# Challenges in genetic counseling for likely pathogenic - low penetrance copy number variants in prenatal diagnosis samples.

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## Introduction

The 15q11.2 (BP1-BP2) microdeletion is associated with developmental delay, abnormal behavior, generalized epilepsy and congenital heart disease.
The area between BP1 and BP2 is approximately 500 kb in size including four genes - NIPA1, NIPA2, TUBGCP5, and CYFIP1 and prone to both microdeletions and microduplications.
This region contains genetic material showing incomplete penetrance or low penetrance of pathogenicity along with variable expressivity.
The penetrance of the 15q11.2 BP1–BP2 microdeletion is estimated to be 10.4%
Patients with the 15q11.2 BP1–BP2 microdeletion can present with developmental and language delay, neurobehavioral disturbances and psychiatric problems. Autism, seizures, schizophrenia and mild dysmorphic features are less commonly seen.
This low penetrance and variable expressivity for such microdeletions makes the process of genetic counseling challenging to predict the exact phenotype or clinical outcomes associated with the CNV.

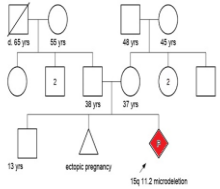
## Aims & Objectives

We present a case where a likely pathogenic, low penetrance CNV was detected during prenatal diagnosis with the aim to:

- Highlight the challenges faced during post counseling.
- Express the importance of genetic counseling in helping such patients to make informed reproductive decisions.

## Case details and Methodology

A non consanguineous married couple underwent NIPT in view of advanced maternal age which was suggestive of high risk for Trisomy 21. Further, prenatal genetic testing by FISH and chromosomal microarray (CMA) 750K to confirm the same was performed on amniotic fluid at 17 weeks 3 days of gestation. The couple has a history of 1 ectopic pregnancy.




## Results

| FISH for Chromosome 13 and 21 | | |
|---|---|---|
| **No of cells analysed** | **Interpretation** | **Result** |
| 50 | 100% cells Negative for aneuploidy of chromosomes 13 and 21 | Normal |

Fish analysis for Chromosome 13 and 21 revealed normal results

| CYTO-ONE ADVANCED (MICROARRAY) | |
|---|---|
| **Summary** | **0.5 MB deletion on chromosome 15** |
| **ISCN format** | arr[GRCh37]15q11.2(22766739-23279684)x1 |
| **Result** | **Likely pathogenic - Low penetrance** |
| **Maternal Cell Contamination** | Negative |

Chromosomal Microarray (High resolution) revealed a 0.5MB deletion on chromosome 15 classified as Likely pathogenic - Low penetrance.

## Discussion

| Concern | Is the fetus affected with Down syndrome? | Clinical Implication of the CNV detected in the microarray report? | Can pregnancy be continued? |
|---|---|---|---|
| **Discussion** | It was discussed that as NIPT is a screening test so there are chances of a false positive result. Further, they were reassured that as the diagnostic tests FISH and CMA report is negative for trisomy 21, which strongly suggests that the fetus is unlikely to be affected by Down syndrome. | They were told that this deletion is common in the general population and often found in asymptomatic individuals. About 90% of people with this deletion show no clinical symptoms. In the remaining 10%, some may have mild neuropsychiatric or behavioral issues, which can vary in severity. Parental analysis to check for the deletion was discussed. It was stressed that even if one partner carries the deletion, predicting whether the current fetus will show symptoms, and how severe they might be, is uncertain. | During genetic counseling, the couple was assured that the decision about their pregnancy was theirs alone, emphasizing respect for their autonomy. They were informed that the identified deletion has low penetrance and variable clinical expression. Detailed explanations of its potential clinical manifestations were provided, empowering them to make an informed decision. Ultimately, they decided to continue the pregnancy. |

## Conclusion

This case underlines the challenges faced during genetic counseling for low penetrance CNV and reflects how perceived risk differs from individual to individual. This case also highlights that non-directive counseling helps individuals make an informed decision if all the relevant information (unbiased facts) are provided to them.

## References

Rafi SK, Butler MG. The 15q11.2 BP1-BP2 Microdeletion (Burnside-Butler) Syndrome: In Silico Analyses of the Four Coding Genes Reveal Functional Associations with Neurodevelopmental Phenotypes. Int J Mol Sci. 2020 May 6;21(9):3296. doi: 10.3390/ijms21093296. PMID: 32384786; PMCID: PMC724644

## Acknowledgment

We would like to thank Neuberg Centre for Genomic Medicine for carrying out the wetlab processes and analysis for the case