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Novel *LSS* variants in alopecia and intellectual disability syndrome: New case report and clinical spectrum of *LSS*-related rare disease traits.

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Abstract

Pathogenic biallelic variants in *LSS* are associated with three Mendelian rare disease traits including congenital cataract type 44, autosomal recessive hypotrichosis type 14, and alopecia-intellectual disability syndrome type 4 (APMR4). We performed trio research exome sequencing on a family with a four-year-old male with global developmental delay, epilepsy and striking alopecia, and identified novel compound heterozygous *LSS* splice site (c.14+2T>C) and missense (c.1357 G>A; p.V453I) variant alleles. Rare features associated with APMR4 as cryptorchidism, micropenis, mild cortical brain atrophy and thin corpus callosum were detected. Previously unreported APMR4 findings including cerebellar involvement in the form of unsteady ataxic gait, small vermis with prominent folia, were noted. A review of all reported variants to date in 30 families with *LSS*-related phenotypes showed an emerging genotype-phenotype correlation.

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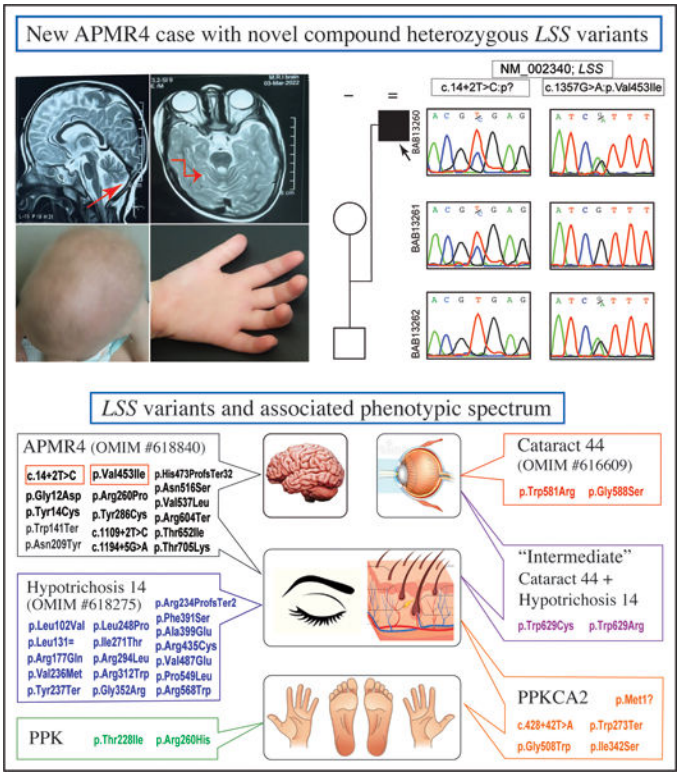
CONFLICT OF INTEREST:

JRL has stock ownership in 23andMe and is a consultant for Genome International.

Our report potentially expands *LSS*-related phenotypic spectrum and highlights the importance of performing brain imaging in *LSS*-related conditions.

Graphical Abstract



Elbendary *et al.* report a new Egyptian patient with alopecia-intellectual disability syndrome type 4 (APMR4) and cerebellar involvement due to novel compound heterozygous *LSS* splice site (c.14+2T>C) and missense (c.1357 G>A; p.V453I) variants. A review of all reported variants to date in 30 families with *LSS*-related phenotypes showed an emerging genotype-phenotype correlation.

