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Neuromotor Deficits in Children With the 22q11 Deletion Syndrome

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Abstract

The 22q11 chromosomal deletion syndrome (22q11DS) is associated with a heterogeneous physical phenotype, neurocognitive deficits, and increased risk of later psychiatric illness. Sporadic clinical reports suggested motor differences, but quantitative studies of movement in children with 22q11DS are rare. If present in a majority of affected school-age children, characterization of neuromotor deficits may prove to be critical for intervention, neurocognitive test interpretation, and understanding etiology. We administered the Movement Assessment Battery for Children to 72 children ages 4.3 to 16.1, including 49 children confirmed positive for the 22q11 deletion and 23 control siblings. We predicted a higher frequency of global and domain impairment in manual dexterity, eye—hand coordination, and balance among affected children. Ninety-four percent of affected children had marked neuromotor deficits, and group scores differed broadly for both global and subarea measures. Secondary analyses showed no impairment differences between younger and older children with 22q11DS, and longitudinal trajectories for 12 affected children suggested stability of deficits over 3-year intervals. Neuromotor deficits in children with 22q11DS occur early in development, continue throughout the school-age years, should be considered in the interpretation of motor-based achievement and IQ tests, and require targeted and ongoing remediation throughout childhood and adolescence. Further studies examining the specificity of motor impairment to 22q11DS are needed.

Keywords

22q11.2; velocardiofacial syndrome; motor impairment; learning disabilities

22q11 deletion syndrome (22q11DS) is a genetic disorder of unknown cause found in approximately 1 in 5,000 live births.¹ The syndrome occurs de novo in over 90% of cases and results from a meiotic deletion at the q11.2 site on chromosome 22.² Congenital anomalies of widely varying severity can be associated with this condition and might include heart defects, immunological deficits, craniofacial dysmorphologies, and/or velopharyngeal defects such as overt or submucous cleft palate.³ Prior to identification of a single associated deletion, distinct clinical labels indicated a child's physical presentation. These have included DiGeorge syndrome (primary immunological deficit), velocardiofacial syndrome (VCFS; including

velopharyngeal, heart, and facial anomalies), and conotruncal anomaly face syndrome (primary heart defect with facial dysmorphologies). The physical phenotype is strikingly heterogeneous, and an unknown number of children may manifest nearly undetectable medical signs.⁴

With regard to cognitive functioning, learning disabilities were among the first characteristics to be described in children and adults with 22q11DS and are consistently estimated to occur in 90% to 100% of cases.^{5,6} Recent reports have provided evidence of specific deficits in executive function,^{7–9} visual attention,^{8,10,11} memory and learning,¹² visuospatial ability,^{13,14} numerical skills,¹³ and speech and articulation disorders.¹⁵ Lowered sensorimotor (startle) gating has also been reported,¹⁶ and associations between sensorimotor gating and visual executive attention have been suggested.¹⁷ The severity of each of these deficits varies widely among individual children. Studies of adults with 22q11DS have suggested that affected children may be at increased risk of later severe psychiatric illness,¹⁸ heightening the urgency for full characterization of early syndrome features.

Marked neuromotor delays and ongoing movement impairment have long been described in children with 22q11DS, although quantitative reports of these have been infrequent. From the first, observational reports described high rates of neuromotor differences among children with 22q11DS.^{19–24} Marked gross and fine motor deficits measured with a standardized battery, and hypotonia, were reported among a majority of affected preschool children,²⁵ and recent evidence has suggested that early motor deficits continue throughout childhood^{4,9,26} and include ongoing hypotonia, poor balance, and gross and fine motor impairment, and extending into oral musculature. Interestingly, unilateral hemispheric polymicrogyria in a child with 22q11 deletion presenting with hemiplegia, cognitive and behavioral disorders was recently described,²⁷ suggesting a possible source of severe motor abnormalities, spasticity, and/or oral—motor deficits in children with extreme manifestations. (Occurrences of symptoms associated with perisylvian polymicrogyria, including seizures, spasticity, and frank mental retardation, are not common in children with 22q11DS.)

