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Original article

# A comparative study of the neuropsychiatric and neurocognitive phenotype in two microdeletion syndromes: Velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes

O. Zarchi [a,b,c], A. Diamond [e], R. Weinberger [a], D. Abbott [e], M. Carmel [d,f], A. Frisch [d,f], E. Michaelovsky [f], R. Gruber [i,j], T. Green [d,g], A. Weizman [d,f,h], D. Gothelf [a,d,*]

[a] The Behavioral Neurogenetics Center, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer 52621, Israel
[b] The Institute for Clinical Neurophysiology and Audiology, Rabin Medical Center, Petah Tikva 49202, Israel
[c] The Interdisciplinary Ph.D. Program in Neuroscience, Tel Aviv University, Tel Aviv 69978, Israel
[d] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel
[e] Department of Psychiatry, University of British Columbia & Division of Child & Adolescent Psychiatry, BC Children's Hospital, Vancouver, Canada
[f] The Biochemical Genetics Laboratory, Felsenstein Medical Research Center, Petah Tikva 49202, Israel
[g] The Nes-Ziyyona–Beer Yaakov Mental Health Center, Nes-Ziyyona 70400, Israel
[h] Research Unit at Geha Mental Health Center, Petah Tikva 49202, Israel
[i] Department of Psychiatry, McGill University, Montreal, Canada
[j] ABS Lab and Douglas Institute Research Center, Verdun, Canada

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ABSTRACT

*Purpose:* 22q11.2 deletion syndrome (22q11.2DS) and Williams syndrome (WS) are common neurogenetic microdeletion syndromes. The aim of the present study was to compare the neuropsychiatric and neurocognitive phenotypes of 22q11.2DS and WS.
*Methods:* Forty-five individuals with 22q11.2DS, 24 with WS, 22 with idiopathic developmental disability (DD) and 22 typically developing (TD) controls were compared for the rates of psychiatric disorders as well as cognitive executive and visuospatial functions.
*Results:* We found that while anxiety, mood and disruptive disorders had an equally high prevalence among individuals with 22q11.2DS, WS and DDs, the 22q11.2DS group had the highest rates of psychotic disorders and the WS group had the highest rates of specific phobia. We also found that the WS group demonstrated more severe impairments in both executive and visuospatial functions than the other groups. WS and 22q11.2DS subjects had worse Performance-IQ than Verbal-IQ, a feature typical of non-verbal learning disorders.
*Conclusion:* These findings offer a wide perspective on unique versus common phenotypes in 22q11.2DS and WS.



## 1. Introduction

Both 22q11.2 deletion syndrome (22q11.2DS) and Williams syndrome (WS) share similar phenotypic manifestations, including calcium dysregulation, cardiovascular anomalies, neuroanatomical aberrations, cognitive deficits and high rates of psychiatric comorbidities [4,28,33], but few studies have compared these phenotypes across the syndromes. Such cross-syndrome studies are important to delineate the specific deficits of each of them. The specific deficits are assumed to be more directly related to the genetic mutation. Thus, identification of the syndrome-specific neurophenotype is a necessary step in understanding the genotype-neurophenotype association of these intriguing syndromes.

To date, only one study compared cognitive functions in a 22q11.2DS vs. WS cross syndrome design, reporting worse Performance-IQ scores coupled with better verbal, social and facial processing skills in WS than in 22q11.2DS [4]. The current study expands this former investigation by having a control group of individuals with idiopathic developmental disability (DD) and by also comparing the psychiatric phenotype among the syndromes as well as executive functions (EF) and visuospatial deficits, two specific aspects of cognition that have been proposed as being especially impaired in 22q11.2DS and WS [24,35,26,21].

We compared the neuropsychiatric and neurocognitive profiles of four groups of participants: 22q11.2DS, WS, individuals with DD and typically developing (TD) controls. Based on findings from

* Corresponding author. The Child Psychiatry Unit, Sheba Medical Center, Tel Hashomer 52621, Israel. Tel.: +972 3 530 2663; fax: +972 77 349 8317.
*E-mail address:* gothelf@post.tau.ac.il (D. Gothelf).

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previous studies, we hypothesized that the neuropsychiatric phenotype of adolescents and young adults with 22q11.2DS would have a higher prevalence of psychotic disorders [14], and that children with WS would have a higher prevalence of anxiety disorders, especially specific phobias, compared to the other groups [11]. We also investigated general neurocognitive functioning and proposed that the WS and 22q11.2DS groups would have significantly higher Verbal-IQ (VIQ) scores compared to Performance-IQ (PIQ) scores and that this would be more pronounced in the WS group [4]. In addition, we considered that individuals with WS and 22q11.2DS would be more impaired than TD and DD controls in performing tasks requiring EF [24,21,29,9]. Finally, we studied visuospatial functions among the study groups and hypothesized that individuals with WS and 22q11.2DS would display greater impairments than TD and DD controls [35,26], and that the WS group would show greater impairment on visuospatial functioning than the 22q11.2DS group.

## 2. Subjects and methods

### 2.1. Participants

The study included 45 participants with 22q11.2DS, 24 with WS, 22 with idiopathic DD and 22 TD controls. The demographic characteristics of the four groups are presented in Table 1. The groups did not differ significantly in mean age or gender distribution. To match the three clinical groups (22q11.2DS, WS and DD) for full-scale IQ (FSIQ), we included subjects with FSIQ in the range of 50–80 (Table 2).

