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Research paper

Steroid sulfatase and filaggrin mutations in a boy with severe ichthyosis, elevated serum IgE level and moyamoya syndrome

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ABSTRACT

X-linked ichthyosis (XLI) is a relatively common, recessive condition caused by mutations in the steroid sulfatase (*STS*) gene. Common loss-of-function mutations in the filaggrin gene (*FLG*) cause ichthyosis vulgaris and predispose individuals to atopic eczema. We report a case of a 6-year-old boy who presented with unusually severe XLI, an increased serum immunoglobulin E level (2120 IU/ml) and moyamoya angiopathy. Whole-exome sequencing identified a gross deletion encompassing the *STS* in Xp22.31 and the p.K4022X *FLG* mutation. The deletion is at least 1.6 Mb in size in the proband, based on real-time quantitative polymerase chain reaction results. No other genetic mutations related to ichthyosis, moyamoya or hyper-immunoglobulin E syndrome were detected. Furthermore, his mother's brothers suffered from mild XLI and only had a deletion encompassing the *STS*. Additionally, his father and older sister suffered from mild ichthyosis vulgaris and had the p.K4022X FLG mutation. We report the first case of XLI with concurrent moyamoya syndrome. Moreover, an IgE-mediated immune response may have triggered the moyamoya signaling cascade in this patient with ichthyosis. Furthermore, our study strengthens the hypothesis that filaggrin defects can synergize with an STS deficiency to exacerbate the ichthyosis phenotype in an ethnically diverse population.

1. Introduction

X-linked ichthyosis (XLI, OMIM # 30810) is a skin genetic disease characterized by widespread dark brown, polygonal scales and generalized dryness. XLI is caused by a deficiency of the enzyme steroid sulfatase (*STS*) due to *STS* mutations (Fernandes et al., 2010) (Elias et al., 2004). STS is highly expressed in the developing adult brain, and it can potentially influence neurodevelopment and ongoing brain function (Chatterjee et al., 2016).

Mutations in filaggrin (*FLG*), the gene encoding profilaggrin/filaggrin, have been demonstrated to be the underlying cause of ichthyosis vulgaris (IV; OMIM #146700) and have been shown to be an important predisposing factor for atopic dermatitis (Sandilands et al., 2006; Nemoto-Hasebe et al., 2009). IV is inherited as a semi-dominant Mendelian trait, wherein heterozygotes may have a mild sub-clinical presentation compared with homozygotes, who present with marked scaling. Moreover, as genetic modifying factors, *FLG* mutations that exacerbate XLI have been reported in 2 families (Liao et al., 2007; Ramesh et al., 2011).

Moyamoya disease (OMIM # 607151) is an idiopathic cerebral vasculopathy characterized by progressive stenosis of the terminal portion of the internal carotid arteries and the development of a

Abbreviation: ACA, anterior cerebral artery; CD, cluster of differentiation; *FLG*, filaggrin gene; Ig, immunoglobulin; IV, ichthyosis vulgaris; MCA, middle cerebral artery; MR, magnetic resonance; qPCR, quantitative polymerase chain reaction; RCN, relative copy number; *STS*, steroid sulfatase; WES, whole exome sequencing; XLI, X-linked ichthyosis

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Fig. 1. Clinical appearance of severe XLI in a boy
A, B: The proband had severe, widespread and hyperpigmented ichthyosis.

network of abnormal collateral vessels (Scott and Smith, 2009). Moyamoya syndrome may be caused by acquired factors (e.g., cranial irradiation) or related to clinically well-characterized genetic diseases (e.g., Alagille syndrome, Noonan syndrome, Neurofibromatosis type 1, Down syndrome, Turner syndrome, and Costello syndrome) (Guey et al., 2015). However, moyamoya syndrome has not previously been described in ichthyosis patients.

