Association Study of Common Mitochondrial Variants and Cognitive Ability

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Abstract Mitochondria are central to optimal functioning of the nervous system and disruption of mitochondrial function is known to lead to cognitive impairment. However, there has been little focus on whether common mitochondrial DNA polymorphisms contribute to normal variation in cognitive phenotypes. In this study, we use methodology for carrying out whole mitochondrial association studies in family cohorts to test whether 69 common mitochondrial variants and 10 common European haplogroups are associated with a number of measures of cognition, including information processing, word recognition and general cognitive ability, in a sample of Australian adolescent twins and their singleton/non-twin siblings. With data from 1,385 individuals from 665 families, this is by far the largest mitochondrial association study of cognition undertaken to date. We find that there is no significant evidence that either common European mitochondrial SNPs or haplogroups are associated with variation in cognitive performance. In spite of the associations not reaching significance, several of the most highly associated SNPs are in mitochondrial genes that have previously been identified as potentially playing a role in cognitive performance in mice. These genes warrant further investigation in both functional and association studies with larger cohorts.

Introduction

Accumulating evidence from a number of different studies suggests mitochondrial DNA (mtDNA) variants account for some of the variation in cognitive functioning. Mitochondria are intracellular organelles that contain their own DNA which is independent of nuclear DNA. The number of mitochondria in a given cell is dependent upon the tissue type, and there can be up to several hundred thousand mitochondria in a cell. Their primary role is to produce energy through the process of oxidative phosphorylation. The mitochondrial DNA encodes 37 genes, 13 of which code for proteins that are essential components of the oxidative phosphorylation complexes. The other genes encode tRNAs and rRNAs essential for translation of the mitochondrial proteins. Mitochondrial DNA is strictly maternally inherited and does not recombine. This lack of recombination means that when a mutation occurs, it is in linkage disequilibrium (LD) with all other variants on the mitochondrial chromosome. Over time, sets of linked variants called haplogroups evolve. Each haplogroup is defined by the presence of a specific set of variants. There are nine major European haplogroups—H, I, J, K, T, U, V, W, and X, and in this paper, we also test for association with the Asian superhaplogroup M, which is found in the Australian

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population. Mitochondrial DNA also mutates at a much higher rate than nuclear DNA and, in many cases, a situation known as heteroplasmy can develop, whereby cells contain a mixture of wild-type and mutant mitochondria.

There are several reasons to think that mtDNA variants may contribute to variation in cognitive ability. Mitochondria play an essential role in the functioning of the nervous system (DiMauro and Schon 2008), and the vast majority of mitochondrial diseases in both mice and man involve brain disorders (Wallace 1999), with variants implicated in both bipolar disorder (Munukata et al. 2004) and schizophrenia (Martorell et al. 2006). In addition, mtDNA has been implicated in neurodegenerative disorders and it has been proposed that the gradual accumulation of mutations in the mtDNA may provide the necessary genetic aging clock to explain the delayed-onset and progressive course of neurological disorders (Wallace 2005). In Alzheimer's disease (AD), a number of lines of evidence show that mtDNA coding region mutations that damage the regulatory functions of the mitochondria are central to the pathology of the disease (Shoffner et al. 1993; Hutchin and Cortopassi 1995; Wallace 2005). A 5 kb deletion in the mtDNA has been found at a 15× greater frequency in cases than controls. (Wallace 2005; Corral-Debrinsky et al. 1994). Mitochondrial association studies have had mixed results, with some groups finding no association with AD (Chinnery et al. 2000; Elson et al. 2006) and others reporting that haplogroup J increases susceptibility, while T has a protective effect (Chagnon et al. 1999). Similarly, there is substantial evidence to suggest that mitochondrial dysfunction is key to the etiology of Parkinson's disease, and a number of association studies have been undertaken to test for a link between mitochondrial variants and Parkinson's. Some have suggested that haplogroups J and K provide a protective effect against Parkinson's disease (van der Walt et al. 2004). Other studies could not confirm such an effect, but did report an association with the 4336C variant (Huerta et al. 2005). Mitochondrial dysfunction has also been implicated in the onset of Huntington's disease. Memory loss in older rats has also been associated with mitochondrial decay (Liu et al. 2002). This combined evidence suggests that mitochondria are essential for normal brain functioning.

