RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Are 22q11.2 Distal Deletions Associated with Math Difficulties?

Maria Raquel Santos Carvalho,[1,2]* Gabrielle Vianna,[1] Lívia de Fátima Silva Oliveira,[3,4] Annelise Julio Costa,[4,5] Pedro Pinheiro-Chagas,[4,5] Rosane Sturzenecker,[6] Paulo Ricardo Gazzola Zen,[7] Rafael Fabiano Machado Rosa,[7] Marcos José Burle de Aguiar,[8] and Vitor Geraldi Haase[3,4]

[1]Pós-Graduação em Genética, Departamento de Biologia Geral, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

[2]Departamento de Biologia Geral, Instituto de Ciências Biológias, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

[3]Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

[4]Departamento de Psicologia, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

[5]Pós-Graduação em Neurociências e Comportamento, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[6]Biocod—Belo Horizonte, Minas Gerais, Brazil

[7]Departamento de Clínica Médica, Universidade Federal de Ciências da Saude de Porto Alegre, Brazil

[8]Departamento de Pediatria, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

Manuscript Received: 6 May 2013; Manuscript Accepted: 22 May 2014

Approximately 6% of school-aged children have math difficulties (MD). A neurogenetic etiology has been suggested due to the presence of MD in some genetic syndromes such as 22q11.2DS. However, the contribution of 22q11.2DS to the MD phenotype has not yet been investigated. This is the first population-based study measuring the frequency of 22q11.2DS among school children with MD. Children (1,564) were identified in the schools through a screening test for language and math. Of these children, 152 (82 with MD and 70 controls) were selected for intelligence, general neuropsychological, and math cognitive assessments and for 22q11.2 microdeletion screening using MLPA. One child in the MD group had a 22q11.2 deletion spanning the LCR22-4 to LCR22-5 interval. This child was an 11-year-old girl with subtle anomalies, normal intelligence, MD attributable to number sense deficit, and difficulties in social interactions. Only 19 patients have been reported with this deletion. Upon reviewing these reports, we were able to characterize a new syndrome, 22q11.2 DS (LCR22-4 to LCR22-5), characterized by prematurity; pre- and postnatal growth restriction; apparent hypotelorism, short/upslanting palpebral fissures; hypoplastic nasal alae; pointed chin and nose; posteriorly rotated ears; congenital heart defects; skeletal abnormalities; developmental delay, particularly compromising the speech; learning disability (including MD, in one child); intellectual disability; and behavioral problems. These results

How to Cite this Article:
Carvalho MRS, Vianna G, Oliveira LFS, Costa AJ, Pinheiro-Chagas P, Sturzenecker R, Zen PRG, Rosa RFM, de Aguiar MJB, Haase VG. 2014. Are 22q11.2 distal deletions associated with math difficulties? Am J Med Genet Part A 164A:2256–2262.

The authors declared that they have no conflicts of interest.
Grant sponsor: FAPEMIG; Grant numbers: APQ-02755-SHA, APQ-03289-10, APQ-02523-11, PPM-00280-12; Grant sponsor: CNPq; Grant numbers: 307006/2008-5, 401232/2009-3, 557664/2010-1, 504891/2010-3; Grant sponsor: CAPES/DAAD.
*Correspondence to: Maria Raquel Santos Carvalho, Departamento de Biologia Geral, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais—UFMG, Av. Antônio Carlos, 6627, 31.270-901, Belo Horizonte, Minas Gerais, Brazil.
E-mail: ma.raquel.carvalho@gmail.com
Article first published online in Wiley Online Library (wileyonlinelibrary.com): 2 July 2014
DOI 10.1002/ajmg.a.36649

suggest that 22q11.2 DS (LCR22-4 to LCR22-5) may be one of the genetic causes of MD. © 2014 Wiley Periodicals, Inc.

Key words: chromosome 22q11.2 deletion syndrome; distal; math difficulties; 22q11.2 DS (LCR22-4 to LCR22-5); developmental dyscalculia; learning disability

INTRODUCTION

Arithmetic is a cultural acquisition based on core biologic abilities, including our capacity to discriminate small amounts without counting (subitizing), to perceive differences between larger sets without counting (number sense); to identify the spatial position of digits in a number (the rightmost place represents the unit, to its left follow the tens, hundreds, and so on), to understand and execute algorithms underlying basic math operations, etc. [Dehaene, 1997]. Schooling provides us with symbolic representations for the quantities, which may be represented as Arabic or oral and written verbal symbols. Persons with math learning disability (MD) or dyscalculia have troubles in these very basic functions with consequences for their everyday life. Indeed, people with dyscalculia have lower income, lower chances to get and keep a job, when compared to typically achieving (TA) persons as well as to persons with dyslexia [Parsons and Bynner, 2005]. A considerable proportion of school-age children experience difficulties learning math (math difficulties or MD) [Mazzocco, 2007]. In 4–6% of these children, these difficulties can be attributed to dyscalculia or math learning disability (MD), a persistent condition not primarily caused by intellectual disability, neurosensorial deficits, or pedagogical and socioemotional problems [Gross-Tsur et al., 1996; Butterworth et al., 2011;].

