

**A nationwide survey of Aicardi-Goutières syndrome patients identifies a strong association between dominant *TREX1* mutations and chilblain lesions: Japanese cohort study**

**Objectives.** Aicardi-Goutières syndrome (AGS) is a rare, genetically determined, early onset progressive encephalopathy associated with autoimmune manifestations. AGS is usually inherited in an autosomal recessive manner. The disease is rare, therefore the clinical manifestations and genotype-phenotype correlations, particularly with regard to autoimmune diseases, are still unclear. Here we performed a nationwide survey of AGS patients in Japan and analysed the genetic and clinical data.

**Methods.** Patients were recruited via questionnaires sent to pediatric or adult neurologists in Japanese hospitals and institutions. Genetic analysis was performed and clinical data were collected.

**Results.** Fourteen AGS patients were identified from 13 families; 10 harboured genetic mutations. Three patients harboured dominant-type *TREX1* mutations. These included two *de novo* cases: one caused by a novel heterozygous p.His195Tyr mutation and the other by a novel somatic mosaicism resulting in a p.Asp200Asn mutation. Chilblain lesions were observed in all patients harbouring dominant-type *TREX1* mutations. All three patients harbouring *SAMHD1* mutations were diagnosed with autoimmune diseases, two with SLE and one with SS. The latter is the first reported case.

**Conclusion.** This study is the first to report a nationwide AGS survey, which identified more patients with sporadic AGS carrying *de novo* dominant-type *TREX1* mutations than expected. There was a

strong association between the dominant-type *TREX1* mutations and chilblain lesions, and between *SAMHD1* mutations and autoimmunity. These findings suggest that rheumatologists should pay attention to possible sporadic AGS cases presenting with neurological disorders and autoimmune manifestations.

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