**LETTERS: NEW OBSERVATIONS**

Movement Disorder Phenotypes in Children With 22q11.2 Deletion Syndrome

The 22q11.2 deletion syndrome (22q11.2DS) is associated with a broad spectrum of clinical phenotypes, including congenital heart defects and immune deficiencies. In addition, there is also an increased risk of psychiatric disorders, cognitive deficits, and functional motor impairments. To date, a systematic examination of movement disorders has not been undertaken in this group.

Nineteen participants with 22q11.2DS (11 male; 8 female; median age, 12.7 years; range, 6.8–17.1 years), and 13 sibling controls (7 male; 6 female; median age, 11.2 years; range, 7.5–17.5 years) were recruited following informed consent. Examinations were reviewed independently by 3 neurologists blinded to all clinical information. Reviewers indicated if a movement disorder was observed and determined its phenomenology and body distribution. A movement disorder was considered present when there was agreement between all neurologists. Statistical analysis was carried out in R, using Fisher’s exact tests, chi-squared tests, Pearson’s correlations, and $t$ tests as appropriate.

Sample demographics are presented in Table 1. There was a higher rate of movement disorders in the 22q11.2DS group compared with controls ($P = 0.0002$), with consensus agreement for a movement disorder in 18 of 19 children with 22q11.2DS (94.7%) compared with 4 of 13 of controls (30.8%). Dystonia was the most common movement disorder subtype, in isolation (94.4%, $n = 17$) and combined with upper limb distal jerks (5.6%, $n = 1$). The limbs and craniofacial region were most commonly affected, with upper limb involvement in all 18 cases (Videos 1–3). Three of 4 controls displayed isolated dystonia, with upper limb involvement in all 4. In the 22q11.2DS cohort, dystonia severity was mild (mean BFMDRS, 24.93/120) but was associated with lower IQ ($r = −0.52$, $P = 0.03$) and higher anxiety symptoms ($r = 0.57$, $P = 0.03$).

This is the first cohort study investigating the prevalence and type of movement disorders in young people with 22q11.2DS. Dystonia was the most commonly observed subtype, although these features were mild and tended to be associated with action. Identification of true movement disorders is often challenging in this age range, but the frequency of dystonic signs in the 22q11.2DS group indicate that they were associated with the 22q11.2DS phenotype, rather than neuromotor immaturity. More severe dystonia was associated with lower IQ and higher levels of anxiety. The 22q11.2 deletion is known to affect brain development, and genes in the region such as COMT are expressed in the brain. Our study is a cross-sectional, longitudinal examination throughout childhood, adolescence, and into adult-life and is required to gain a more comprehensive understanding of the 22q11.2DS motor phenotype. Although this cohort is relatively small, the high rate and preponderance of dystonia indicate that it is likely part of the neurodevelopmental phenotype of 22q11.2DS.

**Author Contributions**

Adam C Cunningham had a major role in the acquisition of data; interpreted the data; and drafted the article for full-scale intelligence quotient (IQ), psychiatric symptoms, and coordination performance. Motor assessment involved a standardized videotaped clinical examination using a modified Burke-Fahn-Marsden Dystonia (BFMDRS) rating scale protocol. Examinations were reviewed independently by 3 neurologists blinded to all clinical information. Reviewers indicated if a movement disorder was observed and determined its phenomenology and body distribution. A movement disorder was considered present when there was agreement between all neurologists. Statistical analysis was carried out in R, using Fisher’s exact tests, chi-squared tests, Pearson’s correlations, and $t$ tests as appropriate.

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## TABLE 1. Cohort demographic, motor, and nonmotor characteristics