Neuromotor impairment has received scant attention as compared with other physical or neurocognitive features of 22q11DS. The lack of recognition regarding possible motor deficits should be of substantial concern. Unrecognized motor impairment among school-age children can lead to a detrimental mischaracterization of academic performance and cognitive potential, as well as subadequate programs of remediation. Unidentified motor deficits confound the validity of cognitive batteries that include subtests with a motor component; when lowered scores from motor-based subtests are included in score summations, they negatively bias global IQ. Comparing the motor performance of children with 22q11DS to neurotypical controls is necessary for determining the extent of their possible deficits. Characterizing motor deficits is necessary for accurate interpretation of test and classroom performance, for determining remediation needs, and for expanding the understanding of syndrome etiology.

We administered the Movement Assessment Battery for Children (MABC)²⁸ to 72 children, 49 with the 22q11 deletion syndrome and 23 typically developing control siblings (Table 1). The MABC provides national norms for global ability, as well as functioning in the areas of manual dexterity, eye—hand coordination, and balance. We predicted that a greater number of affected children would score in the impaired range with regard to both total impairment score and individual subtest scores as compared with neurotypical control siblings. Further, children with 22q11DS have frequently been characterized as developmentally delayed, suggesting that some deficits may resolve with age. For this reason, we compared motor functioning in younger and older children with 22q11DS. In the absence of other evidence, we hypothesized that impairment among affected children would lessen with age, and thus fewer older as compared with younger affected children would have scores in the impaired range.

PATIENTS AND METHODS

Participants

These data were collected as part of a longitudinal study of neurocognitive development in children with 22q11DS. Parents learned of our project through Web site postings, brochures sent to genetic counselors, doctors' offices, speech and language specialists, and parent support groups. Prior to enrollment in the study, all children were confirmed positive for the 22q11 deletion via fluorescence in situ hybridization (FISH) assay. Potential participants were excluded if they or their parents were not fluent in the English language. One child (female, age 13) originally recruited and scheduled for evaluation refused to come for evaluation and was never seen by study staff; one family withdrew from the study after moving out of the country following one completed assessment (female, age 8).

All children were unmedicated at the time of testing. The tests and testing procedures were explained to the parents by study staff and to child participants by their parents. Consent forms were sent to parents for review approximately 1 month in advance of scheduled testing. Child verbal assent and parental informed consent were obtained on the morning of testing prior to the start of assessment procedures. An appropriate institutional review board approved this project prior to data collection.

Procedures

Testing was conducted by a licensed clinical psychologist, or by one of four specially trained neuropsychological testers with a minimum of 2 years of child testing and/or treatment experience at the doctoral level. A licensed clinical psychologist supervised testers. All testing was completed by 1 PM to control for circadian effects. Parents waited immediately outside the testing room for their children and were available to the children as needed.

The MABC measures manual dexterity (three tasks), eye—hand coordination (two tasks), static balance (one task), and dynamic balance (two tasks). Developmentally appropriate tasks for four age bands are provided. Table 2 summarizes the tasks. Research and development leading to the current MABC began in 1966, with the goal of developing a statistically valid and reliable instrument for assessing motor dysfunction in children for both research and intervention. Items for the 1972 version²⁹ were piloted on over 1,000 school-age children in Scotland and Canada. The first published edition (1972) was standardized on 854 Canadian school children, and the 1984 revision³⁰ was standardized on approximately 1,200 children ages 5 to 12 in the United Kingdom and Canada, with equal representation of males and females. No substantial differences by nationality were found. The 1992 version used in this study²⁸ included several enhancements, including more detailed scoring instructions, addition of 4-year-old norms, and U.S. norms for approximately 1,200 neurotypical children ages 4 to 12; this version achieved high validity and also high test—retest reliability.²⁸ A recent study of the MABC also reported high test—retest reliability as well as concurrent validity with the lengthier Bruininks—Oseretsky Test of Motor Proficiency.^{31,32} The MABC was selected for its very large national and cross-national standardization samples, highly stable cutoff scores, and clinical efficiency (completion time is 15–20 minutes). Stanford—Binet Intelligence scales³³ were administered to children for the assessment of cognitive general ability.

