Letter to the Editor
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Identification of Homozygous Likely Pathogenic Variant of *ALDH3A2* in a Korean Boy with Sjögren–Larsson Syndrome

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Dear Editor,

Sjögren–Larsson syndrome (SLS; OMIM 270200) is an autosomal recessive disorder caused by deficiency of fatty aldehyde dehydrogenase (FALDH) owing to mutations in *ALDH3A2* [1]. Patients with SLS usually have ichthyosis after birth, spastic paraplegia, and mental retardation. On ocular examination, crystalline macular dystrophy is often observed, which can result in photophobia or reduced visual sensitivity in affected patients [2, 3]. In Korea, there have been a few case reports on SLS but, as far as we know, none was confirmed by genetic testing [4-7]. Although some patients show typical clinical features of SLS, its phenotype can be variable so that genetic testing of *ALDH3A2* should be performed to make a diagnosis of SLS. We present clinical and genetic findings of a Korean patient with SLS.

A 7-year-old boy was born to non-consanguineous parents at 33+2 weeks gestational age by cesarean section delivery because of maternal preeclampsia. His birth weight was 1,560 g. At birth, he had ichthyosiform skin lesions, sparing the face. Developmental delay was observed; the patient rolled over at eight months, leaned back at 10 months, crawled at 14 months, and walked holding furniture at 23 months. At two years of age, he needed axillary support for standing and walking. At five years of age, he started speaking words, and his enunciation improved after language treatment. At seven years of age, he was able to read, write, and sit unsupported, and could count ~60% of the numbers from 1–100. His expressive language abilities were within the normal range for 6-year-old children.

At seven years of age, the patient's height and weight were 140 cm (<5th percentile) and 39.3 kg (<5th percentile), respectively. Generalized brownish ichthyosis was observed on the skin, except the face, and was prominent in periarticular regions of the upper and lower extremities (Fig. 1A). Pruritus was observed only when sweating or febrile. On motor examination, muscle spasticity and weakness were observed in the proximal lower

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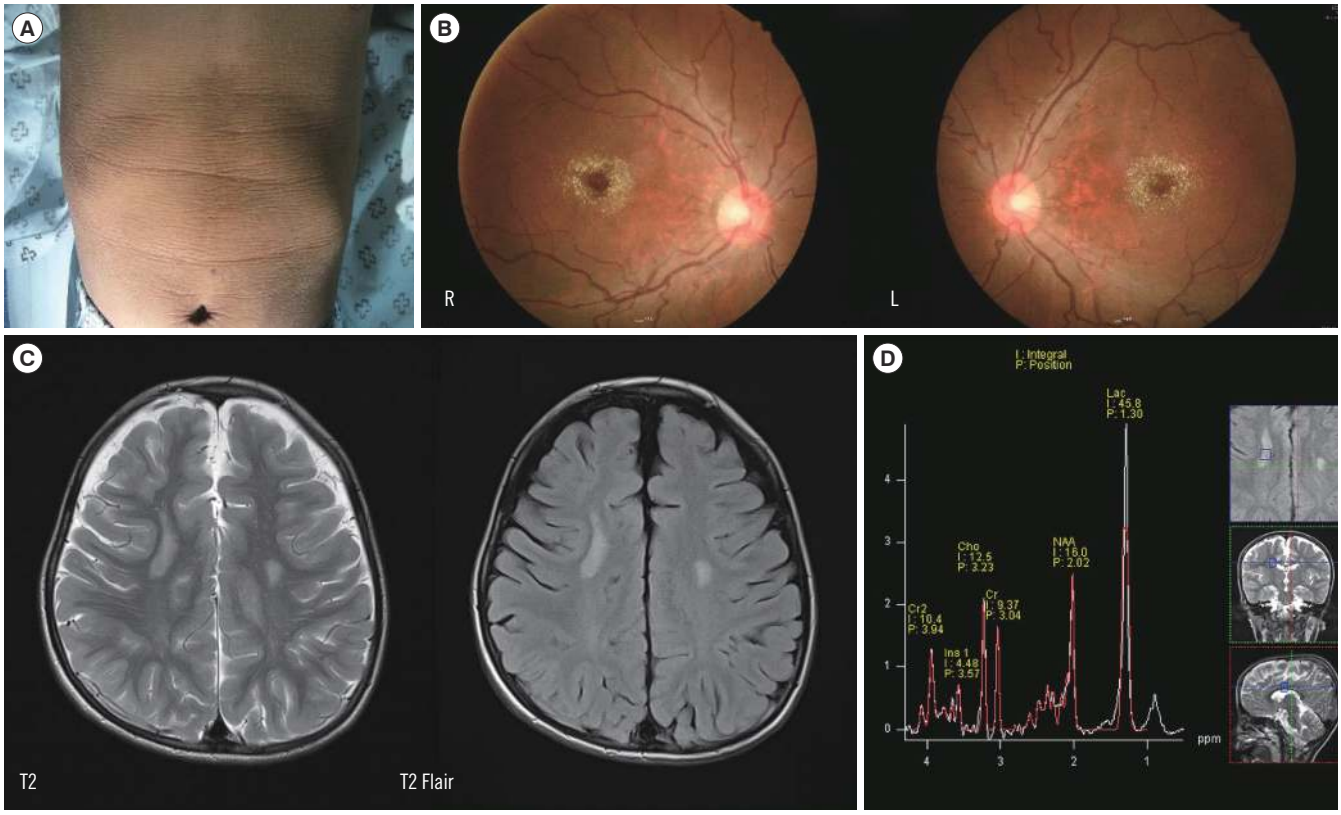

