Karyotype Versus Chromosomal Microarray Analysis in Fetal Demise: An Institutional Evaluation

University of Colorado Anschutz Medical Campus

REBECCA WYMA, MD[1]; CHELSEY PLUCKER, DCLS, MLS(ASCP)[CM 2]; JENNA BODMER, MD[1,2]

[1]University of Colorado Anschutz Medical Campus, Department of Pathology, 12605 E. 16th Avenue, Aurora, CO 80045, USA;
[2]Children's Hospital Colorado, Department of Pathology, 13123 E. 16th Avenue, Aurora, CO 80045, USA

Children's Hospital Colorado

Background

Compared to conventional karyotype chromosomal microarray analysis (CMA) classically shows improved detection of genetic abnormalities in fetal demise, but at higher cost. We aim to distinguish results of karyotype and CMA testing in fetal demise cases to determine the most accurate, efficient, and cost-effective test utilization method for our institution.

Methods

Consult fetal demise autopsy cases from 2020 – 2023 were retrospectively reviewed for karyotype (G-banding, 450 band resolution) and SNP (single nucleotide polymorphism) CMA testing, as well as associated costs. Partial autopsies and non-fetal demise autopsies were excluded from review.

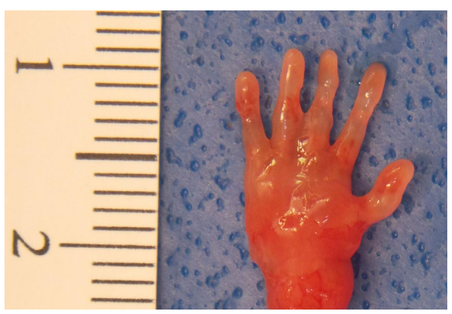

Figure 1. Hand phenotype (webbing of digits 3 and 4) from Case 1 (Table 2) with an abnormal karyotype revealing triploidy (69, XXX).

Results

- A total of 98 cases were reviewed. 47 cases had karyotype testing performed and 51 cases had CMA, with 38 of 98 cases undergoing both. Combined, karyotype testing showed an 84.2% failure rate (55.6% alone) while CMA showed 7.9% (0% alone). Karyotype testing alone demonstrated abnormal results in 25% of completed cases while CMA testing alone demonstrated abnormal results in 7.1% (Table 1).

	Number of Cases	Karyotype Failure	CMA Failure	Abnormal Results	Abnormal Karyotype	Abnormal CMA
Karyotype Only	9 of 98 cases (9.2%)	5 of 9 cases (55.6%)	---	1 of 4 cases (25%)	1 of 4 cases (25%)	---
CMA Only	13 of 98 cases (13.3%)	---	0 of 9 cases (0%)	1 of 13 cases (7.7%)	---	1 of 13 cases (7.7%)
Karyotype & CMA	38 of 98 cases (38.8%)	32 of 38 cases (84.2%)	3 of 38 cases (7.9%)	4 of 38 cases (10.5%)	1 of 4 cases (25%)	3 of 4 cases (75%)

Table 1. Testing rates by case, test failure, and abnormal results.

- 6 cases had abnormal karyotype or CMA results. **Karyotype testing revealed one case with triploidy** (Figure 1; CMA not performed but theoretically would have also detected it) **and one case with a balanced Robertsonian translocation** (CMA normal). **CMA testing revealed 4 cases with variants of unknown significance** (VUS; 3 with karyotype test failure and 1 not performed; **karyotype resolution would not have identified this size of alteration**), which did not obviously correlate with fetal phenotype (Table 2).

Case	Karyotype	CMA	Abnormal Findings	Phenotype and Likely Cause of Demise	Gestational Age	Estimated Demise-to-Delivery Time	Delivery-to-Autopsy Time
1	Abnormal	Not performed	Triploidy (69,XXX)	Webbed digits (Figure 1) and omphalocele; induced demise due to maternal health concerns	15w5d	< 4hr	5d
2	Abnormal	Normal	Balanced Robertsonian translocation of 13,14 (most adults asymptomatic)	Mild fetal growth restriction; likely placental cause of demise (small with accelerated villous maturation, tethered cord)	20w5d	Likely greater than 24hr; examination limited to placenta/external exam	2d
3	Study Failure	Abnormal	Variant of unknown significance (1.6 Mb in 7q31.1); no OMIM disease-associated genes	Fetal growth restriction; likely placental/cord cause of demise (nuchal cord, maternal vascular malperfusion)	37w2d	18hr-14d; examination limited to placenta/external exam	2d 6hr
4	Study Failure	Abnormal	Variant of unknown significance (1.62Mb gain in 13q31.1); includes *SLITRK* (deafness and myopia syndrome)	Unremarkable; unclear cause of demise (evidence of in utero fetal distress, plasma cell deciduitis)	35w6d	1-2d	5d
5	Study Failure	Abnormal	Variant of unknown significance (384 kb gain in 9q34.3); includes *LHX3, CARD9, PMPCA, NOTCH1, INPP5E (*implicated in many diseases including Joubert syndrome)	Unremarkable; likely chromosomal vs. placental/cord cause of demise (hypercoiled and strictured cord)	22w5d	96hr-1w	4d
6	Not performed	Abnormal	13 kb loss in 6p24.3 (7,573,455-7,586,308); includes *DSP* (associated with inherited cardiomyopathies)	Suspected skeletal dysplasia but normal postmortem exam and radiology	30 weeks	<4hr	Tissue stored in freezer until exam

Table 2. Autopsy cases with abnormal karyotype or CMA results, with associated fetal/autopsy findings: phenotype and cause of demise, gestational age, estimated time from demise to delivery, and time from delivery to autopsy.

- The total cost of CMA testing was 3.9 times the cost of karyotype testing, with a significant failure cost associated with karyotype (Table 3). However, limiting karyotype testing would not lead to significant cost savings at our institution (Table 4).

	Number of Cases	Testing Rate	Number of Failed Tests	Test Failure Rate	Cost of Failed Testing	Total Cost
Karyotype	47	49.9%	39	82.9%	$12,992	$16,829
CMA	51	52%	3	5.9%	$999	$65,046

Table 3. Karyotype and CMA cases comparing testing rates, failures, and costs.

	Karyotype	CMA	Total
Current Cost	$16,829	$65,046	$81,875
Cost of Discontinuing Karyotype	$0	$80,058*	$80,058
Cost Difference	-$16,829	+$15,012	-$1,817

Table 4. Estimated cost of discontinuing karyotype and performing CMA testing only. *9 cases with karyotype only testing were added to the 51 CMA cases for a total of 60 CMA cases.

Conclusions

CMA testing was more sensitive and had an overall lower failure rate, though it was more costly. In our limited sample, CMA results (all VUS) did not necessarily contribute to fetal phenotype or demise. The karyotype testing failure rate was significant, however, when successful it led to diagnoses that may have been missed by CMA (Robertsonian translocation). At our institution, discontinuing the use of karyotype testing would not result in significant annual cost savings. Given the limited sample size, as well as increasing utilization of additional techniques such as whole exome or whole genome sequencing, further similar studies are warranted.