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Coexistence of Two Rare Autosomal Recessive Disorders: Activation-Induced Cytidine Deaminase Deficiency and Sjogren-Larsson Syndrome

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Activation-induced cytidine deaminase (AID, gene *AICDA*) is a DNA editing protein which plays an important role in three major events of immunoglobulin (Ig) diversification: somatic hypermutation, class switch recombination (CSR) and Ig gene conversion [1]. Inborn errors in *AICDA* result in the rare autosomal-recessive (AR) primary immunodeficiency disorder (PID) hyper-IgM syndrome type 2 (HIGM2 or AID deficiency, MIM#605258), which is characterized by normal or elevated serum IgM levels, absence of IgG, IgA, and IgE, and results in lymphoid hyperplasia and profound susceptibility to bacterial infections [1]. Sjogren-Larsson syndrome (SLS, MIM#270200) is also a rare AR disorder, manifested by a clinical triad of ichthyosis, mental retardation and spastic diplegia. It is caused by a deficiency of fatty aldehyde dehydrogenase (FALDH), an enzyme that induces oxidation of fatty aldehyde to fatty acid and is encoded by the *ALDH3A2* gene [2].

We report here the coexistence of HIGM2 and SLS in the same consanguineous pedigree. The combined phenotype of both disorders was an obstacle to obtaining the diagnosis. This was overcome by clinical awareness to the unique phenotype of SLS and by the use of the whole-exome sequencing (WES) technique.

PATIENT DESCRIPTION

Patient 1 (PIV1) is a 6 year old boy, the second of two children born to consanguineous Arab parents [Figure 1A]. Since early childhood he suffered from recurrent otitis media and pneumonia. During the first year of life, his skin became dry and he was diagnosed with ichthyosis. His motor and language development was delayed, as he started walking independently at 3.6 years and

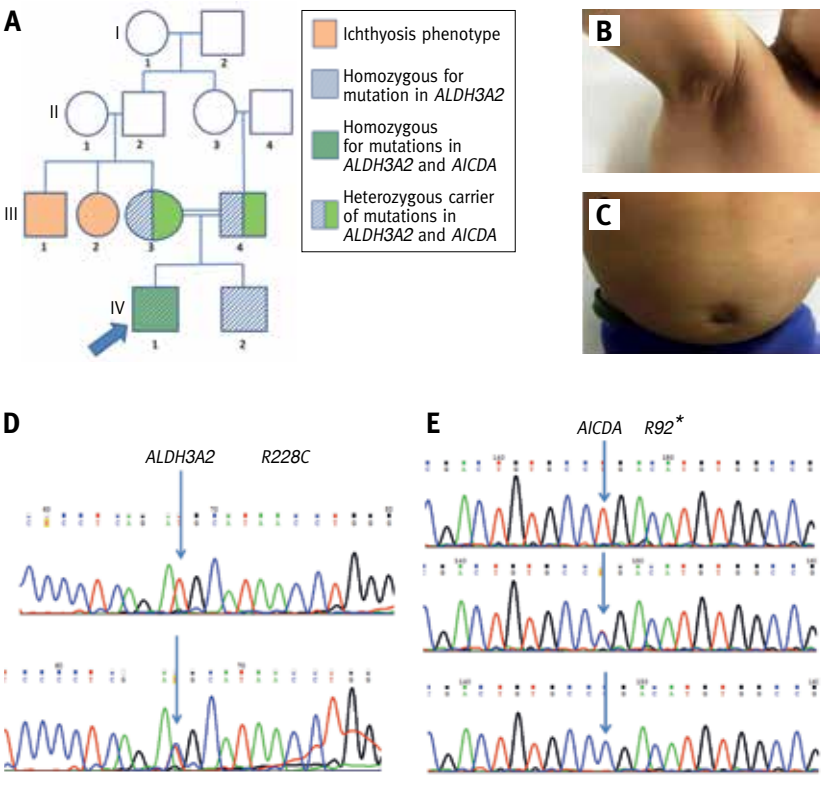

Figure 1. [A] Family pedigree of the patients. Note consanguinity. PIV1 and PIV2 are homozygous to mutation in *ALDH3A2*. PIV1 is also homozygous for mutation in *AICDA*. Both parents are heterozygous carriers of these mutations. PIII1 and PIII2 have ichthyosis with no clear diagnosis of Sjogren-Larsson syndrome. **[B & C]** Cutaneous finding in the patients. **[B]** Lichenified, hyperkeratotic and hyperpigmented plaque involving the right axilla of PIV1. **[C]** Lichenified and dry abdominal skin in PIV2. **[D & E]** Electropherograms of Sanger's sequencing analysis of the patients

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spoke only four words at the age of 4 years. He underwent bilateral tonsillectomy and adenoidectomy at age 1 year due to obstructive sleep apnea caused by enlarged tonsils and adenoids. On physical examination he was noted to have generalized xerotic skin with lichenified, brown and hyperkeratotic plaques affecting the neck, axillae, abdomen and popliteal fossae [Figure 1B]. Nails and teeth were normal. Neurological examination revealed increased deep tendon reflexes in his lower extremities and a clumsy and unstable gait without muscle wasting, consistent with spastic diplegia. At the age of 2 years he was found to have hypogammaglobulinemia, with low IgA (25 mg/dl, normal range 70–400 mg/dl), low IgG (308 mg/dl, normal range 700–1600 mg/dl), normal IgE and normal IgM levels (115 mg/dl, normal range 40–230 mg/dl). The patient's complete blood count was within normal limits. He has been maintained on monthly intravenous immunoglobulin (IVIG) therapy with clinical improvement. Any attempt to discontinue the treatment was followed by recurrence of the infections. Although a primary immunodeficiency disorder (PID) was suspected, his diagnosis was unclear and he was referred to our medical center for further evaluation.

