Disentangling the genetics of lean mass

Disentangling the Genetics of Lean Mass

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Abstract

Lean body mass (LM), consisting mostly of skeletal muscle, plays an important role in mobility and metabolic function. In a previous large scale study we identified five loci associated with LM adjusted for fat mass in kilograms. Such an adjustment may reduce the power to identify genetic signals having an association with both lean mass and fat mass.

To identify additional LM loci and to be able to determine the impact of different fat mass adjustments, we performed genome-wide association analyses for whole body LM (in 20 cohorts of European ancestry with n=38,292) measured using DXA or bioelectrical impedance analysis, adjusted for sex, age, age^2 and height with or without different fat mass adjustments (*Model 1* no adjustment for fat mass; *Model 2* adjustment for fat mass as a percent of body mass; *Model 3* adjustment for fat mass in kilograms). Seven SNPs in/near separate loci, including one novel LM locus (*TNRC6B*), were successfully replicated in 47,227 individuals from 27 cohorts. The lean mass increasing allele of the identified genetic variant in the *TNRC6B locus* was also robustly associated with increased hand grip strength.

Based on the strengths of the associations in *Model 1* vs *Model 3* we divided the LM loci into those with an effect on both lean mass and fat mass in the same direction and refer to those as "*sumo wrestler"* loci (*FTO* and *MC4R*). In contrast, those loci with an impact specifically on lean mass were termed "*body builder" loci* (*VCAN* and *ADAMTSL3).* When evaluated in existing available GWAS databases, LM increasing alleles of SNPs in *sumo wrestler* loci were associated

with an adverse metabolic profile while LM increasing alleles of SNPs in *"body builder"* loci were associated with metabolic protection.

In conclusion, we identified one novel LM locus (*TNRC6B*); our results suggest that genetically determined increase in lean mass might exert either harmful or protective effects on metabolic traits, depending on its relation to fat mass.

keywords: body composition, skeletal muscle, body fat, meta-analysis of genome wide association studies, metabolic profile

ABBREVIATIONS:

BIA - bioelectrical impedance analysis

BMD - bone mineral density

DXA – Dual energy X-ray absorptiometry

EQTL - expression quantitative trait loci

FDR - false discovery rate

GWS - genome-wide significant

KASP - KBioScience Allele-Specific Polymorphism SNP genotyping system

LD - linkage disequilibrium

LM - Lean body mass

MAF - minor allele frequency

Q-Q - quantile–quantile (plots)

sGWS - suggestive genome-wide significance

Introduction

Lean body mass (LM), consisting mostly of skeletal muscle, plays an important role in mobility and metabolic function. It is well established that high fat mass results in insulin resistance, increased risk of Type 2 diabetes and dyslipidemia. Observational studies indicate that lean mass adjusted for weight or fat mass is inversely associated with insulin resistance and metabolic abnormalities.[1] However, the causal effects of lean mass on metabolic traits are unclear. Adipocytes and myocytes share common mesenchymal ancestry[2] and factors (genetic and/or environmental) stimulating the development of mesenchymal stem cells towards the myocyte lineage instead of the adipocyte lineage may lead to more favorable body composition.

In a recent large scale study we identified five loci associated with LM adjusted for fat mass in kilograms.[3] In that study we were primarily interested in genes contributing to lean mass independent of those regulating fat mass.[3] Because lean mass is positively correlated with fat mass and may even be stimulated to increase by the mechanical demands of carrying more fat mass, our previous results adjusted for fat mass in the statistical models. A potential limitation of this strategy of adjusting for fat mass is that the ability to identify genetic signals with an impact on both lean and fat mass will be reduced. Nevertheless, the *FTO* signal was found to be significantly associated with lean mass after fat adjustment and the direction of this association was the same as the association with fat mass found in other studies.[4] To be less restrictive in our quest to identify additional lean mass loci and to gain more insight into the lean-fat mass relationship and its health consequences, in this study we performed different statistical models with either no fat adjustment at all, or with one of two fat adjustment models: fat as a percentage of body mass, or fat in absolute kilograms.

For identified lean mass SNPs, we also aimed to evaluate the associations with a variety of musculoskeletal and metabolic traits. Finally, we aimed to explore if the associations with musculoskeletal and metabolic parameters differed for significant loci identified in models without fat mass adjustment compared with those having the strongest association in models with fat mass adjustment.

METHODS

Study summary: We performed a genome-wide association study meta-analysis on whole body lean mass in a set of discovery cohorts (Stage I), then meta-analyzed the discovery SNPs in replication cohorts (Stage II), followed by a combined analysis with discovery and replication cohorts. The total sample size for the combined analysis was 85,519 individuals of European ancestry from 47 studies.

Study Population

The Stage I Discovery sample comprised 38,292 individuals of European ancestry drawn from 20 cohorts with a variety of epidemiological designs and participant characteristics (Supplementary Table S1 and Supplementary Note 1). Whole body lean mass was measured using DXA (10 cohorts, n=21,074) and BIA (10 cohorts, n=17,218). Of the 20 cohorts, 15 consisted of males and females, while 2 had males and 3 had females only. In total, the cohorts included 22,705 women and 15,587 men.

Twenty-nine additional studies were used for replication with a total sample size of 47,227 subjects of European ancestry. The Stage II, Replication included cohorts with either existing GWAS data that were unavailable at the time of the Stage I Discovery, or cohorts without GWAS data who agreed to undergo *de novo* genotyping. Because some of the replication cohorts performed *de novo* genotyping, there were fewer data points for SNPs that were newly genotyped compared to SNPs that were imputed from already available GWAS studies. All studies were approved by their institutional ethics review committees and all participants provided written informed consent.

Lean Mass Measurements

Lean mass was measured in all cohorts using either DXA or BIA. DXA provides a three compartment body composition assessment based on specific x-ray attenuation properties: bone mineral, lipid (triglycerides, phospholipid membranes, etc.) and lipid-free soft tissue. Each pixel on the DXA scan is quantitatively partitioned into these three tissue types. For the cohorts with

DXA measures, the phenotype used for these analyses was the lipid-free, soft tissue compartment that is referred to as lean mass, and is the sum of body water, protein, glycerol and soft tissue mineral mass. Two lean mass phenotypes were used: whole body lean mass and appendicular lean mass. The latter was obtained by DXA while considering only pixels in the arms and legs collectively, which has been demonstrated to be a valid measure of skeletal muscle mass.[5] Some of the cohorts estimated body composition using BIA, which has been detailed in our previous work.[3] For BIA cohorts with specific resistance and reactance measures, we used the validated equation from Kyle et al. with an R^2 of 0.95 between BIA and DXA to calculate the appendicular lean mass.[6]

STAGE 1: GENOME-WIDE ASSOCIATION ANALYSES IN DISCOVERY COHORTS

Genotyping and Imputation: Genome-wide genotyping was done in each study on a variety of platforms following standard manufacturer protocols. Quality control was performed independently for each study. To facilitate meta-analysis, each group performed genotype imputation with IMPUTE[7] or MACH[8] software using HapMap Phase II release 22 reference panels (CEU or CHB/JPT as appropriate). Overall imputation quality scores for each SNP were obtained from IMPUTE ("proper_info") or MACH ("rsq_hat"). Details on the genotyping platform used, genotype quality control procedures and software for imputation employed for each study are presented in Supplementary Table S2. Because the project started prior to the creation of denser imputation panels, only Hap Map II based imputation was available.

