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## A pilot study of genetic variants in dopamine regulators with indoor tanning and melanoma

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### Abstract

Many people frequently tan indoors despite being aware of the increased risk of melanoma. Ultraviolet radiation is hypothesized to modify biological reward pathways, for example, through the dopamine neurotransmitter system, to reinforce tanning behaviour. In this pilot study, we relied on questionnaire and DNA data from a recently completed case-control study to examine 67 single-nucleotide polymorphisms (SNPs) and related haplotypes in five dopamine receptor and drug metabolism genes in relation to indoor tanning among controls. We also examined the association between individual SNPs and likelihood of melanoma, adjusting for or stratifying on indoor tanning status. In candidate and haplotype gene analyses, variants only in the DRD2 dopamine receptor and ANKK1 signalling genes were positively associated with indoor tanning use among controls; only associations for ANKK1 remained statistically significant ( $P < 0.05$ ) after adjustment. Several SNPs in ANKK1 and DRD2 associated with indoor tanning among controls were also found to be associated with increased risk of melanoma. Upon stratifying for indoor tanning status, one ANKK1 SNP was positively associated with melanoma among non-tanners, while three DRD2 SNPs were positively associated with melanoma among tanners or non-tanners, depending on the SNP. These alleles represent important genomic regions to further explore addictive tanning behaviour.

### Keywords

dopamine; indoor tanning; melanoma; single-nucleotide polymorphisms

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## Introduction

The incidence of cutaneous malignant melanoma continues to increase in all developed countries despite declines in other common cancers (1). Ultraviolet radiation (UVR) is the major aetiologic factor associated with melanoma incidence. While most human exposure to UVR comes from the sun, a significant number of people are exposed to UVR by the purposeful use of indoor tanning devices including sunlamps and tanning beds.

Indoor tanning has become increasingly popular since the 1980s, particularly in adolescents and young adults, and is now widespread in developed countries (2,3). In 2009, the International Agency for Research on Cancer elevated the classification of tanning devices as 'carcinogenic to humans' (4). A meta-analysis review showed a 75% increased risk of developing cutaneous melanoma for those that starting using tanning devices before age 35 (summary relative risk, 1.75; 95% CI: 1.35, 2.26) (5). Although there is now extensive evidence supporting the strong association of indoor tanning with increased risk of melanoma (6–8), many people continue to tan indoors on a frequent basis. Most frequent tanners are knowledgeable about the health risks associated with indoor tanning, and some continue to tan despite having a family history of melanoma (9,10). Frequent indoor tanning behaviour, even in persons with knowledge about the health risks associated with UV exposure, has been compared with an addictive behaviour (10–12).

Frequent indoor tanners report and rationalize many physical and psychological reasons to tan indoors such as for appearance, relaxation, socialization and seasonal affective disorders (11–15). Harrington et al. (10) found that for those frequent tanners that began to tan between the ages of 13–17, 60% of respondents in this category met criteria for addiction to tanning and 80% met criteria for problem tanning. Links between indoor tanning and substance use have also been reported (14,16,17). College students that were addicted to indoor tanning, as measured by the mCAGE and mDSM-IV-TR questionnaires, reported higher alcohol, marijuana and other substance use compared with college students who were not addicted to indoor tanning (14,17). One hypothesis about a relationship between indoor tanning and substance use is that UVR exposure modifies biological reward pathways in the brain, such as through the dopamine system, similar to the effects of nicotine, alcohol or other chemical substances (10,11). In a recent study with a small group of frequent tanners, UVR exposure activated regions of the brain associated with the mesostriatal reward pathway, and when UVR was filtered out, these regions of the brain were significantly less activated. Indoor tanners also reported a decrease in their desire to tan when they received the real UVR treatment but not after sham treatment (18).

Behavioural genetic research, pioneered by Dr. Seymour Benzer, has sought to understand the association of genes with behaviour (19). Current studies suggest that genetic factors play a role in the spectrum of addictive behaviour including risk for initiation, continuity of use and dependency. There is now a growing body of work to support associations of genetic variants from genes involved with dopamine regulation and drug metabolism with addiction (20–24). Associations of variants in DRD2 with dependency for alcohol, cocaine, heroin and nicotine have been verified by meta-analysis (20). To date, no studies have examined the relationship of genetic variants with tanning behaviour. The purpose of this

study was to explore the association of single-nucleotide polymorphisms (SNPs) in candidate genes involved in dopamine regulation and drug metabolism (ANKK1, CYP2A6, CYP2A7, DRD2 and SLCA3) with indoor tanning behaviour for participants in the Skin Health Study. We further examined the associations of these SNPs with melanoma and how they might be related to indoor tanning in a stratified analysis.

