

EP10.73. Prenatal Diagnosis of Citrullinemia Type 1 due to a Novel ASS1 Splice Site Variant in a High-Risk Consanguineous Pregnancy

Sonal O. Gupta 3,1, Kavita Aneja2, Omprakash P. Gupta5,4, Devi Lal 6, Himani Pandey7

isuog2026.24a02d1

Background

- Citrullinemia type 1: autosomal-recessive urea-cycle disorder from biallelic ASS1 variants (OMIM 215700).
- Classic neonatal form: lethargy, seizures, hyperammonemia often lethal without rapid diagnosis.
- Recurrent unexplained neonatal death with consanguinity
- Published estimates exist; reliable nationwide incidence data for India are unavailable.

Case Summary

- G3P2L0A0D2; consanguineous couple.
- G1: FT female, died day 10; newborn screen positive for a metabolic disorder.
- G2: FT male, died day 2 of life.
- G3 (index): GA 13w6d at referral; NT scan normal.
- CVS and parental samples sent for TRIO-WES and genetic evaluation was done.

Genetic Findings WES-TRIOS

Family member	c.271A>C p.Thr91Pro	c.105+1G>A (splice)
Father	Heterozygous	Heterozygous
Mother	Heterozygous	Not detected
Fetus (CVS)	Heterozygous	Heterozygous

- Both variants: Likely Pathogenic (ACMG)

Fetus shares both variants with father - phasing (cis/trans) needed before assigning clinical significance.

Discussion

The combination of consanguinity, recurrent neonatal deaths, and a positive metabolic screen strongly suggested an autosomal recessive urea cycle disorder. Trio whole-exome sequencing established the molecular diagnosis by identifying segregating ASS1 variants. The concordant fetal genotype with the presumed affected siblings strongly supported the prenatal diagnosis of Citrullinemia Type I and enabled accurate recurrence risk assessment and couple counseling for RPL.

Conclusion / Key Message

Trio exome sequencing enabled rapid prenatal genotype-phenotype correlation in a recurrent lethal neonatal phenotype but compound-heterozygous findings must be phased before clinical significance is reported.

Limitations

- Variant phase (cis/trans) not resolved by short-read exome data.
- CNVs, repeats, deep-intronic variants not captured.

References

- Barmore W, Azad F, Stone WL. Physiology, Urea Cycle. [Updated 2023 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. <https://www.ncbi.nlm.nih.gov/books/NBK513323/>
- Lo, R. S., et al. Functional profiling of 2,193 ASS1 missense variants, PMID: 42308225.