Participants with 22q11.2DS and WS were recruited from the Behavioral Neurogenetics Center at a large tertiary referral center in Israel that coordinates research and treatments of individuals with 22q11.2DS and WS throughout the country and referred from genetic departments and parents' associations. The Behavioural Neurogenetics Center coordinates the medical care of these patients, including psychiatric treatments. The diagnosis of 22q11.2DS and WS was confirmed in all participants by fluorescent in situ hybridization (FISH). Participants with DD were recruited from schools for special education for children and adolescents with DD. Subjects with DD were evaluated by a clinical geneticist and their medical records were screened. When indicated, subjects were referred to genetic testing and were excluded from the study if there was any evidence of a genetic syndrome. TD controls were recruited through advertisements within the local community. They were all students in mainstream classes and none had a major psychopathology.

The study was approved by the Institutional Review Board. After providing a complete description of the nature of this study, we obtained written informed consent from all participants and from the parents of minors.

### 2.2. Neuropsychiatric assessment

Participants and their parents were interviewed by trained psychiatrists using the Hebrew version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime (K-SADS-PL), and the adults and their parents were interviewed with the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) as previously described [17].

### 2.3. Neurocognitive assessment

More detailed information can be found in Appendix A.

IQ was measured using the age-appropriate versions of the Wechsler test [39]. Assessment of EF was conducted using a battery of tools designed by Diamond et al. [8]. We chose this battery since it is geared towards preschool TD children and can serve as an appropriate option for our participants with relatively low FSIQ. The battery includes the Heart and Flowers Task (H&F) and the Flanker & Reverse Flanker task (F-RF) which were designed to test working memory, inhibition and mental flexibility [8]. The Mental Rotation task (MR) and the Block-Design subtest of the Wechsler Intelligence Test [39,1] were used to assess visuospatial functions.

### 2.4. Data analysis

All trials with a response faster than 200 ms were omitted as being too fast to be in response to the stimulus. We used exact statistics with non-parametric tests for analyzing the F-RF and H&F results, the Kruskal-Wallis tests for comparing all groups, and the Wilcoxon Mann-Whitney tests for pairwise comparisons (StatXact, Cytel Software, Inc., Cambridge, MA). Psychiatric disorders were clustered in to four domains (Table 3). Differences in the rate of psychiatric disorders among groups were analyzed using $2 \times 3$ chi-square tests with post-hoc $2 \times 2$ chi-square tests. Based on the literature indicating age effects for psychopathology in 22q11.2DS and WS, we conducted analyses of psychosis and mood disorders in individuals from the age of 12 years and older, and analyses of anxiety and disruptive disorders among individuals up to 18 years of age or younger [17].

## 3. Results

### 3.1. Psychiatric evaluation

As hypothesized, there was a significant difference among groups in the rate of psychotic disorders in adolescents and young adults ($\chi^2(2) = 8.1$, $P < 0.05$; Table 3). Post-hoc tests revealed that psychotic disorders were significantly more common in 22q11.2DS (29.2%) than in WS (5.6%; $P = 0.05$) and DD (0.0%; $P = 0.05$). Five of seven cases of psychosis in the 22q11.2DS group fulfilled the DSM-IV criteria for schizophrenia.

The rate of anxiety disorders was similar among groups ($\chi^2(2) = 1.0$, $P = 0.61$), while the rate of specific phobia differed significantly among groups ($\chi^2(2) = 6.2$, $P < 0.05$). Post-hoc tests showed that the rate of specific phobia was significantly higher in WS (45.8%) than in DD (11.8%; $P < 0.05$) and a trend towards significance compared to 22q11.2DS (24.3%; $P = 0.08$).

There were no significant differences in the rate of mood disorders among groups. The rate of disruptive disorders, including attention deficit hyperactivity disorder (ADHD), was similarly high in all three groups (41.2%–48.6%).

**Table 1**
The demographic characteristics of the study groups.

| Variable | 22Q11.2DS | WS | DD | TD | Statistics |
|---|---|---|---|---|---|
| *n* | 39 | 24 | 22 | 22 | |
| Age (mean ± SD) | 16.9 ± 9.2 | 16.8 ± 7.5 | 18.6 ± 6.7 | 17.1 ± 10.0 | F = 0.2; $P = 0.90$ |
| Gender distribution (M/F) | 22/17 | 10/14 | 10/12 | 12/10 | $\chi^2 = 2.0$; $P = 0.57$ |

22q11.2DS: 22q11.2 deletion syndrome; WS: Williams syndrome; DD: idiopathic developmental disabilities; TD: typically developing.

