

# Language skills in children with velocardiofacial syndrome (deletion 22q11.2)

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**Objective:** To further define the language profile of children with velocardiofacial syndrome (VCFS) and explore the influence of parental origin of the deletion on language.

**Study design:** Children and adolescents with VCFS (n = 27) were group-matched for sex, age, and IQ with 27 children and adolescents with idiopathic developmental delay. Fifty-four typically developing control subjects were also included in the analyses investigating word association abilities.

**Results:** Children with VCFS had significantly lower receptive than expressive language skills, a unique finding when compared with IQ-matched control subjects. However, no significant differences in word association were detected. Children with a deletion of paternal origin score significantly higher on receptive language when compared with children with a deletion of maternal origin.

**Conclusions:** The Clinical Evaluation of Language Fundamentals-III results suggest that children with VCFS show more severe deficits in receptive than expressive language abilities. Language skills of children with VCFS could be influenced by parental origin of the deletion and thus related to neuroanatomic alterations at the deletion site. (*J Pediatr* 2002;140:753-8)

Velocardiofacial syndrome (VCFS) is a congenital, autosomal dominant condition typically caused by a de novo deletion at chromosome 22q11.2.<sup>1</sup> Its prevalence is estimated at 1 per 4000 to 4500 live births.<sup>2</sup> The major physical

features of VCFS include cleft palate or velopharyngeal insufficiency, cardiac malformations, and mild facial dysmorphism.<sup>3,4</sup> Recent evidence suggests that individuals with VCFS also are predisposed to a characteristic psychiatric

and neurobehavioral phenotype.<sup>4-7</sup> Studies have documented language impairment in VCFS during infancy, preschool, and childhood.<sup>5,8-10</sup> Specifically, children and young adults with VCFS performed worse on a standardized test of language ability than would have been predicted from their verbal IQ scores and showed a significant discrepancy between receptive and expressive language scores.<sup>8</sup> Preschool-aged and school-aged children with VCFS were found to have significantly lowered expressive than receptive language scores.<sup>8,9</sup>

It has been suggested that within the VCFS population, additional genetic factors may modulate the neurobehavioral phenotype.<sup>4,11,12</sup> One recent report proposed that parental origin of the deletion impacts brain development.<sup>1,2</sup> Moreover, other studies, primarily involving subjects transmitted through maternal germ line cells,

ANOVA	Analysis of variance
CELF-III	Clinical Evaluation of Language Fundamentals-III
DD	Developmentally delayed
VCFS	Velo-cardio-facial syndrome

showed that familial transmission indicates lower cognitive outcomes than de novo cases.<sup>4,11</sup> These studies suggest that the greater severity of disabilities may occur with maternal origin of the deletion rather than familial transmission, which would imply an imprinting effect as the result of the parental origin of the deletion. Imprinting is a genetic mechanism in which gene expression is modulated by the parental origin of the chromosome on which the gene is located.<sup>13,14</sup>

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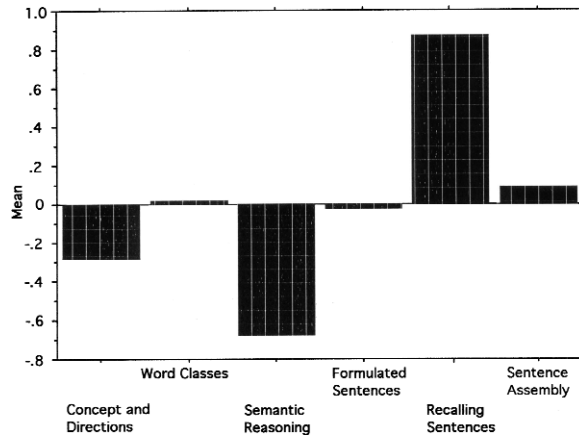
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**Fig 1.** Deviation of CELF-III subtest scores of children with VCFS from a grand mean. Figure illustrates the average language profile by depicting overall strengths and weaknesses. The Word Structure and the Sentence Structure subtests are not included in the figure because they were administered to only 6 of 27 subjects.

