ORIGINAL ARTICLE

Clinical and Molecular Aspects of Sjogren-Larsson Syndrome Reported in an Iranian Consanguineous Family with Triplet Affected Individuals

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Abstract

Background: Sjogren Larsson Syndrome (SLS; OMIM: 270200) is an autosomal recessive neurocutaneous disorder characterized by mental retardation, congenital ichthyosis and spastic paraplegia. SLS is caused by mutations in aldehyde dehydrogenase 3A2 isoform 2 (*ALDH3A2*), which encodes fatty aldehyde dehydrogenase (FALDH). This enzyme metabolizes the NAD-dependent oxidation of long chain aldehyde derived from lipid metabolism. Up to now, more than 72 mutations have been reported in SLS patients.

Methods: DNA was extracted from peripheral blood of all the five patients, one healthy sibling and their parents using standard procedures. SNP genotyping was performed using the GeneChip®. Multipoint linkage analyses and non-parametric linkage analysis was performed too.

Results: Here, we report an interesting family with five affected individuals with a novel splice site mutation (c.1107+1delGTA) in *ALDH3A2*.

Conclusion: In absence of capability to measure FALDH activity in Iran, DNA sequencing of the ALDH3A2 gene could lead to the identification of causative mutation and confirm the diagnosis.

Keywords: Sjogren-Larsson; Skin disease; Mutation; Iran

Introduction

Sjogren-Larsson Syndrome (SLS) was first described in 1956 in a northern Sweden family with a distinctive combination of symptoms consisting of mental retardation, congenital ichthyosis and spastic diplagia.[1,2] Shortly after that the autosomal recessive pattern of this disease in bigger cohorts was established.[1-3] Thirty years later in its initial description, the deficiency of fatty aldehyde dehydrogenase (FALDH) was identified for the disease[4,5] and accumulation of long-chain fatty alcohols and modification of macromolecules by an excess of fatty aldehydes were considered to be the pathophysiologic mechanisms causing the manifestations of SLS.[2,5] Prevalence of SLS is estimated to be 1 in every 1000 mentally retarded cases and 1 in every 2500 dermatologic cases.[6] The clinical features of SLS is developped during fetal and infantile period.[1]

The ichthyosis in SLS has been appeared at birth and it is the first visible sign in the patients. The ichthyosis is generalized and distributed through the flexure areas, neck trunk and extremities.[1,2,6] Erythematous appearance of the skin is often observed in early life and it has a pruritic character.[1] The face is mostly spared.[1] Hair and nails are usually normal. Dermatographic alterations (e.g., simian creases, palmar hyperlinearity) and dental abnormalities like enamel hypoplasia may be seen.[1,6] Neurologic symptoms appear

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during the first two years of life and consist of delay in motor milestone development, spastic diplagia or tetraplagia also; it is more severe in the lower limbs than in other parts of the body.[1,2,7] Fifty percent of patients are unable to walk and in 40% of patients, seizure has been reported.[1] In addition, cognitive deficit and some degree of mental retardation (mild to profound) have been reported in the majority of patients, however some cases have rarely been found with normal intelligence.[1,5,7] Other clinical features including Speech delay and dysarthria are commonly reported. Ophthalmologic manifestations may include glistening white dots, photophobia and myopia.[1,2,5,7] Although retinal inclusions are a particular feature for SLS but it has not been observed in all reported patients.[1] Brain MRI shows white matter changes and magnetic resonance spectroscopy (MRS) reveal an unusual lipid peak in myelin sheath.[1,8]

Lipid accumulation may lead to alteration of the epidermal water barrier and increased transepidermal water loss, subsequently leading to ichthyosis. SLS is caused by mutations in the aldehyde dehydrogenase 3A2 isoform 2 (*ALDH3A2)* gene that encodes fatty aldehyde dehydrogenase (FALDH). This gene is mapped to chromosome 17p11.2 with 31kb length.[9] It consists of 11 exons that are numbered 1-10 with an additional exon (exon9) located between exon 9 and 10.[9]

