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A novel STAG1 variant associated with congenital clubfoot and microphthalmia: A case report

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Abstract

The cohesin protein complex plays a vital role in various cellular processes such as sister chromatid cohesion, chromosome condensation, DNA repair, and transcriptional regulation. It is constituted by SMC1, SMC3, RAD21, STAG1/STAG2 subunits, and several regulatory proteins. Pathogenic variants in these components cause cohesinopathies, with common clinical features including facial dysmorphism, delayed growth, developmental delay, and limb anomalies. Pathogenic variants in the *STAG1* contribute to an emerging syndromic developmental disorder with only 21 reported cases in the literature. We describe a 3-year-old girl presenting with congenital bilateral clubfoot and unilateral microphthalmia—clinical manifestations not previously reported in the literature. Whole exome sequencing revealed a novel *de novo* nonsense variant (c.1183C>T, p.(Arg395*)) in the *STAG1*, expanding the clinical and molecular spectrum of *STAG1*-related cohesinopathy. This patient's unique phenotype highlights the clinical diversity within cohesinopathies, emphasizing their relevance in cases of developmental delay and dysmorphic features. Further studies, including genotype–phenotype correlation analyses and functional investigations, are essential for enhancing our understanding of *STAG1*-related cohesinopathy.

Keywords

STAG1, cohesin, cohesinopathies, developmental delay, congenital clubfoot, microphthalmia

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Introduction

Cohesin is a multisubunit, evolutionarily conserved protein complex that is part of the Structural Maintenance of Chromosomes (SMC) family, alongside condensin and Smc5/6.[1] Cohesin is essential for sister chromatid cohesion, chromosome condensation, DNA repair, and transcriptional regulation.[1,2] The cohesin SMC complex comprises the heterodimer of SMC1, SMC3, the kleisin subunit RAD21, and the HEAT repeat-containing protein Stromal Antigen or SA/STAG.[3] Additional proteins interact with cohesin and regulate its behavior, most importantly NIPBL, PDS5A/B, WAPL, SORORIN, ESCO1/2, HDAC8, and CTCF.[3] Humans have three STAG orthologs—STAG1, STAG2, and STAG3. STAG1 and STAG2 are ubiquitously expressed in somatic cells and STAG3 is found in germ cells only.[4] STAG1 and STAG2 regulate the interaction between the cohesin and the chromosome.[4]

Conditions resulting from pathogenic variants in either the cohesin complex or its interactors are commonly referred to as cohesinopathies, which exhibit both phenotypic similarities and differences.[5] The most common clinical features of cohesinopathy disorders include facial dysmorphism, delayed growth, developmental delay/intellectual disability (DD/ID), and limb pathologies.[6,7] Two of the better studied cohesinopathies are Cornelia de Lange syndrome (CdLS) (OMIM 122470, 300590, 300882, 610759, 614701) and Roberts syndrome (RS) (OMIM 268300).[8,9] Common clinical features of CdLS are DD/ID, growth disturbances, distinctive facial features, and upper limb defects.[8,9] An international consensus statement defines the "CdLS-spectrum" as the classical and non-classical phenotypes caused by pathogenic variants in one of the seven genes encoding the cohesin complex and its

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Figure 1. (a) and (b) Photographs of the patient at 1 month of age showing congenital clubfoot.

regulators.[10] RS is caused by homozygous or biallelic pathogenic variants in the acetyltransferase *ESCO2*. Clinically, RS has a more severe phenotype with profound cognitive impairment, limb anomalies resembling phocomelia, growth delay, and dysmorphic features.[7,11]

Heterozygous pathogenic variants in *STAG1* cause autosomal dominant ID type 47 (MRD47, OMIM #617635). To date, 21 cases of *STAG1*-related cohesinopathy have been reported in the literature.[11–13] All patients had DD/ID accompanied by a wide spectrum of congenital anomalies.

Here, we describe a 3-year-old girl with a novel *de novo* nonsense variant c.1183C>T, p.(Arg395*) in *STAG1* (NM_032217.4) with previously unreported phenotypes of congenital bilateral clubfoot and unilateral microphthalmia.[14] The case expands the clinical and molecular spectrum of *STAG1*-related cohesinopathy.

Case presentation

A 3-year-old girl was referred for genetic evaluation due to DD, facial dysmorphic features, and limb abnormalities. She was born to a healthy mother at 40 weeks of gestation by cesarean section. Her parents are non-consanguineous, and she is the second child, having a healthy older brother. The pregnancy and delivery were uneventful. Her birth weight was 3300 g (46th percentile), length was 50 cm (52nd percentile), and occipitofrontal circumference (OFC) was not reported. She required a neonatal intensive care unit stay for a week due to oral feeding difficulties. At the time of birth, the patient had bilateral clubfoot (Figure 1(a) and (b)). Foot abduction bracing was initiated which led to a significant improvement in position. Her developmental milestones were delayed; she started holding her head at 4 months, could sit independently at 11 months, walked at 26 months, and spoke her first words at 18 months. Currently, at 3 years, she uses approximately 20 words.