## Materials and methods

### Study population

The Skin Health Study was approved by the Institutional Review Board at the University of Minnesota. The Skin Health Study is a population-based case-control study that recruited individuals from Minnesota, ages 25–59, diagnosed with invasive cutaneous melanoma (cases) between 2004 and 2007 as ascertained by the state cancer registry. Controls were randomly selected from the state drivers' licence list and frequency matched (1:1) to cases on age and gender (7). Approximately 68% of cases ( $n = 1380$ ) and 51% of controls ( $n = 1590$ ) were eligible after initial screening. From the eligible participants, 85% of cases ( $n = 1167$ ) and 69% of controls ( $n = 1101$ ) completed the self-administered questionnaire and a telephone interview. Eligible participants ( $n = 1753$ ) submitted mouthwash samples from which DNA was isolated and used for genotyping. This study sample was restricted to 1746 eligible individuals with both genotype and phenotype data.

### Exposure measurement

The development of the instrument for demographic, phenotypic and exposure information has been previously described (7). Detailed information on lifetime indoor tanning behaviour was collected by a mixed-mode instrument consisting of a self- and a telephone-administered questionnaire (7). Standard demographic information included age, sex, income and education. Information was also collected for skin, hair and eye colour, body mass index (BMI), lifetime number of painful sunburns and family history of melanoma. Hair colour, eye colour and inability to tan were used to create a phenotypic index score that has been shown to be associated with increased risk of melanoma (25). Hair colour, eye colour and inability to tan were assigned a numerical value, and the sum of these phenotypes, ranging from 1 to 5, represents the phenotypic index score: hair colour (1 = black/dark brown; 2 = light brown/blond; 3 = red), eye colour (0 = black/brown; 1 = hazel/green/grey/blue) and inability to tan (0 = easily tan; 1 = poorly tan).

### Selection of SNPs

Tagging and functional SNPs were chosen in candidate genes related to dopamine regulation and drug metabolism that were previously shown to be associated with addiction to alcohol, nicotine or other substances (20,22,26). A total of 67 SNPs from five genes (ANKK1, CYP2A6, CYP2A7, DRD2 and SLCA3) were examined. Tagging SNPs were identified using Haploview (27).

### SNP genotyping

Biological samples were collected by mouthwash and mailed directly to the University of New Mexico Molecular Epidemiology Laboratory where DNA was extracted using DNeasy

Qiagen kits (Qiagen, Valencia, CA, USA) per manufacturer protocol. SNPs were genotyped on the Illumina GoldenGate (Illumina, Inc., San Diego, CA, USA) platform at the University of Utah Genotyping Core.

### Quality control

To eliminate potential confounding by race/ethnicity, 46 non-white subjects were removed from the analysis. Seven additional subjects who were missing phenotypic indices were also excluded. Thirty DNA samples with SNP call rates <95%, potentially indicating low-quality samples, were removed from the analysis to minimize genotyping error. The resulting sample set contains 1663 subjects and 67 SNPs, where each SNP has a genotyping rate >95% and each sample also has a genotyping rate >95%. The overall genotyping call rate in the final analysis set was 99.87%. Hardy–Weinberg equilibrium (HWE) was calculated in the control group for each SNP. The genotype distributions for six SNPs showed deviation from the HWE at a  $P$ -value <0.0007. These SNPs were retained for single SNP analysis as deviation from HWE can be due to association (28); however, these SNPs were flagged if they were found to be significantly associated with tanning behaviour and reported as such. SNPs of HWE were not used for haplotype analysis.

### Statistical analysis

Due to possible confounding of tanning behaviour and melanoma, we first assessed the association of SNPs or haplotypes with having ever or never tanned indoors in control participants only. For the analysis of 67 individual SNPs in relation to indoor tanning, an additive genotype model was used, except when the minor homozygote subject count was <10, then a dominant model was used. Logistic regression was used to calculate crude and age- and sex-adjusted odds ratios (OR), 95% confidence intervals and  $P$ -values for the association between each SNP and indoor tanning behaviour.