Family recurrence [Shalev et al., 2001; Landerl and Moll, 2010], twin studies [Kovas et al., 2007; Hart et al., 2009; Willcutt et al., 2010], and genome-wide association studies [Docherty et al., 2010] suggest a complex and heterogeneous etiology for MD. Some environmental and genetic factors have already been identified, such as fetal alcohol [Jacobson et al., 2011], Turner [Bruandet et al., 2004], 22q11.2 deletion (22q11.2 DS) [DeSmedt et al., 2007] and Williams [Krajcsi et al., 2009] syndromes, as well as familial mental retardation 1 (FMR1) in females [Murphy and Mazzocco, 2008].

Learning disabilities in 22q11.2DS have gained increasing attention due to their specific cognitive phenotype, with a pattern of poorer performance in arithmetic than in visual word decoding and spelling tasks [Jacobson et al., 2010]. The 22q11.2 region is prone to rearrangements through non-allelic homologous recombination due to the presence of eight interspersed low-copy repeats (LCR22-2 to LCR22-8). Approximately 90% of 22q11.2DS patients are hemizygous, due to typical deletion region (TDR) microdeletions spanning a 3-Mb chromosomal segment (LCR22-2 to LCR22-4), and almost all the remaining cases result from a 1.5–2 Mb microdeletion (LCR22-2 to LCR22-3a) [Yu et al., 2012]. The region and the associated phenotypes are shown in Figure 1. Atypical microdeletions, either larger or smaller, overlapping the TDR or not, have

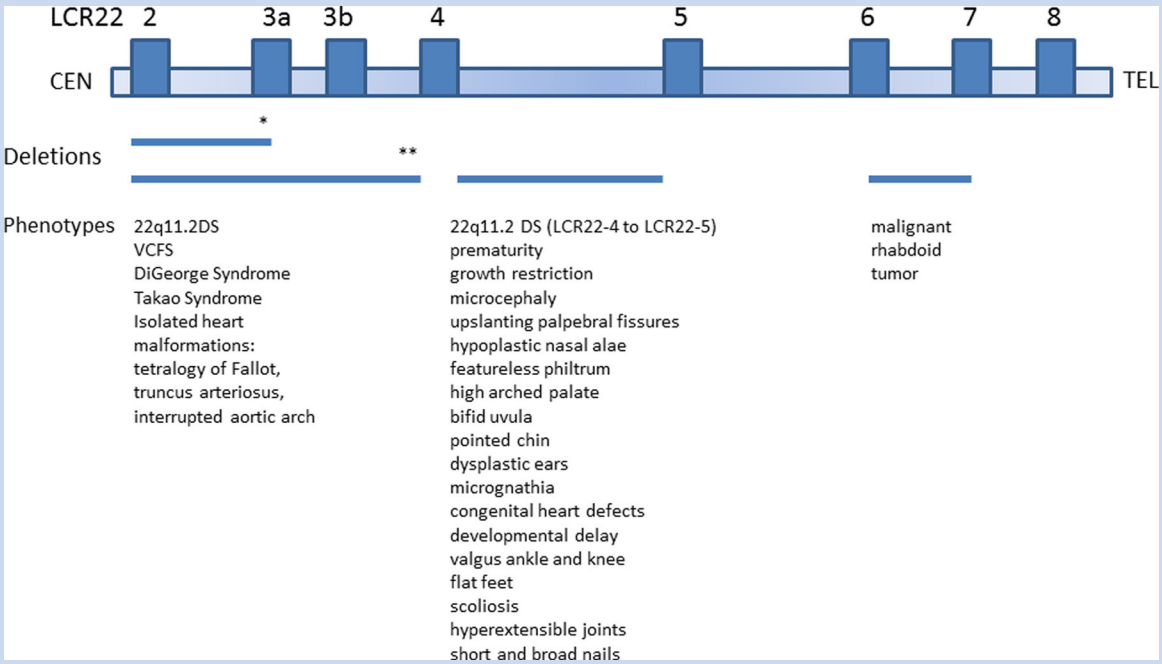

FIG. 1. Map 22q11.2 region showing the distribution of LCRs (low copy region), deletions, and phenotypes. Phenotypes were drawn based on deletions spanning only one interval. No clear phenotype has been associated with deletions spanning the intervals 22q11.2 (LCR22-5 to LCR22-6) and 22q11.2 (LCR22-7 to LCR22-8).

also been found occasionally. Small deletions are found even less frequently. In fact, to the best of our knowledge, 19 patients bearing deletions spanning only the LCR22-4 to LCR22-5 interval have been already described [Saitta et al., 1999; Ben-Shachar et al., 2008; Newbern et al., 2008; Rodningen et al., 2008; Xu et al., 2008; Bruce et al., 2010; Tan et al., 2011; Verhoeven et al., 2011; Fagerberg et al., 2012; Molck et al., 2013]. However, deletions in this interval have also been identified in asymptomatic persons, suggesting that the symptoms are not produced by haploinsufficiency but rather by the exposition of recessive deleterious alleles. Alternatively, this deletion may interfere with the functioning of long-range regulatory elements that are not yet characterized.

