Case Study

MACS Syndrome Associated with a Novel Variant in the RIN2 Gene: A Case Series

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Abstract

MACS (Macrocephaly Alopecia Cutis Lexa Scoliosis) syndrome is a rare autosomal recessive connective tissue disorder caused by mutations in the RIN2 gene. This syndrome is characterized by progressive facial coarsening, gingival hypertrophy, severe scoliosis, sparse hair, and skin and joint hyperlaxity. We describe three siblings (ages 14, 13, and 7) from, Sindh, Pakistan, who presented with the hallmark features of MACS syndrome.

The 14-year-old female exhibited macrocephaly, coarse facial features, thin sparse hair, prominent forehead, puffy droopy eyelids, depressed nasal bridge, hypertelorism, low-set ears, sagging cheeks, gum hypertrophy, and irregular dentition. She also had loose skin hanging in folds and widespread joint hypermobility. Her younger brother, aged 13, presented with similar facial features and additionally had marked kyphosis. The 7-year-old male also displayed similar facial characteristics and joint hypermobility. All three siblings were developmentally normal. Whole exome sequencing identified a novel frameshift homozygous variant C.2243 T>G; P.Ile748 Arg in the RIN2 gene.

This case report provides a comprehensive understanding of MACS syndrome by detailing the clinical features and genetic findings in these three siblings. Early recognition, effective intervention, and holistic care are essential for improving patient outcomes and quality of life for individuals affected by this rare syndrome.

Introduction

Macrocephaly, alopecia, cutis laxa, and scoliosis (MACS) syndrome, also referred as RIN2 syndrome, is an uncommon connective tissue illness. The autosomal recessive syndrome is characterized by striking clinical features such as macrocephaly, coarsening of facial features, fullness of everted lips, fullness of eyelids, gum hypertrophy, irregular dentition, sparse scalp hair, skeletal abnormalities, joint hypermobility, and scoliosis (1) The RIN2 gene, which is found on chromosome 20p11.23, is mutated in MACS syndrome

(1) Fifty-five known or predicted genes were identified in the candidate area. The RIN2 gene encodes a Rab5- and ras-interactor 2 protein, which is hypothesized to be responsible for the autosomal-recessive transmission of the MACS syndrome. (3)

Rab5, a small GTPase involved in early endocytosis, has been demonstrated to interact with RIN2. Rab5 is necessary for the homotypic early endosome fusion as well as the transport and heterotypic fusing of plasma membrane-derived endocytic vesicles to early endosomes. Additionally, it controls the movement of early endosomes along microtubules, assisting in their intracellular dispersion. The trafficking of secretory proteins, such as collagen and elastin, from the endoplasmic reticulum to the Golgi apparatus or from the Golgi to the plasma membrane (4) linked to endosomal tracking may be impaired by RIN2 deficiency (5). (5) RIN2 deficit

was linked to a lack of dermal micro-fibrils and a fibulin-5 deficiency, which may be the cause of the aberrant skin phenotype seen.

Patients with a unique autosomal recessive Geno dermatosis who came from a consanguineous Algerian family were the first to be diagnosed with Mac syndrome (7). The patients were found to have a unique RIN2 deletion of 2 bp (c.1914_1915delGC), which causes nonsense-mediated mRNA degradation. Rather than having the cutis lexa spectrum phenotype, the three affected family members had a clinical, dermatological, and ultrastructural phenotype resembling that of Ehlers-Danlos (OMIM 130060). Despite the clear phenotypic overlap between those patients and the family with a RIN2 deletion that was first reported, the authors proposed a new term for MACS syndrome based on the distinct histology findings of primary collagen involvement in their patients (8,9).

Here we report a patient with a novel frameshift homozygous variant C.2243 T>G; P. Ile748 Arg in the RIN2 gene.

Case Presentation:

Sibling 1 (14-Year-Old Female)

A 14-year-old female presented with macrocephaly, coarse facial features, thin sparse hair, a prominent forehead, puffy droopy eyelids, a depressed nasal bridge, hypertelorism, low-set ears, sagging cheeks, gum hypertrophy, and irregular dentition. Her skin was noted to be loose and hung in folds upon stretching. She exhibited widespread joint hypermobility as indicated by the Beighton grading system. Systemic examination revealed normal symmetrical chest movements with normal vesicular breathing and no added sounds. Cardiovascular examination showed normal heart sounds with S1 and S2 audible. Neurologically, she was well-oriented to time and place with a GCS score of 15/15, normal tone, reflexes, and plantar down-going. Her abdomen was soft and non-tender, with normal bowel sounds, and an umbilical hernia was noted. Genitourinary examination indicated Tanner stage 3 with normal genitalia. Anthropometric measurements were as follows: weight 44 kg (-1.10 z), height 157 cm (-0.87 z), and head circumference 57 cm (97th centile, 1.9 z).

