

## ORIGINAL RESEARCH ARTICLE

# A functional polymorphism in the succinate-semialdehyde dehydrogenase (aldehyde dehydrogenase 5 family, member A1) gene is associated with cognitive ability

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**Succinate-semialdehyde dehydrogenase (SSADH) deficiency is a rare cause of learning disability. We have investigated SSADH to assess its contribution to cognitive ability in the general population in both case-control- and family-based analyses. Sequence analysis of SSADH revealed four changes affecting the encoded protein, only one of which had a minor allele whose frequency is even moderately common. We genotyped this functional polymorphism in 197 high-IQ cases, 201 average-IQ controls and 196 parent high-IQ offspring trios. The minor allele was significantly less frequent in high-IQ cases and was significantly less frequently transmitted by parents to high-IQ subjects than chance expectation. A previous study has shown that the minor allele encodes a lower activity enzyme than the major allele. These data suggest that higher SSADH activity is associated with higher intelligence across the general population. The effect is small, with each allele having an effect size translating to about 1.5 IQ points.**

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## Introduction

Individual performance across a range of cognitive functions, such as memory, spatial ability and verbal ability shows substantial covariance. Indeed, about 40% of the population variance of measures of these individual cognitive processes can be accounted for by a single general intelligence factor.<sup>1</sup> Multivariate genetic analyses indicate that this general intelligence factor is highly heritable, and that the overlap in the genes that influence variance in the individual cognitive processes is twice as great as the overall phenotypic overlap, with genetic correlations averaging about 0.80.<sup>1</sup> This implies that genes associated with one cognitive ability are highly likely to be associated with other cognitive abilities. These quantitative genetic findings make general intelligence an excellent target for molecular genetic research, as indicated in a recent special section of this journal,<sup>2</sup> which included a report of a direct association between normal variation in intelligence and a functional polymorphism in the Cathepsin D (CTSD) gene,<sup>3</sup> and a report of an indirect association (that is, based on linkage disequilibrium) with a

polymorphism in the cholinergic muscarinic 2 receptor gene that has not yet been shown to be functional.<sup>4</sup> These papers add to other recent reports of direct associations between cognitive abilities and functional polymorphisms in the catechol *O*-methyltransferase (COMT) gene<sup>5,6</sup> and the brain-derived neurotrophic factor gene.<sup>6</sup>

Much more is known about the molecular genetic basis of uncommon Mendelian genetic syndromes associated with cognitive and learning impairment than is known about the genes that influence the broader spectrum of ability. One example is a rare inborn error of metabolism known as succinate-semialdehyde dehydrogenase (SSADH) deficiency (OMIM 271980). SSADH (also known as aldehyde dehydrogenase 5 family, member A1; ALDH5A1, accession number NM\_001080) is required for degradation of  $\gamma$ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. SSADH deficiency leads to the accumulation of  $\gamma$ -hydroxybutyric acid and of GABA. The mechanisms underpinning cognitive impairment are uncertain in SSADH deficiency, but are believed to include neurotoxicity caused by this accumulation.<sup>7</sup> Recently, two rare loss-of-function mutations in SSADH have been shown to lead to SSADH deficiency in a small number of individuals.<sup>8</sup>

The degree of impairment resulting from SSADH deficiency is highly variable, from severe neurological

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impairment to mild developmental delay.<sup>9</sup> This led us to postulate that common sequence variants in the gene with less dramatic effects on the SSADH protein might influence cognitive ability across the broader spectrum of cognitive ability. Our interest was also fueled by the observation that the SSADH gene maps to a region of the genome (6p22), showing both genetic linkage and genetic association to the cognitive phenotype dyslexia.<sup>10</sup>

We used two different designs to test for an association between SSADH and intelligence in order to reduce the possibility of a false-positive association and to control for stratification: a case–control design and a transmission disequilibrium test (TDT) design consisting of parent–offspring trios.