Scoring, Database, and Data Analysis

Individual subtest items were scored 0 through 5, with higher scores indicating impairment. Subtest scores were totaled, and the percentile rank equivalent of each total score was determined according to the tables provided.²⁸ Fifth percentile cutoff criteria provided in the manual for each test domain and age group were used to group children dichotomously (impairment yes/no). Data were entered and maintained in a Statview database by a specially

trained research assistant (S.H.M.) and analyzed using Statview version 3.0 for PC or SAS version 6.0 for PC. Testers completed the initial scoring immediately following test administration. Scoring was checked by testers and by the research assistant prior to data entry, final scores were transferred onto data forms, and all data were entered into a Statview database. Entered data were checked at regular intervals during the data collection and entry stage, and the entire sample was reviewed for scoring accuracy prior to data analysis.

Movement was assessed at regular 1-year intervals in affected children and once in control siblings. The database here described included a total of 127 administrations of the MABC. Among affected children, 49 completed one test administration, 43 completed two administrations, and 12 affected children completed three administrations. With regard to siblings, 23 completed one test administration.

t tests were used to examine possible mean age differences between groups. Stem-and-leaf plots were used to examine distributional characteristics of the data. To examine the stability of possible differences, data from affected children at two time points were each compared with data from control siblings. χ^2 analyses were used to examine group frequency differences in the number of children with total and area scores in the impaired range. χ^2 analyses were also used to test associations between age and subtest score performance among younger and older affected children. Because the score distributions of younger and older children matched for total impairment scores, Mann—Whitney *U* tests were used to test for differences among affected children grouped by age. Three-year longitudinal trajectories for 12 children were illustrated with line graphs.

RESULTS

Seventy-two children were included in these analyses, 49 (24 females) with the 22q11 DS and 23 typically developing control siblings (16 females). Affected children ranged in age from 4.3 to 16.1, with a mean age of 8.6 ± 2.9 . Four of the 49 (8%) were over age 12, and 3 were below age 5 (6%). Siblings ranged in age from 5.3 to 12.8, with a mean age of 8.8 ± 2.3 . Stanford—Binet composite IQ scores (mean = 100 ± 16) were consistent with past reports of children with 22q11DS. The IQs of affected children ranged from 62 to 120. The “mildly mentally retarded range” includes scores from 50 to 69. No control siblings and only three affected children had scores in this range (62, 67, and 67). The scores of the remaining 46 affected children and 23 sibling controls were normally distributed from the lower average to superior range (29% of affected children had IQ scores above the mean) (Table 1).

Groups were comparable with regard to mean age (mean difference = 0.19; *df* = 70; *t* = 0.28). Initial review of group data suggested that percentile equivalents of total summary scores and subscale score totals were not normally distributed. Distributions of scores for one or both groups on each of the hypothesized variables were skewed, and for each variable the distributions differed by group. With regard to control siblings, these data characteristics might be expected because the MABC quantifies impairment and thus does not scale movement differences among typically developing children (“ceiling effect”). The heavily skewed distributions for three of four variables for affected children were less predictable and suggested a high level of impairment for a majority of children in the sample. Table 3 compares group medians and interquartile ranges (IQR) for total and subscale score variables.

Nonparametric tests were used for group comparisons. Continuous scale percentile rank for total impairment scores and subscale score totals were dichotomized to indicate impairment (yes/no) using the MABC fifth percentile cutoffs (~2 SDs below the standardization sample mean, one-tailed test). Table 4 shows the impairment frequency counts by group. For descriptive purposes, the total number of impaired areas per affected child was also calculated.