22q11.2DS is the most common microdeletion syndrome in humans, affecting 1:3,000 to 1:6,000 live births [for a review, see Yu et al., 2012]. However, these figures may be underestimates due to factors such as the high costs of molecular diagnosis methods, clinical variability, ascertainment biases, and the intricacies of the etiology of the syndrome itself. Furthermore, despite the large amounts of data presented in the literature reporting MD in patients bearing the 22q11.2DS [DeSmedt et al., 2009a], no studies have investigated the frequency of 22q11.2 deletions among persons with MD. Therefore, we conducted a population-based study to ascertain the frequency of 22q11.2DS among school children with math performance below the 25th centile on a standardized achievement test. Among these children, we found a girl with a 22q11.2 deletion spanning LCR22-4 to LCR22-5. This was an unexpected result, because the studies on MD in 22q11.2 focused on the interval LCR22-2 to LCR22-4. Here, we describe the results of the population screening for 22q11.2 deletions among children with MD, report a child with a 22q11.2 distal deletion spanning LCR22-4 to LCR22-5, and review the literature on this specific class of deletion.

METHODS

Participants

Research procedures were approved by the local research ethics review board, and children participated after informed consent was obtained. Participants were recruited from Belo Horizonte, capital of the Brazilian state of Minas Gerais, with approximately 2.5 million inhabitants, with 366,000 school-age children and adolescents. Approximately 82% of them attend public schools, and the rest attend private schools.

The study was conducted in two phases. Phase I included classroom psychological screening and Phase II included individual neuropsychological assessment and 22q11.2DS genotyping. Phase I was conducted in 16 randomly selected schools, 11 of which are public. A total of 1,520 children were screened in this phase. This sample had a mean age of 9.75 (SD = 1.95) years, 51% were female, and mean formal schooling was 3.39 (SD = 1.66) years.

Three instruments were used in Phase I. Intelligence was assessed using the Brazilian validated Raven's Colored Progressive Matrices [Angelini et al., 1999]. School achievement was assessed using the Arithmetic and Single Word Spelling subtests of the Brazilian School Achievement Test [Teste do Desempenho Escolar, TDE; Stein, 1994; Oliveira-Ferreira et al., 2012]. Behavior was evaluated using Child Behavior Checklist (CBCL) [Achenbach, 2001]. Detailed descriptions of TDE and CBCL are provided in Supplementary Box 1.

In Phase I, we selected 82 children identified with MD and 70 normal, typical math-achieving (TA) children to participate in Phase II. Control and MD cases were matched according to sex, age, grade, and type of school (public or private) in order to avoid socioeconomic differences. Results from this phase have been reported elsewhere [Costa et al., 2011; Ferreira et al., 2012; Haase et al., 2012].

Molecular Assays

DNA was extracted from peripheral blood or saliva as described elsewhere [Miller et al., 1988]. The 22q11.2 copy number variations were ascertained using the SALSA MLPA P250-A1 and P250-B1 kits (MRC-Holland, Amsterdam, The Netherlands), according to the manufacturer's directions. Results were analyzed using a spreadsheet developed by National Genetics Reference Laboratory, Manchester (NGRL; MRC http://www.ngrl.org.uk/Manchester/). A deletion detected by Multiplex Ligation-dependent Probe Amplification (MLPA) in the patient described in detail here was confirmed by array Comparative Genome Amplification (aCGH), using the whole genome Cytosure^{TM}, ISCA V2 array 8 × 60K (Oxforg Gene Technology, OGT, UK) containing ~60,000 oligonucleotides.

RESULTS

Children were not invited to participate in Phase II if their performance was below the 10th centile in the Raven's Colored Progressive Matrices or below the 25th centile exclusively in the TDE Spelling subtest, or if the data were incomplete. Participants were classified according to their performance on the Arithmetic and Spelling subtests. Children who were invited to participate in the TA group performed above the 25th centile in all subtests. Pupils performing below the 25th centile in the Arithmetic subtest were invited to participate in the MD group. No significant differences in TDE Arithmetic performance were found between the subgroups of MD children with and without comorbid TDE spelling difficulties, therefore both groups were collapsed into a single MD group.

MLPA assays were performed to identify copy number variations in the 22q11.2 region that could be connected to the MD phenotype. Normal MLPA results were obtained for all children in the control group and all except one in the MD group, who showed an atypical 22q11.2 deletion (Supplementary Fig. 1), detected by probes from *HIC2* to *TOP3B*, corresponding to the LCR22-4 to LCR22-5 interval. Probes *LZTR1*, proximally, and *RTDR1*, distally, showed normal MLPA profiles. According to aCGH, this deletions spans 947,631 bp [chr22:20,287,395–21,235,025 (NCBI36/hg18)].

