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CDH13 is associated with working memory performance in attention deficit/hyperactivity disorder

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Different analytic strategies, including linkage, association and meta-analysis support a role of *CDH13* in the susceptibility to attention deficit/hyperactivity disorder (ADHD). *CDH13* codes for cadherin 13 (or H-cadherin), which is a member of a family of calcium-dependent cell–cell adhesion proteins and a regulator of neural cell growth. We tested the association between *CDH13* on three executive functioning tasks that are promising endophenotypes of ADHD. An adjusted linear regression analysis was performed in 190 ADHD-affected Dutch probands of the IMAGE project. Three executive functions were examined: inhibition, verbal and visuo-spatial working memory (WM). We tested 2632 single nucleotide polymorphisms (SNPs) within *CDH13* and 20 kb up- and downstream of the gene (capturing regulatory sequences). To adjust for multiple testing within the gene, we applied stringent permutation steps. Intronic SNP rs11150556 is associated with performance on the Verbal WM task. No other SNP showed gene-wide significance with any of the analyzed traits, but a 72-kb SNP block located 446 kb upstream of SNP rs111500556 showed suggestive evidence for association (*P*-value range 1.20E-03 to 1.73E-04) with performance in the same Verbal WM task. This study is the first to examine *CDH13* and neurocognitive functioning. The mechanisms underlying the associations between *CDH13* and the clinical phenotype of ADHD and verbal WM are still unknown. As such, our study may be viewed as exploratory, with the results presented providing interesting hypotheses for further testing.

Keywords: Attention deficit hyperactivity disorder, *CDH13* gene, executive functioning, haplotype analysis, working memory

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Multiple studies point the influence of genetic factors in the etiology of attention deficit/hyperactivity disorder (ADHD; heritability ~70%) (Faraone *et al*. 2005; Nikolas *et al*. 2010). Its etiology is complex: combinations of genetic factors with small effect size interacting with each other and with environmental factors seem to contribute (Faraone *et al*. 2005). So far, only a small part of the genetic component of the complex clinical phenotype of ADHD has been explained (Franke *et al*. 2009). With the recent advent of genome-wide association studies (GWAS), the identification of new genes for multifactorial diseases and traits has become very successful (Manolio *et al*. 2008). However, the performance of GWAS in the psychiatric disorders, including ADHD, has been particularly poor (Franke *et al*. 2009; Manolio *et al*. 2009). One of the reasons probably is the largely suboptimal nature of the clinical psychiatric phenotypes, which are based on a categorization of symptom clusters with no proven biological significance.

Endophenotypes, heritable traits that are associated with a disorder, are hypothesized to be more suitable for detecting risk genes than the clinical phenotypes because they are genetically less complex by being etiologically closer to disease genes (Aron *et al*. 2005; Gottesman *et al*. 2003). Systematic reviews and meta-analyses indicate that response inhibition and both verbal and visuo-spatial working memory (WM) are impaired in subjects with ADHD (Oosterlaan and Sergeant 1998; Oosterlaan *et al*. 1998; Willcutt *et al*. 2005). We and others have found similar impairments in unaffected siblings of ADHD probands and significant between-sibling correlations, indicating these measures to be useful as endophenotypes of ADHD (McInnes *et al*. 2003; Rommelse *et al*. 2008b,d).

ADHD linkage and association studies position Cadherin 13 (*CDH13*; OMIM = 601364) as an interesting candidate gene for ADHD (Franke *et al*. 2009). In a recent ADHD GWAS, single nucleotide polymorphism (SNP) rs6565113, an intronic SNP in *CDH13*, was found to be associated with symptom

count variables (Franke *et al*. 2009; Lasky-Su *et al*. 2008). Moreover, *CDH13* is located in the only genome-wide significant locus identified in a meta-analysis of linkage studies using ADHD-affected status as a phenotype (Asherson *et al*. 2008; Zhou *et al*. 2008) and a SNP near this gene also is part of the top-25 in the ADHD-affected status GWAS (Neale *et al*. 2008). A meta-analysis of four ADHD GWAS also implicated the *CDH13* gene in ADHD (Neale *et al*. 2010).

CDH13 codes for cadherin 13, a member of a family of calcium-dependent cell–cell adhesion proteins (Patel *et al*. 2003) and a regulator of neural cell growth. The broad distribution of H-cadherin in midbrain and telencephalon suggests that it may play an important role in building and maintaining neural circuitry (Takeuchi *et al*. 2000).