The purposes of this study are to provide a detailed description of the strengths and weaknesses of children with VCFS on a standardized language assessment and to examine language development in light of parental origin of the deleted chromosome 22. On the basis of the recruitment bias found in previous studies, we hypothesized that children with a deletion on their maternally derived chromosome 22 would have significantly lower language skills than those with a paternally derived deletion.

## METHODS

### Subjects

Twenty-seven subjects (19 male; 8 female) with VCFS 6 to 19 years of age (mean,  $12.4 \pm 4.1$  years) participated in the study. The sample had a mean full-scale IQ score of 69.4 and a standard deviation of 16.4 (range, 40-105) as measured by the WISC-III or WAIS-III. Subjects were recruited through announcements on Stanford University's Child and Adolescent Psychiatry web site ([www-cap.stanford.edu](http://www-cap.stanford.edu)) and in the Northern California VCFS Association's newsletter. All participants in the study had a deletion of chromosome 22q11.2 as confirmed by fluorescent in situ hybridization technique. Children

with the VCFS clinical phenotype but without the deletion were excluded from the study.

Parental origin of the deletion was confirmed for 21 (14 male; 7 female) of the 27 subjects with VCFS. The mean age of the 21 subjects was  $11.6 \pm 3.5$  years. The 12 subjects (8 male; 4 female) with maternally derived deletions had a mean age of  $11.5 \pm 3.7$  years and a mean full-scale IQ score of  $64.4 \pm 13.7$  (range, 46-81). The nine subjects (6 male; 3 female) with deletions of paternal origin had a mean age of  $11.2 \pm 3.8$  years and a full-scale IQ score of  $76.2 \pm 18.6$  (range, 40-105).

The comparison group of children with idiopathic developmental delay (DD control subjects) consisted of 27 children frequency-matched with the VCFS sample for age (mean,  $11.6 \pm 3.70$  years), sex (18 male; 9 female), and full-scale IQ (mean,  $70.8 \pm 20.5$ ; range, 40-109). The DD control subjects were recruited through advertisements to school programs for children with learning differences and through networks of parents of children with learning disabilities. The primary inclusion criterion for the DD control group was parental report of developmental delay, preferably documented by former standardized assessment. Children whose

primary diagnosis was psychiatric (eg, autism, psychosis) were excluded.

A second comparison group included in the word association analyses consisted of typically developing children, 54 siblings of children with fragile X syndrome genetically identified as normal and recruited as part of an ongoing study conducted by one of the authors. This group had a mean full-scale IQ score of  $105.9 \pm 11.4$  (range, 77-129) and was matched for age (mean,  $11.9 \pm 3.2$  years) and sex (38 male; 16 female) to the VCFS group, using a 2 to 1 ratio of control subjects to children with VCFS. The household incomes for the VCFS, DD, and typically developing groups were comparable. Written informed consent was obtained from the parents of all participants.

### DNA Analysis of Parental Origin

Blood was collected from children with VCFS and their parents. The deletions were verified and their extent determined by two-color fluorescent in situ hybridization, with cosmid probes DO832 (COMT) and N48C12 (D22S264) specific for the proximal and distal deletion regions, respectively [Kurahashi, 1997 No. 23; Karayiorgou, 1995, No. 22]. Parental origin of the deletion was established by genotyping (subjects and parents) for DNA polymorphism (D22S264, D22S941, and D22S944) located within the commonly deleted region.<sup>15</sup> Deletion proved to be de novo in all 21 of the subjects in whom parental origin could be identified. Origin of the deletion could not be determined in six subjects because the biologic parents were not available or the children were adopted.

### Language Assessment

Subjects were administered the complete Clinical Evaluation of Language Fundamentals-III (CELF-III).<sup>16</sup> The CELF-III yields a receptive language score, an expressive language score, and a total language composite score.

