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## Variation in *ITGB3* has sex-specific associations with plasma lipoprotein(a) and whole blood serotonin levels in a population-based sample

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**Abstract** A recent genome-scan identified the Leu33Pro polymorphism in the  $\beta 3$  integrin (*ITGB3*) gene as a quantitative trait locus for whole blood serotonin level in a large Hutterite pedigree. Because both the Leu33Pro polymorphism and the serotonin system have been implicated in cardiovascular disease (CVD) risk and treatment response, we studied additional variation in *ITGB3* and its relationship to intermediate phenotypes associated with CVD in the same population. We examined associations between 15 single nucleotide polymorphisms (SNPs) across *ITGB3* and five CVD-related traits in the Hutterites: plasma levels of high density lipoprotein-cholesterol (HDL-c), triglycerides (TG), low density lipoprotein-cholesterol (LDL-c), and lipoprotein(a) [Lp(a)] and blood pressure or hypertension. Seven of these SNPs in *ITGB3* were associated with whole blood serotonin. Among the intermediate CVD-related phenotypes, only Lp(a) was associated with multiple *ITGB3* SNPs, five of which were also associated with serotonin. A sex-stratified analysis revealed that the

association between *ITGB3* and Lp(a) is present only in females, whereas the association between *ITGB3* and serotonin is concentrated in males. Our results suggest that variation in *ITGB3* in addition to Leu33Pro could contribute to susceptibility to CVD and serotonin in a sex-specific manner.

### Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurochemical and peripheral signaling molecule. Although it is involved in many physiological pathways, the relationship between serotonin and cardiovascular disease (CVD) is particularly intriguing. For example, clinical depression, which is associated with low platelet serotonin level, is an independent risk factor for increased mortality in patients after myocardial infarction (MI), and increased platelet activation has been suggested as the mechanism for this association (Nair et al. 1999). Further, a polymorphism in the serotonin transporter gene (*SLC6A4*) that is associated with increased platelet serotonin uptake (Greenberg et al. 1999) was correlated with increased risk of MI (Fumeron et al. 2002). Lastly, serotonin reuptake inhibitor (SSRI), but not non-SSRI, antidepressant use reduced the risk of MI in a large case-control study (Sauer et al. 2003).

Recently, we identified a novel association between the Leu33Pro single-nucleotide polymorphism (SNP) in the  $\beta 3$  integrin gene (*ITGB3*) and whole blood serotonin level (Weiss et al. 2004b). The *ITGB3* gene product makes up part of the platelet- and megakaryocyte-specific fibrinogen receptor and the widely expressed vitronectin receptor. Because over 99% of blood serotonin is in the platelets, whole blood serotonin is a measure of serotonin contained within platelets. The Leu33Pro polymorphism determines the platelet-specific antigen  $PI^{A1}/PI^{A2}$  (corresponding to Leu33/Pro33, respectively) that can be involved in neonatal alloimmune thrombocytopenia and immune thrombocytopenic purpura (Cines and Blanchette 2002; Rothenberger 2002). In

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addition to being associated with high serotonin level in our study (Weiss et al. 2004b), the protein encoded by the *PLA2* allele has been associated with markers of platelet activation, such as increased and more stable interactions with fibrinogen (Feng et al. 1999; Goodall et al. 1999; Sajid et al. 2002; Undas et al. 2001; Vijayan et al. 2000), enhanced ability of platelets to aggregate and generate thrombin (Carter et al. 1997, 1998; Joven et al. 1998; Mikkelsson et al. 2000, 2001; Pastinen et al. 1998; Wagner et al. 1998; Weiss et al. 1996), and enhanced cell migration (Sajid et al. 2002). Further, the *PLA2* allele has been associated with cardiovascular phenotypes such as coronary thrombosis and atherosclerosis (Mikkelsson et al. 2000, 2001; Weiss et al. 1996), stroke (Carter et al. 1998; Wagner et al. 1998), myocardial infarction (Carter et al. 1997; Pastinen et al. 1998) and high plasma lipoprotein(a) [Lp(a)] concentration (Joven et al. 1998), although these associations were not present in all samples studied [for a negative study of Lp(a), see Batalla et al. 1999, and for other examples of negative studies, see the meta-analysis by Zhu et al. 2000].