Here we report on an Iranian consanguineous family with five mentally retarded individuals including three males and two females (Figure 1) that referred to Genetics Research Center at University of Social Welfare and Rehabilitation Sciences (USWR) in Tehran. Consent form was obtained from the parents, according to the guidelines of local ethic committee of this university. All patients were the product of a normal uneventful term pregnancy. Three out of 5 patients were triplet (a pair of monozygote boys and one heterozygote girl) and the other two were a 34-year-old female and an 18-year-old male. Their parents were first cousin. All affected individuals had severe to profound mental retardation, marked ichthyosis, generalized pruritis on face, trunk and extremities (Figure 2). Severe hyperkeratosis was observed on the palms and soles. The flexures were involved and showed lichenification. The hair and nails were normal and the teeth showed no abnormalities. Neurological symptoms had been started from their infantile period (1-2 years of old) and consist of motor milestone delay due to spastic diplagia. The triplet sibs had more severe spastic diplagia (started around one year of old) and they were never able to walk, while the other two siblings got completely disabled around the age of 15 years. No history of seizure had been reported in all of the patients. Cognitive deficits of the affected individuals, was then measured by standard Wechsler test and they had an average IQ of 15 -35. The triplet affected sibs showed more severity in their cognitive impairment (IQ 20) in comparison with the other two siblings. They also were never able to talk, whereas the other two affected patients had speech delay and dysarthria. In fundoscopy, the retina showed no glistering white dots, which is a pathognomic feature for this neuro-cutaneous disease, although they suffered from photophobia, they did not cooperate for performing Brain MRI.

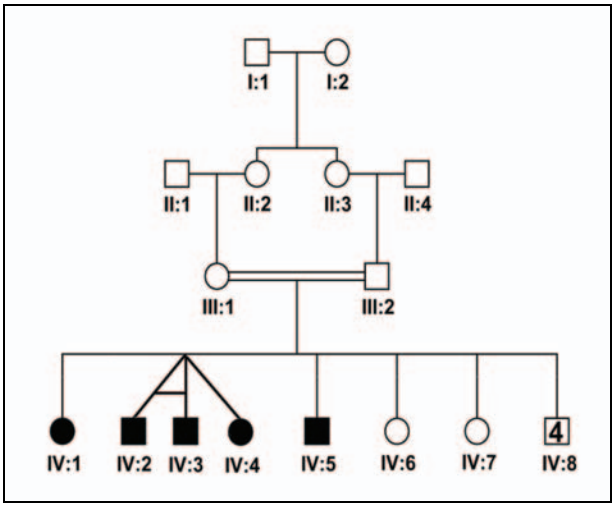

Fig. 1: Pedigree structure of studied family.

Materials and Methods

DNA was extracted from peripheral blood of all the five patients (IV: 1-5), one healthy sibling (IV: 6) and their parents (III: 1 and III: 2) using standard procedures. SNP genotyping was performed using the GeneChip® Mapping 250K Nsp Assay following the protocol of the manufacturer. We performed multipoint linkage analyses, using the Genehunter, Allegro and Merlin software, by assuming a fully penetrated autosomal recessive trait with a disease frequency of 0.001 and no phenocopies. Additionally, non-parametric linkage analysis was performed. Constructed haplotypes by Merlin and Allegro software were visualized using the Haplopainter software. Details of data preparation and quality controls have been published elsewhere.[7] This study was conducted