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**Table 2**
Wechsler intelligence scale scores in individuals with 22q11.2 deletion syndrome, Williams syndrome and controls with idiopathic developmental disability.

| Variable | 22q11.2DS | WS | DD | Statistics | Post-hoc |
|---|---|---|---|---|---|
| *n* | 39 | 24 | 22 | | |
| FSIQ | 67.33 ± 7.17 | 66.59 ± 9.55 | 66.29 ± 9.98 | $F = 0.1$; $P = 0.90$ | |
| VIQ | 71.32 ± 8.02 | 71.38 ± 10.63 | 68.71 ± 9.37 | $F = 0.6$; $P = 0.58$ | |
| PIQ | 67.74 ± 7.15 | 64.76 ± 9.17 | 68.94 ± 10.38 | $F = 1.3$; $P = 0.28$ | |
| Digit span** | 6.11 ± 2.57 | 4.93 ± 2.41 | 3.64 ± 1.91 | $F = 5.0$; $P < 0.01$ | DD < 22q11.2DS |
| Coding* | 4.28 ± 2.26 | 2.90 ± 1.59 | 4.40 ± 2.13 | $F = 3.4$; $P < 0.05$ | WS < 22q11.2DS;DD |
| Arithmetic | 3.69 ± 1.82 | 2.73 ± 2.71 | 3.07 ± 1.98 | $F = 1.5$; $P = 0.24$ | |
| Comprehension | 4.26 ± 1.86 | 3.85 ± 2.21 | 3.07 ± 1.03 | $F = 2.3$; $P = 0.11$ | |
| Similarities | 5.24 ± 2.50 | 6.32 ± 2.67 | 5.93 ± 2.02 | $F = 1.4$; $P = 0.25$ | |
| Information | 6.00 ± 1.86 | 6.00 ± 1.89 | 5.80 ± 2.01 | $F = 0.066$; $P = 0.94$ | |
| Vocabulary* | 4.95 ± 1.99 | 5.91 ± 2.84 | 3.87 ± 1.92 | $F = 3.7$; $P < 0.05$ | DD < WS |
| Block-design | 4.73 ± 1.73 | 3.55 ± 2.41 | 4.40 ± 1.99 | $F = 2.4$; $P = 0.09$ | |
| Picture order | 4.21 ± 1.50 | 3.46 ± 1.71 | 3.93 ± 1.82 | $F = 0.9$; $P = 0.40$ | |
| Picture completion | 4.50 ± 2.58 | 4.50 ± 2.94 | 5.53 ± 3.04 | $F = 0.8$; $P = 0.46$ | |

22q11.2DS: 22q11.2 deletion syndrome; WS: Williams syndrome; DD: idiopathic developmental disabilities; FSIQ: full-scale IQ; PIQ: performance IQ; VIQ: verbal IQ.
* $P < 0.05$.
** $P < 0.01$.

### 3.2. Cognitive evaluation

#### 3.2.1. General cognitive functioning

The groups were matched for FSIQ and did not differ significantly in VIQ or PIQ. We had hypothesized higher VIQ than PIQ scores in subjects with WS and 22q11.2DS and found significant group × VIQ/PIQ interaction on repeated measures ANOVA ($F(2,73) = 4.3$, $P < 0.05$). While the DD group had similar VIQ and PIQ scores ($\Delta = -0.23$ points; paired $t(16) = -0.1$, $P = 0.88$), the 22q11.2DS ($\Delta = 3.58$; paired $t(38) = 3.2$, $P < 0.01$) and WS ($\Delta = 6.62$; paired $t(20) = 3.7$, $P = 0.001$) groups had significantly higher VIQ than PIQ scores (Fig. 1). Comparing the frequency of non-verbal learning disorder (NLD; VIQ > PIQ by 10 points or more [18]), we found a trend toward significant group differences ($\chi^2(2) = 5.1$, $P = 0.08$), showing a higher NLD prevalence in WS (7/21) and 22q11.2DS (6/38) compared to the DD controls (1/17). The comparison between groups on the Wechsler subscales is shown in Table 2.

#### 3.2.2. Executive functions

There were equally high rates of ADHD in the three clinical groups (Table 3). Similar proportions of subjects with comorbid ADHD among the three groups were treated with methyphenidate (six of 17 in the 22q11.2DS group, six of ten in the WS group and three of six in the DD group; $\chi^2(2) = 1.6$, $P = 0.45$). All patients treated with methyphenidate continued their regular treatment in the morning of the cognitive assessment.

We analyzed congruent, incongruent and mixed H&F blocks controlling for gender and age (Table 4). We found significant group differences on the H&F incongruent block, which tests response inhibition ($\chi^2(3,\ N = 125) = 18.4$, $P < 0.001$). Post-hoc analysis showed WS ($\chi^2(1,\ N = 125) = 15.39$, $P < 0.001$, odds ratio = 0.11), DD ($\chi^2(1, N = 125) = 5.6$, $P < 0.05$, odds ratio = 0.23) and by trend 22q11.2DS ($\chi^2(1,\ N = 125) = 3.1$, $P = 0.08$, odds ratio = 0.41) to be significantly less accurate than TD controls. We also found significant group differences on the mixed block, a task that requires mental flexibility in addition to inhibition ($\chi^2(3,$

**Table 3**
The prevalence (%) of psychiatric disorders in individuals with 22q11.2 deletion syndrome, Williams syndrome and controls with developmental disability.

