

When Fetal Anomalies Lead to Prognostic Clarification: An Underrecognized Application of Exome Sequencing



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OBJECTIVE: The aim of this study was to describe a cohort of fetuses with abnormal prenatal findings in whom exome sequencing (ES) revealed genetic diagnoses associated with favorable clinical outcomes, thereby providing reassurance during pregnancy.

METHODS: We retrospectively reviewed all fetal ES studies performed at our center between 2017 and 2025 for structural or biochemical abnormalities detected on prenatal imaging or screening. Cases with a definitive molecular diagnosis were identified, and among them, those in which the expected postnatal phenotype was considered mild, transient, isolated, or surgically correctable were classified as “reassuring.” Clinical findings, inheritance patterns, and predicted postnatal outcomes were analyzed.

CONCLUSION: ES can play a pivotal role not only in identifying severe genetic disorders but also in distinguishing isolated, transient and treatable conditions from complex syndromic etiologies. In selected cases, a molecular diagnosis offers substantial reassurance, reduces uncertainty, and supports informed counseling and pregnancy management.

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RESULTS: Among 1692 fetuses who underwent ES for evaluation of structural or biochemical abnormalities, a molecular diagnosis was identified in 291 cases (17%). Among the diagnosed cases, five (approximately 2%) met criteria for a reassuring outcome: (1) a heterozygous pathogenic variant in *GLI1* associated with isolated postaxial polydactyly; (2) a hemizygous *STS* missense variant causing X-linked ichthyosis in a fetus with markedly low estriol levels; (3) a homozygous pathogenic variant in *DAW1* in a fetus with isolated situs inversus; (4) compound heterozygous variants in *CFAP52* in a fetus with isolated situs inversus totalis; and (5) a hemizygous truncating *MAGED2* variant associated with transient antenatal Bartter syndrome. In all cases, the molecular diagnosis substantially reduced the likelihood of severe syndromic conditions in the differential diagnosis and provided parents with clearer expectations regarding neonatal course and long-term prognosis.

Reassuring Results: Favorable Outcomes in Prenatal Exome Sequencing

Prenatal exome sequencing can reveal reassuring outcomes in approximately 2% of cases, distinguishing manageable conditions from severe syndromic disorders and providing critical clinical clarity.



Isolated Postaxial Polydactyly

Gene: *GLI1*

Confirms an isolated, surgically correctable extra digit, ruling out complex syndromic etiologies.

