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Replication and characterization of *CADM2* and *MSRA* genes on human behavior

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Abstract

Progress identifying the genetic determinants of personality has historically been slow, with candidate gene studies and small-scale genome-wide association studies yielding few reproducible results. In the UK Biobank study, genetic variants in *CADM2* and *MSRA* were recently shown to influence risk taking behavior and irritability respectively, representing some of the first genomic loci to be associated with aspects of personality. We extend this observation by performing a personality "phenome-scan" across 16 traits in up to 140,487 participants from 23andMe for these two genes. Genome-wide heritability estimates for these traits ranged from 5–19%, with both *CADM2* and *MSRA* demonstrating significant effects on multiple personality types. These associations covered all aspects of the big five personality domains, including specific facet traits such as compliance,

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altruism, anxiety and activity/energy. This study both confirms and extends the original observations, highlighting the role of genetics in aspects of mental health and behavior.

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1. Introduction

Progress identifying the individual genes underpinning the heritable component (h^2 = 40–60%) [1] of psychiatric disease and personality has lagged behind that of other complex traits [2]. A number of reasons might explain this lag, including strong evolutionary selection against common alleles with large effects, a lack of large studies with detailed and harmonized trait information, disease misclassification and subjective clinical criteria. Candidate gene studies have yielded few, if any, credible associations that are replicated [2] [3]. In the last few years, suitably powered genome-wide association study (GWAS) meta-analyses have begun identifying handfuls of genetic variants associated with severe psychiatric disease [4] [5]. This success, alongside the arrival of large studies such as UK Biobank [6], prompted the hunt for alleles associated with other behavioral and psychological outcomes. Notably, a recent GWAS on educational attainment [7] identified 74 robustly associated genomic loci, which were subsequently demonstrated to have a causal effect on longevity [8]. Two studies recently reported the first loci convincingly associated with aspects of personality, performing large-scale GWAS in up to ~300,000 individuals for subjective well-being [9], neuroticism [9], depressive symptoms [9], irritability [10] and risk taking [10]. Amongst these loci, *CADM2* and *MSRA* were initially linked with reproductive onset (age at first sex and birth), with subsequent analyses suggesting the mechanism of effect might act through broader personality domains (risk taking and irritability) [10]. The range of personality phenotypes in this original study was however limited and no replication datasets were available at the time. Our present study builds on this initial observation by replicating and extending these prior associations at *CADM2* and *MSRA*, examining 16 personality constructs using independent data from 23andMe, Inc., a personal genetics company.

2. Methods

2.1. Human subjects

All 23andMe research participants included in the analysis provided informed consent and answered surveys online according to a human subjects protocol approved by Ethical & Independent Review Services, a private institutional review board.

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