Study-specific genome-wide association analyses with lean mass and different lean mass models: Details about study-specific genome-wide association analyses and meta-analyses have been described previously.[3] Briefly, in each study, a multiple linear regression model with additive genetic effect was applied to test for phenotype-genotype associations using ~2.0 to 2.5 million genotyped and/or imputed autosomal SNPs. Because lean mass is correlated with fat mass and height, we pre-specified three models of adjustment: model 1: adjustment for sex, age, age^2, height; model 2: adjustment for sex, age, age^2, height, percent fat mass; model 3: adjustment for sex, age, age^2, height, fat mass in kilograms. Other covariates adjusted in the model included

ancestral genetic background using principal components and, when appropriate, study specific covariates such as clinical center for multi-center cohorts. For family-based cohorts, including the Framingham Study, ERF, UK-Twins, Old Order Amish Study and the Indiana cohort, familial relatedness was taken into account in the statistical analysis.[3]

Meta-analyses: Meta-analyses were conducted using the METAL package (www.sph.umich.edu/csg/abecasis/metal/). We used the inverse variance weighting and fixed effect model approach. Prior to meta-analysis, we filtered out SNPs with low minor allele frequency, MAF (< 1%) and poor imputation quality (proper_info < 0.4 for IMPUTE and rsq_hat < 0.3) and applied genomic control correction where the genomic control parameter lambda (λ_{GC}) was > 1.0.

We used quantile–quantile (Q-Q) plots of observed versus expected $-\log_{10}$(p-value) to examine the genome wide distribution of p-values, Manhattan plots to report genome-wide p-values, regional plots for genomic regions within 100Kb of top hits, and forest plots for meta-analyses and study-specific results of the most significant SNP associations. For all three models, a threshold of $p < 5 \times 10^{-8}$ was pre-specified as being genome-wide significant (GWS), while a threshold of $p < 2.3 \times 10^{-6}$ was used to select SNPs for a replication study (suggestive genome-wide significant – sGWS).

STAGE 2: REPLICATION

In each GWS or sGWS locus, we selected the lead SNP with the lowest p-value for replication. In addition, GWS or sGWS SNPs that had low linkage disequilibrium (LD) with the lead SNPs ($r^2 < 0.5$) were also selected for replication. Both *in-silico* replication and *de-novo* genotyping for replication was conducted. *In-silico* replication was done in 24 cohorts with GWAS SNP genotyping that did not have data available at the time of the initial discovery efforts (Supplementary Table S3). *De-novo* replication genotyping was done using KBioScience Allele-Specific Polymorphism (KASP) SNP genotyping system (in OPRA, PEAK25, AGES, CAIFOS, DOPS cohorts), TaqMan (METSIM), Illumina OmniExpress + Illumina Metabochip (PIVUS and ULSAM), or Sequenom's iPLEX (WHI) (Supplementary Table S4). Samples and SNPs that did not meet the quality control criteria defined by each individual study were excluded.

Minimum genotyping quality control criteria were defined as: SNP call rate > 90% and Hardy-Weinberg equilibrium $p > 1x10^{-4}$.

META-ANALYSIS OF REPLICATION AND DISCOVERY STUDIES

In the replication stage, we meta-analyzed results from individuals of European descent only. A successful replication was considered if the association *p-value* in the cumulative-meta-analysis was GWS *and* less than the discovery meta-analysis *p-value*. Using the METAL package we also estimated I^2 to quantify heterogeneity and p-values to assess statistical significance for a total of 12 associations (three SNPs from model 1, four from model 2 and five from model 3) that were replicated in the cumulative-meta-analysis. Appendicular lean mass was available in a subsample of those with whole body lean mass (n=70,690 from 38 studies) and models 1-3 for appendicular lean mass were evaluated for the replicated GWS associations from the whole body lean mass analyses.

ANNOTATION AND ENRICHMENT ANALYSIS OF REGULATORY ELEMENTS

We predicted the function of coding variants by PolyPhen-2. For all replicated variants, we annotated potential regulatory functions based on experimental epigenetic evidence including DNase hypersensitive sites, histone modifications, and transcription factor binding sites in human cell lines and tissues from the ENCODE Project and the Epigenetic Roadmap Project. We first selected SNPs in high LD ($r^2 \geq 0.8$) with GWAS lead SNPs based on the approach of Trynka, et al.[9] We then identified potential enhancers and promoters in the GWAS loci (GWAS SNPs and SNPs in LD with the GWAS SNPs) across 127 healthy human tissues/normal cell lines available in the ENCODE Project and the Epigenetic Roadmap Project from the HaploReg4 web browser[10] predicted by ChromHMM.[11] To evaluate if replicated GWAS loci were enriched with regulatory elements in skeletal muscle tissue, we performed a hypergeometric test. Specifically we tested whether estimated tissue-specific promoters and enhancers in a GWAS locus were enriched in 8 relevant skeletal muscle tissues/cell lines vs. enrichment in non-skeletal muscle tissues (119 tissues/cell lines). The permutation with minimum p-value approach was performed to correct for multiple testing. Permutation *p-values* < 0.05 were considered statistically significant. In addition, we also performed enrichment analyses in smooth muscle

tissues/cells, fat tissue, brain, blood cells and gastrointestinal tract tissues. The 8 skeletal muscle relevant tissues/cells were excluded when conducting enrichment analyses for other tissue types. The detailed information for tissue types and chromatin state estimation is described in the Supplementary Materials (Suppl. Note 2).

CIS-EXPRESSION QUANTITATIVE TRAIT LOCI (EQTL)

We looked up *cis*-eQTL information from GTEx data on the 7 replicated GWS loci, SNPs rs2943656, rs9991501, rs2287926, rs4842924, rs9936385, rs10871777 and rs 733381 with gene expression within 2Mb of the SNP position. Multiple testing was corrected by using false discovery rate (FDR q value < 0.05) to account for all pairs of SNP-gene expression analyses in multiple tissues.

Look-ups of replicated SNPs in GWAS of metabolic and musculoskeletal traits

For the seven replicated lean mass SNPs, we performed look-ups of relevant metabolic and musculoskeletal traits using available results from published GWAS meta-analyses. The metabolic and musculoskeletal traits evaluated included percent fat [12], BMI [4], coronary artery disease [13], type 2 diabetes [14], HOMA insulin resistance [15], triglycerides [16], total cholesterol [16], LDL cholesterol [16], HDL cholesterol [16], hand grip strength [17, 18], bone mineral density (BMD)[19] and fractures (manuscript). (CITE ABSTRACT OF FX GWAS OR TIMING MIGHT BE OK FOR THE FRACTURE PAPER TO BE ACCEPTED AT BMJ) We will keep this in the paper but revisit according to how the timing works out and if other fx paper authors are ok with this.)

