International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Devi LT. Int J Reprod Contracept Obstet Gynecol. 2026 Apr;15(4):1411-1416
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/ 10.18203/2320-1770.ijrcog20260911

Case Report

A novel genetic variant in loss of heterozygosity

L. Thulasi Devi*

Department of Obstetrics and Gynaecology, Military Hospital, Nasirabad, Rajasthan, India

Received: 26 January 2026
Revised: 03 March 2026
Accepted: 05 March 2026

***Correspondence:**
Dr. L. Thulasi Devi,
E-mail: mowgli1974.mt@gmail.com

ABSTRACT

An interesting case of loss of heterozygosity (LOH) and BOH with a history of second degree consanguineous marriage with manifestation of congenital fetal malformation in all her previous pregnancies. A case of missed clinical diagnosis and poor correlation of available clues and data due to lack of awareness, poor history taking and repeated irrelevant investigations, relying mostly on sonography and adhocism. This case is being reported as consanguinity is extremely widespread in the subcontinent and patients seldom get answers to recurrent miscarriages and fetal loss. On evaluation, the affected fetus had novel – likely pathogenic genetic variant not yet classified.

Keywords: LOH, BOH, Consanguinity, Human evolution, Obstetric surveillance, Medical genetics, Genetic screening, MTP services, OMIM

INTRODUCTION

"Loss of heterozygosity" (LOH) is a genetic event where a cell loses one copy of its two alleles of a gene, leading to a heterozygous region manifest as homozygous (as if possessing identical alleles) or completely excluding and losing the gene's expression and contribution. It's a significant contributor in cancer development, often involving the loss of expression of a normal allele (wild-type) and unmasking with dominant expression of a harmful recessive mutation or a tumor suppressor gene's inactivation, leading to uncontrolled cell growth.[1]

Genetic events that lead to LOH are - deletion/loss: a whole chromosome or a large segment is lost, gene conversion: one allele's sequence replaces another, mitotic recombination: errors during cell division, and DNA repair issues: inappropriate repair of DNA breaks.[2]

Importance in cancer and tumour genomics

LOH unmasks recessive mutations that is if one allele has a mutation and the other is normal, it excludes the normal copy, allowing the recessive, undesirable, harmful mutation to express which leads to disease manifestation. It also alters functioning and expression of tumor suppressor genes leading to loss of the working copy of a tumor suppressor gene which normally halts cell growth and tumor progression.

Biomarkers helps identify tumor suppressor gene locations and is a marker of genomic instability, important in cancer diagnostics and therapy.[3]

In colloquial and layman terms losing the "good" copy of a gene can allow the "bad" copy to take over. LOH is a type of mutation that leads to loss of one copy of a segment of DNA (typically containing a gene or group of genes). Usually for most of the genome, human cells have two copies of any genomic segment — one from each parent but in case of LOH, only one copy would be present.

Objectives

To spread awareness regarding dangers of consanguinity and relevance of PIGT, Donor Ovum or Donor Sperm in

such couples for a desirable positive fetal outcome and to diagnose antenatally and enable termination of pregnancy if requested by parents after appropriate genetic counseling.

Health education and awareness among clientele.

To enable patients to receive quality healthcare within available resources and reduce burden of healthcare.

Importance of targeted investigations after detailed history taking and perusal of documents.

Importance of Chromosomal Micro Array as a simple invaluable tool in Obstetrics for genetic screening and diagnosis where all effort should be made to avoid maternal cell contamination and send fetal tissue which is easily possible in late second trimester abortions. (Placenta, cord or membranes do not yield results)

Management of cases as per existing Guidelines within legal framework of PCPNDT Act.

Reporting of rare diseases.

