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STAT5B Deficiency: Impacts on Human Growth and Immunity

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Abstract

Growth hormone (GH) promotes postnatal human growth primarily by regulating insulin-like growth factor (IGF)-I production through activation of the GH receptor (GHR)-signal transducer and activator of transcription (STAT)-5B signaling cascade. The critical importance of STAT5B in human IGF-I production was confirmed with the identification of the first homozygous, autosomal recessive, *STAT5B* mutation in a young female patient who phenotypically resembled patients with classical growth hormone insensitivity (GHI) syndrome (Laron syndrome) due to mutations in the *GHR* gene, presenting with severe postnatal growth failure and marked IGF-I deficiency. Of note, the closely related STAT5A, which share >95% amino acid identity with STAT5B, could not compensate for loss of functional STAT5B. To date, 7 homozygous, inactivating, *STAT5B* mutations in 10 patients have been reported. STAT5B deficient patients, unlike patients deficient in GHR, can also present with a novel, potentially fatal, primary immunodeficiency, which can manifest as chronic pulmonary disease. STAT5B deficiency may be underestimated in endocrine, immunology and pulmonary clinics.

Keywords

STAT5B mutations; IGF-I deficiency; growth hormone insensitivity; T regulatory cell deficiency

Introduction

The 7 human STAT (signal transducer and activator of transcription) family of proteins (STAT1, -2, -3, -4, -5a, -5b and -6) are expressed in multiple cell types, activated by multiple growth factors and cytokines, participating in a diverse set of biological activities(1). With increased accessibility and application of next-generation whole exome sequencing in clinical settings, genetic defects have now been identified for all, but the *STAT5A*, genes, germ-line as well as somatic (2–5). To date, each of the described STAT deficiencies is associated with distinct immuno-deficiencies (2–5). Only STAT5B deficiency (MIM245590)

Conflict of Interest

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present co-morbidities of growth hormone insensitivity (GHI) syndrome (MIM262500), with severe insulin-like growth factor (IGF)-1 deficiency (IGFD) and profound postnatal growth failure(6). Of note, recent reports describe activating, heterozygous, STAT3 mutations associated with growth failure and IGFD, but these features, in contrast to STAT5B defects, was proposed to be secondary to the lymphoproliferation and autoimmunity phenotype(7–9). The present review will focus on the impacts of germ-line *STAT5B* mutations in human growth and immunity.

STAT5B protein

Human STAT5B, typical of members of the STAT family (1), consist of discrete protein modules (Figure 1) of which the modular src-homology 2 (SH2) domain permits STAT5B to bind phosphorylated tyrosines, including those on activated receptors such as the GH receptor (GHR) or interleukin (IL) receptors. Recruited STAT5B itself is activated upon phosphorylation of tyrosine residue, Y699, downstream of the SH2 domain (Figure 1), by kinases such as cytosolic Janus kinase 2, JAK2. The phosphorylation of two serines, S128 and S193, and acetylation of L701, have been reported as other mechanisms for regulating STAT5B activities (10–13).

STAT5B is most closely related to STAT5A, sharing a striking 96% identity at the amino acid residue level. By contrast, STAT5B shares only 24% similarity with STAT3. Interestingly, the genes encoding these 3 STAT proteins lie within ~204 kilobases (kb) region of each other on chromosome 17q11.2, with *STAT5A* and *STAT5B* genes (77.23 kb and 24.4 kb, respectively) only 11 kb apart(14), suggesting the possibility of a gene duplication. The divergence between the translated STAT5B and STAT5A proteins is primarily at the C-terminus of the TAD region, where a 20 amino acid sequence in STAT5A distinguishes it from STAT5B. Indeed, the inability to readily differentiate between these two closely-related proteins, for many years, led them to be considered interchangeable, redundant, entities, designated STAT5. The identification of *STAT5B* mutations associated with the complex clinical syndrome of GHI and immune deficiency firmly established, in humans, that STAT5B and STAT5A have certain distinct and non-redundant roles, despite their high degree of identity. Human mutations in *STAT5A*, as noted above, have yet to be identified.

The Human Growth Hormone Receptor – STAT5B Signaling Pathway

Pituitary-derived growth hormone (GH) promote normal human postnatal growth by regulating the expression of insulin-like growth factor (IGF)-I, both circulating (liver derived) and peripheral. The importance of IGF-I for human growth is supported by clinical conditions of primary IGFD due to GH deficiency (GHD), mutations in the GH receptor (GHR), and rare homozygous inactivating *IGF1* mutations identified in patients characterized by *in utero* and severe postnatal growth failure (height SDS, HtSDS, below −4.9), microcephaly, intellectual impairment, and sensorineural deafness(15–17).

