Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Novel Chromosome 18 Polymorphism Identified through NIPT: A Case Report

Andrea Ramirez

andrea.ramirez@cuanschutz.edu

CU Anschutz Academic Office One

Charlotte Pollack

CU Anschutz Academic Office One

Mikayla Stoeker

CU Anschutz Academic Office One

Leilah Zahedi-Spung

CU Anschutz Academic Office One

Case Report

Keywords: NIPT, Trisomy 18, Variants of Uncertain Significance

Posted Date: August 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10542843/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Trisomy 18 is one of the most common autosomal trisomies observed in live births, and it has serious fetal and neonatal impacts that are most often not compatible with life. The advent of cell-free fetal DNA (cfDNA) testing, also known as non-invasive prenatal testing (NIPT), has significantly enhanced early detection of chromosomal abnormalities.

Case Presentation

We report on a specific patient case whose prenatal genetic testing resulted as concerning for trisomy 18. Further testing revealed that the patient and fetus shared the same triplication in chromosome 18 and neither had phenotypic abnormalities. This case led to a review on chromosome 18 variants that have been previously reported. In conclusion, we report that recognition of the importance of confirmatory testing is critical when prenatal screens come back abnormal.

Conclusion

Our case highlights a specific triplication of chromosome 18 that has never been reported before and has no phenotypic abnormalities. It emphasizes how Variants of Uncertain Significance are important to consider when reviewing novel triplications. In conclusion, we emphasize the importance of confirmatory testing when prenatal screens come back abnormal to guide counseling provided by the obstetrician.

Background

Chromosome aberrations remain a major contributor to failed pregnancies, infant mortality, and lifelong disabilities. Chromosome 18 is one of the 23 pairs of human chromosomes and contains over 76 million base pairs, representing about 2.5% of the total DNA in a human cell. Alterations in chromosome 18, whether structural or numerical, are associated with various conditions, such as Trisomy 18 (Edwards syndrome), Pitt-Hopkins syndrome (PTHS), and partial aneuploidies (1, 2). Trisomy 18 is seen once in every 5000 live births, making it the second most common autosomal trisomy observed in live births (3). Pregnancies complicated by Trisomy 18 have an increased risk of intrauterine fetal demise as well as congenital cardiac, neural, renal, and gastrointestinal abnormalities (4, 5, 6). Survival postnatally is also limited by significant anomalies of these different organ systems.

Trisomy 18 can be broken down into three types: complete trisomy 18, translocations involving Trisomy 18, and trisomy 18 mosaicism (7). Complete trisomy 18, the most common form comprising about 90% of cases, involves every cell containing 3 copies of chromosome 18. Translocations or other rearrangements can cause partial trisomy 18 with highly variable clinical impacts. In Mosaic trisomy 18, individuals carry a complete trisomy 18 in some cells, and others only carry two copies with a wide variety of phenotypes. Despite these known conditions, novel aberrations in chromosome 18 continue to expand our understanding of its genetic complexity and the range of phenotypes it can produce.

Most cases of Trisomy 18 are diagnosed prenatally based on screening or detection of common phenotypic ultrasound abnormalities such as fetal growth restriction, clenched fists, choroid plexus cysts, overlapping fingers, micrognathia, or congenital heart defects (8). The advent of cell-free DNA (cfDNA) testing, also known as non-invasive prenatal testing (NIPT), has significantly enhanced early detection of chromosomal abnormalities. CfDNA testing, performed starting at 10 weeks gestation, involves analyzing small fragments placental DNA circulating in the maternal bloodstream. This technology offers high sensitivity and specificity for common aneuploidies such as Trisomy 18, Trisomy 21, and Trisomy 13, identification of sex chromosomes and Rhesus blood type (9). However, while cfDNA is a powerful screening tool, it cannot confirm or precisely characterize the nature of chromosomal abnormalities, necessitating confirmatory invasive diagnostic procedures when anomalies are detected. The American College of Obstetricians and Gynecologists (ACOG) recommends that diagnostic testing with chorionic villous sampling or amniocentesis should be offered following a positive screening test or detection of fetal structural anomaly (10).

In this case report, we explore known chromosome 18 variants after the discovery of a novel copy number variant on chromosome 18 in a patient case. This review was completed to provide the patient with thorough and appropriate counseling after receiving abnormal screening results. The novel copy number variant of interest was detected through a combination of cfDNA screening, amniocentesis, chromosome analysis, FISH, and chromosomal microarray analysis. This variant expands the known spectrum of chromosomal abnormalities on chromosome 18 and highlights the importance of integrating advanced genomic technologies with traditional diagnostic methods to uncover new genetic variants and their clinical implications.