The most direct evidence of a role for mitochondrial DNA in cognition comes from recent experimental work in mice (Roubertoux et al. 2003). Mice that were essentially identical for all nuclear loci but having different mitochondria were bred by backcrossing for 20 generations. Mice carrying particular mtDNA variants performed better in learning and exploration tasks than mice with the same nuclear genome, but different mitochondria. There was also a clear interaction effect between the mitochondrial and nuclear genomes (Roubertoux et al. 2003).

Given the amount of attention that has been paid to the role of mitochondrial dysfunction in cognitive impairment, it is surprising that there has been very little focus on the potential association between common mitochondrial variants and cognitive phenotypes. An early association study on IQ tested 100 Single Nucleotide Polymorphism (SNP) markers for association in a group of high- and low-IQ Caucasian children (Skuder et al. 1995). A significant association was found with a marker at position 15,925 of the mitochondrial genome in both an initial and replication sample. This polymorphism is found in the D-loop and is therefore unlikely to be functionally important, but the non-recombining nature of the mitochondria means that it may be in LD with a truly causal variant somewhere else in the mitochondrial genome. This study suffered from a small sample size however, with the initial sample consisting of 42 individuals, and the replication sample consisting of 44 individuals. Subsequent studies have failed to replicate the association (Moises et al. 1998; Petrill et al. 1997), but again both of these studies had small sample sizes, and one of them was carried out in a different population which may explain its failure to replicate (Moises et al. 1998).

Here we use methodology for performing family-based mitochondrial association studies to test for an association between a number of measurements of cognitive ability—information processing, reading, and IQ—and common mitochondrial polymorphisms in a sample of Australian adolescent twins and their siblings.

Materials and methods

Sample

Families consisted of adolescent twins and their singleton/non-twin siblings who had been initially recruited as part of a study investigating melanoma risk factors (Zhu et al. 1999) and subsequently agreed to take part in a large ongoing twin study into genetic and environmental influences on cognition (Wright and Martin 2004). A total of 1,385 individuals from 665 families had both cognitive measurements and mitochondrial genotype information. This included 366 DZ pairs, four sets of DZ triplets, 181 MZ pairs and 279 singleton/non-twin siblings. There were 668 males and 717 females. All subjects were assessed on the cognitive test battery as close as possible to their 16th birthday. The mean age of the twins sampled was 15.9 (SD 0.5) years, while the mean age of the siblings was 15.9 (SD 1.1) years. The age range in the sample was 15.6–22.2 years. Participants gave informed consent for both the cognitive assessment and collection of blood. The studies were approved by the QIMR Human Research Ethics Committee.

Genotyping

The details of the genotyping have been described elsewhere (McRae et al. 2008; Byrne et al. 2008), so only a brief description is given here. Saxena et al. 2006, identified 64 mtSNPs that tag all mitochondrial variants of >1% frequency in the European population with an r^2 of at least 0.8. For this study, 61 of the 64 tagSNPs were genotyped as well as an additional 9 SNPs which tag variation at $r^2 > 0.8$, that otherwise required the use of multi-SNP haplotypes using a method described in a previous study (McRae et al. 2008). A common D-loop variant, mt16189, was also genotyped. This gave a total of 71 SNPs, but two were found to be monomorphic in our sample, leaving 69 SNPs in the final analysis. The tagging SNP set that was developed by Saxena et al. has been previously been criticized for not being well grounded in mitochondrial phylogenetics (Elson et al. 2007). However, these tag SNPs tag all the major European haplogroups very efficiently, but also allow for direct testing of variants which may occur on multiple haplogroups. Were such a SNP to be associated with a trait, simple association testing of a specific haplogroup in which that SNP is found may lead to false negative results. The approach used by Saxena et al. and also used here, allows for testing of SNPs without regard to phylogeny. The approach for tagging haplogroups used here differs from that used by Saxena et al. Haplotypes were assigned to haplogroups using a linear discriminant function analysis described in a previous study (McRae et al. 2008). Instead of testing specific SNPs or specific combinations of SNPs, the linear discriminant function analysis can potentially use information from all 69 SNPs to assign haplogroups. Because of missing genotypes, a small number of haplotypes (<1%) could not unambiguously be assigned to haplogroups.