CASE REPORT

Ms. X, G9A8, 33-year-old lady with history of second degree consanguineous marriage (maternal uncle) and previous history of 8 second trimester losses without any confirmed definitive diagnosis and numerous repeated ultrasounds, laparoscopies, routine blood investigations and repeated numerous karyotyping of the couple. There was one chromosomal microarray wherein only maternal tissue was detected with complete absence of fetal tissue. In present pregnancy she reported early with all normal biochemical, haematological and viral markers. Her NIPT, NT/NB, dual markers were normal and within statistical range. At 17-18 weeks bedside USG showed grossly reduced liquor, bilateral cystic kidneys and likely hypoplastic heart. She was sent for detailed USG which confirmed severe oligohydramnios, dysplastic kidneys, subaortic VSD, hypoplastic heart, grossly increased NT – 12.5 mm. These findings were similar to her USG in all her previous adverse outcome pregnancies. Pregnancy was terminated and fetal tissue was sent for chromosomal MicroArray, MCC and whole exome sequencing (Nx-Gen WES) which revealed LOH and hitherto unclassified likely pathogenic genetic variant.

Genetic report

Specimen: Fetal Tissue (limbs: two set of specimens in normal saline).

POG: appx 18 - 20 weeks.

Maternal Cell Contamination: not detected

Chromosomal Microarray.

Nx Gen WES.

Chromosomal microarray

Test methodology

Test methodology used was ICSN, arr (1-22) ×2.[4] The whole genome chromosome SNP microarray analysis was performed using the Affymetrix Cytoscan 750K platform which uses over 550,000 non-polymorphic probes and 200,000 SNP probes. Approximately, 250 ng of genomic DNA extracted from product of conception was digested with Nsp1 and ligated with Nsp1 adaptor. The Titanium Taq amplified PCR products of approximately 120-2000 bp were purified using AMP pure beads and fragmented to 25-125 bp size, biotin labelled and hybridized to the Affymetrix Cytoscan 750K GeneChip. The data was analyzed and reported using chromosome analysis suite (ChAS) software based on the human reference genome (GRCh37/hg19).

The whole genome chromosome SNP microarray analysis revealed a normal chromosome complement with no copy number variations. However, significantly high long continuous regions of homozygosity (LCSH) ranging from ~17.0-40.8 Mb were observed in the chromosomes 5, 9, 12, 14 and 21. The long continuous stretch of homozygosity also confers recessive disease risk.

Interpretation

The whole genome chromosome microarray analysis revealed a normal chromosome complement and did not demonstrate significant DNA copy number changes within the clinically significant criteria for the analysis indicated below. There are however, extended contiguous regions of allele homozygosity ranging from ~17.0-40.8 Mb was observed in the chromosomes 5, 9, 12, 14 and 21. encompassing approximately 5.81% of the genome. Although this result was not diagnostic of a specific condition, it raised the possibility of a recessive disorder with a causative gene located within one of these regions. Additionally, these results could indicate a familial relationship (3rd degree) between individual's parents (which was confirmed on both sides as this was a cultural practice for ages in this community).[5]

Genetic counselling and correlation of the result with family history was recommended which was done.

Positive evaluation criteria

The array detected copy number changes and absence of heterozygosity (AOH), which may be due uniparental disomy (UPD) or identity by descent (IBD). The deletions and duplications smaller than 50 kb were not reviewed. The array detected gains and losses ≥50 kb for clinically relevant deletion/duplication subtelomere and pericentromere region or targeted genes. Significant AOH was reported for stretches of DNA >15 Mb on a single

chromosome, suggestive of UPD or >10 Mb on multiple chromosomes, suggestive of IBD. Benign copy number changes present in >1% of the population were not reported. The test detected gain or loss of entire chromosomes, deletions and duplications of the loci represented on this array. Balanced rearrangements such as Robertsonian translocations, reciprocal translocations and inversions and balanced insertions were not detected by this test. It also did not detect DNA mutations, deletions or duplications below the resolution of this array or disease associations based on linkage analysis. SNP analysis can only detect uniparental isodisomy and some cases of heterodisomy, but this test cannot rule out the presence of UPD caused by heterodisomy. The detection of mosaicism by this array is variable and is dependent on the size of the chromosomal imbalance, type of the array used and the quality of array results.

