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Genome-wide estimate of the heritability of Multiple System Atrophy

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ABSTRACT

Introduction: Multiple System Atrophy (MSA) is a neurodegenerative disease which presents heterogeneously with symptoms and signs of parkinsonism, ataxia and autonomic dysfunction. Although MSA typically occurs sporadically, rare pathology-proven MSA families following either autosomal recessive or autosomal dominant patterns have been described, indicating a heritable contribution to the pathogenesis.

Methods: We used Genome-Wide Complex Trait Analysis (GCTA) to estimate the heritable component of MSA due to common coding variability in imputed genotype data of 907 MSA cases and 3866 population-matched controls. GCTA only assesses the effect of putative causal variants in linkage disequilibrium (LD) with all common SNPs on the genotyping platform.

Results: We estimate the heritability among common variants of MSA in pooled cases at 2.09–6.65%, with a wider range of values in geographic and diagnostic subgroups. Meta-analysis of our geographic cohorts reveals high between-group heterogeneity. Contributions of single chromosomes are generally negligible. We suggest that all calculated MSA heritability among common variants could be explained by the presence of misdiagnosed cases in the clinical subgroup based on a Bayesian estimate using literature-derived rates of misdiagnosis.

Discussion: MSA is a challenging disease to study due to high rates of misdiagnosis and low prevalence. Given our low estimates of heritability, common genetic variation appears to play a less prominent role in risk for MSA than in other complex neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis. The success of future gene discovery efforts rests on large pathologically-confirmed case series and an interrogation of both common and rare genetic variants.

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1. Introduction

Genome Wide Association (GWA) studies have identified risk loci in several neurodegenerative diseases [1–5]. These loci, however only explain a relatively small proportion of the total heritable proportion of disease. Current conservative estimates of the heritable component of Parkinson's Disease are ~30%, whereas the known GWA loci only account for 3–12% of the burden of disease. Clearly, an understanding of the known and unknown heritable component of disease has the power to inform the research community regarding the value of searching for additional genetic risk, and where to look for this risk.

A recently unpublished GWA study for MSA examined more than 5 million single nucleotide polymorphisms (SNPs) tagged to common genetic variants in 1030 MSA samples (Sailer et al., unpublished). The results, which included 918 MSA cases and 3884 controls after quality control, were unable to detect any genome-wide significant associations between tagged SNPs and MSA risk. Though sample size and power were limited in this study, this finding suggests that MSA etiology cannot be easily explained by common SNPs with moderate or large effects. This result, however, does not preclude the role of common variability in MSA;

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particularly for variants that may only have marginal effects, typical of those observed for GWA in complex disease. The genotype data generated as a part of this study afford an opportunity to look beyond the identification of individual risk loci, toward an estimate of the role and extent of common variants as a heritable component of disease risk.

We estimated the total heritability of MSA from common genetic variants (MAF > 0.01) with Genome-Wide Complex Trait Analysis (GCTA). Heritability is defined as phenotypic variation attributable to total genetic variation in all assessed loci. Total genetic variation is estimated in GCTA by generating a 'genetic relatedness matrix', which estimates overall genetic differences in each subject. If cases are more genetically similar to one another than they are to controls, we can quantify this higher relative similarity and use it to estimate the total heritability of the disease phenotype. Notably, this approach is possible only in unrelated populations and requires relatively large sample sizes for requisite statistical power. GCTA can examine only the effect of putative causal variants in LD with all common SNPs on the genotyping platform [6,7].

In this study, we estimated the total heritability of MSA with GCTA in order to guide future genetic research into the disease.

2. Methods

All participants provided written informed consent. Pre-imputation base calling quality control filters were applied using standard conditions. See Supplemental 1 for details. 907 MSA cases, 3866 controls, and 107,447 SNPs passed initial quality control. All principal component (PCA) and IBD analyses were carried out using linkage-pruned SNP sets.

Imputation was accomplished using MaCH to estimate subject haplotypes. In the process of imputation, sample genotype data is inferred using a reference haplotype database. Matching the genotypes to common haplotypes and 'filling in' (imputing) the missing bases based on typical haplotypes allow for millions of intervening nucleotide sequences not captured by the microarray to be incorporated into the overall genetic data for each sample. Further information can be found in Supplemental 1.

