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A QTL on chromosome 3q23 influences processing speed in humans

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Abstract

Processing speed is a psychological construct that refers to the speed with which an individual can perform any cognitive operation. Processing speed correlates strongly with general cognitive ability, declines sharply with age, and is impaired across a number of neurological and psychiatric disorders. Thus, identifying genes that influence processing speed will likely improve understanding of the genetics of intelligence, biological aging, and the etiologies of numerous disorders. Previous genetics studies of processing speed have relied on simple phenotypes (e.g., mean reaction time) derived from single tasks. This strategy assumes, erroneously, that processing speed is a unitary construct. In the present study, we aimed to characterize the genetic architecture of processing speed by using a multi-dimensional model applied to a battery of cognitive tasks. Linkage and QTL-specific association analyses were performed on the factors from this model. The randomly ascertained sample comprised 1291 Mexican-American individuals from extended pedigrees. We found that performance on all three distinct processing-speed factors (*Psychomotor Speed; Sequencing and Shifting* and *Verbal Fluency*) were moderately and significantly heritable. We identified a genome-wide significant QTL on chromosome 3q23 for *Psychomotor Speed* (LOD = 4.83). Within this locus, we identified a plausible and interesting candidate gene for *Psychomotor Speed* ($Z = 2.90$, $p = 1.86\times10^{-03}$).

Keywords

Processing speed; linkage; association; cognition; genetics

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Introduction

Processing speed is “the speed with which an individual can perform (and provide a response to) any cognitive operation” (Salthouse, 1996). Impairments in processing-speed ability have meaningful consequences for everyday tasks, such as reading instructions, calculating a tip, or driving a car (Goverover et al., 2007; Owsley et al., 2002). As early as the 1800s, psychologists recognized the link between individual differences in processing speed and general intelligence (Cattell, 1890; Galton, 1890; O’Brien & Tulsky, 2008). Contemporary research frames processing speed as an integral component of general intelligence (Deary, Der & Ford, 2001; Grudnik & Kranzler, 2001; Sheppard & Vernon, 2008). Processing speed deficits may impede the initial time-dependent aspects of a task, producing insufficient or incorrect information necessary for downstream processing events, and consequently leading to poor task performance (Salthouse, 1996; Madden, 2001). The importance of processing speed is further underlined by its role in developmental trajectories as well as its vulnerability to insult with advancing age and neurological illness. Processing speed is thought to support the development of reasoning ability (the ability to think logically and solve problems) (Ferrer et al., 2013) as well as contributing to the emergence of successful real-world social functioning in adolescents (Bachman et al., 2012). Processing speed declines dramatically with age, and some argue that this explains age-related cognitive decline generally (Finkel et al., 2007; Eckert et al., 2010; Salthouse & Ferrer-Caja, 2003). Reduced processing speed is also considered a hallmark of various neurological and psychiatric disorders, including multiple sclerosis (Chiaravalloti & DeLuca, 2008; Ruet et al., 2013), mild cognitive impairment and Alzheimer’s Disease (Phillips et al., 2013; Tales et al., 2012; Warkentin, Erikson & Janciauskiene, 2008), unipolar and bipolar depressive disorders (McDermott & Ebmeier, 2009; Torres, Boudreau & Yatham, 2007; Glahn et al., 2010) and psychosis (Reichenberg & Harvey, 2007; Dickinson, Ramsey & Gold, 2007; Knowles, David & Reichenberg, 2010; Mathias et al., 2017). Thus, examining the genetic architecture of processing speed should improve our understanding of the biological pathways involved in this key cognitive ability and potentially how these pathways are disrupted in brain-related diseases or aging.

Processing-speed ability is classically measured by the number of correct responses that an individual is able to make when completing a timed task or mean reaction time over a fixed number of trials (Lezak, 2004). Previous genetics studies of processing speed have conformed to this paradigm. Twin studies have found that such measures of processing speed are moderately and significantly heritable, with estimates varying between 0.35 and 0.77 for a wide variety of measures, including simple and complex reaction times, inspection time, Stroop tasks, memory scanning, letter matching, digit-symbol substitution tasks, and parts A and B of the trail making test (TMT) (Vernon, 1989; Baker, Vernon & Ho, 1991; Neubauer et al., 2000; Luciano et al., 2001; Posthuma et al., 2002; Posthuma et al., 2003; Hansell et al., 2005; Lee et al., 2012). Gene-discovery efforts, on the other hand, have resulted in less cohesive findings. There are, to our knowledge, four published genome-wide association (GWA) and two family-based linkage studies of processing-speed ability. Luciano and colleagues meta-analyzed the results of GWA applied to various processing-speed measures (including the digit symbol substitution task, inspection time and reaction