**Table.** Descriptive statistics of Clinical Evaluation of Language Fundamentals-III domain and subtest scores by group

	VCFS (n = 27)	DD (n = 27)	Mat (n = 12)	Pat (n = 9)
CELFI-III:				
Total language	70.4 ± 18.5	67.7 ± 19.6	63.67 ± 15.32	79.89 ± 17.05
Receptive language	69.0 ± 17.3	70.3 ± 19.5	62.5 ± 13.4	78.7 ± 17.3
Concepts and directions	5.6 ± 2.8	5.7 ± 2.6	4.8 ± 2.1	6.9 ± 3.3
Word classes	5.9 ± 2.3	5.8 ± 2.5	5.4 ± 2.0	7.0 ± 2.2
Semantic relations	5.2 ± 2.7	5.2 ± 2.8	4.0 ± 1.6	7.3 ± 3.1
Sentence structure	5.0 ± 3.2	7.7 ± 5.3	4.7 ± 2.9	5.3 ± 4.0
Expressive language	74.0 ± 20.9	67.4 ± 20.1	67.5 ± 18.4	83.2 ± 17.9
Formulated sentences	5.9 ± 2.8	5.4 ± 3.2	5.3 ± 2.6	6.9 ± 2.3
Sentence assembly	6.0 ± 3.4	4.8 ± 2.3	4.9 ± 2.3	6.8 ± 3.1
Word structure	7.0 ± 3.2	7.1 ± 3.7	7.0 ± 4.6	7.0 ± 2.0
Recalling sentences	6.8 ± 3.6	5.5 ± 3.0	5.6 ± 2.9	8.7 ± 3.7

*Mat*, children with 22q11 deletion of maternal origin; *Pat*, children with 22q11 deletion of paternal origin.

Sentence structure and word structure subtests only apply to children <9 years old. Each of the composite scores has a mean of 100 points, with SD of 15 points. All subtests are based on a scale with a mean of 10 and SD of 3.

The receptive language subtests are Concepts and Directions, Word Classes, and Sentence Structure (given only to children 6-8 years old) or Semantic Relationships (given only to children ≥9 years old). The expressive language subtests are Formulated Sentences, Recalling Sentences, and Word Structure (given only to children 6-8 years of age) or Sentence Assembly (given only to children ≥9 years old).

### Oral Test of Word Association

All subjects were administered the Oral Test of Word Association.<sup>17</sup> The test consists of five separate 1-minute trials. In the “letter-naming” trials, the subject generates words that begin with the letter F in the first trial, the letter A in the second trial, and the letter S in the third trial. In the last two trials, the “semantic” trials, the subject generates words that belong to the categories of “food” in one trial and “animals” in the other. The scores on the five trials can be considered in two parts: letter-naming and semantic.<sup>18</sup> The typical “profile” for the word association test consists of the five trial “scores” ranking in the following order: animals > foods > S words > F words > A words.

### Statistical Analyses

The variable distributions were tested for and met the assumptions for parametric statistics including normality and homogeneity of variances. For all statistical analyses, an  $\alpha$  of  $P < .05$  (2-tailed) was the threshold for statistical significance. Based on a general linear model, analyses of variance (ANOVA) were used to compare groups on CELFI-III and word association trials. For the children with VCFS and the DD control subjects, mean scores on the CELFI-III Receptive and Expressive Language Scales were compared by means of a repeated-measures ANOVA. The diagnostic group (ie, VCFS and DD control subjects) was considered as a between-subjects factor and the two language scale scores as a within-subjects factor. With the use of a similar statistical strategy, word association scores of the children with VCFS were compared with scores from two comparison groups (ie, DD and typically developing children) by using a repeated-measures ANOVA with the diagnostic group as a between-subjects factor and the word association trial scores as a within-subjects factor.