2.1. Genome-Wide Complex Trait Analysis

GCTA uses a REstricted Maximum Likelihood (REML) model to estimate the variance in phenotype explained by variance in genotype. Here, we used GCTA's REML model to estimate the phenotypic variance of MSA, adjusting for population substructure using the top 20 European Ancestry population principal components. This heritability estimate was adjusted for actual population prevalence of MSA (estimated at 0.000046) [8,9]. We first ran GCTA using all samples in a pooled analysis, then divided MSA cases into several sample subsets based on geographic region of origin and whether cases had been pathologically confirmed or only clinically diagnosed (Table 1). Each of these groups were tested against matched controls to estimate total heritability of MSA both before and after imputation. We then meta-analyzed these subgroups under a random effects model in order to assess heterogeneity between the cohorts.

2.2. GWAS

Please refer to Supplemental 1 for GWA study methods.

2.3. Bayesian estimate of Parkinson's disease-derived heritability

We estimated rates of false clinical diagnosis from Osaki et al., 2009 [10]. Using values of 6–25% false positive rate, 70% of false positives as Parkinson's cases, and heritability priors of 0.31 for PD and 0.1 for all other disorders, we calculated an expected rate of heritability to due misdiagnosis. Derivation of this formula may be found in Supplemental 1.

Table 1
Summary statistics of all samples included within GCTA following stringent quality control analysis. Component numbers of control subjects do not sum to total due to incomplete annotation (i.e. unknown region of origin). Cases not explicitly labeled as pathologically confirmed were assumed to have only a clinical diagnosis.

Cohort	Number of subjects	Path confirmed/clinically diagnosed
Cases		
United Kingdom	238	141/97
United States	127	108/19
North European	308	28/258
South European	234	14/220
Total	907	291/616
Controls		
United Kingdom	945	–
United States	793	–
North European	944	–
South European	1184	–
Total	3877	

3. Results

MSA cases and their respective geographic cohort controls show an insignificant amount of heterogeneity within each regional cohort (Supplemental 2). After initial quality control (QC) of genotyped data, we imputed the data using 1k Genomes reference haplotypes order to increase power and provide many more variants for assessment of total heritability. Standard errors of the estimates decreased uniformly post-imputation, likely reflecting improved statistical power and increased information content (Fig. 1, Table 2).

We estimated heritability with GCTA using pooled samples, then divided analyses by population cohort and whether subjects were pathologically-confirmed or clinically diagnosed (Fig. 1, Table 2). After estimating heritability of each of these subgroups, we also ran a random effects meta-analysis of all population cohorts in each diagnostic subset: all cases, pathologically-confirmed cases, and cases identified exclusively through clinical diagnosis.

We estimated heritability of pooled MSA samples to be about 4.37% in imputed data (95% CI 2.09–6.65%). Heritability estimates ranged widely in our geographic cohorts, from 0.26% in UK cases to 9.18% in Southern European cases. The UK and US cohorts were composed primarily of pathologically-confirmed cases (Table 1), while the Northern (Germany, Austria, Netherlands, Denmark) and Southern (Italy, Portugal, Spain) European samples were mostly identified by clinical means alone.

MSA, as with many parkinsonian disorders, is often misdiagnosed, making pathologically-confirmed cases significantly more reliable than clinical diagnoses. Therefore, we also estimated the heritability of pathologically confirmed cases alone with the intention of minimizing falsely attributed heritability stemming from genetic underpinnings of other neurodegenerative diseases (i.e. PD, PSP) (Table 2).

In pooled pathologically-confirmed samples, we found heritability to be near zero in genotyped data. However, this estimate increased to around 5.8% (95% CI 0–11.99%) in imputed data, suggesting that the imputed genotypes contribute a great deal to the heritability of MSA. Clinical-only estimates have a pooled heritability of 6.17%, slightly higher than the pooled estimate of all cases and pathologically-confirmed case in the imputed datasets. However, pathologically-confirmed and clinical estimates are