



Research paper

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



Qian Zhang^{a,b,c,d,1}, Nuo Si^{e,1}, Yaping Liu^e, Dong Zhang^{a,b,c,d}, Rong Wang^{a,b,c,d}, Yan Zhang^{a,b,c,d}, Shuo Wang^{a,b,c,d}, Xingju Liu^{a,b,c,d}, Xiaofeng Deng^{a,b,c,d}, Yonggang Ma^{a,b,c,d}, Peicong Ge^{a,b,c,d}, Jizong Zhao^{a,b,c,d,*}, Xue Zhang^{e,**}

^a Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, China 6 Tiantanxili, DongCheng District, Beijing 100050, China

^b China National Clinical Research Center for Neurological Diseases, Beijing, China

^c Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China

^d Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, China

^e McKusick-Zhang Center for Genetic Medicine, State Key Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College, 5 Dong Dan San Tiao, Beijing 100005, China

ARTICLE INFO

Keywords:

X-linked ichthyosis
Ichthyosis vulgaris
Steroid sulfatase
Filaggrin
Moyamoya
Immunoglobulin E

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

* Corresponding author at: Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, China 6 Tiantanxili, DongCheng District, Beijing 100050, China.

** Corresponding author.

E-mail addresses: sinuol02@126.com (N. Si), ypliu_pumc@163.com (Y. Liu), zhangdong0660@aliyun.com (D. Zhang), Ronger090614@126.com (R. Wang),

YanZhang135@163.com (Y. Zhang), captain9858@vip.sina.com (S. Wang), liuxingju006@163.com (X. Liu), windmessenger@126.com (X. Deng), mayonggang12345@163.com (Y. Ma), gepeicong@163.com (P. Ge), zhaojz205@163.com (J. Zhao), xuezhang@pumc.edu.cn (X. Zhang).

¹ These authors contributed equally to this work.

<http://dx.doi.org/10.1016/j.gene.2017.07.030>

Received 23 April 2017; Accepted 10 July 2017

Available online 12 July 2017

0378-1119/ © 2017 Elsevier B.V. All rights reserved.



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

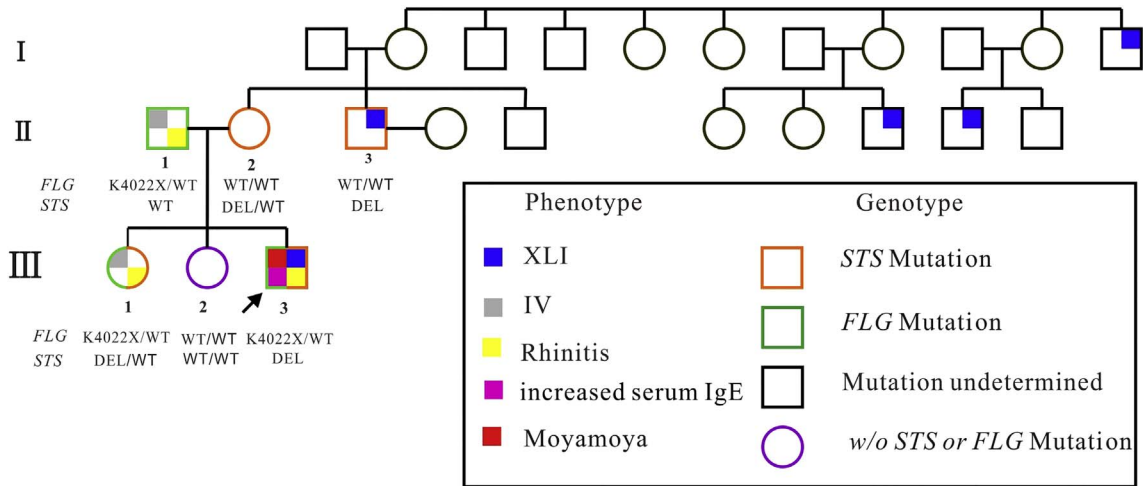


Fig. 2. Family pedigree with classical X-linked recessive inheritance
Disease and mutation statuses are indicated in the figure key. Circles represent women, squares represent men, and arrowheads indicate the proband in the family. The phenotype and genotype are coded and correlate with the figure key.