Keywords

LSS-related phenotypes; intellectual disability; hypogenitalism; cerebellar abnormalities; alopecia

INTRODUCTION

Alopecia-intellectual disability syndrome (APMR) is a rare clinical condition defined by loss of scalp hair, absence of eyebrows, eyelashes, axillary and pubic hair in combination with mild to severe intellectual disability.[1] APMR is classified into four subtypes based on the degree of intellectual disability and the associated clinical manifestations.[1] Alopecia-intellectual disability syndrome type 4 (APMR4, OMIM #618840) is a very rare, neuro-ectodermal syndrome caused by biallelic variants in *LSS* located on chromosome 21q22.[2]

Lanosterol synthase (LSS) is an enzyme involved in the biosynthesis of cholesterol, steroid hormones, and vitamin D.[3] It catalyzes the rate-limiting step in the conversion of (S)-2,3-oxidosqualene into lanosterol.[4] LSS is expressed in many tissues, including the brain, glomerular podocytes, and skin, potentially explaining multi-system involvement and pleiotropic phenotypic manifestations.[5] Biallelic *LSS* variants are associated with three autosomal recessive rare diseases including congenital cataracts type 44, hypotrichosis simplex type 14, and APMR4 (OMIM #616509, #618275, #618840, respectively). APMR4 is characterized by alopecia universalis, scaly skin, and variable degrees of psychomotor delay.[6]

A total of 29 families with all three *LSS*-related disorders have been reported worldwide amongst which are ten families with 15 affected individuals with the APMR4 phenotype.[2,5,7–18]

We describe an Egyptian patient with biallelic novel variants in *LSS* and APMR4 to potentially expand the mutational and phenotypic spectrum of the syndrome.

CLINICAL REPORT

The proband is a four-year-old male and the first child of healthy non-consanguineous parents (Figure 1a,b,c). Normal pregnancy and delivery histories and birth growth parameters were recorded. Baldness and absence of eyebrows were noted since early infancy. At the age of 14 months, he presented with global developmental delay, myoclonic epilepsy, and alopecia. On clinical examination, he was able to support the head, recognized the mother and followed objects. His weight was 10kg (−0.5SD), length 76cm (−0.2SD), and head circumference 45cm (−1.2SD). He had alopecia, sparse hair and eyebrows, prominent forehead, wide-spaced eyes, depressed nose, short philtrum and thin upper lip. Neurological evaluation showed generalized hypotonia with normal reflexes. The genitalia showed micropenis (1.5cm) and bilateral cryptorchidism.

Brain MRI identified mildly dilated lateral ventricles, mild cortical volume loss, and cerebellar vermian hypoplasia. Other investigations such as karyotyping, metabolic work up, biotinidase enzyme activity, EMG and NCV were normal. EEG revealed generalized multifocal epileptiform activity. Abdominopelvic ultrasound showed bilateral inguinal testicles.

During his last assessment at the age of 4 years, he was able to sit at 24 months old, and walk with a wide-based gait at 40 months. Delayed cognitive function was still present and he achieved single syllables. Anthropometric measurements were 15kg for weight (−0.8SD), 94cm for height (−2 SD), and 47.5cm (−2SD) for head circumference. Alopecia was evident. Follow-up brain MRI was quite similar to the previous scans. Ophthalmological and hearing evaluations were normal.

The family was enrolled after informed consent under an Institutional Review Board (IRB)- approved research protocol (H-29697) at the Baylor College of Medicine Genomics Research to Elucidate the Genetics of Rare (BCM-GREGoR) and Medical Research Ethics Committee of NRC, Egypt. Trio research exome sequencing was

performed. Two novel compound heterozygous *LSS* variant alleles were identified in the proband: NM_002340:c.14+2T>C and NM_002340:c.1357G>A:p.(Val453Ile), of paternal and maternal origin, respectively. The missense variant c.1357G>A:p.(Val453Ile) was predicted deleterious by multiple prediction models including Polyphen, SIFT and LRT and had a CADD score of 24.5 and a REVEL score of 0.288. The splicing variant was predicted to cause donor loss with a score of 0.57 by SpliceAI. The variants were absent in homozygous state in available control databases (ARIC; GO-ESP; 1000 Genomes Project; and gnomAD v2.1.1) or in the in-house generated BHCMG database (~13,000 exomes) while the missense variant c.1357G>A:p.(Val453Ile) was present in the heterozygous state in a single control subject of South Asian origin in gnomAD v2.1.1 (minor allele frequency of 0.000004).