SNPs were typed using iPLEX^TM Gold chemistry and analyzed using a Sequenom MassARRAY Compact Mass Spectrometer (Sequenom Inc, San Diego, CA, USA). After PCR reactions, a two-step 200 short cycles program was used for post-PCR extension reaction. The iPLEX reaction products were spotted on a SpectroChip (Sequenom Inc, San Diego, CA, USA), and data were processed and analysed by MassARRAY TYPER 3.4 software (Sequenom Inc, San Diego, CA, USA). All SNPs had a high call rate (>95%). There were 46 (0.05%) "heterozygous" calls out of a total of 93,275 called genotypes, possibly attributable to genotyping error, indicating that there is little heteroplasmy in the sample. Heterozygous calls were treated as missing for the purposes of this study. Any individual with >5% missing genotypes (two individuals) was removed from the analysis.

Traits

The cognitive measures assessed include the digit symbol test (a measure of perceptual motor speed) which is a subtest of the WAIS-R (Wechsler 1981), two reading tests—the Cambridge Contextual Reading Test (Beardsall and Huppert 1994) (a contextualized version of the National Adult Reading Test (NART) (Nelson 1982)) and the Schonell Graded Reading Test (Schonell and Schonell 1960)—both of which test for the ability to pronounce irregular words, and the Multi-dimensional Aptitude Battery (MAB) (Jackson 1984) including 5 IQ subtests—3 verbal tests (information, vocabulary and arithmetic) and two performance tests (spatial and object assembly). Each of the IQ subtests was analysed individually, in addition to analysing the overall scores for verbal (VIQ), performance (PIQ) and full IQ (FSIQ). Further information on these traits can be found in Wainwright et al. (2004) and Luciano et al. (2001). The only trait to deviate from normality was the Schonell reading test, which was transformed using a reverse, logarithmic function (Luciano et al. 2006), whereby all scores were subtracted from the sum of one plus the maximum score, and a logarithm taken of the result. One outlier (any individual with an absolute z-score of >3.5) was removed from the digit symbol analysis and nine were removed from the vocabulary subtest. There were no outliers for any of the other traits.

Analysis

Simple regression of a trait on mitochondrial genotype is not suitable when using family data due to the observations being correlated among family members. The correlation is modeled as being due to sharing of additive genetic variance by using a linear mixed model to model the inheritance of both mitochondrial and nuclear genetic effects. The full model is:

$$y = \mu + \beta x + Zu + e$$

where y is a vector of phenotypes and μ is the mean. The mitochondrial inheritance is modelled as a fixed effect (β), where x is a vector of mitochondrial genotype indicators and β is a scalar containing an estimate of the effect of the mitochondrial variant. The nuclear genetic inheritance is modelled with a random effect Zu, where Z is a matrix relating individuals to phenotypes and u is a vector of nuclear additive polygenetic effects. e is a vector of residuals. The random effects u and e are assumed to be distributed as multivariate normal where $u \sim N(0, A\sigma_a^2)$ and $e \sim N(0, I\sigma_e^2)$ where A is the standard additive genetic relationship matrix, and I is an identity matrix. Age and Sex are included as fixed effects in the model. It was

previously shown that there are age and sex effects on the means of a number of these variables (Luciano et al. 2006). The heritability can be estimated as $\frac{\sigma_a^2}{\sigma_a^2+\sigma_e^2}$. The model above fits an AE variance components model (the variance of u is the Additive genetic variance and the variance of e is the Environmental variance) to explain the phenotypic variance in the sample. This model assumes that there is no variance due to family members, in particular twin-pairs, sharing common environmental factors. If such common environmental variance does exist, it will be confounded with additive genetic variance, leading to an upward bias of heritabilities. The model was fitted using the program Sib-Pair (http://www.qimr.edu.au/davidD/index.html) via the "mit" command, and the effect of the mitochondrial variant was estimated using a likelihood ratio test.

The experiment-wide significance level was set at $P = 6.32 \times 10^{-4}$ (5% significance level with a Bonferroni correction for the 79 tests—69 SNPs and 10 haplogroups—being carried out). Bonferroni correction is an appropriate strategy in this case due to the generally low LD between markers as shown in McRae et al. 2008. However, there is a high level of correlation between the tests of the individual SNPs and those of the haplogroups, so the correction is likely to be slightly conservative. This is counteracted by there being no correction for the analysis of multiple correlated traits. The phenotypic correlations among the variables were moderate to high, ranging from 0.25 to 0.82 (Table 1).

