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Genetic and phenotypic variation in UGT2B17, a testosterone-metabolizing enzyme, is associated with body mass index in males

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Abstract

Objective—A number of candidate gene and genome-wide association studies have identified significant associations between single nucleotide polymorphisms, particularly in *FTO* and *MC4R*, and body weight. However, the association between copy number variation and body weight is less understood. Anabolic androgenic steroids, such as testosterone, can regulate body weight. In humans, UDP-glucuronosyltransferase 2B17 (UGT2B17) metabolizes testosterone to a metabolite, which is readily excreted in urine. We investigate the association between genetic and phenotypic variation in *UGT2B17* and body weight.

Methods—*UGT2B17* deletion was genotyped and *in vivo* UGT2B17 enzymatic activity (as measured by the 3-hydroxycotinine glucuronide to free 3-hydroxycotinine ratio) was measured in 400 Alaska Native individuals and 540 African Americans.

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Conflicts of Interest

N.L.B. serves as a consultant to several pharmaceutical companies that market smoking cessation medications and has been a paid expert witness in litigation against tobacco companies. R.F.T. has consulted for Novartis, McNeil and Apotex. D.H., A.Z.X, L.S.C, J.S.A, and C.C.R declared no conflicts of interest.

Results—In Alaska Native people, *UGT2B17* deletion was strongly associated with lower BMI in males (P<0.001), but not in females, consistent with testosterone being a male dominant steroid. The gender specific association between *UGT2B17* deletion and lower BMI was also observed in African Americans (P=0.01 in males). In both populations, *UGT2B17* deletion was significantly associated with lower measured *in vivo* UGT2B17 activity. In males, lower *in vivo* UGT2B17 activity was associated with lower BMI, as observed in the gender specific genotypic association.

Conclusion—These data suggest that *UGT2B17* deletion leads to reduced UGT2B17 activity, and lower BMI in males. This is consistent with the hypothesis that reduced UGT2B17-mediated testosterone excretion results in higher testosterone levels. Future studies could confirm this hypothesis by directly measuring serum testosterone levels.

Keywords

UGT2B17; body mass index; testosterone metabolism; obesity

Introduction

Obesity is prevalent and can have significant negative impacts on health [1]. In the United States, more than one-third of adults are currently considered obese [2], and obesity contributes to 5 to 15% of deaths each year [3–5]. Currently, there are over 400 million obese adults worldwide [6], and it is predicted that nearly 60% of the World's adult population will be overweight or obese by 2030 [7]. A number of genome-wide association studies (GWAS) have identified significant associations between single nucleotide polymorphisms (SNPs), particularly in *FTO* and *MC4R* genes, and body mass index (BMI) [8–14]. However, little is known about the contribution of structure variants, such as copy number variants (CNV, segments of DNA longer than 1kb that differ in the number of copies between the genomes of different individuals), to the variation observed in BMI.

Anabolic androgenic steroids, such as testosterone, can regulate body weight. Males with lower testosterone levels are 2.4 times more likely to be obese than males with higher testosterone levels [15]. Testosterone levels are consistently inversely correlated with BMI in humans [16–18], and experimental administration of testosterone to rats reduces their body weight [19]. UDP-glucuronosyltransferase 2B17 (UGT2B17) plays an important role in testosterone metabolism in humans [20]. It catalyzes the transfer of UDP-glucuronic acid to the testosterone molecule to increase its renal excretion [21]. UGT2B17 exhibits substantial expression variation within and between populations [22], consistent with the different population prevalence of a ~117kb deletion polymorphism surrounding the *UGT2B17* gene [22]. Individuals with *UGT2B17* deletion(s) have higher serum testosterone levels (by 15%) [23], and lower urinary testosterone excretion (by ~90%) [24–26]. In addition, the *UGT2B17* deletion is associated with a lower urinary testosterone to epitestosterone ratio, which is routinely used to detect testosterone abuse in doping control programs [27, 28]. Furthermore, the *UGT2B17* deletion can alter the risk of testosterone-associated phenotypes including male insulin sensitivity, fat mass, prostate-cancer risk, and osteoporosis risk [23, 25, 29, 30]. The objective of this study was to evaluate the association between *UGT2B17* genotype and UGT2B17 activity and BMI. We hypothesized that

individuals with *UGT2B17* deletion(s) or lower UGT2B17 activity, expected to result in reduced excretion and higher blood levels of testosterone, would have lower BMI.