Case Presentation

A 25-year-old G1P0 initially presented for termination of pregnancy at 15w3d after her prenatal cfDNA results obtained at an outside hospital demonstrated high-risk for Trisomy 18 per her report. Her medical history was notable for asthma, carrier status for cystic fibrosis, and a remote personal medical history of kidney stones. She had no pertinent surgical history. She had been referred to a Complex Family Planning clinic by her primary obstetrician/gynecologist (OBGYN) for termination, as she had been counseled by her provider that these cfDNA results were “99% accurate.” While positive predictive value for QNatal Advanced cfDNA screening is relatively high at ~ 92%, it was discussed with the patient that these results alone are not diagnostic of aneuploidy (11). When stratifying for maternal age, the calculated PPV was 15% with a false positive value of 85% (12). However, on further detailed review of the patient’s original cfDNA report, it stated that the screening test was unable to be completed for Trisomy 18. The chromosomal data pattern interfered with the ability of the test to detect fetal gain of chromosome 18, and the report recommended further expert discussion for alternative screening or diagnostic testing.

At this initial encounter, a rudimentary anatomy ultrasound was performed by a board-certified Maternal Fetal Medicine provider and did show not any expected abnormal findings for Trisomy 18 such as

hypoplastic nasal bone, micrognathia, or thickened nuchal fold, although exact measurements were deferred to a later anatomy scan. After ascertaining that this would be a desired pregnancy in the absence of confirmed trisomy 18, the patient was counseled on her option to undergo confirmatory testing via amniocentesis for which she ultimately consented. The amniocentesis was performed in standard fashion at 15w3d during this same initial encounter without immediate complication. The amniotic fluid sample was sent for fluorescence in situ hybridization (FISH), chromosome analysis, and chromosomal microarray analysis (CMA).

FISH analysis of uncultured amniocytes was normal, suggesting the fetus was not affected with Trisomy 18. Fetal chromosome analysis identified an abnormal banding pattern on 18q (Fig. 1). Chromosome analysis detected an atypical banding pattern on the long arm of chromosome 18. While 5 Mb is typically considered the threshold of cytogenetic visibility of copy number gains and losses, the two additional copies of this region appear to be located in tandem and immediately adjacent to the original DNA. Concurrent single nucleotide polymorphism (SNP) microarray clarified this abnormality to be a 5.2Mb triplication (totaling 4 copies) of chr18:36,723,898 – 41,924,037 (grch37) evidenced by the significantly elevated LogR average and the BAF plot with AAAB, BBAA, and BBBA tracks (Fig. 2).

Chromosome and microarray analysis of the patient's blood specimen determined that the triplication was maternally inherited in that they shared the same triplication. Given the lack of similar variants in the healthy population, patient databases, and published literature, this triplication was classified as a Variant of Uncertain Significance (VUS) by CMA following American College of Medical Genetics and Genomics (ACMG) Technical Standards (13). Inheritance from an unaffected parent was not sufficient to reclassify the copy number variant interpretation, but suggests that the gain may be a rare, possibly benign familial variant. However, the possibility of variable expressivity and/or reduced penetrance could not be excluded by the lab, and further correlation with fetal monitoring was recommended in this highly desired pregnancy.

The patient had a repeat formal anatomy survey at 20 weeks, which continued to reveal an anatomically normal and appropriately grown fetus. The patient was reassured that this fetus did not have traditional Trisomy 18. Unfortunately, at 21 weeks of gestation, the patient presented with previable preterm premature rupture of membranes and an intrauterine fetal demise. She was induced and subsequently delivered a demised fetus via vaginal delivery. Notably, no findings characteristic of Trisomy 18 or other known chromosomal syndromes were seen in the pathological autopsy of the fetus, placenta, or umbilical cord.

Discussion and Conclusion

The case above is notable due to the large size of the triplication with apparent lack of phenotypic findings consistent with Trisomy 18. Trisomy 18 phenotype is commonly due to duplications of the entire chromosome; however, there are few cases that reflect individuals with partial duplications of different regions of chromosome 18. This is an example of a triplication of chromosome 18 (18q12.2q12.3) that

led to a presumed phenotypically normal fetus and phenotypically normal adult with no physical malformations or mental and developmental abnormalities.

