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Pleiotropic Effects of DCDC2 and DYX1C1 Genes on Language and Mathematics Traits in Nuclear Families of Developmental Dyslexia

Cecilia Marino,
Department of Child Psychiatry, Scientific Institute Eugenio Medea, Via don Luigi Monza, 20, 23842 Bosisio Parini, LC, Italy

Centre de Recherche Université Laval Robert-Giffard, Quebec, Canada

Sara Mascheretti,
The Academic Centre for the Study of Behavioural Plasticity, Vita Salute San Raffaele University, Milan, Italy

Valentina Riva,
The Academic Centre for the Study of Behavioural Plasticity, Vita Salute San Raffaele University, Milan, Italy

Francesca Cattaneo,
Department of Child Psychiatry, Scientific Institute Eugenio Medea, Via don Luigi Monza, 20, 23842 Bosisio Parini, LC, Italy

Catia Rigoletto,
Department of Child Psychiatry, Scientific Institute Eugenio Medea, Via don Luigi Monza, 20, 23842 Bosisio Parini, LC, Italy

Marianna Rusconi,
Molecular Biology Laboratory, Scientific Institute Eugenio Medea, Bosisio Parini, Italy

Jeffrey R. Gruen,
Yale Child Health Research Center, Yale University School of Medicine, New Haven, CT, USA

Roberto Giorda,
Molecular Biology Laboratory, Scientific Institute Eugenio Medea, Bosisio Parini, Italy

Claudio Lazazzera, and
Department of Child Psychiatry, Scientific Institute Eugenio Medea, Via don Luigi Monza, 20, 23842 Bosisio Parini, LC, Italy

Massimo Molteni
Department of Child Psychiatry, Scientific Institute Eugenio Medea, Via don Luigi Monza, 20, 23842 Bosisio Parini, LC, Italy

Cecilia Marino: cecilia.marino@bp.lnf.it

Abstract

Converging evidence indicates that developmental problems in oral language and mathematics can predate or co-occur with developmental dyslexia (DD). Substantial genetic correlations have been found between language, mathematics and reading traits, independent of the method of sampling.

Correspondence to: Cecilia Marino, cecilia.marino@bp.lnf.it.

We tested for association of variants of two DD susceptibility genes, DCDC2 and DYX1C1, in nuclear families ascertained through a proband with DD using concurrent measurements of language and mathematics in both probands and siblings by the Quantitative Transmission Disequilibrium Test. Evidence for significant associations was found between DCDC2 and 'Numerical Facts' (p value = 0.02, with 85 informative families, genetic effect = 0.57) and between 'Mental Calculation' and DYX1C1 markers −3GA (p value = 0.05, with 40 informative families, genetic effect = −0.67) and 1249GT (p value = 0.02, with 49 informative families, genetic effect = −0.65). No statistically significant associations were found between DCDC2 or DYX1C1 and language phenotypes. Both DCDC2 and DYX1C1 DD susceptibility genes appear to have a pleiotropic role on mathematics but not language phenotypes.

Keywords

Dyslexia; Association study; Pleiotropy; Mathematics; Language

Introduction

Developmental dyslexia (DD) is a specific learning disability diagnosed in children who fail to develop normal reading skills in spite of normal intelligence, adequate motivation and schooling. It is a common condition with a prevalence ranging from 5 to 15.5% depending on the cutoff imposed on the normal distribution of reading ability and the language orthographic rules (Shaywitz and Shaywitz 2008). Twin studies show that the role of genetic factors is substantial (see Fisher and De Fries 2002 for a review), with estimates of broad heritability ranging between 0.44 and 0.75 (Plomin and Kovas 2005). Converging evidence from high-risk and longitudinal studies indicate that early developmental problems in oral language can predate DD, and/or constitute associated features of DD, with varying degrees of persistence and severity (Bishop and Adams 1990; Nathan et al. 2004; Stothard et al. 1998; Snowling et al. 2000; Lyytinen et al. 2001, 2005; Rescorla 2005). In addition, a positive covariation between poor mathematics skills and poor reading skills has been found in epidemiological samples and as well as in groups ascertained for both types of impairments (Markowitz et al. 2005; Light and DeFries 1995; Knopik and DeFries 1999).