Fig. 1. Patient's clinical, ophthalmological, and radiological findings. (A) Brownish hyperkeratosis in the abdominal area. (B) Crystalline retinopathy in both eyes. (C) Increased signal intensity on T2-weighted images lateral, superior, and posterior to both lateral ventricles, especially in the superior aspect. (D) Sharp lipid peak at 1.3 ppm and a small peak at 0.9 ppm by proton MR spectroscopy (^{1}H-MRS).

limbs, although muscle strength and tone in the distal ankles were intact. Deep tendon reflexes were hyperactive in both lower extremities with positive ankle clonus; the upper extremities were neurologically normal. Ophthalmological examination showed crystalline retinopathy in both macular regions (Fig. 1B). These clinical findings were suggestive of SLS.

Brain magnetic resonance imaging (MRI) showed mild brain atrophy in both frontal lobes and high signal intensity on T2-weighted images lateral, superior, and posterior to both lateral ventricles, especially in the superior aspect (Fig. 1C). A noticeable, sharp lipid peak at 1.3 ppm and a small peak at 0.9 ppm were identified by single-voxel proton MR spectroscopy (1H-MRS) (Fig. 1D). An animal fat-free diet, a topical steroid cream, and a leukotriene receptor antagonist were prescribed to relieve dermatological symptoms, including pruritus and ichthyosis.

His elder brother, who died at seven years of age after acute respiratory failure, had also presented with congenital ichthyosis and severe retardation in motor and language development. From the age of two years, the patient started having several febrile seizure attacks every year. Brain MRI at three years of age revealed brain atrophy with periventricular white matter signal changes that were compatible with leukodystrophy.

To confirm the clinical diagnosis of SLS, *ALDH3A2* was analyzed by Sanger sequencing. After obtaining written informed consent from both parents, genomic DNA was extracted from peripheral blood leukocytes, and all coding exons and flanking introns of *ALDH3A2* were PCR-amplified and sequenced using primer sets designed by the authors (available upon request). The patient was homozygous for the NM_000382.2:c.1157A>G (p.Asn386Ser) variant in *ALDH3A2*, and both parents were heterozygous carriers for the same variant (Fig. 2). This variant has previously been reported in a Japanese family with SLS [8]. Population frequencies of this variant were estimated to be 0.0002311 in East Asians (Exome Aggregation Consortium database) and 0.000909 in the Korean population (Korean Reference Genome database).