In this study, we aimed to examine the relationship of *CDH13* with selected neurocognitive endophenotypes of ADHD and evaluate the association with variation in three tasks of executive functioning in ADHD-affected children from the Dutch subsample of the International Multicentre ADHD Genetics (IMAGE) project (Kuntsi *et al*. 2006).

Methods

Participants

The participating Dutch ADHD-affected probands were part of a larger sample of the International IMAGE study, which were also administered to neurocognitive tasks. This is an international collaborative study in seven European countries (Belgium, Germany, Ireland, Spain, Switzerland, the Netherlands and the United Kingdom) and Israel that aims to identify genes that increase the risk for ADHD using linkage and association strategies. Ethical approval for the study was obtained from National Institutes of Health recognized local ethical review boards and all families gave written informed consent prior to participation. All participants were aged 5–17 and of European Caucasian descent. Exclusion criteria included IQ < 70, presence of autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. Details of the sample collection for this study and screening procedures are described elsewhere (Brookes *et al*. 2006; Kuntsi *et al*. 2006). In short, the children were screened with the following rating scales: parent and teacher Conners' long version rating scales (Conners *et al*. 2003) and the Strength and Difficulties Questionnaire (Goodman 2001). Only clinical cases with an average *T*-score of the DSM-IV total symptom score (*N*-scale) greater than 63 on the Conners scales and scores >90th percentile on the SDQ-hyperactivity scale were recruited into IMAGE. Subsequently, the clinical diagnosis of the probands was verified with the *Parental Account of Childhood Symptoms, PACS* (Taylor *et al*. 1986). PACS is a semi-structured, standardized, investigator-based, parent-informed interview developed as an instrument to provide an objective measure of children's behavior. A standardized algorithm for PACS was applied to all raw PACS data to yield a diagnosis based on operational DSM-IV criteria for ADHD.

Neuropsychological measures

The participants were tested at one of the three sites (Karakter Child and Adolescent University Centre in Nijmegen, Accare Child and Adolescent University Centre Groningen or at the Vrije Universiteit in Amsterdam). Testing required approximately 2–3 h per child and took place in a quiet test room by experienced child and adolescent psychologists and trained undergraduate students. The same protocol at each site was used to reduce variability in instructions. The child and adolescent psychologists and trained undergraduate students were trained by the same chief investigators and every person who applied the test was given a code. During data-cleaning, we checked for extreme outliers which could be because of wrong administration or computer problems. Siblings of the same family were tested simultaneously. The administration of neuropsychological tests was counterbalanced to rule out possible effects of fatigue on the tests. Psychostimulants (e.g. methylphenidate) were required to be withdrawn for at least 2 days prior to neurocognitive assessment, as they may positively influence a variety of neuropsychological functions (Kempton *et al*. 1999). The withdrawal of other medication was carried out depending on plasma half life.

The three measures investigated in this work are the stop signal reaction time and performance on Visuo-Spatial Sequencing and Digit Span backwards. The tasks have been fully described elsewhere (Rommelse *et al*. 2007a,b,c; Rommelse *et al*. 2008b,d). In short, The *Stop Task* aims to measure motor inhibition of an ongoing response (Logan *et al*. 1984). Go-trials consisted of a drawing of a plane that was either pointing to the right or to the left (Scheres *et al*. 2006). Children pressed a response button that corresponded to the direction of the stimulus as quickly and as accurately as possible. Stop-trials were identical to the go-stimulus, but a stop-signal was presented (drawing of a cross that was superimposed on the plane). During the stop-signal trials, children were required to withhold their response. The latency of the stop-process, the stop signal reaction time (SSRT), we used as the independent variable in the current analysis.

The *Visuo-Spatial Sequencing* task was used to measure accuracy of visuo-spatial WM (Rommelse *et al*. 2008c). Nine circles were symmetrically organized in a square (3 × 3). On each trial, a sequence of circles was pointed at by a computer-driven hand. Children were instructed to replicate the exact same sequence of circles, by pointing to them with the small, self-driven hand. Difficulty increased with the number of targets to remember and the complexity of the spatial pattern. The dependent measure we used was the total number of correct targets in the correct order.