Sibling 2 (13-Year-Old Male)

A 13-year-old male presented with macrocephaly, coarse facial features, thin sparse hair, a prominent forehead, puffy droopy eyelids, a depressed nasal bridge, hypertelorism, low-set ears, sagging cheeks, gum hypertrophy, and irregular dentition. His skin was also loose and hung in folds upon stretching. He exhibited widespread joint hypermobility as indicated by the Beighton grading system. In addition, he had marked kyphosis. Systemic examination showed normal symmetrical chest movements with normal vesicular breathing and no added sounds. Cardiovascular examination revealed normal heart sounds with S1 and S2 audible. Neurologically, he was well-oriented to time and place with a GCS score of 15/15, normal tone, reflexes, and plantar down-going. His abdomen was soft and non-tender, with normal bowel sounds. Genitourinary examination indicated Tanner

stage 3 with normal genitalia. Anthropometric measurements were as follows: weight 46 kg (-0.13 z), height 155 cm (-0.49 z), and head circumference 57 cm (95th centile, 1.51 z). Despite his physical manifestations, he was developmentally normal.

Sibling 3 (7-Year-Old Male)

A 7-year-old male presented with macrocephaly, coarse facial features, thin sparse hair, a prominent forehead, puffy droopy eyelids, a depressed nasal bridge, hypertelorism, low-set ears, sagging cheeks, gum hypertrophy, and irregular dentition. His skin was noted to be loose and hung in folds upon stretching. He exhibited widespread joint hypermobility as indicated by the Beighton grading system. Systemic examination showed normal symmetrical chest movements with normal vesicular breathing and no added sounds. Cardiovascular examination revealed normal heart sounds with S1 and S2 audible. Neurologically, he was well-oriented to time and place with a GCS score of 15/15, normal tone, reflexes, and plantar down-going. His abdomen was soft and non- tender, with normal bowel sounds. Genitourinary examination indicated Tanner stage 3 with normal genitalia. Anthropometric measurements were as follows: weight 20 kg (-1.36 z), height 120 cm (-0.826 z), and head circumference 54.5 cm (86th centile, 1.09 z). Despite his physical manifestations, he was developmentally normal.