DISCUSSION

Pathogenic biallelic *LSS* variants cause three autosomal recessive rare diseases with a broad phenotypic spectrum: congenital cataracts 44 (OMIM #616509), hypotrichosis (HYPT14; OMIM#618275), and a severe neuro-ectodermal syndrome APMR4 (OMIM #618840). Table 1 summarizes variant and trait information for published cases with the three *LSS*-associated traits.

LSS pathogenic variants were first associated with a Mendelian trait to cause congenital cataract in rats and humans.[7,16,19] In 2015, Zhao et al. reported two families of European origin with congenital cataract due to biallelic *LSS* variants.[7] This was followed by a report of a Chinese male with an “intermediate phenotype” of co-existing cataract and hypotrichosis due to compound heterozygous missense variants in *LSS.*[16] The first variant c.1025T>G :p.(lle342Ser) localized to the N-terminal domain while the second variant c.1887G>T: p.(Trp629Cys) to the C-terminal domain.

Romano et al. described a number of cases from different ethnicity with the second Mendelian trait, hypotrichosis simplex, due to biallelic *LSS* variants.[5] They hypothesized that the phenotype depends on the pathogenic variants localizing toward the N-terminus lead to hypotrichosis simplex (HS) while those near the C-terminus lead to congenital cataract.[5] This assumption was later questioned after a family from China with both cataract and hypotrichosis and had biallelic *LSS* variants localized toward the N-terminus. [13] Several families with the HS phenotype have been described with the variants spread across both domains.[8–11,14,18] Then the phenotypic spectrum of *LSS* was expanded to include a third and more severe neuro-ectodermal phenotype, APMR4, with a report of eleven patients from seven unrelated families having alopecia and intellectual disability secondary to *LSS* biallelic variants.[2] The described *LSS* variants were distributed across both LSS domains thus providing no clear phenotype-genotype correlation (Figure 1d). Two more patients from Iraq and Egypt with APMR4 have been recently reported.[10,12]

Our proband displayed the core clinical features of APMR4 syndrome including alopecia, developmental delay, and early onset seizures in absence of cataract, hearing loss, nail dysplasia or skin lesions. Early-onset epilepsy is a common feature in reported subjects

(8/15; 53%). Additional common features observed in our subject are absent or poor speech (10/13; 77%) and hypotonia (8/15; 53%).[2,10,12]

Our proband had micropenis, reported in four males with APMR4 and one male with the intermediate phenotype.[2,16] It is proposed to result from the impairment in the cholesterol biosynthesis pathway due to defective LSS which is essential for the development of normal genitalia in early fetal life.[20] Interestingly, normal plasma cholesterol level was reported in several patients with *LSS*-related disorders supporting an alternative pathway for cholesterol synthesis (Table 1S).[2,5,12]

Similar to our subject, patients of Wada et al. had partial agenesis of the corpus callosum; however, their motor and intellectual development was normal. Also, the brain MRI of both our subject and Elaraby et al. showed dilated lateral ventricles and thin corpus callosum.[12] Nevertheless, no specific neuroimaging findings were reported by Besnard et al.[2] Our patient had a small cerebellar vermis with prominent vermian folia, not described with APMR4.

Lately, a more severe end-of-spectrum phenotype, palmoplantar keratoderma with congenital alopecia (PPKCA2), was reported with biallelic *LSS* variants, with in addition, severe hand and feet skin involvement.[15] Palmoplantar keratoderma was a finding in the family described by Ho et al. and initially thought to have “the intermediate phenotype”.[13] Interestingly, the variant c.1025T>C;p.(Ile342Ser) is shared between four unrelated Han Chinese subjects with PPKCA2 and “the intermediate phenotype” with another different variant: c.818G>A ;p.(Trp273Ter), c.3G>A;p.(Met1?) and c.1887G>T;p.(Trp629Cys) respectively.[13,15,16] P.(Ile342Ser) variant found to significantly reduce LSS protein expression and completely abolishes its enzymatic activity resulting in no lanosterol production.[13,15] The p.(Ile342Ser) variant might represent a founder allele in the Han Chinese population possibly predisposing to the intermediate or PPKCA2 phenotypes. Recently, a Chinese subject has been reported with two novel missense *LSS* variants and solely mutilating palmoplantar keratoderma (PPK) confirming the association with PPK but also further adding to the complexity and plethora of the *LSS*-related phenotypic spectrum.[17]

