OTC gene and Ornithine Transcarbamylase Deficiency: Variant penetrance in a national screening context

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Background

- **Newborn screening** in the UK currently uses tandem mass spectrometry (TMS) to screen for nine conditions with **high sensitivity and specificity**
- Advances in whole genome sequencing (WGS) now enable rapid, high-throughput analysis from dried blood spot samples
- Recent studies suggest that **WGS could expand newborn screening** to include hundreds of genetic disorders from a single test
- The **UK Generation Study** is currently evaluating the feasibility of using WGS in newborn screening, including screening for OTCD

OTC deficiency

- Ornithine transcarbamylase deficiency (OTCD) is the most common urea cycle disorder and is caused by **pathogenic variants in the OTC gene** on the X chromosome, resulting in partial or complete **loss of enzyme activity**
- Impaired urea cycle function leads **hyperammonaemia**, **encephalopathy**, and potentially death if untreated
- **Clinical presentation is highly variable**, ranging from severe neonatal-onset disease to late-onset or asymptomatic individuals; approximately 20% of heterozygous females develop symptoms
- **Early diagnosis and treatment**, including protein restriction, ammonia scavengers, and arginine/citrulline supplementation, can substantially **reduce morbidity and mortality**

Neonatal / severe form:

- Following protein intake / milk feed
- Lethargy, reduced feeding
- Vomiting
- Irritability
- Hypotonia
- Seizures
- Hepatomegaly
- Cerebral oedema

Late onset / milder form:

- Hyperammonia during episode of illness
- Vomiting
- Lethargy
- Irritability
- Hyperactivity
- Dysarrthria
- Confusion
- Ataxia

Intellectual disability, developmental delay and cerebral palsy

Image 1. Phenotypic heterogeneity of OTCD

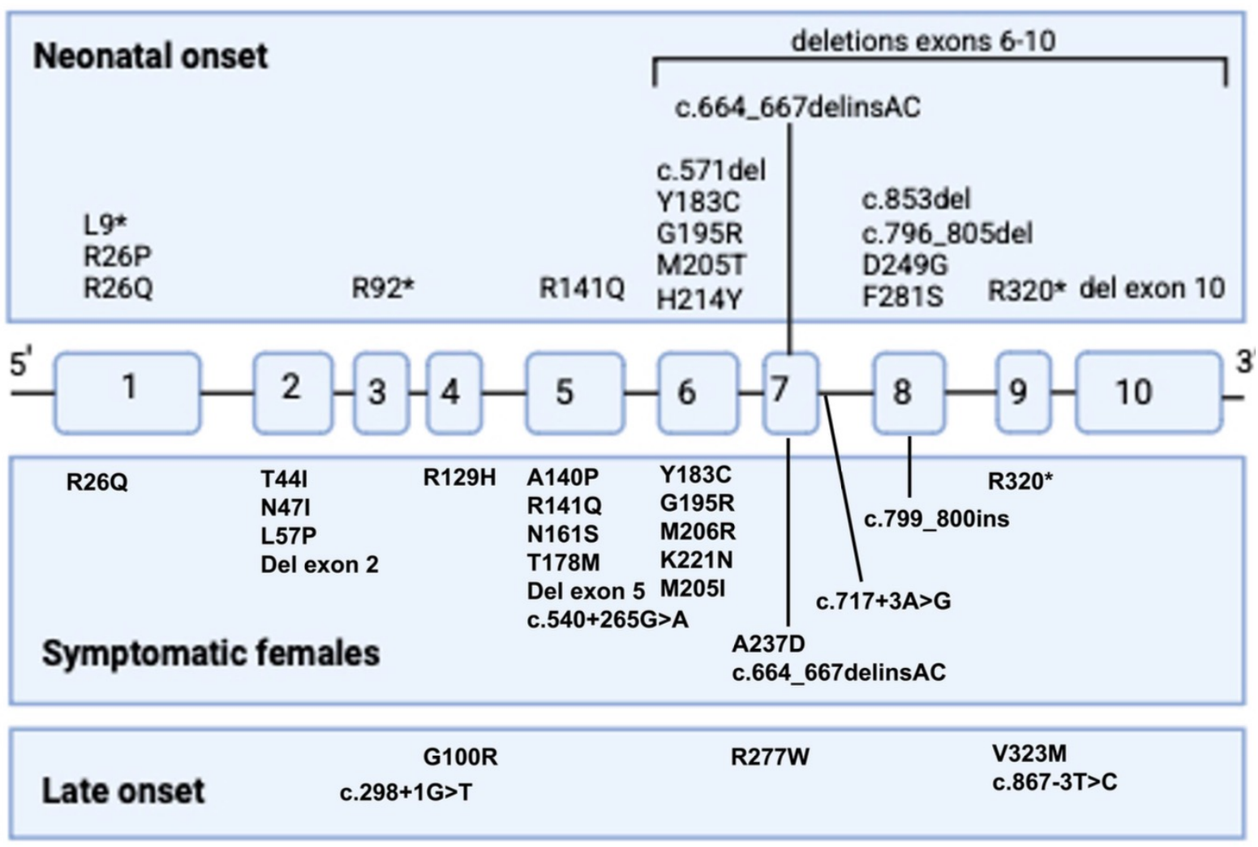
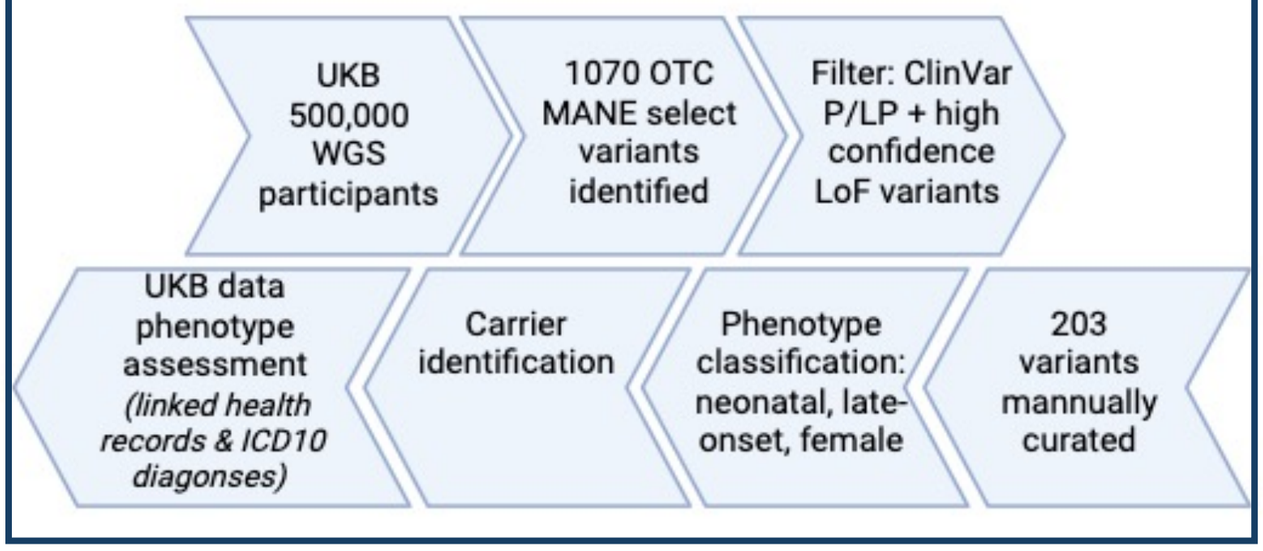