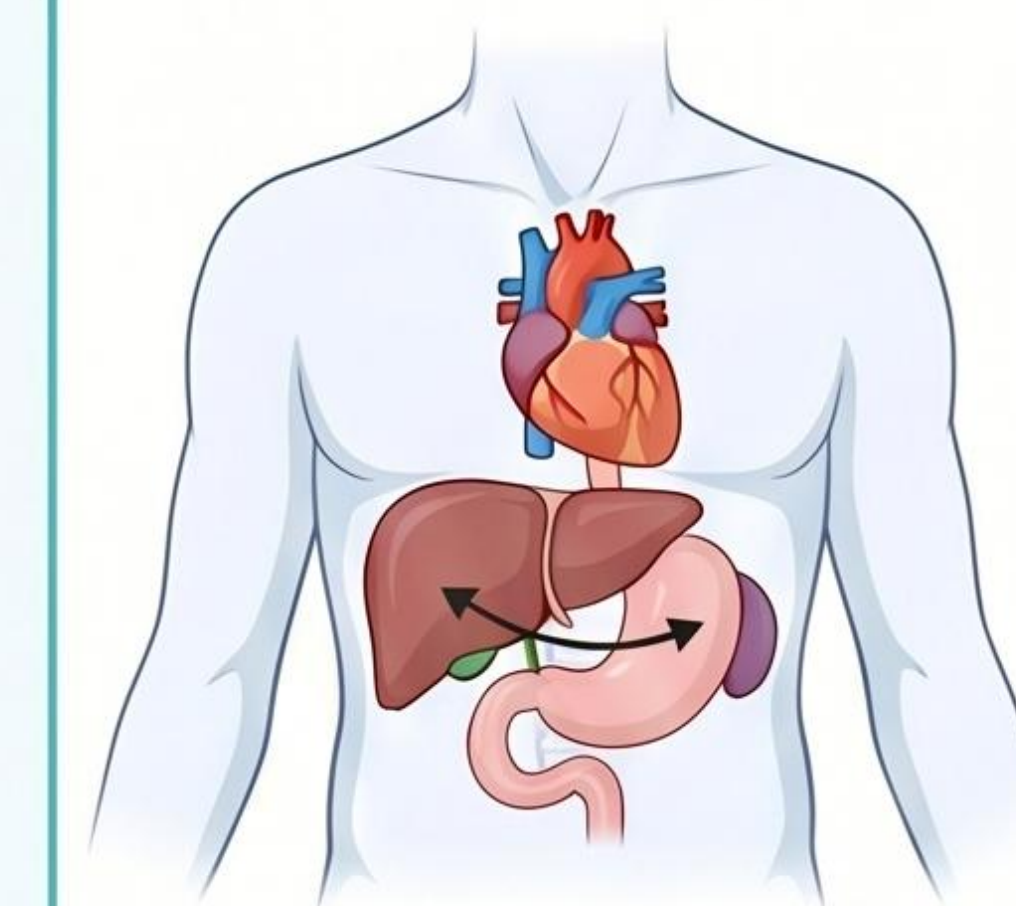
Clinical Indicator:
Low Estriol Levels



X-linked Ichthyosis

Gene: *STS*

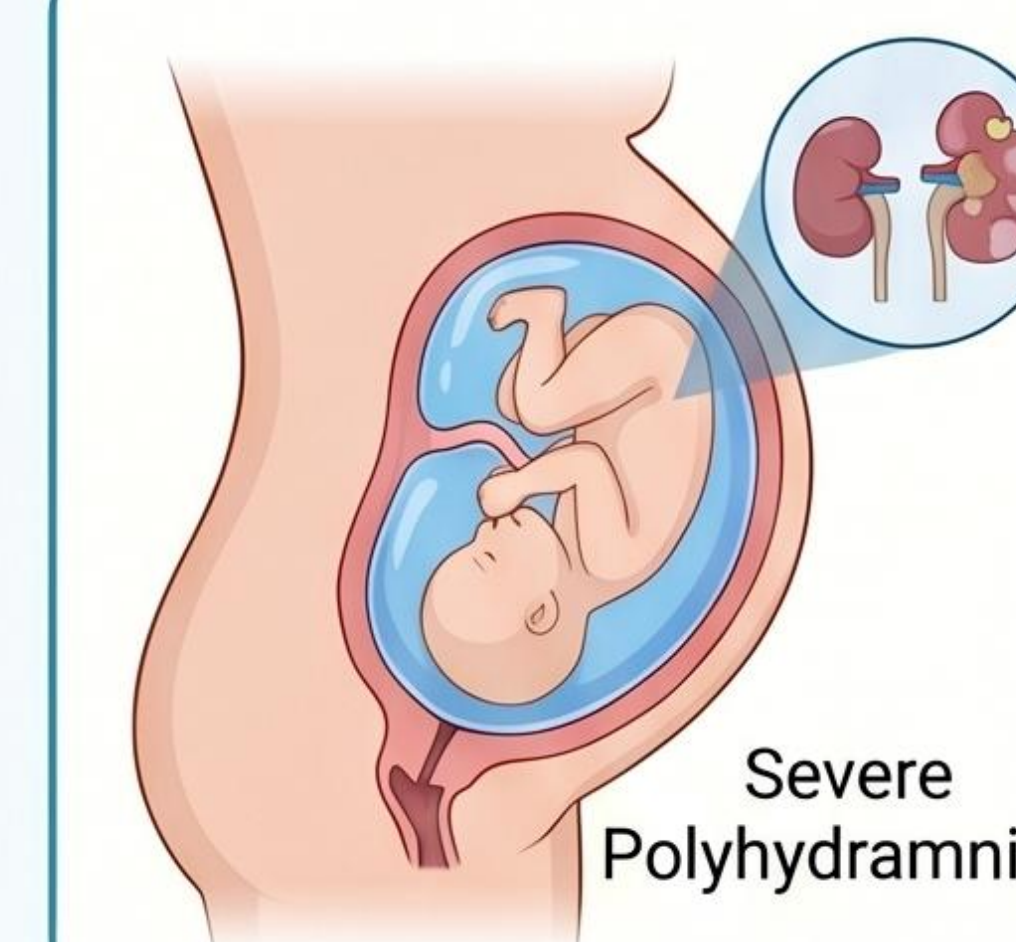
Explains low estriol levels by identifying a mild, manageable skin-scaling condition.



Isolated Situs Inversus Totalis

Genes: *DAW1*, *CFAP52*

Confirms mirror-image organ orientation is isolated, supporting a more favorable prognostic assessment.



Transient Antenatal Bartter Syndrome

Gene: *MAGED2*

Identifies a self-limiting renal condition that resolves spontaneously during the neonatal period.