Functional Characterization of Novel *STAT6* Gain-of-Function Variants Associated with Primary Atopic Disorders (PADs)

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Abstract

- **Identify variants** in the STAT6 protein that cause gain-of-function (GOF) disease
- Overexpress variants in HEK293 cells and **measure STAT6 phosphorylation** via flow cytometry and western blotting
- **Publish the results** publicly to accelerate physician diagnosis and treatment of STAT6 GOF

Introduction

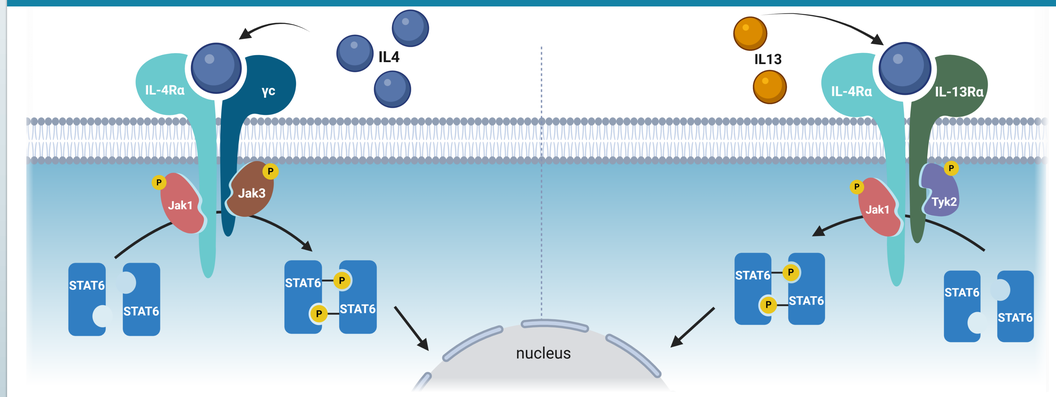

Fig.1: IL-4 and IL-13 stimulation of the Jak/STAT pathway with JAK-mediated STAT6 phosphorylation and nuclear translocation for transcription

