



Utility Of Genetic Testing In Malformed Fetus Who Undergo Termination.

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Introduction

- Prenatal ultrasounds often detect fetal anomalies.
- Genetic tests (karyotyping, CMA) follow but leave 60% undiagnosed.
- Causes: chromosomal issues, gene disorders, multifactorial inheritance.
- WES improves diagnosis (~25% postnatally), now used prenatally.
- Limited data on WES in terminated malformed pregnancies.
- Accurate diagnosis helps prognosis, counseling, and planning.
- Study aim: Evaluate WES utility in terminated fetuses with anomalies.

Aims and objectives

- Assess the utility of genetic testing in fetuses with ultrasound-detected anomalies.
- Evaluate the added diagnostic yield of microarray and whole exome sequencing over standard karyotyping for parental counseling.

Materials and Methods

- **Design:** Prospective study at a metropolitan tertiary hospital.
- **Participants:** Pregnant women opting for termination due to ultrasound-detected fetal anomalies.
- **Inclusion:** Registered/referred cases with malformations.
- **Exclusion:** Continued pregnancies, no consent, known teratogen exposure, normal scans.
- **Ethics:** Institutional approval and informed consent obtained.
- **Sample Size:** 44 (3.2% prevalence, 95% CI, 5% margin of error).
- **Samples:**
 - Fetal tissue (~30 mg: placenta, skin, muscle)
 - Cord/cardiac blood (2 ml in EDTA & heparin)
 - Parental blood if needed
- **Testing:** CMA and WES at Genetic Research Center.
- **Analysis:** Descriptive stats; compare CMA/WES sensitivity and specificity to karyotyping.

Study Overview

- **Total samples studied:** 44 products of conception.
- **Maternal age:** Median 27 years (range 21–50); majority (40.1%) aged 26–30 years.
- **Elderly gravida (>35 years):** 13.6% (n=6).
- **Fetal sex:** 54.5% male, 45.5% female.
- **Median fetal weight:** 300 grams.

Maternal & Obstetric History

- **Primigravida:** 47.7% (n=21).
- **No prior malformations/genetic history:** 100%.
- **No living children:** 70.4% (n=31).
- **History of ≥1 abortions:** 22.7% (n=10).
- **Consanguinity:** Present in 2 cases (4.5%).

Gestational Age at Diagnosis

- **16–20 weeks:** 45.4% (n=20).
- **<16 weeks:** 13.6% (n=6), including 3 detected in 1st trimester.
- **>20 weeks:** 40.9% (n=18) — enabled by MTP Act amendment.

Genetic Testing Results

- **FISH + Karyotype**
- **All 44 underwent FISH:** 15.9% (n=7) positive
 - Trisomy 21: 4 cases
 - Trisomy 13: 3 cases
- **Karyotyping:**
 - Culture failure in 77.2% (n=34)
 - Highlighted need for more reliable methods



Gross and ultrasonography appearance of holoprosencephaly

Chromosomal Microarray Analysis (CMA)

- **Samples tested:** 37 (with normal FISH/Karyotype)
- **Results:**
 - CNVs detected: 6/37 (16.2%)
 - Inconclusive: 2/37 (5.4%)
 - Normal: 29/37 (78.3%)
- **System-specific findings:**
 - CNVs in thorax, abdomen, genitourinary, and skeletal systems
 - Pathogenic CNVs: 2 (on chromosome 17)
 - 3 classified as Variants of Uncertain Significance (VUS)

Whole Exome Sequencing (WES)

- **Samples tested:** 31 (with normal FISH + CMA)
- **Positive findings:** 16/31 (51.6%)
 - **Systems involved:**
 - CNS: 5 (31.2%)
 - CVS: 4 (25%)
 - Multisystem, skeletal: 2 each (12.5%)
 - Others (GU, lymphatic, thorax, abdomen): 1 each
- **Syndromes identified:**
 - Spina bifida → Congenital Hydrocephalus 2
 - Cardiac anomaly → Kabuki Syndrome-1
- **Zygosity:**
 - Heterozygous: 93.7%
 - Inheritance: Mostly autosomal dominant (56.2%)
- **Classification:**
 - Pathogenic variants: 2/16 (12.5%)
 - VUS: 14/16 — require Trio analysis or future reclassification

Type of Anomalies

- **Most common:** CNS anomalies (n=15, 34.1%).
- **Others:**
 - Multiple system defects: 20.5% (n=9)
 - Cardiovascular: 18.2% (n=8)
 - Skeletal: 11.4% (n=5)
- **Frequent CNS anomalies:** Anencephaly, encephalocele, holoprosencephaly, Chiari malformation, open spinal defects, corpus callosum agenesis, etc.
- **Associated malformations:**
 - CNS + other systems: 17 cases (38.6%)
 - CVS anomalies in 3 multisystem cases



Abortus showing encephalocele, Ultrasonography appearance of cystic hygroma.

System-Wise Test Positivity Rate

- **WES highest in:**
 - Genitourinary, thorax, abdomen, lymphatic (100%)
 - Multisystem (88.8%)
 - Skeletal (80%)
- **CNS:** Most frequently affected (46.6% test positivity)
- **CMA vs. WES:**
 - CMA better/similar in genitourinary, thorax, and abdomen

NO	SYSTEM	TOTA FISH/KT	MICR	WES	TOTAL	%	
		L	O		POSITIV	POSITIVE	
		CASE	ARRA		E		
		S	Y				
1	CNS	15	2	1	4	7/15	46.6
2	Craniofacial	1	0	0	0	0/1	-
3	CVS	8	1	1	4	6/8	75
4	Genitourinary	3	0	2	1	3/3	100
5	Lymphatic	1	1	0	0	1/1	100
6	Multiple	9	3	2	3	8/9	88.8
7	Skeletal	5	0	1	3	4/5	80
8	Thorax and abdomen	2	0	1	1	2/2	100

Conclusion

- Majority of patients were aged **26–30 years** (40.1%).
- Most women were **primigravida** (47.7%).
- **Consanguinity** was **not a major risk factor**.
- **CNS anomalies** were the most common in this cohort.
- **Karyotype** had **high culture failure** in abortuses (77.2%).
- **Chromosomal microarray (CMA)** showed better success and utility than karyotyping.
- In **multisystem disorders**, **WES was abnormal in 51.6%**, but only **2/16 had known pathogenic variants**.
- **WES adds value** when karyotype and CMA are normal but is limited by **interpretation challenges**.
- **Variants of unknown significance (VUS)** require cautious interpretation with **parental testing (Trio analysis)**.

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