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Novel gene identified in an exome-wide association study of tanning dependence

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Abstract

Growing evidence suggests that some individuals may exhibit symptoms of dependence to ultraviolet light, a known carcinogen, in the context of tanning. Genetic associations with tanning dependence (TD) have not yet been explored. We conducted an exome-wide association study in 79 individuals who exhibited symptoms of TD and 213 individuals with volitional exposure to ultraviolet light, but who were not TD based on three TD scales. 300,000 mostly exomic single nucleotide polymorphisms primarily in coding regions were assessed using an Affymetrix Axiom Array. We performed a gene burden test with Bonferroni correction for the number of genes examined ($p<0.05/14{,}904 = 3.36\times10^{-6}$). One gene, Patched Domain Containing 2 (*PTCHD2*), yielded a statistically significant p-value of 2.5×10^{-6} (OR = 0.27) with fewer individuals classified as TD having a minor allele at this locus. These results require replication, but are the first to support a specific genetic association with TD.

Background

Recent research involving volitional tanners indicates the presence of behaviors and symptoms that generally fulfill criteria for dependence, and defines tanning dependence (TD) analogous to substance dependence. These behaviors are characterized by continued and frequent tanning despite adverse consequences, such as skin cancer (1), or tanning with

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Author contributions:
BC, JG, SM and AB were responsible for the study concept and design. BC and LF were responsible for the acquisition of survey data. AB was responsible the genetic analysis. AD, LF and BC were responsible for data analysis. BC drafted the manuscript. AD, LF, JG, JS, SM and AB provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

greater frequency than required to maintain a tan. In addition, withdrawal symptoms have been reported in frequent, but not infrequent, tanners treated with naltrexone (2).

Substance dependence diagnostic criteria based on the DSM-IV-TR (3) and the Cut Down, Annoyed, Guilt, Eye-opener (CAGE) Questionnaire for alcoholism (4) have been modified to assess TD (5). The prevelance of TD varies based on the scale used and the population studied. For example, among 229 college-age indoor tanners, 30.6% met the modified CAGE (mCAGE) criteria for TD, 39.3% met the modified DSM-IV-TR (mDSM-IV-TR) criteria, and 21.8% met the criteria on both scales (6) compared to a college-age sample not selected for tanning history or race, among whom only 11% and 23% of 400 individuals were dependent based on the mCAGE and the mDSM-IV-TR, respectively (7).

Alcohol dependence, nicotine dependence and illicit-substance-use disorders have been shown to have a heritable component and to be influenced by genetic factors (8). If TD is similar to these other dependencies, a heritable component is likely.

Questions Addressed

We sought to identify specific TD risk alleles by conducting an exome-wide association study using a panel of ~319,000 single-nucleotide polymorphisms (SNPs), primarily within protein coding regions of the genome. We also conducted a candidate gene analysis of genes previously associated with substance dependence traits (i.e., *POMC, ARVCF, COMT, GABRA2, OPRM1, OPRK1, CHRNA3, CHRNA5, ANKK1, and ADH1B*) to assess their associations with TD.

Experimental Design

Study Population

The parent study for this analysis, a case-control study of early-onset basal cell carcinoma among English speaking individuals under age 40 (9, 10), was specifically designed to assess the role of indoor tanning and various lifestyle and genetic factors in early-onset skin cancer. For these analyses, a subset of participants from the parent study completed an online survey of TD. A total of 548 eligible subjects completed the online survey (81.9% response rate).

Individuals who reported volitional sunbathing or indoor tanning completed three TD scales to assess lifetime TD: the modified CAGE (5, 11), the modified DSM-IV-TR (5, 11), and the Indoor Tanning Affect and Pathology Scale (iTAPS), a new scale developed by one of the authors (JS) to capture dependence symptoms specifically suggestive of an opioid-like model of TD (i.e., loss of control, craving, withdrawal, stress relief, and mood enhancement related to tanning) (2). Participants were classified as TD if they were positively identified as TD on all three TD scales (n = 79) or not TD if they were negative for TD on all three scales (n = 213). This restrictive classification based on multiple scales was used to identify the most homogeneous phenotypes (TD vs. not TD) and increase power. See Figure S1 for the flow of participants in the study.