To explore the hypothesis that *ITGB3* variation in addition to Leu33Pro is associated with increased whole blood serotonin and CVD, we studied additional SNPs in this gene and examined associations with intermediate phenotypes related to CVD in the same population that was the subject of the serotonin genome screen (Weiss et al. 2004b). We studied 15 polymorphisms across the nearly 60-kb *ITGB3* gene, including all nonsynonymous variation, and additional SNPs in each flanking gene. We report significant associations between *ITGB3* and both whole blood serotonin and plasma Lp(a) levels, with opposite sex-specific effects in each.

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## Materials and methods

### Subjects

The Hutterites are a young founder population who practice a communal, farming lifestyle. The Hutterites of South Dakota, the subjects of our studies, are descendants of only 64 ancestors who lived in the early 1700s to the early 1800s in Europe (Ober et al. 1997). Their communal lifestyle attenuates the potential confounding effects of environmental factors. In particular, the Hutterite diet is high in saturated fat, protein, sodium and energy intake (Kant 1990; Rokusek-Kennedy et al. 1987). Individuals typically retire at age 45, after which they lead a sedentary lifestyle. Smoking is prohibited, and as a result, there is virtually no exposure to first-hand or second-hand smoke. The 806 Hutterites in our study are related to each other through multiple lines of descent in a known pedigree. A complete genealogy of these individuals was constructed from a >12,000-member Hutterite pedigree, yielding a 1,623-person pedigree that included all known ancestors of the 806 individuals (Abney et al. 2000).

Our sampling strategy was population-based. We visited nine Hutterite communal farms (colonies) between October, and March of two consecutive years. The nine colonies were selected based on location and to represent the different lines of Hutterite colony descent, but without regard to any particular phenotype (Ober et al. 2000, 2001). Enthusiasm for our studies was high, with >95% of colony members over age 5 participating. Therefore, there are no known ascertainment biases that could influence our results. The mean age of the participants was 28.7 years (SD 17.0 years; range 6–89 years); the mean inbreeding coefficient of the individuals in this sample is 0.034 (SD 0.015), slightly greater than that of 1.5 cousins (Abney et al. 2000).

### Evaluation of phenotypes

Details of our protocols have been described previously (Newman et al. 2003; Ober et al. 2001; Weiss et al. 2004b). Briefly, high density lipoprotein-cholesterol (HDL-c), triglyceride (TG) and Lp(a) levels were measured in plasma from blood samples drawn after an overnight fast in 524 individuals aged 15 or older. Since the Friedewald LDL cholesterol {total cholesterol-[HDL-c+(triglycerides/5)]} includes the cholesterol contained in Lp(a), we estimated the concentration of true LDL cholesterol (LDL-c) by subtracting from the Friedewald value the Lp(a) cholesterol calculated by multiplying Lp(a) protein by 1.3. The LDL-c was not calculated for 33 of the 524 subjects with TG > 300 mg/dl. The concentration of Lp(a) protein in mg/dl was determined using the ELISA procedure of Fless et al. (1989), which is not affected by the apo(a) size polymorphism. Individuals on cholesterol lowering medications or hormone replacement therapy ( $n=37$ ) were excluded from these analyses. Nurses measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) after the subject had been standing for at least 5 min, using mercury-gravity sphygmomanometers and appropriately sized cuffs. Whole blood serotonin was measured in 567 individuals aged 6 and older by HPLC, as described previously (Weiss et al. 2004b; Anderson et al. 1981). Informed consent was obtained for all subjects, and these studies were approved by institutional review boards at The University of Chicago and University of South Dakota.