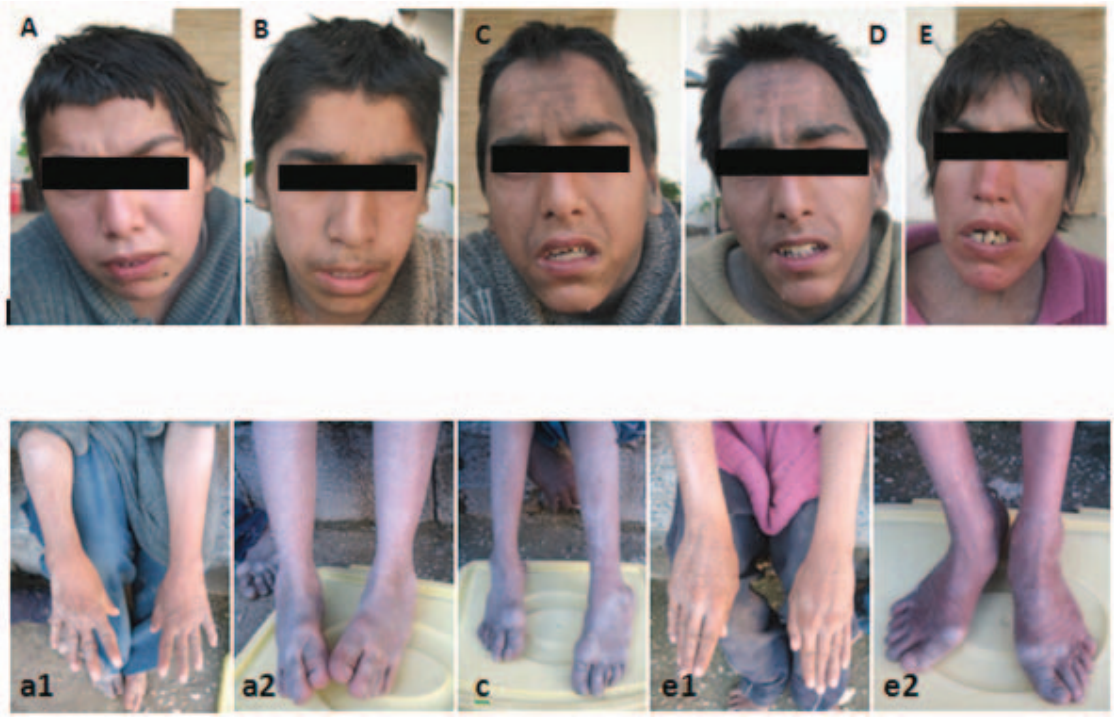

Fig. 2: A-E, facial aspects of affected family members; a1-e2, ichthyosis of the extremities of three affected individuals (a, c, e).

with the approval of the Ethical Committee of University of Social Welfare and Rehabilitation Sciences.

Results

We found single interval on chromosome 17p11.2-q11.2 with a maximum parametric and non parametric LOD scores of 3.2 and 10.3 respectively (Figure 3).

As this region included the *ALDH3A2,* we checked all the exons and exon-intron boundaries of this gene for mutations by direct sequencing and found a c.1107 +1delGTA mutation, which deletes the first three nucleotides after exon 7 (Figure 4). This change destroys the donor-splicing site for exon 7 which can lead to the skipping of exon 7 or retention of intron 7. All affected members were homozygote for the mutation whereas parents who were carriers and the healthy siblings were either carries or homozygously normal.

Discussion

SLS is an autosomal recessive neurocutaneous disorder characterized by severe MR, spastic di-or tetraplegia and congenital ichthyosis.[1,10,11] Ichthyosis is usually evident at birth; neurologic symptoms appear in the first two years of life. The average IQ in most patients is less than 60.[11] Additional clinical features include glistening white spots on the retina, seizures, short stature and speech defects.[1,10,11]

As it mentioned before, there was phenotype variation between our patients. The triplet sibs had more severe spastic diplegia and showed more severity in cognitive impairment in comparison with the other two siblings. Phenotypic variation had been observed among affected siblings with the same mutation in previous studies too.[5,9] This variation suggests there may be unknown genetic or environmental factors that act as a compensating mechanism for the responsible biochemical defect.[5]

The presence of glistening white dots around the macular region of retinal can be seen in 1/3 of the patients. This appears late in life time.[12] Such finding was not observed in our cases. The early diagnosis is easily possible since only cutaneous symptoms are seen at birth. Newborns present ichthyosis followed by neurologic symptoms. The diagnosis can be confirmed by very low level of FALDH activity in skin

