Outcome Following Autosomal Monosomy and Multiple Aneuploidy Results by Noninvasive Prenatal Screening

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Introduction

- A recent study of cytogenetic analysis following spontaneous miscarriage showed that 5% of samples were affected with a multiple aneuploidy.[1]
- An estimated 0.16% of trisomy 21 cases involve a double aneuploidy with either XXX, XXY, XYY or MX. The combination of Down syndrome and Klinefelter syndrome is the most common.[2]
- Full autosomal monosomies are not generally compatible with life; however, partial and mosaic forms of autosomal monosomy have been reported in liveborns
- This study evaluates outcomes of clinical laboratory noninvasive prenatal screening (NIPS) samples from singleton pregnancies receiving multiple aneuploidy and/or autosomal monosomy results

Method

- Database query for all singleton NIPS samples during the study period with one of the following results:
  - Single autosomal monosomy
  - Multiple aneuploidy with aneuploidy detected (AD) and/or aneuploidy suspected (AS) for chromosomes 21,18,13, X and Y
- Outcome information was requested for all cases via:
  - Fax requests
  - Outgoing and incoming phone calls
- Data on 138 samples was reviewed
- Results were classified into one of three categories

Figure 1

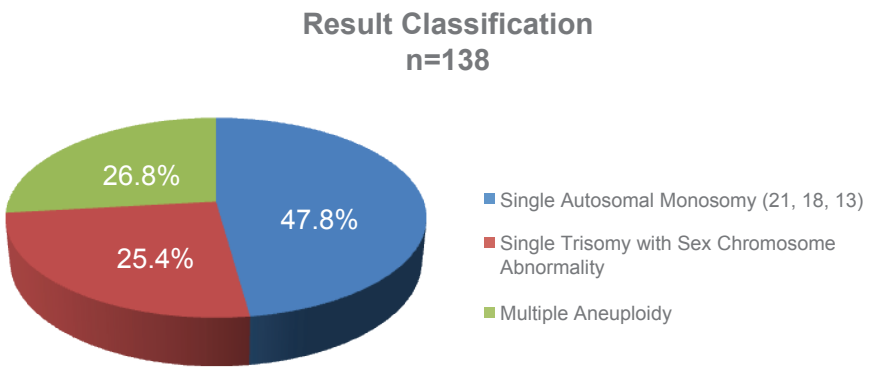

Figure 2

Outcomes

Concordance	Single Autosomal Monosomy	Single Trisomy with Sex Chromosome Abnormality	Multiple Aneuploidy	Total Cohort
Concordant	2	2	1	5
Partially Concordant[1]	0	7	3	10
Discordant	20	10	14	44
Other[2]	7	6	9	22
Outcome Unknown	25	7	10	42
Outcome Unknown, EDD Not Passed[3]	12	3	0	15
Total	66	35	37	138

[1] Concordance confirmed for one aneuploidy
[2] Other outcomes include SAB/TOP/IUFD, maternal conditions and other reported fetal karyotype anomalies
[3] EDD not passed as of data collection

Case Examples

CONCORDANT

Autosomal Monosomy

- Clinical hx: 24 y.o. with Dandy Walker malformation on ultrasound
- NIPS result: full/partial monosomy for chromosome 13
- Prenatal dx: declined
- Outcome: term delivery
- Postnatal array: c/w 9.3Mb deletion on chromosome 13q

CONCORDANT

Multiple Aneuploidy

- Clinical hx: 33 y.o. with echogenic intracardiac focus and shortened long bones on ultrasound
- NIPS result: aneuploidy detected for chromosomes 21 and 18
- Prenatal dx: declined
- Outcome: postnatal fetal karyotype c/w 47,+21; placental analysis c/w mosaic trisomy 18

OTHER

Multiple Aneuploidy

- Clinical hx: 23 y.o. with unilateral multicystic kidney on ultrasound
- NIPS result: aneuploidy detected for chromosomes 21 and 13; full/partial monosomy for chromosome 18
- Prenatal diagnosis: CVS and Amnio c/w 46,XY
- Outcome: Maternal CBC and additional work-up revealed acute lymphocytic leukemia (ALL)

OTHER

Autosomal Monosomy

- Clinical hx: 33 y.o. with cystic hygroma and encephalocele on ultrasound
- NIPS result: full/partial monosomy for chromosome 13
- Prenatal dx: declined
- Outcome: TOP secondary to ultrasound findings; POC karyotype analysis not successful
- Paternal karyotype: c/w 46,XY t(13;20)(q22:q31.1)

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Results

Sample Demographics by Result Classification

	Single Autosomal Monosomy	Single Trisomy with Sex Chromosome Abnormality[1]	Multiple Aneuploidy[1]	Total
Cases	66	35	37	138
Mean Maternal Age (years)	34.4 (19--46)	37.3 (24--47)	35.3 (23--44)	35.4 (19--47)
Mean Gestational Age (weeks)	14.8 (10--32)	12.0 (10--25)	14.0 (10--34)	13 (10--34)
Outcomes Received	29 (43.9%)	25 (71.4%)	26 (70.3%)	81 (58.7%)
EDD not yet passed[2]	12 (18.2%)	4 (11.4%)	1 (2.7%)	17 (12.3%)

[1] Includes AD and AS results
[2] EDD not passed at time of data collection

Summary of Findings

- Overall, full or partial concordance was confirmed in 15 (10.9%) cases
- An additional 13 (9.4%) cases were explained by other biological etiologies, including maternal malignancy (7, 5.1%), maternal karyotype anomalies (1, 0.7%) or other fetal karyotype anomalies (5, 3.6%)
- Some autosomal monosomies were explained by abnormalities in one of the reference chromosomes used to analyze test chromosomes

Conclusions

- Although in most cases, abnormal NIPS results relate to a single trisomy, other results may be reported.
- We anticipate that a portion of multiple aneuploidy and autosomal monosomy findings reflect the fetal karyotype while some may be explained by other etiologies, such as other maternal/fetal chromosomal aberrations, maternal disease, mosaicism or co-twin demise.
- Continued evaluation of outcomes for complex NIPS results is warranted to better understand the biological reasons for such results

References

[1] Subramaniyam S, Pulijaal VR, Matthew S. Double and multiple chromosomal aneuploidies in spontaneous abortions: A single institutional experience. J Hum Reprod Sci. 2014 Oct-Dec; 7(4): 262–268. doi: 10.4103/0974-1208.147494

[2] Kovaleva NV,Mutton DE. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. Am J Med Genet A. 2005 Apr 1;134A(1):24-32.

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