Genetic correlation in LD score regression

We applied LD score regression to estimate genetic correlations across several muscle-related traits from summary-level data of publicly available GWAS. We used LD Hub[20], which is a centralized database of summary-level GWAS results for hundreds of diseases/traits from multiple consortia and online resources, as well as a web interface that automates the LD score regression analysis pipeline [21]. According to Bulik-Sullivan, et al. [22], the genetic correlation for

a set of SNPs S is calculated as $r_S(y_1, y_2) := \rho_S(y_1, y_2) / \sqrt{h^2_S(y_1) h^2_S(y_2)}$, where ρ_S is genetic covariance among SNPs in S, y_1 and y_2 denote phenotypes, and h^2_S, the heritability explained by SNPs in S.

Results

GWAS META-ANALYSES FOR DISCOVERY AND REPLICATION

Descriptions and characteristics of the study populations in the discovery stage and the replication stage are shown in Supplementary Table S1, S5, and Supplementary note 1. The age of the participants ranged from 18 to 100 years. In the GWAS discovery set, comprising 38,292 participants for whole body lean mass, a substantial excess of low p-values compared to the null distribution was observed after genomic control adjustment of the individual studies prior to meta-analysis: λ_{GC} = 1.078 λ_{GC} =1.075and λ_{GC} =1.076, for *Model 1* (not adjusted for fat masss), *Model 2* (adjusted for fat %) and *Model 3* (adjusted for fat mass in kg), respectively (Figure S1A-C).

Tables 1A-C show the genome-wide significant (GWS) and suggestive (sGWS) results for the three models in the discovery set (see also Fig. S2. In *Model 1*, we observed three independent GWS results (in/near *FTO, MC4R* and *CALCR*) and four sGWS results (in/near *HSD17B11, GMPPA, CMTM8 and C10orf39; Table 1A; Fig S2A).* In *Model 2*, we observed three independent GWS results (in/near *HSD17B11, FTO and CALCR*) and 10 sGWS results (in/near *MC4R, TNRC6B, RHOC, GMPPA, NUDT3, AKR1B1, ANGPT2, ZBTB16, ADAMTSL3, SMG6; Table 1B; Fig S2B*).

Data for *Model 3* have already been presented in a previous publication[3] but for comparison we display it in Table 1C. To reiterate, in *Model 3*, we observed one independent GWS result in/near *HSD17B11* and 10 sGWS results (in/near *IRS1, VCAN, ADAMTSL3, FTO, RHOC, PRR16, FRK, AKR1B1, CALCR, KLF12; Table 1C; Fig S2C).*

We selected all GWS and sGWS associations for all three models (Tables 1A, 1B, 1C) to conduct a replication study in a set of 27 cohorts comprising up to 47,227 participants of European descent. Due to limited resources, five of the sGWS signals were evaluated only in the cohorts available for in-silico replication (Tables 1A, 1B, 1C)**.**

The upper parts of each panel in Tables 1A-C show the results for successfully replicated SNPs (defined as combined p-value $<5x10^{-8}$ and lower than discovery P-values) in participants, who were part of the discovery phase, replication phase, and the combined results. For *Model 1*, combined analysis of the discovery and replication cohorts successfully replicated 3 SNPs in/near *HSD17B11*, *FTO* and *MC4R* (P-values between $1.6x10^{-8}$ and 1.8×10^{-30}). For *Model 2*, the same 3 SNPs as reported for Model 1 were successfully replicated and in addition one SNP in/near *TNRC6B* was also successfully replicated (P-values between $7.3x10^{-10}$ and 2.4×10^{-20}). For *Model 3*, combined analysis of the discovery and replication cohorts successfully replicated 5 SNPs in/near *IRS1, HSD17B11, VCAN, ADAMTSL3* and *FTO* (P-values between $1.4x10^{-8}$ and 1.5×10^{-11}; Results of *Model 3* SNPs have been previously reported [3] but are shown here for comparison (Table 1C).

None of the 12 replicated associations (three for Model 1, four for model 2 and five for model 3) had significant heterogeneity at α=0.0042 (0.05/12, Bonferroni corrected for 12 tests). Only mild heterogeneity was indicated for the SNP in/near *FTO* in all three models (*Model 1*, I^2=38%,; *Model 2*, I^2=33%; *Model 3*, I^2=33%; Tables 1A, 1B, 1C).

In total 7 SNPs in independent loci (in/near *IRS1, HSD17B11, VCAN, ADAMTSL3, FTO, MC4R* and *TNRC6B*) were sucessfully replicated in any of the three models and the results for these 7 SNPs in the three different models for whole body lean mass are given in Table 2. The seven SNPs were nominally ($p<0.05$) significant in all three models except for the SNP in/near *IRS1*, which was not associated with lean mass unadjusted for fat mass in model 1. Very similar associations were observed when these 7 SNPs were evaluated for their associations with appendicular lean mass available in up to 70,690 subjects of European descent (Suppl. Table S6).

The impact of fat mass adjustment for lean mass loci - "*sumo wrestler loci* and *body builder loci*"

In general the results from Model 1 and Model 3 differed most from each other while the associations for Model 2 were intermediate. Therefore, in the studies evaluating the impact of fat mass adjustment for lean mass loci, we mainly compared the results between Model 1 and Model 3. Six of the seven loci (*FTO, MC4R, TNRC6B, HSD17B11, VCAN and ADAMTSL3*) had an

impact both on the absolute amount of lean mass (*Model 1*) and the amount of lean mass adjusted for fat mass (*Model 3*). However, the strengths of the associations in *Model 1* vs *Model 3* varied substantially. The *FTO* and *MC4R* signals had high *Model 1*/*Model 3* ratios of Beta values for the association with lean mass (M1/M3 ratio 222-234%), demonstrating that the strengths of the associations were reduced after fat mass adjustment. This suggests that these two loci have an impact on both lean mass and fat mass in the same direction and this is also supported by the fact that they are associated with BMI and fat mass in the same direction as with lean mass (Table 3, Suppl. Table S7). As the alleles of the *FTO* and *MC4R* signals that were associated with greater lean mass also were associated with increased fat mass we named them "*sumo wrestler*" loci (Table 3; Suppl. Table S7).

In contrast, there were two lean mass loci that had a low *Model 1*/*Model 3* ratio of Beta values for the association with lean mass (M1/M3 ratio 64-67%), including the *VCAN* and *ADAMTSL3* loci. For these loci the lean mass associations were stronger after adjustment for fat mass. This means that these two loci have a substantial impact specifically on lean mass with associations in the opposite direction or no association with fat mass (Table 3, Suppl. Table S7). As the alleles of the *VCAN* and *ADAMTSL3* loci that were associated with greater lean mass were associated with slightly reduced fat mass, we named them "*body builder*" loci. The *TNRC6B and HSD17B11 loci* had intermediate *Model 1*/*Model 3* ratios of Beta values for the association with lean mass (M1/M3 ratio 120-125%), suggesting that their impact on lean mass did not appear to be influenced by fat mass, so we called them "*intermediate*" loci (Table 3; Suppl. Table S7).

