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A novel variant in *STAT2* presenting with hemophagocytic lymphohistiocytosis

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Capsule summary:

A novel *STAT2* variant causing complete STAT2 protein abrogation presents with hemophagocytic lymphohistiocytosis (HLH). This is the first report of HLH in association with STAT2 deficiency.

Keywords

STAT2; HLH; Immunodeficiency; mumps

To the Editor:

Frequent viral infections in infancy may signal a primary defect of innate immunity. Signal transducer and activator of transcription 2 (STAT2) is a transcription factor involved in type I interferon signaling. Type I and III interferons are secreted immediately following pathogen exposure by most cells, while type II interferons are secreted primarily by activated T cells, NK cells, plasmacytoid dendritic cells, and macrophages. Activation of STAT2 leads to the expression of genes important for immunity against viral infections.[1] Patients with homozygous mutations in *STAT2* are susceptible to severe recurrent viral infections, including vaccine-strain viruses.[2] Those who survive childhood may mount sufficient anti-viral responses after maturation of their adaptive immune system.[1] Secondary hemophagocytic lymphohistiocytosis (HLH) is a sequela of uncontrolled immune activation typically triggered by infection. HLH is rarely associated with disorders of innate immunity other than chronic granulomatous disease, but has been reported in a single patient with STAT1 deficiency and in two kindreds with IFNGR2 deficiency.[3–6] Here, we describe a

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patient with a novel *STAT2* variant that abrogates protein expression who presented with secondary HLH in the setting of vaccine-strain mumps meningitis.

A non-consanguineous Nepali boy, with normal newborn screen for severe combined immune deficiency (T-cell receptor excision circles >252 copies/μL), was hospitalized five times in the first year of life with dehydration due to common viral illnesses, including respiratory syncytial virus, norovirus, and coxsackie virus. At 12 months of age, he was hospitalized with fever, cough, and emesis occurring seven days after vaccination with the measles, mumps, rubella, and varicella vaccines. He rapidly developed respiratory insufficiency and abdominopelvic ascites accompanied by diffuse adenopathy. Laboratory evaluation did not suggest a cellular or humoral immunodeficiency (Table I). He developed pancytopenia, decreased fibrinogen, elevated ferritin, and increased circulating levels of soluble IL-2 receptor, meeting clinical criteria for HLH (Table E1 in this article's Online Repository).[6] Meningitis due to vaccine-strain mumps was confirmed by PCR of cerebral spinal fluid. High-dose intravenous immunoglobulin (IVIG) treatment (2 g/kg) has been reported to be useful in the management of a STAT2-deficient patient with severe viral infections.[2] Treatment of our patient with high-dose IVIG led to prompt resolution of HLH, with defervescence and normalization of ferritin level and cell counts. He was subsequently started on IVIG (0.5 g/kg) every 3 weeks and now avoids all live viral vaccines. The patient is now two years old and has not had any further infections, hospitalizations, or episodes of HLH.

Targeted next-generation sequencing of the patient's genomic DNA for 207 genes associated with primary immunodeficiency (Primary Immunodeficiency Panel, Invitae Corporation, San Francisco, CA) identified a novel homozygous splice donor variant in *STAT2*(c. 1209+1delG) (Figure IA). His parents are heterozygous for the variant (see Figure E1 in the Online Repository). No mutations were identified in other genes associated with primary HLH or primary immune deficiency. To determine whether the mutation affected splicing of *STAT2*, reverse transcription polymerase chain reactions (RT-PCR) were performed on mRNA from control and patient EBV-transformed B-lymphoblastoid cell lines (BLCLs) (Figure IB). The 533 base pair fragment surrounding the mutation site was identified in the control. In contrast, a lower molecular weight band of approximately 437 base pairs was identified in cDNA from the patient's BLCLs. Sanger sequencing demonstrated abnormal splicing in the patient's cDNA amplicon, resulting in deletion of exon 13 and in-frame splicing of exons 12 and 14 (Figure IC). Immunoblotting of lysates from BLCLs demonstrated abrogation of STAT2 protein expression in our patient without expression of any truncated protein products (Figure ID).