Results

The number of individuals included in the analysis of each trait and the means, SD and heritabilities for each trait in each age group is given in Table 2. Despite being potentially upwardly biased due to the use of an AE variance components model, the estimates of heritability agree with previous studies showing that cognitive ability is a very highly heritable trait (McClearn et al. 1997; Plomin 1999).

Table 3 shows the most significant associations for each trait. There were no significant associations between common mitochondrial variants and any of the traits. Even if the correction for multiple testing is relaxed slightly, there appears to be no convincing associations. A Q-Q plot of the 869 test statistics (79 SNPs and haplogroups, and 11 traits) for each SNP and haplogroup with all traits shows that they deviate slightly from the expected χ^2 distribution (Fig. 1). This deviation is towards lower χ^2 scores than expected. The median χ^2 in the observed distribution is 0.440, whereas the expected median is 0.455. This leads to

Table 1 Phenotypic correlations among the verbal and performance IQ subtests and reading measures

|	Information	Arithmetic	Vocabulary	Spatial	Object assembly	CCRT	Schonell
Arithmetic	0.51						
Vocabulary	0.67	0.44					
Spatial	0.36	0.42	0.29				
Object assembly	0.45	0.44	0.38	0.58			
CCRT	0.63	0.45	0.62	0.32	0.37		
Schonell	0.65	0.46	0.59	0.31	0.34	0.82	
Digit symbol	0.25	0.28	0.24	0.23	0.25	0.25	0.30

Table 2 The number of individuals analysed, and the means, SD and heritabilities for each trait

Trait	Test	Number of individuals	Mean (±SD)	h^2*
IQ subtests	Information	1,376	20.7 (5.6)	0.77
	Arithmetic	1,376	12.3 (2.9)	0.66
	Vocabulary	1,364	17.6 (4.9)	0.61
	Spatial	1,379	30.5 (8.9)	0.57
	Object assembly	1,378	13.1 (3.8)	0.61
	Verbal IQ	1,376	110.3 (11.4)	0.66
	Performance IQ	1,378	112.3 (16.1)	0.70
	Full IQ	1,375	112.2 (12.9)	0.80
Reading	CCRT	1,258	31.5 (7.7)	0.59
	Schonell (transformed)	1,271	1.14 (0.28)	0.82
Processing speed	Digit symbol	1,288	59.7 (10.2)	0.69

* Heritabilities are estimated using an AE model, leading to potential upward bias

Table 3 The most significantly associated variant for each trait and corresponding *P*-values, effect size, and SE