## Materials and methods

### Subjects

The high-IQ cases and the average-IQ controls combine two U S Caucasian samples reported previously.<sup>11</sup> The 197 high-IQ cases have an average IQ greater than three standard deviations above the mean (ie an IQ greater than 145), and include some of the highest-IQ individuals in the US.<sup>12,13</sup> The 201 controls were selected for IQs between 90 and 110, and had an average IQ of 102. As the average IQs are increasing,<sup>14</sup> it is likely that some of these individuals with average IQs according to standardization data for IQ tests in fact have IQs below average. Details of subject selection have been published previously.<sup>11</sup> Although individuals in the case and control samples are all Caucasian, US Caucasian samples are genetically heterogeneous, and thus it is possible that ethnic stratification could nonetheless produce spurious associations. For this reason, our design included a sample of 196 parent–offspring trios that included individuals with IQ scores greater than 145, whose biological mother and father were available to provide DNA. These parent–offspring trios provide a within-family TDT that protects against population stratification as a possible source of quantitative trait loci (QTL) associations. In all, 60% of the offspring from the parent–offspring trios were included as cases in the case–control comparison, and therefore the case–control sample and parent–offspring trio sample are not strictly entirely independent. However, the case–control study is a between-family analysis, whereas the parent–offspring trio analysis is a within-family analysis, and each could yield completely different results even if all the cases included in each analysis were identical. The project was approved by the appropriate institutional review boards, and informed consent was obtained from all participants.

### Measures

Controls were selected with IQ scores between 90 and 110, using the Weschler Intelligence Scale for Children – Revised<sup>15</sup> or the Wechsler Adult Intelligence Scale-III.<sup>16</sup> For 51 of the high-IQ cases, the same measures were used to identify individuals with IQs

greater than 130. The rest of the high-IQ cases and all of the high-IQ offspring in the parent–offspring trios were obtained initially from a nationwide testing program that screened individuals, using the Scholastic Aptitude Test college entrance exam.<sup>12</sup> Their IQ scores have been estimated to exceed 160. Details about the measures have been published previously.<sup>11</sup>

### Laboratory procedures

DNA was extracted either from permanent cell lines established from blood or from buccal swabs.<sup>17</sup> Mutation analysis was performed using well-published and validated protocols based on denaturing high-performance liquid chromatography and sequencing as described.<sup>18</sup> Allele frequency estimation in DNA pools was performed as described previously.<sup>19</sup> For genotyping the CAC(H)538CAT(Y) variant (described below), PCR products were amplified using primers (F) gccgtgttacggagacatcatc; (R) ttccacatccagcaaaagca and digested with 1 U of *BseG1* at 55°C overnight. In the forward primer sequence, the spurious base C (underlined and four bases upstream from the polymorphism) has been introduced instead of T, which is the correct genomic sequence. This forms a *BseG1* recognition site only when the C allele is present at the polymorphic locus.

### Analysis

The  $\chi^2$  test was used to compare the genotypic and allelic frequencies of cases and controls. For the parent–offspring trios, the number of transmitted and nontransmitted target alleles was tested using the TDT.<sup>11</sup> In data simulation and analytic power analyses, we systematically varied effect size and QTL and marker allele frequency. We assumed a normally distributed trait with a sibling correlation of 0.4. For the case–control samples used in the present study, power estimates to detect QTLs that account for 5%, 2.5 and 1% of the variance are, respectively, 100, 100 and 98%, with alpha set at 0.05 when marker and QTL frequencies are 0.25 and the marker is assumed to be the QTL (ie the association between the marker and the QTL is assumed to be 1.0).

## Results

We used standard molecular genetic protocols<sup>18</sup> to screen the SSADH gene for sequence variation in 15 unrelated UK Caucasian individuals with normal intelligence. We screened 2401 bases of sequence comprising all 1608 bases corresponding to protein coding sequence, and a total of 793 bases of untranslated and flanking untranscribed (intronic) sequence. We did not screen the promoter or other putative elements that might affect the amount of expression of SSADH mRNA because, in a previous screen of CNS-expressed genes, we found no evidence that SSADH mRNA expression is commonly influenced by sequence variation in these regions, at least in human brain.<sup>20</sup>

We found four variants that are predicted to change the amino-acid sequence of SSADH. Two were in exon 3 (CAC(H)538CAT(Y); CCG(P)545CTG(L)), and one in each of exons 4 (GCC(A)709TCC(S)) and 6 (GTG(V)961ATG(M)). As the aim of our study is to identify common variants that affect cognitive ability across the general population, we first sought to estimate allele frequencies. Analysis of pooled DNA from 368 UK Caucasian blood donor controls revealed that the least common (or minor) form of each allele was undetectable for all but the first of these. In our hands, this means that the minor allele frequency is less than 3%. Both variants in exon 3 have recently been reported in an independent study.<sup>7</sup> However, in that study, four copies of the minor allele at variant CCG(P)545CTG(L) were found in 54 chromosomes. Given the discrepancy in the estimated frequency with our own pooled data, we individually genotyped this polymorphism in 168 chromosomes from Caucasian control subjects of normal IQ. The minor allele was rare, with a frequency of 1.2%.