This specific triplicated region of interest (chr18:36,723,898 – 41,924,036) contains only three protein-coding genes, *PIK3C3, RIT2*, and *SYT4*, along with several pseudogenes and genes coding for untranslated mRNA molecules as seen in Fig. 3 (14, 15). None of these genes involved are currently known to be associated with disease per the Online Mendelian Inheritance in Man (OMIM) catalog of genes, nor has dosage sensitivity been evaluated by the Clinical Genome Resource. Additionally, the majority of the triplication lies within the heterochromatic 18q12.3 band that is unlikely to experience frequent transcription. The Clinical Genome Resource has not yet evaluated any of the genes for dosage sensitivity, and thus the functions of these noncoding regions are not well understood, so it is unknown how an increase in these regions may or may not be pathologic (15).

A case report published in 1990 details an infant with partial Trisomy 18 due to a noted triplication in part of 18q12(17). This variant was discovered after the patient was thoroughly evaluated for developmental delay at 2 years of life. A 2013 review paper discusses a case of duplication 18q12.1-18q12.2 with a phenotype that was pathogenic for Autistic Spectrum Disorder (18). This duplication is noted to be proximal to the segment that was duplicated in our patient. The are also two published case reports of deletions of this specific chromosome 18 region of interest. There is a reported 5.3Mb deletion within band q12.3 that resulted in expressive dysphagia and a 9.5MB deletion that resulted in a seizure disorder and limited speech (16). A thorough review of existing documented genomic data, using the DECIPHER database was done. There were no documented patients with a similar size triplication as that of our patient. More specifically, there is no associated syndrome or associated morbid disease in this identified segment, nor was there a documented patient with a comparable triplication. We also reviewed the UCSC Genome Browser and the Database of Genomic Variants (DGV). On these reviews, there were no noted morbid genes associated with triplications in our gene segment and no documented similar triplication seen in healthy individuals. These previous cases and our database review may suggest that this specific patient's triplication is uniquely situated in a genetic region less susceptible to pathology from copy number variations. The unique asymptomatic nature of our patient's multiplication suggests that these genes are not pathological in excess, as so many genes closely located on 18q can be due to the heterochromatic nature of it.

Retrospective conversations with a QNatal geneticist detailed that on analysis of chromosome 18, there was some unknown chromosomal data pattern in the background that interfered with detecting a gain or loss of this chromosome in the standard fashion. The geneticist shared that when they have these findings, they are unable to validate the screen and report a copy number. It was emphasized that this often occurs in the setting of copy number variants, and the geneticist was not surprised to hear about the result of the microarray. The geneticist detailed that this affects the validity of this screen even in minuscule aberrations. The cfDNA formal report recommended further discussion for alternative screening or diagnostic testing and that irreversible pregnancy management decisions should not be based solely on these screening results.

In conclusion, cfDNA ordering providers should be aware of the respective positive predictive values of their patients given the potential consideration of pregnancy termination in the setting of abnormal results. This case highlights the importance of effective and productive communication with patients when disclosing negative news. In meeting this patient for the first time when she presented requesting termination, it was left unknown what her initial provider disclosed to her and any potential misunderstanding given the weight and uncertainty of the news. There are various financial and psychological implications that arise when pregnancy termination is being considered; therefore, confirmatory testing must always be offered to guide counseling on possible pregnancy outcomes especially in the context of unclear screening results. Further, the case we shared that led to a database review emphasizes the need for continued molecular characterization of chromosomal abnormalities to help determine the clinical and phenotypical importance of specific genotypes. To our knowledge, this is the only case of a multiplication of this region of chromosome 18 that resulted in phenotypically normal maternal and fetal findings.

Abbreviations

1. Pitt-Hopkins syndrome
PTHS
2. cell-free fetal DNA
cfDNA
3. non-invasive prenatal testing
NIPT
4. American College of Obstetricians and Gynecologists
ACOG
5. Obstetrician/gynecologist
OBGYN
6. Fluorescence in situ hybridization
FISH
7. Chromosomal microarray analysis
CMA
8. Single nucleotide polymorphism
SNP
9. Variant of Uncertain Significance
VUS
10. American College of Medical Genetics and Genomics
ACMG
11. Long non-coding ribonucleic acid
lncRNA
12. Micro ribonucleic acid
miRNAs
13. Database of Genomic Variants

DGV

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable data included in this article. **(will do, will call and then subsequently email the patient the consent form, and upload to her media tab)

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

Andrea Ramirez and Charlotte Pollack contributed equally to this work. Mikayla Stoeker contributed her knowledge and expert review on genetic databases and subsequent interpretations of such. Leilah Zahedi-Spung oversaw and provided guidance and feedback in the development of this case report. All authors read and approved the final manuscript.

