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.

REFERENCES

1 Chahwan C, Chahwan R. Aicardi-Goutieres syndrome: from patients to genes and beyond. Clin Genet 2012;81(5):413-20.

2 Ramantani G, Kohlhase J, Hertzberg C, et al. Expanding the phenotypic spectrum of lupus erythematosus in Aicardi-Goutières syndrome. Arthritis Rheum 2010;62(5):1469-77.

3 Rice G, Patrick T, Parmar R, et al. Clinical and molecular phenotype of Aicardi-Goutieres syndrome. Am J Hum Genet 2007;81(4):713-25.

4 Orcesi S, La Piana R, Fazzi E. Aicardi-Goutieres syndrome. Br Med Bull 2009;89:183-201.

5 Blau N, Bonafé L, Krägeloh-Mann I, et al. Cerebrospinal fluid pterins and folates in Aicardi-Goutières syndrome: a new phenotype. Neurology 2003;61(5):642-7.

6 Crow YJ, Hayward BE, Parmar R, et al. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 cause Aicardi-Goutières syndrome at the AGS1 locus. Nat Genet 2006;38(8):917-20.

7 Crow YJ, Leitch A, Hayward BE, et al. Mutations in genes encoding ribonuclease H2 subunits cause Aicardi-Goutières syndrome and mimic congenital viral brain infection. Nat Genet 2006;38(8):910-6.

8 Rice GI, Bond J, Asipu A, et al. Mutations involved in Aicardi-Goutières syndrome implicate SAMHD1 as regulator of the innate immune response. Nat Genet 2009;41(7):829-32.

9 Rice GI, Kasher PR, Forte GM, et al. Mutations in ADAR1 cause Aicardi-Goutières syndrome associated with a type I interferon signature. Nat Genet 2012;44(11):1243-8.

10 Rice G, Newman WG, Dean J, et al. Heterozygous mutations in TREX1 cause familial chilblain lupus and dominant Aicardi-Goutieres syndrome. Am J Hum Genet 2007;80(4):811-5.

11 Haaxma CA, Crow YJ, van Steensel MA, et al. A de novo p.Asp18Asn mutation in TREX1 in a patient with Aicardi-Goutières syndrome. Am J Med Genet A 2010;152A(10):2612-7.

12 Tüngler V, Silver RM, Walkenhorst H, Günther C, Lee-Kirsch MA. Inherited or de novo mutation affecting aspartate 18 of TREX1 results in either familial chilblain lupus or Aicardi-Goutières syndrome. Br J Dermatol 2012;167(1):212-4.

13 Crow YJ. Type I interferonopathies: a novel set of inborn errors of immunity. Ann N Y Acad Sci 2011;1238:91-8.

14 Obermoser G, Pascual V. The interferon-alpha signature of systemic lupus erythematosus. Lupus 2010;19(9):1012-9.

15 Lee-Kirsch MA, Gong M, Chowdhury D, et al. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nat Genet 2007;39(9):1065-7.

16 Cheng MH, Anderson MS. Monogenic autoimmunity. Annu Rev Immunol 2012;30:393-427.

17 Ramantani G, Häusler M, Niggemann P, et al. Aicardi-Goutières syndrome and systemic lupus erythematosus (SLE) in a 12-year-old boy with SAMHD1 mutations. J Child Neurol 2011;26(11):1425-8.

18 Lee-Kirsch MA, Gong M, Schulz H, et al. Familial chilblain lupus, a monogenic form of cutaneous lupus erythematosus, maps to chromosome 3p. Am J Hum Genet 2006;79(4):731-7.

19 Abe J, Izawa K, Nishikomori R, et al. Heterozygous TREX1 p.Asp18Asn mutation can cause variable neurological symptoms in a family with Aicardi-Goutieres syndrome/familial chilblain lupus. Rheumatology (Oxford) 2013;52(2):406-8.

20 Shintaku H, Asada M, Sawada Y. Diagnosis and treatment of 6-pyruvoyl-tetrahydropterin synthase deficiency. Brain Dev 2000;22 Suppl 1:S118-21.

21 Nishikomori R, Akutagawa H, Maruyama K, et al. X-linked ectodermal dysplasia and immunodeficiency caused by reversion mosaicism of NEMO reveals a critical role for NEMO in human T-cell development and/or survival. Blood 2004;103(12):4565-72.

