# Slimming Down the Genetic Signals for BMI in African Americans

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Obesity is a major risk factor for many chronic diseases. Obesity is also a major public health concern, as more than 1.4 billion adults worldwide are obese. Heritability estimates ranging from 40-70% suggest a strong genetic component. Genome-wide association studies have identified at least 21 genetic loci associated with body mass index (BMI), a common measure of obesity. Since most of these associations were discovered in European Americans, however, it is important to evaluate whether these loci generalize to other ancestry groups. In a recent study published in *The American Journal of Human Genetics*, Dr. Jian Gong and colleagues, under the direction of Dr. Riki Peters in the Public Health Sciences Division, report that some, but not all, of these loci generalize to African Americans.

To investigate these loci, the authors combined the rich data available from eight collaborating studies, totaling more than 29,000 African American participants. Bringing these groups together was instrumental, says senior author Dr. Peters, as "this large study was only possible because of strong collaborations between multiple investigators that have made an effort to include minority groups."

Furthermore, says lead author Dr. Gong, "as we had the unique opportunity to study genetic risk factors in a very large population of African descent, this allowed us to not only identify the strongest genetic risk factors for obesity in African Americans, but also to fine-map these genetic regions". These fine-mapping efforts used the different patterns of linkage disequilibrium between ancestral populations to narrow in on, or fine-map, BMI-related loci. This can winnow down the number of potentially-related variants, honing in on a narrower section of the genome that is more likely to contain the functional variant driving the association. Says Peters, "This will ease subsequent laboratory investigations to identify the underlying causal variant and understand its function".

To evaluate and fine-map genetic associations with BMI, the authors tested 18,000 genetic variants across 21 BMI-associated loci using the Metabochip, a custom Illumina genotyping array focused on metabolic traits. Of these 21 loci previously identified in studies of European Americans, only 8

contained genetic variants showing statistically significant evidence of an association with BMI in African Americans. Overall, most variants showed a direction of effect consistent with the previously reported association. By fine-mapping, the authors were also able to refine the association signals in 7 of these 8 loci, narrowing these regions considerably. In the *MC4R* locus, for example, fine-mapping reduced this region of interest from 184 to 74 kilobases, substantially reducing the number of variants which could be forwarded to functional follow-up efforts in the lab. Furthermore, by running conditional analyses in regions with multiple hits, the authors were also able to identify a potential secondary independent signal in the *GNPDA2* locus. The identification of such secondary signals is important for accurately characterizing the genetic contributions of these loci to BMI and obesity.

In addition to evaluating these known loci, the authors also investigated whether any of the other 177,000 variants on the Metabochip were associated with BMI. This Metabochip-wide analysis revealed two novel BMI-associated loci near the genes*BRE* and *DGKB*. In both loci, the genetic variants identified were much more common in African Americans than in European Americans, potentially explaining why they were not seen in previous genome-wide scans, which were primarily performed in European American populations. Such results help to highlight the benefits of studying multiple populations.

Indeed, says Gong, "it is critical to study the genetic risk factors directly in minority populations, as it can be misleading to extrapolate findings across different ethnicities." While genetic variants are correlated with each other, this correlation can differ between ancestry groups. Therefore, says Gong, "a genetic marker that is a risk factor for obesity in one ethnic group may or may not be a risk factor in another ethnic group". While some loci seem to be population-specific, others appear to be common across groups. Identifying which loci are associated with BMI for each ancestry group, then, will be an important step for preventing the development of health disparities in the application of genetic information. With this in mind the authors are currently working on similar analyses for other population groups, such as Hispanics, Asian or Native Americans, with the goal of further elucidating the genetic underpinnings of obesity.

Other PHS investigators contributing to this project were Drs. Christopher Carlson and Charles Kooperberg, with additional support from Jeff Haessler and Stephanie Rosse.

Gong J, Schumacher F, Lim U, Hindorff LA, Haessler J, Buyske S, Carlson CS, Rosse S, Bůžková P, Fornage M, Gross M, Pankratz N, Pankow JS, Schreiner PJ, Cooper R, Ehret G, Gu CC, Houston D, Irvin MR, Jackson R, Kuller L, Henderson B, Cheng I, Wilkens L, Leppert M, Lewis CE, Li R, Nguyen KD, Goodloe R, Farber-Eger E, Boston J, Dilks HH, Ritchie MD, Fowke J, Pooler L, Graff M, Fernandez-Rhodes L, Cochrane B, Boerwinkle E, Kooperberg C, Matise TC, Le Marchand L, Crawford DC, Haiman CA, North KE, Peters U. 2013. Fine mapping and identification of BMI loci in African Americans. *Am J Hum Genet.* 93(4):661-71.

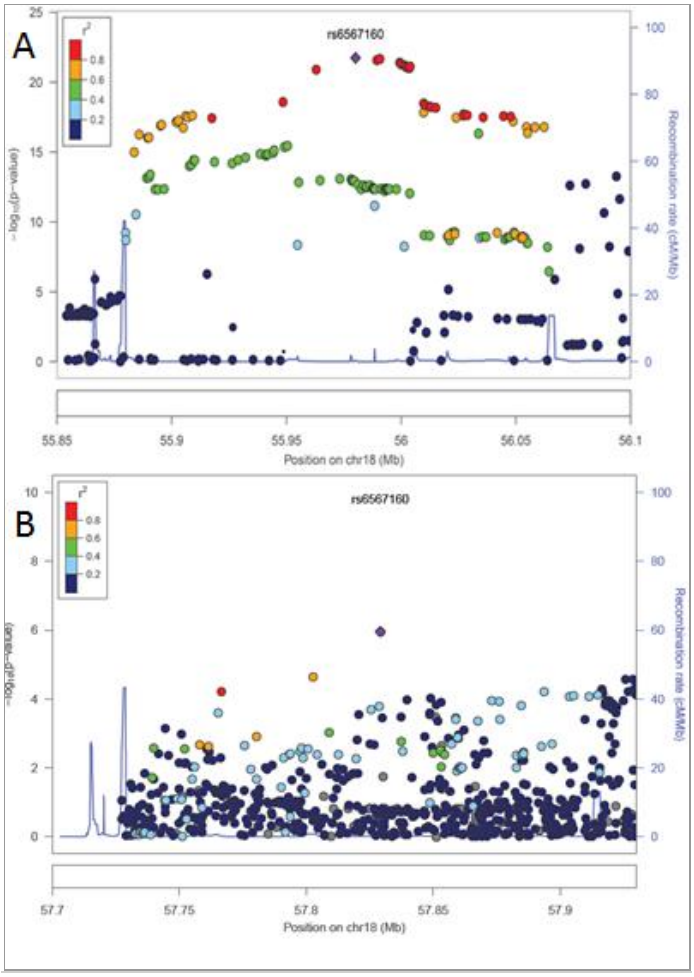


Image provided by Dr. Jian Gong.

Regional association plots of the association with BMI in the MC4R region, in European American (A) and African American (B) populations. On the y-axis are the -log(10) p-values for the association between BMI and each single nucleotide polymorphism (SNP). The x-axis refers to the genomic position, mapped to either NCBI build 36 (A) or 37 (B). Each SNP is color coded according to the correlation between that SNP and the top finding for this region, rs6567160. As can be seen, both the number of highly correlated SNPs and the width of the signal are substantially reduced in the African American group (B) compared to the European American group (A) (note that the y-axis scales are different).