The signal in/near *IRS1* was not associated with lean mass without adjustment for fat mass. As shown in Tables 3 and S7, the lean mass increasing allele in/near *IRS1* was associated with lower fat mass. This association with lower fat mass may indirectly make the association with fat mass adjusted lean mass to be significant in the opposite direction. It is indeed a locus with an impact on the ratio between lean and fat mass but with no significant association with the absolute amount of lean mass when the effect of fat mass is not taken into account. The lean mass increasing allele was associated with reduced BMI and fat mass (Table 3, Suppl. Table S7), suggesting that its inverse association with fat mass is dominant for its effect on BMI, which is influenced by both lean mass and fat mass. We, therefore, named the IRS locus a "*fat-mediated*

lean mass" locus as it primarily appears to impact the amount of fat mass (Table 3; Suppl. Table S7).

Metabolic associations for lean mass increasing alleles

We next evaluated the associations with metabolic traits for the seven replicated lean mass SNPs, using available results from GWAS-meta-analyses of these traits (Table 3; Suppl. Table S7). The lean mass increasing alleles of SNPs in/near the two *sumo wrestler* loci (*FTO* and *MC4R*) were in general associated with an **adverse metabolic profile** both regarding carbohydrate metabolism (higher fasting insulin, higher HOMA-IR and increased risk of diabetes mellitus) and lipid metabolism (higher serum triglycerides and lower HDL cholesterol; Table 3; Suppl. Table S7). In addition, the lean mass increasing allele of the SNP in/near *FTO* was associated with increased risk of coronary artery disease (Table 3). In contrast, the lean mass increasing alleles of the SNPs in the two *body builder* loci (*VCAN* and *ADAMTSL3*) were in general associated with some **metabolic protection** both regarding carbohydrate metabolism (lower fasting insulin or reduced risk of diabetes mellitus) and lipid metabolism (lower serum triglycerides or higher HDL cholesterol; Table 3 presents general direction of associations; Suppl. Table S7 actual beta coefficients). The lean mass signals in the *intermediate* lean mass loci (*TNRC6B and HSD17B11*), not influenced by fat mass adjustment, did not have any major impact on metabolic traits.

As reported previously [23], the lean mass increasing allele of the SNP in the *fat-mediated* lean mass locus *IRS1* was associated with an adverse metabolic profile (Table 3; Suppl. Table S7).

Musculoskeletal associations of lean mass increasing alleles

We also evaluated the associations between the seven replicated lean mass SNPs and musculoskeletal traits. Importantly, the lean mass increasing alleles of the SNPs in/near *TNRC6B* and in/near *ADAMTSL3* were robustly associated with higher hand grip strength (Table 4, Table S8). In general the associations with the other musculoskeletal traits (Table 4 and Suppl. Table S8) were less pronounced compared with the associations with metabolic traits (Table 3 and Suppl. Table S7) and no general pattern for the signals in the *sumo wrestler* loci vs. the signals in the *body builder* loci was observed for the musculoskeletal traits (Table 4; Suppl. Table S8).

Surprisingly the lean mass increasing allele of the SNP in/near *TNRC6B* was associated with lower lumbar spine BMD and increased risk of fractures.

Genetic correlations with lean mass by LD score regression

We next determined the genetic correlations between lean mass phenotypes and a variety of parameters with a focus on metabolic and musculoskeletal phenotypes using LD score regression (Table 5). *Obesity traits*, including both extreme phenotypes, such as childhood obesity and extreme BMI, and quantitative traits, such as BMI and waist-to-hip ratio, demonstrated strong positive genetic correlation with lean mass in the model not adjusted for fat mass (*Model 1*) and as expected these genetic correlations were attenuated after fat mass adjustment (*Model 2 and Model 3;* Table 5).

For all carbohydrate metabolism related traits (type 2 diabetes mellitus, fasting glucose, fasting insulin, fasting proinsulin, HbA1C and HOMA-IR) positive genetic correlations with lean mass in *Model 1* were observed. All these correlations were attenuated after fat mass adjustment in *Models 2 and 3*.

When *lipid metabolism related traits* were evaluated in lean mass *Model 1*, a positive genetic correlation was observed for serum triglycerides and negative genetic correlations were observed for total cholesterol and HDL cholesterol (Table 5). The significant genetic correlation with triglycerides was lost in lean mass *Model 3* adjusted for fat mass in kg. Although the genetic correlations with HDL cholesterol was attenuated after fat mass adjustment (*Model 3*), the correlation was still significant.

There was a modest positive genetic correlation between BMD parameters and lean mass in all three models while the genetic correlation with grip strength, a proxy for muscle function, was observed in *Model 3* but not in *Model 1* (Table 5).

Age at menarche and age at menopause can be regarded as indicators of lifetime sex steroid exposure. Age at menarche but not age at menopause displayed negative genetic correlations with lean mass in all three models although most pronounced in *Model 1* (Table 5).

Annotation and enrichment analysis of regulatory elements

In the enrichment analysis of tissue-specific regulatory elements using experimental epigenetic evidence (DNase hypersensitive sites, histone modifications, and transcription factor-binding sites in human cell lines and tissues from the ENCODE Project and the Epigenetic Roadmap Project), SNPs in the *TNR6CB* locus were significantly enriched in these regulatory elements in blood cells, but not in muscle or other selected tissues after multiple testing correction (Suppl. Table S9). There was no significant tissue specific enrichment of regulatory elements for the *MC4R* locus. The enrichment results for the other loci have previously been presented.[3]

Expression quantitative trait loci

No significant association was found between rs733381 and *TNRC6B* gene expression in the skeletal muscle tissue (p=0.13, N=491) fom GTEx data; although individuals with homozygosity of minor allele G appear to have relatively lower *TNRC6B* gene expression in the skeletal muscle tissue. We also looked at eQTLs of rs733381 in other tissues from GTEx data, but none of the associations achieved statistical significance after multiple testing correction. *MC4R* gene expression is not detectable in the skeletal muscle tissue, whole blood and many other tissue types, except for brain tissues, esophagus and testis from GTEx data. Among those tissues with detectable *MC4R* gene expression, the smallest p-value between rs10871777 and *MC4R* gene expression was found in the frontal cortex brain tissue (p=0.017, N=118). However, no statistical significance was found after multiple testing correction. The eQTL results for the other loci have previously been presented.[3]

Discussion

Body weight consists of lean mass (LM), fat mass and bone mass, each with substantial heritable components and each playing important roles in physical function and metabolism. Since LM is correlated with fat mass, it is difficult to identify genetic determinants specific for LM. In addition, this makes it challenging to determine the metabolic health consequences of LM independent of fat mass. In the present study, we performed large scale GWAS for LM without or with different fat mass adjustments and we identified genetic variants in seven separate loci, including one novel locus *(TNRC6B*), associated with LM. Based on the relative strengths of the associations in models without and with fat adjustments we divided the LM loci that we identified into those with an effect on both LM and fat mass in the same direction (named *sumo wrestler loci*) and those with an impact specifically on LM (named *body builder loci*). LM increasing alleles of SNPs in *Sumo wrestler loci* were associated with an adverse metabolic profile while LM increasing alleles of SNPs in *body builder* loci were associated with metabolic protection.

