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Genome-wide search reveals dopamine-related genetic variation effects on caudate volume replicated in young and elderly populations (N=1198)

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Abstract: There is an urgent quest to identify common genetic variations that influence brain structure and disease risk in large human populations. In one of the largest ever imaging genetics studies, we performed a genome-wide search for common genetic variants associated with the volume of the caudate nucleus - a structure implicated in many neurological and psychiatric illnesses. We automatically identified the caudate nucleus in structural brain MRI scans from 1198 subjects with genome-wide scans, from two cohorts: the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Brisbane Adolescent/Young Adult Longitudinal Twin Study (BLTS). The left and right caudate were automatically delineated in each subject using a highly reliable machine learning algorithm based on Adaboost: intra-class correlation coefficients were >0.98 for the left, right and combined caudate volumes. Caudate volume was highly heritable (average caudate 60.8% heritable; $P=2.31 \times 10^{-10}$) according to structural equation modeling in 85 monozygotic (MZ) and 52 dizygotic (DZ) same-sex twin pairs from the BLTS. To identify sources of this heritability, we conducted a genome-wide association study to find common genetic variants associated with caudate volume in a discovery sample of 734 ADNI subjects and a replication sample of 464 BLTS subjects. Association was conducted using an additive model controlling for age and sex with a standard regression in the ADNI study and a mixed-effects regression in the BLTS study to account for family relationships. The most highly associated SNP in the ADNI ($t=4.76$; $P=2.36 \times 10^{-6}$) was independently replicated in the BLTS sample ($t=2.52$; $P=0.012$). The peak of

association for right caudate volume was found in and around two genes, WDR41 and PDE8B. A region containing this gene is essential for dopaminergic neuron development in Drosophila, consistent with the known density of dopaminergic projections in the caudate. A rare autosomal-dominant type of striatal degeneration is also caused by a mutation in PDE8B. Similar results are found in both cystic fibrosis and obesity where common variants have subtler but similar effects to rare Mendelian mutations. Such replicated genetic hits suggest the power of imaging genomics.
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Briefly explain (500 characters) the timeliness and importance of your research, and the overall theme of your abstract or group.

: Discovering the genetic variants which influence brain structure should also give variants associated with mental illnesses. Here we search the genome for variants associated with caudate volume and replicate our finding in one of the largest ever neuroimaging studies.

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