There are notable racial and ethnic disparities in the prevalence of obesity in the United States; around 35% of the non-Hispanic Whites or Alaska Native peoples are considered obese compared to nearly 50% of African Americans [31, 32]. There is also a high degree of racial variation in prevalence of the *UGT2B17* deletion. The allele frequency of the deletion allele is >90% in Asians, 30–35% in Caucasians, and 25% in African Americans [33]. In this study, we investigated the association between the *UGT2B17* deletion and BMI in 400 Alaska Native individuals, most of whom were tobacco users, recruited near Bristol Bay, Alaska [34]. We then replicated the findings in an independent study of 540 African American smokers recruited as part of a smoking cessation trial in Kansas City, Kansas [35, 36]. Next, we extended the *UGT2B17* genotype findings using measured *in vivo* UGT2B17 activity, confirming the genotype association.

MATERIALS AND METHODS

Study design

Alaska Native Study: The association between the *UGT2B17* gene deletion and BMI was investigated in 400 Alaska Native individuals, most of whom were tobacco users, recruited near Bristol Bay, Alaska. Demographic variables are summarized in Supplementary Table S1. A detailed description of the recruitment procedures has been reported previously [34].

African American Study: The association between the *UGT2B17* gene deletion and BMI was subsequently replicated in 540 African American smokers recruited as part of a cessation trial in Kansas City, Kansas. Demographic variables are summarized in Supplementary Table S1. A comprehensive description of the study has been published elsewhere [35, 36].

Informed consent for genetic analysis was obtained from the genotyped participants. Ethics approval was obtained from Alaska Area IRB, the Bristol Bay Area Health Corporation Board and Ethics Committee, University of California San Francisco, University of Kansas Medical Center and University of Toronto.

UGT2B17 genotyping

UGT2B17 deletion genotypes were determined using Viia 7 real time PCR machine (Applied Biosystems, Foster City, CA). The Taqman probe was specific to *UGT2B17* Exon 1 and will not amplify the highly homologous *UGT2B15* (HS03185327_CN, Applied Biosystems, Foster City, CA). RNase P was used as an endogenous control for the TaqMan Copy Number assay. The threshold cycles of *UGT2B17* were normalized to the threshold cycle of RNase P. The copy number data were analyzed by CopyCaller software version 1.0 (Applied Biosystems, Foster City, CA).

Measuring UGT2B17 activity in vivo

3’-Hydroxycotinine (3HC), a secondary metabolite of nicotine, is metabolized by UGT2B17 to 3HC-glucuronide [37]. Since our participants were mostly tobacco users (88%), we used

the ratio of urinary 3HC-glucuronide over un-metabolized free 3HC (i.e. the ratio of product over substrate) in tobacco users as an indicator of UGT2B17 activity to confirm the association between *UGT2B17* genotype and UGT2B17 activity as well as UGT2B17 activity and BMI. The ratio of urinary 3HC-glucuronide over free 3HC was previously shown to be specific to UGT2B17 [37–39], and was not altered by genetic variation in *UGT2B10* [40].

Statistical analysis

Statistical analyses were performed using STATA version 12 (College Station, TX) and the 'Bioconductor' package in 'R' (R foundation for statistical computing). BMI was calculated by dividing the individual's body weight (kg) by the square of his/her height (meter^2). The association of *UGT2B17* gene deletion with UGT2B17 activity, BMI, body weight were assessed by Kruskal–Wallis or Mann-Whitney tests followed by Jonckheere-Terpstra trend tests. The association between UGT2B17 activity (binned into tertiles to match the number of genotype groups) and BMI was assessed by Kruskal–Wallis tests followed by Jonckheere-Terpstra trend tests.

RESULTS

Descriptive data of the participants

Between the two studies, *UGT2B17* genotype was available in 930 participants. BMI was available in 912 participants and UGT2B17 activity was available in 796 participants. The *UGT2B17* deletion was in Hardy-Weinberg equilibrium in both populations. Supplementary Table S1 summarizes the baseline characteristics of the study participants.

UGT2B17 is significantly associated with lower BMI and body weight in Alaska Native and African American Males

Among the Alaska Native participants, the allele frequency of *UGT2B17* deletion was 93.5% (Supplementary Table S1). Among the Alaska Native participants, the individuals with $UGT2B17^{-/-}$ genotype had significantly lower BMI and body weight compared to the individuals with $UGT2B17^{WT/-}$ genotype (P=0.03 and P=0.01 respectively, Fig. 1A&B). Since testosterone is a male dominant steroid (the normal serum testosterone ranges are 300–1000 ng/dL in males and 15–70 ng/dL in females) [41], we focused our analysis on the association between *UGT2B17* genotype and BMI/body weight in males. As illustrated by Fig. 1C&D, the *UGT2B17* deletion was strongly associated with BMI and body weight in Alaska Native males (both P<0.001, Fig. 1C&D). The *UGT2B17* effect on BMI was very similar in non-smokers and smokers (data not shown). We did not observe any association between *UGT2B17* genotype and BMI or body weight in Alaska Native females (Supplementary Fig. S1A&B).