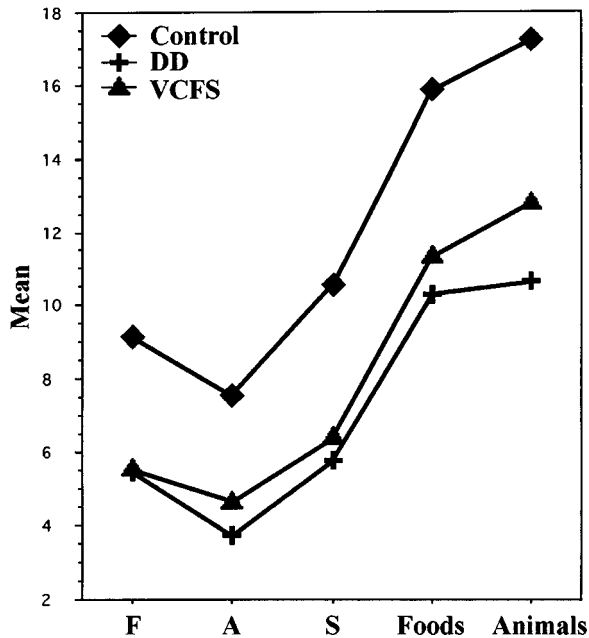
We subsequently divided the VCFS sample into two groups by parental origin of de novo deletion (ie, maternal

and paternal) and compared these groups on the CELFI-III and Oral Test of Word Association. CELFI-III receptive language and expressive language scores were compared by means of a repeated-measures ANOVA model with parental origin as a between-subjects factor and receptive and expressive scores as a within-subjects factor. Because the parental origin groups were not IQ matched, we also ran an analysis of covariance model with IQ used as a covariate to ensure that any obtained differences in language skills or word association skills were not mediated by differences in general cognitive ability.

## RESULTS

### Descriptive Statistics: CELFI-III

The VCFS group (n = 27) and the DD control subjects (n = 27) scored in the “moderately delayed” to “severely delayed” range on the Total Language domain of the CELFI-III (Table). For the children with VCFS, the lowest subtest scores were on Semantic Relationships and Sentence Structure and the highest subtest scores were on Recalling Sentences and Word Structure (Fig 1). Seven of the children with VCFS (1 female; 6 male) and seven of



**Fig 2.** Word association profiles of children with VCFS, children with DD, and typically developing control children (Control).

the DD control subjects (4 female; 3 male) had the lowest possible scores (standard scores of 50) on the Total Language, Receptive Language, and Expressive Language domains. We subsequently divided the VCFS sample into two groups by parental origin of the deletion: the maternal origin group ( $n = 12$ ) and the paternal origin group ( $n = 9$ ). The maternal origin group scored in the "severely delayed" range on Total Language, Receptive Language, and Expressive Language. The paternal origin group scored in the "mildly delayed" range on Total Language, Receptive Language, and Expressive Language.

VCFS and DD control subjects had lower scores on both the letter-naming and the semantic parts of the Oral Test of Word Association (Fig 2). On the letter-naming trials, children with VCFS averaged  $5.6 \pm 4.0$  words beginning with F,  $4.7 \pm 3.8$  words beginning with A, and  $6.4 \pm 4.6$  words beginning with S. DD control subjects averaged  $5.5 \pm 3.6$  words,  $3.7 \pm 2.5$  words, and  $5.8 \pm 3.4$  words, whereas typically developing control subjects averaged  $9.2 \pm 3.7$  words,  $7.6 \pm 3.1$  words, and  $10.6 \pm 4.1$

words, respectively, for these same tasks. Children with VCFS and DD control subjects also scored lower on both of the semantic trials. On the Foods trial, children with VCFS averaged  $11.3 \pm 5.5$  words, DD control subjects averaged  $10.3 \pm 4.5$  words, and those in the control group averaged  $15.9 \pm 5.4$  words. On the Animals trial, children with VCFS averaged  $12.8 \pm 6.1$  words, DD control subjects averaged  $11.0 \pm 6.6$  words, and typically developing control subjects averaged  $17.2 \pm 5.1$  words.

