs of inflammation with cold staphylococcal abscesses or poor or delayed clinical and biological signs of inflammation in the setting of infection. In contrast, patients with ZNF341 deficiency show appropriate clinical and biological signs of inflammation. The immunophenotyping of blood or PBMCs (Peripheral blood mononuclear cells) has shown that both deficiencies are associated with high frequencies of naive $CD4^+$ T cells, and low frequencies of central memory $CD4^+$ and $CD8^+$ T cells, mucosal-associated invariant T cells, memory B cells, and innate lymphocytes (ILC) 1 and ILC2 [18,19,25,35–39]. In addition, the $CD4^+$ T cells of these patients have a biased helper (Th (T helper)) profile, with an abnormally high frequency of Th2 cells, and abnormally low levels of T-follicular helper (Tfh) and of Th17 cells. The high proportion of Th2 cells probably underlies the high serum levels of IgE, eczema, and the other allergic manifestations seen in the patients, as suggested by the spectacular improvement of symptoms and biological parameters in a ZNF341-deficient patient treated with dupilumab, a monoclonal antibody inhibiting signaling via IL-4 and IL-13 [40]. Low proportions of Th17 cells probably underlie CMC, a clinical feature of patients with various inborn errors of IL-17 immunity [41,42]. The low proportions of Tfh and memory B cells probably at least partly account for the severe bacterial infections of the lungs observed in these patients, through the impairment of sustained humoral responses [18]. Intriguingly, despite their low frequency of memory B cells, ZNF341-deficient patients, unlike STAT3-deficient patients, have high plasma levels of IgG and a high frequency of IgG^+ cells among the remaining memory B cells. Finally, unlike STAT3-deficient patients, ZNF341-deficient patients frequently display low NK cell numbers or frequencies among lymphocytes (8% vs. 67%, respectively). The remaining NK cells have a normal pattern of differentiation. Thus, ZNF341 deficiency phenocopies STAT3 deficiency in terms of the immunological phenotype of patients, except that NK cell counts are low in a majority of patients with ZNF341 deficiency but rarely in those with STAT3 deficiency.

ZNF341 controls basal levels of STAT3 expression

Before the discovery of ZNF341 defects in patients with HIES, the function of ZNF341 was unknown in both mice and humans. However, the clinical similarities between ZNF341 and STAT3 deficiencies suggested that the two genes/proteins were probably connected [18,19]. The 12 zinc finger domains and the two predicted nuclear localization sequences present in the ZNF341 protein suggested that it might act as a transcription factor. Indeed, ZNF341 was localized to the nucleus in overexpression studies, and western blots of

cell extracts from primary cells and immortalized cell lines showed it to be ubiquitously expressed [18]. Chromatin immunoprecipitation sequencing (ChIP-seq) of endogenous ZNF341 from control primary T cells and Epstein–Barr virus (EBV)-transformed B (EBV-B) cells showed that ZNF341 did, indeed, bind a ZNF-like DNA-binding motif (GGAAC/GA/GGC) and a SP1-like DNA-binding motif (GGGAGG), potentially forming a high-affinity bipartite motif with the two binding sites separated by 13 or 14 nucleotides ($GGGAGGn_{(13–14)}GGAAC/GA/GGC$) [18,19]. Similar DNA-binding motifs were identified in ChIP-seq data obtained from HEK293T cells transfected with a tagged wild-type (WT) *ZNF341* cDNA, and ZNF341-deficient EBV-B cells stably transduced with WT ZNF341 isoform 1 or 2 [18,43]. Strikingly, the primary DNA- binding sequence most strongly targeted by ZNF341 was found in the *STAT3* promoter. However, ZNF341 exerted subtle control over the expression of the *STAT3* gene, which did not differ markedly between the WT and ZNF341-deficient cell lines (e.g. EBV-B cells or Herpesvirus Saimiri (HVS)-transformed T cells), due to the variability of *STAT3* expression after cell immortalization. The reintroduction of WT *ZNF341* in deficient EBV-B or HVS-T cells induced only a minor, but consistent, increase in STAT3 mRNA and protein levels [18]. By contrast, ZNF341 deficiency had a marked impact on basal levels of STAT3 in the patients' primary cells. All the ZNF341-deficient cell subsets tested, including lymphocytes, monocytes, and fibroblasts, had 50% the normal level of STAT3 mRNA and protein. This resulted in 50% the normal level of STAT3 phosphorylation following cytokine stimulation, in all the primary cell subsets tested. This 50% decrease in STAT3 expression was associated with a decrease in prototypic STAT3 target gene (suppressor of cytokine signaling 3 (*SOCS3*)) induction upon IL-6/IL-6Rα stimulation in primary fibroblasts from patients. However, *SOCS3* induction was normal in naive $CD4^+$ T lymphocytes and monocytes after stimulation with IL-6/IL-6R and IL-10, respectively, for 2–4 h, suggesting that the 50% decrease in basal STAT3 levels had only a modest impact on downstream signaling. Thus, ZNF341 constitutively binds the STAT3 promoter and increases basal levels of STAT3, but has a modest impact on STAT3 signaling in response to cytokine stimulation only.