time indices, plus a composite speed factor) in four cohorts (total N ≈ 3,500) (Luciano et al., 2011). They identified several suggestively significant SNPs in *DCDC2* (reaction time) on chromosome 6p22.3, *TRIB3* (speed factor and reaction time) on chromosome 20p13, and *NFKBIL1* (DSST and speed factor) on chromosome 6p21.33. A meta-analysis of GWAS in three separate samples (N = 1,338) of the trail making test (TMT) by Ising and colleagues (Ising et al., 2014) revealed a suggestively significant SNP, the effects of which were moderated by age, in the *DSG1* gene on chromosome 18q21.1. Ibrahim-Verbass and colleagues (Ibrahim-Verbaas et al., 2016) identified a SNP in the *CADM2* gene on chromosome 3p21.1 for performance on the DSST in a sizeable cohort (N = 32,070), which they replicated at a nominal level of significance in a smaller sample (N = 1,311). Most recently, a GWAS by Davies and colleagues discovered a locus on chromosome 12q24 influencing reaction time containing the genes *SH2B3* and *ATXN2* (Davies et al., 2016). These associations did not replicate, although the replication sample comprised published GWAS of general cognitive function and educational attainment rather than reaction time *per se*. There have been two genome-wide linkage studies of processing speed. Luciano and colleagues did not find genome-wide significant QTLs for the DSST in a sample of 361 families comprising 2-5 siblings per family (Luciano et al., 2006), while a genome-wide linkage study of reaction time (378 families; 2-5 siblings per family) found suggestive linkage on the long arm of chromosome 1 and the short-arms of chromosomes 8, 11, and 22 (Wright et al., 2008). In sum, the genetic architecture of processing-speed requires further investigation.

Previous genetics studies of processing speed used disparate tasks of reaction time or constrained analysis to individual neuropsychological measures of processing-speed ability. This approach implicitly assumes that processing speed is a unitary construct and factor analysis of cognitive test batteries typically reveals a single processing-speed factor (Deary, 2001; Deary, Spinath & Bates, 2006). However, the diversity of test types that load on processing-speed factors suggests that it may actually be a multidimensional construct (Posthuma & Gues, 2008): a complex ability formed from a number of simpler cognitive sub-processes. More specifically, it has been proposed that processing speed can be broken down into simple and complex factors, comprising reaction time and information processing, respectively (Chiaravalloti et al., 2003). In a previous study, we built a model of simple and complex processing speed in the vein of seminal work by Miyake and colleagues (Miyake et al., 2000; Friedman & Miyake, 2017), using a combination of confirmatory factor and structural regression modeling (Knowles et al., 2012). This model comprised a simple factor (*Psychomotor Speed*) plus two complex (*Sequencing and Shifting* and *Verbal Fluency*) factors (Figure 1).

The present study addresses the limitations in the breadth of phenotypes employed in previous gene-discovery studies of processing speed by applying genome-wide linkage, peak-wide association and gene analysis to multiple processing-speed factors derived from a replicated model of processing speed in a sample of 1291 individuals from extended pedigrees. The aim of this study was to replicate our previous model of processing speed and then use that model to characterize the genetic basis of multiple aspects of processing-speed ability and in so doing, isolate potentially interesting candidate genes for the numerous neurological and psychiatric disorders in which it is impaired.

Methods

Participants

The sample comprised 1291 individuals from extended pedigrees (75 families, average size 16.48 people, range = 2-129). The sample was 62.90% female and had a mean age of 45.47 (SD = 14.64; range = 18-97 years). Individuals in this Genetics of Brain Structure and Function (GOBS) cohort have actively participated in research for over 18 years and were randomly selected from the community with the constraints that they are of Mexican American ancestry, part of a large family, and live within the San Antonio region (Knowles et al., 2014). All participants provided written informed consent before participating in any aspect of the study.

Neuropsychological Assessment

Each participant was required to complete a 90-minute neuropsychological test battery consisting of standard and computerized measures (Knowles et al., 2014; Glahn et al., 2007). From this battery, 7 measures taken from 6 neuropsychological tests were similar to those in the processing-speed model previously published by Knowles and colleagues (Knowles et al., 2012). Two of these measures were reaction times, one taken from the Emotion Recognition (Kohler et al., 2003) and Facial Memory tasks. These reaction time measures were chosen because they were normally distributed with few outliers. In addition we included the number and letter sequencing measures from the Trails A, and the Trails B, and verbal and semantic fluency measures; all of these tasks have been described previously (Knowles et al., 2014; Glahn et al., 2007).

Stasticial Analysis

Confirmatory Factor Analysis—One of the aims of the present study was to replicate a previously published model of processing-speed ability (Knowles et al., 2014). To this end, we took analogous measures in our sample and fit the model using confirmatory factor analysis in Mplus (Muthén & Muthén, 2011). Prior to model fitting, z-scores were computed and screened for outliers (z-scores ≥ 3.29 were removed). In order to minimize the impact of missing data on composite scores derived via factor analysis we imputed missing values using the mice package in R (van Buuren & Groothuis-Oudshoorn, 2011). Scores were imputed only for those subjects with less than 50% missing data. The imputation model was based on all available cognitive data plus age and sex. Imputation resulted in a complete dataset of 1291 individuals. In order to appropriately estimate standard errors and X^2 statistics during factor analysis, family structure was taken into account using the *cluster* command in Mplus. Each factor model was assessed in terms of both model fit and the strength and significance of the factor loadings. Given the large sample size a significant X^2, which is typically indicative of poor model fit, was attributed less weight than other fit statistics less biased by sample size (Kline, 2005). The X^2 is a reliable index of fit for models with 75-200 cases, after which it is almost always statistically significant (Kenny, 2003). Thus these additional fit statistics were also included: RMSEA, CFI, TLI and SRMR. For RMSEA (Root Mean Square Error of Approximation) a value which is below 0.05 is considered excellent fit. For CFI (Comparative Fit Index) and TLI (Tucker Lewis Index) a value >0.90 is indicative of good fit and of 0.95 excellent fit. For SRMR (Standardized Root

Mean Square Residual) a value below 0.10 is considered a good fit. For more information on any given fit index readers are referred to excellent resource on model fit by Kenny (Kenny, 2003). Once a factor model was established, factor scores were derived for each individual participant and saved for subsequent analysis.