Automated analysis, using the InterVar program for the clinical interpretation of genetic variants by American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) standards and guidelines, revealed that this vari-

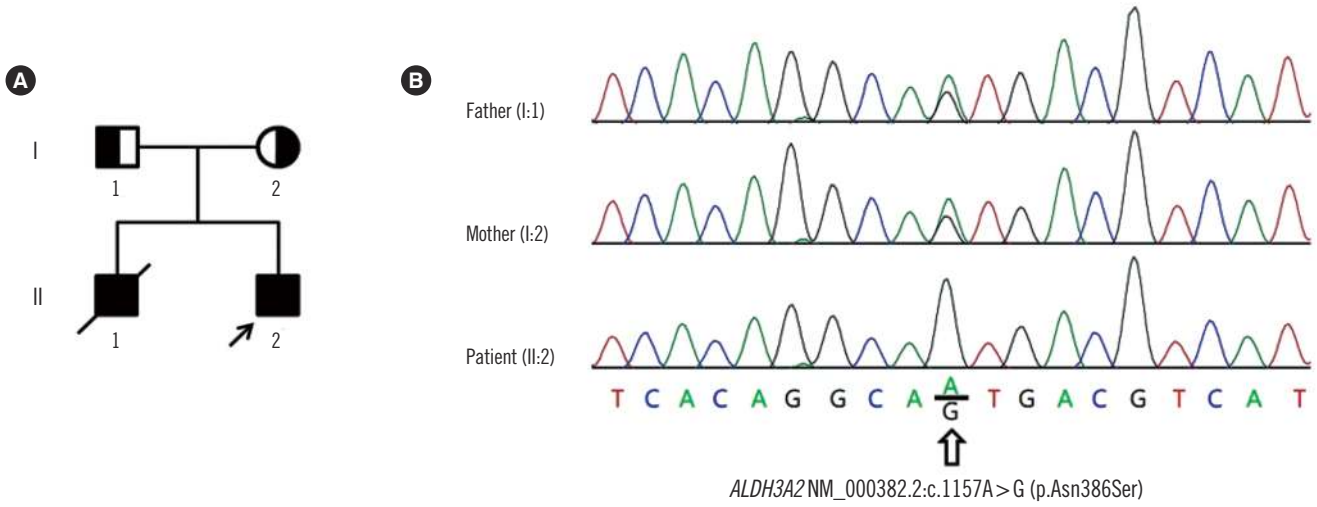

Fig. 2. Pedigree and sequence chromatogram of the *ALDH3A2* variant identified in this family. (A) Family pedigree shows two affected patients. The elder brother of the proband is deceased. Male, square; female, circle; filled symbols, affected; half-filled symbols, heterozygous carriers; arrow, proband. (B) The patient is homozygous for the *ALDH3A2* c.1157A>G (p.Asn386Ser) variant, while both parents are heterozygous carriers of the same variant (arrow).

ant could be classified as a likely pathogenic variant on the basis of the following evidence: located in a well-established functional domain (PM1), extremely low frequency in controls (PM2), deleterious effect on the gene by multiple computational programs (PP3), and listed as a pathogenic variant in reputable sources, including the Human Gene Mutation Database (CM001057) and ClinVar (Variant ID: 1644) (PP5) [9, 10].

In summary, we report a Korean child carrying a homozygous likely pathogenic variant of *ALDH3A2*. He had the triad of SLS, including congenital ichthyosis, spastic diplegia, and mental retardation, as well as crystalline retinopathies in both eyes. 1H-MRS findings were also consistent with SLS. To the best of our knowledge, this is the first genetically confirmed case of SLS in Korea.

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