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Aicardi-Goutières syndrome due to a paternal mosaic *IFIH1* mutation

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Progressive immune-mediated neurodegeneration is a central feature of Aicardi-Goutières syndrome (AGS), a monogenic disorder characterized by chronic activation of antiviral type I interferon (IFN).[1] Typically, AGS presents as subacute infancy-onset encephalopathy with microcephaly, leukodystrophy, and basal ganglia calcification, resulting in global developmental delay. AGS is either caused by loss-of-function mutations in *TREX1*, *RNASEH2B*, *RNASEH2C*, *RNASEH2A*, *SAMHD1*, or *ADAR*, encoding genes involved in the metabolism of nucleic acids, or by gain-of-function mutations in *IFIH1* encoding the cytosolic RNA sensor melanoma differentiation-associated protein 5 (MDA5).[1] The phenotypic spectrum of *IFIH1*-associated mutations includes intracerebral vasculopathy, bilateral striatal necrosis, and isolated spastic paraparesis.

We report the rare case of AGS due to paternal mosaicism for an *IFIH1* mutation in 2 brothers. The study was conducted with approval by the ethics committees of the University of Tübingen and Technische Universität Dresden, and written informed consent was obtained. Both siblings were born at term to healthy nonconsanguineous parents after uneventful pregnancies and with anthropometric birth data within normal limits. Their family history was unremarkable. After a period of normal development, both brothers presented with gait disturbances and progressive microcephaly. Bilateral lower limb spasticity manifested at the age of 18 months in the older brother (II:1) after he had learned to walk unsupported, whereas the younger brother (II:2) became symptomatic at the age of 12 months before learning to walk (figure, A). Apart from mild hypertonicity of the left arm and minor dysarthria in the older brother, neither of the 2 children showed signs of additional motor or cognitive deficits. Brain MRI revealed symmetric hyperintensities within the periventricular white matter in both brothers, with hypomyelination more pronounced in the older sibling (figure, B). Blood counts, inflammatory markers, and liver and renal function tests were unremarkable. Both siblings were clinically diagnosed with hereditary spastic paraplegia. Sequencing of 136 HSP-related genes (HaloPLEX hereditary spastic paraplegia Panel) identified a heterozygous variant of *IFIH1* (NM_022168: c.2336 G>A, p. R779H) in both children. Of interest, the variant was also observed at low abundance in the blood-derived DNA sample of the clinically asymptomatic father. Sanger sequencing confirmed the heterozygous R779H variant in both children, while a weak mutation peak was also observed in the sequence pherogram of the father, confirming that he was mosaic for R779H (figure, C). Thus, both children inherited the R779H mutation through a germline mosaic from the father.

R779H has previously been reported in at least 8 patients with AGS occurring either as a dominant mutation with reduced penetrance or as de novo mutation.[2] We therefore investigated the family for signs of constitutive type I IFN activation in blood. Consistent with AGS, both brothers exhibited a strong IFN signature (IFN score 1,031.19 ± 350.19 in I:1 and 648.21 ± 219.61 in I:2, mean ± SEM; normal range < 12.49). Although the mother showed no signs of IFN activation (IFN score 1.29), the father was also found to have an IFN signature (IFN score 404.04),