Here, we report a novel splice site variant and a novel missense variant. The majority of the reported pathogenic variants were missense. Splicing, frameshift and nonsense variants have been also reported as pathogenic in 9/15 (60%) patients with APMR4, 2/3 (67%) with PPKCA2 and only 2/22 (9%) with hypotrichosis phenotype, with another missense variant. Murata et al. thought that a combination of mutations with their locations can be important for determining the severity of phenotypes.[11] Hua et al. inferred that epigenetic and other modifier genes might be responsible for phenotypic heterogeneity of LSS.[14] By reviewing the reported mutations in aggregate and their associated phenotypes in an attempt to find a phenotype-genotype correlation, we found that the map positions of the individual pathogenic variant alleles were not related to the observed clinical disease. However, cases with a more severe phenotype were more likely to have a biallelic combination of a LoF allele plus a missense. Future studies should evaluate the functional impact of the variants as it is still unclear whether the different phenotypes represent different diseases or a continuum of one disorder due to allelic combinations and allelic severity at the locus.[13]

Our report provides novel *LSS* variants to be added to the list of APMR4 and highlights the clinical heterogeneity of *LSS*-related disorders. Moreover, we suggest that some neuroimaging clues can be relevant for an early diagnosis. We also encourage further studies of the allelic series at this locus to better understand the mechanisms and functions of the altered proteins and the neurectoderm phenotypic variability that arises from *LSS* mutations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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DATA AVAILABILITY

All data are available upon request to corresponding author.

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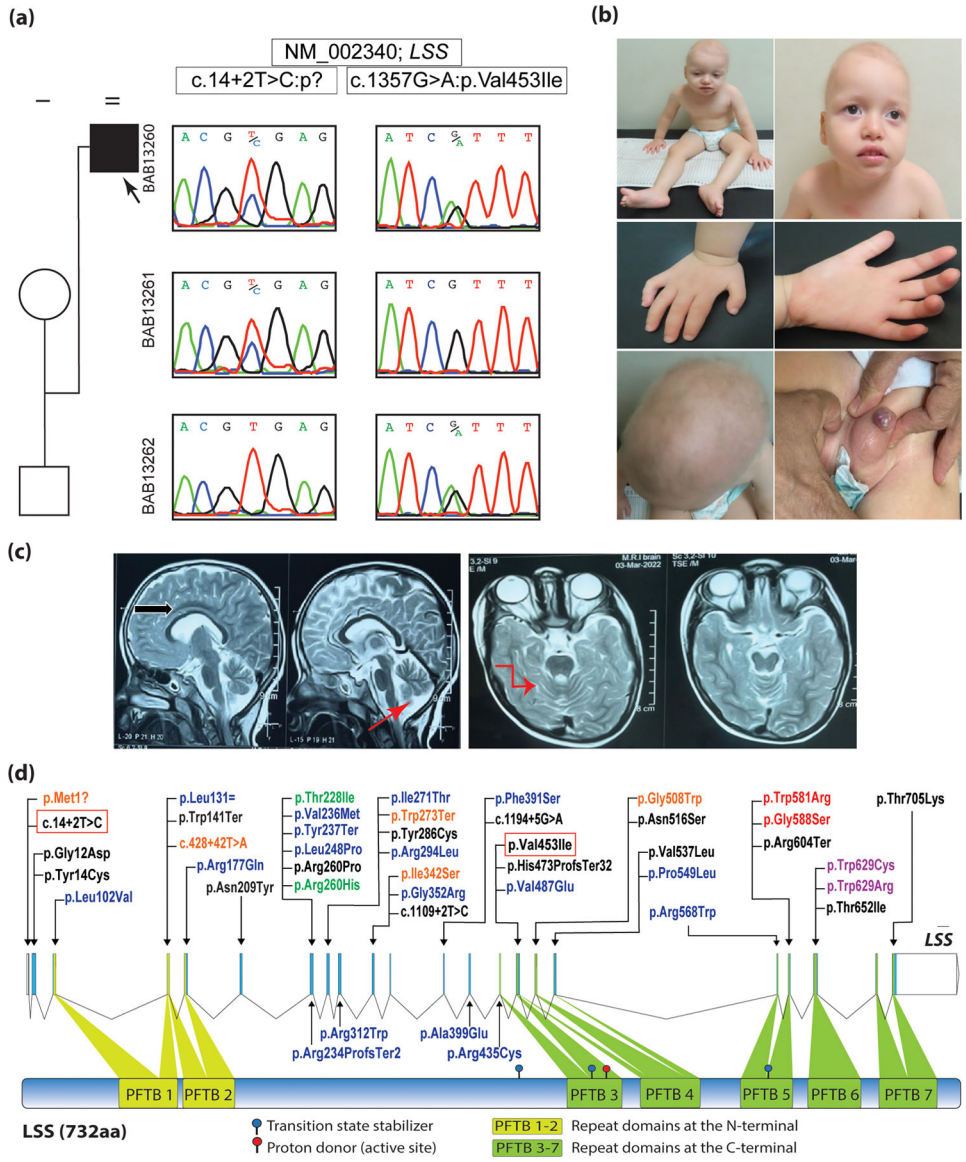