Investigating the extent to which the phenotypic correlations between abilities and disabilities in reading, language and mathematics are attributable to shared genetic backgrounds, and addressing the issue of pleiotropy, are amongst the major aims of contemporary genetic research (Plomin and Kovas 2005). Multivariate genetic analyses have found strong genetic correlations (ranging 0.67–1.0) between language and reading traits in unselected twin samples (Thompson et al. 1991; Hohnen and Stevenson 1999). In selected extreme groups the genetic correlations between language and reading traits are similar, ranging from 0.53 to 0.86 (Bishop 2001). Substantial genetic correlations were also found between reading and mathematics abilities independent of the method of sampling, since the genetic correlation between normally varying reading and mathematics abilities is reported to range between 0.47 and 0.98 (Thompson et al. 1991; Knopik and DeFries 1999; Markowitz et al. 2005; Kovas et al. 2007), the bivariate heritability between reading disability and normally-varying mathematic abilities is 0.55 (Light and DeFries 1995), and the group genetic correlation for the phenotypic co-morbidity of disabilities is 0.67 (Kovas et al. 2007). In 4,000 pairs of twins from the UK Twins Early Development Study (TEDS), genetic correlations between language and general cognitive abilities, as well as between reading and mathematical traits were consistently high (Haworth et al. 2009). The fact that the genetic correlations are stably high in the low extremes as well as across the entire phenotypic distribution, indicates that the degree of overlap in genetic influences is comparable across different regions of the liability distribution. Thus, there are overall

sufficient data to support the view that low performance in one or more of the reading, language, and mathematics phenotypes is likely to represent a quantitative phenotypic extreme of an underlying unitary, or largely shared, liability with many shared elements of genetic influence.

The precise elements of these shared genetic influences are not known. There have been proportionally few molecular genetic studies of language and mathematics (see for a review Grigorenko 2009; Docherty et al. 2010) compared to the extensive molecular genetic literature on DD. The genetic mechanisms proposed to underlie the behavioral manifestation of DD are complex (see for a review Fisher and DeFries 2002). Linkages have been found to chromosome 1 (Rabin et al. 1993; Grigorenko et al. 2001; Tzenova et al. 2004), chromosome 2 (Fagerheim et al. 1999; Francks et al. 2002; Petryshen et al. 2002; Kaminen et al. 2003), chromosome 3 (Nopola-Hemmi et al. 2001), chromosome 6 (Cardon et al. 1994, 1995; Grigorenko et al. 1997; Gayán et al. 1999; Fisher et al. 1999), chromosome 15 (Grigorenko et al. 1997; Schulte-Körne et al. 1998) and chromosome 18 (Fisher et al. 2002). DYX1C1, KIAA0319, DCDC2 and ROBO1 have been consistently reported to be DD candidate susceptibility genes. The proteins encoded by these genes, though diverse, have been found functionally linked to pathways involved in neuronal migration and axon growth (see for a review Galaburda et al. 2006). As part of an ongoing project on the genetics of DD, we have previously studied the association between DD and two candidate susceptibility genes, DYX1C1 and DCDC2, by a family-based approach. In our sample, both DYX1C1 and DCDC2 were found associated with short-term and working memory processes, while only DCDC2 was found associated with word/non word reading. Our findings suggest that while both genes influence individual variation in the retrieval and transient storing of information, only DCDC2 would be implicated in phonological tasks (Marino et al. 2007; Marino et al. submitted). Recent evidence suggests that some of the DD candidate chromosomal regions harbor genes acting pleiotropically, i.e. acting as QTLs that influence language traits or other language disorders. Significant linkage results have been reported for speech sound disorder (SSD) and specific language impairment (SLI) to chromosome 3 and 1p34–p36, 6p22 and 15q regions (Stein et al. 2004, 2006; Smith et al. 2005; Miscimarra et al. 2007; Rice et al. 2009), all of which have been previously implicated in linkage studies of DD. By performing a linkage disequilibrium screen of DCDC2 and KIAA0319 on chromosome 6p22, and of the FOXP2 region of chromosome 7, Rice et al. (2009) reported significant results for five SNPs within KIAA0319 (two SNPs within a possible regulatory region), two SNPs within FOXP2, and one SNP within DCDC2. While the very nature of covariation and comorbidities between DD and language and mathematical (dis)abilities remains obscure with contrasting theories that place different emphasis on commonalities and differences among the cognitive components, initial linkage/association findings corroborate a shared molecular genetic etiology.