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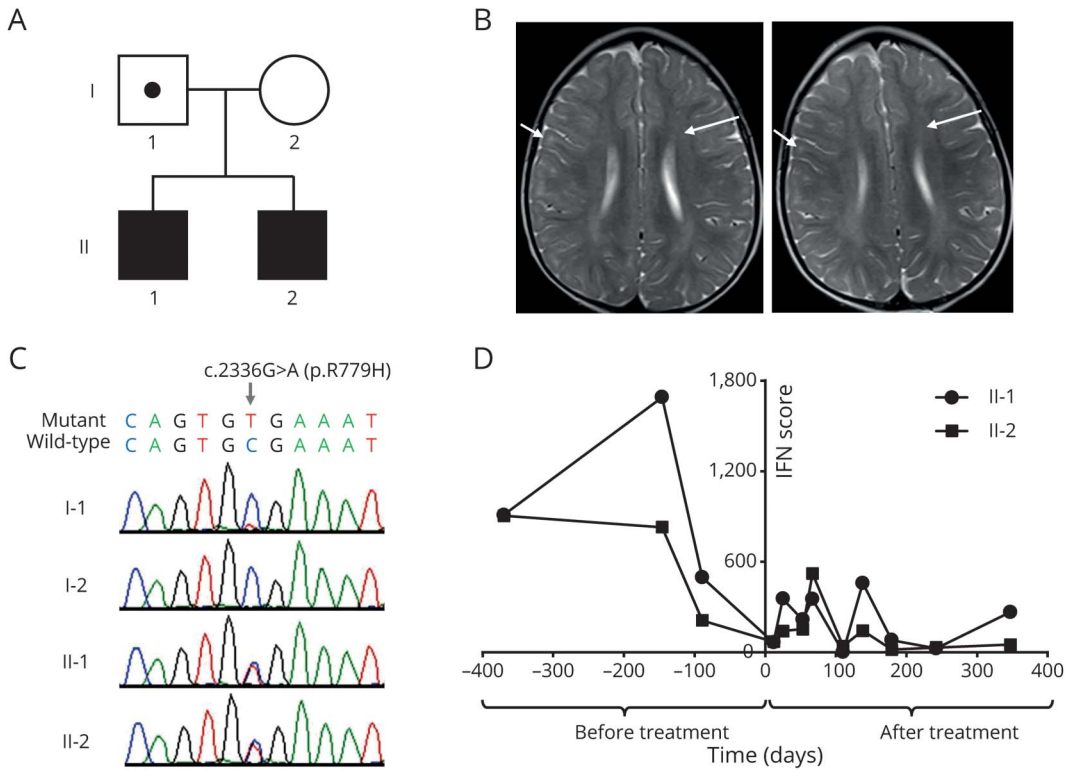
Figure Clinical and molecular findings



(A) Pedigree. (B) MRI of II:1 at 2 years, delayed myelination and white matter hyperintensity (left, white arrows), and unchanged at 5 years (right). (C) Heterozygous *IFIH1* mutations in the children, weak mutation peak in the father (reverse sequence). (D) IFN scores ($p \leq 0.0007$, before vs after ruxolitinib), calculated as described.[3] IFN = interferon.

consistent with the mosaic state of the R779H variant in his blood. Further examination of the father did not reveal microcephaly, vasculitis, or lupus-like symptoms. His blood counts and renal and liver function tests were unremarkable.

Uncontrolled activation of the MDA5 receptor because of activating *IFIH1* mutations results in constitutive type I IFN signaling.[2] Given the disease progression and lack of approved therapeutic options, we initiated off-label treatment with the Janus kinase (JAK) 1/2 inhibitor ruxolitinib, which inhibits downstream signaling at the IFN-α/β receptor. Ruxolitinib started at 5 and 7 years, respectively, with a dose of 0.5 mg/kg was well tolerated without any hematologic or infectious adverse events. Ruxolitinib was increased to 0.75 mg/kg over time. Both children responded with a significant reduction of the IFN signature (figure, D). The parents reported a marked improvement in their childrens' quality of life during ruxolitinib treatment, who were described to be less fatigued and to engage more motivated in physical activities. Improved concentration of the older brother had a positive effect on academic achievements. Both children were able to maintain and even moderately improve their motor abilities, with a progress more noticeable in the younger brother, whose gait using orthoses improved by 40% after 8 months of treatment, as revealed by the dimension "walking, running, and jumping" of the Gross Motor Function Measure.

Clinical improvement observed in the patients supports previous reports, indicating that JAK inhibition may be therapeutically effective in type I IFN-driven disorders.[3–7] Timely diagnosis is of clinical importance because early therapeutic intervention may modify the course of the disease and prevent further neurologic damage. Our findings also suggest that parental germline mosaicism may be more common than previously presumed in patients with AGS with apparent de novo *IFIH1* mutation with significant implications for genetic counseling.

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Disclosure

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Rebecca Schüle, MD	University of Tübingen, Germany	Author	Study design and analysis and interpretation of the data
Min Ae Lee-Kirsch, MD	Technische Universität Dresden, Germany	Author	Study design, clinical assessment, analysis, and interpretation of the data, and drafting of the manuscript

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