The child bearing the 22q11.2 LCR22-4 to LCR22-5 deletion is an 11-year-old girl with MD phenotype. She was adopted at 1 year of age, and no information on pregnancy, delivery, or early development was known to her adoptive parents. At 1 year of age, she was unable to sit or crawl. After 3 months with the adoptive family, she started to walk and to utter her first words. Respiratory and otitis symptoms were frequent in the first years of life, but she was otherwise healthy. The adoptive parents reported math and text comprehension difficulties from the beginning of her school life,

although she can now read and write. Additionally, they report enuresis and difficulties in social interactions that they characterized by her having only one friend (an 18-year-old female cousin) and a tendency not to engage in conversation. The girl was previously diagnosed as having attention deficit hyperactivity disorder (ADHD), but treatment with methylphenidate was not beneficial. At clinical examination, she presents with short stature, normal weight and head circumference, apparent hypotelorism, upslanting palpebral fissures, long nose, submucous cleft palate, bifid uvula, pointed chin, long, thin fingers, short and broad nails, and flat feet (Fig. 2). General clinical, uronephrological, and cardiological exams were normal. A standard neurological exam was normal. Structural magnetic resonance imaging of the brain was normal. The most prominent cognitive-behavioral findings were intelligence in the 60th centile (Raven's raw scores equal to 21 and 30, respectively, at 8 and 11 years) and math achievement at 8 years old below the 25th centile. After one year of neuropsychological rehabilitation, math achievement improved to the average range of performance (TDE Arithmetic >25th centile), but difficulties in school persisted, causing one grade retention. Learning difficulties are restricted to math, with normal results in spelling and reading tests. Parents' complaints of mild phobic symptoms, shyness and social anxiety were corroborated by the attending neuropsychologists. In the CBCL, normal social (T-score = 65) and attention (T-score = 65) behaviors were reported by the parents, and the DSM-IV clinical scores were also normal. In sum, the phenotype was characterized by very mild somatic anomalies, normal intelligence, and non-severe learning difficulties, mainly in the domains of math and text processing.

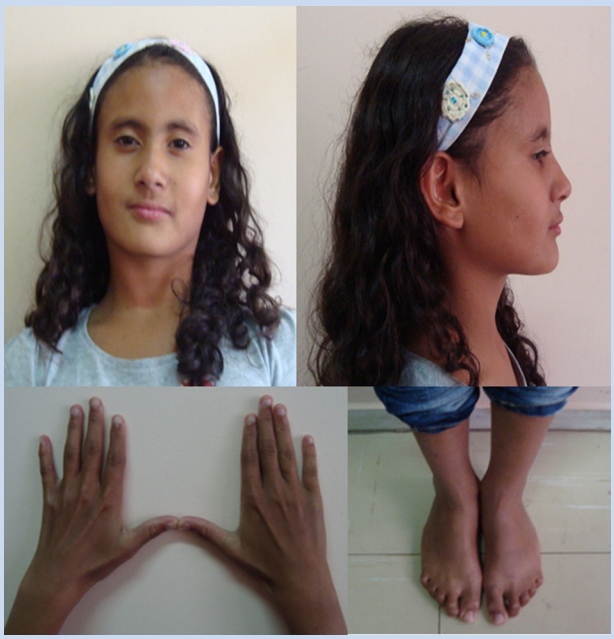

FIG. 2. Patient with a 22q11.2 deletion syndrome spanning only the LCR22-4 to LCR22-5 interval. Observe that she presents subtle anomalies: arched eyebrows, apparent hypotelorism, upslanting palpebral fissures, pointed chin, low-set ears, short nails, and flat feet.

DISCUSSION

This is the first study to be developed to ascertain the frequency of 22q11.2DS among persons with MD. Several studies have suggested that 22q11.2DS children perform better in reading and spelling than in arithmetic tasks [Swillen et al., 1999; Wang et al., 2000; DeSmedt et al., 2007, 2009b]. Verbal abilities and short-term memory are preserved in these children, but they have low performance in visuospatial short-term memory, working memory, and inhibitory control tests [Bearden et al., 2001; Sobin et al., 2004]. Performance in reading numbers and recalling arithmetic facts in one-digit tasks were normal, but magnitude representation and calculation strategies were lower than in controls [DeSmedt et al., 2007]. Children with 22q11.2DS have difficulties in number comparison, calculation strategies, and solving word problems involving semantic manipulations. These findings point to specific deficits in the quantity subsystem in children with 22q11.2 DS. Therefore, it has been suggested that 22q11.2DS is a specific type of math learning disability [DeSmedt et al., 2007].