|                               | 22q11.2DS n (%)/mean (SD) | Sibling controls | 22q11.2DS versus sibling controls | 22q11.2DS cohort: correlation analysis with BFMDRS severity Scores |
|-------------------------------|---------------------------|-----------------|-----------------------------------|---------------------------------------------------------------|
| Total cohort (M:F)            | 19 (11:8)                 | 13 (7:6)        | —                                 | —                                                            |
| Age at examination (years), Median (range) | 12.70 (6.8–17.1)         | 11.12 (7.5–17.5) | 0.79 (–2.8 to 2.2)                | −0.24 (0.34)                                                 |
| FSIQ                          | 78.83 (10.06)             | 109 (15.13)     | <0.0001 (21.16–39.64)             | −0.52 (0.03)                                                 |
| BFMDRS severity score (maximum possible score, 120) | 24.93 (8.17)             | —               | —                                 | —                                                            |
| Medication                    |                           |                 |                                   |                                                               |
| ≥1 Medication prescribed      | 12 (63.2%)                | 0 (0%)          | 0.0004b                           |                                                               |
| Melatonin                     | 5 (26.3%)                 | —               | —                                 |                                                               |
| Antibiotics                   | 4 (21.1%)                 | —               | —                                 |                                                               |
| Laxatives                     | 3 (15.8%)                 | —               | —                                 |                                                               |
| Vitamin/mineral supplementation| 3 (15.8%)                | —               | —                                 |                                                               |
| Antidepressants               | 1 (5.3%)                  | —               | —                                 |                                                               |
| Medical comorbidities         |                           |                 |                                   |                                                               |
| Cardiac defect                | 13 (68.4%)                | 0 (0%)          | 0.0001                            |                                                               |
| ASD/VSD                       | 5 (26.3%)                 | —               | —                                 |                                                               |
| Tetralogy of Fallot           | 4 (21.1%)                 | —               | —                                 |                                                               |
| Other                         | 4 (21.1%)                 | —               | —                                 |                                                               |
| Past/present seizures         | 1 (5.3%)                  | 0 (0%)          | >0.99                             |                                                               |
| Cleft lip/palate              | 6 (31.6%)                 | 0 (0%)          | 0.06                              |                                                               |
| Recurrent respiratory infections| 7 (36.8%)              | 0 (0%)          | 0.02                              |                                                               |
| Recurrent ear infections      | 6 (31.6%)                 | 1 (7.7%)        | 0.20                              |                                                               |
| Psychiatric symptoms          |                           |                 |                                   |                                                               |
| ADHD                          | 7 (36.8%)                 | 1 (7.7%)        | 0.10                              |                                                               |
| Anxiety disorder (overall)    | 5 (26.3%)                 | 1 (7.7%)        | 0.36                              |                                                               |
| Social phobia                 | 3 (15.8%)                 | 0 (0%)          | 0.25                              |                                                               |
| Generalized anxiety disorder  | 1 (5.3%)                  | 0 (0%)          | >0.99                             |                                                               |
| Specific phobia               | 1 (5.3%)                  | 1 (7.7%)        | >0.99                             |                                                               |
| ADHD count score              | 3.39 (3.38)               | 1.00 (3.16)     | 0.07 (–2.39 to 1.3)               | 0.41 (0.10)                                                 |
| Anxiety count score           | 2.13 (3.18)               | 1.75 (2.96)     | 0.78 (–3.17 to 2.42)              | 0.57 (0.03)                                                 |
| Autism trait symptoms score   | 11.43 (5.16)              | 2.50 (2.27)     | <0.0001 (–12.55 to –5.30)         | 0.42 (0.16)                                                 |
| Developmental history         |                           |                 |                                   |                                                               |
| Preterm birth                 | 4 (21.1%)                 | 5 (38.5%)       | 0.43                              |                                                               |
| Failure to thrive             | 8 (42.1%)                 | 0 (0%)          | 0.01                              |                                                               |
| Feeding difficulties          | 16 (84.2%)                | 1 (7.7%)        | <0.0001 (–12.55 to –5.30)         | 0.42 (0.16)                                                 |
| Parental reported clumsiness  | 15 (78.9%)                | 3 (23.1%)       | 0.003                             |                                                               |
| Talking by 2 years of age     | 6 (31.6%)                 | 12 (92.3%)      | 0.0009                            |                                                               |
| Walking by 1.5 years of age   | 11 (57.9%)                | 11 (84.6%)      | 0.14                              |                                                               |
| Statement of educational needs/education and health care plan | 13 (68.4%) | 1 (7.7%) | 0.0009 |                                                               |
| Age at riding a bike (years), median (range) | 6.5 (5–10) | 5 (3.5–7) | 0.09 (–27.6 to 2.1) | 0.02 (0.95) |
| Age at being able to button (years), median (range) | 6.2 | 4 (3–6.5) | 0.008 (–41.6 to –7.0) | –0.10 (0.79) |
| Age at being able to do laces (years), median (range) | 9.75 (6–11) | 6.9 (5–8.7) | 0.008 (–47.3 to 8.4) | 0.20 (0.63) |
| Movement disorder             |                           |                 |                                   |                                                               |
| Evidence of movement disorder on examination | 18 (94.7%) | 4 (30.8%) | 0.0002 |                                                               |
| Dystonia                      | 17 (94.4%)                | 3 (23.1%)       | 0.0002                            |                                                               |
| Distal UL jerks (possible myoclonus/possible chorea) | 1 (5.6%) | 1 (7.7%) | >0.99 |                                                               |
| Body part affected            |                           |                 |                                   |                                                               |
| Eyes                          | 0 (0%)                    | 0 (0%)          | >0.99a                            |                                                               |
| Oromandibular region          | 6 (31.6%)                 | 0 (0%)          | 0.05                              |                                                               |
| Cervical                      | 8 (42.1%)                 | 1 (7.7%)        | 0.05                              |                                                               |
| Upper limbs                   | 18 (94.7%)                | 4 (30.8%)       | 0.0002                            |                                                               |
| Trunk                         | 0 (0%)                    | 0 (0%)          | >0.99                             |                                                               |
| Lower limbs                   | 8 (42.1%)                 | 3 (23.1%)       | 0.45                              |                                                               |

(Continues)
and conceptualized the study, analyzed the data, and drafted the article for intellectual content.

Statistical analysis undertaken by A.C.C. and K.J.P. (both Cardiff University, UK).

Search terms: [161] All Movement Disorders, [162] Dystonia, [228] Developmental Disorders, [230] Child Psychiatry, [91] All Genetics.

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**Supporting Data**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.