We sought to replicate the findings from Alaska Native individuals in African Americans, which is a distinct population with a lower prevalence of the *UGT2B17* deletion. Among the African American participants, the observed allele frequency of *UGT2B17* deletion was 23.4%. African Americans with *UGT2B17* deletion(s) trended toward having a lower BMI (P=0.07, Fig. 1E), but *UGT2B17* genotype was not associated with body weight (Fig. 1F).

However, when the analyses were restricted to males, the *UGT2B17* deletion was significantly associated with BMI and body weight (P=0.01 and P=0.05 respectively, Fig. 1G&H), and there were significant gene-dose associations between the *UGT2B17* copy number and BMI as well as body weight (P_{trend}<0.001 and P_{trend}=0.004 respectively, Fig. 1G&H). We did not observe any association between *UGT2B17* genotype and BMI or body weight in African American females (Supplementary Fig. S1E&F).

Variation in UGT2B17 activity is associated with BMI and body weight in Alaska Native and African American Males

Next, we extended the *UGT2B17* genotype findings using measured *in vivo* UGT2B17 activity. 3'-Hydroxycotinine (3HC), a secondary metabolite of nicotine, is metabolized by UGT2B17 to 3HC-glucuronide [37]. Since our participants were mostly tobacco users (88%), we used the ratio of urinary 3HC-glucuronide over un-metabolized free 3HC (i.e. the ratio of product over substrate) in tobacco users as an indicator of UGT2B17 activity to confirm the relationship between *UGT2B17* genotype and UGT2B17 activity [40], as well as the association between UGT2B17 activity and BMI. The Alaska Native individuals with the $UGT2B17^{-/-}$ genotype had a significantly lower UGT2B17 activity (P=0.002, Fig. 2A). Lower UGT2B17 activity was significantly associated with lower BMI in Alaska Native individuals (P=0.05, P_{trend}=0.01, Fig. 2B). When the analyses were restricted to Alaska Native males, UGT2B17 activity was significantly associated with *UGT2B17* genotype (P<0.001, Fig. 2C), and with BMI (P=0.02, P_{trend}<0.01, Fig. 2D), which was not observed in Alaska Native females (Supplementary Fig. S1C&D).

The African Americans with *UGT2B17* deletion(s) had significantly lower UGT2B17 activity (P=0.001, Fig. 2E). When both male and female African Americans were analyzed together, UGT2B17 activity was not significantly associated with BMI (Fig. 2F). However, when the analyses were restricted to males, UGT2B17 activity was associated with *UGT2B17* genotype and with BMI (P=0.01 and P=0.06 respectively, Fig. 2G&H), which was not observed in African American females.

DISCUSSION

Our findings demonstrated a significant association between *UGT2B17* genotype and BMI in males. A consistent association between *UGT2B17* genotype and BMI was observed in men in two racial groups with distinct allele frequencies of the *UGT2B17* deletion, and with both *UGT2B17* genotype and UGT2B17 activity. The findings identified a novel locus influencing BMI, which had not been identified in previous studies, and illustrated the contribution of gene structure variants to variation in BMI [8–10, 12, 13, 42, 43]. The direction of the association between *UGT2B17* genotype, UGT2B17 activity and BMI was highly consistent with our hypothesis that reduced UGT2B17 activity will decrease testosterone excretion and increase systematic testosterone exposure, which would lead to lower BMI and body weight.