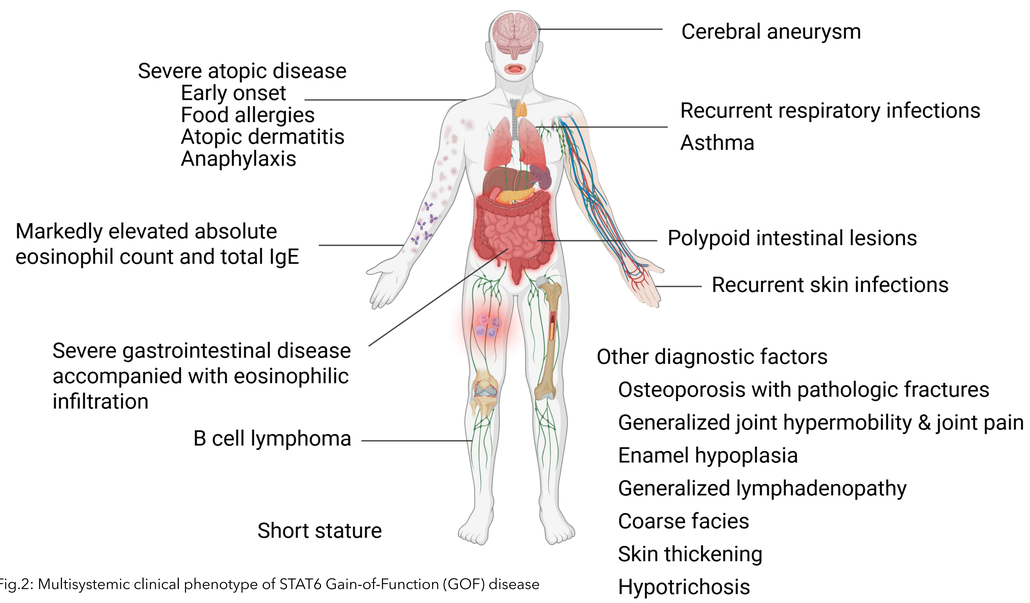

Fig.2: Multisystemic clinical phenotype of STAT6 Gain-of-Function (GOF) disease

Methodology

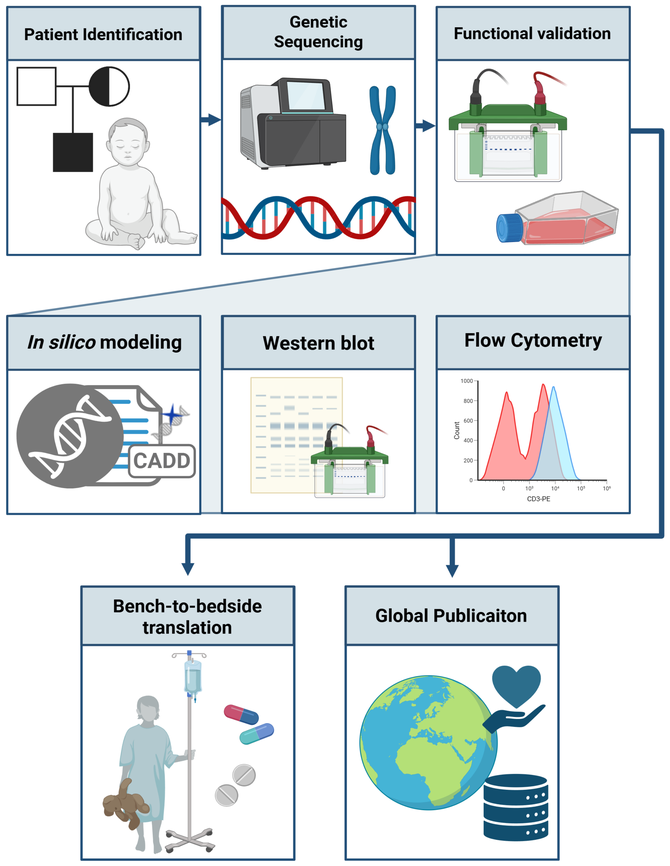

Fig.3: Translational workflow for the identification, validation, and targeted treatment of STAT6 gain-of-function (GOF) variants.

Conclusions

- Once verified, the variants will be **published in journals** and **deposited in** genomic **databases**.
- This will aid physicians in **diagnosing and treating** STAT6 GOF with **preexisting drugs** that target the Jak/STAT pathway

Preliminary Results

	p.Asn420Ser	p.Pro643Leu
c. annotation	c.1259A>G	c.1928C>T
CADD Score	25.4	25.1
Location of Variant	DNA Binding Domain	SH2-TAD Linker Region
Symptoms	• Food allergy • Eosinophilic gastrointestinal disorder (EGID) • Hyper IgE	• Severe Acne & Atrophic Scarring • Diffuse Eczema & Multifocal Viral Warts • Low IgG/IgM & B-cell lymphopenia • Hyper-IgE • Glomerulonephritis
Patient Country	Iran	Sweden

Table 1: Comparative genotypic and clinical profile of (n=2) novel STAT6 GOF variants

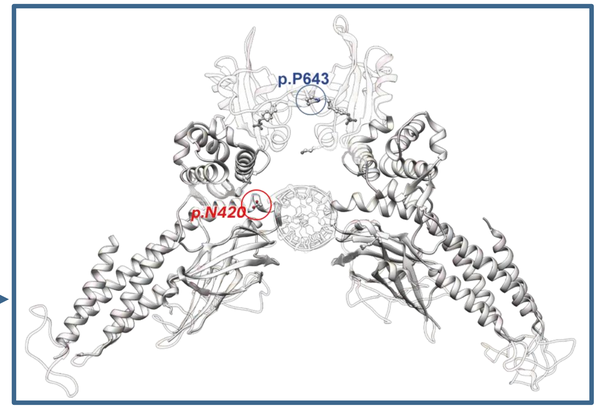

Fig.4: Structural model of the DNA-STAT6 homodimer complex highlighting potentially pathogenic gain-of-function (GOF) variant sites

Fig.5: Schematic representation of STAT6 protein domain architecture mapping reported gain-of-function (GOF) variants and variants of study