We assessed the association between haplotypes and tanning behaviour among controls by performing haplotype trend regression for each haplotype block using an additive haplotype model. Within each haplotype block, we reconstructed the haplotypes from the SNP genotype input data using a Bayesian method (29). To take into account the haplotype phase uncertainty, the probabilities of being different haplotypes for each individual were incorporated as the predictor variable in the haplotype trend regression (30). The analyses were restricted to those haplotypes with estimated frequencies >0.01.

As tanning exposure has been shown to increase the risk of having melanoma in this highly exposed population (7), we also examined the association between each of the 67 SNPs in relation to being a case or a control. We then considered how each SNP was associated with melanoma risk in the presence or absence of indoor tanning exposure. We first tested for differences in the association between each SNP and melanoma risk for tanners and non-tanners using logistic regression that included the product terms of indoor tanning status and individual SNPs. The  $P$ -values for these interactions on the multiplicative scale for all the genotyped SNPs were calculated through likelihood ratio tests, and adjusted for age, sex and phenotypic index. Association and interaction analyses were conducted using the generalized linear model (GLM) function in statistical package R (<http://www.r->

project.org/). If the *P*-value for the interaction was  $<0.05$ , we present analyses for the associations between SNP and melanoma risk stratified on indoor tanning status. In addition to age and sex, OR and related 95% confidence intervals, and *P*-values for the association between each SNP and melanoma risk in the combined or stratified analyses were also adjusted for phenotypic index.

## Results

### Characteristics of control participants and association with having ever or never tanned indoors

The characteristics of control participants from the Skin Health Study ( $n = 769$ ) were examined by ever or never indoor tanning status (Table S1). Compared to non-tanners, study participants who had ever tanned indoors were more likely to be female (72% vs 43%) and under the age of 50 (68% vs 44%). Young adults between the ages of 25–29 years of age were more likely to have ever tanned indoors relative to adults age 50 and above (OR = 7.82; CI: 3.53, 17.29). Participants with a phenotypic index score of 5 (representing those that tan poorly, have red hair colour and have light eye colour) were less likely to have ever tanned indoors compared with those with phenotypic index scores of 1 (OR = 0.23; CI: 0.06, 0.90). BMI was also associated with indoor tanning. Participants with BMIs 30 and above were less likely to have ever tanned indoors compared with participants with BMIs between 18.5 and 24.9 (OR = 0.42; CI: 0.29, 0.62). No association was observed between having a family history of melanoma and tanning behaviour.

### Association of candidate gene SNPs with indoor tanning

Of the 67 SNPs investigated, three SNPs in ANKK1 and one SNP in DRD2 were each positively associated with having ever tanned indoors among controls (unadjusted *P*-value  $< 0.05$ ; Tables 1 and S2). The association between individuals with variants in the three ANKK1 SNPs, rs2734848, rs1003641, rs12422191, with indoor tanning remained significant after adjustment for age and sex. However, with adjustment, the association between individuals with variants in DRD2 SNP rs2440390 and indoor tanning observed in the crude analysis was attenuated and no longer statistically significant. No SNPs in the SLC6A3 and CYP6A or CYP7A genes were associated with tanning behaviour among controls (Table S3).

### Association of haplotypes with indoor tanning

Similar to the individual SNP analysis, haplotypes within ANKK1 and DRD2 were also positively associated with having ever tanned indoors among controls (Table 2). The age- and sex-adjusted OR for the ANKK1 haplotype, which included the three SNPs found to be associated with indoor tanning in the first analysis, and two new SNPs (rs1800497, rs1279490), was 1.68 (95% CI: 1.31, 2.50, *P*-value = 0.01) for having ever versus never tanned indoors. This haplotype association was stronger compared with any of the single SNP associations shown in Table 1. A DRD2 haplotype, comprised of nine SNPs (including rs2440390 from the first analysis), was also positively associated with having ever tanned indoors among controls, but the association was only marginally significant after adjustment for age and sex (*P*-value = 0.06). As was observed for the individual SNPs, no haplotypes in

the SLC6A3 and CYP6A or CYP7A genes were associated with tanning behaviour (Table S3) among controls.