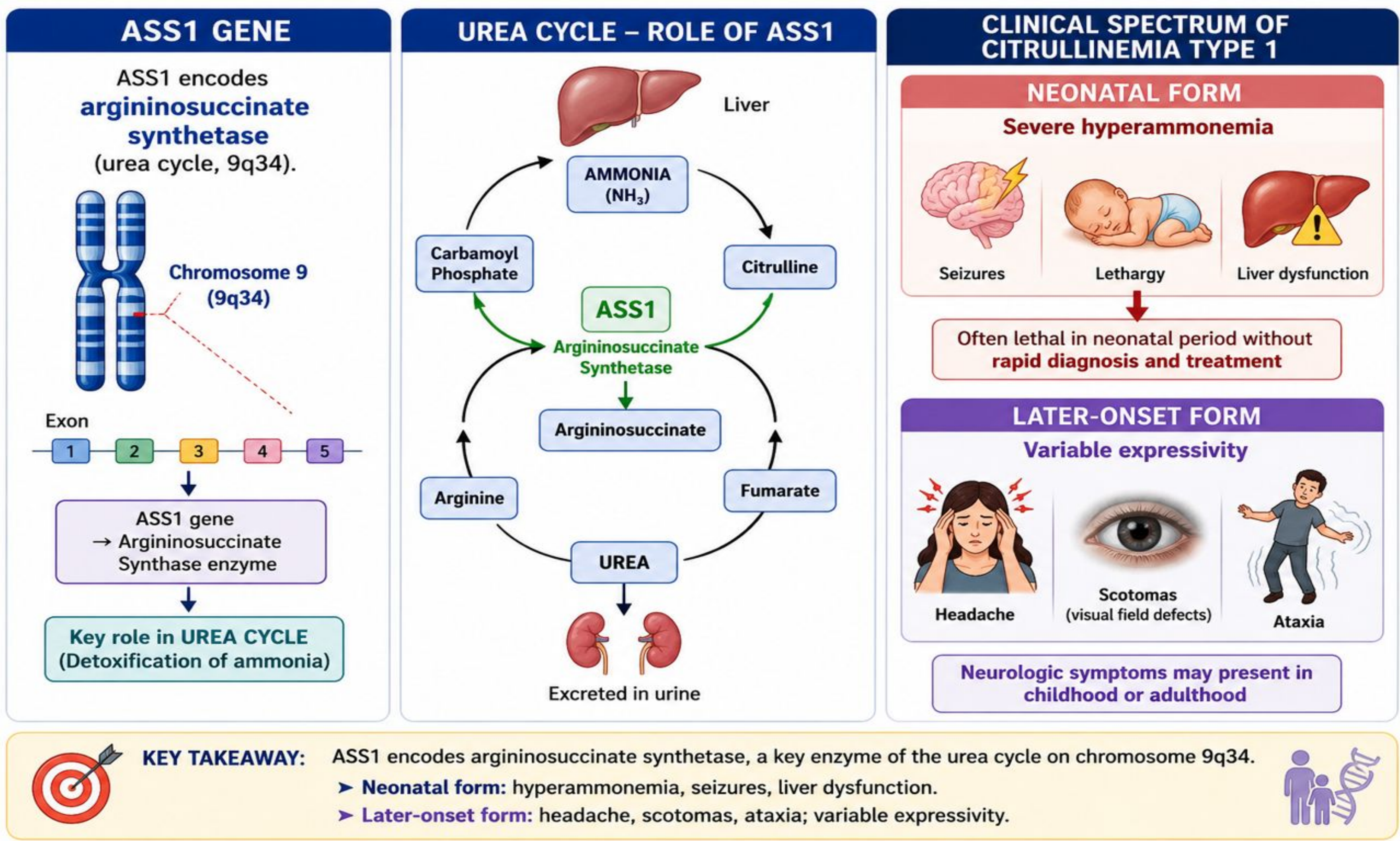


Fig. 1. ASS1 gene, urea-cycle pathway, and clinical spectrum of Citrullinemia Type I.

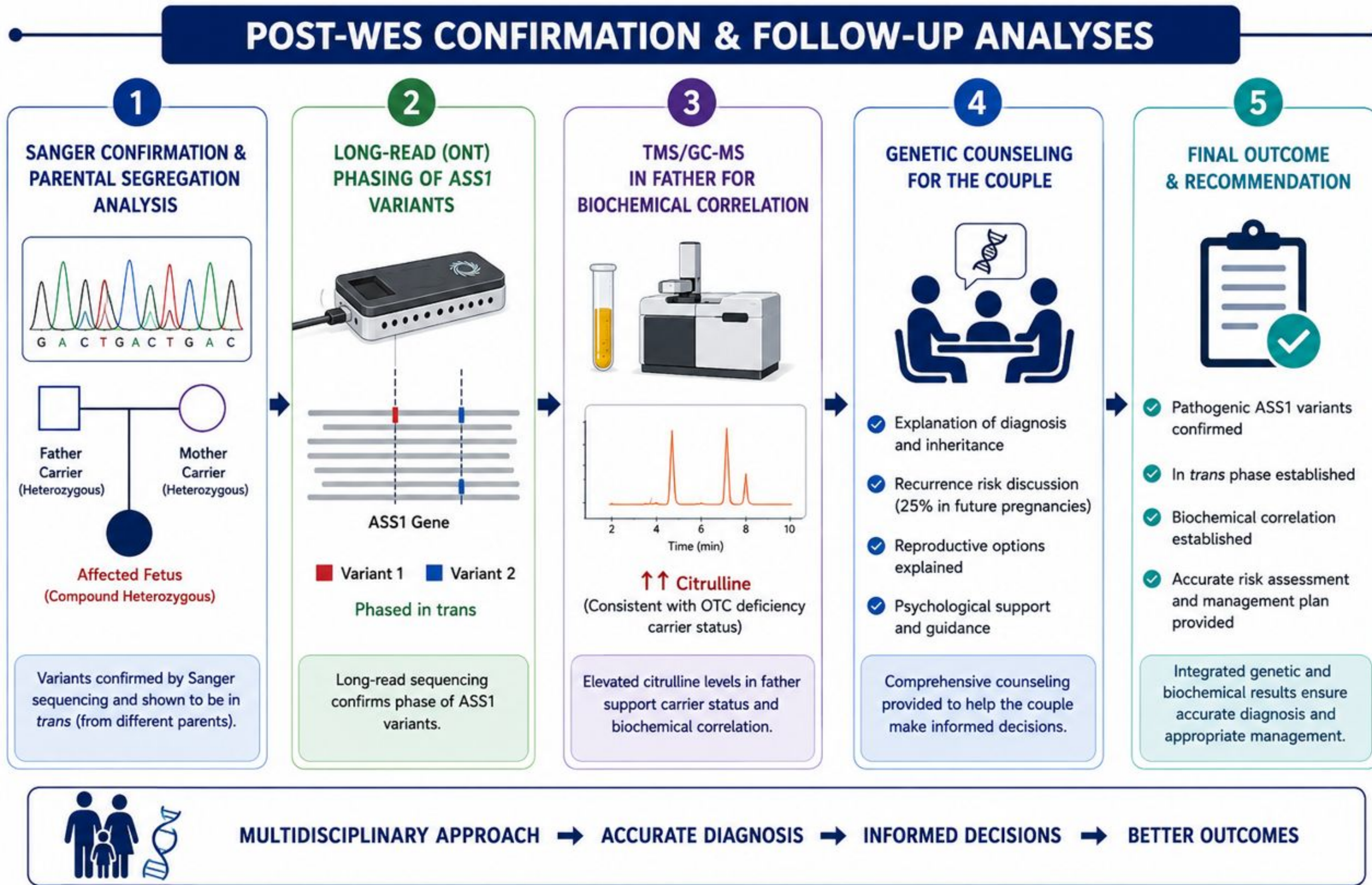


Fig. 2. Post-WES Confirmation & Follow-up