STAT2 deficiency in humans and mice is characterized by defective type I interferon signaling.[1,2,9] The infection and subsequent transformation of B cells with EBV activates STAT2 and upregulates expression of interferon-stimulated genes, including *IFIT1, ISG15* and *IRF7*, which are further increased after exposure to type I interferons.[7,8] Expression of *IFIT1*, *ISG15*, and *IRF7* were severely depressed in the patient's BLCLs compared to controls (time 0 in Figure IE). Furthermore, the patient BLCLs cells failed to upregulate *IFIT1*, *ISG15*, and *IRF7* after IFN-α stimulation (Figure IE), indicating a lack of STAT2-driven signaling in response to type I interferons.

Mouse models of STAT2 deficiency have demonstrated defective responses to viral infections both *in vitro* and *in vivo*.[1] Human STAT2 deficiency has been associated with development of recurrent and severe viral illnesses. After MMR vaccination, one patient developed disseminated vaccine strain measles virus,[1] another patient developed meningitis with vaccine strain mumps virus,[9] and four patients developed post-MMR febrile syndromes with negative viral studies.[1, 2, 9]

This is the first report of HLH in association with STAT2 deficiency. We identified a novel *STAT2* variant in our patient, resulting in abrogation of protein expression and type I interferon response. This report, as well as previously published reports of patients with defects in *STAT1* and *IFNGR2,* demonstrate that secondary HLH can occur with defects in either type I or type II interferon signaling..[4, 5] The rapid improvement of our patient after high-dose IVIG suggests the utility of this intervention in treating secondary HLH triggered by infection. The beneficial effect of IVIG may be ascribed to passive immunization and possibly to its potential anti-inflammatory effect. Our report and other literature[2] suggests patients with STAT2 deficiency may benefit from monthly immunoglobulin replacement during childhood, particularly if they have received live vaccines prior to their molecular diagnosis, until their adaptive immune system matures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

STAT2	signal transduction and activator of transcription 2
HLH	hemophagocytic lymphohistiocytosis
MMR	measles, mumps, rubella
RT-PCR	Reverse transcription polymerase chain reaction
BLCLs	B-lymphoblastoid cell lines
IVIG	intravenous immunoglobulin

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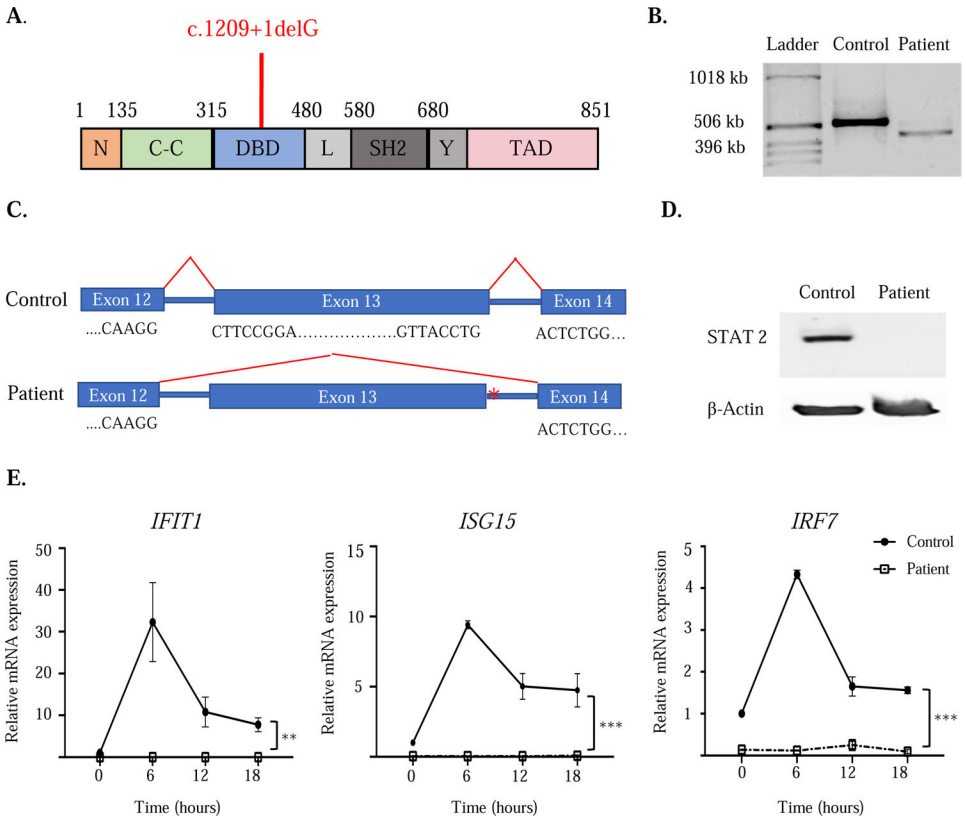

Figure I. The *STAT2* homozygous splice donor variant mutation abrogates protein expression.

