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Title: Genetic Causes of IgA Nephropathy by Next Generation Sequencing

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis. Familial aggregation and ethnic differences in IgAN susceptibility strongly argue for a role of genetic factors in its pathogenesis. Despite ongoing efforts, causative genetic factors responsible for this serious disease have not been identified. We hypothesize that familial IgAN is attributable to rare variants with large effects that are detectable by high throughput sequencing.

Whole exome sequencing has emerged as an efficient way to interrogate the entire coding segment of the genome to identify potentially damaging mutations. We have previously successfully utilized this approach to sequence exomes of two individuals with highly sensitive detection of heterozygous variants. Here, we put forward a pilot study of exome sequencing in familial IgA nephropathy. We propose a cost-effective strategy that combines whole exome sequencing with linkage analysis to identify causative mutations.

Whole exome sequencing will be performed at Columbia and will involve 10 selected IgAN cases from 5 multigenerational families with available linkage data. We will identify functional variants that localize to linkage intervals and co-segregate with the disease. We will validate these variants by finding independent damaging mutations in the same genes in additional cohorts of familial and sporadic IgAN.

Discovery of genes involved in the pathogenesis of IgAN will have a major impact in our field. By identifying causal genes, our study will open doors to targeted therapeutic approaches. The clinical applications of our work may involve genetic screening and diagnosis, improved risk stratification, or the selection of suitable kidney transplant donors based on genetic testing among related individuals. We also hope that this pilot project will provide us with the necessary experience and preliminary data for future R01 applications involving high throughput sequencing at Columbia.