Genotyping—Subjects were genotyped for approximately one million SNPs using Illumina HumanHap550v3, HumanExon510Sv1, Human1Mv1 and Human1M-Duov3 BeadChips, according to the Illumina Infinium protocol (Illumina, San Diego, CA). SNP loci were checked for Mendelian consistency utilizing SimWalk2 (Sobel & Lange, 1996). SNPs or samples exhibiting high calling rate failures or requiring excessive blanking (i.e., if <95% of the genotypes are retained) were eliminated from analyses. Missing genotypes were imputed according to Mendelian laws based on available pedigree data using MERLIN (Abecasis et al., 2002). Maximum likelihood techniques, accounting for pedigree structure, were used to estimate allelic frequencies (Boehnke, 1991). Estimates of allelic frequencies were formally tested and found to be in Hardy-Weinberg equilibrium. For linkage analyses, multipoint identity-by-descent (IBD) matrices were calculated based on 28,387 SNPs selected from the 1M GWAS panel as follows. Using genotypes for 345 founders, SNPs on each chromosome were selected to be at least 1kb apart, MAF >= 5%, and LD within a 100kb sliding window not exceeding |rho| = 0.15. The resulting selection averaged 7-8 SNPs/centimorgan. For each centimorgan location in the genome, multipoint IBD probability matrices were calculated using a stochastic Markov Chain Monte Carlo procedure implemented in the computer package, Loki (Heath, 1997). Each run lasted 100,000 iterations with a burn-in of 10,000 iterations. LM ratio = 0.8 (the LM ratio is parameter in Loki that sets the proportion of “meiosis” vs. “locus” updates, where the former guarantees irreducibility of the sample and the latter improves mixing). Map distances were calculated using the Haldane mapping function (Haldane, 1919).

Quantitative Genetic Analyses—All genetic analyses were performed in SOLAR (Almasy & Blangero, 1998). SOLAR implements a maximum likelihood variance decomposition to determine the contribution of genes and environmental influence to a trait by modeling the covariance among family members as a function of expected allele sharing given the pedigree. In the simplest such decomposition, the additive genetic contribution to a trait is represented by the heritability, or h^2, index. First, univariate variance decomposition analysis was applied to each individual measure, and then to each processing-speed factor derived from the confirmatory factor model. All traits were normalized using an inverse Gaussian transformation. Age, age^2, sex and their interactions were included as covariates and residualized traits were saved for subsequent bivariate polygenic, linkage and association analysis. Second, bivariate analysis was applied to pairs of processing-speed factors where the phenotypic covariance between the traits was decomposed into its genetic and environmental constituents to determine the extent to which they are influenced by shared genetic effects (e.g. genetic correlation, ρ_g).

Genome-Wide Linkage, Peak-Wide Association and Gene-Based Analyses—Quantitative trait linkage analysis was performed to localize specific chromosomal locations influencing processing-speed factors (Almasy & Blangero, 1998). Model parameters were

estimated using maximum likelihood. The hypothesis of significant linkage was assessed by comparing the likelihood of a classical additive polygenic model with that of a model allowing for both a polygenic component and a variance component due to linkage at a specific chromosomal location (as evidenced by the location-specific identity-by-descent probability matrix). The LOD score, given by the log10 of the ratio of the likelihoods of the linkage and the polygenic model, served as the test statistic for linkage. Genome-wide thresholds for linkage evidence were computed with correction for both the number of loci tested per genome. Briefly, using a method derived from (Feingold, Brown & Siegmund, 1993), genome-wide *p*-value thresholds were computed as a function of the average marker density (linkage SNPs per centiMorgan) and the mean recombination frequency given the complexity of the specific pedigrees used in this study. These *p*-values were then converted to LOD scores. In our case, a LOD of 1.69 is required for suggestive significance (likely to happen by chance less than once in a genome-wide scan) and a LOD of 2.9 is required for genome-wide significance.

Any genomic region meeting genome-wide significance for linkage was further assessed using association analysis of the processing-speed domain and the variants within the cM that yielded the greatest LOD because this maximal LOD is the most likely location of the causal variant. Association analyses were run in SOLAR (Blangero, Williams-Blangero & Mahaney, 1993). To control for multiple testing a Bonferroni correction was applied for the effective number of SNPs (Cheverud, 2001), alpha was adjusted for each additional cM added to the search space. In order to yield more information about the SNPs in the region they were annotated for location and functional effects based on RefSeq transcripts using Annovar (Wang, Li & Hakonarson, 2010) applied to the hg19 reference genome (Casper et al., 2018).

Gene-based association analysis were performed using MAGMA (de Leeuw et al., 2015). A gene-based statistic was calculated for the top-ranked gene using the *p*-value associated with each SNP from association analysis. We elected to run gene analysis on the summary SNP statistics rather than on the raw genotype data so that the complex family structure could be appropriately modeled in SOLAR. SNPs were assigned to genes based on their position relative to gene coordinates (35kb upstream and 10kb downstream window to capture possible regulatory regions) outlined by the NCBI 37.3 build. Linkage disequilibrium (LD) was accounted for using the raw genotype data. We evaluated whether any individual SNPs within genes associated with processing speed were eQTL using the online GTEx portal (The GTEx Consortium, 2015; GTEx Consortium et al., 2017).

Results

Processing-Speed Model

Table 1 shows the heritability estimates of the cognitive measures that were included in the processing-speed model. All of these measures were significantly heritable.

