HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2017 September 22.

Published in final edited form as:

Gastroenterology. 2009 May ; 136(5): 1492–1495. doi:10.1053/j.gastro.2009.03.020.

Genetics of Common Obesity and Nonalcoholic Fatty Liver Disease

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Over the last 25 years, the prevalence of obesity has increased to epidemic proportions. Certainly, this rise is in part due to a change in our environment; before the mid 1980s, the prevalence of obesity was relatively constant at about 10%.[1] This increase in obesity is correlated with a higher prevalence of fat deposits in the liver, which leads to a condition called nonalcoholic fatty liver disease (NAFLD). NAFLD encompasses a spectrum of disease that ranges from simple fat deposition (steatosis) to inflammation around the fat (steatohepatitis) and scarring (cirrhosis); some individuals with NAFLD go on to develop liver failure. However, even in today's "obesogenic" environment, not all people become obese. Similarly, why some individuals deposit fat in their liver and others do not and why some of those that deposit fat go on to develop nonalcoholic steatohepatitis, cirrhosis, and liver failure remains to be determined. One possibility is that genetics influence the observed heterogeneity in the development of these traits.

One way to determine the overall genetic contribution to a trait is to measure its heritability.[2] *Heritability* is the proportion of population phenotype variation that is attributable to genetic variation. In simple mathematical terms, phenotype variation is the sum of variation owing to environment plus variation owing to genotype. Heritability is measured relative to the genetic and environmental factors of the population and is not absolute. The degree of relatedness influences the accuracy and degree of heritability estimates; for example, the heritability of BMI studied in twins is usually higher than that obtained from family studies, which is higher than that observed in adoption studies.[3] Heritability describes a population characteristic, not an individual's. For example, if a trait is 40% heritable, then the variation in the population attributable to a familial component genetics is 40%, not the variation found in the individual.

The most commonly used obesity measure is body mass index (BMI). Twin and family studies show that the heritability of BMI ranges from 20% to 90% (reviewed in Maes et al[4]). This suggests that the variation in BMI observed in the population is part of familial origin. Work evaluating the genetic nature of NAFLD has been much more limited. Fatty liver clusters in families,[5,6] suggesting a possible genetic component to the condition. A recent study of fatty liver in 157 individuals with familial combined hyperlipidemia found that the

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Conflicts of interest The author discloses no conflicts.

heritability of fatty liver in this group was 40%.[7] The heritability of fatty liver in individuals without known genetic lipid abnormalities has not been addressed.

The accompanying paper by Schwimmer et al[8] aims to fill this gap in knowledge. The strength of this paper is that the authors took on the challenging task of measuring fatty liver using magnetic resonance imaging in family members of probands with and without biopsy-proven NAFLD. Using variance components methods, they determined that the heritability of fatty liver measured as a continuous trait was 58%; after controlling for age, gender, race, and BMI, it was reduced to 39%. Such a range is often seen with many common traits[9] and suggests that about half of the population variance in fatty liver may have a genetic origin. The authors calculated further the heritability of fatty liver as a dichotomous trait. In this case, they obtained a higher heritability of 85% and, after correction for age, gender, race, and BMI it increased to close to 100%. Both the continuous and dichotomous analyses were done using a multivariate *t*-distribution in SOLAR, a program that uses variance component methods algorithms to determine the contribution of genetic and other influences on a trait. Because both the continuous and certainly the dichotomous fatty liver traits are not normally distributed and the underlying methodology of variance component methods requires normality, analysis of these traits in SOLAR may be limited. Although the multivariate *t*-distribution can be used to model non-normal traits, numerical problems with modeling dichotomous traits in particular may lead to faulty parameter estimates. Thus, the dichotomous analyses of fatty liver should be viewed with caution

The authors go on to show that BMI correlates with fatty liver in individuals with NAFLD whereas BMI correlates less well with liver fat in those without NAFLD. One possible explanation for this nonlinear correlation is that some individuals with a genetic predisposition to develop fatty liver disease with increasing BMI deposit fat in their livers, whereas in those not predisposed it may be harder to accumulate fat in the liver.