A subtest of the WISC-III or WAIS-III, *Digit Span* (*DS*), was used to measure verbal WM (Wechsler 2000; Wechsler 2002). It has two presentations, DS-Forward and DS-Backward, the latter of which is a robust indicator of executive function, requiring the manipulation of information in memory. Forward digit span requires the individual to store and reproduce a digit sequence in its correct serial order, where the number of digits to be remembered is progressively increased over successive trials. Children were instructed to reproduce sequences as accurately as possible. In the backward condition, the child repeated the numbers in the opposite order. The highest number of digits recalled in the backward condition (maximum span backwards) was used as the dependent variable, because this aspect of the task places highest demand on the WM system.

A Van der Waerden transformation was applied (SPSS version 16) to the performance-derived variables for each task for normalization and standardization purposes. The *z*-scores of the performance measures on Digit Span and Visuo-Spatial Sequencing were mirrored, so that all dependent measures would have the same meaning, with a higher score reflecting a worse performance.

DNA collection, genotyping and association analysis

Directly after collection, blood samples were sent to Rutgers University Cell and DNA Repository, NJ, USA, where DNA was extracted from part of the blood or from immortalized cell lines. Details of the genotyping and data cleaning process have been reported elsewhere (Neale *et al*. 2008). In short, genome-wide genotyping was performed by Perlegen Sciences using the Perlegen platform. The Perlegen Array has 600 000 tagging SNPs designed to be in high linkage disequilibrium (LD) with untyped SNPs for three HapMap populations (CEU, YRB and CHB/JPN). Genotype data cleaning and quality control procedures were performed by The National Center for Biotechnology Information (NCBI) using the GAIN QA/QC Software Package (version 0.7.4) developed by Gonçalo Abecasis and Shyam Gopalakrishnan at the University of Michigan. Data were excluded on the basis of the following quality control metrics: (1) call rate < 95%; (2) gender discrepancy; (3) per-family Mendelian errors > 2; (4) sample heterozygosity < 32%; (5) genotype call quality score cut-off < 10; (6) a combination of SNP call rate and minor allele frequency (MAF) [(a) 0.01 ≤ MAF < 0.05 and call rate ≥ 99%; (b) 0.05 ≤ MAF < 0.10 and call rate ≥ 97% and (c) 0.10 ≥ MAF and call rate ≥ 95%]; (7) Hardy–Weinberg equilibrium *P*-value < 0.0001 and (8) duplicate

sample discordance. With this filtering, 438 784 SNPs were retained in the final dataset.

To increase coverage in the targeted genomic areas, we used the imputation approach implemented in MACH software (http://www.sph.umich.edu/csg/yli/mach/download/) and imputed Hapmap II release 22 genotypes into our dataset. The imputed data underwent an extra QC step in which SNPs with an imputation score (RSQR in MACH) < 0.3 and MAF < 0.05 were excluded. After this step, we ended up with a total of 2 182 904 SNPs across the genome. Genotypes for the *CDH13* gene were extracted from this SNP set. Genotypes and neuropsychological measures were available for 190 ADHD-affected children.

Descriptive information on age, gender, Conner's scores and the three measures investigated was analyzed using SPSS v16 for windows. Association for the QC-approved 190 datasets was performed using the linear regression option in PLINK v1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/) adjusting by age and gender. We tested 2632 SNPs within *CDH13* and 20 kb up- and downstream of the gene (aiming to capture many of the relevant regulatory sequences that might be involved with the *CDH13* gene). To adjust for multiple testing, we ran 10 000 max(*T*) permutation tests for all SNPS using the -mperm command in PLINK and used a threshold for significance = 0.05 for the empirical *P* value. This is achieved by comparing the observed test statistic against the maximum of all permuted statistics for each replicate. The *P*-value now controls for multiple comparisons because it indicates the probability of detecting a test statistic this large, given the total number of tests performed.

We also performed a haplotype analysis for the *CDH13* SNPs. Given the analytical limitations of estimating haplotypes for 2632 SNPs, we restricted our analysis to SNP rs11150556 and its 10-kb flanking region. Haplotypes were estimated using the 'haplo.em' functions implemented in the haplo.stats package (Schaid *et al*. 2002). Haplotype association analyses were carried out in a 3-SNP sliding window design scanning the effect of the selected *CDH13* SNPs using the haplo.score.slide function implemented in haplo.stats. This approach allows adjustment for covariates. This analysis was corrected for multiple testing by applying the simulate = TRUE parameter in haplo.score.slide (Schaid *et al*. 2002).