Figure 1:S1

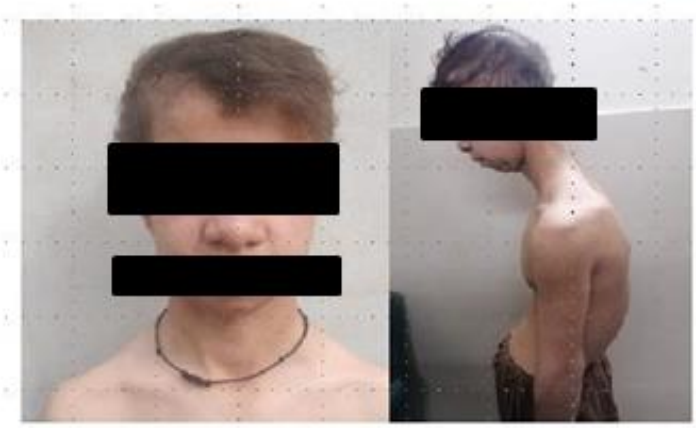

Figure 2: S2

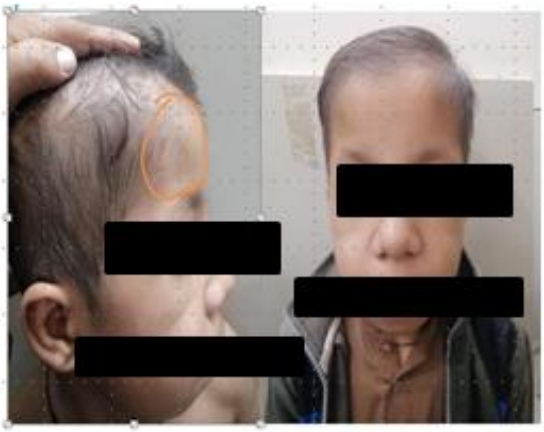

Figure 3:S3

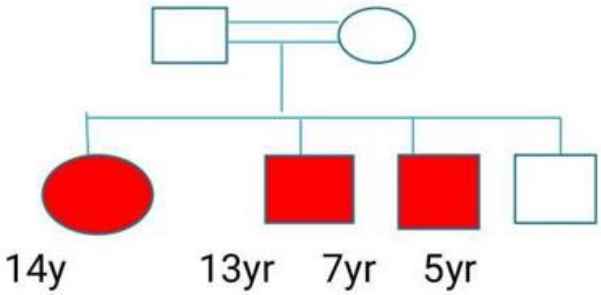

Figure 4: Family Pedigree

Genetic Analysis

Whole exome sequencing of the siblings revealed a novel frameshift homozygous variant C.2243 T>G; P.Ile748 Arg in the RIN2 gene. This variant is predicted to cause a change in amino acid Ile to Arg at codon 748. The variant is not present in gnomAD and is absent from the local database. This variant is not listed in ClinVar.

Results: A homozygous uncertain significance variant was identified in the RIN2 gene. The genetic diagnosis of autosomal recessive MACS syndrome (macrocephaly, alopecia, cutis laxa, and scoliosis) is possible.

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
RIN2	c.2243T>G; p.Ile748Arg	Hom	VUS	MACS syndrome	AR

Figure 5: Genetic Reports

	Gene/OMIM	*RIN2/610222*
	Genomic coordinate (GRCh38)	chr20:19996721T>G
	ID Transcript	NM_018993.4
	HGVS nomenclature	c.2243T>G
	Protein change	p.Ile748Arg
	Location	exon 12/13
	Zygosity	Hom
	Function	Missense
	Impact	High
	ClinVar	N/A
Allele Frequency	Local Database	N/A
	gnomAD	N/A
In silico Predictors	REVEL	0.872
	CADD (PHRED)	29.4
	Splice-AI	0.01
	Clinical significance	Uncertain significance
	ACMG Criteria	PM2, PP3

HGVS= Human Genome Variation Society; gnomAD= Genome Aggregation Database; ACMG= American College of Medical Genetics and Genomics; REVEL score (combination from 13 individual tools; rages from 0 to 1)= higher scores reflect greater likelihood that variant is disease- causing; CADD (PHRED)= Combined Annotation Dependent Depletion scoring, ranging from 1 to 99, Splice-AI= deep neural network that accurately predicts splice junctions from an pre-mRNA transcript (using 0.8 as high-precision cut-off).
**: The ACMG criteria are described under Methods /Variant interpretation section.*

Figure 6: Variant Details

Discussion

MACS (Macrocephaly Alopecia Cutis Laxa Scoliosis) syndrome is an autosomal recessive connective tissue disorder characterized by distinctive physical and facial abnormalities, as well as joint and skin issues. (1) The three siblings described in this report presented with key clinical features such as progressive facial coarsening, gingival hypertrophy, severe scoliosis, sparse hair, and joint hyperlaxity. These findings are consistent with previous descriptions of MACS syndrome, further highlighting the phenotypic variability and the significant impact of the disorder on multiple systems.

The identification of a novel frameshift homozygous variant C.2243 T>G; P.Ile748 Arg in the RIN2 gene in these siblings underscores the importance of genetic testing in the diagnosis and management of rare syndromes like MACS. Genetic analysis not only confirms the diagnosis but also aids in understanding the molecular mechanisms underlying the disorder. This, in turn, can pave the way for potential targeted therapies in the future.

Currently, specific therapies for MACS syndrome remain undetermined. However, multidisciplinary approaches can play a crucial role in managing the symptoms and improving the quality of life for affected individuals. Physical therapy is essential in alleviating musculoskeletal symptoms and enhancing mobility. Regular physiotherapy sessions can help manage joint hyperlaxity and prevent the progression of scoliosis. Additionally, plastic surgery can have a significant impact on enhancing facial aesthetics, which can improve self-esteem and social interactions in patients with hereditary cutis lexa.

