IRF4 p.T95R Combined Immunodeficiency: Clinical Features and Transplant Outcomes

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Introduction

Interferon regulatory factors (IRFs)

Nine transcription factors vital for:

- **Interferon signaling**
- **Immune development**

IRF4 promotes:

- **Lymphocyte development**
- **B cell function**
- **Th1:Th2 balance**

Associated with **several inborn errors of immunity (IEIs)**

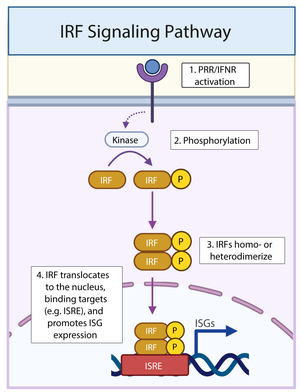


Figure 1: IRF Signaling.

IRF4 p.T95R disrupts DNA-binding

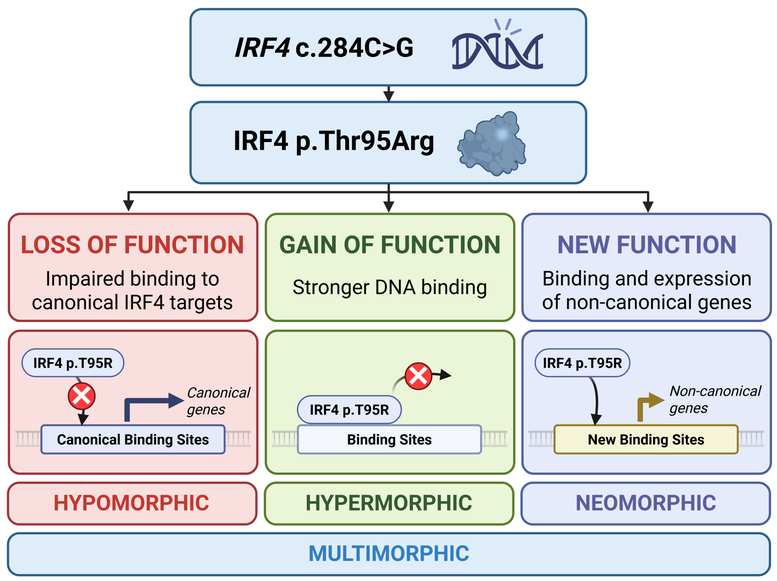


Figure 2: Multimorphic effects of IRF4 p.(Thr95Arg).

Objectives

- Refine the **clinical understanding** of IRF4 T95R
- Improve **treatment outcomes, including HSCT**



Figure 3: Objectives.

Methods

- Patients identified by **next-generation sequencing**
- **Comprehensive clinical reports** were analyzed
- **Aggregate *in silico* scoring** calculated with CADD, REVEL, AlphaMisense, and SpliceAI



Figure 4: Methods.

Results

The IRF4 T95R Consortium: A global collaboration

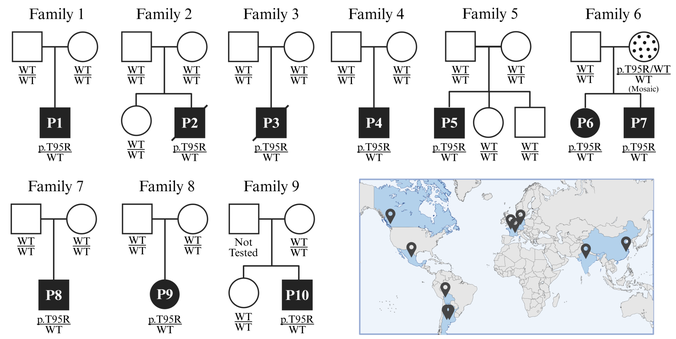


Figure 5: Pedigrees and global distribution of our cohort.