The binding of GH to cell surface homo-dimeric GHR(18) activates the associated JAK2, which initiates signaling cascades including four STAT pathways (STAT1, STAT3, STAT5A

and STAT5B), the MAPK (mitogen-activated protein kinase) and the PI3K (phosphoinositide-3 kinase) pathways. Recent studies indicate that three of the seven intracellular tyrosines in the human GHR (mature peptide: Y516, Y548, Y609) are necessary, individually or in combination, for STAT5B signaling(19). This redundancy in tyrosine utilization by STAT5B may explain why, of the more than 80 *GHR* mutations associated with GHI syndrome(20,21), only a handful are located within the intracellular domain of the GHR(22) and why damaging mutations frequently involve frameshifts that abrogate the JAK2 binding site and/or the three critical GHR tyrosines(23).

Surprisingly little is known regarding the DNA elements recognized by STAT5B in the transcriptional regulation of the human *IGF1* gene. In the rat *Igf1* gene locus, 7 Gh-induced Stat5b response elements were recently reported (24). Interestingly, 3 of these Gh response elements (GHRE) were located well upstream of the *Igf1* gene (63 kb, 73kb and 86 kb from the *Igf1* start site), and 4 were intronic (one in intron 2 and three in intron 3). These rat GHREs did not align with established canonical response elements (GAS, γ-interferon-activated sequences) that are frequently recognized by members of the STAT family. Although both human STAT5B and STAT5A associated with these rat elements in *in vitro* gel-shift binding assays (25), it remains unclear whether variations of these rat elements, found in the human *IGF1* gene (24,26), are utilized by STAT5B for regulating *IGF1* expression.

The *Stat5b*$^{-/-}$ mouse model for growth

The experimental disruption of each of the seven Stat proteins in rodent models implicated Stat5b, in particular, as important for postnatal growth. *Stat5b*$^{-/-}$ mice displayed loss of sexually dimorphic growth, with a concomitant reduction of serum Igf-I concentrations by 30–50% (27,28). While male *Stat5b*$^{-/-}$ mice were reduced in size to wild-type female mice, no differences were observed between *Stat5b*$^{-/-}$ and *Stat5b*$^{+/+}$ female mice, suggesting a critical role for Stat5b in male/female differential growth in mice. Disruption of both *Stat5b* and the *Stat5a* genes imparted a more pronounced effect on growth, affecting both male and female mice, with growth phenotypes similar to those observed in mice deficient for either Gh or the Ghr (28,29). This growth restriction, together with observed profound immune deficiency, recapitulated the human STAT5B deficient condition (see below) but suggested that, in mice, Stat5a can partially compensate for loss of Stat5b.

Molecular defects in the human *STAT5B* gene

Molecular defects along the human GH-IGF-I axis are extremely rare. The identification of *STAT5B* mutations associated with severe growth failure, marked IGF-I deficiency, and insensitivity to GH, provided the first definitive demonstrations that the STAT5B signaling pathway is critical for GH-induced IGF-I production and normal growth in humans (Table 1; (30,31)). The first *STAT5B* mutation, reported in 2003, was identified in a 16 year old female from a consanguineous pedigree who presented biochemistries, a growth profile, and facial features, similar to Laron syndrome (classical GHI), but had wild-type *GHR* and additional presentations of chronic pulmonary disease (Table 1, (32)). An autosomal recessive, homozygous missense mutation, p.Ala630Pro located in the SH2 domain of

STAT5B, was subsequently identified. The p.Ala630Pro substitution disrupted the core of anti-parallel β-sheets that forms the pocket for binding phosphate groups(33), causing loss of thermodynamic stability, as well as aberrant folding and aggregation of the mutant STAT5B protein(34,35). Quantitative real-time-PCR (polymerase chain reaction) amplification analysis of primary dermal fibroblast cells derived from the patient, furthermore, demonstrated that the loss of functional STAT5B correlated to loss of GH-induced IGF1 expression(32) which was not restored by activation of endogenous STAT5A(36). Altogether, these *in vitro* analyses supported *in vivo* presentations of IGF deficiency and GH resistance in the patient.

Six other homozygous *STAT5B* mutations have been described to date, identified in 9 subjects(37–41), including 2 sets of siblings(42,43). All the mutations were autosomal recessive, suggesting that haploinsufficiency of STAT5B has modest, or minimal, effects on IGF-I expression, growth, and immune complications (30). The mutations, located in different domains of the STAT5B protein (Figure 1), include one nonsense mutation and 4 frameshifts (deletions or insertions), all of which is predicted to result in early protein termination. Only one other missense mutation, p.Phe646Ser, has been identified. Similar to p.Ala630P, p.Phe646Ser is located within the SH2 domain, but In contrast to p.Ala630Pro, loss of function was due to an inability to drive transcription(41).

