Lumping, splitting and mapping: assessing linkage in different ethnic groups for albuminuria and glomerular filtration rate in the HyperGen study

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The ability to map genes that predispose to complex disease has been an ongoing area of research for more than a decade, but results have often been less than satisfying in terms of discovering genes of major importance. One likely reason is that the phenotypes used in many linkage analyses have heterogeneous genetic causes, so that different loci may confer susceptibility in different families. Such a situation can lead to the inability to identify loci in studies, or alternatively, loci found in one study may not replicate in others. An example of this kind of situation is found in the genetic study of hypertension, where multiple genome screens have identified a variety of loci, several of which do not replicate [1,2]. How can investigators deal with such heterogeneity?

In their article in the current issue of NDT, Leon et al. [3] use two potentially important methods to help address the problem. They report on linkage mapping for two traits that may be related to each other and to hypertension: albuminuria (measured as albumin to creatinine ratio, ACR) and glomerular filtration rate (GFR) in two large family-based samples from the HyperGEN cohort. One sample is African-American (AA) and the other is European-American (EA). This study is important because of the approaches and because of the large size of each of the samples (1251 AA and 1129 EA). Another interesting feature of this study is that it attempted to identify loci that affect both traits simultaneously. This last feature is interesting in that it tests for pleiotropy, a type of genetic variation rarely assessed in linkage or association studies.

First, Leon et al. [3] chose presumably more homogenous populations in terms of geographic origin and with presumably more similar genetic risk factors. Such analyses involve defining ethnicity prior to analyses and analysing groups by this criterion. However, this approach may still fail because even within a homogeneous population, the complexity of the factors that predispose to disease may be dependent on a variety of factors that are left unmeasured. These unmeasured factors can provide the critical context in which the susceptibility genes function; context being defined broadly as variations in other genes and/or environmental parameters. Failure to assess context may make results difficult to reproduce across studies [4–6]. Second, they mapped presumably more homogenous phenotypes that underlie at least some of the risk of clinical disease. It is possible that this approach will be better at identifying loci that can replicate across studies, because the loci identified are likely to be closer to underlying gene action.

Splitting and lumping by geographic origin

In linkage analyses it is common practice to pool all samples collected, regardless of ethnicity. This is done because of the need to increase power by increasing sample size. This approach is understandable when sample sizes are limited, but in the case of Leon et al. [3] the sample size of both AA and EA cohorts is large enough that it is possible to analyse the cohorts separately (splitting), and they do so. Of importance is the fact that they identify linkage signals in both of the cohorts, and the signals do not overlap. For GFR, evidence for linkage in AA was found for chromosomes 7, 14 and 19. Similar regions on the same chromosomes have been observed in previous linkage results for hypertension, although the previous results are for samples of different ethnic origins (reviewed in [2]). No significant findings were obtained for GFR in EA. For ACR several interesting signals were observed for both AA (chromosomes 8, 16 and 17) and EA (chromosomes 18 and 19). A previous analysis of some HyperGEN samples, as well as Family Blood Pressure Program samples, also detected linkage at the...
same site on chromosome 19 for ACR in hypertensive families [7]. It is of note that there was no overlap between AA and EA signals. This reinforces the potential importance of assessing these groups independently.

The results of Leon et al. can also be compared with recent work by Krolewski et al. [8] and Turner et al. [9], who assessed linkage in traits related to kidney disease. Krolewski et al. studied ACR, and detected a linkage peak on chromosome 7. Turner et al. examined both estimated GFR and urine ACR in both AA and EA, using the GENOA cohort, with sample sizes comparable with that of Leon et al. They found a linkage signal for eGFR in AA on chromosome 7, in a location close to that reported by Leon et al. for ACR. Additionally, Turner et al. found a peak for UACR on chromosome 7, but not near the locus found by Leon et al. As with the results of Leon et al., the results of Turner et al. indicate different linkages in AA and EA.

In an alternative analysis, Leon et al. pooled the AA and EA samples and did another linkage analysis. In the combined analysis, additional signals to those found for each group separately were detected, for ACR (chromosome 19) and for GFR (chromosomes 14, 15 and 16). Although the chromosome 16 and 19 results are the same as reported in the separate analysis, the other two chromosomes are not found in either of the samples alone. Therefore, although there are likely to be some loci that differ among groups, there is also evidence for common signals that can only be found in the larger analyses. Therefore, by both splitting and lumping, different potentially important linkage signals can be detected.