### Association of candidate SNPs with melanoma

In the analysis comparing cases and controls, two SNPs in ANKK1 (including rs1003641 from the individual and haplotype analyses) and three SNPs in DRD2 (all part of the DRD2 haplotype) were positively associated with increased risk of melanoma after adjustment for age, sex and phenotypic index (Table 3). Age- and sex-adjusted OR ranged from 1.17 to 1.27, and all confidence intervals excluded the null value. None of the associations for the two ANKK1 and three DRD2 SNPs with melanoma were significantly modified by adjusting for having ever or never tanned indoors (data not shown).

### Examination of the relationship of SNPs with risk of melanoma in ever and never indoor tanners

When we assessed the interaction of all candidate SNPs with tanning behaviour on the risk of melanoma, none of the associations between SNPs and melanoma in Table 3 were found to vary by indoor tanning status. However, three SNPs in DRD2 and one SNP in ANKK1 were significant with a *P*-value for the interaction equal to 0.03 or less (Table 4). Two DRD2 SNPs, rs12805897 and rs12364283, were associated with increased risk of melanoma in participants who had ever tanned indoors, but only weakly associated with decreased risk of melanoma in participants who had never tanned indoors. Neither of these SNPs had been individually associated with indoor tanning, nor were they identified as part of the DRD2 haplotype, among controls. Conversely, ANKK1 SNP rs12422191 and DRD2 SNP rs2440390 were associated with increased risk of melanoma in those that had never tanned indoors while being only weakly associated with a decreased risk of melanoma in those that had ever tanned indoors. These two SNPs were linked to indoor tanning among controls in both the candidate gene and haplotype analyses.

## Discussion

This is the first study to examine the relationship of variants in genes involved in dopamine regulation and drug metabolism with tanning behaviour in a highly exposed population. Given the relatively small sample size and multiple comparisons, chance cannot be ruled out as an explanation for any associations. However, consistent associations of SNPs in the ANKK1 and DRD2 genes with indoor tanning persisted across single SNP and haplotype analysis. A SNP in ANKK1 was also associated with risk of melanoma and could be important to the relationship between other addictive exposures and melanoma risk. No consistent associations were found for SNPs in the SLC6A3 dopamine receptor gene or the CYP2A6 and CYP2A7 drug metabolism genes. This hypothesis-generating study points to genomic regions that may be of interest for future investigations with large populations of frequent indoor tanners, preferably those that have also been evaluated for addiction to indoor tanning by validated instruments.

The DRD2 gene encodes the D2-type dopamine receptor, one of five types of dopamine receptors. Dopamine is the primary neurotransmitter of the brain's reward pathway that



mediates feelings of pleasure and overall well-being. Low dopamine function leads to increased risk of impulsive, compulsive and addictive behaviours (31). D2 receptors have been found to be involved in the ability to inhibit an ongoing response (response inhibition). Participants with greater D2 receptor availability, as measured by radioligand affinity in the brain, were able to stop more quickly during a behavioural stop-signal task (32). Theoretically, dysregulation of dopamine receptor function could modify the reward response from UV exposure and increase the desire to tan. Furthermore, catecholamine biosynthesis is linked to melanogenesis (33,34) and to the production of peripheral dopamine in pigmented mice (35). Plasma levels of L-DOPA are increased in patients with melanoma and may be useful to predict melanoma progression (36). These studies reveal complex interconnected pathways involving melanogenesis and dopamine regulation that are currently under-researched.

The protein encoded by the ANKK1 gene belongs to the Ser/Thr protein kinase family and functions in signal transduction (26). The ANKK1 and DRD2 genes are adjacent to one another on chromosome 11 and share common block structure. A cluster of genes in this region is thought to function in neurotransmission pathways (21). SNPs that were found to be associated with substance dependency were originally attributed to the DRD2 dopamine receptor gene but were later found to lie within the ANKK1 gene. As SNPs in this region are in high linkage disequilibrium (data not shown), other SNPs may be contributing to these associations. We examined smaller haplotype blocks associated with the ANKK1 and DRD2 genes; however, as several haplotype alleles have high LD at this region, a more detailed analysis of this large region should be considered in future studies. Future molecular or brain imaging studies could help to determine whether the dopamine receptor is regulated by UV exposure.

