The classic paradigm of autoimmune disease pathogenesis describes the role of an environmental insult to a genetically predisposed individual, which results in miscommunication between the innate and adaptive immune systems, breakdown of tolerance, and the recognition of self-antigens as the target of a damaging immunologic response. This paradigm is perhaps best exemplified by the interaction of HLA genotype and smoking in the development of autoantibodies to citrullinated peptides and the onset of rheumatoid arthritis (1). It is assumed that similar pathogenic mechanisms are involved in other autoimmune diseases, although few are so well delineated as in this example.

In antiglomerular basement membrane (anti-GBM) disease, the components of the aberrant adaptive immune response that are involved in disease pathogenesis are clearly described, such as pathogenic autoantibodies directed to a well defined autoantigen supported by a population of autoreactive T cells (2,3). The putative environmental triggers, however, and how they interact with the known genetic determinants of disease susceptibility to initiate this aberrant response are not fully understood.

These genetic determinants of anti-GBM disease are increasingly well described. Although there has not been an undirected genetic survey, such as a genome-wide association study, perhaps reflecting the overall rarity of anti-GBM disease, targeted genetic analysis has been informative. Polymorphisms in certain non-HLA genes, such as those encoding Fcγ-receptors, are associated with disease susceptibility (4,5), consistent with the contribution of pathogenic autoantibodies in mediating organ damage, whereas polymorphisms in \textit{COL4A3}, the gene encoding the target autoantigen, have been excluded from playing a significant role (6). Better characterized are the HLA associations of anti-GBM disease, with 80% of patients inheriting an HLA-DR2 haplotype. Genotyping studies have identified a hierarchy of associations with particular DRB1 alleles: DRB1*1501, DRB1*03, and DRB1*04 are positively associated with disease, whereas DRB1*01 and DRB1*07 seem to confer a dominant negative protective effect (7). These susceptibility alleles, however, are associated with other autoimmune diseases (such as multiple sclerosis and Sjogren syndrome), and they are common in most populations, whereas anti-GBM disease remains exceptionally rare, highlighting the importance of other factors, including environmental exposures, in the development of this specific condition. Previous reports of clustering or outbreaks of anti-GBM disease (8) and seasonal variations in disease incidence (9) support a role for environmental factors, such as infection, in triggering disease onset, although they are limited to anecdotal observation. The report by Canney et al. (10) in this issue of the \textit{Clinical Journal of the American Society of Nephrology} is the first to assess geographic or temporal clustering using formal statistical methods in a national cohort of patients.

In this well-designed study, Canney et al. (10) systematically identified all patients with anti-GBM disease in Ireland over an 11-year period by screening results from referral immunology laboratories and using a national renal histopathology database. This allowed them to define, for the first time, a national incidence rate for this rare condition. This rate is higher than previous estimates in other European populations, as discussed by Canney et al. (10), most likely reflecting the methodologic inadequacies of previous studies, which were prone to ascertainment bias and unable to accurately define at-risk populations. It might also reflect the moderate over-representation of the DR2 haplotype and DRB1 risk alleles in the Irish population (11) or perhaps a genuine increase in the frequency of anti-GBM disease in recent years compared with historical cohorts.

The study, in addition, has used variable window scan statistics and Bayesian spatial modeling methods to identify temporal and geographic clustering of patients, respectively. These formal statistical methods confirm the prior anecdotal experience of many other authors. Notably, some differences in disease phenotype were observed in the two clusters. It is striking, for example, that the temporal cluster had a very high prevalence of positivity for ANCA (found in >70% of patients), particularly in view of the strict diagnostic criteria used by Canney et al. (10) that excluded patients who had overt clinical features of vasculitis. Double positivity for ANCA and anti-GBM antibodies is a well-recognized phenomenon, with previous studies estimating that approximately 30% of patients with anti-GBM disease have a concurrent ANCA (12), consistent with overall prevalence reported in the entire Irish cohort. The fact that the temporal cluster had an over-representation of ANCA suggests that a different
disease mechanism may be acting in these patients or as suggested by Canney et al. (10), that the disease may present variably in different subpopulations. This is perhaps in keeping with other recent reports that have identified atypical presentations of anti-GBM disease, such as those associated with IgG4 anti-GBM antibodies (13) or what might be termed idiopathic linear Ig deposition (14), and it illustrates the challenges in reliably characterizing the full phenotypic spectrum of a very rare disorder.