Lumping of phenotypic categories

In the above descriptions, the two phenotypes were analysed separately (univariate). In a separate bivariate analysis, Leon et al. looked for loci that simultaneously affect both traits. This approach was also used by Turner et al. [9]. Loci that are identified in this way are said to exhibit pleiotropy, or multiple effects of a single gene. In this analysis, perhaps the locus of the most significance is chromosome 7. This region of chromosome 7 was identified in the univariate analyses for GFR in AA and for UACR in AA by Turner et al. and for GFR in AA by Leon et al. [3]. No loci were identified that were not found in at least one of the univariate analyses. These results indicate that this approach will be fruitful in detecting loci for genes that affect separate but related phenotypes. Such an approach may become commonplace as large datasets, such as the HyperGEN study, become available.

However, the bivariate analysis of these two traits poses some interesting limitations/opportunities. Although as noted by Leon et al., GFR and ACR may be negatively correlated, this is an oversimplification of the relationship between the two phenotypes. Specifically, it has been shown that although increased urinary albumin excretion (UAE) poses a risk for altered GFR, the nature of this alteration in GFR is not simple [10,11]. Specifically, small increases in UAE increase risk of both increased AND decreased GFR [11]. A likely scenario is that initial, small increases in UAE initially increases GFR and then over time leads to decreased GFR. If this is the case, then an analysis as performed runs the risk of confounding these two GFR outcomes [11]. Therefore, although similar genetic pathways may (or may not) lead to the two phenotypes, the relationship may be based on age or time after an increase in ACR. Interestingly, although this was not accounted for in the study of Leon et al., they still detected significant evidence for loci affecting both traits, likely justifying this exploratory analysis.

The report of Leon et al. provides an excellent example of how large scale family-based studies can be used to map putative loci for complex, but related phenotypes. Their study had several important features: first, the size of both the AA and EA cohorts. Clearly, size does matter in linkage and this study was among the largest so far reported. Second, they examined more than one phenotype related to clinical disease, but ones that are more likely to have a simpler relationship to the genes. Lastly, Leon et al. performed a series of analyses that used the entire dataset and appropriate subdivisions. This last feature may be very important in understanding ethnic disparities in common disease, as well as identifying common genetic risk factors across populations.

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References

Poor performance of diagnostic tests for atherosclerotic renal artery stenosis—discrepancies between stenosis and renal function

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Introduction

Both from a pathophysiological point of view and from a clinical standpoint, atherosclerotic renal artery stenosis (RAS) remains an enigmatic disorder. With its capricious clinical presentations, it is often overlooked and diagnosed only at a very late stage. To a certain degree, the latter may be attributable to a lack of enthusiasm amongst clinicians to search for RAS. The basis for this nihilistic attitude mainly lies in the failure of several prospective studies to show a large enough benefit of surgery or angioplasty (with or without stent placement) on blood pressure and renal function. Surely, exposing a patient to diagnostic tests can be justified only when the outcome of these tests are relevant for further clinical decision making. In the case of RAS, however, the situation is a bit more complicated than outcome trials would have us believe. Indeed, even though the effect of balloon angioplasty may be relatively small [1], there are probably subgroups of patients who would benefit more than others from such treatment [2]. Moreover, at present, we do not know whether the seemingly disappointing results of angioplasty are attributable to an inherent ineffectiveness of this form of treatment, or to inappropriate indications. Since the presence of atherosclerotic RAS is associated with an excessive cardiovascular risk [3], it may well be that by the time this degree of stenosis has been reached, ischaemia-induced intra-renal lesions would have become irreversible. A critical appraisal of the current state of affairs is therefore mandatory. In this respect, we should focus on some pathophysiological aspects of RAS that may underlie the fallibility of diagnostic modalities and the poor response to treatment.

When should we think of renal artery stenosis?

The two main causes of RAS are atherosclerosis and fibromuscular dysplasia (FMD). Both conditions clearly differ with respect to patient characteristics and prognosis. For instance, FMD is considered to be a disease of the young, especially women, with a good chance of recovery after percutaneous dilatation. The latter is supported by data from Alhadad and coworkers [4] who, in a retrospective analysis of 69 patients (mean age 44 years), found that nearly 25% of patients were completely cured, while the remainder showed significant falls in blood pressure and serum creatinine and a reduced need for antihypertensive drugs. Whether the concept of FMD occurring mainly...