Many of the BMI-altering genes identified by GWAS, such as *MC4R*, *FTO* and *GNPDA2*, are highly expressed in the brain. This suggested that the brain plays important role in weight regulation possibly by altering appetite and energy expenditure [13, 44]. The

association between *UGT2B17* (which is predominantly expressed in the liver) and BMI suggests that variation in the peripheral metabolism of steroids can also alter BMI. Interestingly, the per allele effect size of the *UGT2B17* deletion was greater than those observed with *FTO* or *MC4R* [13]. For example, each copy of the *UGT2B17* deletion was associated with an 1 kg/m^2 BMI reduction in African Americans. In comparison, GWAS SNPs in *FTO* or *MC4R* generally altered BMI by 0.1 to 0.3 kg/m^2 [9, 43]. The larger effect size observed with *UGT2B17* could be due to the fact that the GWAS SNPs in *FTO* and *MC4R* were "tag" SNPs rather than functional SNPs; the effect size of functional SNPs in these genes could be greater than that captured by "tag" SNPs. Another possible explanation is the relatively high average BMI in our study populations (~30) compared those in previous GWAS [9, 10, 12, 13, 43]; the effect of the *UGT2B17* deletion could be more apparent in individuals with higher BMI.

The association between *UGT2B17* and BMI was observed only in males. This is consistent with the fact that testosterone is a male dominant steroid, and the normal serum testosterone levels in females are substantially lower than males [41]. We observed faster UGT2B17 activity in males than in females, consistent with UGT2B17's role in testosterone metabolism and the molecular data demonstrating that the androgen receptor can regulate the expression of UGT2B17[45, 46].

Previous GWAS had implicated a few loci on chromosome 4 (*UGT2B17* is at 4q13.2). The most consistently replicated locus was *GNPDA2* on 4p12 [12, 13, 43]. It is unlikely that the association we observed between *UGT2B17* and BMI was due to a linkage disequilibrium between *UGT2B17* and *GNPDA2* since these two genes are a significant distance apart (*GNPDA2* is at Chr4:44.7Mb and *UGT2B17* is at Chr4:69.4Mb). The observed association between UGT2B17 activity and BMI also would be inconsistent with linkage disequilibrium with *GNPDA2* being responsible for the association.

Our study should be interpreted in the context of the existing literature. The focus on African Americans and Alaska Native individuals is a major strength of our study. However, this also makes direct comparison to previous investigations in Caucasians challenging [25]. Secondly, we were not able to measure serum testosterone levels in this study to directly test whether *UGT2B17* genotype altered testosterone levels. The association between *UGT2B17* genotype and testosterone is observed in some but not all studies [23, 25, 47, 48]. The discrepancies between studies could be due to the different racial composition of the studies (the *UGT2B17* deletion is less prevalent in Caucasians compared to Asians, thus a study in Caucasians may not be sufficiently powered to detect the impact of homozygous *UGT2B17* deletions on testosterone levels), the different study designs (i.e. endogenous testosterone levels vs. testosterone pharmacokinetics after an experimental administration), and the different methods of testosterone detection (i.e. enzyme-linked immunosorbent assay vs. mass spectrometry assays). Properly powered pharmacokinetic/pharmacogenetic studies are needed to directly examine the association between testosterone levels and *UGT2B17* genotype, and further to BMI, to provide further support for our hypothesis rather than the association being mediated by the metabolism of an alternative UGT2B17 substrate. Another limitation of this study is that BMI may not be fully reflective of body composition. Testosterone should increase lean body mass and decrease fat. Of note, we saw very high

correlations between BMI and waist circumference (R^2=0.883) resulting in very similar associations between *UGT2B17* genotype and waist circumference as with BMI. Future studies could further clarify the relative impact of *UGT2B17* genotype on fat and muscle mass.