To ascertain the contribution of 22q11.2DS to the MD phenotype, we adopted a two-step strategy. In Phase I, we applied a widely used educational achievement test to a representative sample of school-age children, composed of 1,529 subjects [Costa et al., 2011; Ferreira et al., 2012]. From this sample, 70 TA and 82 MD children were selected to take part in a second round of neuropsychological and molecular screening tests. Copy-number variations in 22q11.2 region were assessed using MLPA, which allowed the detection of a small deletion in one subject of the MD group. Interestingly, this deletion spanning the interval between LCR22-4 and LCR22-5, and *not* extending into the typically deleted region in 22q11.2DS, the interval between LCR22-2 and LCR22-4, usually associated to MD.

A genomic condition associated with the 22q11.2 distal deletion syndrome has been proposed based on the analyses of patients with deletions spanning from LCR22-4 to LCR22-8 [Fernández et al., 2009]. Due to the small number of reported patients bearing such deletions, previous studies included patients with different, but not always overlapping, deletions. Therefore, there are two major open questions: Do 22q11.2 distal deletions, spanning the interval LCR22-4 to LCR22-5 only, have a specific phenotype? Is a math learning disability a part of this phenotype?

To answer these questions, we reviewed the literature focusing specifically on this deletion [Saitta et al., 1999; Ben-Shachar et al., 2008; Newbern et al., 2008; Rodningen et al., 2008; Xu et al., 2008; Bruce et al., 2010; Tan et al., 2011; Verhoeven et al., 2011; Fagerberg et al., 2012; Molck et al., 2013]. In Supplementary Table I, we present a detailed description of each patient, including the present one; in Supplementary Table II, we present a list of findings reported only once among those patients.

Clearly, there is high phenotypic variability among persons with a deletion only in the interval LCR22-4 to LCR22-5. The most frequent findings are prematurity, prenatal and postnatal growth restriction, microcephaly, apparent hypotelorism, short upslanting palpebral fissures, hypoplastic nasal alae, featureless philtrum, congenital heart defects, and developmental delay. Skeletal abnormalities are also

common and include valgus ankle, valgus knee, flat feet, scoliosis, hyperextensible joints, short and broad nails, and minor radial defects. Thin upper lip vemilion, high palate, bifid uvula, pointed chin, posteriorly rotated ears, abnormal external ears, and retro/micrognathia were reported in at least three of the 20 patients.

Speech developmental delay was reported far more frequently than motor developmental delay. Intellectual disability is not a frequent finding (3 out of 18 patients), but learning disability is (7 out of 7). Moreover, there is a clear association of this deletion with a wide range of behavioral phenotypes, including ADHD, social difficulties, gagging and oral aversion, lumpy food difficulties, panic disorder, anxiety, uncontrolled aggression, and craving for food. One patient had drug-responsive nocturnal epileptogenic activity [Rodningen et al., 2008].

In addition to these 20 patients presenting a deletion only in the LCR22-4 to LCR22-5 interval, 29 patients presented other deletions in this chromosomal region [review by Fagerberg et al., 2012]. These include 23 patients bearing larger deletions including the interval LCR22-4 to LCR22-5 and extending distally. In these patients, clinical manifestations were quite similar to those observed in patients with deletions only in the interval LCR22-4 to LCR22-5. Except for the susceptibility to malignant rhabdoid tumor, which maps to the LCR22-6 to LCR22-7 interval, all findings reported for those larger deletions have already been described in patients with deletions covering only the LCR22-4 to LCR22-5. This suggests that the LCR22-4 to LCR22-5 interval is the critical region for the phenotype (Fig. 1).

On the other hand, only four patients who present deletions in the interval between LCR22-5 and LCR22-6 have been identified so far. Three of these patients had isolated phenotypes. One had a congenital heart defect, while his father only had low-set ears [Rauch et al., 2005], and the third patient had DD/MR/LD. However, the fourth patient had a more complex phenotype, characterized by postnatal growth restriction, congenital heart malformation, cleft palate, Müllerian dysplasia, hypoplastic thumbs, hypoplastic middle phalanx, and some absent phalanges. Interestingly, this clinical picture resembles that of some patients with LCR22-4 to LCR22-5 deletions, particularly the Müllerian dysplasia and radial defects [Tan et al., 2011]. These are not common findings, and have also been reported in other patients with deletions only in the LCR22-4 to LCR22-5 interval. Phenotypic overlapping, among patients with deletions in non-overlapping chromosomal segments, suggests the existence of long-range regulatory effects that are characteristic of genomic diseases [Carvalho et al., 2010].

The most straightforward genotype-phenotype correlation in the 22q11.2 region has been described for deletions spanning the LCR22-6 to LCR22-7 interval and malignant rhabdoid tumor [reviewed by Fagerberg et al., 2012]. Considering that all patients reported so far with deletions spanning this region have developed this neoplasia, this seems to be a true haploinsufficiency effect.