Results

A total of 238 ADHD children were available in our study. Complete data: performance on the WM tasks and the inhibition task, and SNP genotypes, were available for 190 ADHD-affected probands of the Dutch IMAGE sample. Table 1 shows the descriptive statistics of our study sample including the performance measures on WM tasks, the SSRT and the clinical ADHD variables. A total of 98.7% of our sample was affected with the ADHD combined subtype and 84.9% was male.

Table 1: Descriptive information of the study group

Dutch IMAGE sample	
Probands (*n*)	238*
% combined ADHD type	98.7
Mean Inattention Conner's Score (SD)	71.12 (8.43)
Mean Hyperactive-Impulsive Conner's Score (SD)	79.11 (9.25)
Mean Verbal working memory Task Score (SD)	0.034 (0.86)
Mean Visio-spatial working memory Task Score (SD)	0.123 (0.86)
Mean Inhibition Task Score (SD)	0.069 (1.00)
Mean age in years (SD)	11.99 (2.50)
% males	84.90

*One hundred and ninety children have available GWAS data.

Table 2 shows the correlation measures between the ADHD variables and the three measures investigated: as expected, the Conner's Hyperactive/Impulsive and the Conner's Inattentive scores showed the highest correlation (0.486, $P < 0.01$). The correlation between the neurocognitive endophenotypes of ADHD ranged from 0.405 to 0.261, *P* value <0.01. Interestingly, the correlations between the verbal WM task and ADHD were low and non-significant (Table 2).

All SNPs showing association with at least one neurocognitive task at uncorrected *P*-values <1.00E-02 (1 df linear test from the – linear command in plink) plus SNPs associated with ADHD status from the meta-analysis of Neale *et al*. (2010) as well as SNP rs6565113 associated with ADHD quantitative phenotype (Lasky-Su *et al*. 2008) are shown in Table 3. Analysis of the 2632 *CDH13* SNPs identified SNP rs11150556 to be gene-wide significantly associated with performance on the Verbal WM task (after 10 000 Max(*T*) permutations). Carriers of the C/C genotype showed a significantly worse performance

Table 2: Correlation between working memory tasks and ADHD scores and symptom count

Trait		Conner's Hyperactive/ Impulsive Score	Verbal working memory Task	Visio-spatial working memory Task	Inhibition Task	Hyperactive-impulsive symptom count	Inattentive symptom count
Conner's Inattentive Score	ρ (*N*)	**0.486**** (238)	0.27 (238)	0.24 (238)	−0.036 (210)	−0.080 (237)	**0.174**** (237)
Conner's Hyperactive-Impulsive Score	ρ (*N*)		−0.68 (238)	−0.064 (238)	**0.183**** (210)	**0.226**** (237)	0.022 (237)
Verbal working memory Task	ρ (*N*)			**0.405**** (238)	**0.261**** (210)	0.103 (237)	−0.040 (237)
Visio-spatial working memory Task	ρ (*N*)				**0.238**** (210)	**0.104*** (237)	−0.66 (237)
Inhibition Task	ρ (*N*)					0.039 (209)	−0.24 (209)
Hyperactive-impusive symptom count	ρ (*N*)						**0.155*** (237)

*Correlations significant at the 0.05 level (in bold).
**Correlations significant at the 0.01 level (in bold).

Table 3: Association between SNPs in *CDH13* and working memory in ADHD-affected children