Thus, we focused on the CAC(H)538CAT(Y) SNP in exon 3. This results in a change in amino-acid number 180 from a common histidine (H) to a tyrosine (Y) in the rarer form. This particular polymorphism has been reported to have functional consequences, with *in vitro* studies, suggesting that the 180Y protein encoded by the T allele has 82% of the enzyme activity of the 180H protein encoded by the C allele.<sup>21</sup> Given that SSADH deficiency is associated with cognitive impairment, we postulated that the lower SSADH activity T allele might be associated with lower cognitive ability, and, conversely, that the high-activity C allele would be more common in individuals with exceptionally high IQ than in the normal IQ population.

To test this hypothesis, we used two association study designs. In order to reduce the possibility of a false-negative result, we first used a case-control design as this generally has greater power to detect association than the second, family-based design. Table 1 shows genotypic and allelic frequencies for the high-IQ cases and average-IQ controls. All

**Table 1** Case (high-IQ) vs control (average-IQ) analysis

	Average-IQ controls		High-IQ cases		$\chi^2$	P-value
	%	N	%	N		
<i>Genotypes</i>						
CC	42.7	79	55.8	96	12.9	0.002
CT	44.3	82	40.7	70		
TT	13.0	24	3.5	6		
Total	100.0	185	100.0	172		
<i>Alleles</i>						
C	64.9	240	76.2	262	10.9	0.001
T	35.1	130	23.8	82		
Total	100.0	370	100.0	344		

**Table 2** TDT for parent-offspring trios with high-IQ offspring

Transmissions (allele C)		Nontransmissions (allele C)		$\chi^2$	P-value
%	N	%	N		
59.3	80	40.7	55	4.63	0.03

genotypes are in Hardy-Weinberg equilibrium. Both genotypic ( $P=0.002$ ) and allele distributions ( $P=0.001$ ) differ significantly between the cases and controls. As predicted, the high-activity C allele was significantly more common in the high-IQ cases than in the average-IQ controls.

Case-control analysis potentially runs the risk of false positives arising from poor genetic matching of cases and controls. However, we have previously shown using allele frequencies from multiallelic simple sequence repeat markers relatively evenly distributed throughout the genome that our samples are well matched,<sup>11</sup> an analysis that we have now extended to 1154 markers (data not shown). Thus, the observed association is unlikely to be attributable to poor case and control matching. Nevertheless, as an extra precaution, and as a replication of the result using a different design and data set, family-based association analysis was also performed. A sample of parent-offspring trios was created by obtaining DNA from both biological parents of 196 high-IQ individuals. The parent-offspring trios provide a within-family design that is completely robust to inadequate genetic matching,<sup>22</sup> although the penalty is often a considerable reduction in power.

Of the 196 trios, 104 families were informative for a TDT in that at least one parent was heterozygous. A total of 60 families were noninformative, and for 32 families at least one individual could not be genotyped despite repeated PCR attempts. The TDT results (Table 2) indicate that the C allele is transmitted from parent to offspring more frequently than the chance expectation of equal probabilities for transmission and nontransmission ( $P=0.03$ ).

## Discussion

Both our case-control- and family-based data sets provide significant evidence for association between a functional SNP in SSADH and general intelligence. The high-IQ group had a significantly greater frequency of the high-activity allele than the average-IQ group, and *post hoc* analysis of genotypes shows that the high-IQ group also had significantly fewer homozygotes for the low-activity allele ( $\chi^2=10.4$ , 1 df,  $P=0.001$ ). Excess transmission of the high-activity allele was confirmed in the family analysis showing that this result is not attributable to stratification. In terms of biological plausibility, the association

between high-activity alleles and high IQ is as we predicted from previous findings that rare forms of SSADH deficiency are associated with lower cognitive ability.