In the context of these studies, we hypothesize that DD susceptibility genes could have pleiotropic effects on both language and mathematics performance. To test this hypothesis, in the current study we test for pleiotropic effects on association with markers spanning two DD susceptibility genes, DCDC2 encoded on 6p and DYX1C1 encoded on 15q, using concurrent measurements of language and mathematics in nuclear families ascertained through a proband with DD.

Materials and methods

Sample

Participants were drawn from a sequential cohort of 203 nuclear families ascertained through DD probands (Marino et al. 2005; Marino et al. submitted) at the Department of Child Psychiatry of the Scientific Institute ‘Eugenio Medea’, Bosisio Parini, Lecco, Italy.

Our ascertainment scheme and diagnostic criteria for DD have been reported in detail elsewhere (Marino et al. 2005). Briefly, dyslexic probands were included if they had: (1) either accuracy or speed 2.0 SD at or below expected grade level on standardized text/word/nonword reading tests (Cornoldi and Colpo 1981; Sartori et al. 1995), and (2) total IQ C 85 (Wechsler 1981), and (3) absence of neurological or sensorial disorders. Siblings were included regardless of their reading performance and if the mean score of vocabulary and block design subtests of the Wechsler Intelligence Scale for Children, Revised (Wechsler 1981) was ≥7. For the present study, all 203 families were contacted by phone and asked to participate in a new phase including an assessment of language and mathematics abilities. 180 nuclear families accepted and gave informed written consent. DNA samples were already available for all subjects (Marino et al. 2005). This protocol was approved by the Scientific Institute 'Eugenio Medea' Ethics Board.

Assessment

We administered a battery of psychometric tests to all probands and siblings in each family. Language abilities were assessed with the 'Batteria per l'esame del linguaggio nel bambino dai 4 ai 12 anni' (Fabbro 1999), a clinical tool widely used in Italy for the identification, diagnosis, and follow-up evaluation of language impairments in school-age children which provides language scores for each subscales for children from 4 to 12 years of age. For the current purposes, only three receptive (auditory comprehension tapping syntax, vocabulary and semantic relationships) and three expressive tests were considered:

1. Semantic Comprehension (SC; translated and adapted from the 'British Picture Vocabulary Scale', De Agostini et al. 1998) assesses the child's vocabulary size through a list of 32 words (nouns, adjectives, and verbs). Participants are asked to indicate as rapidly and accurately as possible which picture out of four (the target, two phonological and one semantic distractors) corresponds to the word orally presented by the examiner. A score of 1 is given to correct answers within 1 min, otherwise the score is 0. The total score is the sum of obtained points at each command.
2. Token Test (TOKEN; adapted from Benton 1969) assesses verbal comprehension through a list of 21 commands of increasing syntactic complexity. 20 tokens of different shapes (i.e., circle and square), colours (red, blue, yellow, green and white) and sizes (two sizes) are presented. Participants are asked to execute as rapidly and accurately as possible a command orally given by the examiner. A score of 1 is assigned to correct performance within 5 s at first attempt and of 0.5 to correct performance within 5 s at second attempt; otherwise the score is 0. The total score is the sum of obtained points at each command.
3. Syntactic Comprehension (SYC; 'Test di Comprensione Grammaticale' TCGB; Chilosi and Cipriani 1995) assesses verbal comprehension through a list of 76 sentences with increasing syntactic complexity. Participants are asked to indicate which picture out of four (the target and one grammatical, one lexical and one visual distractors) corresponds to the sentence orally presented by the examiner. Correct answers are scored 0; wrong answers are scored 0.5 at first and 1.5 at second attempt. The total score is the sum of obtained points at each command.
4. The Word Repetition (WR) and NonWord Repetition Test (NWR; De Agostini et al. 1998) were used to assess phonological short-term memory skills. Participants were asked to repeat 15 multisyllabic real and 15 multisyllabic nonsense words in response to the oral presentations by the examiner. The total score is the sum of words correctly repeated.

5. Rapid Automatized Naming (RAN; De Agostini et al. 1998) assesses phonological retrieval and processing speed. Participants are asked to name a visually presented stimuli as rapidly and accurately as possible. The stimuli adopted consisted of colors and objects. Colors are small 8×4 cm^2; they are orange, yellow, pink and red. The objects are line drawings of 32 objects. A score of 1 is assigned to correct naming regardless of articulation errors within 10 s, otherwise the score is 0. The total score is the sum of obtained points at each command.