### Genotyping

Following our genome screen, which included Leu33Pro (Weiss et al. 2004b), 14 additional SNPs in the *ITGB3* gene were chosen from dbSNP (<http://www.ncbi.nlm.nih.gov/SNP/>) to achieve an average spacing of 5 kb (with the largest gap not exceeding 15 kb), spanning from 5 kb upstream to 5 kb downstream of the gene (Fig. 1). Two SNPs in the 5'-flanking gene, *MYL4*, and seven in the 3'-flanking gene, *FLJ40342*, were chosen in

a similar manner (Table 2). All SNPs were genotyped by DNAPrint Genomics (<http://www.dnainprint.com/>), using the orchid SNP Stream-UHT (Ultra High Throughput) platform. To date, no other coding variation in *ITGB3* has been found by sequencing DNA from 12 Hutterites who represent haplotypes with frequency > 0.01 (data not shown). This is not surprising because no coding variation at frequency >0.03 was found in at least two other populations that have been studied (<http://pga.swmed.edu/Data/SNPs/PGA/ITGB3.html>; <http://www.ncbi.nlm.nih.gov/SNP/>).

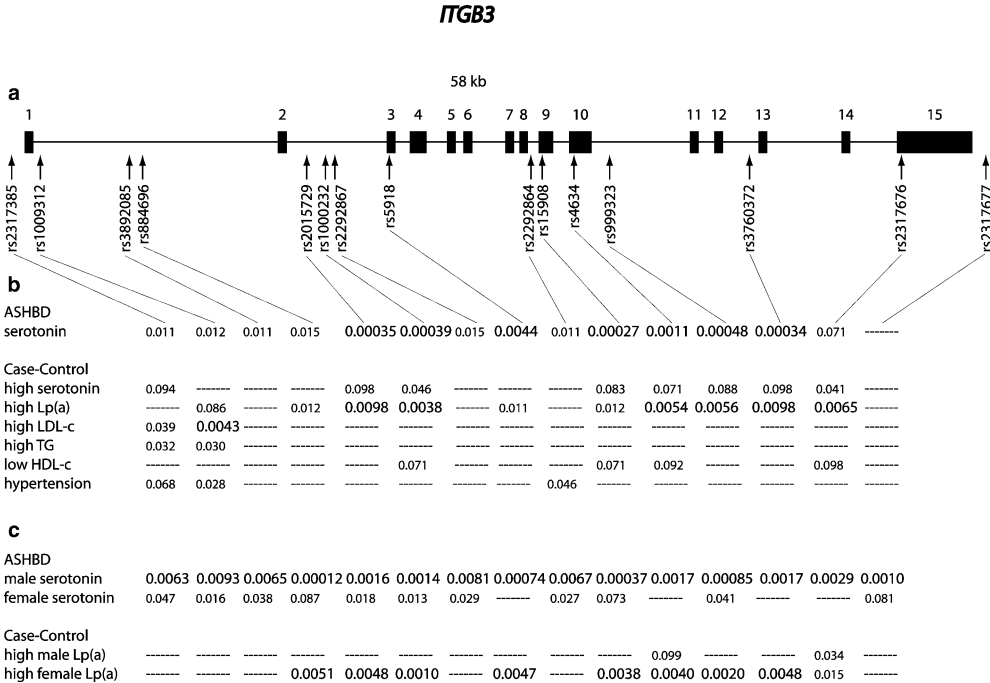
Statistical analysis

We used two approaches that take into account the relatedness between pairs of individuals in the sample to test for association with CVD-associated intermediate phenotypes and serotonin. These two approaches will be most powerful for traits acting under different models, and are therefore complementary tests in the Hutterites. The first involves case-control tests that take into account the relatedness between all individuals in the pedigree (Bourgain et al. 2003). Using this approach, we