The elder brother of PIV1 is a 7 year old boy who has suffered from ichthyosis since infancy and also has a clumsy and unstable gait. The parents denied a history of recurrent infections. On physical examination the patient had dry skin with dark, lichenified plaques over the neck, axillae, abdomen, antecubital and popliteal fossae [Figure 1C]. Neurological examination was consistent with spastic diplegia. Immunoglobulin levels were normal.

The parents reported that the maternal uncle and aunt were known to have ichthyosis. Since the combined phenotype of PID due to hypogammaglobulinemia, ichthyosis and neurological abnormalities has not been previously described, WES was utilized in search of the causing gene/genes. Whole-exome sequencing of genomic DNA of PIV1 was performed at Otogenetics Corporation (USA) using the Roche NimbleGen V2 (44.1 Mbp) paired-end sample preparation kit and Illumina HiSeq2000 at a 50x coverage. Sequence reads were aligned to the human genome reference sequence (build hg19) and variants were called and annotated using the DNAnexus software package. We assumed an autosomal-recessive (AR) mode of inheritance and searched for homozygous mutations associated with hypogammaglobulinemia and ichthyosis. A novel homozygous nonsense mutation (c.274C>T, R92X) in *AICDA* was identified in PIV1. The mutation causes early termination of transcription and results in a truncated protein. It is not listed in dbSNP (www.ncbi.nlm.nih.gov/SNP), 1000 Genomes (www.1000genomes.org) or the EXAC Genome Browser (exac.broadinstitute.org). The Mutationtaster software tool (http://www.mutationtaster.org) predicts that this mutation causes disease, with a score of 1. Sanger sequencing performed on the ABI 3130 automated genetic analyzer (Applied Biosystems, Foster City, CA, USA) confirmed the presence of the mutation in a homozygous state in PIV1 and in a heterozygous state in the parents [Figure 1D & E]. PIV2 was not found to carry this mutation. A homozygous missense mutation in *ALDH3A2* (c.682C>T, R228C, rs72547566) was identified in both PIV1 and PIV2. This is a known disease causing mutation of SLS (HGMD accession number CM993310). Sanger sequencing confirmed that the mother and father are heterozygous for the mutation.

COMMENT

In this study we present a family with two rare and unrelated AR disorders. The combination of hypogammaglobulinemia with lymphoid hyperplasia, ichthyosis and neurological abnormalities has not been previously reported. Its coexistence in a single patient (PIV1), originating from a consanguineous family, raised the possibility that a novel monogenic AR disease may be responsible for this unusual phenotype. His brother, PIV2, could have been oligosymptomatic for this disorder. However, the unique clinical association of ichthyosis, mainly affecting flexures, with spastic diplegia seen in SLS, led us to suspect that PIV1 was manifesting a combined phenotype of SLS and a PID. Meticulous clinical characterization together with WES allowed us to focus our search on specific genes and show that the cause of PIV1's immunological, cutaneous and neurological abnormalities stem from two separate homozygous mutations in *AICDA* and *ALDH3A2* genes, causing a combined phenotype of HIGM2 and SLS, respectively. PIV2 was shown to suffer only from SLS.

To the best of our knowledge this is the first description of an associated phenotype of HIGM2 and SLS. In HIGM2, there is a defect in the ability of B cells to undergo class switch recombination (CSR) and somatic hypermutation. AID is expressed by B cells and deaminate cytosines from exposed single strands of DNA, which are essential for triggering both CSR and somatic hypermutation. The absent or low serum IgG, IgE and IgA levels in these patients can be explained by the intrinsic inability of activated B cells to undergo class switch recombination [3]. Patients suffering from HIGM2 tend to develop lymphoid hyperplasia. This is thought to result from continuous proliferation of B cells by antigen in the absence of successful Ig somatic mutation [3]. The patient described here (PIV1) presented an immunological phenotype consistent with HIGM2 syndrome. He was found to be homozygous for a novel nonsense mutation in *AICDA*, expected to produce a truncated non-functional protein, resulting in AID deficiency.

SLS results from a deficiency of fatty aldehyde dehydrogenase, encoded by *ALDH3A2,* which metabolizes fatty aldehydes to fatty acids. Defective fatty aldehyde causes accumulation of fatty aldehydes, fatty alcohols and related lipids in keratinocytes. This results in abnormal formation of lamellar bodies in the stratum granulosum and impaired delivery of their precursor membranes to the stratum corneum. The epidermal water barrier is disrupted and ichthyosis is observed clinically, affecting mainly the neck, lower abdomen and flexures [4]. PIV1 and PIV2 presented flexural ichthyosis accompanied

by spastic diplegia and in PIV1 also by developmental delay due to a homozygous mutation in *ALDH3A2,* which confirmed the diagnosis of SLS in both patients.

In populations where consanguinity is common, a corresponding increase in the frequency of AR diseases is usually found due to increased risk of homozygosity for ancestral haplotypes, which harbor pathogenic alleles. Homozygous regions associated with recessive disorders may reach approximately 11% of the genome in inbred populations [5], enabling two rare diseases to present in a single patient or pedigree. The clinical diagnosis of this state could be misleading. Careful and detailed clinical evaluation combined with the WES technique is crucial for deciphering this complex phenotype.

In conclusion, we believe this to be the first report of coexisting HIGM2 and SLS in one patient and family, revealed by the combination of a detailed phenotype and the use of WES. It further demonstrates the growing importance of WES as a powerful technology in the service of clinical genetics.

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