Our previously published three-factor confirmatory factor model (Knowles et al., 2012) was fit to the data (Figure 1). Although X^2 was significant (X^2_{11} = 43.70, p<.01), other fit indices

suggested that the model was a good fit to the data (RMSEA = 0.048 (95%CI = 0.034-0.063, p = .559), CFI = .99, TLI = .98, SRMR = .021). All factor loadings were significant at the p<.0001 level. The distribution of each factor score is shown in the supplemental material (Figures S1–3).

The heritability estimate for each factor derived from the model are shown in Table 1, all factor scores were moderately and significantly heritable. In general, these factors were more heritable than the individual tests that loaded on them. Both the phenotypic and genetic correlations were significant between all factor pairings. The correlations between both *Psychomotor Speed* and *Sequencing and Shifting* (ρ_p = 0.50, se = 0.02, $p = 2.33\times10^{-71}$; ρ_g = 0.70, se = 0.07, $p = 1.00\times10^{-11}$) and *Verbal Fluency* (ρ_p = −0.49, se = 0.02, $p = 4.61\times10^{-68}$; ρ_g = −0.76, se = 0.06, $p = 1.32\times10^{-14}$) were large, as was the correlation between *Shifting and Sequencing* and *Verbal Fluency* (ρ_p = −0.85, se = 0.01, $p = 9.31\times10^{-84}$; ρ_g = −0.94, se = 0.02, $p = 2.99^{-32}$). While the strength of the relationships between each factor was sizeable, the overlap was not complete, suggesting dissociable aspects of processing speed ability both at the phenotypic and genetic level. This was true even for the genetic correlation between *Shifting and Sequencing* and *Verbal Fluency*, which was high, but also significantly different from −1 ($p = 3.10\times10^{-05}$).

Univariate Linkage Analysis of Processing Speed Factors

Figure 2 shows the multipoint plot for the univariate linkage runs of each processing-speed factor. For Psychomotor Speed one genome-wide significant locus was observed on chromosome 3 at 150cM (LOD = 4.83), the same location had some influence on both Sequencing and Shifting (LOD = 0.41) and Verbal Fluency (LOD = 0.59). No genome-wide significant loci were observed for the other processing-speed factors. Suggestively significant LODS were observed for Sequencing and Shifting on chromosome 4 at 108 cM (LOD = 2.49) and for Verbal Fluency on chromosomes 7 at 90 cM (LOD = 2.57) and 8 at 144 cM (LOD = 2.36).

QTL-Specific Association and Gene-Based Analysis for Psychomotor Speed

The focal cM of the linkage peak (LOD = 4.83) for Psychomotor Speed spanned approximately 760kb (3:140884683..141644558). There were 266 variants in the GWA data with sufficient copies (MAC ≥ 5) in this region and the region contained 6 genes (Figure 3). First, univariate association analysis was applied to all variants under the peak for *Psychomotor Speed*. No SNP withstood a multiple testing correction (LD-adjusted Bonferroni-corrected $\alpha = 3.35\times10^{-04}$). Table 2 shows the top ten association results for all tested SNPs for Psychomotor Speed. Inspection of Table 2 shows that of the top-ten ranked SNPs for *Psychomotor Speed*, 1 SNP was located in the upstream region of the gene *RASA2*, 6 were located in introns of *RASA2*, one was a synonymous variant located in an exon of *RASA2*, and two were located intergenically between *ZBTB38* and *RASA2*. However, Table 2 also shows that of the top-ten variants associated with Psychomotor Speed nine were eQTLs for *ZBTB38* in thyroid, *ZBTB38* neighbors the gene *RASA2* (Figure 3).

We applied gene-based analysis to the association summary statistics for *Psychomotor Speed* for the six genes under the peak. The top-ranked gene was *RASA2* (Z = 2.90, p =

1.86×10^{-03}; Table 3) containing 51 SNPs and survived Bonferroni correction for the number of genes that were tested ($\alpha = 8.33\times10^{-03}$). Despite the top-ranked gene being *RASA2*, of those SNPs associated with RASA2 in this analysis 10 were eQTLs for *RASA2* and 10 were eQTLs for *ZBTB38* in thyroid and nerve tissues respectively (Table S1). These eQTL identifications suggest that *Psychomotor Speed* can be linked to both genes. Applying gene-based analysis to summary statistics from association analysis of *Sequencing and Shifting* and *Verbal Fluency* showed that the gene, *RASA2*, was not significantly associated with either *Sequencing and Shifting* ($Z = -0.01$, $p = 0.50$) or *Verbal Fluency* ($Z = 0.43$, $p = 0.33$).

Discussion

We investigated the genetic underpinnings of processing-speed ability using a combination of a multi-dimensional processing-speed model and genetic analysis in extended pedigree data. We replicated a previously published model of processing-speed ability from a different data set (Knowles et al., 2012), and using factor scores derived from that model, we identified a new genomic locus that influences a simple aspect of processing-speed ability, *Psychomotor Speed*, on chromosome 3q23. Furthermore, within the 3q23 locus we identified two genes *RASA2* and *ZBTB38* that were associated with *Psychomotor Speed* performance.