On physical examination at 3 years old, her height was 98 cm (81 percentile), weight was 19 kg (99 percentile), and OFC was 49.5 cm (73 percentile). She had prominent dysmorphia including brachycephaly, micrognathia, wide nasal bridge, anteverted nares, large fontanelle, thick and bushy eyebrows, low-set ears, and high palate. She also had hallux valgus, left-sided microphthalmia, strabismus, and ptosis. Hearing evaluations were normal. She had a loss of vision in the affected eye. Electrophysiological tests were not performed.

Brain magnetic resonance imaging performed at the age of 8 months was unremarkable, and cardiac and abdominal ultrasounds were normal.

Routine G-banded karyotype analysis showed a normal female karyotype (46, XX). Whole exome sequencing (WES) (Blueprint Genetics, Seattle, Washington, USA) identified a novel heterozygous nonsense variant c.1183C>T, p.(Arg395*) in *STAG1* (NM_032217.4), classified as "Likely Pathogenic" based on American College of Medical Genetics criteria.[15] The coverage of the coding regions of the *STAG1* gene, including ±10 base pairs, at a 20× nucleotide reading depth was 99.24%. The sequence variant was confirmed using bi-directional Sanger sequencing. Parental segregation study confirmed the *de novo* nature of the variant. Currently, the patient is under the care of a multidisciplinary team involving orthopedic, ophthalmology, behavioral, and pediatric specialists. She is undergoing physical, occupational, and behavioral therapy.

Discussion

The cohesin complex in humans is a ring-shaped structure composed of the SMC1A, SMC3, RAD21, and either the STAG1 or STAG2 subunit.[3] STAG proteins establish a connection with RAD21 and SMC, playing a crucial role in the cohesin complex's association with DNA.[5] Latest studies have unveiled diverse functions of cohesin beyond its role in sister chromatid cohesion (SCC), including transcription regulation, DNA damage repair, chromosome condensation, homolog pairing, and more.[3,5] Pathogenic variants in the subunits of the cohesin complex or its regulators have been associated with an increasing number of rare human diseases known as cohesinopathies.[8]

The STAG1 protein functions in shaping chromatin architecture. In addition, STAG1 is suggested to be necessary for normal development, implying a potential role in gene regulation crucial for embryonic development.[3,5] To date, 21 cases of *STAG1*-related cohesinopathy have been described in the literature. Lehalle et al.[11] first reported 17 individuals from 16

families with a mean age of 2–33 years. From this cohort, four individuals had a microdeletion encompassing *STAG1*, three individuals from two families had an intragenic *STAG1* deletion, and 10 individuals had de novo heterozygous missense/frameshift variants. All patients shared common facial dysmorphic features, four individuals had microcephaly and seven had epilepsy. Yuan et al.[12] reported a further three patients with heterozygous *de novo* variants in STAG1, which included a frameshift and two missense variants. Di Muro et al.[13] reported a 5-year-old female patient with ND, mild ID, dysmorphic features, and congenital anomalies, in which WES revealed a *de novo* novel pathogenic variant c.2769_2770del p.(Ile924Serfs*8) in the exon 26 of *STAG1*. This variant causes frameshift with a resultant premature stop codon formation.

Our patient has a novel variant c.1183C>T, p.(Arg395*) in *STAG1* (NM_032217.4), which is absent in gnomAD. The variant generates a premature stop codon in *STAG1* exon 12 (a total of 34 exons) and is predicted to lead to loss of normal protein function, either through protein truncation or nonsense-mediated mRNA decay. The variant is located downstream of the stromalin conserved domain of *STAG1*, where most of nonsense *STAG1* variants are found.[13] *In silico* tools (Mutation Tester, SIFT, PolyPhen) predict the variant to be damaging. It has not been reported in disease-related variation databases such as ClinVar or Human Gene Mutation Database (HGMD). In addition, the pLI value of the *STAG1* in the gnomAD reference population is 1, indicating that the gene is intolerant to loss-of-function variation. Genes with a pLI value >0.90 are considered extremely intolerant for loss of function, as they show a very low amount of loss-of-function variation compared to the gene size.