Of greater significance, the identification of these disease clusters also supports a role for an environmental trigger in anti-GBM disease. Many such environmental triggers have been suggested previously. Perhaps best known is the association of cigarette smoking with the development of lung hemorrhage (15). Inhalation of hydrocarbons has also been associated with anti-GBM disease (16), and an interesting report of identical twins who both developed anti-GBM disease after hydrocarbon exposure supports a link between genetics and environmental factors (17). It is hypothesized that localized airway inflammation induced by smoking or inhaled hydrocarbons may disrupt the architecture of the alveolar basement membrane, revealing usually sequestered epitopes in type 4 collagen, thus permitting access to pathogenic autoantibodies. Whether these factors have a role in the initiation of the autoimmune response per se, however, is not so clear. A similar process of conformational transition of the autoantigen within the kidney has been suggested to account for the association of anti-GBM disease with other glomerular lesions (such as ANCA-associated GN and membranous nephropathy) and lithotripsy for renal stones, which may disrupt the quaternary structure of GBM (18).

These associations with smoking and other specific diseases, however, are not likely to account for the clustering of diseases that has been confirmed in this study. Some of the early series reported a seasonal variation in disease incidence, with peaks in spring and early summer, which in the absence of any reported association with atopy, suggest an infectious trigger (9). It is of historical interest that Ernest Goodpasture’s original description of GN associated with alveolar hemorrhage was in the context of the influenza outbreak of 1919, although it is not clear whether his patient had genuine anti-GBM disease (19). There are some more recent reports of disease outbreaks associated with influenza virus, such as a series of four patients presenting during an influenza A2 epidemic in the early 1970s, although in these patients, confirmatory virologic or serologic evidence of infection was not shown (20). There is a small number of additional isolated patients in whom influenza infection was serologically confirmed reported in the same era (21,22). Other specific infectious associations with anti-GBM disease, however, have not been reported, and the precise mechanisms through which infection might initiate disease are not defined. It is conceivable that nonspecific inflammation at the time of respiratory or systemic infection may result in the release of sequestered epitopes in the lung or kidney, akin to the mechanisms implicated for smoking in the induction of disease. Alternatively, T or B lymphocytes that are autoreactive to GBM antigens (the presence of which are confirmed in healthy individuals [23–25]) may undergo bystander activation at the time of intercurrent infection, thus initiating anti-GBM disease. More specific molecular mechanisms may also be at work, and observations in a more common form of crescentic GN that associated with ANCA may be informative. A variant ANCA type directed against LAMP2, a human protein that bears a high degree of homology to FimH (a protein expressed in fimbriated Gram-negative bacilli), has been identified in human patients with ANCA-associated vasculitis and is purported to arise via a process of molecular mimicry after bacterial infection (26). It has also been shown that certain Staphylococcus aureus peptides bear high homology to complementary PR3, and it is, thus, suggested that anti-PR3 antibodies may arise via a process of idiotype-anti-idiotype interactions after Staphylococcal infection (27). Although there are no specific mechanisms suggested for the infectious induction of anti-GBM antibodies, it is notable that comparable idiotype-anti-idiotype interactions have recently been described in the induction of experimental anti-GBM disease in a rodent model (28).

Canney et al. (10) do not comment on the potential infectious, occupational, or other environmental exposures that may have initiated disease in their cohort, and exploring these features in more detail may be informative in the future. In addition, analysis of concurrent patterns of infectious disease, such as influenza, in the general population during the study period might be considered. It may also be of interest to determine the pattern of disease in the adjacent six counties of Northern Ireland, particularly in view of the shared border with the spatial cohort of patients described by Canney et al. (10) in Donegal, because this may identify additional patients in the same region, providing additional opportunity to identify shared exposures in a larger cohort of patients.

This study is notable for being the first to accurately determine the frequency of anti-GBM disease in any country, and Canney et al. (10) are to be commended on their collaborative approach, which enabled capture of systematically identified and strictly defined patients at a national level, and their thoughtful use of statistical methodology to identify disease clusters over time and by geographic region. The challenge now is to determine how these data can be used to identify putative environmental factors that trigger disease and may account for these clusters and how these factors interact with known (or yet to be identified) genetic determinants to initiate disease. This might then allow the development of early detection and preventative or more targeted treatment strategies for this rare but potentially devastating condition and other comparable renal and autoimmune disorders with a presumed environmental trigger.

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Disclosures
None.

References


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