Figure 1. Cohorted OTCD variants associated with neonatal, late onset and female phenotypes

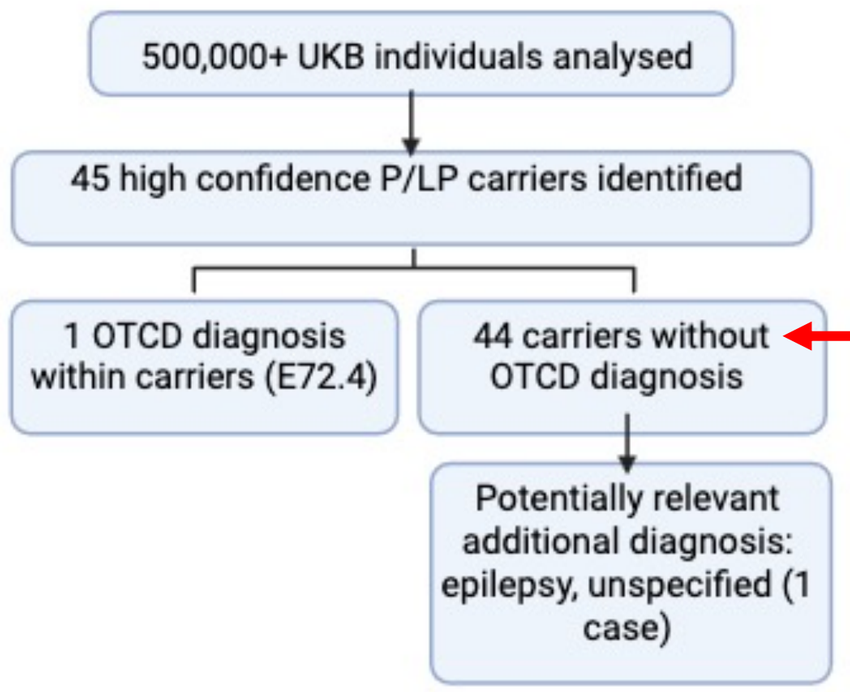
AIMS

- Assess the **clinical relevance of pathogenic OTC variants** by analysing their frequency, associated phenotypes, and recorded diagnoses in a large population cohort (**UK Biobank**)
- Evaluate implications for incorporating WGS into newborn screening

Methods



Results



- UK Biobank cohort 40- 69 year olds
- Extensive phenotype, health records, imaging and WGS data
- Survivor bias
- Lack of genotype-phenotype correlation in these patients

Observed vs expected incidence of OTCD in Biobank cohort

Observed OTCD diagnosis	1 in 500,000
Expected OTCD incidence	1 in 14,000 - 1 in 80,000
Observed OTCD high confidence P/LP variant carriers	45 in 500,000 (1 in 11,000)

Conclusion

- **WGS can identify OTC variants** but may have limited predictive value for clinical disease when used in isolation
- The low detection of clinically confirmed OTCD among variant carriers underscores **challenges in applying genome-wide screening for rare, variably penetrant disorders**
- Further evaluation through prospective studies, including the Generation Study, is needed to determine feasibility, cost-effectiveness, and integration into national screening programmes

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