Trait	Test	Most associated variant	Minor allele	MAF	SNP location (from http://mitowheel.org/mitowheel.html)	*P*-value	Beta	SE
IQ subtests	Information	mt13105	G	0.01	ND5 gene, subunit of NADH dehydrogenase (complex 1). Isoleucine257. First nucleotide in codon ATC	0.0055	3.75	1.35
	Arithmetic	mt5426	C	0.01	ND2 gene, subunit of NADH dehydrogenase (complex 1). Histidine 319. Third nucleotide in codon CAT	0.0404	1.90	0.63
	Vocabulary	mt9093	G	0.01	ATP6 gene, subunit of ATP synthase (complex V). Threonine189. Third nucleotide in ACA	0.0331	4.24	1.48
	Spatial	mt13965	C	0.01	ND5 gene, subunit of NADH dehydrogenase (complex 1). Leucine543. Third nucleotide in codon CTT	0.0035	−8.01	2.44
	Object assembly	mt13965	C	0.01	ND5 gene, subunit of NADH dehydrogenase (complex 1). Leucine543. Third nucleotide in codon CTT	0.0236	−2.54	1.02
	Verbal IQ	mt13105	G	0.01	ND5 gene, subunit of NADH dehydrogenase (complex 1). Isoleucine257. First nucleotide in codon ATC	0.0331	6.17	2.39
	Performance IQ	mt13965	C	0.01	ND5 gene, subunit of NADH dehydrogenase (complex 1). Leucine543. Third nucleotide in codon CTT	0.0063	−13.61	3.98
	Full IQ	mt13965	C	0.01	ND5 gene, subunit of NADH dehydrogenase (complex 1). Leucine543. Third nucleotide in codon CTT	0.0092	−10.34	3.47
Reading	CCRT	mt3348	G	0.01	ND1 gene, subunit of NADH dehydrogenase (complex 1). Leucine19, third nucleotide in codon CTA	0.0338	−13.73	4.47
	Schonell	mt3348	G	0.01	ND1 gene, subunit of NADH dehydrogenase (complex 1). Leucine19, third nucleotide in codon in CTA	0.0215	31.15	10.55
Processing speed	Digit symbol	mt12705	T	0.10	ND5 gene, subunit of NADH dehydrogenase (complex 1). Isoleucine123. Third nucleotide in codon ATC	0.0096	−1.95	0.46
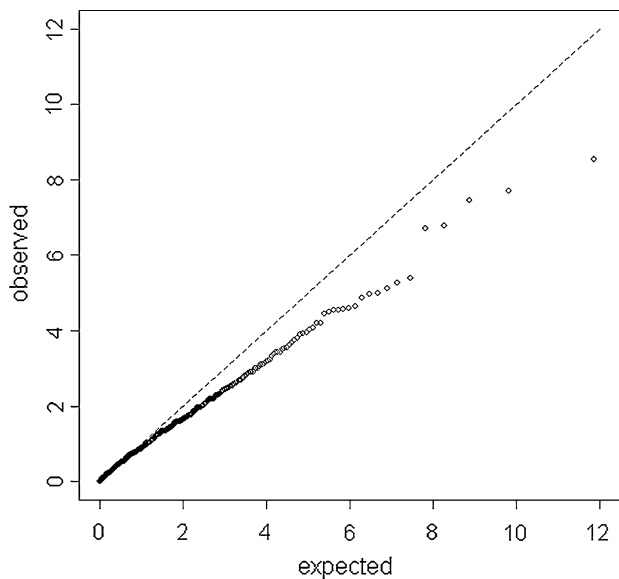
Fig. 1 Q-Q plot of distribution of expected versus observed distribution of test statistic

an "inflation factor" of 0.97. Hence, there is no evidence of an increased number of large test statistics.

As noted in Table 3, the majority of the most highly associated SNPs are in found in the 3rd nucleotide position of codons, indicating that they are synonymous changes. As such, these polymorphisms are unlikely to be functional themselves but may tag other functional variants.

There are no strong associations with any of the common European haplogroups (Table 4).

Discussion

We have carried out a family-based mitochondrial association study on a number of measures of cognitive ability in Australian adolescent twins. This is the largest mitochondrial association study of cognition so far undertaken. Given the wealth of evidence to support a role for mitochondrial DNA in cognition, it is likely that this will be the first of several such studies.

While family-based mitochondrial association studies are not ideal from the point of view of statistical power due to the lack of within-family segregation—all children will have the same genotype as the mother—they allow for the use of family data which has already been collected for large-scale linkage studies of cognitive phenotypes. As the latest genotyping chips contain mitochondrial variants, there will be opportunities to perform mitochondrial association studies in addition to whole-nuclear genome studies. The differing inheritance patterns of the two genomes means that data from the two genetic systems require different methodology for association analysis, and the methodology described here can be used for analysing the mitochondrial variation.

We find no significant evidence to suggest that common European mitochondrial SNPs or haplogroups contribute to variation in cognitive phenotypes in adolescent twins. While the strongest associations found here do not reach significance, they are at least good candidates which may be replicated in future studies. It is interesting to note that all of the most highly associated SNPs (with the exception of mt9093) are found in NADH dehydrogenase genes. Roubertoux et al. 2003 found that many of the differences in mitochondrial DNA between the strains of mice with different cognitive phenotypes were concentrated in the NADH genes. In particular, they noted that the strains differed by two amino acids in the Nad2 and Nad5 genes. They also found differences in the expression of these genes between the different mitochondrial strains of mice. Mt5426 is found in the Nad2 homologue in humans, and mt12705, mt13105, and mt13965 are found in the Nad5 homologue. It may be simply coincidence that these SNPs come out as the most highly associated with cognitive phenotypes in our sample, particularly given the fact that these genes are among the largest in the mitochondrial genome. In addition, because of the non-recombining nature of mitochondria, there is no correlation between LD and distance in the mitochondrial genome, and so these SNPs may actually correlate with causative SNPs in other genes. This is the case for mt5426 and mt12705. They do, however, also tag other SNPs in the same gene (Saxena et al. 2006). mt13105 and mt13965 do not tag other SNPs. These SNPs are certainly interesting candidates for association. Unfortunately, it is not as easy to carry out gene expression studies in human brain tissue as it is in mice, so it will be difficult to test whether there are similar changes in gene expression due to SNPs in these genes in humans.