In this study, all of the SNPs that were associated with higher likelihood of tanning and increased risks of melanoma map to the ANKK1 and DRD2 alleles. The SNP rs1003641 was consistently associated with increased likelihood to have ever tanned indoors in single SNP analyses and in haplotype analyses and with increased risk of melanoma. Other SNPs in ANNK1 and DRD2 were also associated with increased risk of melanoma. To examine whether or not indoor tanning was in the causal pathway between these addiction genes and melanoma, we adjusted for having ever or never tanned indoors. However, adjustment for indoor tanning use did not attenuate the association of these SNPs with the risk of melanoma, perhaps because indoor tanning use may be correlated with other addictive behaviours that also increase the risk of melanoma but were not measured in the Skin Health Study. The positive associations we observed between some addiction SNPs in ANKK1 and DRD2 and risk of melanoma among non-tanners is surprising. Other factors related to addictive behaviour such as frequent sun exposure, and alcohol, smoking or other substance use should be considered in the development of melanoma in never tanners with ANKK1 and DRD2 variants.

Mining of The Cancer Genome Atlas (TCGA) database provided ancillary support for a role of DRD2/ANKK1 in melanoma ([http://www.cbioportal.org/public-portal/cross\\_cancer.do](http://www.cbioportal.org/public-portal/cross_cancer.do)). Interestingly, when we queried the TCGA skin cutaneous melanoma data set for mutations and copy number variations (CNVs) in DRD2 and ANKK1 using the cBio Cancer Genomics

portal (37), we found that nearly 12% of the skin cutaneous melanomas contained DRD2/ANKK1 mutations or CNVs, the highest prevalence compared with other cancers studied thus far, including lung cancer for which there are published studies suggesting an association of DRD2 SNPs with smoking status (38) and lung cancer risk (39). There was a strong tendency for mutations and CNVs in DRD2 and ANKK1 to occur together (i.e. were not mutually exclusive of one another). Although it is unclear how DRD2 somatic genetic variants might influence tanning behaviour, these results suggest that the DRD2 dopamine receptor gene and ANKK1 signalling genes are intriguing candidates for association with tanning behaviour.

This study utilizes exposure information and biological samples from a well-defined and highly exposed population of indoor tanners to explore posited candidate SNP associations with tanning behaviour. The results should be interpreted cautiously. The Skin Health Study did not collect information on addictive behaviour, such as from the CAGE questionnaire or DSM-IV that would allow us to identify individuals who meet criteria for addiction. Participants from the Skin Health Study were originally recruited as participants with melanoma (cases) and participants without melanoma (controls). Although the control participants reported a high prevalence of indoor tanning (51%), this was consistent with indoor tanning results from a Minnesota statewide survey. Over-reporting of indoor tanning in the Skin Health Study was found to be similar in cases and controls who had talked with their physician about the study (7). It therefore seems unlikely that recall bias would strongly impact the association of SNPs with tanning behaviour in controls. The *P*-values for the SNP associations in this study were not corrected for multiple comparisons. However, this SNP association study considered distinct biological pathways for the association of genetic variants with tanning behaviour. SNPs were identified in single SNP and haplotype analyses making them interesting candidates for future hypothesis-driven investigations to understand addictive or problem tanning behaviour.

This study highlights a unique and important hypothesis regarding genetic predisposition to addiction linked to indoor tanning behaviour. Our study narrows a genomic region for future investigations and implicates complex confounders to consider for this line of research. Recent efforts have been made to validate measures of tanning dependence (40). Few studies have collected the extensive information necessary to fully address the genetic, biological and psychological relationship between addictive behaviour, indoor tanning and risk of melanoma. Thus, the opportunity to validate our results is currently limited. In addition to known factors associated with melanoma, future ideal cohorts may consider tanning behaviour, brain imaging, chronic and intermittent UV exposure, addiction or other psychological criteria, smoking, alcohol or other drug intake and biological samples. The validation and replication of these findings in larger populations are necessary. A long-term goal of this line of research is to understand the extent of psychological, biological and genetic factors associated with indoor tanning behaviour and to develop interventions to decrease indoor tanning considering these complex factors.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.



