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PHOSPHOMEVALONATE KINASE DEFICIENCY EXPANDS THE GENETIC SPECTRUM OF SYSTEMIC AUTOINFLAMMATORY DISEASES

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Introduction: In the isoprenoid biosynthesis pathway, mevalonate is phosphorylated in two subsequent enzyme steps by mevalonate kinase (MVK) and phosphomevalonate kinase (PMVK) to generate mevalonate pyrophosphate that is further metabolized to produce sterol and non-sterol isoprenoids. Biallelic pathogenic variants in the *MVK* gene result in the autoinflammatory metabolic disorder MVK Deficiency (MKD). So far, however, no patients with PMVK deficiency due to biallelic pathogenic variants in the *PMVK* gene have been reported.

Objectives: This study aims to report the first patient with proven PMVK deficiency, including the clinical, biochemical and immunological consequences of a homozygous pathogenic variant in the *PMVK* gene.

Methods: We performed whole exome sequencing and functional studies in cells from a patient who, upon clinical and immunological evaluation, was suspected of an autoinflammatory disease.

Results: We identified a biallelic homozygous variant in the *PMVK* gene of the patient *(*NM_006556.4: c.392T>C, p.Val131Ala). Pathogenicity was confirmed by functional studies in patient cells, which revealed a markedly reduced PMVK enzyme activity due to a virtually complete absence of PMVK protein. Clinically, the patient showed various similarities but also distinct features compared to MKD patients, and responded well to therapeutic IL-1 inhibition.

Conclusion: In this study we report the first patient with proven PMVK deficiency due to a homozygous loss-of-function variant in *PMVK* leading to an autoinflammatory disease. PMVK deficiency expands the genetic spectrum of the systemic autoinflammatory diseases (SAID), characterized by recurrent fevers, arthritis and cytopenia and thus should be included in the differential diagnosis and genetic testing for SAIDs.

Trial registration identifying number: -

Patient Consent: Yes, I received consent

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Disclosure of Interest: None declared