| Variable | 22q11.2DS | WS | DD | Statistics | Post-hoc |
|---|---|---|---|---|---|
| *n* | 39 | 24 | 22 | | |
| Psychotic disorders[a,*] | 7 (29.2) | 1 (5.6) | 0 (0) | $\chi^2 = 8.1$; $P < 0.05$ | WS, DD < 22q11.2DS |
| Schizophrenia | 4 (16.7) | 0 (0) | 0 (0) | | |
| Schizoaffective | 1 (4.2) | 0 (0) | 0 (0) | | |
| Schizophreniform | 0 (0) | 0 (0) | 0 (0) | | |
| Brief psychotic disorder | 1 (4.2) | 0 (0) | 0 (0) | | |
| Psychotic disorder NOS | 1 (4.2) | 1 (5.6) | 0 (0) | | |
| Anxiety disorders | 15 (40.5) | 12 (50.0) | 6 (35.3) | $\chi^2 = 1.0$; $P = 0.61$ | |
| Separation anxiety[b] | 1 (2.7) | 3 (12.5) | 1 (5.9) | | |
| GAD | 5 (13.5) | 2 (8.3) | 5 (29.4) | | |
| OCD | 3 (8.1) | 1 (4.2) | 2 (11.8) | | |
| PTSD | 1 (2.7) | 1 (4.2) | 0 (0) | | |
| Social phobia | 5 (13.5) | 0 (0) | 2 (11.8) | | |
| Specific phobias* | 9 (24.3) | 11 (45.8) | 2 (11.8) | $\chi^2 = 6.2$; $P < 0.05$ | DD < WS |
| Mood disorders | 7 (18.9) | 1 (4.2) | 1 (5.9) | $\chi^2 = 3.8$; $P = 0.15$ | |
| MDD | 3 (8.1) | 0 (0) | 1 (6.7) | | |
| Dysthymia | 4 (10.8) | 1 (4.2) | 0 (0) | | |
| Disruptive disorders | 18 (48.6) | 11 (45.8) | 7 (41.2) | $\chi^2 = 0.3$; $P = 0.88$ | |
| Any ADHD | 17 (45.9) | 10 (41.7) | 6 (35.3) | $\chi^2 = 0.5$; $P = 0.76$ | |
| ADHD combined | 9 (24.3) | 5 (20.8) | 4 (23.5) | | |
| ADHD inattentive | 7 (18.9) | 6 (25.0) | 2 (11.8) | | |
| ADHD hyperactive | 1 (2.7) | 0 (0) | 0 (0) | | |
| ODD | 9 (24.3) | 4 (16.7) | 2 (11.8) | | |
| Conduct disorder | 0 (0) | 0 (0) | 1 (5.9) | | |

22q11.2DS: 22q11.2 deletion syndrome; WS: Williams syndrome; DD: idiopathic developmental disabilities; ADHD: attention-deficit/hyperactivity disorder; GAD: generalized anxiety disorder; NOS: not otherwise specified; OCD: obsessive-compulsive disorder; ODD: oppositional defiant disorder; PTSD: posttraumatic stress disorder.
[a] Solely for individuals older than 12 years.
[b] Solely individuals younger than 18 years.
* $P < 0.05$.

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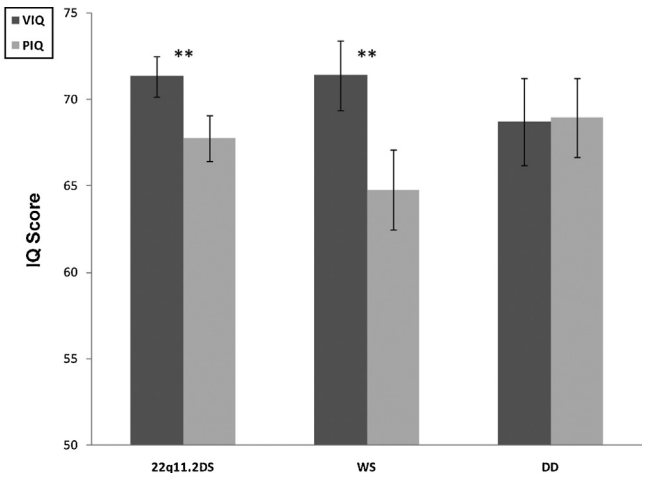


**Fig. 1.** Verbal to Performance IQ differences (VIQ and PIQ, respectively) in Williams syndrome (WS) and 22q11.2 deletion syndrome (22q11.2DS). A significant group by VIQ/PIQ interaction is shown. Whereas the developmental disability group (DD) had similar VIQ and PIQ scores, the 22q11.2DS and WS groups had significantly higher VIQ than PIQ scores.

$N = 125) = 48.4$, $P < 0.001$). Post-hoc analysis showed that WS ($\chi^2(1, N = 125) = 48.3$, $P < 0.001$, odds ratio = 0.24), 22q11.2DS ($\chi^2(1, N = 125) = 24.4$, $P < 0.001$, odds ratio = 0.36), and DD ($\chi^2(1, N = 125) = 17.5$, $P < 0.001$, odds ratio = 0.34) were significantly less accurate than TD controls. No group differences were found on the congruent block ($\chi^2(3, N = 125) = 3.2$, $P = 0.36$). There was a significant group × block interaction ($\chi^2(6, N = 125) = 13.1$, $P < 0.05$), showing that while all groups performed similarly well on the congruent block and declined on the incongruent and mixed blocks, the WS decline on the incongruent block was very abrupt, and much sharper than the slopes of the three other groups (Fig. 2A).