Roubertoux et al. also found that the effects of the mitochondrial variants were modified by the nuclear genome. It is possible that if nuclear variation were controlled for, that the association signals would be stronger. Given the amount of cross-talk between the two genomes, and the reliance of mitochondria on nuclear genes for normal functioning, it is unsurprising there are interaction effects. This interaction is a significant limitation of mitochondrial association studies. However, analysing data from MZ twins may go some way to resolving this problem. If somatic mutations in mitochondrial DNA could be detected in MZ twins, this allows for direct testing of the effects of mitochondrial variants, as their nuclear genomes will be the same. This approach has previously been used in studying the Mendelian disorder neurofibromatosis (Detjen et al. 2007). This may be a particularly good strategy in the cognition studies in elderly twins as they may have developed differences in mitochondrial DNA over the

Table 4 Association results for common European haplogroups

Haplogroup	tagSNPs	Frequency (%)	Trait P-values										
			Information	Arithmetic	Vocabulary	Spatial	Object assembly	VIQ	PIQ	FIQ	CCRT	Schonell	Digit symbol
H	7028C	43.7	1.00	0.31	0.67	0.46	0.40	0.35	0.54	0.64	0.04	0.78	1.00
I	7028T, 10238C, 1719A	4.0	0.47	0.50	0.54	0.46	0.31	0.29	0.49	0.89	0.60	0.45	0.47
J	7028T,12705C, 13708A, 12372G, 11812A	10.9	0.40	0.40	0.89	0.71	0.51	0.81	0.19	0.81	0.89	0.78	0.40
K	10084T, 12372A, 13966A, 14798C	8.6	0.64	1.00	0.42	0.20	0.05	0.71	0.69	0.62	0.84	1.00	0.64
M	1189T, 15043A, 15924A, 11812A, 10238T, 12705T	1.0	0.81	0.67	0.19	0.58	0.62	0.58	0.48	0.64	0.75	0.60	0.81
T	4126C, 10084T, 10398A	9.4	0.58	0.38	0.38	0.32	0.24	0.81	0.42	0.89	0.56	0.69	0.58
U	12372A, 12705C, 14798T	12.1	0.40	1.00	0.89	0.21	1.00	0.75	0.38	0.34	0.19	1.00	0.40
V	11719G,15043G, 15218A	6.9	0.42	0.71	1.00	0.25	0.71	0.32	0.64	1.00	0.07	0.35	0.42
W	1719G, 10238T,12705T, 13966A,15043G	1.5	0.64	0.89	0.16	0.33	0.13	0.71	0.45	0.73	1.00	0.69	0.64
X	709G,1719A, 10238T,12705T,15043G	1.8	0.38	0.84	1.00	0.21	1.00	0.50	0.89	0.54	0.10	0.57	0.38

course of their lifetime. Such a study design would be able to more directly test the validity of the mitochondrial theory of ageing. The present study cannot directly test this theory. The relatively young age of the subjects in this study means that it is unlikely that any cognitive decline would have occurred, or that sufficient mitochondrial mutations would have accumulated to bring about such a decline. In addition, the energy demands and consequent oxidative stress differ depending on the region of the brain examined. To test the mitochondrial theory of ageing, a direct examination of the amount of heteroplasmy in different regions of the brain, as well as a larger battery of cognitive tests which specifically test those regions would be required in an older sample than the one analysed here.

The discovery of the interaction effect by Roubertoux et al. also suggests a future direction for mitochondrial studies of cognition. Given that there is a lot of information on which nuclear genes are expressed in mitochondria, an association study encompassing mitochondrial variants and SNPs found in mitochondrially-expressed nuclear genes may shed light on the role of mitochondria in cognition. In addition, epistasis between these genes could be examined.

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