In general, processing speed is considered a unitary construct, measurable using individual —and interchangeable—tasks. However, processing speed, like most cognitive abilities, is probably better described as a multi-faceted or multi-dimensional construct (Posthuma & Gues, 2008; Chiaravalloti et al., 2003). The implication here is that while on the surface processing-speed impairment leads to decrements in performance on speeded cognitive measures and related real-life tasks, the origins of those impairments might be heterogeneous (Mathias et al., 2017; Rochat et al., 2013). This might easily be dismissed as an argument of semantics (Keefe & Harvey, 2015), except that when it comes to genetics, ignoring such complexities at the phenotypic level could muddy the waters when attempting to identify the polygenic architecture of complex traits. To this end we replicated a factor model of processing-speed ability (Knowles et al., 2012) comprising both simple (*Psychomotor Speed*) and complex (*Sequencing and Shifting* and *Verbal Fluency*) processing-speed factors, and used the factor scores from this model to interrogate the genome. The use of such a model is advantageous because, where each latent variable encapsulates the overlapping variance of all measures that load on it, it is in essence a multivariate approach which is more powerful than a univariate one when searching for genes (Schmitz, Cherny & Fulker, 1998). We would argue that this encapsulation of shared variance explains why the heritability of the factors was greater than that of the individual measures that loaded on them. More specifically, the factor score represents a what is shared between multiple individual measures rather than the multiple sources of variance captured by individual tests which include those that are not necessarily relevant to the construct of interest.

We found that the scores from all three processing-speed factors were moderately and significantly heritable. We identified a region of chromosome 3q23 that influenced *Psychomotor Speed* via univariate linkage analysis. No individual SNP met peak-wide

significance, but the majority of the top-ranked SNPs were in or near the gene *RASA2*. Gene-based association analysis within the focal point of the peak revealed that the gene *RASA2* was significantly associated with *Psychomotor Speed*. There was no evidence that *RASA2* influenced Sequencing and Shifting or Verbal Fluency. Gene-based analysis is a more powerful method than testing individual SNPs (Wang et al., 2011) since it allows converging evidence from multiple genetic variants from the same gene to be assessed, thus enabling detection of signal that might not be detected when focusing on individual SNPs (Sniekers et al., 2017). By testing the joint association of all the variants in a gene it is possible to identify effects comprising many weaker signals that would otherwise be overlooked (de Leeuw et al., 2015). Thus, while no individual SNP met peak-wide significance, the gene-based analysis allowed us to collapse the signal of the multiple variants in *RASA2*, which were also enriched in the top-ranked SNPs from the single variant analysis.

The gene *RASA2* (RAS p21 Protein Activator 2) is expressed in human brain (mean RPKM = 2.6 ± 0.38 (NCBI, 2016)), and particularly in the cerebellum and hypothalamus (Allen Institute for Brain Science). *RASA2* encodes a RAS protein, these proteins (a large family of GTP-binding proteins) are in control of pathways that control cellular signaling, including those responsible for growth, migration, adhesion, cytoskeletal integrity, survival and differentiation (Rajalingam et al., 2007). Activation of RAS signaling is tightly controlled because alterations in cellular proliferation have dire repercussions for normal cell growth. Indeed, RAS genes have been identified as oncogenes, with cancer occurring when there are defects in these signaling mechanisms (Downward, 2003). Approximately 20% of all tumors have undergone an activating mutation in one of the *RAS* genes (Downward, 2003; Bos, 1989). The gene RASA2 has been previously associated with the development of melanoma (Arafeh et al., 2015). In addition rare variation in RASA2 has been associated with Noonan syndrome (NS) (Chen et al., 2014). NS is the most common of several developmental disorders termed “RASopathies” caused by mutations in genes encoding RAS signaling pathway components (Chen et al., 2014; Rauen, 2013). NS occurs in familial and sporadic forms and is characterized by numerous physical features (e.g. facial and musculoskeletal abnormalities, short stature), increased risk for various diseases (e.g. hematological and oncological), as well as neurological, behavioral and cognitive issues (Romano et al., 2010). There is also an increased incidence of cognitive impairment and learning disability in individuals with NS (Sharland et al., 1992; van der Burgt et al., 1999). Interestingly, a subset of individuals with NS exhibit slowed speed of information processing and manual motor speed, and reduced dexterity (Pierpont et al., 2009; Wingbermuhle et al., 2012). These impairments in psychomotor speed have been suggested to be the most common neuropsychological deficit in individuals with NS (Pierpoint, 2016). Thus while variation in *RASA2* has not previously been explicitly associated with processing speed the results of the present study that it is an interesting and plausible candidate gene.

Several of the variants within the gene RASA2 were eQTLs affecting the expression of a neighboring gene *ZBTB38*, thus also implicating this gene in *Psychomotor-Speed* performance. The gene *ZBTB38* (zinc finger and BT domain containing 38) is expressed in human brain (RPKM = 7.3 ± 0.42 (NCBI, 2016)), and particularly in the cerebellum and thalamus (Allen Institute for Brain Science). This gene encodes a Kaiso-like methyl-CpG

binding protein that is an epigenetic regulator (Clouaire & Stancheva, 2008). It has been shown that the ZBTB38 protein represses the transcription of methylated DNA, at least in transcription assays (Filion et al., 2006; Sasai, Nakao & Defossez, 2010; Pozner et al., 2018). DNA methylation is an epigenetic mechanism that inhibits transcription (Bogdanovic & Veenstra, 2009). It is part of normal development, for example it is involved in X-chromosome inactivation (Bird, 2002). Methylated DNA sites recruit methyl-CpG binding domain proteins, for example ZBTB38, and establish silent chromatin, or regions of the chromosome that are not being actively transcribed (Bogdanovic & Veenstra, 2009). Unsurprisingly it has been shown that *ZBTB38* is important for genome stability (Miotto et al., 2014; Miotto et al., 2018). Variation in *ZBTB38* has been associated with prostate cancer (Kote-Jarai et al., 2011). It has also been associated consistently with stature in both cattle (Liu et al., 2013) and humans (Wang et al., 2013; Gudbjartsson et al., 2008; Lin et al., 2017). This gene has not been previously associated with either processing speed or general cognitive ability.

