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Case Report

Expansion of Phenotype of Lanosterol Synthase-related Disease: A Case Report and Literature Review

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Abstract There are currently fewer than 14 reported families with members suffering from Lanosterol synthase (LSS)-related disease who presented with either cataract or hypotrichosis and non-obligatory mental retardation and/or ectodermal presentation. There is currently only one reported case with an intermediate phenotype of co-existing cataract and hypotrichosis. In this case report, we wish to illustrate a patient suffering from molecularly confirmed LSS-related disease with an intermediate phenotype. In addition, she also has ectodermal manifestations but without any intellectual disability.

Key words *Epidermolytic; Cataract; Hyperkeratosis; Hypotrichosis*

Clinical Report

The proband (Figure 1) was a 14 years old Chinese girl born at term after an uncomplicated pregnancy and delivery. Parents were non-consanguinous and phenotypically normal. There was no family history. She suffered from alopecia totalis since birth and developed generalised desquamation over the body and limbs (except hands and feet) at day 3-4 of life but had complete recovery at 2 months of age. At 6 months of age, she started to have recurrent episodes of desquamation that began at her fingertips and extended to involve her fingers and palms. Her toes and soles were also affected. Thick scales started to form with time and her fingers developed contractures. The clinical picture and biopsy findings were consistent with palmoplantar hyperkeratosis seen in ichthyosiform erythroderma. She also suffered from congenital cataract diagnosed at 2 months of age with lens extraction done. She had normal development and enjoyed good health otherwise. On physical examination, she had total alopecia with sparse eyebrows and eyelashes but her nails and teeth were normal. There were thick scales and desquamation over her hands and feet. There were mild joint contractures over the proximal and distal interphalangeal joints of all her fingers.

Investigations

Medical exome sequencing was performed on DNA extracted from peripheral blood of the patient. It revealed biallelic pathogenic variants in NM_001001438.2(LSS): c.818G>A (p.Trp273*) [PVS1, PM3] and c.1025T>G (p.Ile342Ser) [PM2, PM3, PP3, PP5]. The c.1025T>G (p.Ile342Ser) missense variant was previously reported but the c.818G>A (p.Trp273*) nonsense variant was novel. Parents were asymptomatic heterozygous carriers. Both variants were classified as pathogenic according to the ACMG guideline. The diagnosis of LSS-related disease was substantiated. As LSS protein is involved in the cholesterol synthesis pathway, her blood cholesterol levels were tested and revealed no decrease in cholesterol levels or its intermediates.

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Discussion

The LSS protein is involved in the biosynthesis of cholesterol, steroid hormones, and vitamin D. It catalyses the rate limiting step in the conversion of (S)-2,3-oxidosqualene into lanosterol. Mutations of the LSS protein have been reported to be associated with cataract 44 (OMIM 616509) and hypotrichosis (OMIM 618275), both inherited in the autosomal recessive manner. There are also reported patients with intellectual disability and ectodermal manifestations.[1]

Cataract was the first described phenotypical presentation for LSS-related diseases. Two families with members suffering from cataracts were found to harbour homozygous mutation of the *LSS*.[2] Subsequent in vitro and in vivo experiments proved that the LSS mutants failed to demonstrate any cyclase activity and led to a decrease in lanosterol production. The addition of lanosterol, on the other hand, helped reduce the intracellular crystalline aggregation and increase the transparency of the lens. The notion of LSS-related mutations could cause cataracts was therefore substantiated.

LSS mutations related hypotrichosis was reported by Romano et al in 2018.[3] Three families suffering from LSS-related hypotrichosis simplex were described. LSS played an essential role in hair follicle biology by encoding the