Among affected children, 4 of 49 had no measurable motor impairment. Among the remaining 45, 6 had impairment in only manual dexterity, 22 had impairment in manual dexterity and one additional area (more frequently than not, in balance), and 17 had impairment in all three areas tested.

χ^2 analysis was used to test differences in the frequency of impairment between affected children in year 1 and year 2 as compared with control siblings tested at one time point. χ^2 analysis of total score was significant for year 1 ($\chi^2_{(1; n=72)} = 55.4; P < 0.01$) and also for year 2 ($\chi^2_{(1; n=66)} = 53.6; P < 0.01$).

A similar strategy was used to test differences between groups for the three subscale scores. For manual dexterity, the fifth percentile (impairment) for 4- to 5-year-olds was indicated by scores higher than 9.5, and higher than 6.5 for those 6 years and older. For ball skills, fifth percentile was indicated by scores higher than 6.0 for 4- to 5-year-olds, and higher than 5.0 for those 6 years and above. For balance, the fifth percentile was indicated by scores higher than 9.0 for 4- to 5-year-olds, and higher than 7.5 for those 6 years and above. χ^2 tests were calculated for each of the subtests for year 1, and all tests for differences were significant using Fisher's exact P values: manual dexterity $\chi^2_{(df=1; n=72)} = 39.1, P < 0.001$; ball skills $\chi^2_{(df=1; n=72)} = 12.8, P < 0.001$; balance $\chi^2_{(1; n=72)} = 33.8, P < 0.001$. Findings for year 2 were roughly equivalent to those from year 1: manual dexterity $\chi^2_{(df=1; n=66)} = 39.8, P < 0.001$; ball skills $\chi^2_{(df=1; n=66)} = 9.4, P = 0.002$; balance $\chi^2_{(df=1; n=66)} = 24.4, P < 0.001$.

Motor Function in Younger and Older Children With 22q11 Deletion Syndrome

Data from 49 children (year 1) were used for comparisons among subgroups of affected children. Two age groups were assigned, including children ages 4 to 7 years and children ages 8 and above. This split separated children in the period of early rapid development (4–7 years) from older children and coincidentally resulted in approximately even cell sizes in this particular sample. The distribution characteristics differed markedly between younger and older affected children for all subscales, but for total impairment scores were matched (negatively skewed) and of equal variance (variance ratio = 1.17; numerator $df = 22$; denominator $df = 25$; $P = 0.71$). Mann–Whitney U tests were used to examine possible differences in total impairment by age group. Contrary to the hypothesis, no differences were apparent (age group: $z = -0.95$; $P = 0.34$). To examine the possible associations between age and motor competence on individual subscales, χ^2 analyses using Fisher's exact P values were calculated. No differences between age groups were apparent (manual dexterity $\chi^2_{(df=1; n=49)} = 0.34, P = 0.70$; ball skills $\chi^2_{(df=1; n=49)} = 0.21, P = 0.78$; balance $\chi^2_{(df=1; n=49)} = 0.51, P = 0.53$).

Longitudinal Trajectories

Data from three time points were available for 12 of the affected children. Their developmental trajectories were plotted and are presented in Figure 1. Over 3 years, total movement scores for 10 of 12 children do not exceed the fifth percentile (impairment). For 6 of 12 children, movement impairment remains at or below the first percentile. Two of 12 children, both females, scored well above the fifth percentile for initial testing(s) at a young age but dropped below the fifth percentile by testing year 3. Thus, for the two subjects who demonstrated expected movement ability at an earlier age, skills typical of their peers were not maintained over the 3-year interval examined.