Although it has been proposed that one of the mechanisms for the neurological and cognitive impairments observed in severe SSADH deficiency is neurotoxicity,<sup>7</sup> there may be others. GABA plays a pervasive role in acute synaptic inhibition and also influences the development of long-term potentiation (LTP).<sup>23–26</sup> Even in the absence of neurotoxicity, GABA is therefore well placed to contribute to information processing, memory acquisition, learning and other cognitive processes.<sup>27</sup> Interestingly, the learning deficits in an animal model of neurofibromatosis type I have recently been attributed to deficits in LTP, resulting from increased GABA-mediated inhibition.<sup>28</sup> Moreover, as the LTP and learning deficits were reversed by GABA antagonist, the impairment is not likely to be attributable to neurotoxicity. This finding is again compatible with our observation of association between higher activity SSADH alleles (which are expected to reduce GABA) and higher general intelligence.

The significant evidence for association in our case–control- and family-based samples, our prior evidence against poor matching of our case–control sample, our strong prior hypothesis based on SSADH deficiency, and our use of a functional SNP are all pointers to our data representing a true association. Nevertheless, fully independent replication is required to claim definitively that the SSADH locus influences normal variation in cognitive ability.<sup>29</sup> The effect sizes of most QTL are likely to be very small, with each locus accounting for perhaps less than 1% of the variance. Most association studies have very low power to detect effect sizes of this magnitude reliably.<sup>30–32</sup> Since our design compares high-IQ cases with average-IQ controls, it is difficult to estimate a precise population effect size for the association between SSADH and intelligence. However, we have estimated that in our design, the approximately 10% allele frequency difference between high and average IQ subjects corresponds to a 1% population effect size.<sup>11</sup> This translates to about 1.5 IQ points because IQ scores are standardized to have a population mean of 100 with a standard deviation of 15. In other words, in an unselected population, the average IQ of individuals with one copy of the C allele will be about 1.5 IQ points greater than the average IQ of individuals with no copy of the C allele. Assuming that QTLs operate continuously throughout the distribution, an unselected sample of 1000 will be needed to reach 80% power to replicate an association with this effect size at  $P=0.01$  even allowing for a one-tailed test.<sup>33</sup>

Higher power can be obtained not only from increased sample size, but also by selecting subjects from the extremes of the distribution because most of the power of an association comes from these subjects, assuming that QTLs have a continuous effect

throughout the distribution. For this reason, we selected cases from the extreme of the intelligence distribution. The average IQ of our cases is more than three standard deviations above the population mean, and therefore these subjects represent the highest 0.15% of the IQ distribution. Put another way, our high-IQ sample represents the high end of an unselected sample of more than 100 000 subjects. As a consequence, we estimate that our case–control study has 98% power to detect an association of this magnitude.<sup>11</sup>

We selected cases from the high extreme rather than the low extreme of the intelligence distribution, not because our goal is to find genes for genius, but because it is our hypothesis that extremely high ability requires the presence of a high proportion of alleles that are beneficial for cognitive ability. We also think it is implausible that high cognitive ability is conferred by rare alleles with Mendelian effect sizes. In contrast, low ability can be brought about not only by alleles with small detrimental effects on intelligence, but also by rare mutations of large effect size, nonheritable chromosomal abnormalities and by idiosyncratic environmental events.<sup>1</sup> Thus, our hypothesis is that QTLs will be associated with intelligence throughout the distribution, but this is likely to be less so at the lowest end of the distribution. In support of this hypothesis, severe mental retardation is less heritable than either the categorical phenotype of mild mental retardation or the quantitative IQ phenotype across the normal range.<sup>34</sup>

Genetic research on general intelligence has important implications for neuroscience. Neuroscience has assumed that cognitive functioning is modular, whereas general intelligence suggests that the brain functions as an integrated whole.<sup>35</sup> Magnetic resonance imaging studies are beginning to find general structural<sup>36</sup> and functional<sup>37</sup> correlates of general intelligence in the brain. Identifying genes responsible for the high heritability of general intelligence will provide windows through which we can view these brain pathways between genes and cognition.<sup>38</sup> Our study suggests that variation in GABAergic neurotransmission might play a key role in IQ differences in the population, and that genetic variation in other genes encoding relevant proteins, such as biosynthetic and catabolic enzymes, receptors and signal transducers might contribute to the high heritability of this trait. Such a key role for GABAergic neurotransmission in many cognitive processes is perhaps to be expected given that its anatomical ubiquity and its role as the major inhibitory neurotransmitter in the CNS.

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