STAT3 autoinduction: a physiologically relevant mechanism under the control of ZNF341

At least 95% of the 150 pathogenic variants of STAT3 tested act through negative dominance [5,6], and there is no strong evidence that haploinsufficiency at the *STAT3* locus causes HIES. Furthermore, ZNF341 deficiency had only a modest impact on *SOCS3* induction in the primary cell types tested. The 50% decrease in STAT3 protein levels in ZNF341-deficient cells is therefore not sufficient to explain the HIES phenotype. We sought a complementary mechanism that might explain the pathogenesis of ZNF341 deficiency. Studies in mice have shown that, following stimulation with IL-6, STAT3 can bind to its own promoter, inducing the production of its own mRNA and protein in a tissue- and cell-specific manner, including in T cells [44,45]. In particular, a study of a knock-in mouse model with a homozygous mutation of the Stat3-binding element (SBE) within the *Stat3* promoter showed that Stat3 autoinduction was required for the optimal induction of selected IL-6-dependent genes in specific organs, tissues, or cells [45]. Kwon *et al.* demonstrated that Stat3 protein induction upon IL-6 and T-cell receptor (TCR) costimulation was dependent on protein kinase C (PKC)-θ, and that stimulation with phorbol-myristate acetate (PMA), an agonist of PKC-θ, increased Stat3 protein levels [46]. This PKC-θ-mediated *Stat3*

transcription was dependent on the activator protein 1 (AP-1) and nuclear factor- kappa B (NF-κB) signaling pathways, through the binding of at least c-fos and p65 to the STAT3 promoter. More importantly, Th17 differentiation was found to require Stat3 autoinduction [46]. The data obtained in this study thus indicated that PKC-θ acts downstream from the TCR and Th17-priming cytokines (e.g. IL-6) to upregulate *Stat3* via NF-κB and AP-1, resulting in Th17 differentiation. In humans, the STAT3-binding site within the *STAT3* promoter located just upstream from the ZNF341-binding site (Figure 1e). We showed that STAT3 autoinduction in human T cells also required IL-6 and TCR costimulation [18]. STAT3 autoinduction was abolished in ZNF341-deficient naive T cells stimulated under these conditions, but not in STAT3-deficient naive T cells [18]. Consistent with the findings of Kwon *et al.,* this defective STAT3 autoinduction was associated with low levels of Th17 cells in ZNF341-deficient patients, both *ex vivo* and after differentiation in vitro [18,19]. Overall, these data suggest that *STAT3* autoinduction in human T cells is dependent on ZNF341 and, probably, PKC-θ signaling for Th17 differentiation (Figure 1f). Interestingly, impaired STAT3 autoinduction was also observed in ZNF341-deficient naive B cells following CD40L and IL-21 costimulation, and was associated with a severe impairment of immunoglobulin production [18]. Thus, decreased STAT3 basal levels coupled to impaired STAT3 autoinduction probably underlie the CMC and bacterial infections of the lungs observed in patients with ZNF341 deficiency. The underlying mechanism remains incompletely understood but probably involves the impairment of Th17 and B-cell differentiation, respectively.