Acknowledgements

We are grateful to Mikayla Stoecker and QNatal Geneticists for their assistance with interpretation of genetic reports. We are also grateful to the patient for permission to report on her pregnancy.

References

1. Nusbaum C, Zody MC, Borowsky ML et al. DNA sequence and analysis of human chromosome 18 [published correction appears in Nature. 2005;438(7068):696. O'Neill, Keith [added]]. *Nature*. 2005;437(7058):551–555. 10.1038/nature03983

2. Zweier C, Peippo MM, Hoyer J, et al. Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). Am J Hum Genet. 2007;80(5):994–1001. 10.1086/515583.
3. Kosho T, Nakamura T, Kawame H, Baba A, Tamura M, Fukushima Y. Neonatal management of trisomy 18: clinical details of 24 patients receiving intensive treatment. Am J Med Genet A. 2006;140(9):937–44. 10.1002/ajmg.a.31175.
4. Bruns D, Campbell E. Twenty-two survivors over the age of 1 year with full trisomy 18: presenting and current medical conditions. Am J Med Genet A. 2014;164A(3):610–9. 10.1002/ajmg.a.36318.
5. Goel N, Morris JK, Tucker D, et al. Trisomy 13 and 18-Prevalence and mortality-A multi-registry population based analysis. Am J Med Genet A. 2019;179(12):2382–92. 10.1002/ajmg.a.61365.
6. Rosa RF, Rosa RC, Zen PR, Graziadio C, Paskulin GA. Trisomy 18: review of the clinical, etiologic, prognostic, and ethical aspects. Rev Paul Pediatr. 2013;31(1):111–20. 10.1590/s0103-05822013000100018.
7. Edwards JH, Harnden DG, Cameron AH, Crosse VM, Wolff OH. A new trisomic syndrome. Lancet. 1960;1(7128):787–90. 10.1016/s0140-6736(60)90675-9.
8. Cereda A, Carey JC. The trisomy 18 syndrome. *Orphanet J Rare Dis*. 2012;7:81. Published 2012 Oct 23. 10.1186/1750-1172-7-81
9. Raj H, Yelne P. Cell-Free Fetal Deoxyribonucleic Acid (cffDNA) Analysis as a Remarkable Method of Non-Invasive Prenatal Screening. Cureus. 2022;14(10):e29965. Published 2022 Oct 5. 10.7759/cureus.29965
10. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics, Committee on Genetics, and Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020;136(4):e48–69.
11. Strom CM, Anderson B, Tsao D, Zhang K, Liu Y, Livingston K, Elzinga C, Evans M, Nguyen Q, Wolfson D, Rowland C, Kolacki P, Maxwell M, Wang JC, Rabin D, Catanese J, Owen R, Braastad C, Sun W. Improving the Positive Predictive Value of Non-Invasive Prenatal Screening (NIPS). PLoS ONE. 2017;12(3):e0167130.
12. NIPT Cell-Free DNA Screening Predictive Value Calculator. URL https://ppv.geneticsupportfoundation.org/ [10/14/2025]
13. Riggs ER, Andersen EF, Cherry AM, Kantarci S, Kearney H, Patel A, Raca G, Ritter DI, South ST, Thorland EC, Pineda-Alvarez D, Aradhya S, Martin CL. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med. 2020;22(2):245–257. Epub 2019 Nov 6. Erratum in: Genet Med. 2021;23(11):2230.
14. Clinical Genome Resource. https://search.clinicalgenome.org/kb/genes?page=1&size=50&search=rit2&byName=0 [10/14/2025]
15. UCSC Genomics Browser. https://genome.ucsc.edu/ [10/14/25].