Impact of STAT5B deficiency on Growth

Auxology

Birth size, where documented for the STAT5B deficient subjects, was normal for gestation (Table 1), similar to patients who carry *GHR* mutations. Postnatal growth failure was significant and consistent with the degree of IGF deficiency. Growth profiles were indistinguishable from those with GHI (or Laron) syndrome (44). At first report, height SDS ranged from −3.0 SDS to −9.9 (Table 1). Bone age, when measured, was considerably delayed (39,43). Puberty was also consistently delayed (Table 1), reflecting the low levels of circulating IGF-I (Table 1) and a state of chronic illness (see below). Mild facial dysmorphic features, such as a prominent forehead, depressed nasal bridge and high-pitched voice, were noted for some of the STAT5B deficient subjects (32,39,43).

Hormonal Evaluations

The severe post-natal growth failure of STAT5B deficient patients correlated with the clinical endocrine profile (Table 1). Basal GH levels were normal, and when stimulated, GH concentrations were frequently elevated. Serum IGF-I, IGFBP-3 and ALS concentrations in all cases were abnormally low (Table 1), and remained low after GH treatment in an IGF-I generation test (32,37,45) or during GH therapy (38,43). Some of the subjects underwent growth hormone therapy (1yr to 4yr), but growth response was uniformly poor (32,43). Interestingly, serum prolactin levels, when recorded, were abnormally high (Table 1). Pugliese-Pires *et al* determined that the hyperprolactinemia state for Cases 9 and 10 was not a result of macroPRL or of pituitary tumor (43). It is likely that the *STAT5B* mutations disrupted the negative feedback loop for PRL production, although the mechanisms involved remain to be clarified.

Impact of STAT5B deficiency on Immunity

Immune deficiency phenotype

A distinguishing feature in the patients carrying *STAT5B* mutations from those carrying *GHR, IGFI, IGF1R* or *IGFALS* mutations was symptoms of immune dysfunction. Shared symptoms in 8 of the 10 patients include severe eczema, chronic pulmonary disease manifesting as early as the first year of life (39,40,43), and confirmed lung fibrosis and/or lymphoid interstitial pneumonia (LIP), a condition of unknown etiology that is rare in children and often associated with autoimmune disease (46). Corticosteroid and oxygen treatments temporarily stabilize worsening pulmonary functions, but three of the patients, including the first described case of STAT5B deficiency (carrying p.Ala630Pro)(47), succumbed and died as consequences of progressive pulmonary fibrosis and respiratory failure (40) (Dr Merih Berberoglu, personal communication). Only one of the patients has undergone a lung transplantation at age 17.5 years that appeared to have successful alleviated impaired pulmonary function and the requirement for oxygen (43).

Interestingly, two of the patients lacked severe pulmonary problems, although both had symptoms of mild immune dysfunction: the patient carrying *STAT5B c.1102insC* was reported to have contracted haemorrhagic varicella at 16 years of age and had congenital ichthyosis and erythema, but, otherwise, appeared relatively healthy(38), and the patient carrying *STAT5B* p.Phe646Ser(41) had autoimmune thyroiditis, psoriasis, atopecia and was diagnosed with Celiac disease at age 20 yr(47). The explanation for the lack of chronic pulmonary disease in these two patients remains to be elucidated.

Immunological evaluations

Unlike the endocrine profiles that showed an absolute association between *STAT5B* mutations and IGF deficiency, the abnormalities in the immunological profile, where evaluated, was variable, even between siblings who carried the same homozygous *STAT5B* mutation(43). Nevertheless, hypergammaglobulinemia and T-cell lymphopenia were common observations, with both CD4+ and CD8+ T-cells often below normal ranges(39,41,43,47,48). In particular, a subset of CD4+ cells, the CD4+CD25$^{\mathbf{high}}$ cells or T regulatory cells (Treg), is significantly diminished. CD25$^{\mathbf{high}}$ is the α-subunit of the heterotrimeric IL-2 receptor (IL2R) complex and its expression permits IL2 to bind IL2R complex with high affinity. Perturbations of Tregs, which are essential for the propagation and homeostasis of T-cell populations (49), most likely lead to an abnormal accumulation and proliferation of lymphocytes in extra-lymphoid tissues. The increased susceptibility to opportunistic infections could also be related to decreased CD25 on all T cells, as has been reported in humans with severe CD25 deficiency (50). The forkhead-box family of transcription factor, FOXP3, shown to be regulated by STAT5 (51,52), is highly expressed in Treg, but was significantly reduced in STAT5B deficient Treg (48,53). Altogether, the reduced CD25$^{\mathbf{high}}$ and FOXP3 expression associated with homozygous *STAT5B* mutations appears likely to have contributed to the novel immunodeficiency observed in these patients.