Controlling for gender and age, we next compared groups for F-RF accuracy on the blue, pink and mixed blocks, a task that demands selective attention (Fig. 2B) and found significantly lower accuracy rates for the WS group for all three blocks. Providing central cuing, the blue block analysis yielded significant group differences ($\chi^2(3, N = 93) = 34.9$, $P < 0.001$). Effect-size analysis showed that WS had significant lower accuracy rates than 22q11.2DS ($\chi^2(1, N = 93) = 11.2$, $P < 0.001$, odds ratio = 5.22) and TD controls ($\chi^2(1, N = 93) = 33.8$, $P < 0.001$, odds ratio = 57.21), and a tendency towards significantly lower scores than DD ($\chi^2(1, N = 93) = 2.9$, $P = 0.09$). Providing peripheral cuing, the pink block results also produced significant group differences ($\chi^2(3, N = 93) = 42.2$, $P < 0.001$): WS subjects were significantly less accurate than 22q11.2DS ($\chi^2(1, N = 93) = 7.1$, $P = 0.01$, odds ratio = 2.34), DD ($\chi^2(1, N = 93) = 6.1$, $P = 0.01$, odds ratio = 2.73) and TD controls ($\chi^2(1, N = 93) = 41.6$, $P < 0.001$, odds ratio = 10.51). Significant group differences were also found for the mixed block task ($\chi^2(3, N = 93) = 50.0$, $P < 0.001$). WS subjects were significantly less accurate than 22q11.2DS ($\chi^2(1, N = 93) = 7.9$, $P = 0.005$, odds ratio = 1.91), DD ($\chi^2(1, N = 93) = 5.5$, $P < 0.05$, odds ratio = 1.98) and TD controls ($\chi^2(1, N = 93) = 46.7$, $P < 0.001$, odds ratio = 6.84). There was a significant group × block interaction ($\chi^2(6, N = 93) = 17.3$; $P < 0.01$), demonstrating that the WS group had poorer performance in the blue and pink blocks

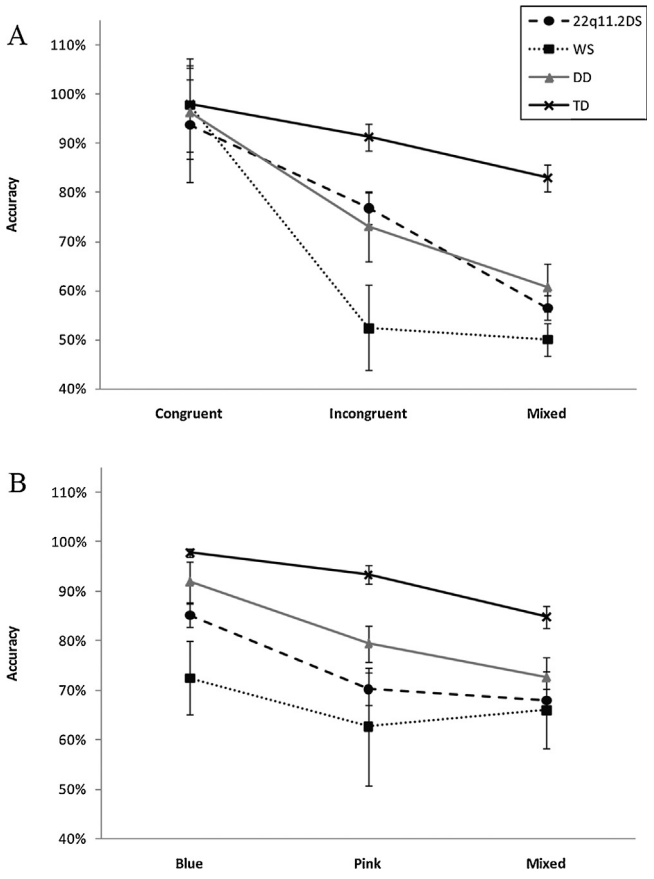


**Fig. 2.** Mean group accuracy and standard errors on the Heart and Flowers (H&F; A) and on the Flanker & Reverse Flanker (F-RF; B) tasks. A. A significant group by block interaction on the H&F task is shown. The Williams syndrome slope of decline on the incongruent block was much steeper than the slopes of the other groups. B. The Williams syndrome group had significantly lower accuracy rates than the other groups on the blue (central cuing), pink (peripheral cuing) and mixed blocks in the F-RF task.

**Table 4**
Executive functions scores in individuals with 22q11.2 deletion syndrome, Williams syndrome, controls with idiopathic developmental disability and typically developing controls.