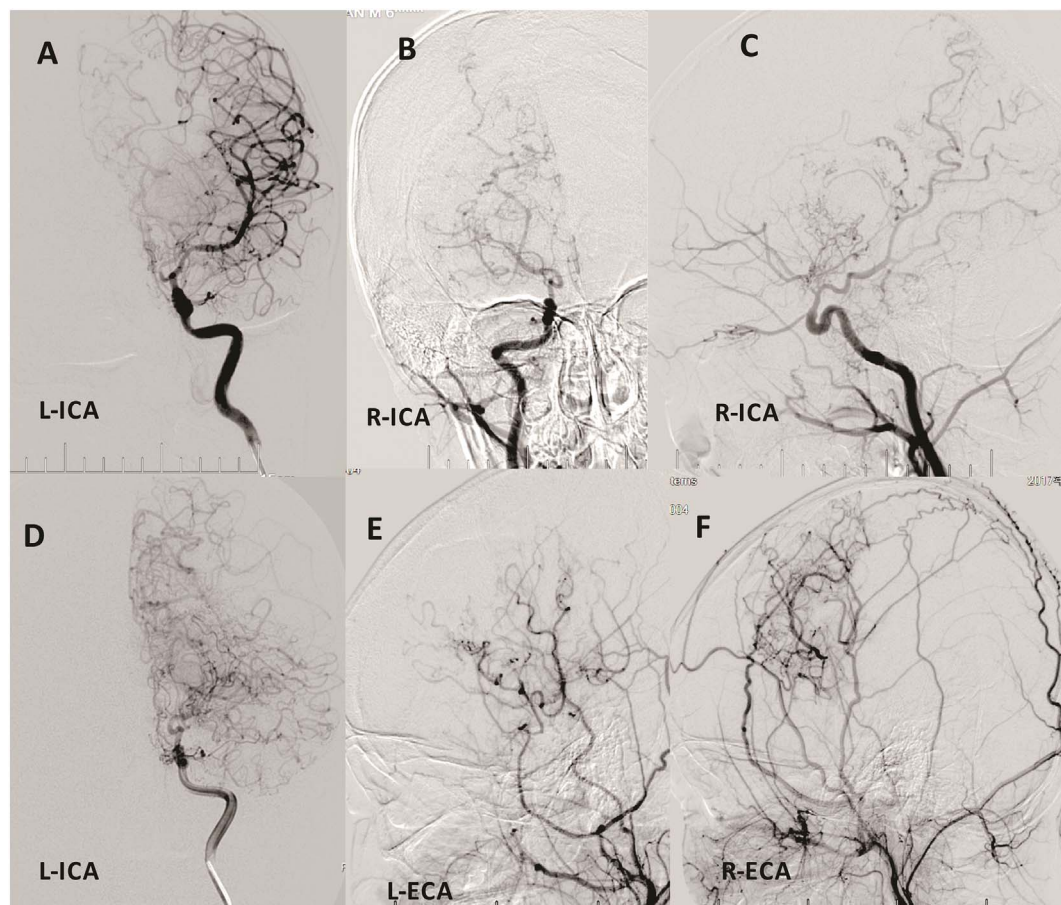


Fig. 3. Preoperative and follow-up angiographic images

A: Preoperative anteroposterior view of the left carotid angiogram showed complete occlusion of the left ACA and mildly developed moyamoya vessels. B, C: Anteroposterior and lateral views of the right carotid angiogram demonstrate the occlusion of the right MCA and ACA at their proximal locations as well as moyamoya vessels. D: Six months later, follow-up carotid angiography revealed left rapid progression and formation of collateral moyamoya vessels in the MCA region. E, F: Angiographic image after surgical treatment of the patient showed abundant filling of the bilateral MCA region by the external carotid arteries.

written informed consent was obtained. The Ethics Committee of Beijing Tiantan Hospital, Capital Medical University approved the study. Written consent was obtained from the parents for the publication of photographs.