The 7 SNPs that were were reproducibly associated with LM in any of the three models used were in independent loci (in/near *IRS1, HSD17B11*, *VCAN*, *ADAMTSL3*, *FTO, MC4R* and *TNRC6B*). Five of these SNPs (in/near *IRS1, HSD17B11*, *VCAN*, *ADAMTSL3* and *FTO*) were identified in the model adjusted for fat mass in kilograms and the results from this model have been previously reported[3]. However, in the present study, we could determine how the strengths of the LM associations for these five SNPs were affected in different models without or with fat mass adjustement, enabling us to divide them into *Sumo wrestler loci* or *body builder loci*.

A genetic variant in the *MC4R* locus was in the present study GWS associated with LM in the model not adjusted for fat mass while the association was weaker in the model adjusted for fat mass in kilograms, and consequently this locus was categorized as a *Sumo wrestler* locus. The *MC4R* locus has not previously been identified as a LM locus in a GWAS on LM. However, in a GWAS on fat mass, the *MC4R* locus was found to be associated with not only fat mass but also in secondary analyses with LM in the same direction.[24] These findings indicate that the *MC4R locus* has a pleiotropic effect, regulating both fat mass and lean mass in the same direction.

Importantly, the *TNRC6B (Trinucleotide Repeat Containing 6B)* locus was in the present study identified as a novel LM locus and comparison of the strengths of the associations in the different models of fat mass adjustments demonstrated that its LM association was only modestly affected by different fat mass adjustments. *TNRC6B* is a protein coding gene in pathways related to cellular senescence, innate or adaptive immune system, *Wnt* signaling, and calcium modulating pathways (GO:0007223). In addition to the LM, BMI, HDL, grip strength, LS-BMD, and fracture associations presented here, other GWAS have reported the *TNRC6B* locus GWS associated with a "chronotype" (defined as "Morningness" or "Eveningness") phenotype[25], uterine fibroids[26], and mammographic density[27]. Understanding the mechanisms by which *TNRC6B* variants relate to body composition and this multitude of phenotypes may be useful for mitigating a wide range of aging and disease states.

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The LM increasing allele of SNPs in the *Sumo wrestler loci* (*FTO* and *MC4R*) were associated with higher fasting insulin, higher HOMA-IR, increased risk of diabetes mellitus, higher serum triglycerides and lower HDL cholesterol. In addition, the LM increasing allele of the SNP in the *FTO* locus was associated with inceased risk of coronary artery disease. Thus, genetically determined increase in LM by genetic variants in *Sumo wrestler loci* is clearly associated with an adverse metabolic profile. In contrast, the LM increasing alleles of SNPs in the *body builder loci* (*VCAN* and *ADAMTSL3*) were in general associated with a beneficial metabolic profile both regarding carbohydrate metabolism (lower fasting insulin or reduced risk of diabetes mellitus) and lipid metabolism lipid metabolism (lower serum triglycerides or higher HDL cholesterol). The intermediate *loci* (*TNRC6B* and *HSD17B11)* were not associated with a clear metabolic profile. These findings suggest that a genetically determined higher LM per se without affecting fat mass has favorable metabolic effects while a genetically determined higher LM that is associated with a higher fat mass as well has adverse metabolic consequences. Alternatively the described associations with metabolic traits could be explained by pleiotropic effects of the respective genes.

While we could divide the SNPs that we found associated with LM in the different models into categories based on a relation with LM and fat mass or LM only, we found that the SNP in *IRS1* behaved differently from the other genes. The LM increasing allele in/near IRS1 was associated

with lower fat mass and lower BMI but had no significant effect on the absolute amount of LM when the effect on fat mass was not taken into account. We, therefore, named the *IRS* locus a "*fat-mediated lean mass" locus* as it primarily appears to impact the amount of fat mass.

Besides cross-phenotype analyses, we determined the genetic correlations between LM phenotypes and a variety of parameters with a focus on metabolic and musculoskeletal phenotypes using LD score regression. Genetic correlation in LD score regression is (asymptotically) proportional to Mendelian randomization estimates[22]. This method has an advantage for several reasons: it does not require individual genotypes, is not restricted to genome-wide significant SNPs, and there is no need for LD-pruning (which loses information if causal SNPs are in LD)[22]. LD score regression analyses revealed strong positive genetic correlations between LM and several obesity traits and carbohydrate metabolism related traits such as type 2 diabetes mellitus, fasting glucose and fasting proinsulin. These genetic correlations were attenuated in models adjusted for fat mass in kilograms, supporting the notion that genes that determine both fat mass and LM have a stronger genetic overlap with genes that determine obesity and glucose intolerance than genes that determine LM irrespective of fat mass. Similar obeservations with stronger genetic correlations in models not adjusted for fat mass were made for the positive genetic correlations with serum triglycerides and the negative genetic correlations with HDL cholesterol.

Cross-phenotype analyses revealed that the LM increasing alleles of the SNPs in/near *TNRC6B* and in/near *ADAMTSL3* were robustly associated with higher hand grip strength, suggesting that increased muscle mass resulted in increased muscle strength. This notion is supported by our finding of a positive genetic correlations between LM and grip strength in models adjusted for fat mass. In general, fat mass adjustment attenuated the genetic correlations between LM and metabolic traits, whereas the same adjustment enhanced or did not change the genetic correlations between LM and musculoskeletal traits.

Interestingly, age at menarche but not age at menopause displayed negative genetic correlations with LM in all three models but was most pronounced in Model 1, implying that genes related to both fat mass and LM are correlated with genes determining age at menarche. One may speculate

that the amount of LM is involved in the onset of menarche. Alternatively it is possible that augmented sex hormone status might be the link between early menarche and high LM.

There are limitations to our study. The X chromosome, harboring the androgen receptor gene, was not included in the present meta-analysis, which is notable since androgens have a major impact on muscle mass. Another potential weakness of this study is our decision to meta-analyze body composition results using two different techniques (BIA and DXA). Nevertheless, the two methods are highly correlated,[6] and by combining them power to detect GWS *loci* was greatly enhanced.

In conclusion, we identified one novel LM locus (*TNRC6B*) and our results suggest that genetically-determined increase in LM might exert either harmful or protective effects on metabolic traits, depending on its relation to fat mass.

Legends to supplemental figures

Figure S1. Quantile-quantile plots of the genome-wide association results of the inverse-variance weighted meta-analysis.

Total lean mass according to Model 1 (A; not adjusted for fat masss), Model 2 (B; adjusted for fat %)) and Model 3 (C; adjusted for fat mass in kg).

Figure S2. Manhattan plots for the genome-wide meta-analysis results.

Total lean mass according to Model 1 (A; not adjusted for fat masss), Model 2 (B; adjusted for fat %)) and Model 3 (C; adjusted for fat mass in kg). Blue line indicates $p = 5 \times 10^{-8}$. Red line indicates suggestive genome-wide significant $p=2.3 \times 10^{-6}$.