In the present study, we explored the genetic architecture of processing speed using our previously constructed model. We have shown previously that identifying genes that influence cognitive factors is more tractable than finding genes for either general intelligence or individual neuropsychological tasks (Knowles et al., 2014). The linkage and association findings presented in this manuscript highlight a novel genetic locus for *Psychomotor Speed*, a simple aspect of processing-speed ability. We also identified the gene *RASA2* within this locus, which was associated with *Psychomotor Speed* performance. Increased understanding of the genetic architecture of processing speed has implications for understanding the biologic underpinnings of intelligence, cognitive aging, and psychiatric disorders. Thus, the present study generates the testable hypothesis that *RASA2* is a potential candidate gene for cognitive enhancement, as well as a target for the amelioration of cognitive aging. *RASA2* may also be a putative candidate for neurological and psychiatric disorders for which processing-speed impairment is a key feature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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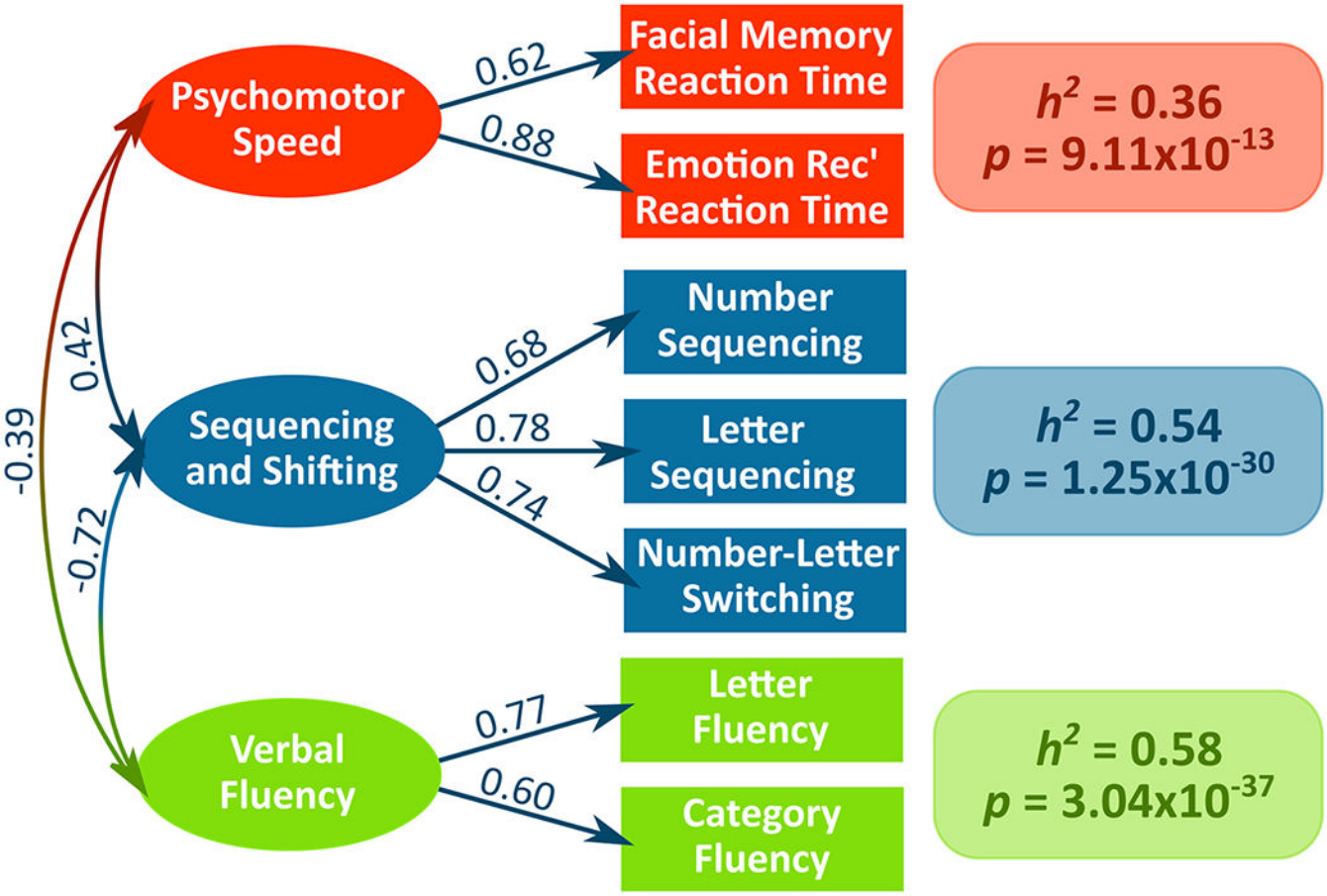

Figure 1.
Confirmatory factor model of processing-speed ability.