The finding that BMI and NAFLD are heritable suggests that there are genetic components that predispose to these traits. Finding genetic variants that affect population traits has been challenging and elusive until recently. Several publications have reported reproducible associations of single nucleotide polymorphisms with BMI. The first common genetic variants convincingly associated with BMI were found in the first intron of the gene *FTO* (Table 1).[10,11] These variants confer an increased odds of being overweight or obese of about 1.14 and 1.25 per risk allele.[12] Since that time, another 10 variants have been reported.[12,13] Many of these variants have small effect sizes and often map to noncoding regions of the genome. Thus far, common single nucleotide polymorphisms captured by current genotyping platforms with large effect sizes for affecting BMI have not been uncovered in the populations being studied. Finally, 1 study[12] has found recently an association of a deletion with increased BMI, suggesting that other forms of genetic variation may contribute to variation in BMI.

Although these associations implicate some genes known previously to associate with body weight, they also implicate novel loci whose contribution to BMI was heretofore unsuspected. Two variants that affect BMI map near the genes *MC4R* and *BDNF*. Severe mutations in these genes both in humans and in mice are associated with hyperphagia and

obesity.[14–17] Other variants that are reproducibly associated with BMI map near the gene *SH2B1*, a member of the leptin signaling pathway. Sh2b1-null mice develop obesity and hyperphagia.[18] The detection of variants near candidate genes that are clearly involved in the regulation of body weight by an unbiased scan of the human genome serves as a positive control, and illustrates that this approach is likely to yield loci that have real effects on BMI. Excitingly, 8 more loci have been reproducibly associated with BMI; however, the precise genes that mediate these effects and their mechanism of action remain to be determined. Seven of the 8 genes located closest to the strongest signals of association are expressed in the cerebral cortex and hypothalamus,[12] suggesting a possible contribution of the central nervous system to the influence of body weight. Furthermore, these new loci in aggregate account for <1% of the population variation in BMI, suggesting that many more BMI-influencing variants remain to be discovered.

In support of the proposed contribution of genetic inheritance to NAFLD, nonsynonymous variants in *PNPLA3* have been associated recently with this phenotype.[19] The investigators measured fat in the liver using proton magnetic resonance spectroscopy in 2,111 European, African, and Latino individuals. They conducted an association analysis of nonsynonymous variants across the genome with NAFLD and discovered a missense variant in *PNPLA3* (rs738409, encoding I148M) that associated with hepatic fat. Hepatic fat was >2-fold higher in individuals carrying 2 alleles of this variant than in those who did not carry any. They identified other variants by resequencing the coding region of *PNPLA3* in individuals at the extremes of the liver fat distribution, and genotyped the 6 most common of these in their full sample. One of them (rs6006460, encoding S453I) was associated with decreased hepatic fat content. *PNPLA3* encodes a protein of unknown function with homology to lipid acyl hydrolases of the patanin-like phospholipase family. These associations with *PNPLA3* need to be replicated in other samples with a direct measure of fat in the liver, but variants near this region were also associated with population based levels of ALT,[20] a nonspecific marker for liver insult, including NAFLD, suggesting that they may be real. Furthermore, the precise mechanisms by which variation around this locus leads to development of NAFLD remain to be determined. Nevertheless, these findings and the paper by Schwimmer et al[8] in this issue of GASTROENTEROLOGY suggest that a human genetic approach to the study of NAFLD is feasible and tractable. Possible overlap in the contribution of variants to obesity and NAFLD is an active area of research. The upcoming years hold great promise for using a human genetic approach to not only get new insights into the biology of obesity and NAFLD, but also into possible new targets for therapeutic intervention.

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Table 1

Variants That Associate With Increasing Body Mass Index (BMI) or Steatosis

Single nucleotide polymorphism	Chorosome	Position	BMI/Steatosis increasing allele	Nearest gene
BMI				
rs9939609	16	52378028	A	*FTO*
rs6548238	2	624905	C	*TMEM18*
rs17782313	18	56002077	C	*MC4R*
rs10938397	4	45023455	G	*GNPDA2*
rs7498665	16	28790742	G	*SH2B1*
rs11084753	19	39013977	G	*KCTD15*
rs10838738	11	47619625	G	*MTCH2*
rs2815752	1	72524461	A	*NEGR1*
rs4074134	11	27603861	G	*BDNF*
rs7647305	3	187316984	C	*ETV5*
rs10913469	1	176180142	C	*SEC16B*
Steatosis				
rs738409	22	42649628	G	PNPLA3
rs6006400	22	28925243	G	PNPLA3

NOTE. Data from references [12], [13] and [19].