| Variable | 22q11.2DS | WS | DD | TD | Statistics | Post-hoc |
|---|---|---|---|---|---|---|
| H&F Congruent | 98 ± 5 | 100 ± 1 | 96 ± 7 | 99 ± 3 | $X^2 = 3.2$; $P > 0.05$ | |
| H&F Incongruent*** | 84 ± 26 | 57 ± 47 | 75 ± 37 | 92 ± 14 | $X^2 = 18.4$; $P < 0.001$ | WS;DD < TD |
| H&F Mixed*** | 67 ± 43 | 59 ± 46 | 67 ± 42 | 86 ± 23 | $X^2 = 48.4$; $P < 0.001$ | WS;22q11.2DS;DD < TD |
| H&F interaction* | | | | | $X^2 = 13.1$; $P < 0.05$ | |
| F-RF Blue*** | 94 ± 38 | 75 ± 121 | 89 ± 65 | 99 ± 4 | $X^2 = 34.9$; $P < 0.001$ | WS < 22q11.2DS;TD |
| F-RF Pink*** | 83 ± 62 | 67 ± 95 | 85 ± 54 | 96 ± 18 | $X^2 = 42.2$; $P < 0.001$ | WS < 22q11.2DS;DD;TD |
| F-RF Mixed*** | 78 ± 40 | 65 ± 53 | 78 ± 38 | 93 ± 16 | $X^2 = 50.0$; $P < 0.001$ | WS < 22q11.2DS;DD;TD |
| F-RF Interaction** | | | | | $X^2 = 17.3$; $P < 0.01$ | |

22q11.2DS: 22q11.2 deletion syndrome; WS: Williams syndrome; DD: idiopathic developmental disabilities; TD: typically developing; H&F: The Heart and Flowers Task; F-RF: The Flanker & Reverse Flanker task.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

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compared to the three other groups, but were comparable to the other groups for the mixed block task (Fig. 2B).

*3.2.3. Visuospatial functions*

Hypothesizing more robust visuospatial impairments in WS and 22q11.2DS than in DD and TD, we compared group performances on the Hands MR task and the Wechsler Block-Design subtest. There were significant group differences in the MR results ($F(3.53) = 15.4$, $P < 0.001$), with all clinical groups performing significantly worse than TD ($Ps < 0.001$). In addition, WS had a tendency towards significantly lower scores compared to DD ($P = 0.06$). The results of the Block-Design revealed a trend for significant group differences ($F = 2.4$, $P = 0.09$), demonstrating lower scores in WS than in 22q11.2DS and DD.

There were no age- or gender-based interactions for any of the EF or visuospatial measures among the groups.

The results of the subtests of the Wechsler Intelligence scale other than the Block-Design subtest yielded significant group differences on the Digit Span, Coding and Vocabulary subscales. Table 2 displays the comprehensive subscale comparison results.

## 4. Discussion

We report the first cross-syndrome study to investigate psychiatric as well as cognitive executive and visuospatial functions in individuals with 22q11.2DS and WS. The cross-syndrome and two control groups design provides this study with an expanded perspective of the psychiatric and cognitive impairments of WS and 22q11.2DS, differentiating syndrome-specific phenotypes from non-specific impairments.

We found that 22q11.2DS, WS and individuals with DD share several common psychiatric phenotypes, including high rates of anxiety as well as mood and disruptive disorders, and that the two syndromes but not the individuals with DD present PIQ ≤ VIQ discrepancy. We also identified unique neurophenotypes in 22q11.2DS and WS, i.e., high rates of psychosis in 22q11.2DS and high rates of specific phobias in WS. Moreover, we detected more impaired response-inhibition and visuospatial functions in WS than in 22q11.2DS and in individuals with DD and TD.

Some of the abnormal neural pathways identified in both syndromes could be associated with phenotypic expression [4,16,5,3,36,27,15]. The two syndromes have relatively preserved volumes of frontal cortex and more pronounced decreased volumes in parieto-occipital regions [4,16,15]. The parieto-occipital deficits could explain the PIQ < VIQ observed in both of the syndromes. Moreover, cortico-striatal aberrations (leading to ADHD) have also been identified in WS and in 22q11.2DS [5,3]. The unique predisposition to psychosis in 22q11.2DS has been associated with reduction in fronto-temporal volumes in adults with 22q11.2DS who developed psychosis [36]. There is increased amygdala volume in WS, and amygdala reactivity is elevated in response to socially irrelevant stimuli but reduced in response to threatening social stimuli: this is in accordance with our findings of a tendency for high specific phobia and low social phobia in WS [27].

Human and animal studies have proposed several genes from the WS and 22q11.2DS-deleted regions as suspected contributors to the cognitive and behavioral phenotypical impairments of the syndromes. The most studied candidate genes in 22q11.2DS were *COMT* and *PRODH*, which are responsible for dopamine and proline degradation, respectively [14,38]. In WS, haplo-insufficiency of *LIMK1*, *CLIP2*, *GTF2I* and *GTF2IRD1*, that are involved in neuronal maturation and migration and in the regulation of gene expression, have been suggested as potential contributors to the WS neural phenotype [19,30], but there is still no definitive answer to the question as to which genes are responsible for the neural phenotypes in both syndromes.

High rates of psychotic disorders have been described for several neurogenetic syndromes, including 22q11.2DS, Huntington's disease, and Prader-Willi syndrome [14,6,37]. However, to the best of our knowledge, no previous study has compared the rate of psychotic disorders between two neurogenetic conditions. Such a comparison is important for learning about the specificity of the association between neurogenetic syndromes and predisposition to psychosis. Both WS and 22q11.2DS share phenotypical expressions that could lead to increased risk for psychosis [28,33], yet we observed higher rates of psychotic disorders in 22q11.2DS (29.2%) compared to WS (5.6%) and DD (0.0%). These findings suggest that there are unique pathways leading from a gene or several genes that are missing from the 22q11.2 deletion region to the evolution of psychosis in 22q11.2DS.

