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Genetic and functional studies reveal a novel noncoding variant in *GALT* associated with a false positive newborn screening result for galactosemia

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## Highlights

- â€¢ We conducted follow-up studies of an infant with a positive NBS for galactosemia.
- â€¢ We identified a novel non-coding variant of *GALT* in the child and both parents.
- â€¢ We demonstrated that this variant does not reduce *GALT* mRNA levels in the child.

â€¢ We demonstrated that galactose metabolism in the child remains apparently normal.

â€¢ Our results illustrate the complexities of diagnosis of galactosemia.

## Abstract

### Background

Classic galactosemia (CG) is a potentially lethal genetic disorder that results from profound loss of galactose-1-phosphate uridylyltransferase (GALT). CG is detected by newborn screening (NBS) in many countries; however, conclusive diagnosis can be complex due to broad and overlapping ranges of GALT activity. Molecular studies can also be complex due to allelic heterogeneity at the *GALT* locus.

### Methods

We conducted both biochemical and molecular follow-up studies for an infant flagged by NBS for possible galactosemia. To clarify the diagnosis we also conducted biochemical and RNA studies of lymphoblasts prepared from the child and one parent.

### Results

We identified a novel noncoding *GALT* variant, c.377+17C>T, that was homozygous in the child and heterozygous in both parents. The child and both parents also showed diminished GALT activity in red blood cells, and transformed lymphoblasts from the child and one parent further showed diminished GALT activity. However, qRT-PCR studies demonstrated apparently normal *GALT* mRNA levels in lymphoblasts, and Gal-1P values measured in the child following galactose exposure in infancy and at 1Â year were normal.

### Conclusions

These results highlight the existence of rare but apparently benign variants in *GALT* and underscore the need for functional studies to distinguish pathogenic from benign variants.



## Abbreviations

CG, classic galactosemia; GALT, galactose 1-phosphate uridylyltransferase; NBS, newborn screening; qRT-PCR, quantitative reverse transcription polymerase chain reaction; Gal-1P, galactose-1-phosphate; GALE, UDP-galactose 4'-epimerase; GALK, galactokinase; EBV, Epstein Barr virus

## Keywords

Galactosemia; Newborn screening; Non-coding variant; Functional studies; qRT-PCR

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