6. Semantic Fluency (FLUENCY; De Agostini et al. 1998). Participants were asked to produce as many words as possible from two semantic categories (i.e., animals and objects) in a 1-min interval each. The total score is the sum of words produced in the best trial.

Language scores were standardized (mean = 0, SD = 1) on norms provided from a sample of 160 subjects aged from 6 to 12 years of Italian ancestry and language, belonging to public and private school in Milan and Lecco. Since these language tests are most appropriate for children younger than 13, only a subset of the sample, i.e. 122 families with 146 offspring, was considered eligible for the language assessment to avoid as much as possible skewed distributions or ceiling effects.

Mathematics abilities were measured with ‘Test di valutazione delle Abilità di Calcolo’ (AC-MT) (Cornoldi et al. 2002) a standardized clinical tool widely used in Italy for the identification, diagnosis, and follow-up evaluation of mathematics impairments in school-age children which provides grade-normed scores for each subscales (mean = 0, SD = 1; Cornoldi and Lucangeli 2004). For the current purposes, only the following tests were considered:

1. Mental calculation (MC) in which participants are asked to solve mentally and to give a verbal response as rapidly and accurately as possible to an orally presented list of two-digit addition, subtraction and multiplication increasing gradually in difficulty. A score of 0 is assigned to correct solutions within 30 s, otherwise the score is 1. Both speed (s) and accuracy (number of errors) are measured.

2. Written Calculation (WC) in which participants are asked to solve by writing as many as possible of a written presented list of two-digit addition, subtraction and multiplication increasing gradually in difficulty. A score of 0 is assigned to correct solutions, otherwise the score is 1. Both speed (s) and accuracy (number of errors) are measured.

3. Number Dictation (ND) in which participants write to dictation a list of numbers in the Arabic format increasing gradually in difficulty. This test gives information about syntactic and lexical mechanisms underlying number production. A score of 1 is assigned to correct solutions, otherwise the score is 0. The total score is the sum of obtained points at each command.

4. Numerical Facts (NF) taps the knowledge of addition and subtraction with one-digit numbers and multiplication tables; participants are asked to solve mentally and to give a verbal response as rapidly and accurately as possible to an orally presented list of addition, subtraction and multiplication with one-digit numbers increasing gradually in difficulty. A score of 0 is assigned to correct solutions within 5 s, otherwise the score is 1. The total score is the sum of obtained points at each command.

Raw scores were converted into grade-adjusted standard deviation units from the norm by application of the standard norms in the test protocol (Cornoldi et al. 2002).

All these measures have acceptable reliability and validity and good psychometric properties (Fabbro 1999; Cornoldi et al. 2002). In all subsequent analyses standardized scores for both language and mathematics measures were used.

Genotyping

Nuclear families ascertained through DD probands have been previously genotyped for the DCDC2 and DYX1C1 gene (Marino et al. 2007; Marino et al. submitted). Exons 2 and 10 of the DYX1C1 gene were amplified from genomic DNA (primer sequences and amplification protocols are available from the authors on request). We decided that direct sequencing of both exons was the best approach. A 0.5 ll aliquot of each amplified DNA sample was labelled with a BigDye Terminator cycle sequencing kit (Applied Biosystems, Monza, Italy) and sequenced on an ABI3100 Avant Genetic Analyzer (Applied Biosystems). Sequences were aligned with Autoassembler (Applied Biosystems) and scored for known and new polymorphisms. Subjects were scored for polymorphisms at −3GA, 1249GT, and 1259CG. DCDC2 was investigated for the intron 2 deletion/compound STR polymorphism (BV677278) and genotyping was performed as described by Meng et al. (2005). Briefly, the common 2,445 bp deletion was genotyped by allelic-specific amplification with a combination of three primers in one reaction, while the compound STR was genotyped by sequencing PCR products. Sequence traces results were analyzed and alleles assigned by comparing samples to reference traces after alignment. Unassigned alleles were cloned in pCR4-TOPO and individually sequenced.