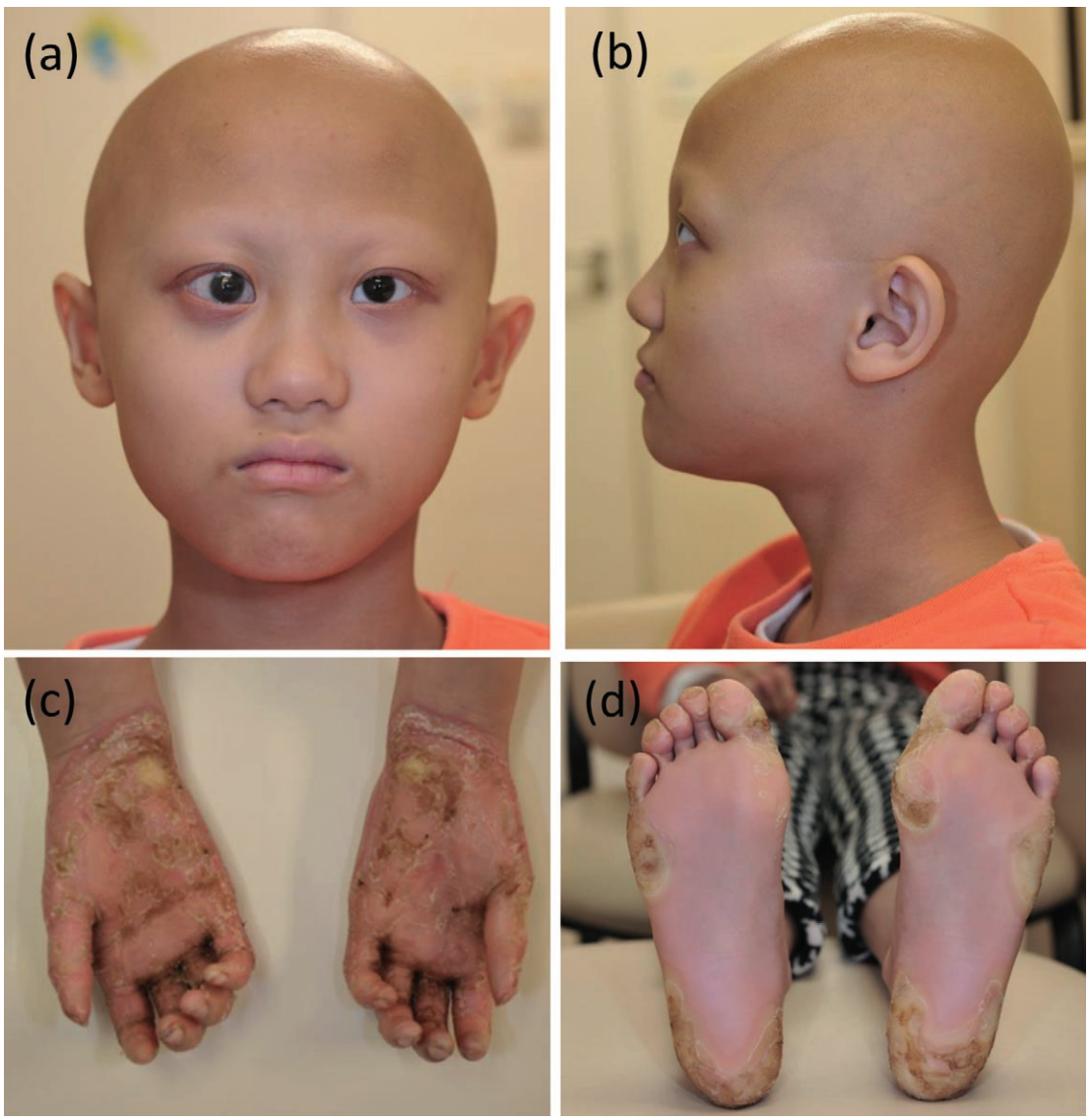

Figure 1 The proband aged at 10 years old. (a, b) Facial views showing baldness and absence of eyelashes and eyebrows. (c) Palms with hyperkeratosis. (d) Soles with hyperkeratosis.

key enzyme in the cholesterol biosynthetic pathway. It was postulated by Romano et al[3] that the mutations caused an intracellular mislocalisation of the LSS protein, leading to a degree of cell toxicity only capable of triggering hair follicle damage without disruption of other cholesterol pathways.

However, the notion of *LSS* mutation only capable of causing hypotrichosis was disproved when Besnard et al reported 7 unrelated families with members suffering from LSS-related alopecia and intellectual disability in 2019. In addition, affected individuals with LSS-mutations were also described to have variable ectodermal manifestations (e.g. ichthyosis and erythroderma), genital abnormalities (e.g. hypospadias, micropenis), visual or hearing impairment, variable neurological symptoms and abnormal MRI findings. The article concluded that defects in cholesterol biosynthesis could also lead to male genitalia anomalies and have neurodevelopmental implications.