SNP rs number	Position on chromosome 16 in BP	MAF	*P* inhibition task	*P* visio-spatial working memory task	*P* verbal working memory task	Emp *P* verbal working memory task
rs16957848	81200541	0.07303	9.48E-02	**6.25E-03**	2.67E-01	NS
rs12922394	81229828	0.05277	**7.89E-03**	9.52E-01	2.22E-01	NS
rs12444015*	81254805	0.3012	9.00E-02	4.35E-01	5.44E-01	NS
rs9936363*	81264849	0.07569	8.80E-01	8.00E-01	5.80E-01	NS
rs8054295*	81267473	0.07676	9.97E-01	8.95E-01	5.41E-01	NS
rs4081995*	81271375	0.1429	7.88E-01	5.82E-01	6.71E-01	NS
rs8048202*	81273739	0.2127	7.82E-01	5.70E-01	7.17E-01	NS
rs8055389*	81275531	0.1333	5.95E-01	7.80E-01	4.32E-01	NS
rs8060937*	81277337	0.1226	8.30E-01	9.96E-01	6.19E-01	NS
rs13334902*	81280799	0.1354	8.59E-01	7.59E-01	5.80E-01	NS
rs12932203*	81281593	0.1354	8.59E-01	7.59E-01	5.80E-01	NS
rs13336758*	81283227	0.1349	8.59E-01	7.59E-01	5.80E-01	NS
rs7195110	81283985	0.4035	**1.88E-03**	4.26E-01	6.87E-01	NS
rs1015972	81289305	0.4392	**6.16E-03**	1.65E-01	2.89E-01	NS
rs10514564	81298757	0.3726	**7.05E-03**	4.90E-01	2.18E-01	NS
rs12444845	81308855	0.08209	2.33E-01	7.37E-02	**9.37E-04**	NS
rs9936126	81310332	0.08475	1.99E-01	9.49E-02	**6.20E-04**	NS
rs1870843	81316815	0.3833	5.36E-01	9.82E-01	**9.47E-03**	NS
rs11150491	81318003	0.3747	4.68E-01	7.97E-01	**5.73E-03**	NS
rs8044520	81321339	0.08475	1.99E-01	9.49E-02	**6.20E-04**	NS
rs2169446	81326564	0.2884	2.75E-01	8.67E-01	**2.64E-03**	NS
rs16958387	81327165	0.08582	1.99E-01	9.49E-02	**6.20E-04**	NS
rs16958392	81327773	0.08582	1.99E-01	9.49E-02	**6.20E-04**	NS
rs10514560	81328576	0.2527	3.71E-01	8.56E-01	**8.83E-03**	NS
rs12600020	81329152	0.08582	1.99E-01	9.49E-02	**6.20E-04**	NS
rs12447571	81329890	0.09648	1.30E-01	1.25E-01	**1.73E-04**	NS
rs16958435	81331360	0.09648	1.30E-01	1.25E-01	**1.73E-04**	NS
rs16958471	81338447	0.08156	2.49E-01	3.50E-01	**7.93E-04**	NS
rs7206687	81342326	0.1397	4.56E-01	4.92E-02	**5.71E-03**	NS
rs1870847*	81349970	0.2265	5.40E-01	8.47E-01	1.14E-01	NS
rs12449008	81357449	0.08369	2.49E-01	3.50E-01	**7.93E-04**	NS
rs726122	81358889	0.08369	2.49E-01	3.50E-01	**7.93E-04**	NS
rs7200332	81360593	0.08475	2.49E-01	3.50E-01	**7.93E-04**	NS
rs16958587	81366499	0.08475	2.49E-01	3.50E-01	**7.93E-04**	NS
rs8061163	81372531	0.08475	2.49E-01	3.50E-01	**7.93E-04**	NS
rs16958616	81373798	0.08475	2.49E-01	3.50E-01	**7.93E-04**	NS
rs7185386	81379173	0.08422	2.49E-01	3.50E-01	**7.93E-04**	NS
rs7186123	81379253	0.08422	2.49E-01	3.50E-01	**7.93E-04**	NS
rs9989405	81381715	0.08369	2.90E-01	2.94E-01	**1.20E-03**	NS
rs10514565	81385422	0.07836	**8.01E-03**	9.05E-01	9.30E-01	NS
rs17278385	81389006	0.4536	9.92E-02	8.07E-01	**9.03E-03**	NS
rs9932137	81391528	0.2249	**7.41E-03**	8.85E-01	1.03E-01	NS
rs7192135*	81468190	0.1194	7.64E-01	3.83E-01	4.23E-01	NS
rs17674039*	81469875	0.1199	6.51E-01	3.72E-01	4.45E-01	NS
rs16958826*	81483050	0.2143	4.54E-01	9.51E-02	2.93E-01	NS
rs16958834*	81490402	0.1279	9.39E-01	2.34E-01	4.10E-01	NS
rs9646331*	81491933	0.1279	9.39E-01	2.34E-01	4.10E-01	NS
rs17674776*	81495401	0.1279	9.39E-01	2.34E-01	4.10E-01	NS
rs16958840*	81497693	0.1279	9.39E-01	2.34E-01	4.10E-01	NS
rs7199681	81652360	0.4099	**9.17E-03**	9.39E-01	6.54E-01	NS
rs6565113†	81665147	0.4659	5.15E-01	9.57E-01	8.77E-01	NS
rs12446149	81666760	0.1413	**9.51E-03**	2.94E-01	7.05E-01	NS
rs4453471	81672439	0.1397	**9.51E-03**	2.20E-01	7.19E-01	NS
rs4284625	81683892	0.1871	**5.63E-03**	2.92E-01	1.91E-01	NS
rs4128843	81709227	0.4051	8.59E-01	**5.44E-03**	5.57E-01	NS
rs7203576	81745773	0.1183	8.15E-01	6.01E-01	**2.84E-03**	NS