ZNF341 functions beyond the control of STAT3 expression

ZNF341 was shown to interact significantly with UBTF, PCM1, and PAF1 in HEK293T cells transfected with a vector encoding GFP-tagged WT ZNF341, in an affinity purification and mass spectrometry experiment (AP-MS) [43]. These interactions have not been confirmed or investigated further with other techniques, but, interestingly, both UBTF and PAF1 play important roles in transcription. ChIP-seq of ZNF341 identified 1457 binding regions in primary T cells, and 5842 and 6570 binding regions in ZNF341-deficient EBV-B-cell lines transduced with vectors encoding WT ZNF341 isoforms 1 and 2, respectively [18]. In total, 228 DNA-binding regions common to primary T cells and EBV-B cells were identified [18]. Thus, in addition to controlling *STAT3*, ZNF341 probably controls the transcription of a large number of genes, starting with *ZNF341* itself. Indeed, ChIP-seq experiments revealed a peak in *ZNF341* intron 1 [18]. A detailed analysis showed that *ZNF341* intron 1 contains six canonical ZNF341-binding sites spaced 4–30 nucleotides apart (Figure 1g). RNA sequencing and RT-qPCR on ZNF341-deficient B and T cells showed high levels of *ZNF341* mRNA, suggesting that ZNF341 downregulates its own expression and potentially that of other genes. Two ZNF341-binding sites were identified within the *STAT1* promoter, including one approximately 400 nucleotides upstream from the transcription start site (TSS), as in the *STAT3* promoter (Figure 1h) [18]. ZNF341 upregulates STAT1 mRNA and protein levels, as demonstrated by the lower levels of STAT1 in ZNF341-deficient cells, and the upregulation of *STAT1* expression upon WT ZNF341 overexpression in ZNF341-deficient cells [18]. AR complete and partial STAT1 deficiencies are associated with susceptibility to mycobacterial and viral infections, whereas AD STAT1 deficiency is associated with isolated susceptibility to mycobacteria [47–51].

None of the ZNF341-deficient patients described to date has been reported to have suffered unusual or severe viral diseases or to have developed adverse clinical events following vaccination with live attenuated BCG. However, at least two patients have been reported to have suffered tuberculosis [18]. Thus, despite the lack of haploinsufficiency at the *STAT1* locus [52], we cannot rule out the possibility that ZNF341-deficient patients are susceptible to virulent environmental mycobacteria due to a partial impairment of STAT1 signaling. It remains unknown whether *STAT1* can undergo autoinduction such as that displayed by *STAT3*, but STAT3 has been shown to act in synergy with nuclear EGFR to enhance *STAT1* expression [53]. It would be interesting to investigate whether this STAT3-dependent induction of *STAT1* expression is dependent on ZNF341, and to determine whether STAT1 can undergo autoinduction. Finally, one of the most important binding sites in all ChIP-seq datasets for ZNF341 was that within the *KAT6A* promoter. As for *STAT3* itself, *KAT6A* mRNA levels were not significantly modulated by ZNF341 complementation in ZNF341-deficient EBV-transformed B cells. However, as for STAT3, it remains possible that the alterations to KAT6A levels in ZNF341-deficient cells are more visible in primary cells. Interestingly, DN variants of *KAT6A* are associated with Arboleda–Tham syndrome [54,55], a neurodevelopmental disorder with extrahematopoietic features also observed in AD STAT3, AR LIFR, and AR complete IL6ST deficiencies [25,56,57]. It would be interesting to determine whether *KAT6A* expression is controlled by STAT3/ ZNF341 in a LIF-dependent manner (or in a manner dependent on another IL-6 family cytokine). These examples highlight the elusive role of ZNF341 beyond the control of *STAT3* expression, and the possible interaction between STAT3 and ZNF341 in the control of expression for various target genes remains to be tested.