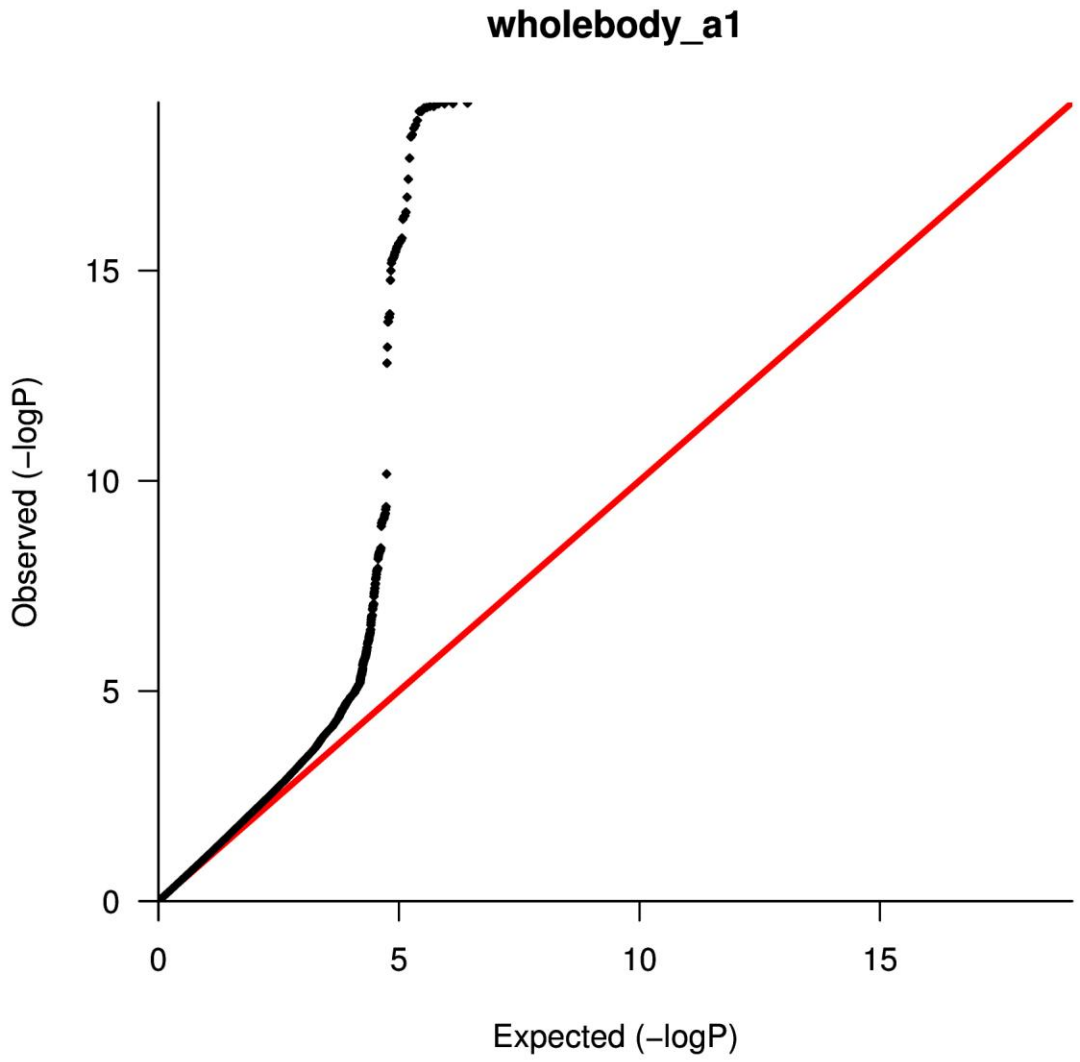


Figure S1A

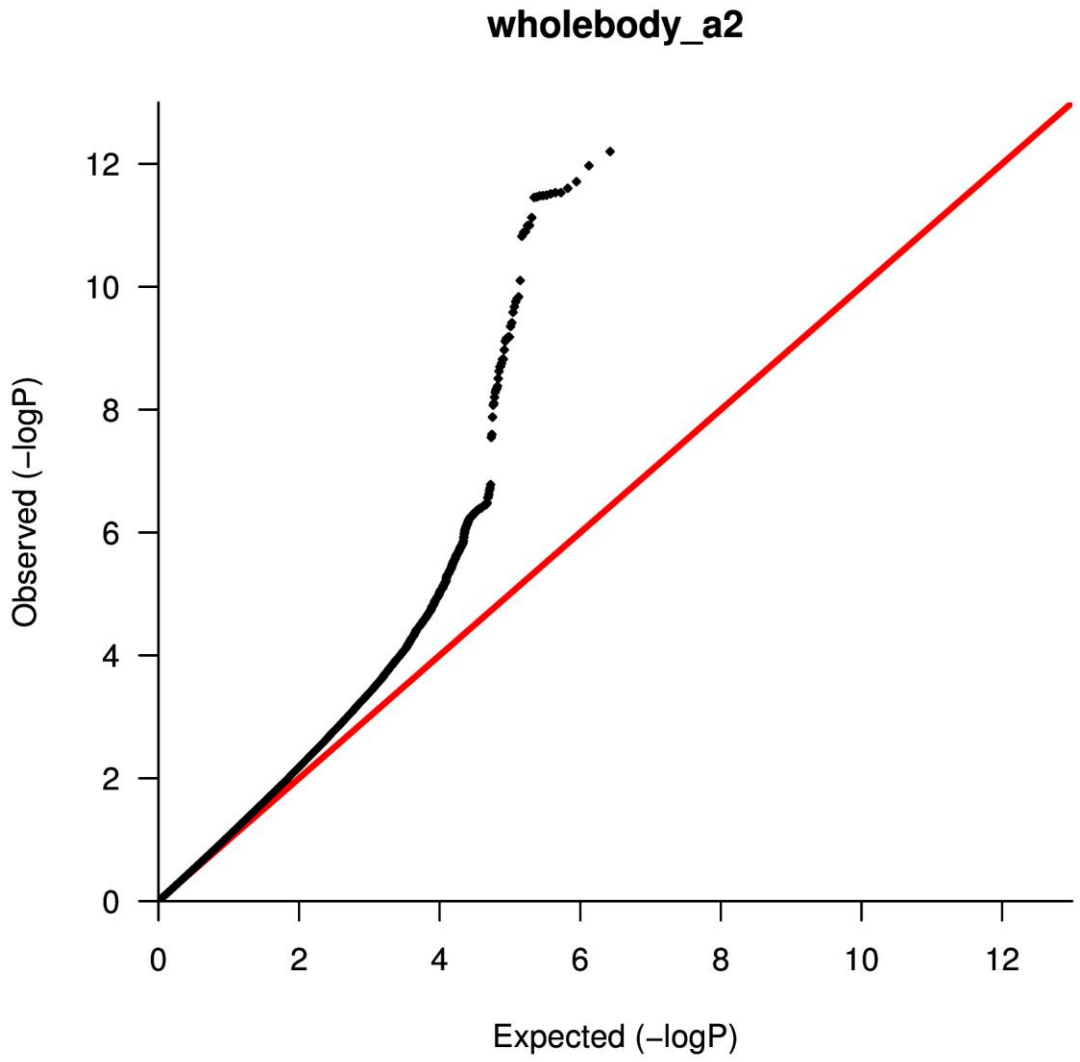


Figure S1B

