A novel gene defect affecting actin dynamics reveals unexplored links between immunodeficiency and autoinflammation

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**BACKGROUND**

The study of inborn errors of the immune system (IEI) has revealed several key regulators of cytoskeleton dynamics, essential in human immunity. Given that many of the identified genes signal through common pathways, the variety of clinical and experimental phenotypes arising from defects in single actin regulators is striking1. Our study identifies novel variants in a hitherto poorly studied actin-regulatory protein as the underlying cause of a novel immune dysregulation syndrome with severe anemia in three unrelated patients.

**Identification of genetic variants in index patients**

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Patient</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
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</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Thrombocytopenia</td>
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<td>X</td>
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<td>Recurrent infections</td>
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<tr>
<td>Systemic inflammation</td>
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<tr>
<td>Neurological disease</td>
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Figure 1. Pedigrees and clinical phenotype of patients

**Morphological and functional assays to dissect the protein's function in actin cytoskeleton regulation in T cells**

**Zebrafish model to investigate role of actin cytoskelton regulation in hematopoiesis**

Cas9 protein + 3x sgRNA 80% KO in F0

Transgenic line to study role in erythropoiesis

Figure 5. Generation of zebrafish KO model to study role in hematopoiesis

**OUTLOOK**

- Reconstitution of wild-type expression for rescue experiment using CRISPR/Cas9 knock-in strategy
- GFP tagging of endogenous protein for interactome studies
- Analysis of cytokine production upon stimulation in T cells
- Assessment of erythroid progenitor populations in bone marrow aspirate and zebrafish model

**REFERENCES**