Conclusions

Although generally milder, AR ZNF341 deficiency is a hardly distinguishable clinical phenocopy of AD STAT3 deficiency in the absence of genetic testing. ZNF341 and STAT3 deficiencies have several biological phenotypes in common, the exceptions being the frequently decreased NK cell counts and the appropriate clinical and biological signs of inflammation observed in patients with ZNF341 deficiency. ZNF341 is a ubiquitous nuclear protein that may repress or activate target gene expression. Its major role appears to be the control of *STAT3* expression, explaining why AD STAT3 and AR ZNF341 are phenocopies. In AD STAT3 deficiency, DN STAT3 proteins interfere with the remaining activity of the WT STAT3 proteins. In AR ZNF341 deficiency, the lack of ZNF341 function reduces the basal expression of STAT3 and impairs STAT3 autoinduction ‘boost’. In both cases, the resulting impaired STAT3 signaling leads to similar B-cell and Th17 defects, underlying the bacterial and fungal infections. STAT3 autoinduction in T cells is probably dependent on cosignaling via AP-1 and NF-kB in the PKC-θ pathway. The role of ZNF341 beyond the control of *STAT3* expression remains unclear. This protein has been shown to bind thousands of regions in the human genome, with cell-type specificities. ZNF341 may act as a bridge between STAT3 and other signaling pathways, by binding to promoters other than the *STAT3* promoter, such as the *STAT1* and *KAT6A* promoters. Furthermore, the interaction partners of ZNF341 remain unknown, although several excellent candidates have been proposed (e.g. UBTF, AP-1, and NF-κB). Despite the many molecular, cellular,

immunological, and clinical similarities between AD STAT3 and AR ZNF341 deficiencies, ZNF341 may function beyond the control of STAT3 expression and autoinduction. For instance, ZNF341-dependent STAT1 expression may underlie susceptibility to virulent environmental mycobacteria (Mycobacterium tuberculosis) reported in some patients. Additional case reports and studies are required to fully understand the functions of this transcription factor.

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Data Availability

Data will be made available on request.

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Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

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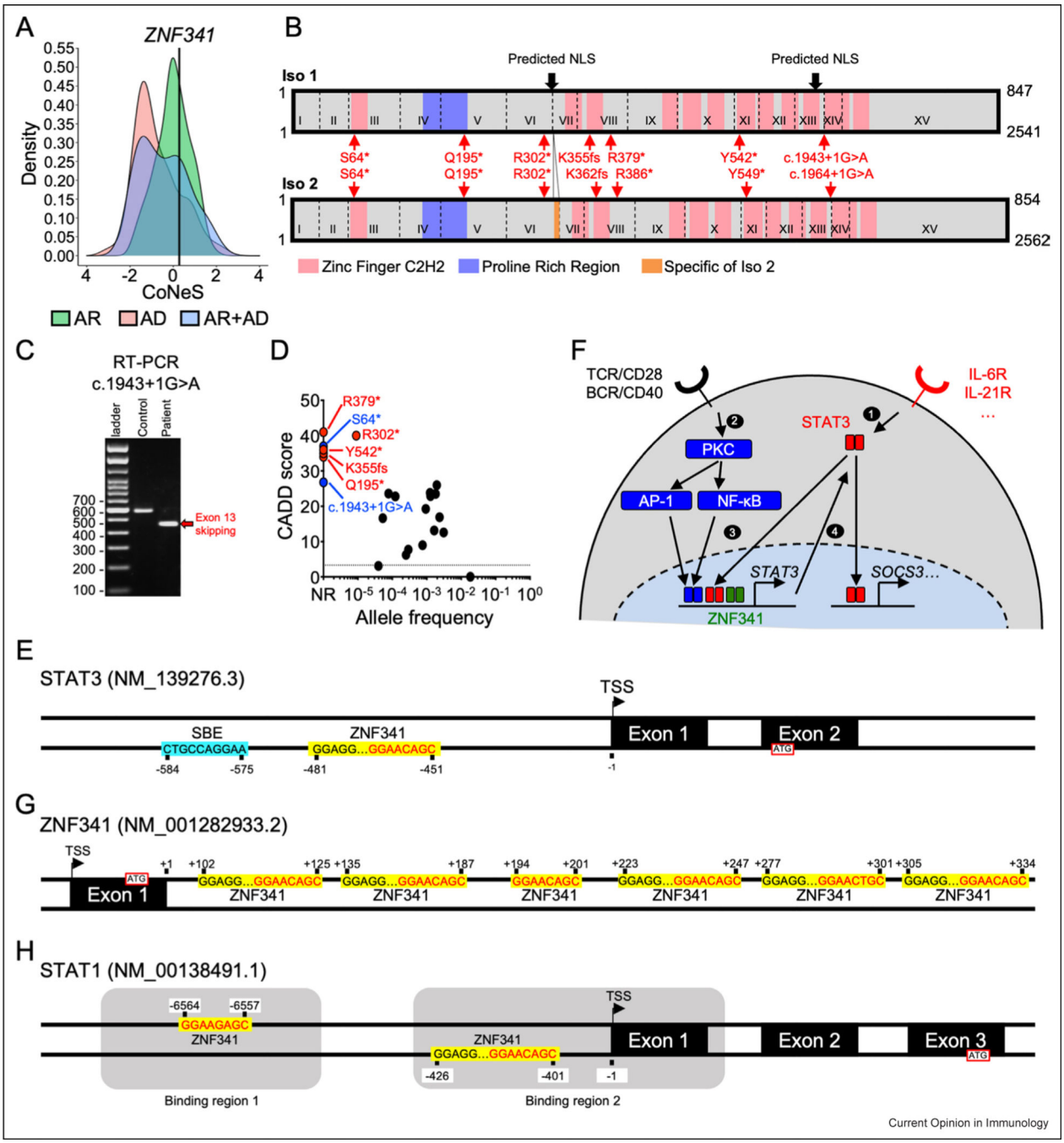

