Classical Galactosaemia — A modifiable glycosylation disorder?

Coss KP[1], Doran PP[1], Byrne JC[2], Adamczyk B[3], Rudd PM[3] and Treacy EP[4]

[1]*University College Dublin, Clinical Research Centre, Mater Misericordiae University Hospital, Dublin, Ireland*
[2]*Royal College of Surgeons, Dublin, Molecular and Cellular Therapeutics, Ireland*
[3]*NIBRT Dublin-Oxford Glycobiology Group, Mount Merrion, Blackrock, Ireland*
[4]*National Centre for Inherited Metabolic Disorders and Trinity College Dublin, Ireland*

Background: Classical Galactosaemia, GALT deficiency (E.C. 2.7.7.12), has been screened for in Ireland as part of the National Newborn Screening Programme since 1972. Treatment, in the form of life-long restriction of dietary galactose is life-saving in the neonate. However, despite early diagnosis and initiation of treatment, long-term complications persist in our treated cohort; including cognitive impairments with full scale IQs $\leq$79 in 56.5% of 85 subjects, speech and language abnormalities in 58% of all subjects $\geq$2.5 yrs, and hypergonadotrophic hypogonadism in 91.2% of all female subjects $\geq$13 yrs. The complications observed are irrespective of genotype, age of initiation of treatment or birth order (Hughes et al., J. Paediatr, 2009). The ability of some individuals to utilize auxiliary pathways of galactose metabolism may play

a role in the variability seen in outcomes. *N*-glycan assembly and processing defects have been reported in Classical Galactosaemia. While the gross *N*-glycan assembly defects in the untreated neonate largely correct upon introduction of dietary treatment, processing defects persist in treated subjects (Coman et al., Pediatr Res, 2010; Coss KP et al., MGM in press).

Aim: To examine if whole serum and IgG *N*-glycan profiling could be used to monitor galactose liberalization and variations in glycosylation in treated adult subjects, in parallel with T-lymphocyte gene expression analysis to identify genes of interest.

Results: IgG, the most abundant glycoprotein in human serum, was informative in identifying ongoing *N*-glycan processing defects in treated Gal subjects and has identified individual optimum galactose tolerance levels in a number of subjects ($n = 4$). We studied specific galactose incorporation into IgG *N*-glycans by measuring G0/G1 and (G0/G1)/G2 ratios. The G0/G1 and (G0/G1)/G2 ratios for pooled healthy adult controls ($n = 100$) are 0.5 and 0.01 respectively. Classical Galactosaemia patients on a galactose restricted diet (<300 mg/day) had a G0/G1 ratio mean of 0.81 (95% CI 0.69–0.92); and (G0/G1)/G2 ratio mean of 0.03 (95% CI 0.02–0.03). Significant variability was observed in the glycosylation profiles within treated subjects with more profound galactosylation deficiencies noted in a number of subjects. Differential galactose tolerance levels and variability were also observed in specific subjects.

Gene expression analysis from T-cell RNA identified dysregulation of 36 glycan biosynthesis genes by at least 2-fold.

Conclusions: Our studies suggest that Galactosaemia is a systemic modifiable glycosylation defect offering new insights into the ongoing pathophysiology with possible new treatment targets.