### Comparisons of VCFS and DD Groups: CELF-III

Repeated-measures ANOVA indicated a significant interaction for language scores (Receptive Language and Expressive Language) by diagnostic group (VCFS and DD) ( $F = 10.50$ ;  $df = 1,52$ ;  $P = .002$ ). Follow-up analyses indicated that Receptive Language scores were significantly lower than Expressive Language scores in the VCFS group ( $F = 6.55$ ;  $df = 26$ ;  $P = .017$ ), whereas Expressive scores were lower than Receptive scores in the DD comparison group ( $F = 3.96$ ;  $df = 26$ ;  $P = .057$ ).

### Comparisons of VCFS, DD, and Typically Developing Groups: Word Association

The repeated-measures ANOVA indicated a significant within-subjects effect in word association performance ( $F = 162.3$ ;  $df = 4$ ;  $P < .0001$ ) and a significant between-subjects effect of diagnosis ( $F = 18.9$ ;  $df = 2, 104$ ;  $P \leq .0001$ ). Post hoc analyses (Scheffe test) revealed significant differences between children with VCFS and typically developing control subjects ( $P \leq .0001$ ) as well as significant differences between the DD group and the typically developing control subjects ( $P < .0001$ ). However, there was no significant difference between the scores of the DD control subjects and children with VCFS on the word association test. Even though the children with VCFS and the DD control subjects scored significantly lower than the typically developing control subjects, all three groups demonstrated similar word association profiles with semantic scores higher than letter-naming scores. Specifically, the repeated-measures ANOVA indicated no significant diagnosis by trial score interaction ( $F = 1.47$ ;  $df = 8, 416$ ;  $P = .17$ ).

### Comparison of Parental Origin Within the VCFS Group on CELF-III and Word Association

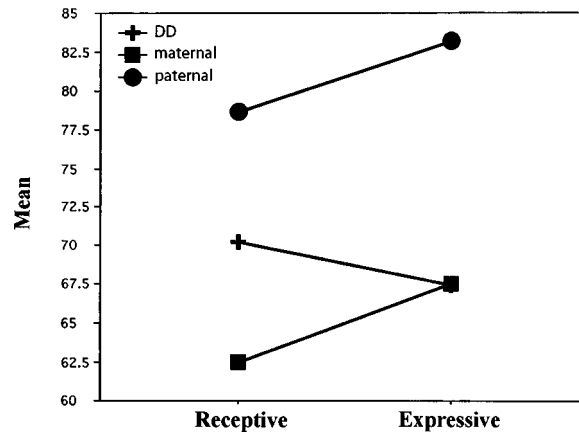
For the two VCFS parental origin subgroups (ie, maternal and paternal), a repeated-measures ANOVA indicated a statistically significant effect between subjects for parental origin ( $F = 5.1$ ,  $df = 1,19$ ,  $P = .035$ ; maternal < paternal) and a significant within-subjects effect for CELF-III Receptive and Expressive Scales ( $F = 4.5$ ,  $df = 1,19$ ,  $P = .046$ ; expressive > receptive) (see Fig 3). However, the interaction of subgroup (ie, maternal and paternal) by language scale was not significant. Follow-up ANOVA comparisons indicated that the maternal origin subgroup scored lower on both the Receptive ( $F = 5.85$ ,  $df = 19$ ,  $P = .026$ ) and Expressive Scales ( $F = 3.82$ ,  $df = 19$ ,  $P = .065$ ), although the difference

reached statistical significance only for the Receptive Scale. A repeated-measures analysis of covariance, with IQ as a covariate, indicated that the between-subjects effect was no longer statistically significant after adjusting for IQ differences ( $F = 2.02$ ,  $df = 1, 18$ ,  $P = .17$ ).

The repeated-measures ANOVA comparing the word association scores of the maternal origin subgroup and paternal origin subgroup revealed no between-subjects effect for parental origin ( $F = .07$ ,  $df = 1, 19$ ,  $P = .78$ ) and no significant group by word association trial interaction ( $F = .47$ ;  $df = 4, 72$ ;  $P = .50$ ).