DNA from saliva samples was quantified using a Hoefer DyNA Quant 200 fluorometer and arrayed at a concentration of 10 ng/μl for analysis on Axiom Exome 319 Array Plates from Affymetrix (http://www.affymetrix.com).

Results

In the exome-wide analysis, one gene, Patched Domain Containing 2 (*PTCHD2*), yielded a statistically significant p-value of 2.5×10^{-6} on the gene-based burden analysis after Bonferroni correction (OR = 0.27) (Table 1). We observed significantly fewer individuals who were TD with a minor allele in this gene compared to individuals who were classified as not TD. Details of the variants are shown in Table S1.

Aldehyde dehydrogenase 1 family, member B1 *ALDH1B1* was the second highest gene associated with TD; the association was not statistically significant with correction for multiple comparisons. Other top genes in the gene burden analysis are presented in Table 1.

Of the 35 SNPs which passed QC and had a MAF greater than 0.01 in the ten genes in the candidate gene analysis, four SNPs had a p-value less than 0.05; none reached statistical significance following correction for multiple comparisons (Table 2).

No individual SNP surpassed the Bonferroni corrected exome-wide significance threshold, but the most significant single SNP, rs861204, a missense variant mapped to transmembrane (C-terminal) protease, serine 12 (*TMPRSS12*), had a p-value of 4.10×10^{-5} (OR=2.29). All SNPs with a p-value less than 0.0005 are also shown in Table S3.

Conclusions

We evaluated a panel of over 300,000 rare and common exomic variants in this first, large-scale, unbiased association study of TD, and identified one gene (*PTCHD2*) that met exome-wide significance for TD. *PTCHD2* is a gene of unknown function whose product is expressed mainly in the brain. In our candidate gene analysis, three of four SNPs within the Ankyrin Repeat and Kinase Domain Containing 1 (ANKK1) gene had a $p<0.05$. This gene has repeatedly been shown to be strongly associated with substance and alcohol dependence (12–14), and very recently been reported to be associated with ever (versus never) indoor tanning, however TD was not assessed in that study (15).

A suggested mechanism for TD involves UV-induced p53 protein expression, which results in increased levels of beta-endorphin and adrenocorticotrophic hormone, via stimulation of the pro-opiomelanocortin (*POMC*) gene promoter (16). With several studies supporting this mechanism (2, 17–19), the nominally-significant association we observed with a SNP in the Opioid Receptor, Mu 1 gene (*OPRM1*), which encodes the main target of naltrexone, is of possible interest. However, our data do not lend support to the hypothesis that SNPs in the *POMC* gene are associated with TD (all p-values > 0.25), in contrast to to findings from substance dependence studies (20), although our sample size is comparatively small.

These results are provocative in suggesting genetic associations with TD, but due to the relatively small sample size, replication in larger samples is necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The studies have been performed according to the Declaration of Helsinki, and have been approved by Yale University's Institutional Review Board. Subjects provided written informed consent.

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Table 1

Genes with the strongest association with tanning dependence (TD) resulting from a gene-based analysis of rare and common variants

Gene	TD[1] (n=79) n (%)	Not TD[1] (n=213) n (%)	P-value for Fisher's Exact Test
PTCHD2	32 (40.5)	152 (71.4)	2.50E-06
ALDH1B1	36 (45.6)	149 (70.0)	1.99E-04
INHBC	18 (22.8)	98 (46.0)	2.75E-04
MYLK3	38 (48.1)	153 (71.8)	2.80E-04
SMC5	41 (51.9)	61 (28.9)	3.07E-04
PRPH2	50 (63.3)	87 (40.8)	9.05E-04

[1]Number having one or more minor alleles at a missense, non-sense or splice site SNP within the gene

Table 2

Association (p<0.05) with tanning dependence of SNPs within and around substance dependence candidate genes

Gene	SNP	Chromosome	BP	OR[1]	P-value[1]	AA Change
OPRM1	rs650662	6	154198159	0.61	0.0181	upstream
ANKK1	rs7118900	11	113266821	1.86	0.0131	Ala239Thr
ANKK1	rs4938016	11	113270015	0.62	0.0264	Gly442Arg
ANKK1	rs2587543	11	113279119	0.65	0.0431	downstream

[1]From logistic regression model adjusted for age and sex.