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Reply to Qiu et al.: Hunting for leadership "causal" genes: Mission possible?

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In their letter, Qiu et al. (1) showcase potential "causal" genes at genome-wide association study (GWAS) loci for leadership phenotypes, using expression quantitative trait loci (eQTL) mapping. Using the transcriptome-wide association study (TWAS) approach, the *MST1R* genetic region at chromosome 3p21.31 exhibits a significant association between gene expression and managing demands in several brain tissues. The top transcriptome genes (*MST1R, MST1, RNF123, UBA7*, and *APEH*) are overlapped with the GWAS locus (lead single-nucleotide polymorphism: rs9848497) reported in our study (2). Among them, *MST1R* transduces signals in the Hippo-YAP pathway by binding to the downstream gene *MST1* ligand, which emerges as a key modulator of neurodegenerative disorders such as depression initiated by chronic stress (3). Other pinpointed genes were recently reported to constitute a network interacting with estrogen receptors for anxiety and depressive disorder (4). Interestingly, the rs9848497 T allele was also the top variant associated with job attainment phenotypes (e.g., job autonomy, innovation) in our other recent GWAS paper (5). Whether this allele, positively associated with leadership and job attainment traits, exerts a beneficial effect in stress-induced depression merits further functional research.

Delineating causal genetic variants and biological mechanisms underlying the observed associations for leadership is noteworthy, given pleiotropic genes identified for several mental disorders and various well-being phenotypes. A next question to ask is, How much farther can we go? To pinpoint causal genes is a challenging endeavor in the biomedical domain. For social and behavioral outcomes, the difficulty is even greater (6). For example, the standard gene knockout experiment can hardly be applied in social sciences, due to the absence of similar phenomena in animals, or ethical concerns. Although there are leadership studies on social animals, such as wolves and chimpanzees, exploring those in the herds that play dominating or leading roles (7), and social dominance studies on mice (8), which are the animal often used in knockout studies, establishing an animal model to study human leadership "causal" genes is expected to be a tremendously challenging task.

Previous GWAS studies and ours show that social and behavioral phenotypes tend to be highly polygenic, which means that thousands of genetic loci are relevant, but each contributes a tiny effect (9). For the purposes of explanation and prediction, a single variant will be far from sufficient; instead, aggregate indices, such as polygenic scores (PGSs), are commonly adopted (10). Large collections of GWAS data or summary statistics allow us to have a stable estimation of genetic effects in calculating PGS. With bioinformatics approaches, we can also integrate GWAS data with omics genomes such as gene expression, proteomics in brain tissues and cells, and brain image to pinpoint potential regulatory effects and biological mechanisms. We can characterize how influences of the genetic lottery (e.g., through PGSs) unfold in shaping social and behavior phenotypes longitudinally, while taking into account momentary environmental influences (e.g., G*E correlations and interactions). This may help guide the development of more effective and personalized prevention programs.

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