Cell, Volume *180*

Supplemental Information

FAMIN Is a Multifunctional Purine Enzyme

Enabling the Purine Nucleotide Cycle

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Supplemental Table 1. FAMIN variation linked to human disease

Rare variants – monogenic disorders	Clinical presentation	Laboratory findings	Classification	Age of onset	Background	Ref
c.T850C p.C284R autosomal recessive	Quotidian fever, erythematous maculopapular rash; symmetrical polyarthritis of small and large joints; 9/13 with persistent systemic manifestation with intermittent fever and active polyarthritis; 4/13 with short-lived systemic manifestation and polyarticular subtype	Leukocytosis, thrombocytosis, high inflammatory markers; 8/13 ANA; 5/13 weak RF	**sJIA** (Still's disease)	3.2±1.8 yrs	13 patients in 5 consanguineous Saudi Arabian families	(Wakil et al., 2015)
c.T850C p.C284R autosomal recessive	Early-onset Crohn's disease; severe debilitating arthropathy		**Early-onset inflammatory bowel disease**	< 10 yrs	4 patients in consanguineous Saudi Arabian family	(Patel et al., 2014)
c.128_129delGT p.C43Yfs*6 autosomal recessive	RF-negative polyarticular juvenile idiopathic arthritis: chronic, symmetric polyarthritis of large and small joints, erosive in 2/3. No fever, skin rash, uveitis, or other extra-articular manifestations.	Leukocytosis, thrombocytosis, anaemia, high inflammatory markers	**JIA**	2-4 yrs	3 patients in consanguineous Moroccon family	(Arostegui et al., 2015)
c.827delC p.T276fs*2 autosomal recessive	Child 1: at 16 months severe polyarthritis of small & large joints, lymphadenopathy, quotidian fever without serositis or exanthema. Precursor B cell acute lymphoblastic leukaemia at age 6. Child 2: large joint arthritis, later systemic polyarthritis	Leukocytosis, high inflammatory markers	(1) **sJIA** (Still's disease) (2) extended oligoarticular **JIA**	15 and 16 months	2 siblings in consanguineous Lebanese family	(Kallinich et al., 2016)
c.3G>A p.0 autosomal recessive	Polyarticular arthritis; 1/4 with fever or rash; 3/4 chronic, 1/4 episodic; 1/4 growth retardation		Polyarticular **JIA**	<1 yr (3/4); 2 yr (1/4)	4 patients in consanguineous family	(Karacan et al., 2018)
c.1240C>T p.R414X autosomal recessive	Chronic polyarticular arthritis; 1/3 fever or rash; 2/3 splenomegaly		Polyarticular **JIA**	<1 yr (2/3); 2.5 yr (1/3)	3 patients in consanguineous family	(Karacan et al., 2018)
c.988_990del p.I330del autosomal recessive	Fever, rash, pericarditis; chronic polyarticular arthritis; growth retardation		**sJIA** (Still's disease)	<1yr and 2 yrs	2 patients in consanguineous family	(Karacan et al., 2018)
Compound: Het: c.1109G>A p.C370Y; Hom: c.760A>G [rs3764147] p.I254V	1/2 episodic enthesitis-related juvenile arthritis; 1/2 episodic oligoarticular juvenile arthritis; 1 unaffected sibling with identical genotype		**JIA**	10 and 7 yrs	2 patients in consanguineous family	(Karacan et al., 2018)

Common variants	Minor allele frequency	Odds ratio	Disease risk		Population	Ref
rs3764147 c.760A>G p.I254V	~0.26	1.25	**Crohn's disease**		Caucasian	(Barrett et al., 2008)
rs3764147 c.760A>G p.I254V	~0.35	1.68	**Leprosy**		Han Chinese	(Zhang et al., 2009)
rs2121033 (intronic) (rs9316059, intronic)	~0.28	0.69 – 0.79	**Behçet's disease**		Turkish, Iranian and Japanese	(Takeuchi et al., 2017)

p.I254V: reduced ROS production, oxygen consumption (oxidative phosphorylation) and extracellular acidification (glycolysis) (Cader et al., 2016)
p.C284R: loss-of-function, phenotype indistinguishable from knock-out allele (Cader et al., 2016)
Abbreviations: ANA, anti-nuclear antibody; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor; ROS, reactive oxygen species; sJIA, systemic juvenile idiopathic arthritis