A- A+

PgmNr 2556: IFIH1 gain of function variants: Further delineation of multiple faces of type I Interferonopathy.

Authors:
S. Shimada [1]; J. Stephen [2]; S. Nampoothiri [3]; L.A. Wolfe [1,4]; C. Toro [1,4]; C.J. Tifft [1,4]; D.R. Adams [1,4]; W.A. Gahl [1,2]; MCV. Malicdan [1,2,4]

View Session Add to Schedule

Affiliations:
1) 1.NIH Undiagnosed Disease Program, Common Fund, Office of the Director and the National Human Genome Research Institute, National Institutes of Health, Bethesda, USA; 2) 2.Medical Genetics Branch, national Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA; 3) 3.Department of Pediatric Genetics, Amrita Institute of Medical Sciences and Research Center, Kerala 682041, India; 4) 4.Office of the Clinical Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

IFIH1 encodes the protein interferon-induced helicase C domain-containing protein 1, otherwise known as melanoma differentiation-associated protein 5 (MDA5), which is a cytosolic sensor of double-stranded(ds) RNA as innate immune receptor. Enhanced type I interferon signaling secondary to gain-of-function mutations in *IFIH1* results in a range of neuroinflammatory phenotypes including Aicardi-Goutieres syndrome (AGS) and multi-system phenotypes like Singleton-Merten syndrome (SMS). Here we describe the clinical spectrum of three patients from three independent families with gain of function *IFIH1* mutations identified by exome sequencing.
All three probands have a typical AGS phenotype with various neurological and systemic manifestations, and brain imaging consistent with intracranial calcification. Probands 1 and 2, harboring heterozygous *IFIH1* variants (c.1009A>G;p.Arg337Gly and c.2342G>A;p.Gly781Glu, respectively) presented with an AGS and SMS overlapping phenotype, manifesting with abnormal dental findings (periodontitis and moderate enamel hypoplasia) and cutaneous findings (psoriasis and chilblain lesions). Atypical presentations were also noted; proband 1 had recurrent non-diabetic pancreatitis while proband 2 had axonal sensory motor neuropathy. Proband 3, with a heterozygous c.2335C>T;p.Arg779Cys variant, showed early-onset epileptic encephalopathy (EOEE) with severe global developmental delay.
To determine the cellular consequences of these variants, we measured the interferon activity in mammalian cells overexpressing the different mutations as compared to full length, wild-type IFIH1. Based upon this luciferase-based reporter assay, all three variants had increased interferon activities, confirming a gain?of?function mechanism. We hypothesize that these variants will lead to the upregulation of interferon-stimulated gene transcription.
Our results further delineate the spectrum of IFIH1-associated type 1 interferonopathy, ranging from neuroinflammation in SMS to an autoimmune phenotype.