compared either individuals with trait values at the extremes of the distribution of quantitative measurements or affected and unaffected individuals for qualitative traits, in order to find genes that could act as major risk (or protective) factors for CVD. For quantitative traits, cases were defined as individuals in the highest quartile of the distribution for LDL-c (mean = 177.8 mg/dl), Lp(a) (mean = 7.3 mg/dl), TG (mean = 253 mg/dl), and serotonin (mean = 288 ng/ml) and the lowest quartile of the distribution for HDL-c (mean = 33 mg/dl); controls were individuals in the lowest quartile for LDL-c (mean = 93.2 mg/dl), Lp(a) (mean = 0.6 mg/dl), TG (mean = 64 mg/dl) and serotonin (mean = 115 ng/ml) and the highest quartile for HDL-c (mean = 65 mg/dl), after adjusting for age and sex (72, 93, 121, 142 and 121 cases and an equivalent number of controls for each phenotype, respectively), as described previously (Newman et al. 2004). The 110 hypertension cases were either (1) adults taking antihypertensive medication or stage 1 or higher hypertension as defined by the World Health Organization-International Society of Hypertension (1999) or (2) children with high blood pressure as defined by Council on Cardiovascular Disease in the Young (Williams and Poulton 2002). The cases were compared with 84 controls (age and gender matched normotensive controls for all individuals under age 40 and all normotensive adults over age 40).

A second approach was also used to test for association with quantitative traits in order to identify genes responsible for normal variation in the population. This multipoint approach is particularly powerful for identifying loci with recessive effects, because the test relies on the existence of regions that are homozygous by descent (HBD) in inbred individuals to detect QTLs that act in a recessive manner. However, loci

**Fig. 1a-c** Association of variation in *ITGB3* with whole blood serotonin and plasma Lp(a) levels. **a** The genomic structure of *ITGB3* is shown (not to scale), with exons depicted as boxes, and arrows identified by rs# in the approximate locations of the variation genotyped. **b** Below, *P* values <0.10 are shown for the association of this variation with whole blood serotonin and CVD-associated intermediate phenotypes. *P* values <0.01 are in larger font. **c** *P* values <0.10 are shown for the association of this variation with whole blood serotonin and Lp(a) in the sex-split samples. *P* <0.01 are in larger font



with strong dominant or additive effects may also be detected by this method, as phenotype values for homozygotes of the associated allele may still differ from the phenotype values of other genotypes at this locus. In this allele-specific HBD (ASHBD) test, the effect of an allele was represented as a main effect in a linear model, as previously described (Abney et al. 2002). A given individual's multilocus genotype information and the complete pedigree information were used to estimate the individual's conditional probability of HBD for specific marker alleles, via a hidden Markov model (HMM) method. The ASHBD method tests for association of the marker alleles with deviations from the mean of the quantitative trait. This method is the only multipoint association method available capable of analyzing the Hutterite pedigree unbroken. Age and sex were included as covariates and the trait values were transformed to have a normal distribution (see Ober et al. 2001 for details). The  $P$  values were not formally corrected for multiple testing. Because many of the phenotypes (HDL-c, LDL-c, TG, and SBP, DBP) and most of the genotypes are correlated and we have used two different tests of association, it is difficult to determine the number of truly independent tests performed.

To test for correlations between quantitative phenotypes, we used a Pearson correlation coefficient. Because the test does not adjust for the genetic correlation in the sample (i.e. the relatedness of individuals in the sample), it is likely to be anticonservative and estimate a downwardly biased  $P$  value.

## Results

### Serotonin

In our genome-wide association analysis by ASHBD, an association with *ITGB3* Leu33Pro met criteria for suggestive significance (Weiss et al. 2004b). We therefore used the same method here to test for association, but now including 14 additional markers in *ITGB3* and nine in the flanking genes. Seven SNPs in *ITGB3* were associated with serotonin level (ASHBD,  $P < 0.01$ ) (rs2012759, rs1000232, rs5918, rs15908, rs4634, rs999323, rs3760372) (Table 1; Fig. 1). Six SNPs had smaller  $P$  values than Leu33Pro (rs5918), the SNP identified in our original genome screen (Weiss et al. 2004b), indicating that the  $PI^{A1}/PI^{A2}$  antigen does not by itself account for the association, but that additional variation in *ITGB3* contributes to the association signal. None of the SNPs in the flanking genes were associated with serotonin levels ( $P > 0.01$ ; Table 2), further suggesting that the association with *ITGB3* is not the result of linkage disequilibrium (LD) with SNPs in the neighboring genes (data not shown). Two of the SNPs in *ITGB3* were also modestly associated ( $0.01 < P < 0.05$ ) with serotonin by the case-control test (Fig. 1).