To date, there were 13 reported families with members suffering from LSS-related diseases worldwide (Table 1). All of them have normal blood cholesterol levels except for one (Table 1). It was postulated there is an alternative pathway for cholesterol homeostasis.[2] Affected members in the same family appear to consistently exhibit same phenotype (i.e. cataract, hypotrichosis with developmental delay or hypotrichosis without developmental delay). However due to the limited number of families involved, whether this could extend to the conclusion of limited intrafamilial variation in expressivity requires further studies. Amongst all affected individuals with LSS-related disease, only one patient reported by Chen et al[4] and our patient has the intermediate phenotype, with coexisting cataract and hypotrichosis. In addition to the intermediate phenotype, our proband also has epidermolytic ichthyosis, palmoplantar type, but without intellectual disability. Interestingly, our proband and the patient reported by Chen et al[4] shared the c.1025T>G mutation. Whether this is a common mutation amongst the Chinese population and whether it contributes to a particular phenotype requires further studies. All the reported mutations appeared to be evenly distributed between the two terminals (Figure 2). It was proposed by Romano et al that the intermediate phenotype in Chen et al's reported patient might be related to the location of the respective nucleotide changes; with one variant in the N-terminus and the other more towards the C-terminus. However, in our patient, both variants were localised towards the N-terminus and thus disproves this hypothesis (Figure 2). Majority of the reported mutations were missense mutations although splice site variants and nonsense variants had also been reported as pathogenic. Further studies are required to arrive at genotype-phenotype correlations.

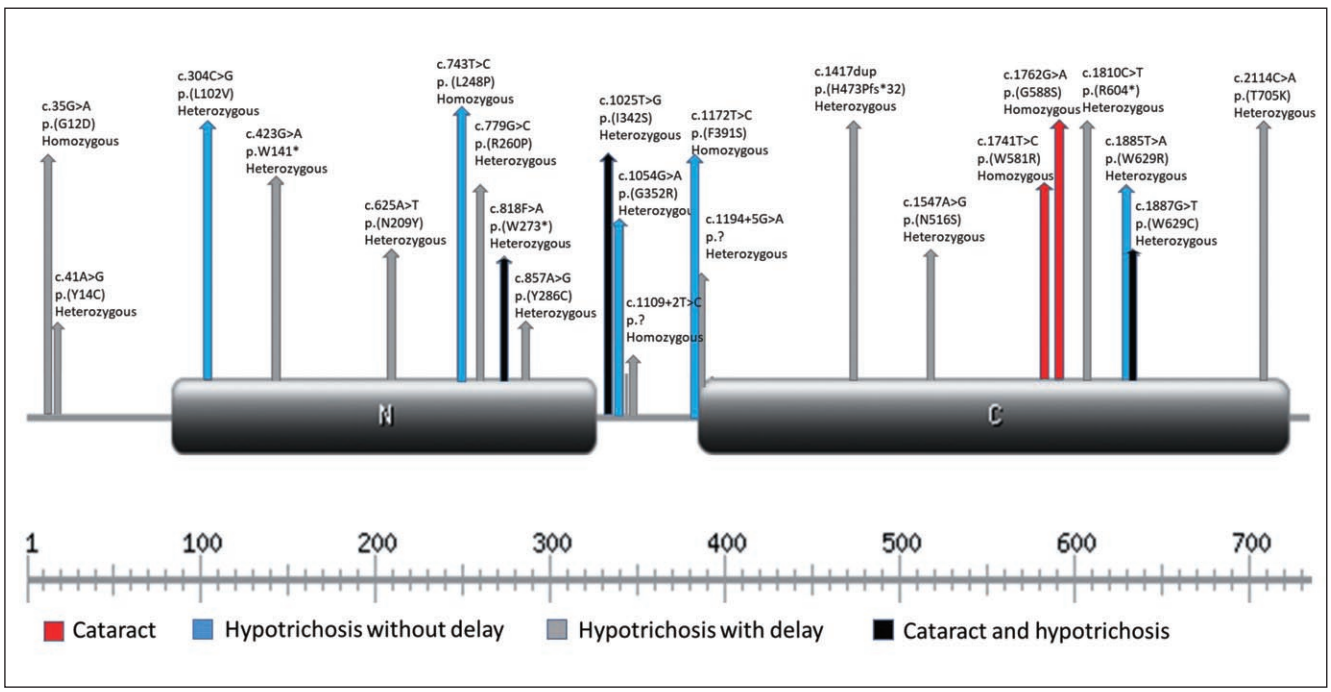

Figure 2 Schematic diagram of structure of the LSS protein and summary of all reported mutations.