Another point to stress is that, despite the wide range of phenotypes associated with the 22q11.2 deletions restricted to the LCR22-4 to LCR22-5 interval, some patients do clinically resemble each other. However, despite the subtle anomalies reported for these patients, there is a conspicuous facial resemblance among some of them [see Fig. 2 and also patient photographs in Rauch et al., 2005; Ben-Shachar et al., 2008; Tan et al., 2011; Verhoeven et al., 2011; Fagerberg et al., 2012]. This facial resemblance suggests that there is a specific syndrome associated with this deletion. The 22q11.2 DS (LCR22-4 to LCR22-5) microdeletion syndrome is characterized by the following: prematurity, pre- and postnatal growth restriction, microcephaly, apparent hypotelorism, short upslanting palpebral fissures, hypoplastic nasal alae, featureless philtrum, thin upper lip vermilion, pointed chin and nose, posteriorly rotated/abnormal external ears, congenital heart defects, subtle skeletal abnormalities, hyperextensible joints, developmental delay, particularly compromising the speech, learning disability (including math learning disability), intellectual disability in some cases, and behavioral problems.

The specific relationship between MD and the LCR22-4 to LCR22-5 interval is suggested by the fact that 2 out of 18 of the cases reported so far have MD. Indeed, we report the second patient with a distal 22q11.2 deletion syndrome spanning the interval between LCR22-4 and LCR22-5 and presenting with normal intelligence and math learning disabilities. Recently, another girl was reported to present with normal intelligence, difficulties in planning, concentration, calculation, visuospatial perception, and chronic anxiety disorder [Verhoeven et al., 2011]. However, because MD is a widespread condition, this association may be coincidental.

On the other hand, we found one individual with a LCR22-4 to LCR22-5 deletion among the 82 children with MD. This frequency (1.2%) is amazingly high, raising the question as to whether the 22q11.2 distal is indeed a rare event and not an underdiagnosed one. Indeed, until recently, the probes used in molecular studies such as FISH spanned only the LCR22-2 to LCR22-3a interval. It is only since the introduction of new methods, such as MLPA, aCGH, and qPCR, that it is possible to investigate the LCR22-4 to LCR22-5 interval. This has broadened the possibilities for the investigation of the contribution of specific genomic diseases to complex, common phenotypes.

In conclusion, although math learning disabilities have been extensively researched, the genetic causes remain elusive [Butterworth et al., 2011]. It is plausible that the LCR22-4 to LCR22-5 deletion may be one of the genetic components involved with the MD phenotype. Additionally, other than the math learning disability, the child reported here showed only subtle dysmorphias that, alone, would not justify referral for a clinical genetic evaluation. Currently, molecular tests are indicated only when relatively severe phenotypes are present, such as intellectual disability, autism, malformations, or combinations such as neurodevelopmental delay *plus* facial abnormality. Our results suggest that it may be worth screening patients with subtle clinical manifestations, such as learning disabilities, for microdeletions/microduplications. Although it is too early to adopt microdeletions/microduplications screening for persons with MD without associated congenital malformations or anomalies in the clinical practice, the results presented here open a new investigative field.

ACKNOWLEDGMENTS

We thank to Prof. Carla Rosenberg for performing aCGH. This research was funded by FAPEMIG (APQ-02755-SHA, APQ-03289-10,

APQ-02523-11, PPM-00280-12), CNPq (307006/2008-5, 401232/2009-3, 557664/2010-1, 504891/2010-3), and CAPES/DAAD. VGH and MRSC have been awarded CNPq research productivity fellowships 308157/2011-7 and 307975/2010-0, respectively. The authors thank the Program for Technological Development in Tools for Health-PDTIS/FIOCRUZ for use of its facilities.

REFERENCES

Achenbach TM. 2001. Manual for the child behavior checklist/6 and 18 profile. Burlington: University of Vermont.

Angelini AL, Alves ICB, Custódio EM, Duarte WF, Duarte JLM. 1999. Matrizes progressivas coloridas de Raven—Escala especial. São Paulo: Centro Editor de Testes e Pesquisas em Psicologia.

Bearden CE, Woodin MF, Wang PP, Moss E, McDonald-McGinn D, Zackai E, Emannuel B, Cannon TD. 2001. The neurocognitive phenotype of the 22q11.2 deletion syndrome: Selective deficit in visual-spatial memory. J Clin Exp Neuropsychol 23:447–464.

Ben-Shachar S, Ou Z, Shaw CA, Belmont JW, Patel MS, Hummel M, Amato S, Tartaglia N, Berg J, Sutton VR, Lalani SR, Chinault AC, Cheung SW, Lupski JR, Patel A. 2008. 22q11.2 distal deletion: A recurrent genomic disorder distinct from DiGeorge syndrome and velocardiofacial syndrome. Am J Hum Genet 82:214–221.

Bruandet M, Molko N, Cohen N, Dehaene S. 2004. A cognitive characterization of dyscalculia in Turner syndrome. Neuropsychologia 42: 288–298.