Pathogenic variants are interpreted based on the recommendations and guidelines of American College of Medical Genetics (ACMG, 2021) and International Standard of Cytogenomics Arrays (ISCA).[4,6] Pathogenic variants category include copy number variants (CNVs) which overlap with clearly established clinical significance. This usually means that a suspected disorder for which testing had been requested has been confirmed. Other categories are likely pathogenic which include CNVs, that overlaps with a genomic region consistent with a syndrome containing OMIM morbid genes as well as deletions that overlap autosomal recessive genes (which may unmask a recessive allele associated with a syndrome/disorder). Some are variants of unknown significance which include CNVs, within a region which are not associated with genetic syndromes or symptoms of disease, deletions that overlap autosomal recessive genes (which may unmask a recessive allele but are not associated with a syndrome/disorder), de novo CNVs with no OMIM genes or genes associated with diseases as yet.

Other subcategories are likely benign and benign which include CNVs which overlap with the genome listed as benign in ISCA or other database based on large patient samples and heterozygous duplication with no known OMIM morbid genes; Benign category includes CNVs which are known not to be responsible for disease. Generally, no further action is warranted on such detections.

Nx gen whole exome sequencing

Test methodology

Genomic DNA was extracted from the sample submitted and libraries were prepared using Twist exome 2.0 kit. Target exonic regions (GRCh38) were captured using standard hybridization-based target enrichment protocol. The libraries were sequenced at a mean coverage of >90x on the Illumina NovaSeqX Plus sequencing platform. Variant calling was performed using DRAGEN (Dynamic Read Analysis for GENomics) pipeline, version v4.3.13.[7]

Secondary findings: Negative: ACMG (v3.3)

Incidental findings: Negative: None Variant calling and prioritization

All disease-causing variants reported in OMIM and ClinVar, as well as all variants with minor allele frequency (MAF) below 0.05 in ExAC, 1000 GENOMES and gnomAD database are considered.[9,10] In addition, provided family history and clinical information may be used to evaluate identified variants with respect to their pathogenicity and causality, and are categorized into classes 1-5 according to ACMG guidelines.[11] All variants related to the phenotype of the patient, except benign or likely benign variants, are reported.

Detailed analysis

Detailed analysis is given in Tables 1 and 2.

Variant summary- interpretation

CRELD1 NM_001077415.3: c.778C>T; p.Gln260* Likely Pathogenic.

A heterozygous nonsense variant was detected in the CRELD1 gene (c.778C>T; p.Gln260*). Clinical phenotypes of this patient overlap with the manifestations of the condition associated with CRELD1 gene.

It is absent in gnomAD database and has not been previously reported in ClinVar database. This variant is classified as likely pathogenic according to ACMG classification. Further clinical evaluation of the patient will give more insight into the phenotypic overlap.

Variant coverage statistics: ref allele coverage - C=11; alt allele coverage - T=12.

OMIM gene and disease association

CRELD1 (CRELD disulfide isomerase 1)

Gene: CRELD1 (CRELD disulfide isomerase 1) is a protein coding gene. Diseases associated with CRELD1 include atrioventricular septal defect 2 and Jeffries-Lakhani neurodevelopmental syndrome. Gene ontology (GO) annotations related to this gene include calcium ion binding. An important paralog of this gene is CRELD2.[12]

Table 1: Variant details.

Gene/ REFSEQ	Coord (GRCh38)	Variant (23X)	Exon/ Intron	Variant type	Zygosity/ Inheritance	OMIM/ phenotype	CLASSFN/ ACMG/AMP
CRELD1/ NM_001077415.3	**chr3: 9942857**	**c.778C>T p.Gln260***	**Exon 8**	**Nonsense**	**Heterozygous/ AD**	**Atrioventricular septal defect, partial, with heterotaxy syndrome (OMIM# 606217)**	**Likely pathogenic**

Table 2: Statistical analysis.

