Published in final edited form as:

J Hypertens. 2009 May ; 27(5): 939–940. doi:10.1097/HJH.0b013e328329fca3.

Are isolated populations better for studying genes that predispose to hypertension?

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Genomics is best defined as a study of functions and interactions of all the genes in the genome, including their interactions with environmental factors [1]. Established methods for detecting genetic polymorphisms underlying common complex traits include family-based linkage and population-based association strategies as well as candidate gene and genome-wide studies. It should be noted that the underlying genetic architecture for hypertension and other complex traits includes dozens and potentially hundreds of risk alleles for each disease or trait [2]. Some of these alleles are common and of small effect, whereas others are rare and of large effect.

Genome-wide association (GWA) studies constitute a watershed in genomics, enabling genetic variants at specific loci to be associated with particular diseases and traits [1]. As summarized recently by Donnelly [3], more than 300 replicated associations have now been reported for more than 70 common diseases, conditions and biological measurements. For example, there are 30 loci associated with Crohn's disease and nearly 20 loci associated with type 2 diabetes [1]. It is of interest that the great majority of loci identified so far did not belong to the known candidate genes for these diseases [3]. The modern GWA studies typically genotype hundreds of thousands to a million of single nucleotide polymorphisms (SNPs) in thousands of cases and controls. Careful power calculations predict that the selection of extreme phenotypes increases the power and chance of success of such analyses [4].

However, there are alternative strategies, which might be helpful to track genes with small effects as expected in hypertension. One of such classic strategies is described by Hoffman *et al.* [5] in this issue of the journal and involves the analysis of an isolated population, the Sorbs. Sorbs are a Slavic population isolate in Germany whose history dates back to the 5th and 6th Century A.D. The Sorbs retained their Slavic language and culture and remained separated till today with classic features of a founder population. The study recruited 283 participants from 87 multigenerational families and genotyped 1040 polymorphic microsatellite markers rather than hundreds of thousands of SNPs. The results are interesting, as they point to a locus on chromosome 1p36, which reaches genome-wide significance ($\text{LOD} = 3.45$; $P = 0.00003$). These results assume even greater importance in light of previous published data documenting that the same locus is implicated in diabetes, hyperlipidaemia, obesity and body mass index [5]. However, it should be noted that the majority of these studies have been seriously underpowered and some had a very poor marker coverage. Moreover, finding a large locus linked to the phenotypic trait, in this case hypertension, is only the first step in gene identification. Current genomic resources will allow for rapid fine mapping with SNPs, for example, using tailored genotyping chips

(<http://bmic.upenn.edu/cvdsnp/>) that cover genes implicated in cardiovascular disease as well as direct sequencing utilising massive parallel sequencing technologies. These technologies, although feasible, are still challenging and expensive.

The current study on Sorbs follows previous classic studies on isolated populations such as the French-Canadians, Icelandic and western China populations. It remains to be established whether findings from these studies can be easily translated to out-bred populations. However, the clustering of hypertension and metabolic phenotypes at the 1p36 locus provides an interesting opportunity to gain further insights into metabolic syndrome and cardiovascular risk in a wider context.

Acknowledgments

Work in our laboratory is funded by the BHF Chair and Programme Grant BHFRG/07/005/23633, Wellcome Trust Cardiovascular Functional Genomics Initiative 066780/2/012, and European Union InGenious HyperCare Grant LSHM-CT-2006-037093.

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