2.3. Genotyping

Genomic DNA from the subjects was extracted from blood leukocytes using a QIAamp blood kit (QIAGEN, Hilden, Germany). WES was performed on an Illumina HiSeq 2000 platform by BGI (Shenzhen, China). Coverage of the target region is 99.4% and the fraction of the target covered at least $20\times$ is 97.6%. (The detailed experimental pipeline and result of WES are available.) A point mutation in *FLG* was confirmed by Sanger sequencing, while a gross deletion encompassing *STS* was identified by real-time quantitative polymerase chain reaction (qPCR) in the proband and other available family members.

3. Results

3.1. Clinical findings

An indirect revascularization of the boy's right hemisphere was first performed. Six months after his first surgery, carotid angiography revealed abundant filling of the right MCA region by the external carotid artery as well as rapid progression of left hemisphere (Fig. 3). A left-sided pial-synangiosis was performed with an uncomplicated post-operative course. In the follow-up period of 6 months after his second

surgery, he had no further ischemic events. The patient's relatives were free of cerebral vascular disease, stroke and increased serum IgE levels.

3.2. Genetic results

WES suggested a gross deletion encompassing the *STS* in Xp22.31. The deletion was at least 1.6 Mb in length in the proband according to real-time qPCR results. The left and right breakpoints were harbored in 11 kb and 38 kb regions, respectively (Fig. 4). A gross deletion was also detected in three family members, including the proband's mother, oldest sister and uncle. Meanwhile, WES detected a nonsense mutation in *FLG* (c.1206A > T, p. K4022X). In addition to the proband, a nonsense mutation was also identified in his father and oldest sister, but the mutation was not detected in other relatives (Fig. 5). The mutation was documented as pathogenic for psoriasis and atopic dermatitis in the human gene mutation database. It was also observed in 167/8652 alleles in the Exome Aggregation Consortium database, and all mutation carriers were of East Asian origin. No other gene mutation related to ichthyosis (*TGM1*, *ALOX12B*, *ALOXE3*, *ABCA12*, *CYP4F22*, *NIPAL4*, *LIPN*, *CERS3*, *PNPLA1*, *ST14*, *FATP4* or *ABHD5*), moyamoya (*RNF213*, *ACTA2*, *GUCY1A3* or *BRCC3*) or hyper-immunoglobulin E syndrome (*STAT3*, *DOCK8*, *PGM3*, *SPINK5* or *TYK2*) were detected (Nomura et al., 2009; Ben Khelifa et al., 2013; Maruthappu et al., 2014; Guey et al., 2015; AlKhater, 2016; Zhang et al., 2017).