DISCUSSION

Approximately 50 observational and empirical reports of development in children with 22q11DS have been published since 1966. Of these, eight observational reports described

uniformly high percentages of affected children with marked early neuromotor delays and deficits; one study measured neuromotor function in pre-schoolers using a standardized battery,²⁵ and only one study thus far has considered motor performance as a possible confound in neurocognitive testing.¹³

To increase awareness and understanding of movement impairment in children with 22q11DS, motor functions were measured in 72 children, including 49 with 22q11DS and 23 typically developing control siblings. Affected children had greatly increased rates of global movement impairment and increased rates of impairment in all individual areas assessed, including manual dexterity, eye—hand coordination, and balance. With regard to possible developmental change, younger and older affected children did not differ with regard to total movement impairment, nor with regard to the frequency of impairment in the three subareas assessed.

Though rarely evaluated, marked neuromotor deficits are common in children with 22q11DS, from early childhood through adolescence, and do not appear to lessen with age. These conclusions are based on the stability of the cross-sectional findings from year 1 and year 2, and on the very small range of summary values among affected children. Three-year longitudinal data from 12 children provide additional support for these conclusions. Large-scale longitudinal studies are needed to examine how and when specific deficits emerge, and to explore the interplay between neuromotor deficits at different ages and the development of particular cognitive functions. Whether these deficits are specific to 22q11DS awaits further study.

Manual dexterity (fine motor dexterity and precision, as well as graphomotor control) was the most uniformly impaired function among affected children. In younger children, hand movements tended to be very imprecise and pincer grasp was weak; movements were often jerky and unsteady, and this greatly reduced efficiency and completion speed. Among older children, grasp strength was unregulated and was either very weak or overly tensed, both of which lessened control. For the oldest children, even exceedingly slow completion did not improve accuracy.

Younger and older affected children varied the most on tests of eye—hand coordination assessed by tasks requiring ball skills. Those who completely failed had little perception of the force or trajectory of their throws, and they could not adapt subsequent tries based on earlier errors. Grasp timing when attempting to catch was poor. Of special note, those who had ongoing involvement in games that required ball skills, regardless of their proficiency in these sports or lack thereof, performed notably better. Thus, these very common symptoms may also be remediable, and full assessment followed by targeted long-term intervention is indicated.

Children who performed most poorly on balance tasks did not use compensatory arm movements or eye gaze to establish balance. These children teetered wildly, some with very exaggerated movements. Affected children who did better often had one poor trial and one trial where they were suddenly able to secure a balance point.

Overall, affected children greatly enjoyed the motor tasks despite their frequent difficulties and failures, and compliance was near 100%. The children welcomed the active and concrete nature of the tasks, suggesting that this aspect of functioning is very clinically accessible in children with 22q11DS.

Given the frequency and severity of neuromotor deficits among children and adolescents with 22q11DS, measures of neuromotor function should be included in all neuropsychological and neurocognitive studies of children with 22q11DS and integrated into research programs investigating the syndrome's biological basis. IQ batteries with subtests that attempt to assess nonmotor aspects of cognitive development via timed subtests requiring manipulation of

objects or writing instruments may be invalid for children and adolescents with 22q11DS. Alternative subtests that do not include a motor component must be substituted. Fine and gross motor deficits can directly impact classroom performance, self-care, activity-based social interactions, and can negatively influence others' perceptions. Difficulty in these areas can lower a child's self-evaluation, create debilitating and embarrassing dependence, and have a lasting impact on a child's self-esteem. Once movement impairment has been identified, it is essential to provide targeted long-term intervention.

Study Limitations

This sample included comparisons with neurotypical siblings with no history of cognitive or developmental delay. This type of comparison is important for establishing the extent of deficits in a given atypical population. However, this comparison provides no information regarding the specificity of motor deficits to children with 22q11DS. Given the marked deficits identified in this report, additional studies are warranted for determining the nature and specificity of these deficits to children with 22q11DS. Studies comparing children with 22q11DS to cognitively matched controls with no known genetic abnormality, and to cognitively matched controls with genetic disorders other than 22q11DS (e.g., fragile X, William's, Prader—Willi), would be especially valuable for exploring the etiology of 22q11DS.