In conclusion, we observed a consistent association between genetic and phenotypic variation in UGT2B17 and BMI in males of two populations with distinct prevalences of the *UGT2B17* deletion and of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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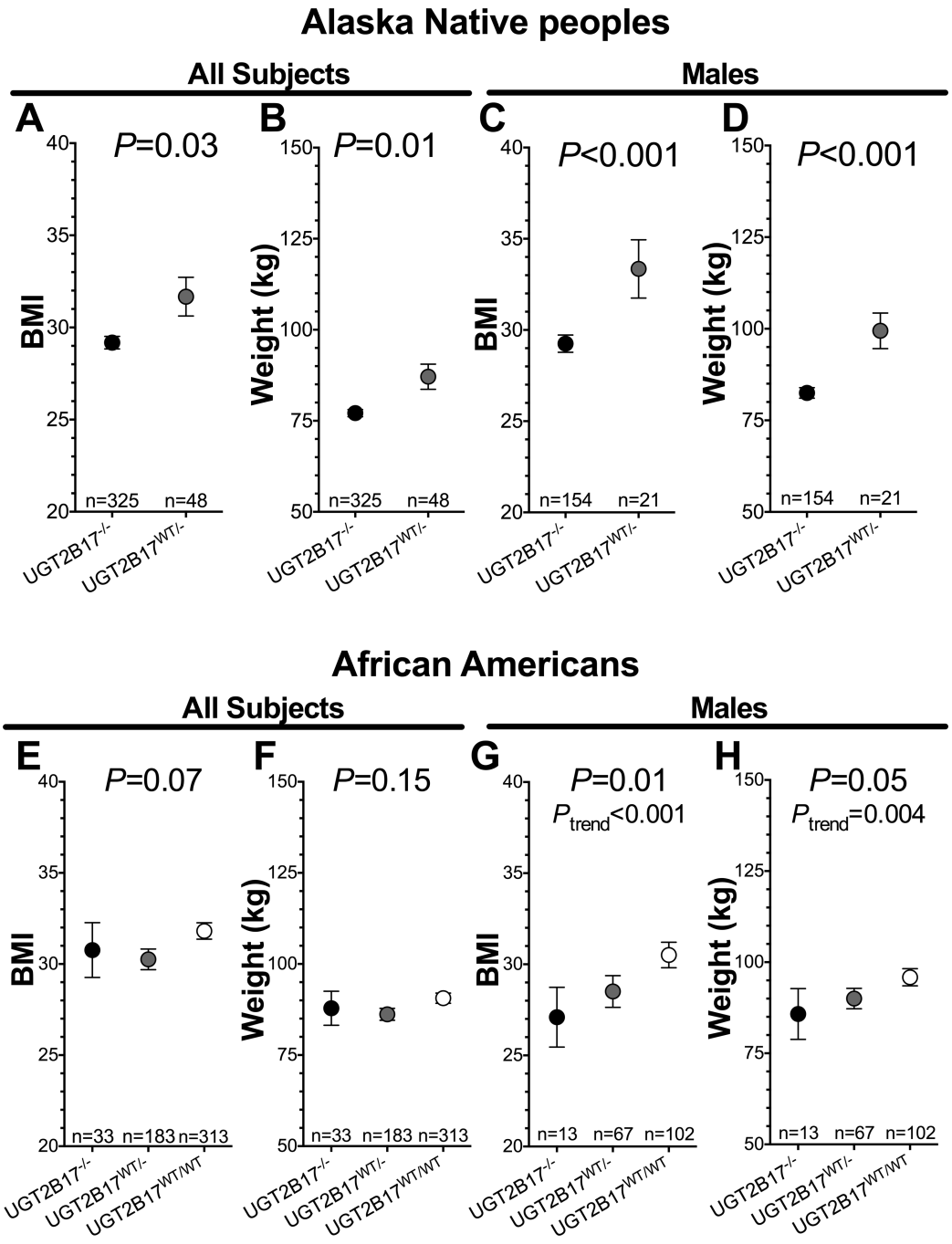

Figure 1.

UGT2B17 copy number variation is associated with BMI and body weight in Alaska Native individuals and African Americans. **Alaska Native individuals** with *UGT2B17*$^{-/-}$ genotype had lower BMI **(A)** and body weight **(B)**. Alaska Native *males* with *UGT2B17*$^{-/-}$ genotype had lower BMI **(C)** and body weight **(D)**. **African Americans**: In all African American participants, *UGT2B17* gene deletion(s) were not significantly associated with BMI **(E)** and body weight **(F)**. African American *males* with *UGT2B17* gene deletion(s) had lower BMI **(G)** and body weight **(H)**. The associations were assessed by Kruskal–Wallis or Mann-

Whitney tests followed by Jonckheere-Terpstra trend tests. Values represent Median ± interquartile range. The UGT2B17$^{WT/WT}$ genotype was not found in this population of Alaska Native individuals. BMI data were available for 373 individuals in the study of Alaska Native individuals

