Genotype-Phenotype Correlations in Patients with STAT1 Gain-of-Function Mutations: A Case Series

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BACKGROUND

- STAT1 gain-of-function (GOF) mutations lead to chronic mucocutaneous candidiasis (CMC) and a wide range of complications, including bacterial/viral infections, autoimmunity, endocrinopathies, lymphoproliferation, and malignancies.
- Severe complications such as invasive infections, cerebral aneurysms, and malignancies are key predictors of poor prognosis.
- Understanding genotype-phenotype correlations is essential for early risk stratification and guiding personalized therapeutic strategies.

OBJECTIVE

- This study characterizes genotype-phenotype correlations in patients with STAT1 GOF mutations and evaluate how specific mutations impact clinical presentation, disease severity, and treatment response.

METHODS

- **Study Design:** Retrospective cohort study of Mayo Clinic Health System records.
- **Timeline:** January 2009 to December 2024.
- **Inclusion criteria:** Patients of all ages with genetically confirmed heterozygous STAT1 gain-of-function mutations.
- **Data Collection:** Demographics, clinical history, immunologic evaluations, genetic testing results, disease manifestations, treatments and clinical outcomes.

RESULTS

- Five patients (1 male, 4 females; mean age at diagnosis: 21.7 years) were identified with heterozygous STAT1 GOF mutations.

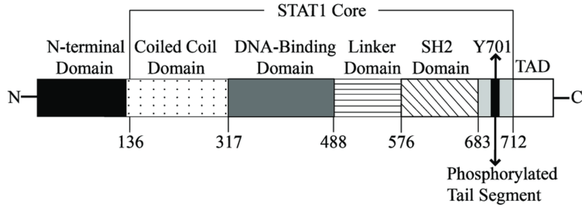

Figure 1. Structural Domains of the STAT1 Protein

Table I. Demographics

N	Age (yrs)	Age at Dx (yrs)	Gender	Mutation	AA Change	Domain Properties △
1	6	3.5	F	c.1154C>T	p.Thr385Met	DBD B > A
2	24	17.2	M	c.1154C>T	p.Thr385Met	DBD B > A
3	34	31.8	F	c.1154C>T	p.Thr385Met	DBD B > A
4	31	30.3	F	c.1310C>T	p.Thr437Ile	DBD B > A
5	30	25.7	F	c.856A>G	p.Lys286Glu	CCD D > C
Avg	**25**	**21.7**				

Abbreviations: DBD = DNA-Binding Domain; CCD = Coiled Coil Domain; AA = Amino Acid
Amino acid side chain properties: A = Hydrophobic; B = Hydrophilic, non-charged; C = Hydrophilic, negatively charged; D = Hydrophilic, positively charged

Table II. Genotype-Phenotype Correlation by Mutation Group

Phenotypic Feature	c.1154C>T p.Thr385Met (N=3)	c.1310C>T p.Thr437Ile (N=1)	c.856A>G p.Lys286Glu (N=1)	Total (N=5)
Chronic mucocutaneous candidiasis	3	1	1	5
Recurrent sinopulmonary infections	3	1	1	5
Multidrug-resistant infections	0	0	1	1
Histoplasmosis	0	1	0	1
Bronchiectasis	2	0	0	2
Autoimmunity	3	0	0	3
Neurologic complications	0	0	1	1
Deceased	0	0	1	1

RESULTS

- All patients had chronic mucocutaneous candidiasis and recurrent sinopulmonary infections.
- **Mutation distribution:**
  - Three patients had c.1154C>T (p.Thr385Met)), in the DBD
    - Early-onset infections, severe autoimmunity (e.g., pancytopenia, enteropathy), and bronchiectasis.
    - All required ruxolitinib; one with poor response was transitioned to tofacitinib.
  - One had c.1310C>T (p.Thr437Ile), in the DBD
    - Late childhood onset of symptoms, later complicated by persistent histoplasmosis.
  - One had c.856A>G (p.Lys286Glu) in the Coiled Coil Domain (CCD)
    - Severe multidrug-resistant infections, coagulopathy, neurologic complications, poor ruxolitinib response, and death from MSSA pneumonia and Monkeypox.

DISCUSSION

- Genotype-phenotype correlations in STAT1 GOF mutations highlight a diverse mutation-specific clinical patterns.
- DBD mutations are linked to more severe phenotypes—early-onset immunodeficiency, autoimmunity, and invasive infections—due to enhanced STAT1 activity from impaired dephosphorylation and nuclear accumulation.
- CCD mutations demonstrate broader multisystem involvement and poor treatment response, reflecting the heterogeneity of this condition.
- JAK inhibitors show therapeutic promise but require personalized dosing, ongoing monitoring, and continuous administration.
  - Limited impact on underlying epigenetic abnormalities, and response may not be strictly mutation-specific.
- Early genetic diagnosis is critical with consideration for hematopoietic stem cell transplantation in severe or refractory cases.

CONCLUSION

- Genotype-specific insights in STAT1 GOF are essential to inform prognosis and tailor individualized treatment strategies.