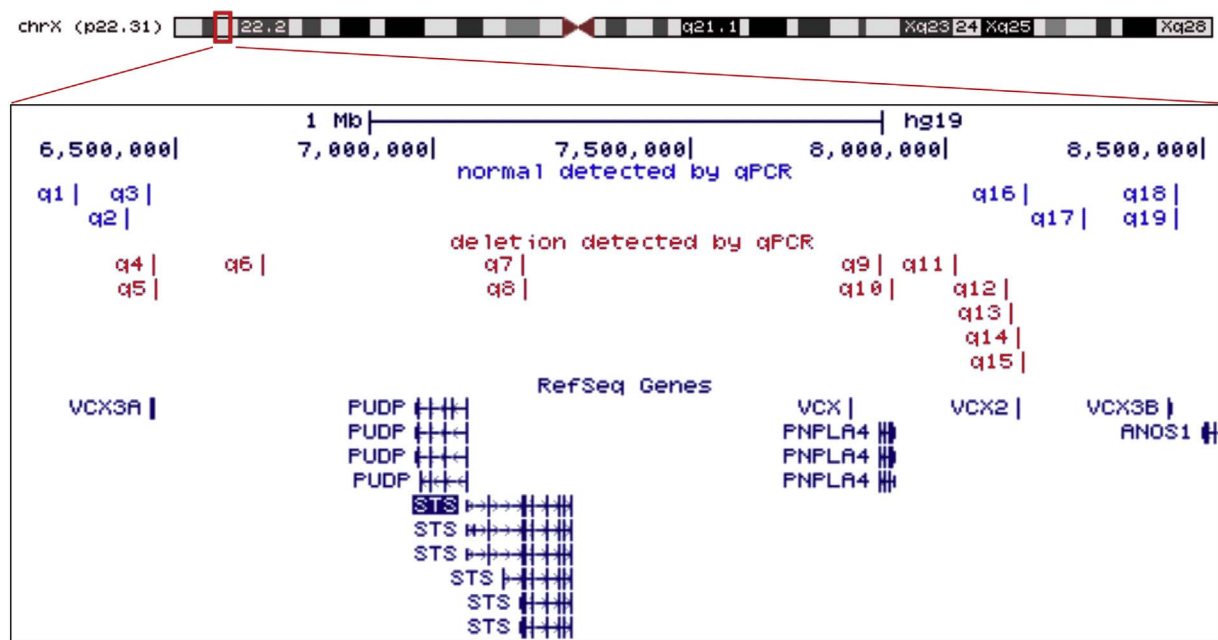


Fig. 4. Schematic diagram of the gross deletion identified by quantitative polymerase chain reaction (qPCR). Positions of the RefSeq genes and qPCR amplicons (q1–q19) are shown. qPCR amplicons in red represent the deletion regions in the proband, while the blue amplicons represent the normal regions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Our case highlights the occurrence of *STS* and *FLG* mutations in a boy with severe ichthyosis, an increased serum IgE level and moyamoya angiopathy. Functionally, *STS* deficiency impacts the biogenesis of stratum corneum lipids (Elias et al., 2008), whereas filaggrin haploinsufficiency or complete deficiency impacts the protein components of the stratum corneum (Sandilands et al., 2009). Therefore, one would

predict that *FLG* and *STS* mutations would be additive and lead to a more severe phenotype due to deficiencies in both the protein and lipid components of the skin barrier, as previously suggested (Liao et al., 2007; Ramesh et al., 2011). The boy in our study was a heterozygous carrier of the p.K4022X *FLG* mutation and an *STS* deletion. Moreover, his father and oldest sister had a p.K4022X heterozygous mutation and suffered from mild IV; the mutation was absent in his uncle, who presented with milder, more typical XLI. Of note, immunohistochemical