### CVD-associated intermediate phenotypes

We next examined associations between variation in *ITGB3* and five CVD-related intermediate phenotypes. Six SNPs spanning *ITGB3* from the second intron to the 3'UTR were associated with Lp(a) level using the case-control test, five of which coincide with the serotonin-associated SNPs (Table 1; Fig. 1). The five SNPs that were associated with both Lp(a) and serotonin levels are in strong LD with each other ( $r^2 > 0.9$ ), so may represent a haplotype or SNP (typed or untyped) within the haplotype that is associated with both traits. A SNP in intron 1 (rs1009312, A allele), was associated with high LDL-c ( $P < 0.01$ ), but not with Lp(a) or serotonin levels (Fig. 1). No association was observed using the ASHBD test for any CVD-associated intermediate phenotype, suggesting that either variation in *ITGB3* contributes more to extremes of the Lp(a) phenotype than the full distribution of variation or that the ASHBD method is not powerful for the specific model of association between *ITGB3* and Lp(a). For example, while serotonin had a large non-additive component in its heritability ( $h^2 = 0.52$ ,  $H^2 = 0.99$ ), Lp(a) was estimated to have only additive genetic variance (Ober et al. 2001), which could explain the lack of power of the ASHBD method to detect association with Lp(a).

### Further examination of serotonin and Lp(a) levels

The finding that the same variation in *ITGB3* was associated with both serotonin and Lp(a) led us to investigate whether serotonin levels and Lp(a) might be associated with each other independent of *ITGB3*. To assess the relationship between serotonin and Lp(a) levels, we first examined the correlation between the two traits in 324 individuals with phenotype data for both traits. The correlation between the ln-transformed values of serotonin and Lp(a), adjusted for age and sex, was not significant (Pearson correlation coefficient =  $-0.01$ ,  $P = 0.86$ ).

The fact that these phenotypes were not correlated in the sample, despite their strong association with the same variation in *ITGB3*, was puzzling. However, we recently reported that on a genome-wide level, whole blood serotonin has a sex-specific genetic architecture, with the linkage and association evidence at *ITGB3* present primarily in males (Weiss et al. 2004a). In addition, a study of metabolic syndrome (obesity, high triglycerides, low HDL-c, high blood pressure and high fasting glucose) reported association at many loci, including *ITGB3*, only in females (McCarthy et al. 2003). Therefore, we next examined these phenotypes more closely in the Hutterites. Lp(a) and serotonin level were both sexually dimorphic, with levels of each higher in females than males [median Lp(a): female = 1.99 mg/dl, male = 1.50 mg/dl,  $P = 0.054$ ; median serotonin: female = 195 ng/ml, male = 161 ng/ml,  $P = 2.4 \times 10^{-9}$ ].



**Table 1** SNPs in *ITGB3* included in this study (rs# from dbSNP <http://www.ncbi.nlm.nih.gov/SNP/>). The SNPs are shown as base change from consensus sequence in contig NT\_035424

rs #	Location in gene	Position in contig NT_035424	Associated allele <sup>a</sup>	Frequency in Hutterites
rs2317385	5' region	841140G → A	A	0.20
rs1009312	intron 1	843598G → A	A	0.20
rs3892085	intron 1	851938A → G	G	0.14
rs884696	intron 1	852702C → A	A	0.22
rs2015729	intron 2	865951G → A	A	0.39
rs1000232	intron 2	868019T → C	C	0.37
rs2292867	intron 2	868947C → T	T	0.14
rs5918	exon 3	872188T → C (L33P)	C	0.21
rs2292864	intron 8	879139C → T	T	0.14
rs15908	exon 9	879795A → C	C	0.38
rs4634	exon 10	881247G → A	A	0.36
rs999323	intron 10	883061T → C	C	0.36
rs3760372	intron 12	891460T → C	T	0.39
rs2317676	3'UTR	899741A → G	G	0.08
rs2317677	3' region	904865G → A	A	0.22

