

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

Jana Block<sup>1,2,3</sup>, Christina Rashkova<sup>1,3,4</sup>, Irinka Castanon<sup>3</sup>, Rouven Schoppmeyer<sup>5</sup>, Loïc Dupré<sup>1,6#</sup>, Kaan Boztug<sup>1,2,3,4,7#</sup>

<sup>1</sup>Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Vienna, Austria; <sup>2</sup>CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria; <sup>3</sup>St. Anna Children's Cancer Research Institute, Vienna, Austria; <sup>4</sup>Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria; <sup>5</sup>Molecular Cell Biology, Sanquin Research, Amsterdam, The Netherlands; <sup>6</sup>Center for Pathophysiology of Toulouse Purpan, INSERM UMR1043, CNRS UMR5282, Paul Sabatier University, Toulouse, France; <sup>7</sup>St. Anna Children's Hospital, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria; # These authors contributed equally to this work.

## 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 striking<sup>1</sup>. 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

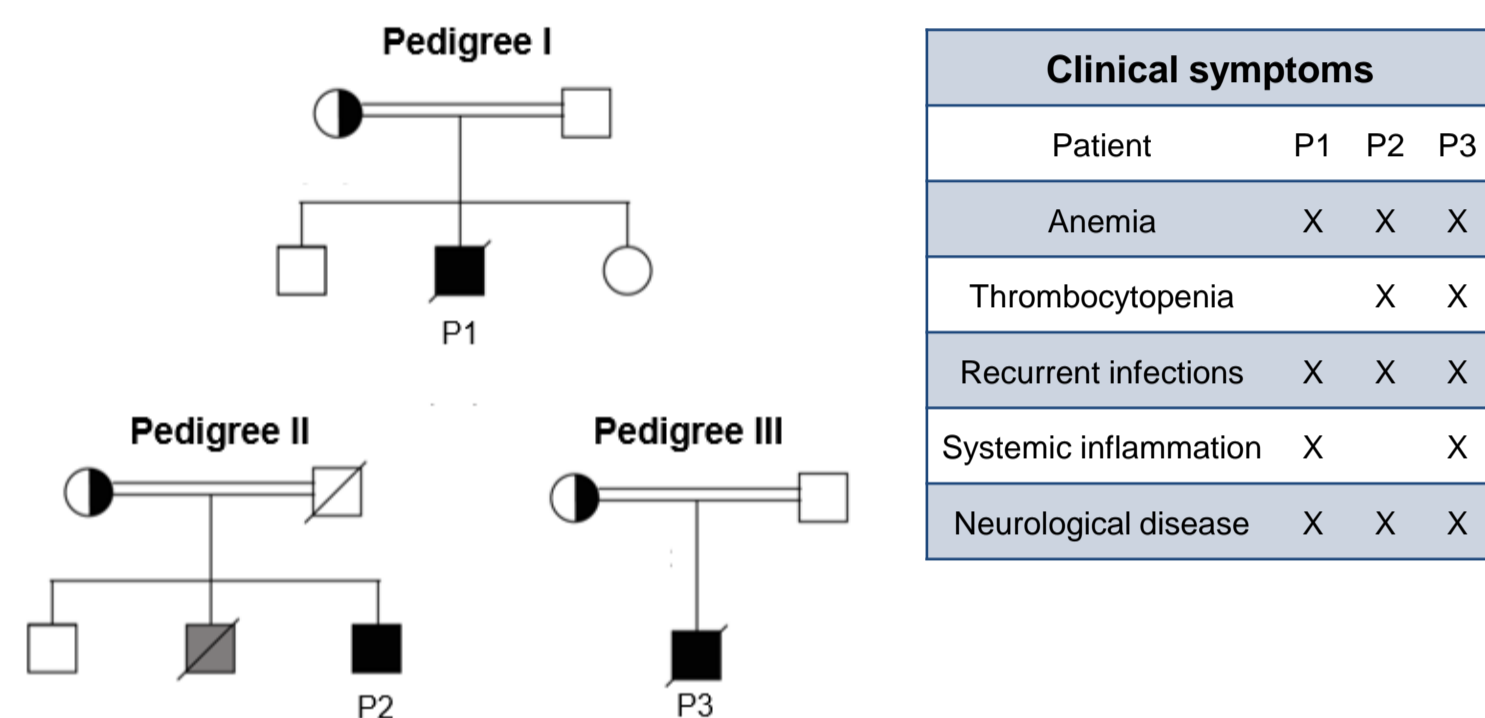


Figure 1. Pedigrees and clinical phenotype of patients

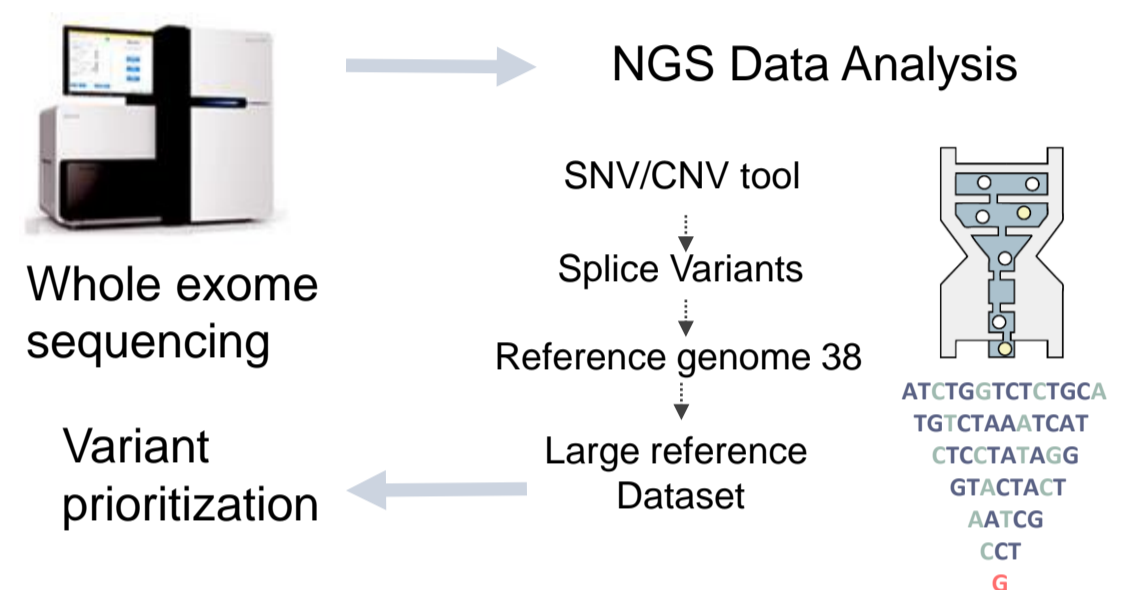


Figure 2. Schematic illustration of whole exome sequencing and filtering pipeline