Statistical analyses

Marker-trait association was investigated by the Transmission Disequilibrium Test (TDT), a test of linkage in the presence of association that was originally developed for dichotomous traits (Spielman et al. 1993). We adopted the TDT as modelled by Abecasis et al. (2000), which allows for the analyses of quantitative traits and is supported by the QTDT package version 2.5.1. For QTDT, the number of informative families for each marker depends upon the number of families with at least one heterozygous parent. Marker-trait association was assessed by the “orthogonal association” option (Abecasis et al. 2000). We performed a genotype-permutation procedure within QTDT to verify the results from the orthogonal test and to correct for the biasing effects of trait nonnormality or small sample size. Given the exploratory nature of the study, empirical *p* values are presented. Seven phenotypes in the language (SC, TOKEN, SYC, WR, NWR, RAN, FLUENCY), and six in the mathematics domain (MC accuracy, MC speed, WC accuracy, WC speed, ND, NF) were analyzed as quantitative traits. We followed the approach proposed by Meng et al. (2005) and combined the BV677278 minor alleles (alleles with a frequency ≤ 0.07, i.e. alleles 2, 5, 6, 10, 15, 19 and the deletion) to avoid the extremely low number of informative families for minor alleles association analyses. Given that both mathematics and language covary phenotypically with reading ability, the distribution of mathematics and language traits is often skewed in the sample of probands (Table 1); to obtain a better distribution and gain power, we thus performed all analyses of quantitative traits in the whole offspring sample. The mean Pearson’s bivariate correlations for language and mathematics measures with word/non word reading performance in the offspring sample were 0.17 and 0.23 respectively. We reasoned that the hypothetical pleiotropic effect of DD genes to language and mathematics phenotypes may become more clear once the variance shared with reading is removed; thus, we used both accuracy and speed of word/nonword reading tests (Sartori et al. 1995) as covariates in all quantitative genetic analyses. Descriptive and correlation analyses were performed by SPSS version 12.0.

Results

The sample consisted of 180 nuclear families, including 28 parent–child pairs, 94 triads, 48 families with two, 9 with three, and 1 with four offspring, yielding a total of 581 participants, all of Italian ancestry and native language, 249 of which were offspring (mean age 10.8 ± 2.6 years, male:female sex ratio 3:1) and 332 parents. Families who agreed to take part in this study did not differ from families who declined acceptance for children age, number, or severity of probands with DD. Offspring mean total IQ was 101.67 ± 11.98. Strong ceiling effects in the WR and NWR tests were observed across all ages, with the vast majority of subjects who made no errors and yielding a coefficient of variation of only 3%. Therefore, these measures were not used in subsequent analyses. Probands with DD tended to perform consistently in the below-average ranges in most cognitive tasks only for the mathematics domain whereas performance in the language domain was close to the average. Tables 1 and 2 show the descriptive statistics for language and mathematics measures. Partial bivariate correlations between language and mathematical measures—adjusted for word/non word reading performance—were overall modest (mean value = 0.19; Table 3). Eight families were excluded from the analyses due to mendelian errors. Genotype distribution in the parents did not significantly deviate from Hardy–Weinberg equilibrium (*p* values range: 0.36–0.99). Tables 4 and 5 show the marker-trait associations yielded by the QTDT analyses. Evidence for significant associations was found between the DCDC2 BV677278 marker and numerical facts (*p* value = 0.02; 85 informative families; genetic effect = 0.57) and between ‘Mental Calculation, Accuracy’ and DYX1C1 markers −3GA (*p* value = 0.05; 40 informative families; genetic effect =−0.67, minor allele) and 1249GT (*p* value = 0.02; 49 informative families; genetic effect = −0.65, minor allele). No statistically significant associations were found between DCDC2 or DYX1C1 markers and language phenotypes.

Discussion

In a genetically informed study of families ascertained through a child with DD, we explored the hypothesis that two measured genes known to influence the familial transmission of DD could also be associated with individual variation in two independent—but DD correlated—cognitive domains, namely language- and mathematics skills, across the whole distribution of liability.

Our data show that DCDC2 on chromosome 6p and DYX1C1 on chromosome 15q are respectively associated with the cognitive phenotypes of ‘numerical facts’ and ‘mental calculation’, suggesting that not only can these genes account for part of the disabilities of DD (i.e., memory and phonological processes: Marino et al. 2007; Marino et al. submitted), but also for part of the reduced mathematical skills that are observable in these children. In order to enhance specificity of the associations, all analyses were conducted with reading skills as covariates. Thus, inasmuch as the variance shared with reading abilities was successfully partialled out, our results suggest pleiotropic effects for both DCDC2 and DYX1C1 on mathematical skills. Alternatively, it could be the case that variation at these genes accounts for function at some—not yet identified— intermediate phenotype, which would act as a latent pathway common to memory, phonological and mathematical abilities. Given the unprecedented nature of these results, however, these data need both prudent consideration and independent replication. In the only study that to our knowledge addressed a similar question, by adopting a GWA strategy in the extended British TEDS twin cohort, Docherty et al. (2010) found SNPs associated with mathematical skills in chromosomal regions that do not pertain to the two genes examined in this hypothesis-driven study.