This sample included a very broad age range. Comparisons revealed no differences between age groups; however, because of the data characteristics, we were unable to examine whether particular motor functions fluctuate with age. This sample also included relatively few typically developing male siblings. Future studies should include larger numbers of control siblings with balanced numbers of males and females. The sample included mostly Caucasian children, and the application of these findings to children of other racial backgrounds cannot be assumed.

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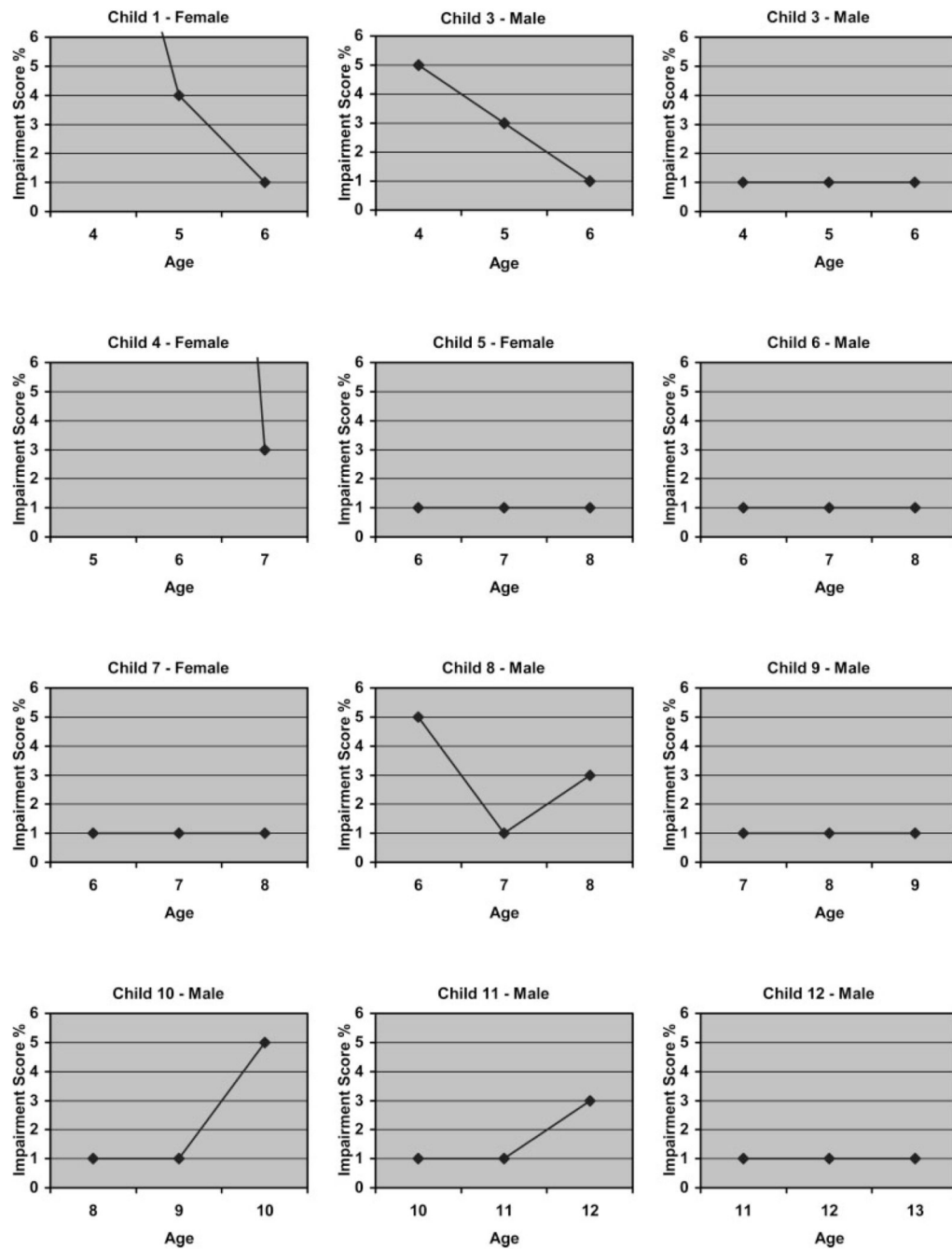


FIG. 1.
Developmental trajectories of neuromotor deficit in 12 children with the 22q11DS.