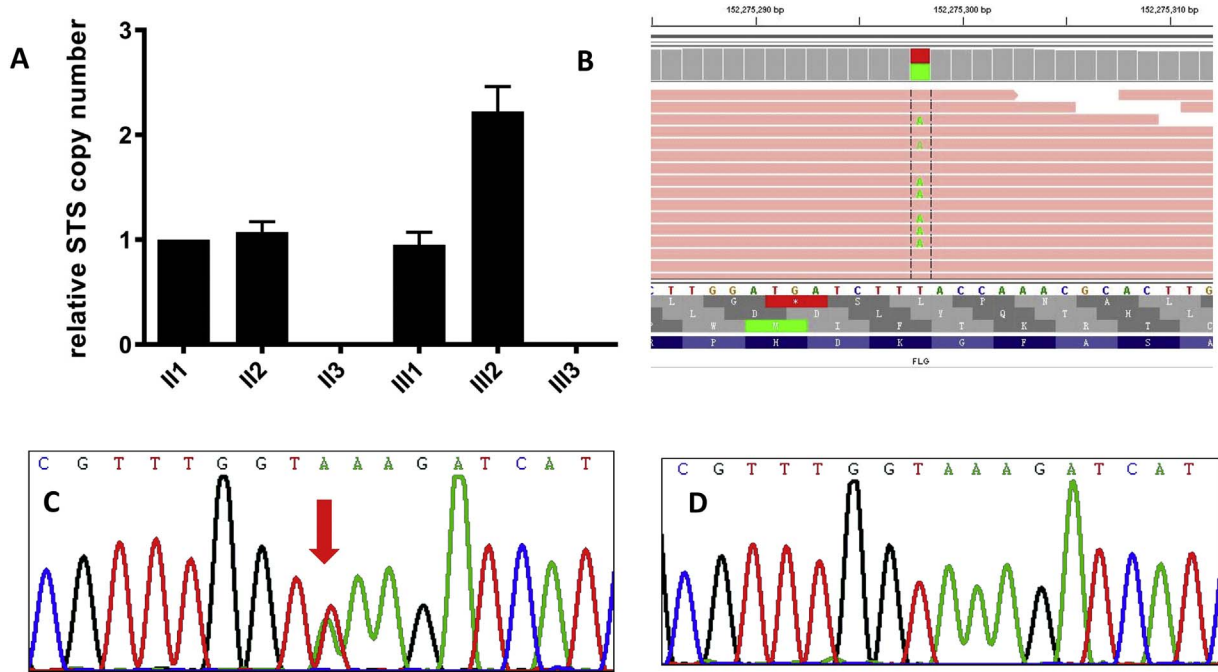


Fig. 5. Genetic findings in the family with ichthyosis and moyamoya. A: Relative copy number (RCN) changes tested with primers in *STS* using a qPCR assay. RCN was determined based on the comparative $\Delta\Delta CT$ method with the male family member (III1) as the calibrator. A normal male (RCN = 1), normal female (RCN = 2), affected male (RCN = 0) and affected female (RCN = 1) are shown. B: WES results of the proband via IGV viewer. The *FLG* mutation c.1206A > T (p. K4022X) was detected as demarcated by dotted lines. C, D: *FLG* sequencing results in carriers (left) and non-carriers (right) in the family. The red arrow indicates the *FLG* mutation (c.1206A > T, p. K4022X). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

staining for filaggrin revealed that the p.K4022X mutation contributes to a remarkable reduction in filaggrin protein expression in patients' epidermis (Nemoto-Hasebe et al., 2009). The *FLG* mutations R501X and 3672del4, which exacerbate XLI, were reported to be genetic modifying factors in a Scottish boy and an Indian girl (Liao et al., 2007; Ramesh et al., 2011). The presence of population-specific *FLG* mutations in European, Japanese, Korean and Chinese populations has been reported (Palmer et al., 2006; Hsu et al., 2009; Nemoto-Hasebe et al., 2009; Nomura et al., 2009; Hu et al., 2012; On et al., 2017). Moreover, R501X, 3672del4 and p.K4022X mutations all occurred in exon 3 of *FLG*, which codes for the majority of the polyprotein profilaggrin, consisting of 10–12 tandem repeats of the 37-kDa filaggrin peptide (Hsu et al., 2009; Nemoto-Hasebe et al., 2009; On et al., 2017). Our results and previous reports support the hypothesis that filaggrin defects can synergize with an STS deficiency to exacerbate the ichthyosis phenotype in ethnically diverse populations.

In our study, the boy and his oldest sister, who carried a heterozygous p.K4022X mutation, suffered from rhinitis. This finding was in line with previous results indicating that p.K4022X in the C-terminal imperfect filaggrin repeat is a predisposing factor for atopic dermatitis (Palmer et al., 2006; Nemoto-Hasebe et al., 2009). Epicutaneous sensitization with a protein allergen has been shown to induce a Th2-type immune response with concomitant high IgE production in mice (Palmer et al., 2006). These findings in mice imply that the presence of a heritable defect in the skin barrier may lead to increased susceptibility to transepidermal allergen transfer, therefore amplifying the epidermal-driven Th2 response and provoking the onset of atopic disease (Palmer et al., 2006).