Turning to our negative results regarding language phenotypes, our data contrast with three previously published studies of comparable sample sizes (Smith et al. 2005; Stein et al. 2006; Rice et al. 2009) reporting pleiotropic effects of DD loci/genes on chromosome 6 and 15, although direct comparisons should be considered cautiously since two of them investigated linkage (Smith et al. 2005; Stein et al. 2006) instead of association. When examining this discrepancy, however, both careful examination of the datasets and a developmental perspective become helpful. The fact that we failed to find association with the language phenotypes could be connected to the age of the subjects in our study and the type of tests that constitute adequate measures at different ages. The studies that yielded positive results (Smith et al. 2005; Stein et al. 2006; Rice et al. 2009) assessed age-appropriate language skills in children of a much younger age than in our study and therefore substantively different skills than we assessed, even though they all fall into the class of 'language'. Thus, relative to other studies, our measures of language abilities may have turned out to be insensitive to association with DCDC2 and DYXC1 for three, non mutually exclusive explanations. First, the deficits in language skills measured by the previous positive studies may undergo spontaneous catch-up with time and development, so that by assessing older children we found linguistically better performances for crucial phenotypes. Second, our language tests were simply not measuring the same types of deficits as measured by the previous positive studies. Third, the DCDC2 and DYX1C1 genes may exert a time-dependent effect on language skills that are detectable in younger children, but become less detectable when children grow older. Furthermore, in our study—compared to previous investigations—–we assessed a smaller number of markers (Smith et al. 2005; Stein et al. 2006; Rice et al. 2009). This fact brings about further caveats in interpreting the lack of consistency between our and previous findings, together with sample power issues. However, we checked the conditional power to detect association between all polymorphisms, i.e., −3GA, 1249GT, 1259CT and BV677278 and continuous traits within various genetic models (additive, dominant and recessive) with the PBAT Power Calculator (http://www.biostat.harvard.edu/~fbat/pbat.htm). Assuming an explained proportion of genetic variance of 0.05, for the sample with language phenotypes (n = 122) the power at a significance level of 5% was at best 50%, a figure that should be considered as a limitation and suggests cautious interpretation of results, especially in the context of complex traits such as language phenotypes.

In summary, these findings likely indicate shared biological or cognitive processes that underlie reading and mathematics and represents initial evidence in favour of a pleiotropic effect of the DCDC2 and DYXC1 genes on mathematics skills in a sizable sample of families ascertained for DD. Nevertheless, it should be viewed with some limitations in mind. First, the results of these univariate association analyses should be considered exploratory, and in the future, the relationship between potential risk loci and the various aspects of these traits may be better explored using newly developed methods for multivariate association analyses of multiple related traits. Second, as with all analyses of complex traits, the significance of the current association findings should be interpreted cautiously until they can be replicated in an independent sample of DD or selected directly for Developmental Mathematics Disorder.

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Table 1

Descriptive statistics of the language phenotypes in the offspring sample

Traits	Total sample (*n* = 146)					Probands (*n* = 122)					Siblings (*n* = 24)				
	Min	Max	Mean (SD)	Skew	Kurtosis	Min	Max	Mean (SD)	Skew	Kurtosis	Min	Max	Mean (SD)	Skew	Kurtosis
SC	−4.20	3.03	−0.04 (1.48)	−0.128	0.081	−4.20	2.54	−0.41 (1.31)	−0.36	0.52	−2.99	3.03	0.89 (1.49)	−0.47	−0.22
TOKEN	−3.91	2.14	−0.37 (1.25)	−0.716	0.364	−3.68	2.14	−0.48 (1.29)	−0.50	0.03	−3.91	1.09	−0.03 (1.12)	−1.49	3.03
SYC	−7.95	1.00	−0.95 (1.64)	−1.62	3.06	−6.78	0.80	−1.07 (1.54)	−1.31	1.66	−7.95	1.00	−0.64 (1.89)	−2.34	6.28
RAN	−4.19	1.77	0.68 (1.05)	−1.39	3.35	−4.19	1.77	0.69 (1.04)	−1.69	5.11	−2.40	1.77	0.64 (1.09)	−0.73	0.79
FLUENCY	−2.28	2.40	−0.23 (1.01)	0.401	−0.084	−2.14	2.29	−0.28 (0.99)	0.40	−0.13	−2.28	2.40	−0.11 (1.05)	0.40	0.78