The rate of anxiety disorders was similarly high in 22q11.2DS, WS and DD, however in terms of types of anxiety, there were higher rates of specific phobias in WS (45.8%) compared to both 22q11.2DS (24.3%) and DD (11.8%). Previous studies found that fears and specific phobias are salient manifestations of the WS phenotype, at a reported rate of 36%-56% in WS individuals [11,22,23]. While those comprehensive studies assessed psychiatric and, particularly, anxiety disorders in large samples of individuals with WS, our study is the first to compare WS with both neurodevelopmental disorder controls of idiopathic and of chromosomal deletion etiology, showing that specific phobias (e.g., noise or blood tests), but not other anxiety disorders, are a unique phenotype of WS.

Investigation of EFs revealed that while all three clinical groups performed worse than TD controls, the WS group performed significantly worse than all other groups, especially on tasks that tested inhibition. The results of the H&F task clearly demonstrated a sharp decline in accuracy by the WS group, when a demand for response inhibition was introduced (incongruent block) in addition to the working memory demand (equally present on the congruent and incongruent blocks). Response inhibition is mediated by fronto-striatal circuitry, and maturation of this circuitry is thought to underlie the development of response-inhibition abilities in TD children [10]. The particular response-inhibition impairments in our WS group are in line with a functional magnetic resonance imaging investigation which demonstrated reduced engagement of fronto-striatal circuits during the performance of a response-inhibition task in individuals with WS [29]. Taken together with our results, atypical development of response inhibition seems to be a hallmark phenotype of WS. Moreover, our finding of impaired response inhibition (as indicated in the H&F task) may be relevant to the social disinhibition typical of WS [24]. This observation is supported by a twin study which showed a genetic association between impaired executive response inhibition and behavioral social disinhibition [41].

Our WS group also performed more poorly than the other groups on the F-RF task. While also involving inhibitory demands, the F-RF task requires the participant to selectively focus on the central (blue block) and periphery (pink block) stimuli, thus evaluating visual selective attention in particular. Our results showed that in comparison to the other groups, the WS group encountered more difficulties in selectively allocating visual attention, whether that meant ignoring all the flankers or ignoring the central stimulus. It may be that this profound selective visual attention dysfunction is related to parietal lobe impairments, which are well-established in imaging studies of individuals with WS [26]. Indeed, in addition to the crucial role of the frontal lobe in EF, the parietal lobe underlies selective attention and inhibitory processes, particularly when stimuli and/or responses are in the

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visuospatial domain [25]. We hypothesized that 22q11.2DS would be more impaired in dopaminergic EF, e.g., inhibition and mental flexibility than TD and DD controls. Because subjects with 22q11.2DS are hemizygote for the *COMT* gene, they putatively have excess prefrontal dopamine levels [14]. EF have been shown to be optimal within a narrow range of prefrontal dopamine levels, with too low or too high levels impairing of EF performance [13]. Our findings showed that 22q11.2DS performed worse than TD but similar to DD both on H&F and F-RF tasks. These results suggest that the putatively high prefrontal dopamine levels may still efficiently serve EF in 22q11.2DS. A few studies have reported EF impairments in 22q11.2DS (e.g. [21,9,2,40]). Most of them, however, did not include DD controls, which did not enable the determination of whether the EF impairments seen in 22q11.2DS are a unique phenotype of the syndrome or unspecific impairments of individuals with DD [21,9,2,40]. Our results support the second option by showing that individuals with 22q11.2DS do not present worse EF performances from IQ-matched DD controls and are better than IQ-matched individuals with WS.

We found visuospatial performances to be significantly worse in all three clinical groups compared to TD controls. The WS group, however, showed more severe visuospatial impairments, performing even worse (although with only a tendency towards significance) than the DD and 22q11.2DS groups on the visuospatial tasks-mental rotation and the Wechsler Block-Design subtest. MR abilities, which are required in both of our visuospatial tasks, have been reported to be even weaker in WS than other abilities in the non-verbal domain, and are suggested to reflect an inability of individuals with WS to use mental imagery [12]. Neuroimaging studies of TD subjects have consistently demonstrated MR performance to be associated with superior parietal lobe function [7], supporting the notion that a dorsal stream impairment underlies the salient MR impairments found in WS. Indeed, a selective dorsal stream dysfunction was suggested to explain WS's unique cognitive profile of impaired visuospatial construction yet spared object recognition [26]. Imaging studies show visuospatial dysfunctions in WS to be associated with atypical parietal lobe structure and function, including reduced gray matter in the superior parietal and the intraparietal sulcus, abnormal gyri and connectivity of the parietal lobule and hypo-activation in the parietal portion of the dorsal stream during visuospatial tasks [26,31,20,32].

We found PIQ to be significantly worse than VIQ in both the WS and 22q11.2DS groups but not in the DD group, with a more marked VIQ-PIQ discrepancy in WS. Furthermore, while only 5.9% of the DD controls met the criteria for NLD, 33.3% of the WS and 15.8% of the 22q11.2DS participants did meet NLD criteria. In agreement with our findings, a NLD profile was previously reported in WS and 22q11.2DS [4,31]. Taken together with reports of non-verbal impairments in other neurogenetic syndromes, such as fragile X and Turner syndromes [34], it seems that there may be common pathways leading to parietal lobe circuitry impairments in several neurogenetic syndromes.