Summary

The identification of patients with unequivocal defects in the GH-induced STAT5B signaling has furthered our understanding of the molecular basis of growth failure associated with primary IGF deficiency. The *STAT5B* mutations identified to date were autosomal recessive, suggesting that haploinsufficiency of STAT5B has minimal effects on IGF-I expression and growth. Significantly, in humans, unlike in rodent models, the presence of STAT5A cannot compensate for the loss of STAT5B, thus supporting the hypothesis that GH-induced regulation of IGF-I production is mediated predominantly by STAT5B. In addition to severe IGFD and profound growth failure, mutation in the *STAT5B* gene cause a novel form of primary immune deficiency involving Treg dysfunction and associated pulmonary diseases. The lack of chronic pulmonary diseases in two of the patients supported the hypothesis STAT5B deficiency may be underestimated in endocrine, immunology and pulmonary clinics.

At present, therapeutic options to improve both poor statural growth and immunodeficiency are non-existent. A lung transplantation appeared to have alleviated problems caused by the chronic pulmonary disease (43), although prognosis remains unclear for the long-term. Bone marrow transplants and its use in clinical settings of autoimmunity and alloimmunity have been intensely studied (54), and may be a therapeutic option for deficiencies in T cells related to STAT5B deficiency. For statural growth, the resistance to GH therapy suggested that recombinant human IGF-I treatment could be a therapeutic option, although response was poor in the one report where the proband was on rhIGF-I therapy for one year(43). The poor response to rhIGF-I was attributed to complications associated with the immuno-compromised status of the subject. Continued clinical evaluations of patients carrying these rare *STAT5B* mutations and elucidating the impact of these mutations on structure and function of the STAT5B protein, is important to understanding the pathophysiology of this complex disease.

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Highlights

- Rare autosomal recessive STAT5B mutations are associated with severe growth failure, marked IGF-I deficiency and growth hormone insensitivity (GHI) syndrome.
- STAT5B deficiency can lead to potentially fatal primary immunodeficiency.
- The closely related STAT5A cannot compensate for loss of STAT5B in humans.

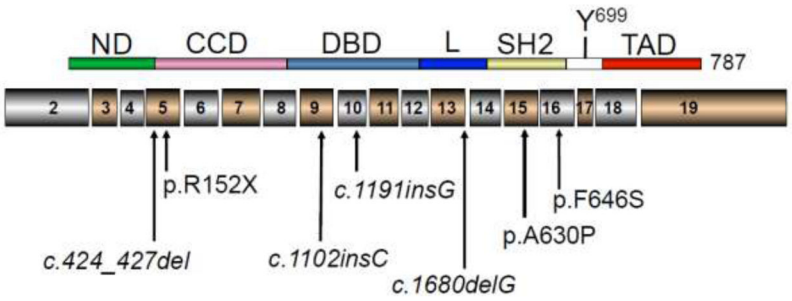

Figure 1.

Homozygous human STAT5B mutations identified. Schematic of the human STAT5B peptide (upper schematic) and encoding exons (lower schematic). Mutations identified are indicated. Tyrosine 699 (Y699) that can be phosphorylated by JAK2 and other kinases is shown. The domains indicated: ND, N-terminal domain; CCD, coil-coiled domain; DBD, DNA binding domain; L, linker domain; SH2, Src-homology 2 domain; TAD, transactivation domain.

Table 1

Phenotype of patients carrying homozygous STAT5B mutations. Phenotype was as described in reports. The nonsense mutation, p.Arg152*, was identified in two unrelated subjects.

STAT5B Mutation Homozygous	Gender	Age, yr	Height SDS	Birth	GHI	IGFD	Prolactin Elevated	Hypergamma-globulinemia	T-cell lymphopenia	Pulmonary Disease	Reference
p.Ala630Pro[1]	F	16.5	−7.5	AGA	+++	+++	+++	+++	+++	+++	28, 43, 44
c.1191insG[1]	F	16.4	−7.8	AGA	+++	+++	ND	ND	ND	+++	33
p.Arg152*	F	15.3	−9.9	unknown	ND	ND	+++	+++	+++	+++	35
p.Arg152*[1]	F	12	−5.3	SGA	+++	+++	Normal	No	No	+++	36
c.1102insC	M	31	−5.9	AGA	+++	+++	+++	No	No	No	34, 41
c.1680delG[2]	F	2	−5.8	AGA	+++	+++	ND	ND	ND	+	38
c.1680delG[2]	F	4	−5.6	AGA	+++	+++	ND	ND	ND	+	38
c.424_427del[3]	M	6	−5.6	AGA	+++	+++	+++	+	+++	+++	39
c.424_427del[3]	M	2	−3.0	AGA	+++	+++	+++	No	+++	+++	39
p.Phe646Ser	F	14.8	−5.95	unknown	+++	+++	+++	+++	+++	No	37

[1]Deceased as of this review;

[2]Siblings;

[3]Siblings.

AGA, appropriate for gestational age; ND, not determined

+ to +++, increasing severity of indications