16. Bouquillon S, Andrieux J, Landais E, et al. A 5.3Mb deletion in chromosome 18q12.3 as the smallest region of overlap in two patients with expressive speech delay. Eur J Med Genet. 2011;54(2):194–7. 10.1016/j.ejmg.2010.11.009.
17. Wilson GN, Heller KB, Elterman RD, Schneider NR. Partial trisomy 18 with minimal anomalies: lack of correspondence between phenotypic manifestations and triplicated loci along chromosome 18. Am J Med Genet. 1990;36(4):506–10. 10.1002/ajmg.1320360427.
18. Wang P, Carrion P, Qiao Y, et al. Genotype-phenotype analysis of 18q12.1-q12.2 copy number variation in autism. Eur J Med Genet. 2013;56(8):420–5. 10.1016/j.ejmg.2013.05.006.

Figures

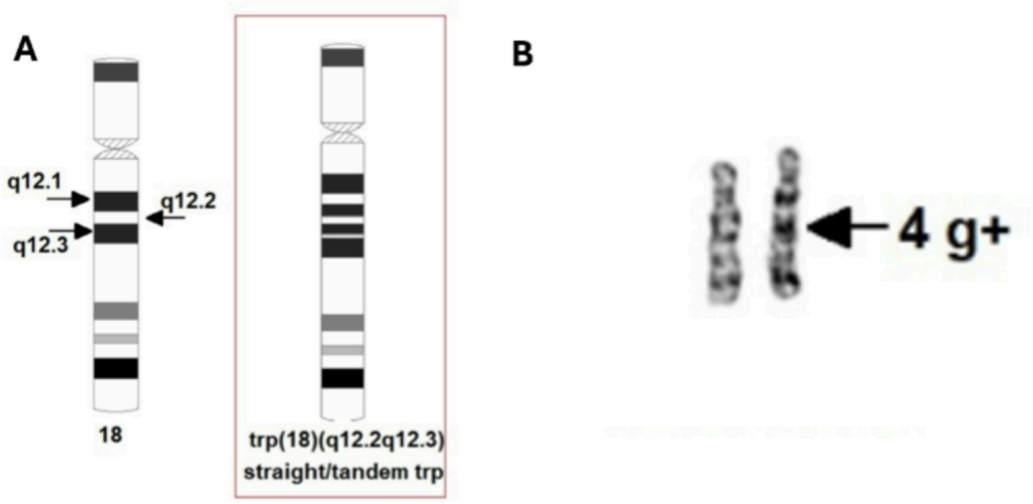


Figure 1

A) Idiogram of the typical chromosome 18 banding pattern (left) in contrast with the atypical pattern caused by the triplication of q12.2-q12.3 (right, in red box). B). G-banded normal 18 (left) and triplicated 18 (right)