There are several limitations in our study. Since individuals with WS typically have lower IQs than those with 22q11.2DS, we included participants with IQs in the range of 50–80. This matching procedure may have resulted in some bias in the 22q11.2DS phenotype, i.e., toward relatively low-FSIQ 22q11.2DS subjects. Thus, it is possible that in our attempt to increase the comparability of the 22q11.2DS subjects to the subjects in the WS and DD groups, other factors (e.g., postoperative stroke) could affect the cognitive performance of our 22q11 subjects. Another limitation of the study is the lack of FISH testing in the DD group. Nevertheless, all subjects with DD had been evaluated by a clinical geneticist and referred to further genetic testing if any genetic condition were suspected, thereby minimizing the possibility of including subjects with WS or 22q11.2DS in the DD group.

## 5. Conclusion

This study investigated the psychiatric manifestations and the cognitive executive and visuospatial functions in 22q11.2DS and WS. Our results demonstrated a unique psychiatric phenotype in 22q11.2DS and WS, showing a specific association between 22q11.2DS and psychosis and between WS and specific phobia. We revealed a unique cognitive profile of individuals with WS who showed salient impairments in inhibition and in visuospatial abilities. We also suggest that a VIQ > PIQ discrepancy leading to NLD in some cases may be a common characteristic of the two genetic syndromes, distinguishing them from idiopathic DD. The specific psychiatric and cognitive deficits found in each of the syndrome should be the focus of future psychiatric and cognitive remediation intervention studies.

## Contributors

A. Diamond, D. Gothelf, A. Weizman and O. Zarchi designed the study and D. Gothelf wrote the protocol.

M. Carmel, A. Frisch and E. Michaelovsky managed the genotyping assays and analyses.

T. Green and D. Gothelf carried out the psychiatric evaluation and T. Green, R. Weinberger and O. Zarchi carried out the cognitive evaluation and analyses.

A. Diamond, A. Weizman, D. Gothelf, R. Gruber and O. Zarchi managed the literature searches and D. Abbott and O. Zarchi carried out the statistical analyses.

O. Zarchi wrote the first draft of the manuscript and D. Gothelf, A. Diamond, R. Gruber, A. Weizman and A. Frisch assisted in further preparation of the manuscript. All authors contributed to and have approved the final manuscript.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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## Appendix A. Detailed neurocognitive materials

### A.1. Assessment of executive functions

Executive functions were evaluated using a battery of tools adopted from Diamond et al. [8]:

The Heart and Flowers Task (H&F; previously called the Dots Task) was designed to test working memory, inhibition and mental flexibility. Stimuli are simple line drawings either of a red heart or a red flower presented either on the left or right on each trial. Participants were instructed to respond on the same side as the heart stimulus and on the side opposite to a flower stimulus. An initial block of 20 congruent trials (with all responses on the same

side as the stimulus) was followed by a block of 20 incongruent trials (with all responses on the side opposite to the stimulus), and then by a mixed block of 20 trials where congruent and incongruent trials were randomly intermixed. Memory is required on all trials of the H&F task to remember the rules (i.e., whether to respond on the same or opposite side as the stimuli). Manipulation of that recalled information (i.e., working memory) is required to translate "same" and "opposite" into a right or left response. Inhibition is required on incongruent trials to inhibit the prepotent response to respond on the same side as the visual stimulus. A change in response rules demands mental flexibility on the mixed block test [8].

The Flanker & Reverse Flanker task (F-RF) is another task that tests working memory, inhibition and mental flexibility. In the Flanker trial block, a row of five blue fish appears in the center of the screen, and the child's job is to help in "feeding" the middle fish. Here, the child should selectively attend to the fish in the center and ignore the others. In the Reverse Flanker trial block, the child's job is to ignore the center fish and help in "feeding" the other ones (the pink fish block). The child is told to feed the relevant fish by pressing a key on his right or left, corresponding to the direction in which the relevant fish are pointing. On congruent trials, all fish are pointing in the same direction; on incongruent trials, the irrelevant fish are pointing in the direction opposite to that of the relevant fish. Other trials include (a) no irrelevant fish or (b) irrelevant fish pointing in a direction (up or down) not associated with any response on the task. A third block, the "mixed" condition, consists of blue (focus on the center) and pink (focus on the outside) trials, demanding additional mental flexibility resources for rule switching [8].

### A.2. Assessment of visuospatial functions

The Mental Rotation task (MR) is a visual working memory task sensitive to impairments of the fronto-parietal network, suggested as being impaired in WS and 22q11.2DS [1]. To assess mental rotation, eight hand photographs were used (four each of a right and left hand, two palm up and two palm down), first shown at 0° rotation and then all rotated 180°. For each of the 16 trials, the children indicated whether the photograph showed a right or left hand. Their own hands were concealed under a cloth with a turtle sticker on one arm and a bunny sticker on the other; they could respond by saying "right/left hand" or "turtle/bunny hand".

The Wechsler Block-Design subtest of the Wechsler Intelligence Test was adopted as part of the visuospatial assessment [39].

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