Serum IgA1 Hinge Region O-Glycosylation is a Heritable Trait in Caucasians

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Background

IgA nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide. The condition is characterised by the deposition of IgA in the glomerulus leading to mesangial cell proliferation and synthesis of extracellular matrix proteins. Patients with the disease have a variable prognosis, 30% patients develop end stage renal disease within 20 years of diagnosis. IgAN has a complex aetiology with genetic and environmental components. Changes in the galactosylation of the hinge region of serum IgA1 have been widely reported to be important in the pathogenesis of IgAN[1,2]. We have presented data previously to show that the pattern of serum IgA1 *O*-glycosylation remains unchanged over time in both healthy subjects and patients with IgAN. This observation, along with reports of large pedigrees of familial IgAN, increased occurrence of the disease in relatives of affected individuals and geographical variations in disease prevalence suggest a genetic contribution to the pathogenesis of IgAN and possibly IgA1 *O*-glycosylation.

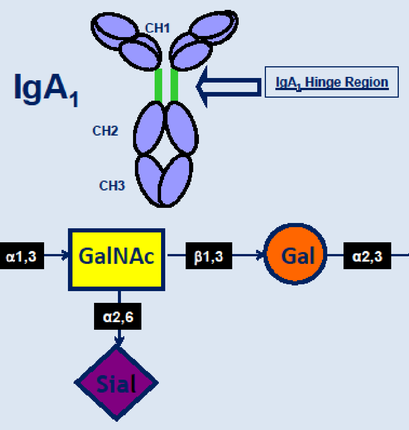

Figure 1:Diagrammation representation of the structure of IgA1 and the sugars which attach to the hinge region.

Aim

To assess the hereditability of serum IgA1 *O*-galactosylation by measuring relative levels of serum IgA1 *O*-galactosylation in 136 parent-child trios identified from the UKGDB IgAN cohort using an established ELISA-based Helix aspersa (HA) lectin binding method.

Methods

The UK Glomerulonephritis DNA Bank (UKGDB) IgAN cohort was established in 2000. Participants of European ancestry were recruited through four UK centres (Glasgow, Leicester, London, and Oxford) through probands with renal biopsy-proven IgAN, <50 years of age at the time of diagnosis and >18 years of age at the time of recruitment. Individuals with evidence of liver disease or Henoch-Schonlein purpura were excluded. Diagnosis was confirmed in all cases by direct review of renal biopsy histopathology reports and clinical case records. Where available, samples were also collected from the healthy parents of singleton affected individuals and, in some cases, other nuclear family members, to enable a study of family-based association. The UKGDB IgAN cohort comprises 914 serum samples, including 136 complete parent-child trios and 39 parent-child pairs.

An established elisa-based IgA1-HA lectin binding assay was used: captured IgA was treated with 75mU/ml neuramindase to remove terminal sialic acid residues. The desialylated IgA was incubated with biotin labelled HAA and developed. Absorbance at 492nm was measured. As a standard curve was not used in this study plates were normalised using serum samples with known lectin binding values. Increasing HA lectin binding to IgA1 correlates with lower O-galactosylation of the IgA1 hinge region. The samples were analysed in duplicate by 2 independent scientists achieving a coefficient of variance of <3% between samples. Hereditability (the proportion of observed variability in IgA glycosylation that is inherited) was estimated using parent-off-spring standardised regression.

Results

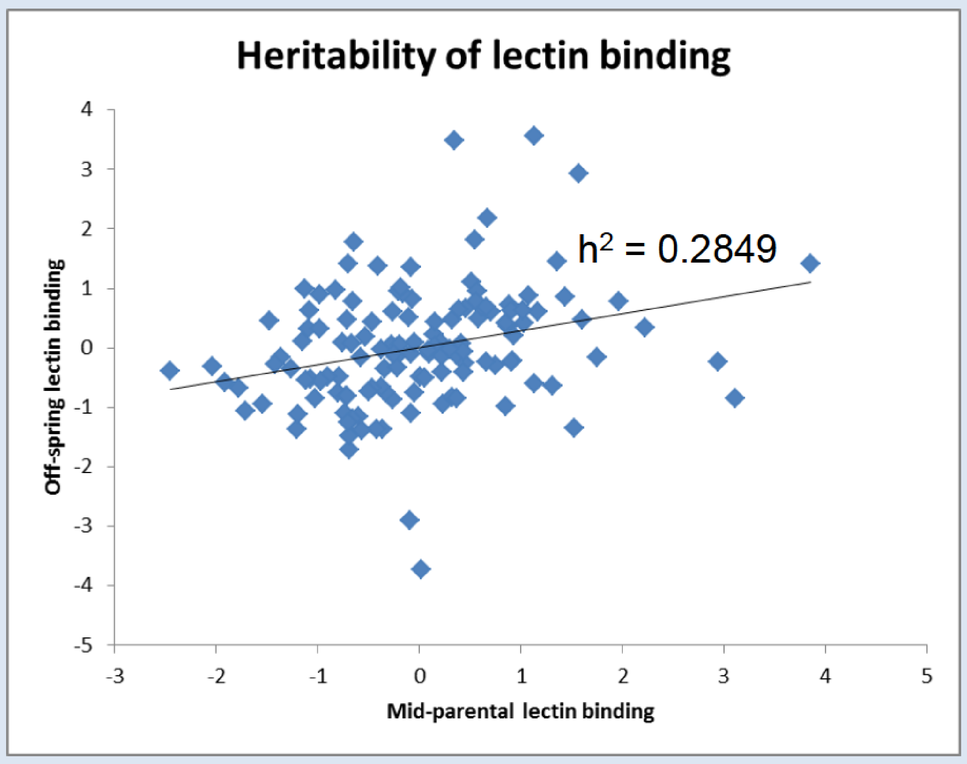

Figure 2: Proband mean lectin binding compared with mean parental lectin binding

Narrow sense heritability (h^2) was 0.28 (R^2 = 0.08; p = 0.0008)

Conclusions

This result strongly implies that genetic factors play an important role in determining the pattern of IgA1 *O*-galactosylation in Caucasians. These results are consistent with findings in familial IgAN and sporadic IgAN in other ethnic groups.[3]

Separately at this meeting we present data showing that the pattern of serum IgA1 *O*-galactosylation in patients with biopsy-proven IgAN and non-progressive disease is not significantly different from that seen in healthy subjects. The extent of IgA1 *O*-galactosylation was however significantly associated with the severity of renal injury and risk of developing progressive renal failure in IgAN. IgA1 *O*-glycosylation therefore appears to be more strongly associated with disease severity (or risk of progression) than it is with susceptibility. Together, these findings imply that as yet undefined genetic determinants of IgA1 *O*-glycosylation may influence the risk of renal failure in IgAN.

References

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