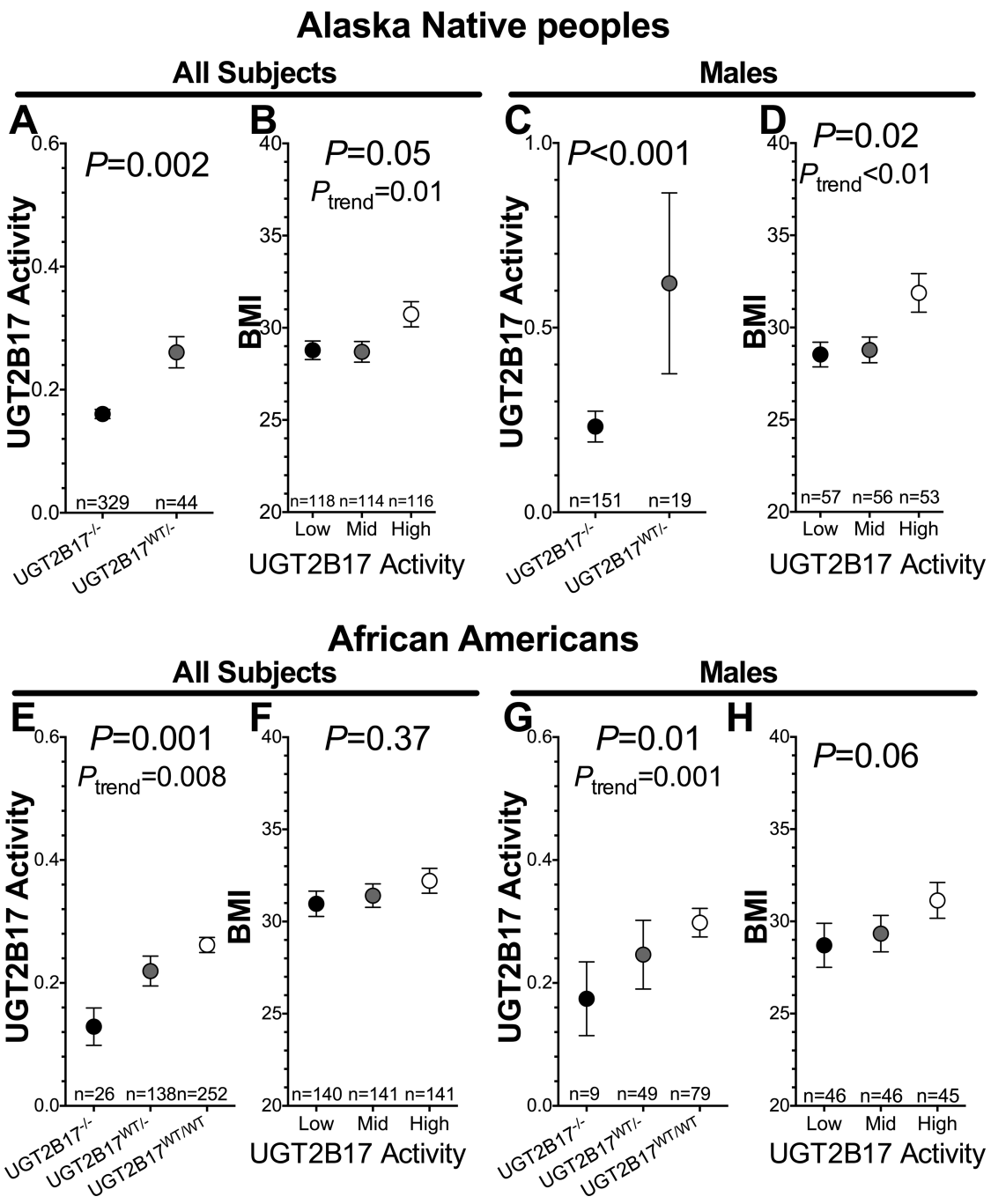

Figure 2.

UGT2B17 activity is associated with BMI in Alaska Native peoples and African Americans. **Alaska Native individuals** with *UGT2B17*$^{-/-}$ genotype had lower UGT2B17 activity **(A)** and lower UGT2B17 activity (binned into tertiles) was associated with lower BMI **(B)**. Alaska Native *males* with *UGT2B17*$^{-/-}$ genotype had lower UGT2B17 activity **(C)** and lower UGT2B17 activity (binned into tertiles) was associated with lower BMI **(D) African Americans**: African Americans with *UGT2B17* gene deletion(s) had lower UGT2B17 activity **(E).** *UGT2B17* activity (binned into tertiles) was not significantly associated with

BMI when both male and female African Americans were analyzed together **(F)**. African American *males* with *UGT2B17* gene deletion(s) had lower UGT2B17 activity **(G)** and lower UGT2B17 activity (binned into tertiles) was associated with lower BMI **(H).** The association between UGT2B17 activity (binned into tertiles to match the number of genotype groups) and BMI was assessed by Kruskal–Wallis tests followed by Jonckheere-Terpstra trend tests. Values represent Median ± interquartile range. The $UGT2B17^{WT/WT}$ genotype was not found in this population of Alaska Native individuals. UGT2B17 phenotype data were available for 373 individuals, and BMI was available for 373 individuals in the study of Alaska Native individuals; phenotype and BMI together were available for 348 individuals