SC semantic comprehension, *TOKEN* token test, *SYC* syntactic comprehension, *RAN* rapid automatized naming, *FLUENCY* semantic fluency. Measures are in SD units, relative to the age-appropriate Italian population norm

Table 2

Descriptive statistics of the mathematics phenotypes in the offspring sample

Traits	Total sample (249)					Probands (*n* = 180)					Siblings (*n* = 69)				
	Min	Max	Mean (SD)	Skew.	Kurtosis	Min	Max	Mean (SD)	Skew.	Kurtosis	Min	Max	Mean (SD)	Skew.	Kurtosis
MC accuracy	−3.63	1.30	−0.26 (1.16)	−0.62	−0.42	−3.63	1.30	−0.37 (1.15)	−0.47	−0.42	−2.98	1.30	−0.03 (1.15)	−0.98	−0.01
MC speed	−10.23	2.18	−1.09 (2.17)	−1.47	2.26	−10.23	2.18	−1.57 (2.26)	−1.33	1.75	−6.20	2.07	−0.11 (1.59)	−1.99	4.64
WC accuracy	−5.63	1.48	−0.52 (1.45)	−0.84	0.32	−5.63	1.48	−0.65 (1.47)	−0.73	0.05	−5.39	1.48	−0.25 (1.39)	−1.12	1.37
WC speed	−12.38	1.80	−1.53 (2.17)	−1.56	3.76	−12.38	1.80	−1.79 (2.33)	−1.46	3.42	−7.23	0.95	−1.02 (1.71)	−1.48	2.33
ND	−20.33	1.24	−2.22 (4.68)	−2.28	4.67	−20.33	1.24	−2.88 (5.04)	−1.89	2.75	−19.27	1.24	−0.84 (1.47)	−4.06	18.71
NF	−4.56	1.41	−1.04 (1.56)	−0.38	−0.90	−4.56	1.15	−1.40 (1.48)	−0.15	−0.92	−4.05	1.41	−0.31 (1.44)	−1.17	0.61

MC mental calculation, *WC* written calculation, *ND* number dictation, *NF* numerical facts. Measures are in SD units, relative to the age/grade-appropriate Italian population norm

Table 3

Partial bivariate correlations among mathematical and language measures in the offspring sample considered eligible for the language assessment (n = 146)

Traits	MC accuracy	MC speed	WC accuracy	WC speed	ND	NF
SC	0.22 (0.13)	0.23 (0.12)	0.02 (0.92)	0.20 (0.18)	0.38** (0.01)	0.26 (0.08)
SYC	0.33 (0.03)	0.18 (0.23)	−0.23 (0.12)	−0.10 (0.49)	−0.03 (0.87)	0.15 (0.32)
TOKEN	0.29 (0.05)	0.28 (0.06)	−0.021 (0.89)	0.04 (0.78)	0.35* (0.02)	0.31* (0.03)
RAN	0.17 (0.27)	0.13 (0.4)	0.025 (0.87)	0.04 (0.81)	0.17 (0.25)	0.09 (0.55)
FLUENCY	0.32* (0.03)	0.24 (0.11)	0.12 (0.43)	0.30* (0.04)	0.3* (0.04)	0.09 (0.54)

All correlations are controlled for reading related traits, i.e. word/nonword reading accuracy and speed measures. Between parentheses are the *p* values for two-sided tests and not adjusted for multiple comparisons.