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**Table 1**  
**Significant associations of SNPs with having ever or never tanned indoors among controls**

Loci	SNP	Minor Allele	Major Allele	MAF	OR (95% CI)	$P^a$	OR (95% CI)	$P^b$
ANKK1	rs2734848	G	A	0.19	1.45 (1.07, 1.95)	0.01	1.38 (1.00, 1.90)	0.05
ANKK1	rs1003641	A	G	0.30	1.28 (1.01, 1.62)	0.04	1.33 (1.04, 1.71)	0.03
ANKK1	rs12422191 <sup>I</sup>	A	G	0.10	1.60 (1.11, 2.32)	0.01	1.58 (1.06, 2.35)	0.02
DRD2	rs2440390 <sup>I</sup>	A	G	0.13	1.45 (1.03, 2.03)	0.03	1.31 (0.91, 1.89)	0.14

<sup>a</sup>  $P$ -value, crude.

<sup>b</sup>  $P$ -value, adjustment for age and sex.

<sup>I</sup> Association was tested using a dominant model.

**Table 2**  
**Significant associations of haplotypes with having ever or never tanned indoors among controls**

Gene	SNPs	Haplotype	Freq	OR (95% CI)	<i>P</i> <sup>a</sup>	OR (95% CI)	<i>P</i> <sup>b</sup>
ANKK1	rs2734848, rs1800497, rs1279490, rs1003641, rs12422191	GGGAA	0.09	1.69 (1.17, 2.44)	0.005	1.68 (1.31, 2.50)	0.01
DRD2	rs2440390, rs1800499, rs2734836, rs2734831, rs12799083, rs4436578, rs11214606, rs4648318, rs4245145	AGGACAGGA	0.12	1.54 (1.10, 2.15)	0.01	1.41 (0.98, 2.02)	0.06

<sup>a</sup> *P*-value, crude.

<sup>b</sup> *P*-value, adjustment for age and sex.

**Table 3**  
**Significant associations between variation in SNPs and likelihood of melanoma**

Loci	SNP	Minor Allele	Major Allele	MAF	OR (95% CI)	$P^a$	OR (95% CI)	$P^b$
ANKK1	rs12360992	A	C	0.45	1.16 (1.01, 1.33)	0.03	1.18 (1.02, 1.35)	0.02
ANKK1	rs1003641	A	G	0.30	1.17 (1.00, 1.36)	0.05	1.20 (1.03, 1.40)	0.02
DRD2	rs2734831	A	C	0.39	1.18 (1.02, 1.35)	0.03	1.17 (1.02, 1.35)	0.03
DRD2	rs4436578 <sup>J</sup>	G	A	0.12	1.26 (1.00, 1.59)	0.05	1.27 (1.01, 1.60)	0.05
DRD2	rs4648318	G	A	0.25	1.19 (1.00, 1.40)	0.05	1.20 (1.02, 1.42)	0.03

<sup>a</sup>  $P$ -value, crude.

<sup>b</sup>  $P$ -value, adjustment for age, sex and phenotypic index.

<sup>J</sup> Association was tested using a dominant model.

**Table 4**  
**Stratified analysis of the association of addiction SNPs with melanoma by indoor tanning behaviour**

SNP	Gene	Ever tanners			Never tanners		
		OR (95% CI)	P-value <sup>a</sup>	P-value <sup>b</sup>	OR (95% CI)	P-value <sup>b</sup>	Interaction P-value <sup>b</sup>
rs12422191	ANKK1	0.77 (0.55, 1.06)	0.11	0.04	1.50 (1.01, 2.24)	0.04	0.01
rs2440390	DRD2	0.85 (0.63, 1.15)	0.30	0.03	1.48 (1.03, 2.11)	0.03	0.03
rs12805897	DRD2	1.71 (1.16, 2.53)	0.01	0.60	0.89 (0.58, 1.37)	0.60	0.03
rs12364283	DRD2	1.7 (1.16, 2.49)	0.01	0.66	0.91 (0.59, 1.39)	0.66	0.03

<sup>a</sup> P-value adjusted for age and sex.

<sup>b</sup> P-value adjusted for age, sex and phenotypic index.

All SNP associations were tested using a dominant model.