

EP11.08: Importance of Whole Exome Sequencing in Prenatal Diagnosis of Arthrogryposis



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Background

- Arthrogryposis multiplex congenita (AMC) is defined by congenital contractures in ≥ 2 joints in the body.
- AMC is a descriptive term rather than a single diagnosis and is genetically and phenotypically heterogeneous.
- Prenatal ultrasound is the primary tool for AMC detection, including lack of fetal movement, abnormal posturing of extremities, and increased amniotic fluid.

Objective

- To describe a case series of four fetuses with AMC, highlight the utility of whole exome sequencing (WES) in prenatal diagnosis, and review the relevant literature.

Methods

- Retrospectively reviewed the electronic health record of all mothers and their offspring with prenatally diagnosed AMC at a large, academic hospital between August 2019 and December 2024
- Conducted a literature review using PubMed.

Conclusion

- Given its clinical utility, WES is recommended when AMC is suspected, and cytogenetics is normal.
- Prenatal WES is crucial for prognosis, recurrence risk, and family counseling.
- Future research is needed to identify novel genetic variants and interventions to improve outcomes.

Results: Case Series

	Patient 1	Patient 2, Pregnancy 1	Patient 2, Pregnancy 2	Patient 3
Maternal Information				
Maternal Age (years)	31	22	23	42
Gestational Age at US diagnosis	14w1d	23w5d	20w0d	17w4d
Ultrasound Findings				
Cardiac	Ventricular septal defect	Enlarged left atrium	Ventricular septal defect	None
Movement	None	None	None	None
Contractures	Yes	Yes	Yes	Yes
Amniotic Fluid	Polyhydramnios	Polyhydramnios	Normal AFI	Normal AFI
Other	Fetal hydrops	Fetal hydrops	Fetal hydrops	None
Genetic Diagnoses				
Genetic Testing	Amniocentesis (24w): Normal CMA, positive WES	Amniocentesis (24w): Normal CMA, positive WES	Chorionic villus sampling (10w): normal CMA, positive prenatal targeted TTN variant analysis	Postnatal: normal CMA, positive WES
Gene	ACTA1	TTN	TTN	RYR1
Variant	c.536G>T	c.3875del and c.59451 dup	c.3875del and c.59451 dup	c.14818G>A
Mode of inheritance	AD	AR and AD	AR and AD	AD
Disease(s)	Severe infantile congenital myopathy 2C	AR skeletal myopathy, AD cardiomyopathy	AR skeletal myopathy, AD cardiomyopathy	Central core disease, Malignant hyperthermia susceptibility
Variant Classification	Likely pathogenic	Pathogenic	Pathogenic	Pathogenic
Family history	De novo	Both parents heterozygous	Both parents heterozygous	Paternally inherited
Pregnancy Outcomes				
GA at birth	31w5d	28w3d	28w0d	37w5d
Neonatal outcome	Intrapartum fetal demise	Neonatal demise	Neonatal demise	Discharged home and living

Table 1. Demographic, clinical, genetic, and pregnancy outcome data from our case series.

CMA (chromosomal microarray analysis), WES (whole exome sequencing), AR (autosomal recessive), AD (autosomal dominant)

Results: Literature Review

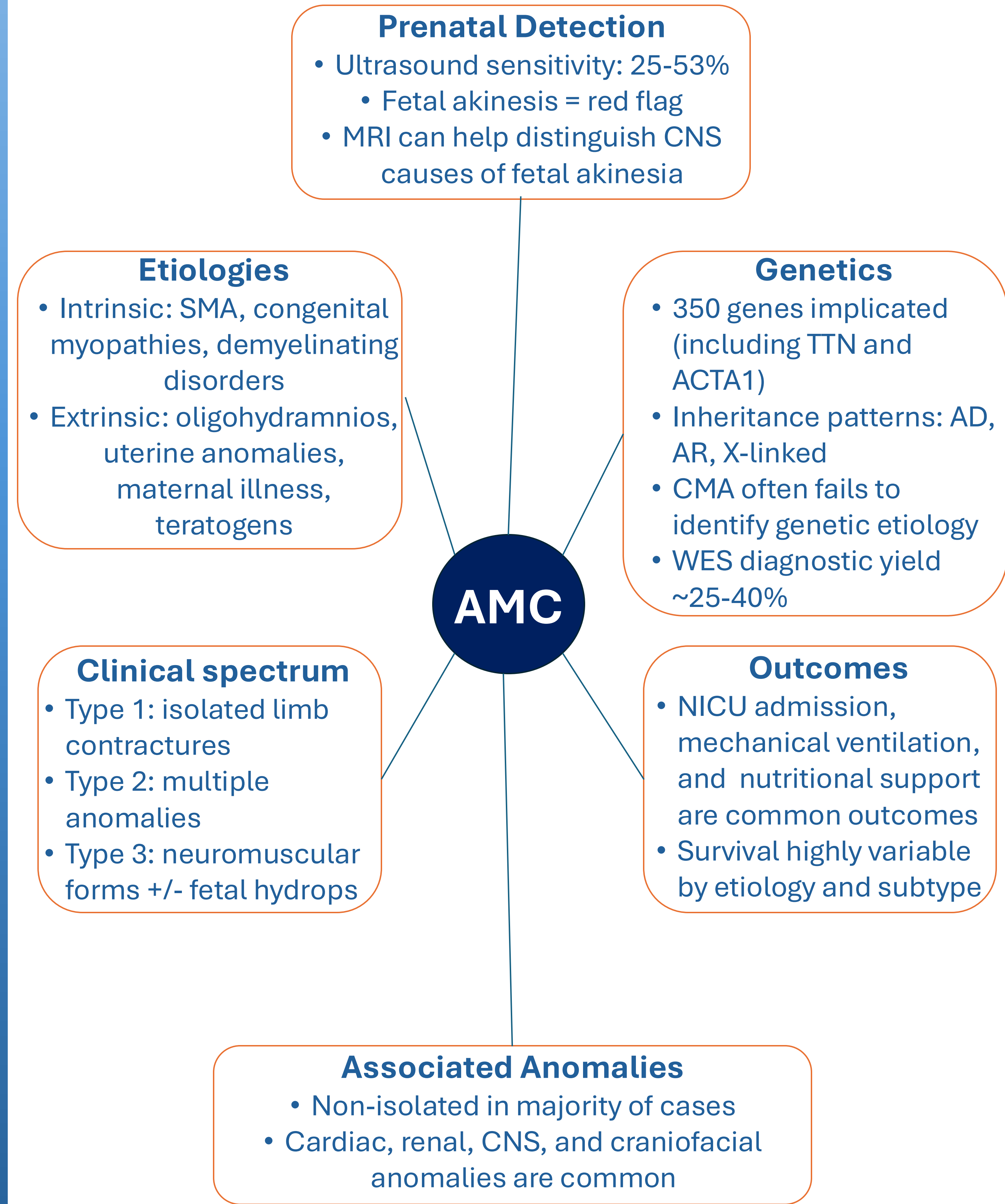


Figure 1. Overview of results from literature review (16 studies).

AMC (Arthrogryposis multiplex congenita), CMA (chromosomal microarray analysis), WES (whole exome sequencing), AR (autosomal recessive), AD (autosomal dominant), NICU (neonatal intensive care unit), SMA (spinal muscular atrophy)



References