TABLE 1

Demographics

	22q11DS (n = 49)	Siblings (n = 23)
Female	24/49 (49%)	16/23 (70%)
Caucasian	46/49 (94%)	20/23 (87%)
22q11DS FISH-positive	49/49 (100%)	0
Median age of detection	29.0 months (IQR 4.9)	
History of learning disabilities and/or milestone delays	49/49 (100%)	0
Hypotonia with motor delays before age 3	45/49 (92%)	0
Age	8.6 ± 2.9	8.8 ± 2.3
Stanford—Binet composite IQ ^a	88.0 ± 13.9	119.4 ± 11.8

^aMean = 100 ± 16.

TABLE 2
 Descriptions of tasks on the Motor Assessment Battery for Children

Age band	Subtest	Description
4–6	Manual dexterity	Coin posting, threading beads, pencil bicycle trail
	Eye—hand coordination	Catching bean bag, rolling ball into goal
	Static balance	One-leg balance
	Dynamic balance	Walking heel raised, jumping over chord
7–8	Manual dexterity	Placing pegs, threading lace, pencil flower trail
	Eye—hand coordination	One-hand bounce and catch, throwing bean bag in box
	Static balance	Stork balance
	Dynamic balance	Hopping in squares, heel toe walking
9–10	Manual dexterity	Shifting pegs, threading nuts, pencil flower trail
	Eye—hand coordination	Two-hand catch, throwing bean bag in box
	Static balance	One-board balance
	Dynamic balance	One foot hopping in squares, walking ball balance
11–12	Manual dexterity	Turning pegs, cutting out elephant, pencil flower trail
	Eye—hand coordination	One-hand catch, throwing ball at wall target
	Static balance	Two-board balance
	Dynamic balance	Clapping jump over chord, backward heel toe walking

TABLE 3
Descriptive statistics for percentile rank of total impairment and subscale scores

	22q					
	Year 1 (n = 49; mean age = 8.5 ± 2.9)		Year 2 (n = 43; mean age = 9.2 ± 2.3)		Siblings (n = 23; mean age = 9.0 ± 2.2)	
	Males (n = 25)	Females (n = 24)	Males (n = 21)	Females (n = 22)	Males (n = 7)	Females (n = 16)
Percentile median (IQR)						
Total impairment	1.0 ± 0.25	1.0 ± 0	1.0 ± 0	1.0 ± 0	45.0 ± 61.3	47.0 ± 55.0
Subscale median (IQR)						
Manual dexterity	12.0 ± 6.0	10.0 ± 4.5	12.0 ± 5.3	12.0 ± 4.5	2.0 ± 5.0	0.3 ± 3.3
Ball skills	3.0 ± 5.2	5.8 ± 4.0	3.0 ± 6.0	5.5 ± 4.0	0.0 ± 0.9	1.75 ± 3.3
Balance	9.5 ± 5.2	8.5 ± 3.8	10.0 ± 5.6	10.0 ± 7.0	0.0 ± 0.8	1.3 ± 3.0

TABLE 4

Frequency counts for scores in the impaired range by group

	Total score impaired (%)	Manual dexterity impaired (%)	Ball skills impaired (%)	Balance impaired (%)
22q (n = 49)				
Year 1	46/49 (93.9) ^a	42/49 (85.7) ^a	23/49 (47.0) ^a	36/49 (73.5) ^a
Year 2	41/43 (95.3) ^a	38/43 (88.3) ^a	17/43 (39.5) ^a	27/43 (62.8) ^a
Sibs (n = 23)	1/23 (4.3)	2/23 (8.7)	1/23 (4)	0

^a χ^2 significant $P < 0.01$.