<sup>a</sup>Allele associated with high serotonin and Lp(a) level (or the allele with the smaller *P* value if neither were associated)

We then repeated the association analyses of *ITGB3* with serotonin and Lp(a) stratifying by sex. As previously reported, the *ITGB3* Leu33Pro association with serotonin level were much stronger in males (Weiss et al. 2004a). Here, we further show that the other SNPs across *ITGB3* that are associated with serotonin level are also associated more strongly in males (Fig. 1). In contrast, the *ITGB3* associations with Lp(a) were even more significant in females, with virtually no association in males (Fig. 1). It is notable that in both cases, despite smaller sample sizes, *P* values were more significant in one sex, indicating that the evidence for association is likely all coming from males for serotonin and females for Lp(a). In light of these results, the lack of correlation between the two phenotypes is not unexpected.

**Table 2** The SNPs in directly flanking genes are shown with distance in base pairs from *ITGB3* (M3599) based on the Human Genome Project (<http://www.genome.ucsc.edu>). For *MYL4*, this distance is from the 5' end and for *FLJ40342*, this distance is from the 3' end

rs#	Gene	Base pairs from <i>ITGB3</i>	Minor allele frequency
rs908359	<i>MYL4</i>	49,885	0.39
rs867859	<i>MYL4</i>	32,801	0.38
rs2271803	<i>FLJ40342</i>	11,238	0.19
rs1912483	<i>FLJ40342</i>	53,824	0.38
rs2292348	<i>FLJ40342</i>	65,262	0.07
rs2292345	<i>FLJ40342</i>	65,899	0.07
rs2136750	<i>FLJ40342</i>	66,430	0.38
rs3752864	<i>FLJ40342</i>	81,558	0.07
rs3883318	<i>FLJ40342</i>	100,581	0.23

## Assessing potential relationships between serotonin and Lp(a)

We next explored whether there may be common pathways that influence serotonin and Lp(a) levels. To investigate whether other genes known to influence whole blood serotonin level also influence plasma Lp(a) level, we examined associations between Lp(a) level and variation in the serotonin transporter gene (*SLC6A4*, also known as *5HTT* and *SERT*), which has been associated with serotonin uptake in outbred samples (Greenberg et al. 1999) and with serotonin level in the Hutterites (Weiss et al. 2004b). We did these tests in the whole sample and sex-stratified samples, and in each case, the association was strongest in the sex-stratified sample. An intronic SNP in *SLC6A4* (rs2066713 C/T) was modestly associated with Lp(a) level in females (case-control test, T allele, *P*=0.021), but not males. Neither a second SNP (rs2020936 C/T), nor the promoter length polymorphism (5HTTLPR long/short) (Kim et al. 2002) was associated with Lp(a) level in either sex (*P*>0.05).

Finally, we tested for associations between the *LPA* locus and serotonin level. We used a nearby microsatellite, D6S305, as a surrogate for the *LPA* gene, because this microsatellite was highly associated with low Lp(a) level in the Hutterites (*P*=7.9×10<sup>-11</sup>) (Ober et al. 2001). This locus was (more modestly) associated with decreased serotonin level in females (case-control test, *P*=0.01), but not in males.

## Discussion

Our study, showing that variation in *ITGB3* is associated with Lp(a) level in a population with uniform but high environmental risk factors for CVD, suggests that the αIIbβ3 integrin receptors, which play key roles in platelet activation, could contribute to the relationship between Lp(a) and thrombosis, particularly in females. In fact, coding variation in the gene for another coagulation initiator, factor VII (F7), was associated with Lp(a) level in a Canadian Hutterite population (Hegele et al. 1997). Interestingly, this same polymorphism in F7, R353Q (rs6046), as well as a 10-bp insertion/deletion polymorphism (rs5742910) in the 5'-flanking region were associated with Lp(a) level in females (*P*=0.018 and 0.0012, respectively) but not males in the S. Dakota Hutterites (unpublished data). These combined data suggest a more general connection in females between Lp(a) and proteins traditionally thought of as relevant to coagulation.