All 10 known IRF4 p.T95R patients share similar phenotypes

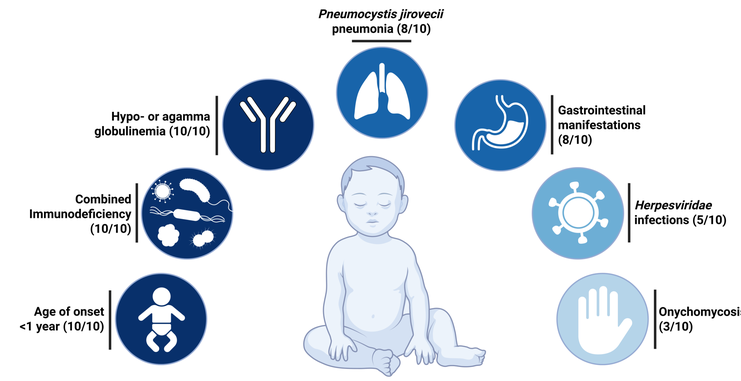


Figure 6: Prevalence of clinical phenotypes.

Treatments and hematopoietic stem cell transplant (HSCT) outcomes for IRF4 p.T95R patients

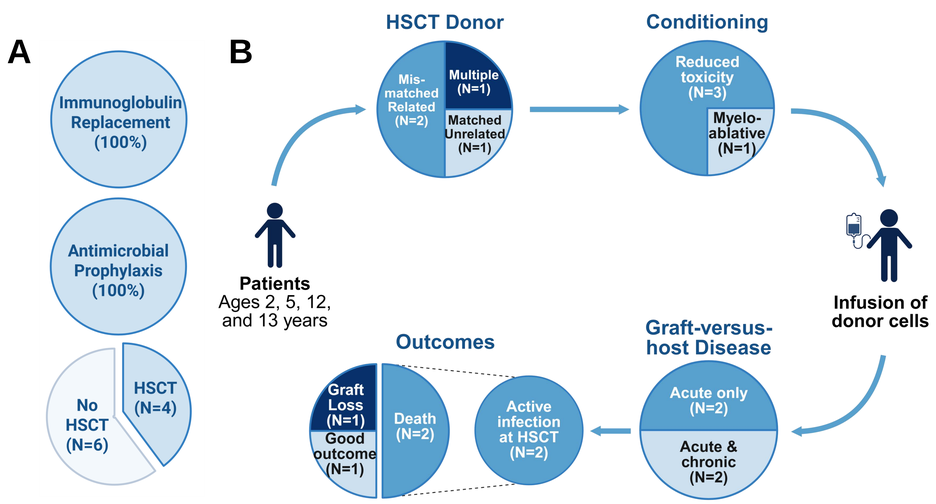


Figure 4: Treatments and outcomes. (**A**) Treatment distribution. (**B**) HSCT outcomes.

Results (cont.)

In silico models cannot predict the clinical severity of IRF4 variants

MOST SEVERE — LEAST SEVERE

Genotype	p.V405Gfs Ter127	p.T95R	p.F359L	p.R98W p.R25S
Phenotype	**CID with syndromic features** Fatal in early life (1/1)	**Combined Immunodeficiency** Fatal in some cases (2/10)	**Combined Immunodeficiency** Severe recurrent infections	**Susceptibility to Whipple's Disease** Whipple's disease with incomplete penetrance
Onset	Infancy	Infancy	Infancy to early childhood	Late adulthood
Mechanism (Inheritance)	Loss of function (AR via UPD)	Multimorphic (AD)	Multimorphic (AD)	Loss of function (AD)
Aggregate *in silico* prediction	Deleterious	Deleterious	Deleterious	Deleterious

Figure 7: Disease severity across IRF4-associated IEIs.

Discussion

IRF4 T95R CID is characterized by:

- **Profound CID**
- **Early-onset infections**
- **Clinical heterogeneity**

HSCT is potentially curative

- Ideally, **early, before infection**

Interpreting IRF4 variants

- Mechanistically and clinically **divergent phenotypes**
- **Variant-specific interpretation** is crucial for guiding management



Figure 5: Management of IRF4 deficiencies.

Acknowledgments

Thank you to the **patients and their families**.

Affiliations & References