Table 1 Summary of clinical characteristics

Family	**1**	**2**	**3**	**4**		**5**		**6**				**7**	
Reported by	Zhao et al (2015)[2]	Zhao et al (2015)[2]	Chen et al (2017)[4]	Romano et al (2018)[3]		Romano et al (2018)[3]		Romano et al (2018)[3]				Besnard et al (2019)[1]	
Gender	F	M	M	F	F	M	F	M	F	M	M	F	F
Consanguinity	✓	✓	✖	N/A	N/A	✖	✖	✖	✖	✖	✖	✖	✖
Family history	2 younger brothers	✖	✖	1 younger sister	1 elder sister	1 younger sister	1 elder brother	Father, paternal uncle, 1 Sibiling		Elder brother Son and daughter	Younger brother	1 younger sister and niece	1 elder sister
Cataract	✓	✓	✓	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖
Hypotrichosis	N/A	N/A	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ectodermal manifestation	N/A	N/A	✖	✖	✖	✖	✖	✖	✖	✖	✖	Ichthyosis	✖
Developmental delay	N/A	N/A	✖	✖	✖	✓	✓	✖	✖	✖	✖	✓	✓
Genital abnormalities	N/A	N/A	Micropenis	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖
Blood cholesterol profile	N/A	N/A	Normal	N/A	N/A	N/A	N/A	Normal for all affected individuals in the family				Normal	Normal
LSS mutation	Homozygous c.1762G>A (p.G588S)	Homozygous c.1741T>C (p.W581R)	Heterozygous c.1025T>G (p.I342S) c. 1887G>T (p.W629C)	Homozygous c.1172T>C (p.F391S)		Heterozygous c.625A>T (p.N209Y) c.423G>A (p.W141*)		Heterozygous c.304C>G (p.L102V) c.743T>C (p.L248P)				Heterozygous c.1547A>G (p.N516S) c.2114C>A (p.T705K)	
Location	C-term	C-term	Towards N-term C-term	C-term		N-term		N-term				C-term	

Family	**8**		**9**		**10**		**11**	**12**	**13**			**14**
Reported by	Besnard et al (2019)[1]		Besnard et al (2019)[1]		Besnard et al (2019)[1]		Besnard et al (2019)[1]	Besnard et al (2019)[1]	Li et al (2019)[5]			Our patient
Gender	M	F	F	M	M	M	M	F	F	F	F	F
Consanguinity	✓	✓	✓	✓	✖	✖	✖	✓	✖	✖	✖	✖
Family history	1 younger sister	1 elder brother	Younger brother	Elder sister	Younger brother	Elder brother	✖	✖	3 affected sisters			✖
Cataract	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	✓
Hypotrichosis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ectodermal manifestation	✖	✖	Ichthyosis at birth Follciular keratosis at adolescence	Ichthyosiform congenital erythroderma	✖	✖	✖	Icthyosis	Papular lesions for all affected individuals			Epidermolytic Ichthyosis, PS type
Developmental delay	✓	✓	✓	✓	✓	✓	✓	✓	✖	✖	✖	✖
Genital abnormalities	Hypospadias	✖	✖	✖	Hypospadias	Hypospadias	✖	✖	✖	✖	✖	✖
Blood cholesterol profile	N/A	N/A	Low	Normal	N/A	N/A	Normal	N/A	N/A for the family			Normal
LSS mutation	Heterozygous c.779G>C (p.R260P) c.1194+5G>A (p.?)		Homozygous c.1109+2T>C (p.?)		Heterozygous c.857A>G (p.Y286C) c.1810C>T (p.R604*)		Heterozygous c.1417dup (p.H473Pfs*32) c.41A>G (p.Y14C)	Homozygous c.35G>A (p.G12D)	Heterozygous c.1054G>A (p.G352R) c.1885T>A (p.W629R)			Heterozygous c.818 G>A (p. W273*) c. 1025T>G (p.I342S)
Location	N-term Towards C-term		Towards N-term		N-term C-term		C-term N-term	N-term	Towards N-term C-term			N-term Towards N-term

Compliance with Ethical Standards

Conflict of Interest

All authors have disclosed no conflicts of interest.

Informed Consent

Informed consent for publishing clinical photo and clinical information was obtained from proband and her parents.

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