Population-Specific Manifestation of Insulin Signaling/Action Pathways: A Case Study of Chronic Metabolic Diseases in Colombians

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Abstract

Although the dysregulation of insulin signaling/action pathways are a well-known phenomenon in metabolic diseases such as type 2 diabetes and dyslipidemia, the manifestation of such pathways have a complex interaction with population-specific variables including life-style and ancestry. Here we use bipartite networks to analyze how SNPs on genes linked to insulin resistance, are associated with key demographic and clinical variables in Colombians with metabolic disease. The results revealed subsets of patients that were strongly associated with a heterogeneous subset of genes related to insulin resistance, with significantly high and low triglyceride levels explaining two of those associations. The results demonstrate how bipartite networks of genes from known pathways can rapidly elucidate their population-specific manifestations, with the goal of translation to contextually relevant therapeutics.

Introduction

While the role of insulin signaling/action pathways has been well-studied across chronic metabolic diseases (type 2 diabetes, obesity, hypertension, and dyslipidemia), their association with population-specific variables such as life-style and ancestry have yet to be fully elucidated. We therefore posed the question: *How do single nucleotide polymorphisms (SNPs) in candidate genes involved in insulin signaling/action co-occur across Colombian patients with one or more metabolic diseases?*

Method

Colombian patients (n=340) with one or more metabolic diseases in the age range of 20-84 were genotyped for 10 SNPs on 6 candidate genes known to be associated with insulin signaling/action pathways[1]. Furthermore, we recorded clinical variables (triglycerides, waist circumference) and demographic variables (admixture, age, gender and socioeconomic status) for each patient. These data were analyzed using a bipartite network where nodes represented patients or SNPs, and edges represented the genetic association between each patient-SNP pair using the recessive model. We used bipartite modularity to determine the clusteredness (in comparison to random networks of the same size) of patient or node clusters, and the Mann Whitney *U* test to analyze which clinical and demographic variables were significant across the molecularly-defined patient clusters.

Results and Conclusion

As shown in Figure 1, the bipartite network analysis was highly clustered (patient modularity= 0.382, SNP modularity=0.488), with each of the 5 patient clusters being associated to 1 or 2 SNPs. This result suggests that in the Colombian population, there are many entry points into the insulin signaling/action pathways. For example, Patient-Cluster-A was strongly associated with two SNPs on the KLF14 gene which regulates gene expression in adipocytes; Patient-Cluster-C (green nodes) strongly associated with two SNPs on the GCKR gene involved in the regulation of glucose phosphorylation in liver cells. Furthermore, Patient-Cluster-A (red nodes) had significantly lower triglycerides (U=6749.5, $p<0.01$, two-tailed) suggesting the presence of metabolic dysfunctions in absence of hypertriglyceridemia. In contrast, Patient-Cluster-C had significantly higher triglycerides compared to the rest (U=5872.5, $p<0.0005$, two-tailed) suggesting dysregulation of lipids metabolism in liver. The other 3 patient clusters had no variables that were significantly different compared to the rest of the patients, suggesting that in addition to having heterogeneous entry points into insulin dysregulation, these patients' responses were also heterogeneous[1]. The network therefore enabled us to examine a complex set of associations in a known pathway but in a new population. In future research we plan to analyze other pathways in chronic metabolic diseases using the same approach to elucidate the similarities and differences of pathways across populations.

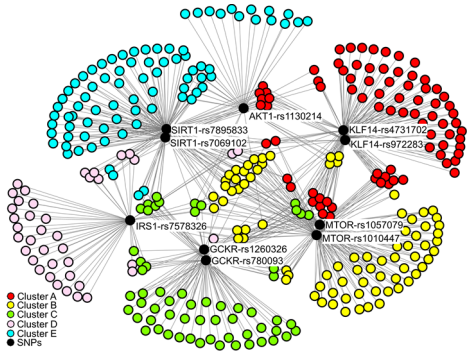

Figure 1. Bipartite network showing how candidate SNPs co-occur across Colombian patients with one or more metabolic diseases.

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References

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