Bruce S, Hannula-Jouppi K, Puoskari M, Fransson I, Simola KOJ, Lipsanen-Nyman M, Kere J. 2010. Submicroscopic genomic alterations in SilvereRussell syndrome and SilvereRussell-like patients. J Med Genet 47:816–822.

Butterworth B, Varma S, Laurillard D. 2011. Dyscalculia: From brain to education. Science 332:1049–1053.

Carvalho CMB, Zhang F, Lupski JR. 2010. Genomic disorders: A window into human gene and genome evolution. Proc Natl Acad Sci 107: 1765–1771.

Costa AJ, Lopes-Silva JB, Pinheiro-Chagas P, Krinzinger H, Lonnemann J, Willmes K, Wood G, Haase VG. 2011. A hand full of numbers: A role for offloading in arithmetic learning. Front Psychol 2:368.

Dehaene S. 1997. The number sense. How the mind creates mathematics. Oxford: Oxford University Press. 274p.

DeSmedt B, Swillen A, Devriendt K, Fryns JP, Verschaffel L, Ghequière P. 2007. Mathematical disabilities in children with velo-cardio-facial syndrome. Neuropsychologia 45:885–895.

DeSmedt B, Reynvoet B, Swillen A, Verschaffel L, Boets B, Ghesquière P. 2009. Basic number processing and difficulties in single-digit arithmetic: Evidence from Velo-Cardio-Facial syndrome. Cortex 45:177–188.

DeSmedt B, Swillen A, Verschaffel L, Ghesquière P. 2009. Mathematical learning disabilities in children with 22q11.2 deletion syndrome: A review. Dev Disabil Res Rev 15:4–10.

Docherty SJ, Davis OS, Kovas Y, Meaburn EL, Dale PS, Petrill SA, Schalkwyk LC, Plomin R. 2010. A genome-wide association study identifies multiple loci associated with mathematics ability and disability. Genes Brain Behav 9:234–247.

Fagerberg CR, Graakjaer J, Heinl UD, Ousager LB, Dreyer I, Kirchhoff M, Rasmussen AA, Lautrup CK, Birkebaek N, Sorensen K. 2012. Heart defects and other features of the 22q11 distal deletion syndrome. Eur J Med Genet 56:98–107.

Fernández L, Nevado J, Santos F, Heine-Suñer D, Martinez-Glez V, García-Miñaur S, Palomo R, Delicado A, Pajares IL, Palomares M, García-Guereta L, Valverde E, Hawkins F, Lapunzina P. 2009. A deletion and a duplication in distal 22q11.2 deletion syndrome region. Clinical implications and review. BMC Med Genet 10:48–60.

Ferreira FO, Wood G, Pinheiro-Chagas P, Lonnemann J, Krinzinger H, Willmes K, Haase VG. 2012. Explaining school mathematics performance from symbolic and nonsymbolic magnitude processing: Similarities and differences between typical and low-achieving children. Psychol Neurosci 5:37–46.

Gross-Tsur V, Manor O, Shalev RS. 1996. Developmental dyscalculia: Prevalence and demographic features. Dev Med Child Neurol 38: 25–33.

Haase VG, Júlio-Costa A, Pinheiro-Chagas P, Oliveira LFS, Micheli LR, Wood G. 2012. Math self-assessement, but not negative feelings, predicts mathematics performance of elementary school children. Child Dev Res Article ID 982672, 10 pages, doi: 10.1155/2012/982672 (http://www.hindawi.com/journals/cdr/2012/982672/).

Hart SA, Petrill SA, Thompson LA, Plomin R. 2009. The ABCs of math: A genetic analysis of mathematics and its links with reading ability and general cognitive ability. J Educ Psychol 101:388.

Jacobson C, Shearer J, Habel A, Kane F, Tsakanikos E, Kravariti E. 2010. Core neuropsychological characteristics of children and adolescents with 22q11.2 deletion. J Intellect Disabil Res 54:701–713.

Jacobson JL, Dodge NC, Burden MJ, Klorman R, Jacobson SW. 2011. Number processing in adolescents with prenatal alcohol exposure and ADHD: Differences in the neurobehavioral phenotype. Alcohol Clin Exp Res 35:431–442.

Kovas Y, Petrill SA, Plomin R. 2007. The origins of diverse domains of mathematics: Generalist genes but specialist environments. J Educ Psychol 99:128–139.

Krajcsi A, Lukács A, Igács J, Racsmány M, Pléh C. 2009. Numerical abilities in Williams syndrome: Dissociating the analogue magnitude system and verbal retrieval. J Clin Exp Neuropsychol 31:439–446.

Landerl K, Moll K. 2010. Comorbidity of learning disorders: Prevalence and familial transmission. J Child Psychol Psychiatry 51:287–294.