## DISCUSSION

The finding of lower receptive language than expressive language in children with VCFS differs from the results of the IQ-matched comparison group and the findings of other studies. Specifically, Moss et al<sup>8</sup> and Gerdes et al<sup>9</sup> previously found that children with VCFS scored higher on receptive language than expressive language in younger populations. The contradictory language findings and mean age differences suggest several possibilities. First, these differences may indicate unique developmental patterns. Perhaps as children with VCFS become older, their expressive language skills continue to improve (possibly as a result of language interventions) and their receptive skills plateau by comparison. Alternatively, the differences could be due to the way in which the CELF-III test is constructed. The Semantic Reasoning subtest is administered only to children 9 years of age and older<sup>16</sup> and is the receptive language subtest on which our subjects scored the lowest. Because it was administered to a greater proportion of the subjects in our sample than in previous studies, it is possible that the lower receptive language scores are strongly driven by this subtest. A related explanation could be that by 9 years of age, children with VCFS have not



**Fig 3.** Mean scores on CELF-III Receptive and Expressive Language scales of children with VCFS with a deletion of maternal origin, children with VCFS with a deletion of paternal origin, and control subjects with DD.

gained the abstract reasoning skills and cognitive sophistication required to complete more advanced receptive language tasks such as the Semantic Reasoning subtest. Perhaps the group's lower receptive than expressive language is related to the population's weakness in abstract reasoning, which is not as noticeable when the children are younger and given more concrete tasks.<sup>5</sup>

Structural brain findings provide further support for lower receptive than expressive language in children with VCFS. In a study of children with VCFS, magnetic resonance imaging demonstrated reductions of the left parietal lobe<sup>19</sup> and a decrease of the temporal lobe,<sup>20</sup> regions of the brain involved in receptive language. In addition, a relative preservation of the frontal lobe was reported,<sup>19</sup> which is one of the areas of the brain commonly associated with expressive language.

As could be expected from their delayed language fundamentals scores, the performances on the test of word association of the children with VCFS and the DD control group were poorer than the performance of the typically developing control group. However, the word association profiles of the children with VCFS and the DD control group were consistent with the typically developing control group and with previous studies of typically developing control

subjects.<sup>18</sup> Both groups produced more words in the semantic trials than in the letter-naming trials.<sup>18</sup> The fact that there were no significant differences between the children with VCFS and the DD control subjects signifies that their weakness in word association is most likely related to overall level of cognitive impairment.

Previous studies have reported that familial transmission of the deletion 22q11 in VCFS results in more severe intellectual disabilities than those seen in de novo cases.<sup>4,11</sup> However, it is unclear whether this result is due to familial transmission or to a recruitment bias for children of affected mothers. The current study may provide support for an alternate interpretation of the familial transmission findings. Subjects with a maternally deleted chromosome 22 had more impaired language abilities than those with a paternally deleted chromosome 22, as shown by a significant difference on the CELF-III Receptive Language Scale and a trend toward significance on the Expressive Language Scale. This finding suggests an effect of imprinting on the regions of the brain associated with language ability and is supported by a report that reduction of gray matter development in patients with VCFS was associated with maternal origin of the deletion 22q11.<sup>12</sup> There is only a single case report of paternal uniparental disomy.<sup>21,22</sup> Previous

reports have not assessed cognitive abilities with the use of standardized tools.<sup>22-25</sup> In the current study, accounting for full-scale IQ made the effect of parental origin on receptive and expressive language nonsignificant. This leaves the relation among parental origin of the deletion, language, and overall cognitive ability uncertain. It could be hypothesized that structural brain differences evidenced in previous studies are associated with differences in IQ between the groups.<sup>12</sup>

It will be essential for investigators in the future to explore parental origin of the genetic deletion on larger subject samples with the use of new quantitative investigation tools such as functional magnetic resonance imaging. It also will be important for future studies to further explore the effects of parental origin of the genetic abnormality on cognition, behavior, and brain function in individuals with VCFS.

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