Understanding SPENCD: How genetic variants in *ACP5* cause dysfunction in the immune and skeletal systems

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Introduction

Spondyloenchondrodysplasia (SPENCD) is a rare inborn error of immunity causing:

1. Immune overactivity
2. Abnormal bone development
3. Neurological dysfunction

SPENCD is linked to damaging *ACP5* variants

- ACP5 produces **tartaric-acid-resistant acid phosphatase (TRAP)**

Case Summary

2-Year-Old Male Patient

- Autoimmune hemolytic anemia
- Splenomegaly

- Skeletal dysplasia
- Short stature

- Autism spectrum disorder
- Intracranial calcification

Compound heterozygous *ACP5* variants
- **c.550C>T (p.Q184*)**
- **c.740T>G (p.L247R)**

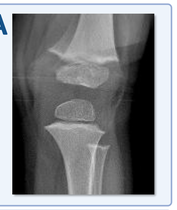

Figure 1: Patient imaging demonstrating phenotypic markers of SPENCD. (A) Skeletal dysplasia on radiography **(B)** Intracranial calcification on CT.

Objective

Elucidate the functional impact of **two ACP5 variants** and expand **SPENCD's disease mechanism.**

Methods

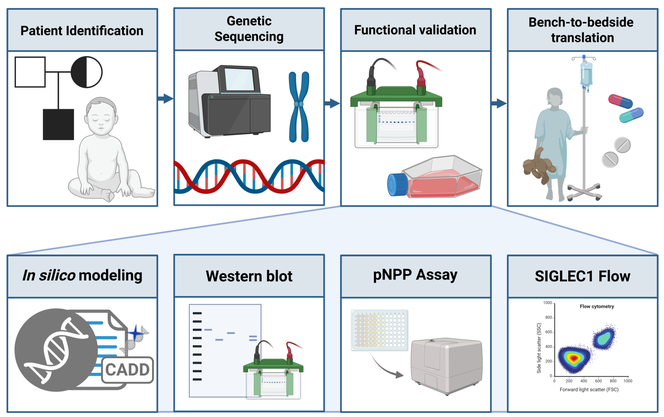

Figure 2: Methods.

Results

Patient variants are pathogenic *in silico* and segregate with disease

A

Variant		Databases		*In Silico* Models		
C. DNA	Protein	ClinVar	GnomAD	CADD	REVEL	AlphaMissense
Patient Variants						
c.550C>T	p.Q184*	Pathogenic	0 homozygotes	41	N/A	N/A
c.740T>G	p.L247R	Not found	Not found	25.7	Deleterious	Deleterious
Literature SPENCD Variants						
c.369C>A	p.T123*	Pathogenic	Not found	37	N/A	N/A
c.721G>A	p.D241N	Pathogenic	Not found	28.9	Deleterious	Deleterious
c.266C>T	p.T89I	Pathogenic	Not found	29.8	Deleterious	Deleterious
Healthy Population Variant						
c.598G>A	p.V200M	Benign	10,108 homozygotes	7.906	Uncertain	Benign

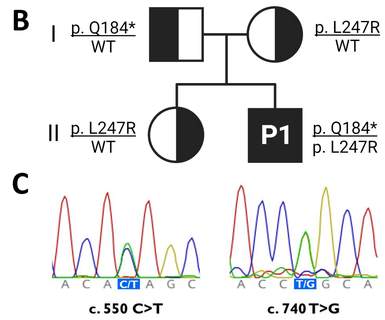

Figure 3: Identification of compound heterozygous *ACP5* variants. (A) *In silico* modeling. **(B)** Segregation. **(C)** Sanger sequencing.

SPENCD variant protein is produced but has impaired phosphatase activity

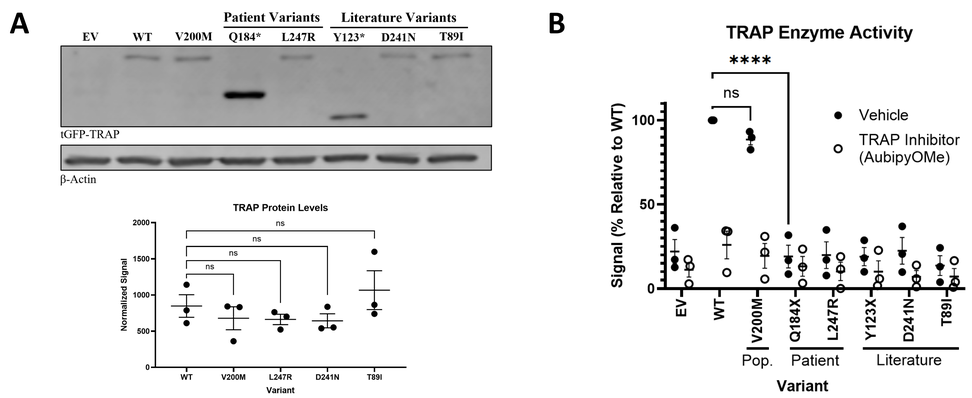

Figure 4: Functional assessment. (**A**) Western blotting. (**B**) p-Nitrophenyl phosphate (pNPP) phosphatase activity assay.