Some of the overlapping features between our patient and previously described individuals with *STAG1* variants include DD, failure to thrive, brachycephaly, micrognathia, wide nasal bridge, anteverted nares, large fontanelle, thick and bushy eyebrows, low-set ears, and high palate. Our patient presented with bilateral clubfoot and unilateral microphthalmia with vision loss, features that have not been previously reported in the literature. Genomic testing did not reveal any other findings to explain these observations. In addition, there was no history of oligohydramnios or other prenatal complications. These findings expand the phenotypic spectrum of *STAG1*-related cohesinopathy. However, long-term follow-up is needed to better characterize the clinical spectrum of this condition. Further studies involving a large number of patients and genotype–phenotype correlation analyses are important to enhance our understanding of the *STAG1*-related clinical spectrum. Lehalle et al.[11] and Di Muro et al.[13] propose that the clinical manifestations and severity of the *STAG1*-related syndrome are independent of the nature or type of the gene variant. Instead, they suggest that these manifestations result from transcriptional dysregulation caused by depletion or defects in the cohesin complex. Additional functional studies using cellular and/or animal models, along with analyses of gene expression profiles and episignatures will be helpful to strengthen this emerging evidence on the etiopathogenetic mechanisms.

Conclusion

In summary, we describe a novel *de novo* nonsense variant c.1183C>T, p.(Arg395*) in the *STAG1*, identified in a 3-year-old girl exhibiting novel clinical findings of congenital bilateral clubfoot and unilateral microphthalmia. This variant expands the mutational spectrum of *STAG1*-related cohesinopathy. Our findings emphasize the phenotypic diversity of this rare syndrome and highlight the importance of considering cohesinopathies in patients with DD and dysmorphic features. Further studies involving large cohorts and functional analyses are crucial for refining our understanding of *STAG1*-related cohesinopathy, potentially leading to improved diagnosis and management.

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Author contributions

T.T. evaluated and provided care for the patient. K.B., A.S., M.L., E.M., and T.T. wrote the manuscript. All co-authors reviewed and approved the final submitted version of the manuscript.

Declaration of conflicting interests

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Ethical approval

Because all findings were a consequence of routine clinical evaluation and diagnostics, and further research did not require further individual investigations, ethical review board evaluation was not required.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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References

1. Choudhary K and Kupiec M. The cohesin complex of yeasts: sister chromatid cohesion and beyond [published correction appears in *FEMS Microbiol Rev*. 2023 Mar 10;47(2):]. *FEMS Microbiol Rev* 2023; 47(1): fuac045.
2. Zhu Z and Wang X. Roles of cohesin in chromosome architecture and gene expression. *Semin Cell Develop Biol* 2019; 90: 187–193.
3. Alonso-Gil D, Cuadrado A, Gimenez-Llorente D, et al. Different NIPBL requirements of cohesin-STAG1 and cohesin-STAG2. *Nat Commun* 2023; 14: 1326.
4. Casa V, Moronta Gines M, Gade Gusmao E, et al. Redundant and specific roles of cohesin STAG subunits in chromatin looping and transcriptional control. *Genome Res* 2020; 30(4): 515–527.
5. Piché J, Van Vliet PP, Pucéat M, et al. The expanding phenotypes of cohesinopathies: one ring to rule them all!. *Cell cycle* 2019; 18(21): 2828–2848.
6. Zakari M, Yuen K and Gerton JL. Etiology and pathogenesis of the cohesinopathies. *Wiley Interdiscip Rev Dev Biol* 2015; 4(5): 489–504.
7. Barbero JL. Genetic basis of cohesinopathies. *Appl Clin Genet* 2013; 6: 15–23.
8. Avagliano L, Parenti I, Grazioli P, et al. Chromatinopathies: a focus on Cornelia de Lange syndrome. *Clin Genet* 2020; 97(1), 3–11.
9. Kaur M, Blair J, Devkota B, et al. Genomic analyses in Cornelia de Lange Syndrome and related diagnoses: novel candidate genes, genotype-phenotype correlations and common mechanisms. *Am J Med Genet A* 2023; 191(8): 2113–2131.
10. Kline AD, Moss JF, Selicorni A, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. *Nat Rev Genet* 2018; 19(10): 649–666.
11. Lehalle D, Mosca-Boidron AL, Begtrup A, et al. STAG1 mutations cause a novel cohesinopathy characterised by unspecific syndromic intellectual disability. *J Med Genet* 2017; 54(7): 479–488.
12. Yuan B, Neira J, Pehlivan D, et al. Clinical exome sequencing reveals locus heterogeneity and phenotypic variability of cohesinopathies. *Genet Med* 2019; 21(3): 663–675.
13. Di Muro E, Palumbo P, Benvenuto M, et al. Novel STAG1 frameshift mutation in a patient affected by a syndromic form of neurodevelopmental disorder. *Genes (Basel)* 2021; 12(8): 1116.
14. Tkemaladze T, Kvaratskhelia E, Bregvadze K, et al. Expanding the phenotypic and mutational spectrum of STAG1-related cohesinopathy. *Eur J Hum Genet* 2024; 32: 530–531.
15. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17(5): 405–424.