Figure 1:

(a) Family pedigree, along with the Sanger validation and segregation next to each corresponding individual.

(b) Facial, hand, and genital images of the proband at the age of 4 years. Note sparse, lanugo-like scalp hair, sparse eyelashes and eyebrows, clinodactyly and micropenis.

(c) Brain MRI at 4ys old (T2W sagittal and axial cuts) showing thinning of the corpus collosum (black arrow), and mild superior cerebellar vermian volume loss (red arrows).

(d) Schematic representation of *LSS* gene (NM_002340) and of LSS protein (NP_002331); arrows point to the locations of the reported variants corresponding to each coding exon. Variants are color coded according to each phenotype sub-category as follows: **Red**; Cataract 44, **Purple**; Cataract 44 + Hypotrichosis 14, **Blue**; Hypotrichosis 14, **Black**: Alopecia-intellectual disability syndrome (APMR), **Orange**; PPKCA2, and **Green**: PPK.

The current variants (c.14+2T>C) and (c.1357G>A:p.Val453Ile) are highlighted in red rectangles.

Table 1:

Review of published cases identified to date

OMIM phenotype	Family #	No. affected subjects	Clinical features	c.DNA Change (NM_002340.6)	Amino acids change	Zygosity	Ethnicity	Reference
Cataract 44	1	3	Cataract	c.1762G>A	p.Gly588Ser	Hmz	European	Zhao et al., 2015
	2	1	Cataract	c.1741T>C	p.Trp581Arg	Hmz	N/A	
"Intermediate" Cataract 44 + HS 14	3	1	Cataract, hypotrichosis	c.1025T>G;c.1887G>T	p.Ile342Ser;p.Trp629Cys	cHet	Chinese	Chen et al., 2017
HS 14	4	2	HS	c.1172T>C	p.Phe391Ser	Hmz	Arab	Romano et al. 2018
	5	4	HS	c.304C>G;c.743T>C c.743T>C	p.Leu102Val;p.Leu248Pro p.Leu248Pro	cHet Hmz	Afghani	
	6	3	HS	c.1054G>A;c.1885T>A	p.Gly352Arg;p.Trp629Arg	cHet	Chinese	Li et al. 2019
	7	2	HS ,midline anomalies, ACC, cleft palate	c. 530G>A; c.701_716del	p.Arg177Gln;p.Arg234ProfsTer2	cHet	Japanese	Wada et al., 2020
	8	2	HS	c.934C>T;c.881G>T	p.Arg312Trp;p.Arg294Leu	cHet	Georgian	Cesarato et al.,2021
	9	1	HS	c.1702C>T	p.Arg568Trp	Hmz	Syrian	
	10	1	HS	c.393G>A	p.Leu131=	Hmz	Afghani	
	11	1	HS	c.530G>A;c.1460T>A	p.Arg177Gln;p.Val487Glu	cHet	Japanese	Murata et al., 2021