Table 3: *Continued*

SNP rs number	Position on chromosome 16 in BP	MAF	*P* inhibition task	*P* visio-spatial working memory task	*P* verbal working memory task	Emp *P* verbal working memory task
rs8045006*	81813774	0.0597	9.84E-01	9.27E-01	6.13E-01	NS
rs8045365*	81819599	0.05064	4.15E-01	6.14E-01	4.66E-01	NS
rs12917991*	81822613	0.05171	3.00E-01	6.76E-01	3.01E-01	NS
rs11150556	81828042	0.4755	4.52E-01	2.38E-01	**4.58E-05**	***3.60E-02***
rs7184058*	81828083	0.2729	6.87E-01	2.55E-02	**3.83E-02**	NS
rs7186143	81828118	0.3582	1.96E-01	2.41E-01	**1.66E-03**	NS
rs17756260	81847518	0.09542	5.62E-01	**8.43E-03**	5.25E-02	NS
rs16960006	81854762	0.06183	4.25E-01	**7.20E-03**	1.10E-01	NS
rs9930051	81946193	0.2729	**9.74E-03**	9.72E-01	4.22E-01	NS
rs7198902	81957144	0.2431	**7.73E-03**	9.12E-01	6.39E-01	NS
rs12149286	82024892	0.4781	**7.84E-03**	4.00E-01	4.07E-01	NS
rs17288787	82039158	0.2543	3.08E-01	**3.33E-03**	6.63E-01	NS
rs7189706	82040601	0.2644	3.31E-01	**3.86E-03**	6.55E-01	NS
rs17288955	82040676	0.2543	3.08E-01	**3.33E-03**	6.63E-01	NS
rs7193606	82041019	0.2489	4.19E-01	**5.32E-03**	7.10E-01	NS
rs12931303	82170815	0.1956	4.13E-01	4.63E-01	**7.97E-03**	NS
rs16961799	82379839	0.1802	1.47E-01	9.88E-01	**9.27E-03**	NS
rs2326025	82385302	0.1796	1.47E-01	9.88E-01	**9.27E-03**	NS
rs3743617	82386045	0.185	1.76E-01	8.98E-01	**9.17E-03**	NS
rs456699	82391190	0.2756	5.48E-01	9.52E-01	**1.30E-03**	NS

Association *P*-values at the *CDH13* locus for working memory tasks in 190 ADHD affected children. SNPs were included in the table if they showed association with at least one of the task at $P < 1.00E\text{-}02$ (in bold). In gray SNP rs11150556 that showed study-wide significant association after correction for multiple testing using correction for effective number of SNPs (LD < 0.35; $n = 313$). *P*-value in italics shows the SNP that showed significant empirical *P*-value after 10,000 permutations.
Positions on the chromosome are according to Genome Build 36.3.
NS = Not Significant.
*SNPs associated with ADHD status from the meta-analysis of Neale *et al*. (2010b). Bold *P*-values are < 0.05.
†SNP that showed genome-wide significant association with a quantitative ADHD phenotype (Lasky-Su *et al*., 2008).

compared to C/T and T/T carriers (TEST STAT = 4.177, $\beta = 0.3523$, additive model $P = 4.58E-05$, Fig. 1). This intronic SNP is located less than 100 bp downstream of SNP rs7184058, which showed nominally significant association with ADHD status ($P = 0.001121$) in the meta-analysis by Neale *et al*. (2010). Permutation analysis showed that the association of this SNP with Verbal WM was significant ($\text{Emp}P_{10000\ \text{permutations}} = 0.036$, Table 3). This association signal remained significant after including Conner's inattentive and hyperactive-impulsive scores in the analysis (TEST STAT = 4.031, $\beta = 0.3426$, additive model $P = 8.21E-05$).