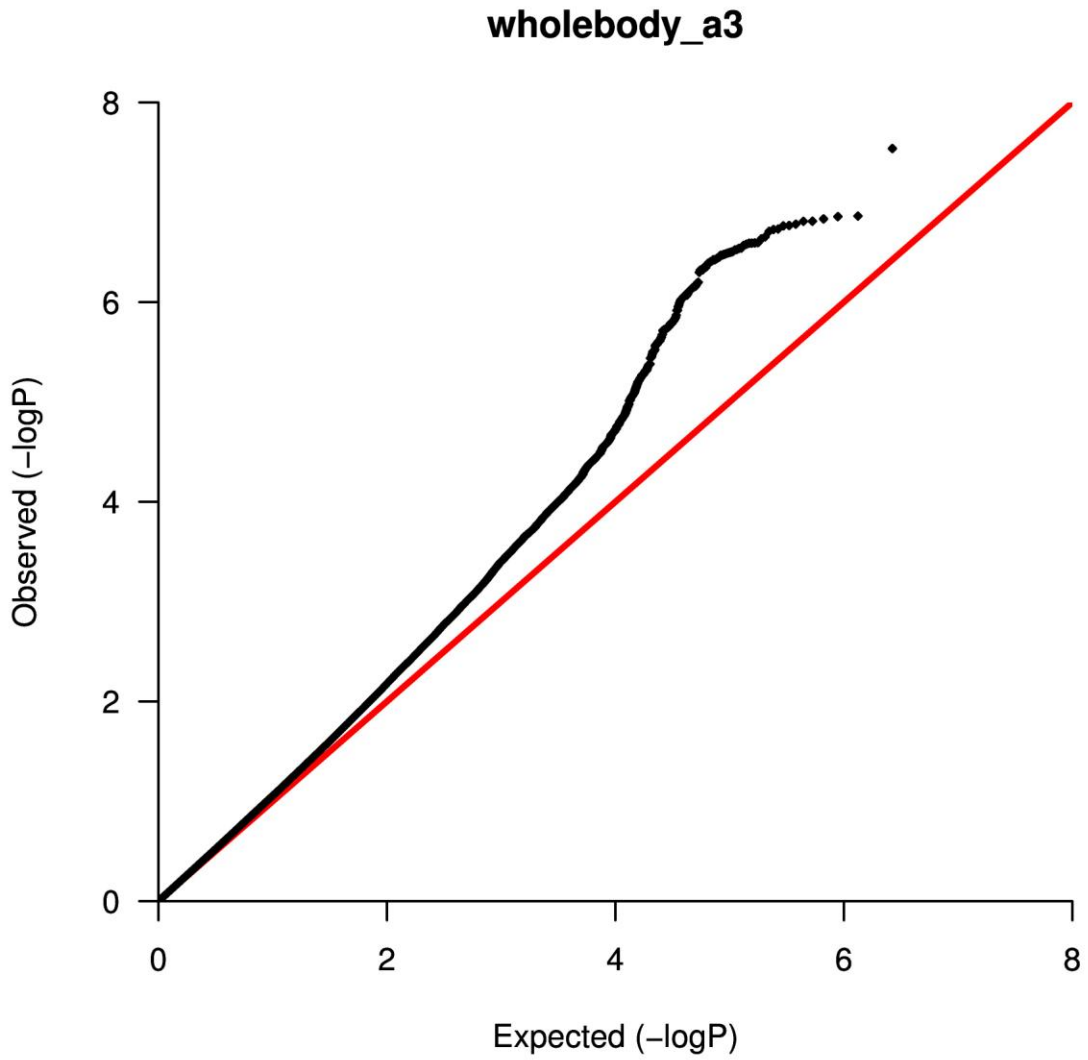


Figure S1C

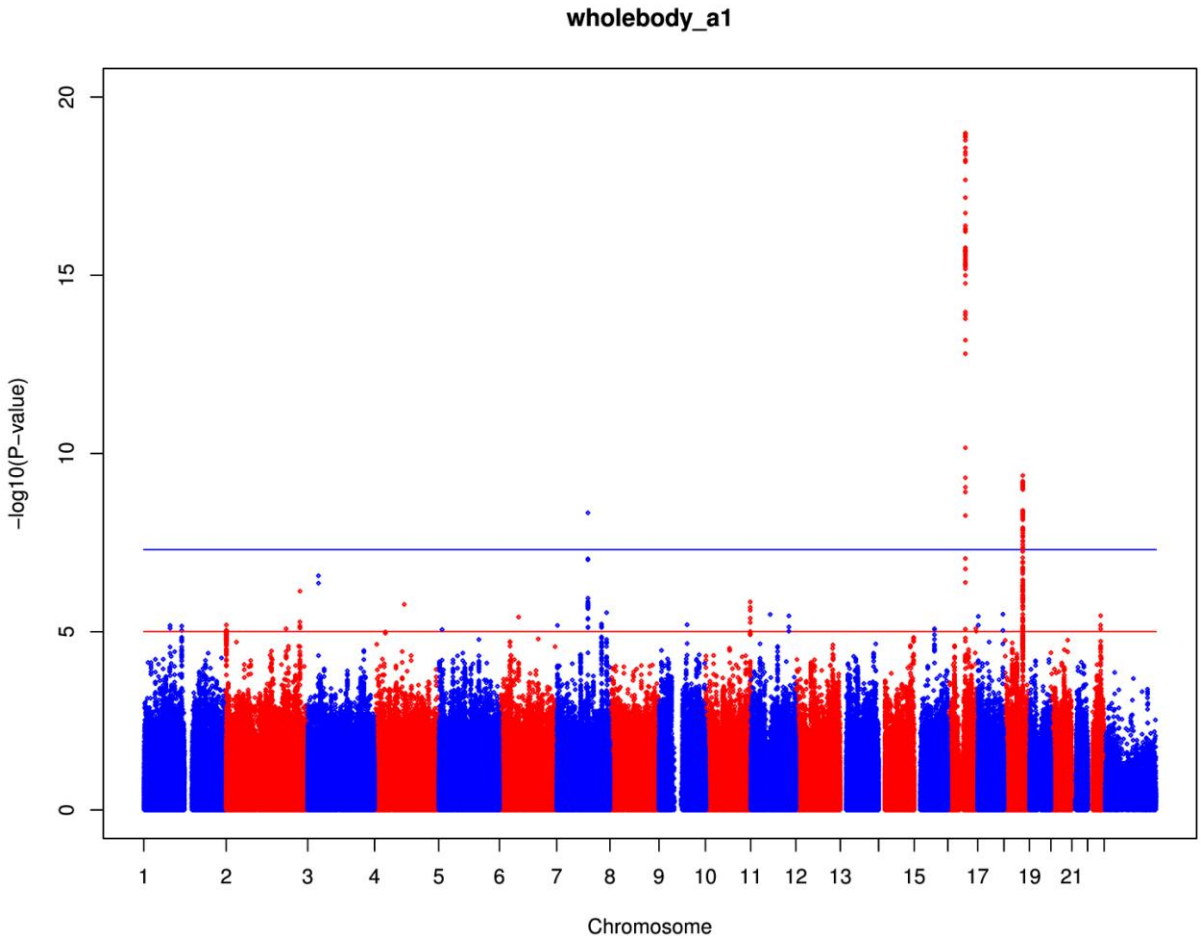
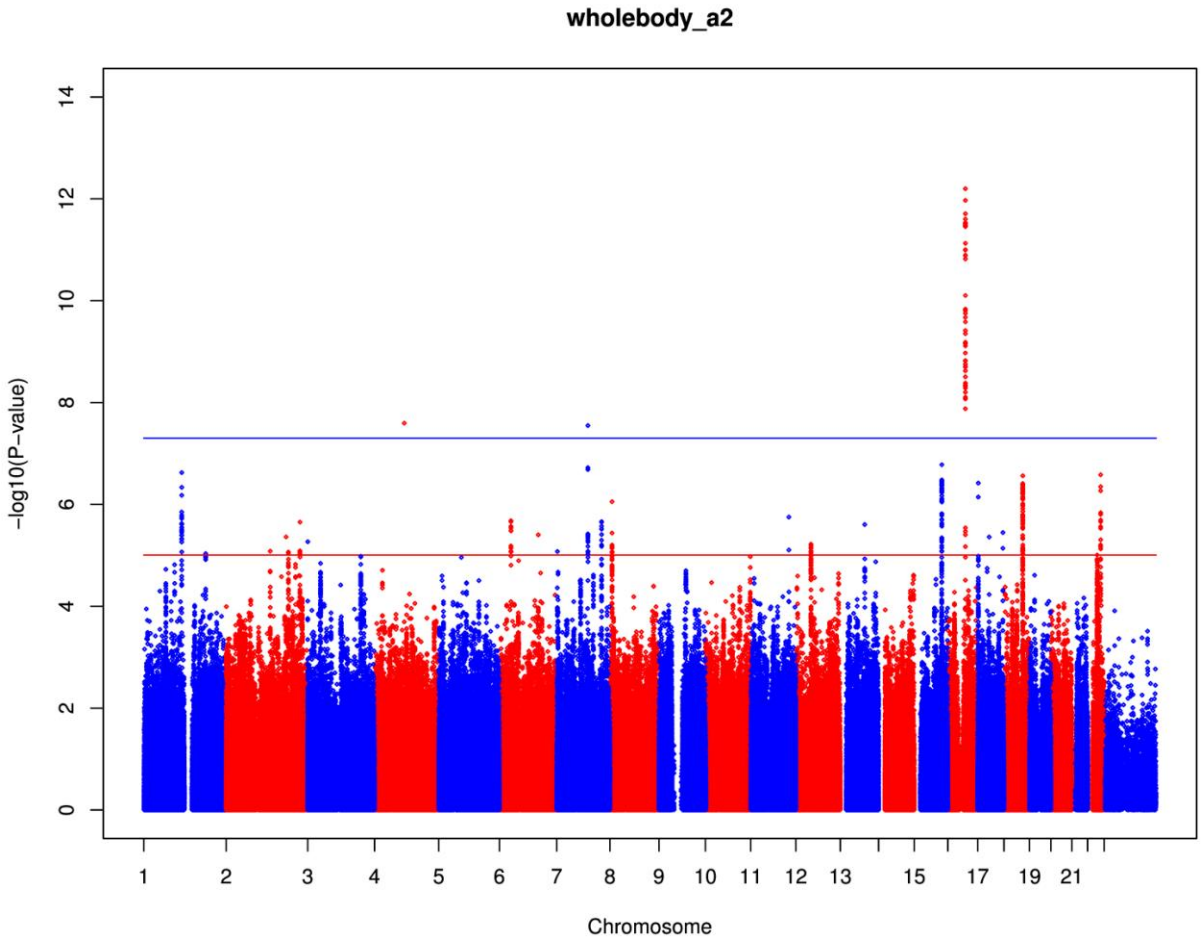