	12	1	HS	c.711C>G;c.1646C>T	p.Tyr237Ter;p.Pro549Leu	cHet	Japanese	
	13	2	HS	c.706G>A;c.1196C>A	p.Val236Met;p.Ala399Glu	cHet	Chinese	Hua et al., 2021
	14	1	HS	c.1303C>T;c.1887G>T	p.Arg435Cys;p.Trp629Cys	cHet	Chinese	
	15	2	HS	c.812T>C	p.Ile271Thr	Hmz	Chinese	Zhao et al., 2023
APMR4	16	2	HS + ID	c.625A>T;c.423G>A	p.Asn209Tyr;p.Trp141Ter	cHet	Swiss	Romano et al., 2018
	17	2	Alopecia with ID	c.1547A>G;c.2114C>A	p.Asn516Ser;p.Thr705Lys	cHet	N/A	Besnard et al.,2019
	18	2	Alopecia with ID	c.779G>C;c.1194+5G>A	p.Arg260Pro;p.?	cHet	Turkish	
	19	2	Alopecia with ID	c.1109+2T>C	p.?	Hmz	N/A	
	20	2	Alopecia with ID	c.857A>G;c.1810C>T	p.Tyr286Cys;p.Arg604Ter	cHet	N/A	
	21	1	Alopecia with ID	c.41A>G;c.1417 dup	p.Tyr14Cys; p.His473ProfsTer32	cHet	N/A	
	22	1	Alopecia with ID	c.1955C>T;?	p.Thr652Ile;?	cHet	N/A	
	23	1	Alopecia with ID	c.35G>A	p.Gly12Asp	Hmz	Qatari	

OMIM phenotype	Family #	No. affected subjects	Clinical features	c.DNA Change (NM_002340.6)	Amino acids change	Zygosity	Ethnicity	Reference
	24	1	Alopecia with ID	c.530G>A	p.Arg177Gln	Hmz	Iraqi	Cesarato et al., 2021
	25	1	Alopecia with ID GR and teeth mineralization defect, thin CC	c.1609G>T	p.Val537Leu	Hmz	Egyptian	Elaraby et al., 2022
	26	1	Alopecia with ID GR, ACC ,hypogenitalism	c.14+2T>C;c.1357G>A	p?;p.Val453Ile	cHet	Egyptian	This Report 2022
PPKCA2	27	1	Cataract, hypotrichosis , PPK	c.818G>A;c.1025T>G	p.Trp273Ter;p.Ile342Ser	cHet	Chinese	Ho et al., 2022
	28	1	PPK with Alopecia, Cataract, pseudoainhum, ACC	c.3G>A; c.1025T>G	p.Met1?;p.Ile342Ser	cHet	Chinese	Yang et al., 2022
	29	1	PPK with Alopecia, Cataract, pseudoainhum, ACC	c.1522G>T;c.428+42T>A	p.Gly508Trp;p.?	cHet	Chinese	
PPK	30	1	PPK	c.683C > T; c.779G > A	p.Thr228Ile;p.Arg260His	cHet	Chinese	Zhou et al., 2023

APMR4; Alopecia-intellectual disability syndrome type 4, ACC; agenesis of corpus callosum, CC; corpus callosum. cHet; compound heterozygous, GR; growth retardation, Hmz; homozygous, ID; intellectual disability, HS; hypotrichosis simplex, PPK; palmoplantar keratoderma, PPKCA2; palmoplantar keratoderma-congenital alopecia syndrome type 2.