

# IgAN Genetic Risk Score in the Clinical Setting



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IgA nephropathy (IgAN) is the most common form of primary biopsy-proven glomerulonephritis in the world.<sup>1</sup> IgAN prevalence varies in different parts of the world, being higher in people of East Asian ancestry, followed by Caucasians, and is relatively low in individuals of African descent. This variability could be ascribed to differences in access to health care, in health screening policies (i.e., systematic urine screening for asymptomatic hematuria and/or proteinuria routinely performed in some countries), or due to differences in biopsy practice, that is, when more patients with minor urinary abnormalities are subjected to renal biopsy, more IgAN patients will be identified.<sup>1,S1</sup> Conversely, genetics plays a part in disease prevalence, as reported in a single-center study from the United States in which biopsy practice was same across ethnic groups, and individuals of East Asian ancestry were reported to have higher IgAN rate.<sup>S2</sup>

The strong genetic involvement of IgAN is also demonstrated by the

strong familial clustering. Furthermore, routine urine analysis carried out on first-degree relatives shows a higher occurrence of urinary abnormalities, such as persistent microhematuria and/or mild proteinuria. Frequently, relatives with these minor urinary abnormalities refuse kidney biopsy; therefore, the precise diagnosis for these subjects can never be obtained.<sup>S3</sup> Moreover, first- and second-degree relatives have also been found to have a higher risk of developing IgAN.<sup>S4</sup>

In the past decade, genome-wide association studies (GWAS) have identified common inherited susceptibility variants associated with common complex disorders; each variant associated with a disease may underpin a gene or biologically relevant pathway related to the disorder. On the other hand, variants also can be used to predict disease risk, each common variant is known to have a relatively small effect.<sup>2</sup> Therefore, a genetic tool for the assessment of the cumulative effect of multiple genetic markers on disease risk are now being developed, that is, genetic risk scores (GRS).<sup>3</sup>

The GWAS approach has been successfully applied in IgAN, associated variants show a strong participation of the human leukocyte antigen system and genes

involved in innate immunity. Seven variants identified through GWAS have already been used for constructing a genetic risk score explaining 4.7% of overall IgAN risk.<sup>4</sup> A later GWAS study by the same authors identified additional susceptibility variants in a large European cohort,<sup>5</sup> and on the whole the GWAS studies pointed out that variants associated with IgAN (i) are common to other inflammatory and immune-mediated diseases, (ii) explain only a proportion of the disease risk worldwide, (iii) contribute to the geographic variation in disease prevalence, and (iv) confirm the polygenic and multiple-susceptibility-gene nature of IgAN.

Sukcharoen *et al.*<sup>6</sup> developed an IgAN-GRS and applied it to estimate the prevalence of IgAN in people with hematuria, hypertension, and microalbuminuria. The IgAN-GRS was generated using 14 of the 15 variants identified in the largest GWAS conducted on the European population.<sup>5</sup> The authors tested it on 2 European cohorts: the UK Glomerulonephritis DNA biobank and the UK Biobank, the latter representing an enormous resource of clinically ascertained genotyped individuals from the United Kingdom. Although there was a clear difference in mean IgAN-GRS between cases and controls, the individual discriminative power of the IgAN-GRS was modest, with an area under the receiver operating curve of 0.60. These results align with other GRS, often characterized by a modest predictive power for many other complex genetic phenotypes, such as schizophrenia, in which the authors evaluated the capacity of GRS to predict the case-control status reaching a modest area under the receiver operating curve value of 0.62.<sup>S5</sup>