Flag * marks significant correlations,

** significant at the 0.01 level (2-tailed),

* significant at the 0.05 level

SC semantic comprehension, *TOKEN* token test, *SYC* syntactic comprehension, *RAN* rapid automatized naming, *FLUENCY* semantic fluency, *MC* mental calculation, *WC* written calculation, *ND* number dictation, *NF* numerical facts. Measures are in SD units, relative to the grade/age-appropriate Italian population norm

Table 4

Market-trait association *p* values in 180 nuclear families (249 offspring) for DYX1C1 markers

Markers	DYX1C1								
	−3GA			1249GT			1259CT		
	0.09[a]			0.13[a]			0.12[a]		
Traits	**Informative families**	***F* statistic (df)**	**Empirical *p* value**	**Informative families**	***F* statistic (df)**	**Empirical *p* value**	**Informative families**	***F* statistic (df)**	**Empirical *p* value**
SC	16	0.82 (77)	0.49	22	0.77 (76)	0.46	27	0.27 (76)	0.64
TOKEN	22	0.00 (85)	0.96	29	0.23 (84)	0.64	32	1.32 (84)	0.20
SYC	18	0.03 (78)	0.9	25	0.21 (77)	0.7	27	2.02 (77)	0.13
RAN	16	1.42 (78)	0.56	22	0.29 (77)	0.54	28	2.54 (77)	0.13
FLUENCY	17	3.79 (79)	0.12	24	1.26 (78)	0.33	28	0.42 (78)	0.49
MC Accuracy	40	3.75 (142)	0.05	49	4.19 (141)	0.02	55	2.13 (141)	0.17
MC Speed	40	0.67 (143)	0.36	49	0.20 (142)	0.62	55	1.75 (142)	0.26
WC Accuracy	40	0.07 (142)	0.81	49	0.33 (141)	0.58	55	0.20 (141)	0.62
WC Speed	40	0.13 (141)	0.71	49	0.06 (140)	0.81	54	0.04 (140)	0.86
ND	40	1.05 (141)	0.21	49	0.12 (140)	0.9	53	2.36 (140)	0.07
NF	40	2.13 (143)	0.19	49	1.51 (142)	0.3	55	0.04 (142)	0.82

[a]Minor allele frequency among parents. All measures are adjusted for reading related traits, i.e. word/nonword reading accuracy and speed measures

df degrees of freedom, *SC* semantic comprehension, *TOKEN* token test, *SYC* syntactic comprehension, *RAN* rapid automatized naming, *FLUENCY* semantic fluency, *MC* mental calculation, *WC* written calculation, *ND* number dictation, *NF* numerical facts

Table 5

Market-trait association *p* values in 180 nuclear families (249 Offspring) for the DCDC2 marker, Bv677278

Traits	df	Allele 1			Allele 2			Allele 3			Allele 4		
		0.61[a]			0.22[a]			0.07[a]			0.1[a]		
		Informative families	*F* statistic	Empirical *p* value	Informative families	*F* statistic	Empirical *p* value	Informative families	*F* Statistic	Empirical *p* value	Informative families	*F* Statistic	Empirical *p* value
SC	85	59	2.76	0.16	50	0.26	0.71	15	0.39	0.47	29	1.06	0.49
TOKEN	95	67	0.68	0.50	52	0.61	0.49	16	0.02	0.86	34	0.48	0.51
SYC	88	63	1.38	0.33	52	0.15	0.68	17	1.19	0.26	33	0.87	0.33
RAN	85	59	1.83	0.37	51	1.70	0.21	16	0.0	0.98	29	0.15	0.74
FLUENCY	88	61	0.13	0.75	51	0.21	0.71	16	0.92	0.30	30	0.04	0.84
MC Accuracy	167	105	0.40	0.54	84	0.19	0.68	29	0.01	0.88	56	0.02	0.89
MC Speed	168	105	3.45	0.12	85	0.20	0.70	30	2.96	0.17	56	0.94	0.30
WC Accuracy	141	105	1.15	0.33	85	0.04	0.88	30	1.21	0.35	56	0.24	0.62
WC Speed	166	105	0.11	0.71	85	0.01	0.91	30	1.59	0.28	56	0.32	0.45
ND	166	103	0.13	0.55	83	0.00	0.94	28	0.00	0.95	54	0.18	0.50
NF	168	105	3.77	0.06	85	4.66	0.02	30	0.40	0.51	56	0.39	0.52

[a] Allele frequency among parents. All traits are adjusted for reading related measures, i.e. word/nonword reading accuracy and speed

df degrees of freedom, *SC* semantic comprehension, *TOKEN* token test, *SYC* syntactic comprehension, *RAN* rapid automatized naming, *FLUENCY* semantic fluency, *MC* mental calculation, *WC* written calculation, *ND* number dictation, *NF* numerical facts. allele 2 alleles with a frequency < 0.07, i.e. alleles 2, 5, 6, 10, 15, 19 and the deletion