Conclusion

The most striking clinical features of MACS syndrome include progressive facial coarsening, gingival hypertrophy, severe scoliosis, sparse hair, and joint hyperlaxity. While specific therapies for MACS syndrome are still undetermined, the potential role of physical therapy in alleviating musculoskeletal symptoms and the significant impact of plastic surgery on enhancing facial aesthetics are noteworthy. By providing a comprehensive understanding of MACS syndrome, this case report aims to facilitate early recognition, effective intervention, and holistic care for affected individuals and their families, thereby improving overall patient outcomes and quality of life. Early diagnosis, coupled with a multidisciplinary approach to management, is key to addressing the complex needs of patients with this rare disorder.

References

1. Kameli R, Ashrafi MR, Ehya F, Alizadeh H, Hosseinpour S, Garshasbi M, Tavasoli AR. Leukoencephalopathy in RIN2 syndrome: Novel mutation and expansion of clinical spectrum. Eur J Med Genet. 2020 Jan;63(1):103629. doi: 10.1016/j.ejmg.2019.02.002. Epub 2019 Feb 13. PMID: 30769224.
2. Basel-Vanagaite L, Sarig O, Hershkovitz D, Fuchs-Telem D, Rapaport D, Gat A, Isman G, Shirazi I, Shohat M, Enk CD, Birk E, Kohlhase J, Matysiak-Scholze U, Maya I, Knopf C, Peffekoven A, Hennies HC, Bergman R, Horowitz M, Ishida-Yamamoto A, Sprecher E. RIN2 deficiency results in macrocephaly, alopecia, cutis laxa, and scoliosis: MACS syndrome. Am

J Hum Genet. 2009 Aug;85(2):254-63. doi: 10.1016/j.ajhg.2009.07.001. Epub 2009 Jul 23. PMID: 19631308; PMCID: PMC2725231.

3. Saito K, Murai J, Kajiho H, Kontani K, Kurosu H, Katada T. 2002. A novel binding protein composed of homophilic tetramer exhibits unique properties for the small GTPase Rab5. J Biol Chem 277: 3412–3418.
4. Aslanger AD, Altunoglu U, Aslanger E, Satkın BN, Uyguner ZO, Kayserili H. Newly described clinical features in two siblings with MACS syndrome and a novel mutation in RIN2. Am J Med Genet A. 2014 Feb;164A(2):484-9. doi: 10.1002/ajmg.a.36277. Epub 2013 Oct 29. PMID: 24449201.
5. Kameli R, Ashrafi MR, Ehya F, Alizadeh H, Hosseinpour S, Garshasbi M, Tavasoli AR. Leukoencephalopathy in RIN2 syndrome: Novel mutation and expansion of clinical spectrum. Eur J Med Genet. 2020 Jan;63(1):103629. doi: 10.1016/j.ejmg.2019.02.002. Epub 2019 Feb 13. PMID: 30769224.
6. Syx D, Malfait F, Van Laer L, Hellemans J, Hermanns-Lê T, Willaert A, Benmansour A, De Paepe A, Verloes A. The RIN2 syndrome: a new autosomal recessive connective tissue disorder caused by deficiency of Ras and Rab interactor 2 (RIN2). Hum Genet. 2010 Jul;128(1):79-88. doi: 10.1007/s00439-010-0829-0. Epub 2010 Apr 28. PMID: 20424861.
7. Syx D, Malfait F, Van Laer L, Hellemans J, Hermanns-L^e T, Willaert A, Benmansour A, De Paepe A, Verloes A. 2010. The RIN2 syndrome: A new autosomal recessive connective tissue disorder caused by deficiency of Ras and Rab interactor 2 (RIN2). Hum Genet 128:79–88.
8. Verloes A, Benmansour A, Mortier G, Pierard GE, Le Merrer M. 2005. A new recessive connective tissue disorder with swelling of lips, lid and cheeks, macrocephaly, hyperextensible skin and severe scoliosis. In: 55th annual meeting
9. Basel-Vanagaite L, Sarig O, Hershkovitz D, Fuchs-Telem D, Rapaport D, Gat A, Isman G, Shirazi I, Shohat M, Enk CD, Birk E, Kohlhase J, Matysiak-Scholze U, Maya I, Knopf C, Peffekoven A, Hennies HC, Bergman R, Horowitz M, Ishida-Yamamoto A, Sprecher E. RIN2 deficiency results in macrocephaly, alopecia, cutis laxa, and scoliosis: MACS syndrome. Am J Hum Genet. 2009 Aug;85(2):254-63. doi: 10.1016/j.ajhg.2009.07.001. Epub 2009 Jul 23. PMID: 19631308; PMCID: PMC2725231.