Our analysis also identified suggestive evidence of associations with Verbal WM performance for a SNP-cluster in high LD spanning 72 kb and located 446 kb upstream of rs11150556 (Table 3 and Fig. S1, Supporting Information). The minor allele frequencies in this cluster range from 8 to 38% and were not in apparent LD with rs11150556 (Fig. S1).

In a haplotype analysis of 62 3-SNP haplotypes (64 SNPs included by selecting SNP rs11150556 and the 10-kb flanking regions), we found a total of five haplotypes associated with WM (maximum simulated $P \leq 0.05$; Table S1 and Fig. S2, Supporting Information). Haplotypes containing SNP rs11150556 showed the most significant associations with WM, this result is consistent with the results of the single SNP analysis (Fig. S2).

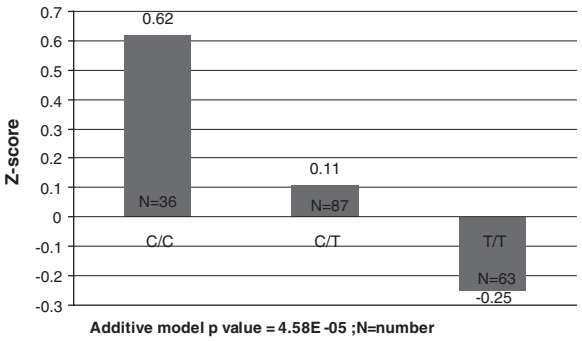

Figure 1: Mean values of Verbal working memory Task by SNP rs1115056 genotypes.

We found no significant associations between *CDH13* SNPs and visuo-spatial WM and the SSRT tasks.

Discussion

CDH13 has been identified as a candidate gene for ADHD using different analytic strategies. We tested the association between *CDH13* on three executive functioning tasks that

are promising endophenotypes of ADHD. Our adjusted linear regression analysis of SNPs on *CDH13* in 190 ADHD-affected Dutch children showed that SNP rs11150556 is gene-wide significantly associated (including haplotype analysis) with verbal WM (independently from ADHD severity) and that a 80-kb SNP block, 446 kb upstream of SNP rs111500556 showed suggestive evidence of association with the same Verbal WM task.

The relationship between ADHD and WM deficits and inhibition are well proven (Willcutt *et al*. 2005). The correlation values observed between neuropsychological and symptom measures were therefore surprising, however, not unexpected. A previous study from our group (Rommelse *et al*. 2008a) shows that: (1) an endophenotypic construct significantly predicts the diagnostic status (affected, non-affected and control) and (2) affected children portray a more severe ADHD phenotype than one would expect based on their cognitive dysfunctioning. In other words, group differences at an endophenotypic level and phenotypic level are not directly comparable for affected children (Nigg *et al*. 2005).

This study is the first to examine *CDH13* in neurocognitive functioning and the first to help explain the mechanisms underlying the association between *CDH13* and the clinical phenotype of ADHD. The broad expression of H-cadherin in the midbrain and telencephalon suggests that it plays an important role in building and maintaining neural circuitry (Takeuchi *et al*. 2000). More specifically, H-cadherin may be responsible for cell–cell adhesion (Patel *et al*. 2003) and the regulation of neural cell growth (Takeuchi *et al*. 2000). Deficient functioning of the H-cadherin system may therefore lead to a lower number of neurons and negatively affect neuronal growth affecting the structure and/or the number of neuronal connections (Poelmans *et al*., unpublished observations).

We found *CDH13* genetic variation to specifically affect WM (single SNPs and haplotypes). WM is one of the major executive functions supported by the frontal lobes (Pennington *et al*. 1996) and seems to be mediated by a complex network of brain structures including fronto-striatal dopaminergic circuits (Frank *et al*. 2007; Goldman-Rakic 1996). Furthermore, the dorsolateral prefrontal cortex appears to be involved in tasks tapping the central executive (CE) (Collette *et al*. 2002; D'Esposito *et al*. 1995), as well as in verbal and spatial WM tasks.

