A novel loss-of-function mutation in *LACC1* underlies hereditary juvenile arthritis with extended intra-familial phenotypic heterogeneity

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ABSTRACT

Objective: To investigate phenotypic and molecular characteristics of a consanguineous family with autosomal-recessive, polyarticular, juvenile idiopathic

arthritis (JIA) with extra-articular manifestations, including renal amyloidosis and Crohn's disease, associated with a novel homozygous truncating variant in *LACC1*.

Methods: Whole exome sequencing (WES) or targeted Sanger verification were performed in 15 participants. *LACC1* expression and cytokine array were analyzed in patient-derived and CRISPR/Cas9-generated *LACC1*-knockout macrophages (Mϕ).

Results: A homozygous truncating variant (p.Glu348Ter) in *LACC1* was identified in three affected and one asymptomatic family member, and predicted harmful by causing premature stop of the LACC1 protein sequences, and by absence from ethnically-matched controls and public variation databases. Expression studies in patient-derived macrophages (Mϕ) showed no endogenous p.Glu348Ter-LACC1 RNA transcription or protein expression, compatible with nonsense-mediated mRNA decay. WES analysis in the asymptomatic homozygous subject for p.Glu348Ter-LACC1 detected an exclusive heterozygous variant (p.Arg928Gln) in complement component C5. Further complement activity analysis suggested a protective role for the p.Arg928Gln-C5 variant as a phenotypic modifier of LACC1-associated disease. Finally, cytokine profile analysis indicated increased levels of pro-inflammatory cytokines in LACC1-disrupted as compared to wild-type Mϕ.

Conclusions: Our findings reinforce the role of LACC1 disruption in autosomal-recessive JIA, extend the clinical spectrum and intra-familial heterogeneity of the disease-associated phenotype, indicate a modulatory effect of complement factor C5 on phenotypic severity, and suggest an inhibitory role for wild-type LACC1 on pro-inflammatory pathways.