A. Linear map of *STAT2* with the patient's variant (c.1209+1delG)indicated in red. **B**. RT-PCR amplification of *STAT2* mRNA encompassing the patient mutation site. **C**. Sanger sequencing of cDNA in the region surrounding the mutation in patient and control. Asterisk indicates mutation location. **D.** STAT2 protein expression in lysates from BLCLs from patient and control. **E.** Quantitative PCR analysis of *IFIT1*, *ISG15* and *IRF7* mRNA at baseline and after IFN-α stimulation of EBV-transformed BLCLs from the patient and controls (n=3). Values were normalized to *GAPDH* and expressed relative to the mean of unstimulated controls. Symbols and bars in E represent mean and SEM. ** $p<0.01$, *** $p<0.001$. Similar results were obtained in two independent experiments in B, D and E.

Table I.

Immunologic profile of the patient.

Variable	Age at time of testing*	
Hemogram 10^3 cells/μL (normal)	**12 months**	**14 months**
White blood cells (7.73–13.12)	**3.71**	13.06
Neutrophils (2.47–6.41)	**0.91**	4.35
Lymphocytes (2.32–5.49)	2.36	**6.99**
Monocytes (0.25–1.15)	0.20	0.46
Hemoglobin (10.4–12.5)	7.9	10.2
Hematocrit (30.5–36.4)	23.6	29.8
Platelets (223–461)	**89**	**474**
Lymphocyte subsets		
$CD3^+$, 10^3 cells/μL (1,900–6,200)	**804**	3,651
$CD3^+CD4^+$, 10^3 cells/μL (1,300–3,400)	**261**	1,070
$CD45RA^+CCR7^+$, % $CD4^+$ (66.3–89.4)	66.8	**52.4**
$CD45RA^-CCR7^+$, % $CD4^+$ (9.2–22.4)	**22.6**	**28.2**
$CD45RA^-CCR7^-$, % $CD4^+$ (1.3–9.4)	**9.5**	**18.1**
$CD45RA^+CCR7^-$, % $CD4^+$ (0.2–29)	0.9	15
$CD3^+CD8^+$, 10^3 cells/μL (620–2,000)	**505**	**2,328**
$CD45RA^+CCR7^+$, % $CD8^+$ (57.8–82.9)	**55.9**	70.4
$CD45RA^-CCR7^+$, % $CD8^+$ (1.7–8.5)	6.5	**1.5**
$CD45RA^-CCR7^-$, % $CD8^+$ (5.1–25.1)	9.5	13.2
$CD45RA^+CCR7^-$, % $CD8^+$ (6.4–20.8)	14	15
$CD19^+$, 10^3 cells/μL (610–2,600)	**465**	2,375
$CD27^-IgD^+$, % $CD19^+$ (76.5–94.7)	ND	90.9
$CD27^+IgD^+$, % $CD19^+$ (3–10.7)	ND	4.5
$CD27^+IgD^-$, % $CD19^+$ (1.4–11.9)	ND	2.7
$CD3^-CD56^+$, 10^3 cells/μL (160–1100)	216	**1,136**
Immunoglobulins (mg/dL)		
IgG, (300–1500)	884	1,386
IgM, (25–115)	80	87
IgA, (16–100)	52	28
Proliferation (counts per minute)		
Concavalin A (65,6999–239,344)		**34,503**
Phytohemagglutinin (96,090–358,179)		229,096
Anti-CD3 (62,927–217,761)		76,757
T cell mitogen Background (204–2,104)		264
Tetanus (8,544–102,895)		**5,530**

Variable	**Age at time of testing***	
Candida (6,231–197,940)		25,213
T cell antigen Background (689–9,034)		3,502

*At 12 months of age, testing was done while he was acutely ill and before starting IVIG replacement; at 14 months of age testing was done after recovery from HLH and after IVIG was initiated. Proliferation was not performed at 12 months due to lymphopenia and critically ill state. Bold values are outside the normal range.

**Prior to intravenous immunoglobulin replacement