The most influential and supported model of WM is Baddeley's multi-component model (Baddeley 2010) which postulates the existence of two short-term storage systems, one for visual material, the visuo-spatial sketchpad, and one for verbal-acoustic material, the phonological loop. The CE control system regulates the two storage systems (Baddeley 2010; Castellanos *et al*. 2006). The CE component of WM controls and manipulates the stored information, and acts on information retrieved from long-term memory to support complex cognitive activities (Martinussen *et al*. 2005). While the forward condition of the Digit Span task assesses only the phonological loop capacity (Baddeley 2010; Gathercole 1999), the backward condition used in this study requires both storage (phonological loop) and transformation (processing) of material within WM (Gathercole 1999), and has been extensively employed in the WM literature to index CE resources (Gathercole 1998; Gathercole *et al*. 2000; Thomason *et al*. 2009). The principal role of the CE system is to coordinate attention and not necessarily to hold information in mind, nevertheless it is considered a part of WM. In ADHD, it is thought that impairments observed in complex tasks of WM (Pennington *et al*. 1996) may be attributable to a dysfunction in the CE component rather than in the verbal or spatial buffers or rehearsal processes (Karatekin 2004). Consistent with this, children with ADHD perform worse than other children on Backward but not Forward Digit Span (McInnes *et al*. 2003). Since we found an association between *CDH13* and the Digit Span backwards, it may be possible that *CDH13* is related to the CE component of WM. This is also consistent with the fact that an association between *CDH13* and lower WM performance was found for verbal WM but not for spatial WM, as the visuo-spatial WM task used in our study relies more on the maintenance of information and less on processing/manipulation (Crone *et al*. 2006). However, we explored the relationship between SNP rs11150556 and forward digit span by testing (post hoc) the association. Our results show a significant P value = 0.0134 with ADHD children carriers of the CC genotype also showing worse performance. This result might imply that *CDH13* is associated with verbal WM in a global way. In other words, it may rely on both the maintenance and processing of verbal information. In addition, we could speculate that *CDH13* may be associated with verbal WM in contrast to visuo-spatial WM.

This study is limited by the relatively small sample size, and replication of our findings in independent datasets is needed. We addressed the problem of multiple testing by performing very stringent permutation test to our three WM tasks association results. Also, the sample selection may affect results in different ways. A homogeneous group (combined type, almost all boys) is advantageous in finding an association between a gene and neurocognitive functioning in ADHD. On the other hand, the combined type may reflect the more severe phenotype which lies at the end of the ADHD continuum and therefore limiting the possibility to find an association. Furthermore, the literature is not straightforward whether ADHD subtypes differ on neurocognitive functioning. Some find no differences (O'Brien *et al*. 2010; Schweitzer *et al*. 2006; Seidman *et al*. 2005), while others do (Solanto *et al*. 2007).

CDH13 has been extensively studied in relation with cancer (Berx *et al*. 2009) and has been identified as a susceptibility locus for high blood pressure (Org *et al*. 2009) but, to our knowledge, our study represents the first attempt to investigate the relationship of the *CDH13* gene with neuropsychological performance in children with ADHD. The association found between *CDH13* and verbal WM is consistent with its expression pattern in the brain, especially in mature cerebral cortex and medulla (Takeuchi *et al*. 2000) and may help to increase our understanding of how this gene contributes to ADHD susceptibility, in particular, because WM is one of the main deficits and an important endophenotypes in ADHD (Arnsten 2011; Jacobson *et al*. 2011; Kofler *et al*. 2011; Pauli-Pott *et al*. 2011).

Intronic SNP associations are particularly difficult to relate with a specific clinically relevant trait but GWAS results found and replicated the association of several intronic SNPs

in *CDH13* with an ADHD quantitative phenotype (Lasky-Su *et al*. 2008), methamphetamine dependence (Uhl *et al*. 2008) and alcohol dependence (Treutlein *et al*. 2009). This further strengthens the evidence for a role of this gene in ADHD, as substance abuse/dependence is a common comorbidity of ADHD. Our study may be viewed as exploratory, with the results presented to be considered hypothesis-generating and our findings require caution and should be replicated in other cohorts for final confirmation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1: Linkage disequilibrium plot of the *CDH13* gene.

Figure S2: CDH13 3-SNP sliding window haplotype associations with WM.

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