It is also notable that *ITGB3* Leu33Pro, which has been previously associated with CVD phenotypes (Carter et al. 1997, 1998 Joven et al. 1998; Mikkelsen et al. 2000, 2001; Pastinen et al. 1998; Wagner et al. 1998; Weiss et al. 1996), was not among the strongest associations for serotonin or Lp(a) levels, by either method. This suggests that the P1<sup>A2</sup> allele may be a marker for an

associated haplotype (or an allele on that haplotype), but is unlikely to be the sole causative SNP for the association with serotonin level in the Hutterites. Because there were no other coding SNPs identified in *ITGB3*, our results would indicate that at least one functional SNP may have regulatory roles in transcription, splicing or mRNA stability for this gene. Additional genetic variation in *ITGB3* may also be relevant for CVD phenotypes previously associated with Leu33-Pro. In this study, it was not possible to separate out the effects of individual SNPs, because the SNPs that were most highly associated with Lp(a) and serotonin were in strong LD in the Hutterites ( $r^2 > 0.9$ ). It is interesting to note, however, that for the most part, the same variation was associated with both serotonin and Lp(a) levels in this sample. Such pleiotropic effects of single genes are not uncommon. For example, the same polymorphism in the *APOE* gene influences cholesterol level and CVD risk as well as predisposition to Alzheimer's disease and dementia (Corder et al. 1993; Eichner et al. 2002). It is possible that our results reflect such pleiotropy.

In one light, our examination of the relationship between Lp(a) and serotonin yielded results that seem contradictory. There was no correlation between the two measures, and in fact the associations were strongest in opposite sexes, which suggests that variation in *ITGB3* regulates serotonin and Lp(a) levels through independent mechanisms. This could occur, for example, if fibrinogen receptors ( $\alpha$ IIb $\beta$ 3) influenced serotonin storage in the platelet in males, but vitronectin receptors ( $\alpha$ v $\beta$ 3) on endothelial tissue could influence Lp(a) level in females. However, the genetic associations between a microsatellite near *LPA* and serotonin level and between the serotonin transporter gene and Lp(a) levels in females suggest an underlying relationship between Lp(a) and serotonin, at least among females. In this case, variation in *ITGB3* could directly influence serotonin level, which in turn regulates Lp(a) level, or variation in *ITGB3* could directly influence Lp(a) level, which in turn regulates serotonin level. In these latter cases, a sex-specific epistatic effect could blur a direct correlation between Lp(a) and serotonin measured in the periphery. In fact, such epistasis may be mediated by estrogen, which can both suppress *ITGB3* mRNA levels (Kimmins et al. 2003) and lower circulating levels of Lp(a) (Espeland et al. 1998; Farish et al. 1996). Therefore, it is possible that differences in circulating levels of estrogen in males and females obscure the evidence for genetic associations between *ITGB3* and serotonin in females and between *ITGB3* and Lp(a) in males, despite a common pathway at the cellular level.

In view of our results, it is intriguing that several studies have recently suggested that in older adults, elevated Lp(a) levels are predictive of stroke and of vascular disease-related deaths in men but not in women (Ariyo et al. 2003; Scanu 2003; Sunayama et al. 1996). Our finding of different genetic etiologies of increased Lp(a) levels in men and women may underlie the difference in Lp(a)-associated morbidity and mortality

observed in large population studies, although our sample did not have a large enough number of older individuals to specifically examine age or age-sex interaction effects, particularly relating to symptomatic coronary artery disease. Further unraveling of the sex-specific genetic architecture of these traits could provide insight into the mechanism by which high plasma concentration of Lp(a) is a major risk factor for atherosclerosis and CVD in only some individuals (de la Pena-Diaz et al. 2000).

In conclusion, we have shown that common variation in *ITGB3* is associated with both plasma Lp(a) in females and whole blood serotonin levels in males. These results provide a new candidate, the  $\beta$ 3 integrin receptor, to further understand Lp(a) biology, to dissect sex-specific risk factors for cardiovascular disease, and to develop more informed therapeutic approaches to treat Lp(a) related cardiovascular disease.

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