Variable	Analysis	Variable	Analysis
Exome coverage ≥20x	96.66%	**Variant read depth**	23x
Target genes/regions coverage at 20x	98.30%	**Variant allele frequency**	66.66%
Exome coverage ≥50x	53.19%	**Total reads generated (millions)**	37
Target genes/regions coverage at 50x	65.68%	**Total reads aligned**	99.28%

DISCUSSION

Atrioventricular septal defect, partial, with heterotaxy syndrome (OMIM# 606217)

Atrioventricular septal defect (AVSD), also called atrioventricular canal defect, common atrioventricular canal, or endocardial cushion defect, is a spectrum of congenital heart malformations defined by a common atrioventricular (AV) junction with deficient AV septation. Defective growth and fusion of the superior and inferior endocardial cushions produce abnormalities of the atrial septum, ventricular septum, and AV valves, creating connections excess blood flow to the lungs. Two principal anatomic patterns are described: ostium primum ASD, in which the atria communicate but the right and left AV valvular orifices remain separate despite a common junction; and complete AVSD, in which a single common AV valve is present. AVSD may occur isolated or as part of syndromes, most commonly Down syndrome and Ivemark syndrome.

Clinical/anatomic variants[13]

Atrial-level shunt only

Interatrial communication above the AV valve, no interventricular communication; bridging leaflets are bound down to the crest of a scooped-out ventricular septum so shunting occurs at the atrial level only.

Ventricular-level shunt only

Interventricular communication below the AV valve, no interatrial communication; bridging leaflets are bound to the atrial septum so shunting occurs at the ventricular level only.

Both atrial and ventricular communications

Interatrial communication above and interventricular communication below the AV valve; these may be restrictive or unrestrictive. In unrestrictive interventricular communications there is no interventricular pressure gradient and the bridging leaflets often float within the defect.

Restrictive interventricular communication

Small VSD immediately below the AV valve.

Unbalanced ventricles

One ventricle markedly larger than the other; distinct from unbalanced commitment of the common AV valve to the ventricles, which should be coded separately.[13] Further reading and detailed understanding of ICD – 11 of the classification is recommended by the author.

Jeffries-Lakhani neurodevelopmental syndrome (JELANS) is an autosomal recessive disorder characterized by hypotonia, early-onset seizures, and global developmental delay apparent from infancy. Affected individuals have motor delay, speech delay, and impaired intellectual development, and about half of patients are non-ambulatory and/or nonverbal. Some patients have cardiac arrhythmia, but congenital cardiac septal defects are only rarely observed. Additional features may include feeding difficulties, recurrent infections, ocular defects, and nonspecific dysmorphic features. Premature death due to cardiac arrhythmia or epilepsy may occur. An autosomal recessive neurodevelopmental disorder characterized by developmental delay, early-onset epilepsy, and hypotonia apparent from infancy. Clinical features include motor delay, speech delay, and impaired intellectual development. About half of patients

are non- ambulatory and/or non-verbal. Some patients have cardiac rhythm disturbances, and some experience recurrent infections. Premature death due to cardiac arrhythmia or epilepsy may occur.[14,15]

The present genetic variant does not match JELANS as reported in OMIM, or ClinVar Database. However, phenotypic and clinical variant overlaps with JELANS; therefore, author has detailed a short summary.

Inheritance

Autosomal dominant (AVSD)/autosomal recessive (JELANS).

Age of onset

Infancy, neonatal, antenatal (in-utero).

Orphanet

98722 (AVSD), JELANS (not available).

OMIM

606217, 620771.

ICD-10

Q21.2 - Atrioventricular septal defect, Q89.7 - congenital malformations, not elsewhere classified (JELANS).

ICD-11

LA87.4 - Common atrioventricular junction with atrioventricular septal defect, not available for JELANS.

Diagnostic methods available are antenatal surveillance via diligent history taking, targeted USG, chromosomal microarray and WES. Prognosis is grave and termination is advised if detected antenatally. Her pregnancy was terminated uneventfully on request and she was discharged on the same day. Couple was counseled regarding donor gametes and legal avenues of adoption.

