GENETICS

FORGET ABOUT GENES II

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Blood pressure seems to have a complicated regulation according to a recent nature medicine editorial

> If you ask a physiologist what organs are involved in blood pressure regulation, you will probably be told the kidney, the brain or the blood vessels. The kidney is responsible for handling sodium … The brain integrates afferent signals from peripheral sites such as the kidney … systemic vascular resistance is elevated in almost all adults with hypertension, suggesting that arteriolar vasoconstriction has an important role in this disease.

The editorial accompanies a new mechanistic report how a high-salt diet leads to interstitial hypertonic Na+ accumulation by activation of tonicity-responsive enhancer binding protein (TonEBP) binding the promoter of the gene encoding vascular endothelial growth factor-C (VEGF-C). As far, as good, if Nature genetics would not just publish SNP associations for blood pressure from the Global BPgen Consortium (n = 34,433) in a long list of genes

> ATP2B1, CYP17A1, PLEKHA7, SH2B3, CACNB2, CSK-ULK3, SH2B3, TBX3-TBX5, ULK4

Another abstract claims to be originating from the same cohort (plus a follow up in 71,225 individuals of European ancestry and 12,889 Indian Asian ancestry) with association found in

> CYP17A1, CYP1A2, FGF5, SH2B3, MTHFR, c10orf107, ZNF652, PLCD3

while not providing any data that would link these genes with functional pathways (although it would be great to double blind test now TonEBP and VEGF-C :-). The authors of the last paper even acknowledge that

exposures such as dietary sodium and potassium intake or excessive alcohol use also contribute to interindividual differences in blood pressure. These were measured in a minority of our samples and thus we could not meaningfully adjust for them in our study.

So, why forget about genes (at least by now)?

The huge misclassification is only one answer. More answers come with the recent malaria gene paper that did not identify any of the well-known erythrocyte variants that have been selected by malaria, other than HbS.

… the lack of GWA signals corresponding to previously reported .. associations can at least in part be explained by low tagging efï¬ciency of the Affymetrix 500K array in this population and other causes of low statistical power, particularly low allele frequencies. However these data also raise the question of how many previously reported associations may have been false positives. In some cases an authentic association may fail to replicate because the effect size was overestimated in initial reports (â€˜winnerâ€™s curseâ€™); because the frequency of the causal variant varies between populations; because LD between the marker SNP and the causal variant varies between populations; or because the effect is complex, for example, due to allelic heterogeneity or epistasis. ciency of the Affymetrix 500K array in this population and other causes of low statistical power, particularly low allele frequencies. However these data also raise the question of how many previously reported associations may have been false positives. In some cases an authentic association may fail to replicate because the effect size was overestimated in initial reports (â€˜winnerâ€™s curseâ€™); because the frequency of the causal variant varies between populations; because LD between the marker SNP and the causal variant varies between populations; or because the effect is complex, for example, due to allelic heterogeneity or epistasis.

~~The summary is trivial: garbage in, garbage out~~. Most of my fears come, however, with the last explanation – too complex, yea, yea.