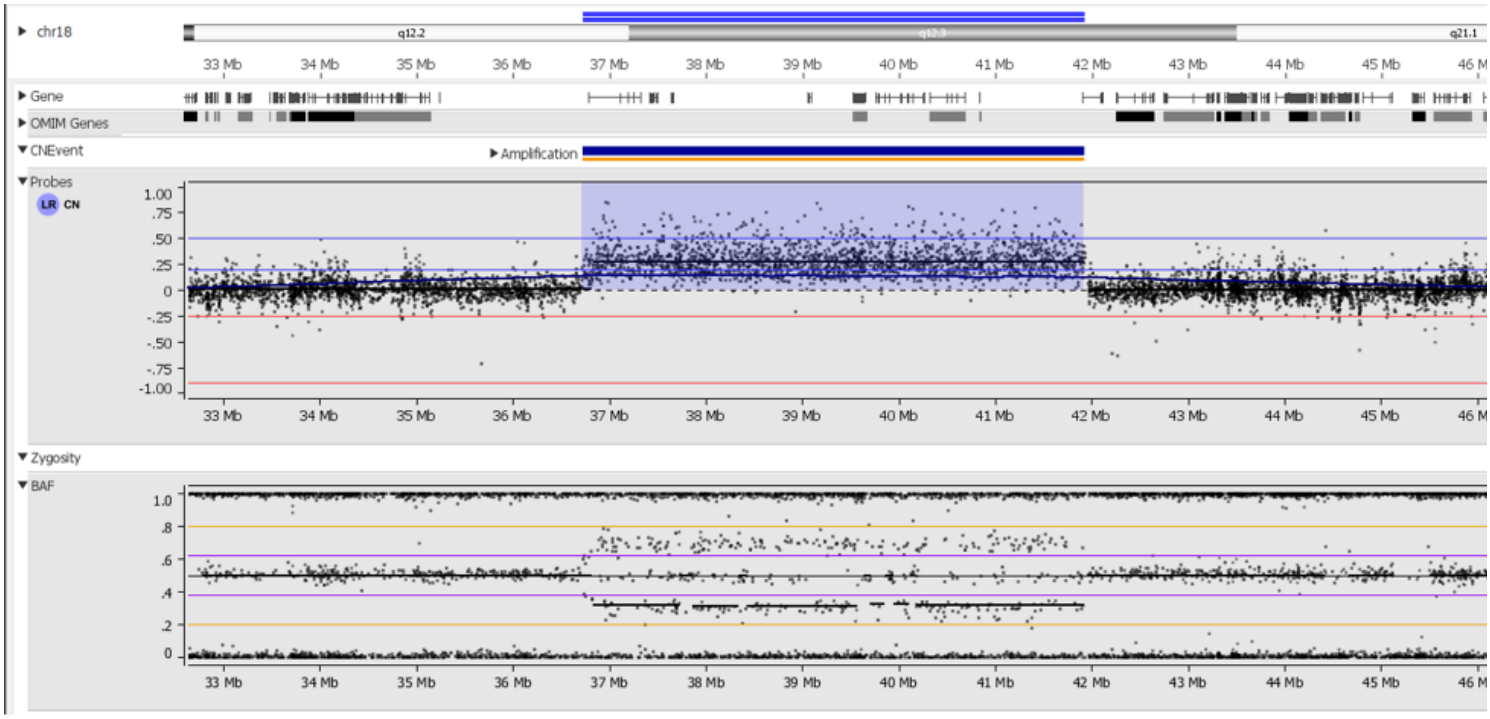


Figure 2

SNP chromosomal microarray (CMA) results from cultured amniocytes run on Illumina® Infinium Global Diversity bead array platform and processed with NxClinical software (Bionano INC.)

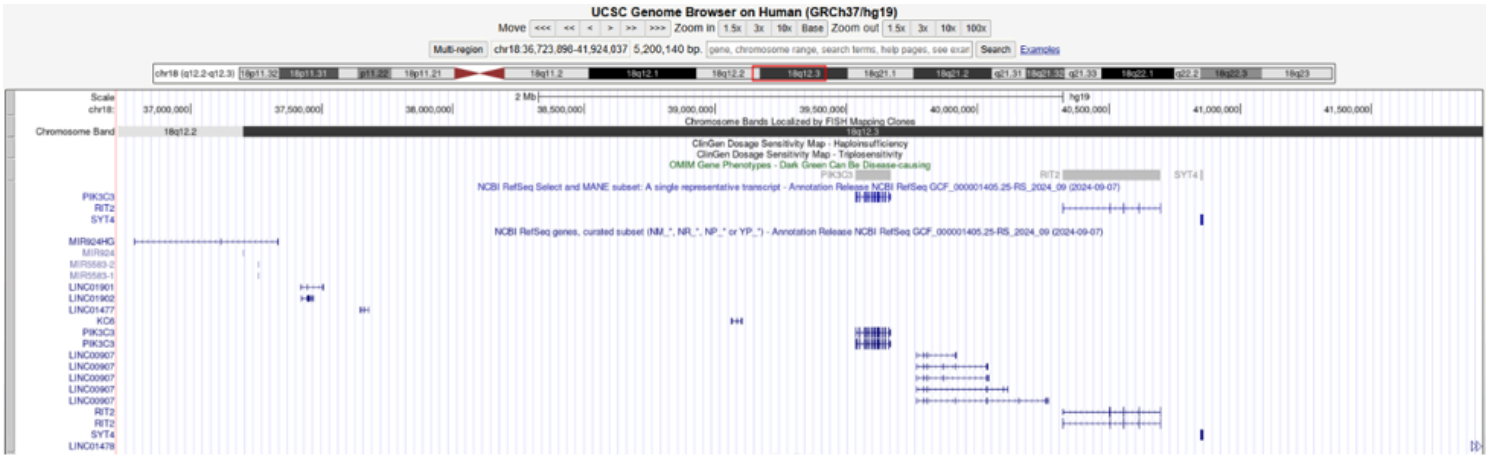


Figure 3

According to the UCSC Genome Browser, the only protein-coding genes in the triplicated region are *PIK3C3, RIT2,* and *SYT4,*although many non-protein-coding genes and pseudogenes can be found, such as the lncRNAs (LINC) and miRNAs (MIR) shown in the browser image.