Sex Chromosome Abnormalities Are a Major CMA and Chromosome Diagnostic Finding for Ambiguous Genitalia

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Background

Ambiguous genitalia refers to external genitalia that cannot be clearly classified as male or female and is commonly caused by Differences of Sex Development (DSDs), arising from disrupted sex differentiation early in development. Timely and accurate diagnosis of DSDs in newborns is important to guide best inform care. However, broad phenotypic variability and genetic heterogeneity often require advanced cytogenomic testing beyond standard chromosome analysis.

Objectives and Methodology

To evaluate the frequency and spectrum of chromosomal abnormalities detected by **Chromosomal Microarray Analysis (CMA)** and **chromosome analysis (CA)** in individuals with the indication of ambiguous genitalia, we performed a retrospective analysis of a large cohort of individuals with this indication tested at our clinical laboratory.

Results – Chromosomal Microarray Analysis (CMA)

- Among 153 individuals tested by CMA, chromosomal variants were identified in 51 cases. (~33%).
- Sex chromosome involvement was identified in 10 of these cases (~20%). These included mosaic loss of the entire Y chromosome with the presence of X chromosome (N=3), complete or segmental copy number gain of Y chromosome, with or without loss of X chromosome (N=4), absence of heterozygosity (AOH) on X chromosome encompassing the androgen receptor gene (*AR*) (N=1), Xq25q26 duplication syndrome (N=1), and copy number gain in Xq26.1q26.2 (N=1).
- Additionally, 45 cases demonstrated autosomal chromosomes involvement including AOH regions > 5M and/or deletion/duplication associated with uncertain clinical significance, known microduplication syndrome, established disease regions, or previously reported phenotypes. Four cases showed concurrent sex and autosomal chromosome involvement.
- Parental testing was performed in 11 cases. Identified events were indicated to be de novo in 3 cases and inherited from one or both parent(s) in 8 cases.

Results – Chromosome Analysis (CA)

- Among 210 individuals tested by CA, chromosomal structural or numerical variation was identified in 31 cases. (~15%).
- 14/31 (~45%) cases had sex chromosome involvement including mosaicism for a monosomy X cell line and a second cell line with XX or XY or XYY or idic(Y)/psu idic(Y) (N=7), constitutional or mosaic Klinefelter syndrome (N=2), Mosaic Klinefelter syndrome with an additional 46,XX cell line (N=1), triploidy (69,XXY) (N=1), additional chromatin material of unknown origin on the distal short arm of one X chromosome (N=1), and variable regions involving either X or Y chromosome (N=2).
- 17/31 cases involved autosomal chromosomes. Of these, 3 cases were consistent with Down Syndrome, one patient was diagnosed with Cat-Eye-Syndrome, while the remaining cases demonstrated various balanced or unbalanced structural rearrangements such as addition of material with unknown origin, unbalanced translocation, isodicentric or ring chromosome.

Figure 1: Distribution of cases with CMA and CA assessment

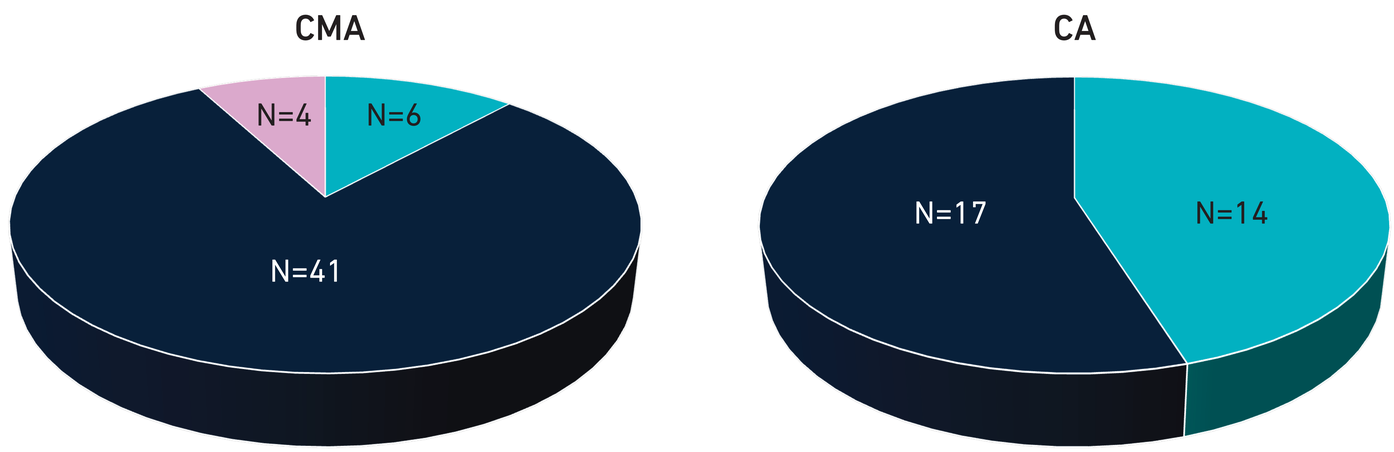

Figure 2: Variants identified by CMA vs. CA

CMA Variants	N
Mosaic loss of the entire Y with the presence of X	3
Complete or partial copy number gain of Y w/wo loss of X	4
AOH > 5Mb on X (including *AR* gene)	1
Xq25q26 duplication syndrome	1
Copy number gain of Xq26.1q26.2	1
Deletions/duplications or AOH >5 Mb in autosomal chromosomes	45
Concurrent sex and autosomal chromosome involvement.	4

CA Variants	N
Mosaicism for Monosomy X and XX or XY or XYY	3
Mosaicism for monosomy X and idic(Y)/psu idic(Y)	4
Complete or mosaic Klinefelter syndrome	2
Mosaic Klinefelter with an additional 46,XX cell line	1
Triploidy (69,XXY)	1
46,X,add(X)	1
Variable region on X or Y	2
Down syndrome	3
Cat-Eye-Syndrome	1
Balanced or unbalanced rearrangements of autosomal chromosomes	13

Conclusions

- This study demonstrates that sex chromosomes are involved in a substantial proportion of variants identified by CMA (~20%) and by chromosome analysis (45%) in patients with ambiguous genitalia.
- We further demonstrate that the percentage of cases with CMA-detected variants (~33%) is significantly higher than that identified by chromosome analysis (~15%), in the clinical evaluation of patients with ambiguous genitalia.
- Additionally, our data indicates that the most frequent sex chromosome variant detected by chromosome analysis is mosaic monosomy X (50%).

Presented at the American College of Medical Genetics & Genomics (ACMG) Annual Meeting, Mar 10-14, 2026, Baltimore, MD USA.