Figure S2A Figure S2A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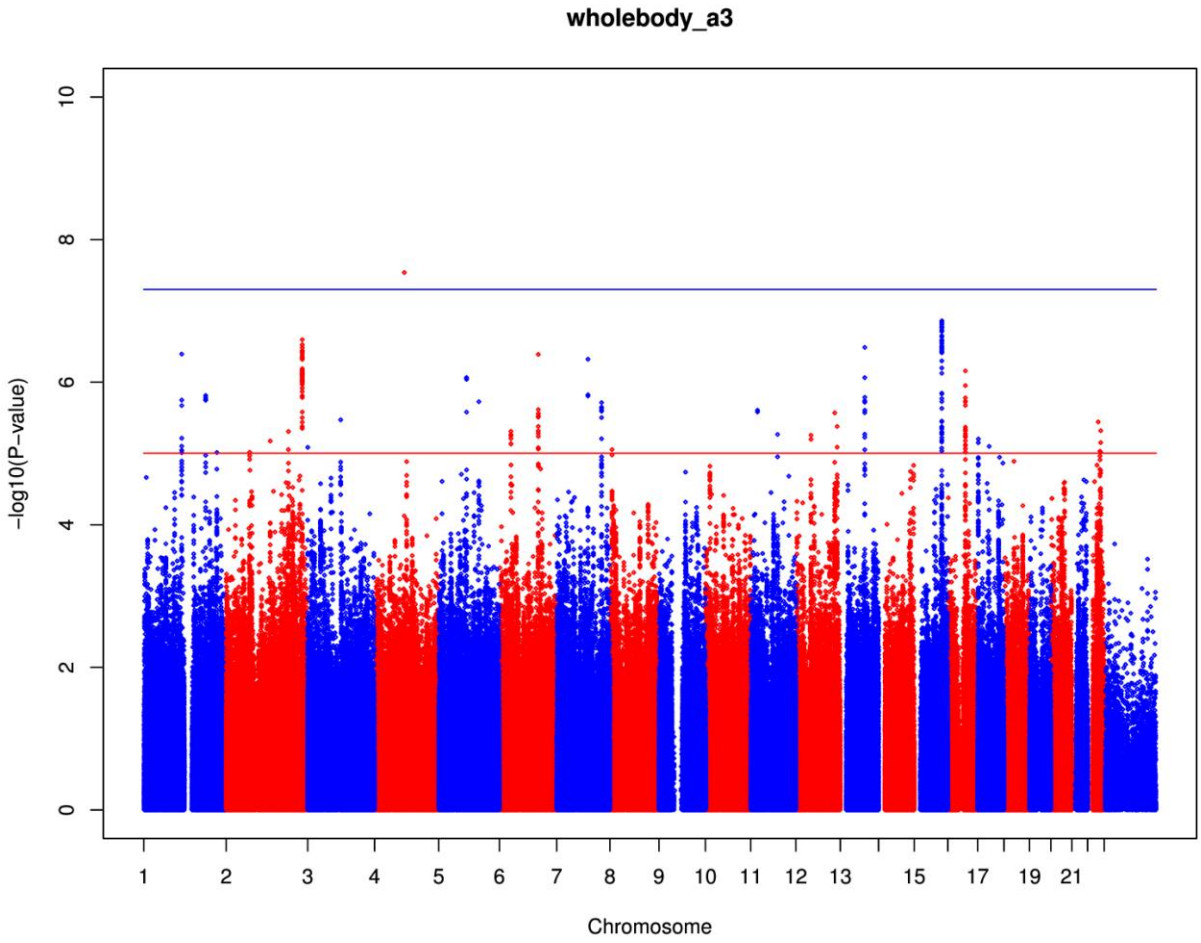
Chromosome

Figure S2B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Chromosome

Figure S2C

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