The unique moyamoya phenotype identified in the boy with severe ichthyosis raises the question of whether a common pathophysiologic mechanism exists between these two diseases. Identification of the genes involved in moyamoya disease and several monogenic moyamoya syndromes revealed different pathways that are involved in the development of moyamoya angiopathy, such as the NO-Sgc pathway (with *GUCY1A3* mutations), RAS pathway (with Neurofibromatosis type 1, Noonan, and Costello syndromes) or NOTCH pathway (with Alagille syndrome), as well as pathways involved in genomic stability (with *RNF213*, Pericentrin and other genes involved in dwarfism, or *BRCC3*) (Guey et al., 2015). However, WES did not identify mutations in the genes involved in moyamoya in the proband presented in this study. Interestingly, recent reports of central nervous system vasculitis in hyper-immunoglobulin E syndrome indicate a potential link between these two diseases (Alkhatir, 2016). Various vascular anomalies have been reported in both forms of hyper-immunoglobulin E syndrome, including aneurysms, vascular ectasia, moyamoya and vascular thrombotic events (Freeman et al., 2007). The boy in our study with a p.K4022X mutation in *FLG* suffered from severe XLI, rhinitis and an increased IgE level. Moreover, in mice sensitized with ovalbumin, cutaneous exposure of this allergen autoimmunity was caused by partial T cell deficiency, resulting in dysregulation and leading to elevated risks of developing both systemic and central nervous system vasculitis (Palmer et al., 2006). Additionally, cerebral arteriostenosis associated with elevated serum IgE levels was observed in young adults without risk factors for ischemic stroke (Guo et al., 2014). Therefore, we speculated that the IgE-mediated immune response triggered moyamoya signaling cascade in this boy with ichthyosis.

Approximately 80–90% of XLI cases are caused by complete or partial deletion of the *STS*. The typical deletion encompasses *STS* and a small number of adjacent genes (including members of the *VCX* family, *HDHD1A*, and *PLPNA4*), while larger deletions can encompass the *KAL* and *NLGN4X* (Kent et al., 2008). Larger gene deletions can be associated with symptoms of contiguous gene syndromes, including epilepsy, mental retardation, skeletal and craniofacial abnormalities, hypogonadotropic hypogonadism and anosmia (Ben Khelifa et al., 2013; Nagai et al., 2017). The deletion size of XLI in the patient presented here was at least 1.6 Mb, including the entire *STS* and nearby *VCX*,

VCX2, *PUDP* and *PNPLA4*. Ischemic symptoms and rapid progression of moyamoya were observed. This case highlights the need to recognize moyamoya syndrome in patients with ichthyosis, and early surgical revascularization should be pursued to prevent symptom progression.

5. Conclusion

Here, we report the first XLI case with concurrent moyamoya syndrome. Moreover, the IgE-mediated immune response may have triggered the moyamoya signaling cascade in this patient with ichthyosis. Early surgical intervention should be considered to prevent symptom progression later in life. Furthermore, our study strengthens the hypothesis that filaggrin defects can synergize with *STS* deficiency to exacerbate the ichthyosis phenotype in an ethnically diverse population.

Sources of funding

This study was funded by the National Science and Technology Major Project of China (2006BAI01A13, 2015BAI12B04), Program of the National Natural Science Foundation of China (81371292), Programs of Capital Medical University Basic - Clinical Cooperation (17JL44) and CAMS Innovation Fund for Medical Sciences (CIFMS) (2016-I2M-1-002).

Disclosures

None.

Acknowledgements

We thank the patients for their participation in this study.