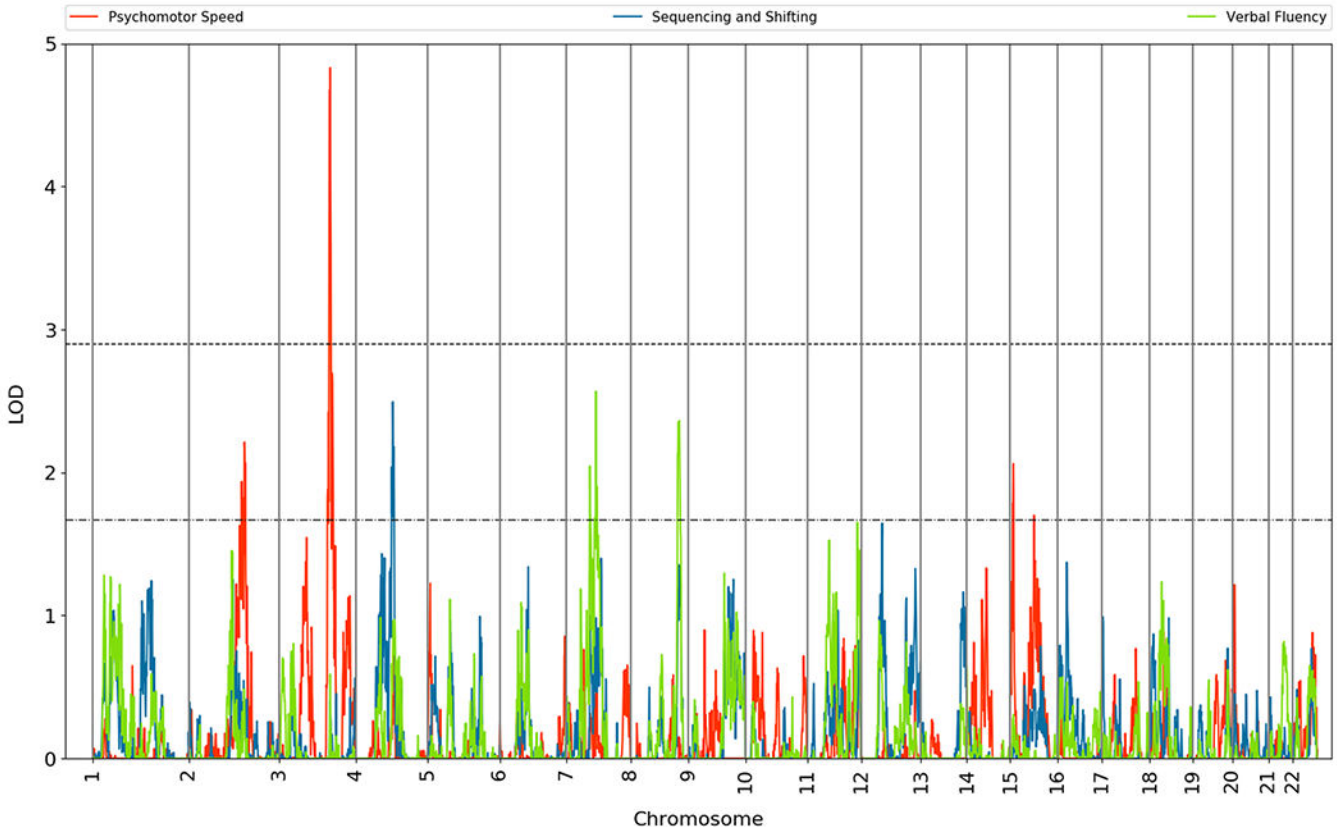

Figure 2.
Genome-wide multipoint plot of processing-speed domains.