Patient samples show evidence of elevated type I interferon signaling

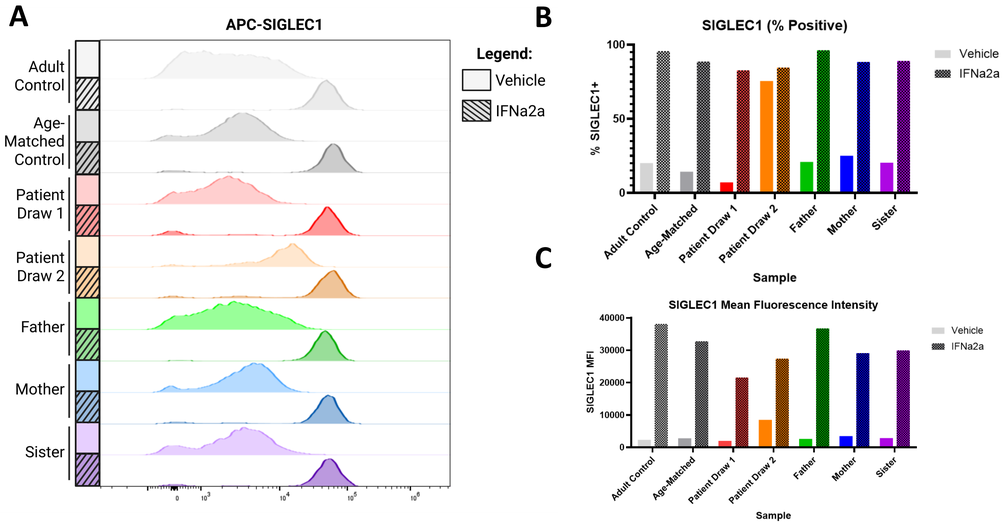

Figure 5: Flow cytometry assessment. (A) APC-SIGLEC1 histograms. **(B)** SIGLEC1 percent positive. **(C)** SIGLEC1 MFI.

Discussion

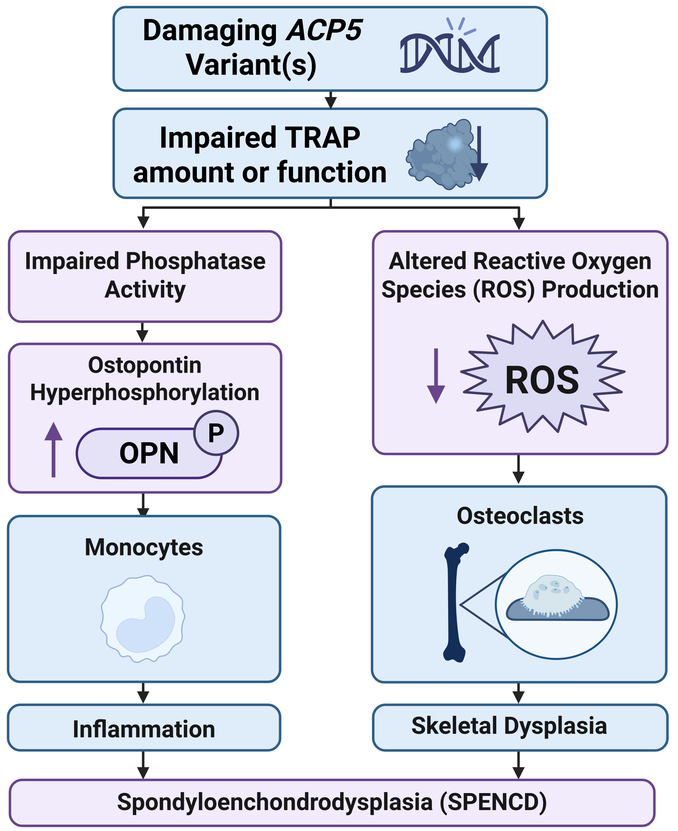

Figure 6: The proposed impact of *ACP5* variants in SPENCD.

Ongoing & Future Steps

- Link phosphatase impairment to **osteopontin (OPN)**
- **Quantify inflammation** in response to a JAK inhibitor
- Assess variant TRAP's ability to generate **reactive oxygen species (ROS)**

Conclusion

This study presents a **novel SPENCD case** and provides insight into **SPENCD's mechanism of disease.**

Acknowledgments

Thank you to the **patient and their family**.

References