2. Subjects and methods

2.1. Case presentation

The proband was a 6-year-old boy who presented to our hospital with a history of ichthyosis diagnosed at 4 months of age and who had experienced a recurrent motor weakness in the left upper and lower extremities at age 4. Dark scales on the head, trunk and limbs were observed (Fig. 1). He also suffered from rhinitis. No other clinical findings, such as corneal opacities, anosmia, cerebellar ataxia, cryptorchidism, or mental retardation, were observed. The history of a similar skin condition in the patient's male maternal relatives helped establish the diagnosis of XLI (Fig. 2). X-ray, abdominal ultrasound, echocardiogram, coagulation and autoantibody studies as well as thyroid function were normal. Immunoglobulin (Ig) and cytokine studies identified a high level of serum IgE at 2120 IU/ml (normal 0–200 IU/ml) and interleukin (IL)-6 at 17 pg/ml (normal 0–3.4 pg/ml). The IL-8, IL-1B and IL-10 levels were normal. Lymphocyte subgroup detection showed a slight decrease in cluster of differentiation (CD)3 + and CD4 + -T lymphocyte (23.51%). CD3 + and CD8 + -T lymphocyte, CD3- and CD19 + -B lymphocyte, CD3-cell, and CD16 + 56 + natural killer cell levels were normal. Brain magnetic resonance (MR) imaging and MR angiography confirmed a normal parenchyma with marked steno-occlusive lesion at the bilateral internal carotid artery terminus. MR perfusion showed delay in the mean transit time of the bilateral frontal, right temporal and occipital lobes. Initial carotid angiography revealed right occlusion of the proximal anterior cerebral artery (ACA) and middle cerebral artery (MCA), left severe narrowing of the proximal ACA, and the formation of mild moyamoya vessels (Fig. 3). Due to a lack of an underlying diagnosis in the setting of a complex phenotype, including XLI, increased serum IgE level, moyamoya and rhinitis, clinical whole-exome sequencing (WES) was performed.

2.2. Other subjects

The patient's mother and older sister are clinically unaffected, but his father and oldest sister have dry skin and subtle signs of IV. Moreover, one of his mother's brothers suffered from mild XLI. Magnetic resonance angiography and serum Ig tests were performed on these relatives. Blood samples were collected from the relatives after

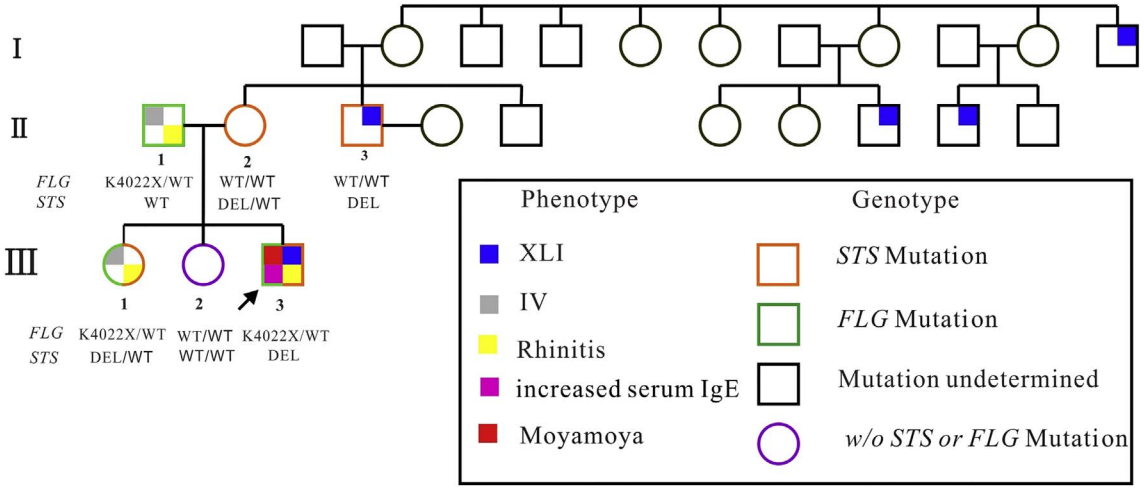

Fig. 2. Family pedigree with classical X-linked recessive inheritance
Disease and mutation statuses are indicated in the figure key. Circles represent women, squares represent men, and arrowheads indicate the proband in the family. The phenotype and genotype are coded and correlate with the figure key.