Figure 1.

ZNF341 isoforms, population genetics, schematic signaling model, and DNA binding sites in *STAT1*, *STAT3* and *ZNF341* genes. **(a)** The CoNeS score of ZNF341 is compatible with an AR trait. **(b)** Schematic representation of ZNF341 isoforms 1 (top) and 2 (bottom). The exons are indicated by Roman numerals, and the exon boundaries are indicated with dashed lines. Predicted nuclear localization sequences are indicated by black arrows. The seven reported mutations underlying HIES are indicated in red for both isoforms. **(c)** Reverse transcription PCR (Polymerase Chain reaction) showing that the newly reported c.1943+1G

> A mutation is responsible for exon-13 skipping. **(d)** Population genetics of ZNF341. All HIES variants are highly deleterious and only the R302* mutant has been reported in the heterozygous state in a public database. CADD: combined annotation-dependent depletion score. **(e)** Schematic representation of the *STAT3* promoter. The SBE (STAT3 binding element) is indicated by a blue box. ZNF341-binding sites are indicated by yellow boxes. The TSS (Transcription start site) is indicated. The position of each binding site is indicated relative to the TSS. **(f)** Model for the ZNF341-dependent signaling pathway. BCR: B-cell receptor. **(g–h)** Schematic representation of the *ZNF341* exon 1 and intron 1 **(g)**, and *STAT1* promoter **(h)**, as in E. The *STAT1* promoter contains two binding regions indicated by gray boxes.

Table 1

Clinical/biological features of human ZNF341 and STAT3 deficiencies.