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

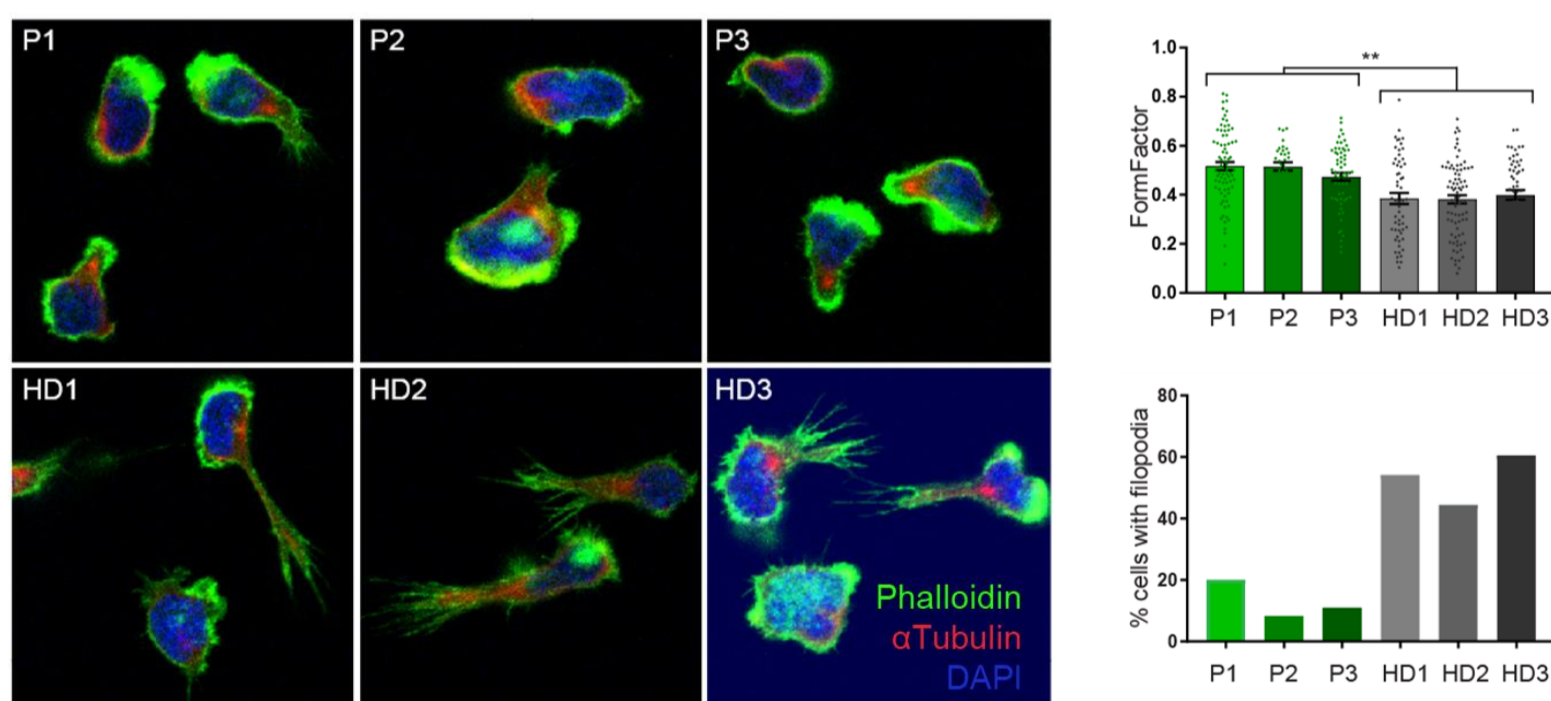


Figure 3. Patient cells display reduced filopodia formation

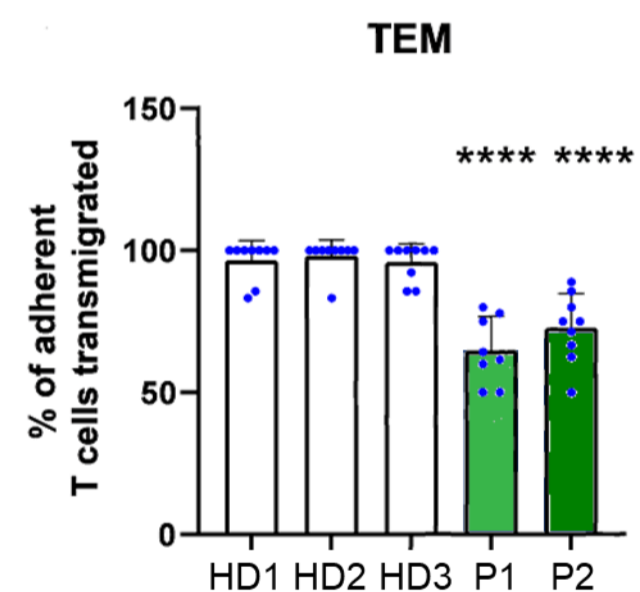


Figure 4. Patient T cells display reduced transendothelial migration

## Zebrafish model to investigate role of actin cytoskeleton regulation in hematopoiesis

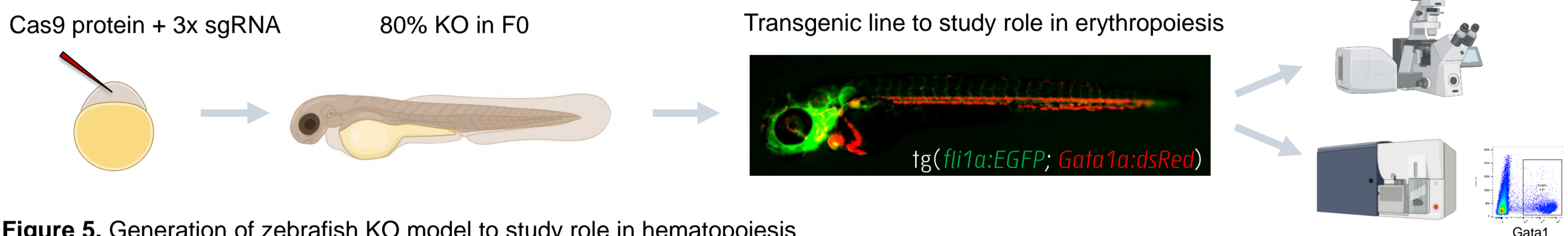


Figure 5. Generation of zebrafish KO model to study role in hematopoiesis

## 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