Mazzocco MMM. 2007. Defining and differentiating mathematical learning disabilities and difficulties. In: Berch DB, Mazzocco MMM, editors. Why is math so hard for some children? The nature and origins of mathematical learning difficulties and disabilities. Baltimore: Brookes. pp 29–47.

Miller SA, Dykes DD, Polesky HF. 1988. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16:1215.

Molck MC, Vieira TP, Sgardioli IC, Simioni M, Santos AP, Souza J, Monteiro FP, Gil-da-Silva-Lopes VL. 2013. Atypical copy number abnormalities in 22q11.2 region: Report of three cases. Eur J Med Genet 56:515–5520.

Murphy MM, Mazzocco MM. 2008. Mathematics learning disabilities in girls with fragile X or Turner syndrome during late elementary school. J Learn Disabil 41:29–46.

Newbern J, Zhong J, Wickramasinghe SR, Li X, Wu Y, Samuels Y, Cherosky N, Karlo JC, O'Loughlin B, Wikenheiser J, Gargesha M, Yong Qiu, Doughman YQ, Charron J, Ginty DD, Watanabe M, Saitta SC, Snider WD, Landreth GE. 2008. Mouse and human phenotypes indicate a critical conserved role for ERK2 signaling in neural crest development. Proc Natl Acad Sci 105:17115–17120.

Oliveira-Ferreira F, Souza-Costa D, Micheli LR, Oliveira LFS, Pinheiro-Chagas P, Haase VG. 2012. School achievement test: Normative data for a

representative sample of elementary school children. Psychol Neurosci 5:157–164.

Parsons S, Bynner J. 2005. Does numeracy matter more? London: University of London, Institute of Education National Research and Development Centre for Adult Literacy and Numeracy (http://www.nrdc.org.uk/download.asp?f=2979&e=pdf, www.nrdc.org.uk/download.asp?f=2979&e=pdf).

Rauch A, Zink S, Zweier C, Thiel CT, Koch A, Rauch R, Lascorz J, Hüffmeier U, Weyand M, Singer H, Hofbeck M. 2005. Systematic assessment of atypical deletions reveals genotype-phenotype correlation in 22q11.2. J Med Genet 42:871–876.

Rodningen OK, Prescott T, Eriksson AS, Rosby O. 2008. 1.4 Mb recurrent 22q11.2 distal deletion syndrome, two new patients expand the phenotype. Eur J Med Genet 51:646–650.

Saitta SC, McGrath JM, Mensch H, Shaikh TH, Zackai EH, Emanuel BS. 1999. A 22q11.2 deletion that excludes UFD1L and CDC45L in a patient with conotruncal and craniofacial defects. Am J Hum Genet 65:562–566.

Shalev R, Manor O, Kerem B, Ayali M, Badichi N, Friedlander Y, Gross-Tsur V. 2001. Developmental dyscalculia is a familial learning disability. J Learn Disabil 34:59–65.

Sobin C, Kiley-Brabeck K, Daniels S, Blundell M. 2004. Networks of attention in children with the 22q11 deletion syndrome. Dev Neuropsychol 26:611–626.

Stein LM. 1994. TDE—Teste de Desempenho Escolar. Manual para aplicação e interpretação. São Paulo: Casa do Psicólogo.

Swillen A, Vandeputte L, Cracco J, Maes B, Ghesquière P, Devriendt K, Fryns JP. 1999. Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): Evidence for a nonverbal learning disability? Child Neuropsychol 5:230–241.

Tan TY, Collins A, James PA, McGillivray G, Stark Z, Gordon CT, Leventer RJ, Pope K, Forbes R, Crolla JA, Ganesamoorthy D, Burgess T, Bruno DL, Slater HR, Farlie PG, Amor DJ. 2011. Phenotypic variability of distal 22q11.2 copy number abnormalities. Am J Med Genet Part A 155A:1623–1633.

Verhoeven W, Egger J, Brunner H, De Leeuw N. 2011. A patient with a de novo distal 22q11.2 microdeletion and anxiety disorder. Am J Med Genet Part A 155A:392–397.

Wang PP, Woodin MF, Kreps-Falk R, Moss EM. 2000. Research on behavioral phenotypes: Velocardiofacial syndrome (deletion 22q11.2). Dev Med Child Neurol 42:422–427.

Willcutt EG, Pennington BF, Duncan L, Smith SD, Keenan JM, Wadsworth S, Defries JC, Olson RK. 2010. Understanding the complex etiologies of developmental disorders: Behavioral and molecular genetic approaches. J Dev Behav Pediatr 31:533–544.

Xu J, Fan YS, Siu VM. 2008. A child with features of Goldenhar syndrome and a novel 1.12 Mb deletion in 22q11.2 by cytogenetics and oligonucleotide array CGH: Is this a candidate region for the syndrome? Am J Med Genet Part A 146A:1886–1889.

Yu S, Graf WD, Shprintzen RJ. 2012. Genomic disorders on chromosome 22. Am J Med Genet Part A 24:665–671.

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article at the publisher's web-site.