References

- Alkhatir, S.A., 2016. CNS vasculitis and stroke as a complication of DOCK8 deficiency: a case report. *BMC Neurol.* 16, 54.
- Ben Khelifa, H., Soyah, N., Ben-Abdallah-Bouhjar, I., Gritly, R., Sanlaville, D., Elghezal, H., Saad, A., Mougou-Zerelli, S., 2013. Xp22.3 interstitial deletion: a recognizable chromosomal abnormality encompassing *VCX3A* and *STS* genes in a patient with X-linked ichthyosis and mental retardation. *Gene* 527, 578–583.
- Chatterjee, S., Humby, T., Davies, W., 2016. Behavioural and psychiatric phenotypes in men and boys with X-linked Ichthyosis: evidence from a worldwide online survey. *PLoS One* 11, e0164417.
- Elias, P.M., Crumrine, D., Rassner, U., Hachem, J.P., Menon, G.K., Man, W., Choy, M.H., Leyboldt, L., Feingold, K.R., Williams, M.L., 2004. Basis for abnormal desquamation and permeability barrier dysfunction in RXLI. *J. Invest. Dermatol.* 122, 314–319.
- Elias, P.M., Williams, M.L., Holleran, W.M., Jiang, Y.J., Schmuth, M., 2008. Pathogenesis of permeability barrier abnormalities in the ichthyoses: inherited disorders of lipid metabolism. *J. Lipid Res.* 49, 697–714.
- Fernandes, N.F., Janniger, C.K., Schwartz, R.A., 2010. X-linked ichthyosis: an oculocutaneous genodermatosis. *J. Am. Acad. Dermatol.* 62, 480–485.
- Freeman, A.F., Collura-Burke, C.J., Patronas, N.J., Ilcus, L.S., Darnell, D., Davis, J., Puck, J.M., Holland, S.M., 2007. Brain abnormalities in patients with hyper-immunoglobulin E syndrome. *Pediatrics* 119, e1121–e1125.
- Guey, S., Tournier-Lasserre, E., Herve, D., Kossorotoff, M., 2015. Moyamoya disease and syndromes: from genetics to clinical management. *Appl. Clin. Genet.* 8, 49–68.
- Guo, R., Liu, H., Li, M., Liu, L., Yang, F., Yin, Q., Xu, G., Zhang, R., Liu, X., 2014. Cerebral arteriostenosis associated with elevated serum-immunoglobulin E level in young adults without risk factors for ischemic stroke: a possible manifestation of cerebral vasculitis? *J. Clin. Neurosci.* 21, 95–99.
- Hsu, C.K., Akiyama, M., Nemoto-Hasebe, I., Nomura, T., Sandilands, A., Chao, S.C., Lee, J.Y., Sheu, H.M., McLean, W.H., Shimizu, H., 2009. Analysis of Taiwanese ichthyosis vulgaris families further demonstrates differences in *FLG* mutations between European and Asian populations. *Br. J. Dermatol.* 161, 448–451.
- Hu, Z., Xiong, Z., Xu, X., Li, F., Lu, L., Li, W., Su, J., Liu, Y., Liu, D., Xie, Z., Peng, Y., Kuang, Y., Wu, L., Zhang, J., Pan, Q., Tang, B., Chen, X., Xia, K., 2012. Loss-of-function mutations in filaggrin gene associate with psoriasis vulgaris in Chinese population. *Hum. Genet.* 131, 1269–1274.
- Kent, L., Emerton, J., Bhadravathi, V., Weisblatt, E., Pasco, G., Willatt, L.R., McMahon, R., Yates, J.R., 2008. X-linked ichthyosis (steroid sulfatase deficiency) is associated with increased risk of attention deficit hyperactivity disorder, autism and social communication deficits. *J. Med. Genet.* 45, 519–524.
- Liao, H., Waters, A.J., Goudie, D.R., Aitken, D.A., Graham, G., Smith, F.J., Lewis-Jones, S., McLean, W.H., 2007. Filaggrin mutations are genetic modifying factors exacerbating