	This paper		Béziat et al [18]	Frey-Jakobs et al [19]	Total ZNF341	STAT3 deficiency [25]
Kindred	**1 Kindred**	**1 Kindred**	**6 Kindred**	**4 Kindred**	**12 Kindred**	
Number of patients	**1 patient**	**1 patient**	**7 patients**	**11 patients**	**20 patients**	**60 patients**
Mutant allele (isoform 1)	c.1943 + 1 G > A (essential splice site, skipping of exon 13)	p.Ser64 *	p.Gln195*(*n* = 1) p.Arg302*(*n* = 4) p.Lys355Serfs*28 (*n*= 1) p.Tyr542*(*n* = 1)	p.Arg302 * (*n* = 8) p.Arg379 * (*n* = 3)		
Age at evaluation — median (range)	29	2	23 (14–47)	17 (0.5–30)	21 (2–47)	n.d.
Sex	m	m	4f/3 m	6f/5 m	10f/10m	30f/30m
HIES NIH score — median (range)	24	25	26 (11–54)	33 (12–62)	28.5 (11–62)	64 (14–86)
IgE levels > 1000 IU	1/1	0/1	6/7	10/11	17/20 (85%)	96%
High IgG levels (> 16 g/L)	1/1	0/1	7/7	7/9	15/18 (83%)	27%
Eosinophilia	0/1	1/1	3/7	7/10	11/19 (58%)	80%
Low NK cell (count or % of lymphocytes)	0/1	0/1	6/7	4/6	10/15 (67%)	8%
Low memory B-cell levels (% of B cells)	0/1	ND	4/6	6/6	10/13 (77%)	94,5%
Low Th17-cell levels	ND	ND	5/5	4/6	9/11 (82%)	93%
Allergy (food or respiratory)	0/1	ND	4/7	0/11	4/19 (21 %)	22%
Atopic dermatitis	1/1	1/1	7/7	11/11	20/20 (100%)	92%
Skin abscesses	1/1	1/1	3/7	10/11	15/20 (75%)	73%
Recurrent skin infection	0/1	1/1	6/7	8/9	15/18 (83%)	100%
CMC	0/1	0/1	6/7	6/11	12/20 (60%)	85%
- Oral thrush	0/1	0/1	5/7	4/11	9/20 (45%)	63%
- Onychomycosis	0/1	0/1	3/7	2/11	5/20 (25%)	57%
- Other	0/1	0/1	3/7	4/11	7/20 (35%)	n.d.
Upper respiratory tract infections	1/1	0/1	1/7	9/10	11/19 (58%)	90%
Lung involvement	1/1	0/1	4/7	6/7	11/16 (69%)	n.d.
- Recurrent infections	1/1	0/1	4/7	4/7	9/16 (56%)	n.d.
- Pneumonia	1/1	0/1	2/7	6/7	9/16 (56%)	90%
- Bronchiectasis	0/1	0/1	2/7	4/8	6/17 (35%)	65%
- Pneumatocele	0/1	0/1	1/7	1/8	2/20 (10%)	52%

	This paper		Béziat et al [18]	Frey-Jakobs et al [19]	Total ZNF341	STAT3 deficiency [25]
Kindred	**1 Kindred**	**1 Kindred**	**6 Kindred**	**4 Kindred**	**12 Kindred**	
Number of patients	**1 patient**	**1 patient**	**7 patients**	**11 patients**	**20 patients**	**60 patients**
Alopecia	0/1	0/1	1/7	1/11	2/20 (10%)	n.d.
Connective-tissue abnormalities	0/1	0/1	6/7	9/11	15/20 (75%)	n.d.
- Facial abnormalities	0/1	0/1	2/7	8/10	10/19 (53%)	95%
- High palate	0/1	0/1	4/7	5/11	9/20 (45%)	53%
- Scoliosis	0/1	1/1	0/7	1/11	2/20 (10%)	38%
- Joint hyperextensibility	0/1	0/1	2/7	1/11	3/20 (15%)	50%
- Bone fractures with minimal trauma	0/1	0/1	1/7	1/11	2/20 (20%)	42%
- Dental abnormalities	0/1	0/1	2/7	4/7	6/16 (38%)	n.d.
- Deciduous tooth retention	0/1	0/1	0/7	4/7	4/16 (25%)	65%
- Craniosynostosis	0/1	0/1	0/7	0/11	0/20 (0%)	3%
Newborn rash	0/1	0/1	1/7	1/4	2/13 (15%)	48%
Neoplasia (any type)	0/1	0/1	0/7	1/11	1/20 (5%)	7%
Growth retardation	0/1	0/1	1/7	2/11	3/20 (15%)	n.d.
Mental delay	0/1	0/1	0/7	7/10	7/19 (37%)	n.d.

n.d.: no data.