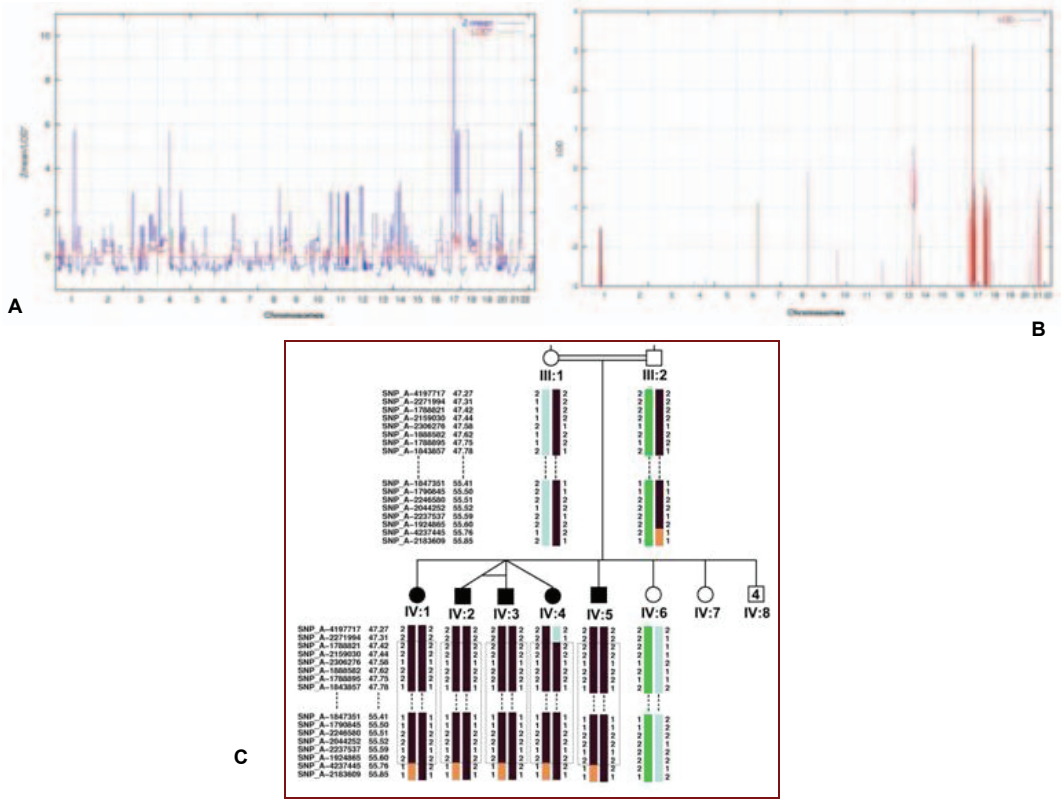

Fig. 3: Whole genome parametric (A) and non-parametric (B) linkage results (Merlin software) and haplotype of the only linkage interval with significant parametric and non-parametric LOD scores of 3.2 and 10.3 respectively (C). About 10 subsequent markers from both ends of the interval and the first adjacent heterozygous SNPs are shown.

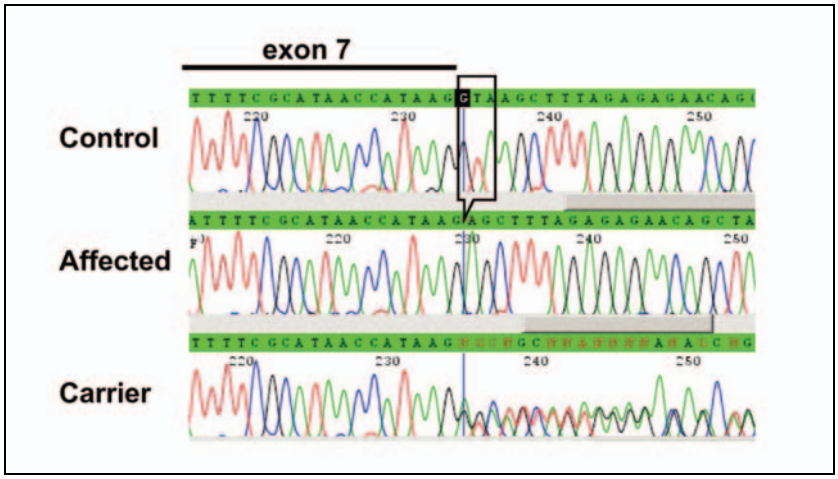

Fig. 4: Sequence chromatogram of the c.1107 +1delGTA mutation in ALDH3A2. chromatograms for the region containing the mutation in a control (Control), a patient (Affected) and one of the parent (Carrier) are shown.

fibroblasts. Very high prevalence of SLS has been observed in north east of Sweden where an incident of 8.3:100,000 births have been reported.[3] SLS has been reported in many different populations worldwide, but no other clusters of patients have been reported elsewhere. Overall, its prevalence is estimated as 0.4 per 100,000 or lower.[6] However, there are no data on its frequency in the Iranian population. The

mutation in the gene for FALDH has been reported as nucleotide substitutions to splicing defects and small insertions of deletions. In patient with European origin, the 943C>T mutation and 1297-1298delGA mutation are responsible for a large part of identified mutations. The 943C>T mutation result in the substitution of serin for the highly conserved proline at position 315 in the FALDH protein.[9] Although insertion mutations are rarely found in SLS, deletion mutations are quit common in this syndrome. We found a c.1107+delGTA mutation in ALDH3A2 gene, in which deletion of the first three nucleotides of intron 7 (Figure 4) has been occurred. The presence of the c.1107+delGTA deletion in our five patients with the classic features of SLS supports its pathogenic significance. Most of the reports on molecular finding of SLS published so far were with no phenotypes details. However some reports indicated that the slight differences between patients could be found. There are few studies comparing the clinical disease among patients with the same ALDH3A2 genotype, either within or across kindreds. In our patients, despite identical ALDH3A2 genotypes in our family, triplet affected showed more severity in their cognitive impairment as well as speech problems in comparison with the other two siblings. The same results observed in six siblings of a consanguineous Arab family with early childhood-onset SLS who carry the homozygous 682C>T mutation in exon 5 of ALDH3A2 gene. In absence of capability to measure FALDH activity in Iran, DNA sequencing of the ALDH3A2 gene could lead to the identification of causative mutation and confirm the diagnosis. The wide variety of mutation in SLS, however, complicated efforts to develop simple DNA screening methods for the routine diagnosis of this disease.

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Conflict of interest: None declared.

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