Severe IGF-I deficiency and multi-organ autoimmune disease associated with novel germline STAT3 mutations.

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Background

Primary IGF-I deficiency can result from molecular defects in genes encoding for the GH receptor, IGF-I, STAT5b and AL5. Heterozygous, activating mutations in the STAT3 gene have been recently described in children with severe growth failure associated with a spectrum of early-onset autoimmune disease (1,2).

Patient 1

- Congenital hypothyroidism with persistant antibodies to TSH
- Severe growth retardation with high basal GH and low IGF-I
- Pulmonary hypoplasia (2/3)

Oral side effects
Oral ciscixtia
IV Gamaglobulin
Prophylaxis TPN

No STAT3 mutation

Patient 2

- Pulmonary distress
- Failure to thrive (PTT)
- Chronic diarrhea
- Chronic vomiting
- Abdominal distention
- Severe Eczema
- History of colitis
- Prevalence – intraepithelial lymphocytosis

No FOP99 mutation

Endoscopy: asphagogus – normal stomach – normal duodenum – mild lymphoid nodularity

Hypothyroidism diagnosed T4 started – poor compliance

STAT3 Luciferase assay

Patient 1 (WES performed in index case and unaffected father, mother and sister)

- 26260 variants (51135 genes)
- 15315 variants (11730 genes)
- 10796 variants (5916 genes)
- 1245 variants (669 genes)

Patient 2 (WES performed on index case, unaffected father and mother)

- 12751 variants (12054 genes)
- 12762 variants (12054 genes)
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Molecular studies

- 12762 variants (12054 genes)
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Candidate gene sequencing

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Methods

- Candidate gene study by Sanger sequencing (STAT5B / FOPX3)
- Whole Exome Sequencing (WES): Illumina HiSeq 1500.
- Functional studies: In HEK293 cells transfected with highGH expression vector, transcriptional activity of WT and C426H E616D STAT3 variants was assessed via a STAT3-responsive dual Firefly/Renilla Luciferase Cignal reporter system (Qiagen). The activity was measured before and 30 minutes after rGH (200ng/ml). Previously reported L0423Q-STAT3 mutation was used as negative control (3).

References


Conclusions

- Although the gene-candidate approach has been useful to identify the genetic defect of several immune dysregulation and autoimmune diseases (STAT5B, FOPX3, CD25, IFIT) only the application of WES techniques has been successful to characterize novel genetic defects.
- Activating STAT3 mutations represent a novel monogenic defect presenting multi-organ autoimmune disease associated with severe growth retardation as the result of marked IGF-I deficiency. In contrast to STAT5b deficiency, patients carrying activating STAT3 mutations appear to preserve partial GH responsiveness.

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