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Abstract:
Immunoglobulin A (IgA) is an important component of the immune system that provides local defense against mucosal pathogens. Increased production of IgA is frequently observed in patients with active mucosal inflammation due to respiratory or gastrointestinal infections. High levels of IgA are also observed in patients with IgA nephropathy (IgAN), which commonly coincides with mucosal infections. IgAN is the most common form of primary glomerulonephritis worldwide and progresses to end-stage renal disease in up to 40% of cases. More specifically, individuals with IgAN have elevated levels IgA1 subclass that is predominantly
galactose-deficient. A reliable lectin-based biomarker assay for quantification of serum galactose-deficient IgA1 (Gd-IgA1) has been developed and used in our laboratory.

We have previously demonstrated high heritability of serum Gd-IgA1 (50-70%), suggesting that this biomarker is, in part, genetically determined. Gd-IgA1 promotes formation and mesangial deposition of IgA1-containing immune complexes. Our recent study suggests that elevated serum levels of Gd-IgA1 may also
predict renal disease progression. Moreover, our data demonstrate that high Gd-IgA1 levels are frequently present in asymptomatic relatives of patients with IgAN, as well as in a fraction of apparently healthy individuals from the general population. Therefore, we postulate that this defect may represent a quantitative risk factor for IgAN with a strong genetic component, but by itself it is insufficient to cause nephritis. The genetic causes of high Gd-IgA1 are currently not known. Similarly, it is not known to what degree the asymptomatic individuals with high Gd-IgA1 levels are at risk of developing kidney disease later in life.

We propose to perform a rigorous population-based analysis of serum IgA, IgA1, and Gd-IgA1 levels in three well-powered multi-ethnic prospective cohorts, totaling 6,000 individuals. We will compare the distributions of these traits between different ethnicities of study participants. We will examine their association with renal function and cardiovascular outcomes. Utilizing available genome-wide SNP data, we will perform a GWAS for serum IgA, IgA1, and Gd-IgA1 to identify common genetic determinants of these traits. We will validate our GWAS findings in additional replication cohorts available to us.