22 Izawa K, Hijikata A, Tanaka N, et al. Detection of base substitution-type somatic mosaicism of the NLRP3 gene with >99.9% statistical confidence by massively parallel sequencing. DNA Res 2012;19(2):143-52.

23 Tanaka N, Izawa K, Saito MK, et al. High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: Results of an international multicenter collaborative study. Arthritis Rheum 2011;63(11):3625-32.

24 Orebaugh CD, Fye JM, Harvey S, Hollis T, Perrino FW. The TREX1 exonuclease R114H mutation in Aicardi-Goutières syndrome and lupus reveals dimeric structure requirements for DNA degradation activity. J Biol Chem 2011;286(46):40246-54.

25 Brucet M, Querol-Audí J, Serra M, et al. Structure of the dimeric exonuclease TREX1 in complex with DNA displays a proline-rich binding site for WW Domains. J Biol Chem 2007;282(19):14547-57.

26 Brucet M, Querol-Audí J, Bertlik K, et al. Structural and biochemical studies of TREX1 inhibition by metals. Identification of a new active histidine conserved in DEDDh exonucleases. Protein Sci 2008;17(12):2059-69.

27 Bailey SL, Harvey S, Perrino FW, Hollis T. Defects in DNA degradation revealed in crystal structures of TREX1 exonuclease mutations linked to autoimmune disease. DNA Repair (Amst) 2012;11(1):65-73.

28 Kavanagh D, Spitzer D, Kothari PH, et al. New roles for the major human 3'-5' exonuclease TREX1 in human disease. Cell Cycle 2008;7(12):1718-25.

29 Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25(11):1271-7.

30 Miyawaki S. [Revised Japan criteria for Sjögren syndrome]. Ryumachi 2000;40(1):48-53.

31 Yao Y, Liu Z, Jallal B, Shen N, Rönnblom L. Type I interferons in Sjögren's syndrome. Autoimmun Rev 2013;12(5):558-66.

32 Lee-Kirsch MA, Chowdhury D, Harvey S, et al. A mutation in TREX1 that impairs susceptibility to granzyme A-mediated cell death underlies familial chilblain lupus. J Mol Med (Berl) 2007;85(5):531-7.

33 Bachmeyer C, Farge D, Gluckman E, Miclea JM, Aractingi S. Raynaud's phenomenon and digital necrosis induced by interferon-alpha. Br J Dermatol 1996;135(3):481-3.

34 Campo-Voegeli A, Estrach T, Marti RM, et al. Acrocyanosis induced by interferon alpha(2a). Dermatology 1998;196(3):361-3.

35 Stetson DB, Ko JS, Heidmann T, Medzhitov R. Trex1 prevents cell-intrinsic initiation of autoimmunity. Cell 2008;134(4):587-98.

36 Chowdhury D, Beresford PJ, Zhu P, et al. The exonuclease TREX1 is in the SET complex and acts in concert with NM23-H1 to degrade DNA during granzyme A-mediated cell death. Mol Cell

2006;23(1):133-42.

37 de Silva U, Choudhury S, Bailey SL, et al. The crystal structure of TREX1 explains the 3' nucleotide specificity and reveals a polyproline II helix for protein partnering. J Biol Chem 2007;282(14):10537-43.

38 Lehtinen DA, Harvey S, Mulcahy MJ, Hollis T, Perrino FW. The TREX1 double-stranded DNA degradation activity is defective in dominant mutations associated with autoimmune disease. J Biol Chem 2008;283(46):31649-56.

39 Fye JM, Orebaugh CD, Coffin SR, Hollis T, Perrino FW. Dominant Mutations of the TREX1 Exonuclease Gene in Lupus and Aicardi-Goutieres Syndrome. J Biol Chem 2011;286(37):32373-82.

40 Gall A, Treuting P, Elkon KB, et al. Autoimmunity initiates in nonhematopoietic cells and progresses via lymphocytes in an interferon-dependent autoimmune disease. Immunity 2012;36(1):120-31.

41 Saito M, Fujisawa A, Nishikomori R, et al. Somatic mosaicism of CIAS1 in a patient with chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheum 2005;52(11):3579-85.

42 Saito M, Nishikomori R, Kambe N, et al. Disease-associated CIAS1 mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients. Blood 2008;111(4):2132-41.