CONCLUSION

Evaluation of consanguineous marriages involves detailed perusal of all previous clinical data, correlation of clues to inherited syndromes, complete ancestry and their evaluation if available. Chromosomal microarray, QF-PCR, MCC Nx GEN WES and Sanger sequencing should be advised and recommended in all unexplained fetal losses, congenital malformations and stillbirths. Genetic testing should be made mandatory in absence of clues under government aegis for population studies and eugenics. It greatly helps in clinical management of couples with consanguineous marriages looking for answers and spending lakhs on investigations and treatments which are at present not available with medical science. Government and ASHA workers should discourage consanguineous marriages at their community level to avoid poor obstetric outcomes in such alliances. Such marriages are often related to economic hardships in the community due to dowry and property related concerns in small land parcel owners and farmers. Such family alliances are also common in rich and affluent to avoid distribution of their wealth. Healthcare education and community level participation is required to explain the dangers of inbreeding and prevent such mishaps.

ACKNOWLEDGEMENTS

Author wishes to acknowledge the wholehearted technical support of Lal Path Labs (India) and team, in enabling Genetic Testing in Ajmer Dist (Rajasthan) at AFMS Hospital.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Naeim F, Rao PN, Grody WW. Chapter 3 - Principles of Cytogenetics, Hematopathology. Academic Press. 2008;57-64.
2. Schwab M. Loss of Heterozygosity. Encyclopedia of Cancer. Springer, Berlin, Heidelberg. 2011.
3. Ryland GL, Doyle MA, Goode D, Boyle SE, Choong DYH, Rowley SM, et al. Loss of heterozygosity: what is it good for? BMC Med Genomics. 2015;8:45.
4. McGowan-Jordan J, Hastings R, Moore S. Re: International System for Human Cytogenetic or Cytogenomic Nomenclature (ISCN): Some Thoughts. Cytogenetic Genome Res. 2021;161(5):225-6.
5. Hoppman N, Rumilla K, Lauer E, Kearney H, Thorland E. Patterns of homozygosity in patients with uniparental disomy: detection rate and suggested reporting thresholds for SNP microarrays. Genet Med. 2018;20(12):1522-7.
6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, 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):405-24.
7. Behera S, Catreux S, Rossi M, Truong S, Huong Z, Ruehle M, et al., Comprehensive genome analysis and variant detection at scale using DRAGEN, Nat Biotechnol 2024;2382.
8. Lee K, Abul-Husn NS, Amendola LM, Brothers KB, Chung WK, Gollob MS, et al. ACMG SF v3.3 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025;27(8):101454.

9. Amberger JS, Bocchini CA, Schiettecatte F, Scott AF, Hamosh A. OMIM.org: Online Mendelian Inheritance in Man (OMIM®), an online catalog of human genes and genetic disorders. Nucleic Acids Res. 2015;43:D789-98.
10. Landrum MJ, Chitipiralla S, Brown GR, Chen C, Gu B, Hart J, et al. ClinVar: improvements to accessing data. Nucleic Acids Res. 2020;48(D1):D835-44.
11. Rehder C, Bean LJH, Bick D, Chao E, Chung W, Das S, et al. Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1399-415.
12. Stelzer G, Rosen R, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses. Curr Protocols Bioinformat. 2016;54:30-3.
13. Rappaport N, Twik M, Plaschkes I, Nudel R, Stein TI, Levitt J, et al. MalaCards: an amalgamated human disease compendium with diverse clinical and genetic annotation and structured search. Nucleic Acid Res. 2017;45(D1):D877-87.
14. Jeffries L, Mis EK, McWalter K, Donkervoort S, Brodsky NN, Carpier J-M, et al. Biallelic CRELD1 variants cause a multisystem syndrome, including neurodevelopmental phenotypes, cardiac dysrhythmias, and frequent infections. Genet Med. 2024;26(2):101023.
15. MalaCards-Human Disease Database. Atrio-ventricular Septal Defect (AVSD). Available at: https://www.malacards.org/card/atrioventricular_septal_defect?search=CRELD1#TraitsCategories. Accessed on 12 January 2026.

Cite this article as: Devi LT. A novel genetic variant in loss of heterozygosity. Int J Reprod Contracept Obstet Gynecol 2026;15:1411-6.