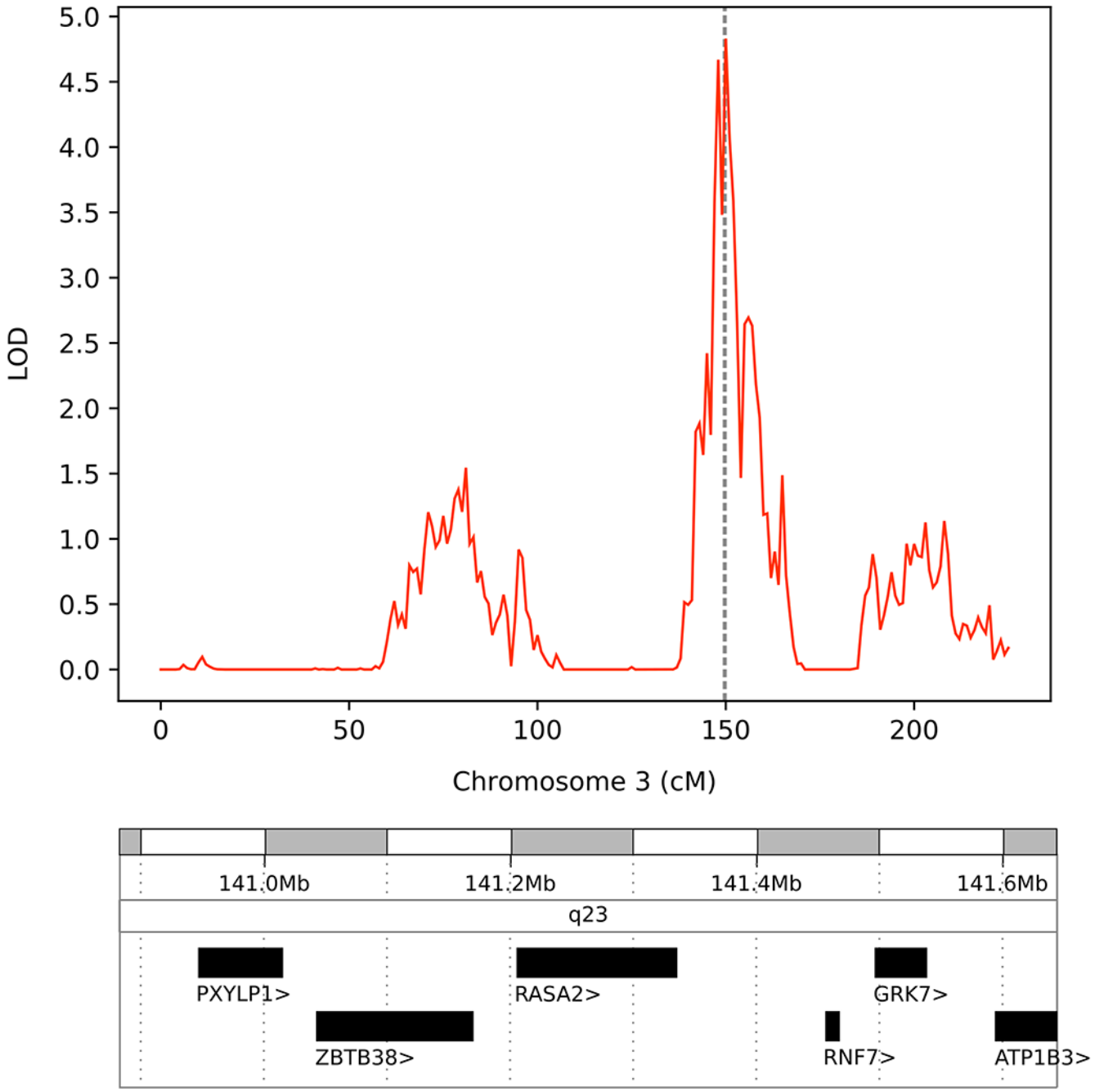

Figure 3.
Multipoint plot of Psychomotor Speed on chromosome 3 and genes falling within the 150cM region with the maximal LOD.

Table 1.

Heritability estimates (and standard errors and *p*-values) for individual cognitive measures and processing-speed domains.

Cognitive Measure	h^2 *(se)*	*p*-value	Cognitive Domain	h^2 *(se)*	*p*-value
Facial Memory RT	0.28 (0.06)	1.81×10^{-09}	Psychomotor Speed	0.36 (0.06)	9.11×10^{-13}
Emotion Recognition RT	0.32 (0.06)	4.23×10^{-10}			
Number Sequencing	0.22 (0.05)	1.00×10^{-07}	Sequencing and Shifting	0.54 (0.06)	1.25×10^{-30}
Letter Sequencing	0.31 (0.06)	1.88×10^{-11}			
Number-Letter Switching	0.56 (0.06)	1.34×10^{-33}			
Letter Fluency	0.49 (0.05)	2.31×10^{-28}	Verbal Fluency	0.58 (0.05)	3.04×10^{-37}
Category Fluency	0.36 (0.06)	5.29×10^{-15}			

Table 2.

Top-ten ranked peak-wide univarite association results for Psychomotor Speed.

rsid (basepair)	X^2 (*p*-value)	Function	(Closest) Gene(s)	Ref/Alt	GTEx eQTL (*p*-value)	MAC	MAF
rs3821712 (3:141205185)	10.34 (1.30×10^{-03})	Upstream	*RASA2*	C/T	*ZBTB38* (2.4×10^{-05})	1127	0.44
rs295323 (3:141327474)	10.11 (1.48×10^{-03})	Exonic (Synonymous)	*RASA2*	G/A	*ZBTB38* (1.1×10^{-05})	1103	0.43
rs9813177 (3:141212518)	10.00 (1.57×10^{-03})	Intronic	*RASA2*	A/G	*ZBTB38* (3.2×10^{-05})	1127	0.44
rs7632308 (3:141196260)	9.71 (1.83×10^{-03})	Intergenic	*ZBTB38;RASA2*	T/C	*ZBTB38* (2.2×10^{-05})	1109	0.44
rs7643837 (3:141209867)	9.46 (2.10×10^{-03})	Intronic	*RASA2*	T/C	*ZBTB38* (3.7×10^{-05})	1137	0.45
rs6785874 (3:141244816)	9.43 (2.14×10^{-03})	Intronic	*RASA2*	G/A	*ZBTB38* (2.3×10^{-05})	1140	0.45
rs6800122 (3:141249398)	9.29 (2.31×10^{-03})	Intronic	*RASA2*	C/T	*ZBTB38* (5.8×10^{-05})	1137	0.45
rs1366042 (3:141183944)	9.07 (2.60×10^{-03})	Intergenic	*ZBTB38;RASA2*	G/A	*ZBTB38* (4.9×10^{-05})	1114	0.44
rs6767158 (3:141228874)	8.83 (2.96×10^{-03})	Intronic	*RASA2*	C/T	*ZBTB38* (2.4×10^{-05})	1131	0.44
rs3821710 (3:141301451)	8.71 (3.16×10^{-03})	Intronic	*RASA2*	G/A	None	1083	0.43

Table 3.

Results of gene-based analyses for Psychomotor Speed.

Gene	Start	Stop	Number of SNPs	*Z*	*p*
RASA2	141170891	141344186	51	2.90	1.86×10^{-03}
ATP1B3	141560424	141655382	29	2.06	0.02
RNF7	141422051	141475645	23	1.31	0.10
GRK7	141462043	141545892	29	0.74	0.23
PXYLP1	140915682	141023486	47	0.07	0.47
ZBTB38	141008055	141178634	48	−0.05	0.52