- X-linked ichthyosis. *J. Investig. Dermatol.* 127, 2795–2798.
- Maruthappu, T., Scott, C.A., Kelsell, D.P., 2014. Discovery in genetic skin disease: the impact of high throughput genetic technologies. *Genes (Basel)* 5, 615–634.
- Nagai, K., Shima, H., Kamimura, M., Kanno, J., Suzuki, E., Ishiguro, A., Narumi, S., Kure, S., Fujiwara, I., Fukami, M., 2017. Xp22.31 microdeletion due to microhomology-mediated break-induced replication in a boy with contiguous gene deletion syndrome. *Cytogenet. Genome Res.* 151 (1), 1–4.
- Nemoto-Hasebe, I., Akiyama, M., Nomura, T., Sandilands, A., McLean, W.H., Shimizu, H., 2009. FLG mutation p.Lys4021X in the C-terminal imperfect filaggrin repeat in Japanese patients with atopic eczema. *Br. J. Dermatol.* 161, 1387–1390.
- Nomura, T., Akiyama, M., Sandilands, A., Nemoto-Hasebe, I., Sakai, K., Nagasaki, A., Palmer, C.N., Smith, F.J., McLean, W.H., Shimizu, H., 2009. Prevalent and rare mutations in the gene encoding filaggrin in Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J. Investig. Dermatol.* 129, 1302–1305.
- On, H.R., Lee, S.E., Kim, S.E., Hong, W.J., Kim, H.J., Nomura, T., Suzuki, S., Shimizu, H., Kim, S.C., 2017. Filaggrin mutation in Korean patients with atopic dermatitis. *Yonsei Med. J.* 58, 395–400.
- Palmer, C.N., Irvine, A.D., Terron-Kwiatkowski, A., Zhao, Y., Liao, H., Lee, S.P., Goudie, D.R., Sandilands, A., Campbell, L.E., Smith, F.J., O'Regan, G.M., Watson, R.M., Cecil, J.E., Bale, S.J., Compton, J.G., DiGiovanna, J.J., Fleckman, P., Lewis-Jones, S., Arseculeratne, G., Sergeant, A., Munro, C.S., El Houate, B., McElreavey, K., Halkjaer, L.B., Bisgaard, H., Mukhopadhyay, S., McLean, W.H., 2006. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat. Genet.* 38, 441–446.
- Ramesh, R., Chen, H., Kukula, A., Wakeling, E.L., Rustin, M.H., McLean, W.H., 2011. Exacerbation of X-linked ichthyosis phenotype in a female by inheritance of filaggrin and steroid sulfatase mutations. *J. Dermatol. Sci.* 64, 159–162.
- Sandilands, A., O'Regan, G.M., Liao, H., Zhao, Y., Terron-Kwiatkowski, A., Watson, R.M., Cassidy, A.J., Goudie, D.R., Smith, F.J., McLean, W.H., Irvine, A.D., 2006. Prevalent and rare mutations in the gene encoding filaggrin cause ichthyosis vulgaris and predispose individuals to atopic dermatitis. *J. Investig. Dermatol.* 126, 1770–1775.
- Sandilands, A., Sutherland, C., Irvine, A.D., McLean, W.H., 2009. Filaggrin in the frontline: role in skin barrier function and disease. *J. Cell Sci.* 122, 1285–1294.
- Scott, R.M., Smith, E.R., 2009. Moyamoya disease and moyamoya syndrome. *N. Engl. J. Med.* 360, 1226–1237.
- Zhang, Q., Liu, Y., Zhang, D., Wang, R., Zhang, Y., Wang, S., Yu, L., Lu, C., Liu, F., Zhou, J., Zhang, X., Zhao, J., 2017. RNF213 as the major susceptibility gene for Chinese patients with moyamoya disease and its clinical relevance. *J. Neurosurg.* 126, 1106–1113.