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Furthermore, differently from monogenic disorders that are caused by high penetrance mutations, in complex disorders, the discriminative ability of GRS is compromised by the relatively small effect of common variants and by the nongenetic multifactorial contributors that concur to the pathogenesis of a complex disease. Other well-established risk prediction models include clinical, biochemistry, lifestyle, and historical risk factors. They, used in combination, achieve a good prediction (area under the receiver operating curve of 0.80–0.85) as seen in cardiovascular diseases.<sup>56</sup> Therefore, IgAN-GRS may benefit if combined with other well-established clinical parameters, such as estimated glomerular filtration rate, blood pressure, and proteinuria at biopsy,<sup>57</sup> or serum biochemical parameters such as microRNA biomarkers.<sup>58</sup>

The IgAN-GRS, characterized by a poor discriminatory value between cases and controls, cannot be used alternatively to biopsy for diagnosis, but if used correctly, it may represent an additional valuable information for patient stratification in clinical practice. Furthermore, the use of GRS could improve health outcomes by accelerating diagnosis. Specifically, cohorts with a higher *a priori* probability of disease, for example in IgAN family members with persistent minor urinary abnormalities, a high IgAN-GRS score could represent the tip of the balance toward a kidney biopsy and a prompt therapeutic intervention (i.e., corticosteroid therapy in the presence of active renal lesions). On the other hand, diagnosis may be encouraged if the routine school screening urinalysis is associated to IgAN-GRS score influencing clinical decision making in favor of a kidney biopsy.

Despite the modest discriminative ability of IgAN-GRS, the score could be important for patient

stratification and for improving screening programs in the general population; specifically, a high IgAN-GRS value in an individual does not necessarily imply the invasive procedure of a kidney biopsy, but this value could simply be used to stratify individuals and define the age and the screening interval for urinalysis.

Cohorts with a higher prior probability of disease (i.e., first- and second-degree relatives with minor urinary abnormalities) and a high IgAN-GRS without biopsy confirmation could be invited to modify their diet and lifestyle to prevent a potential deterioration of their renal function. Low-protein diets could be promoted as the reduction of glomerular hydraulic pressures slow renal functional loss.<sup>59</sup> Also sodium intake should be limited, preventing renal ultrastructural damage related to high blood pressure.<sup>510</sup> Weight loss should be encouraged in overweight patients,<sup>511</sup> and smoking should be discouraged, as it is a dose-dependent risk factor for progressive renal function decline.<sup>512</sup>

Furthermore, the use of GRS could improve health outcomes by matching patients to a more tailored treatment.<sup>513</sup> Many common variants that make up the IgAN-GRS are located within specific genes that have been found to be aberrantly expressed in different gene expression studies.<sup>514</sup> Future studies will need to identify novel treatments able to revert the altered gene and pathways in IgAN. For example, the dysregulation of the proteasome-immunoproteasome axis has been seen in mononuclear cells of patients with IgAN<sup>7</sup> and the same aberrant genes have been found in GWAS studies.<sup>8</sup> A new randomized controlled clinical trial is currently under way (<https://clinicaltrials.gov/>; NCT01103778) to test the safety and efficacy of

bortezomib, a semiselective plasma cell proteasome inhibitor used in the treatment of multiple myeloma, in patients with severe IgAN. Furthermore, pharmacogenetic studies also will need to be done to test how genetic variants affect the response to specific treatments, with the aim of assisting treatment choices to maximize efficacy and minimize side effects.

A major problem related to the applicability of the IgAN-GRS in clinical decision making is that it is applicable to individuals belonging to the same genetic background used for variant discovery. It is well established that the overrepresentation of participants of European ancestry in human genetics<sup>9</sup> and the minority ethnic groups who are underrepresented in genetic research could be unintentionally discriminated, favoring health care inequality. IgAN GWAS studies have been performed only on the European,<sup>5</sup> Southern Chinese Han,<sup>9</sup> and recently Korean<sup>515</sup> populations and other populations have not been taken into consideration. This important issue of minority ethnic group underrepresentation in genetic studies may hinder our efforts toward precision medicine and should be tackled promptly before IgAN-GRS can be used in the clinical setting.

## DISCLOSURE

All the authors declared no competing interests.

## SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary References.](#)

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