

## Intellectual abilities in a large sample of children with Velo–Cardio–Facial Syndrome: an update

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### Abstract

**Background** Learning disabilities are one of the most consistently reported features in Velo–Cardio–Facial Syndrome (VCFS). Earlier reports on IQ in children with VCFS were, however, limited by small sample sizes and ascertainment biases. The aim of the present study was therefore to replicate these earlier findings and to investigate intellectual abilities in a large sample of children with VCFS. In addition, we aimed to identify factors that may contribute to within-syndrome variability in cognitive performance, such as the mode of inheritance of the deletion, sex, the presence of a heart defect and psychiatric morbidity.

**Method** IQ data of 103 children with VCFS (56 males, 47 females) were collected. Psychiatric diagnosis was additionally recorded.

**Results** Children with VCFS had a mean full-scale IQ (FSIQ) of 73.48 (range: 50–109). There were no effects of sex, presence of a heart defect and psychiatric condition on intellectual profile. Inheritance of the deletion affected cognitive performance in VCFS, with children with familial deletions having significant lower FSIQ than children with a *de novo* deletion.

**Conclusions** Learning disabilities are very common in children with VCFS, although marked within

syndrome variability is noted. One factor contributing to this variability seems to be the mode of inheritance of the deletion.

**Keywords** cognitive phenotype, intellectual disability, intelligence, 22q11 deletion, Velo–Cardio–Facial Syndrome

### Introduction

Velo–Cardio–Facial Syndrome (VCFS) is the most frequent microdeletion syndrome in man, with a prevalence of at least 1:6000 (Botto *et al.* 2003). The syndrome is caused by a submicroscopic deletion in region q11 of chromosome 22, which is detectable by means of fluorescence *in situ* hybridization (FISH). The deletion occurs mainly as a *de novo* event, but familial inheritance is noted in about 15% of the patients (Swillen *et al.* 1998). Although the clinical presentation is quite variable, the major characteristics of the syndrome include velopharyngeal abnormalities, cardiac anomalies, mild facial dysmorphism and learning disabilities (for a review, see Shprintzen 2000). In recent years, considerable progress has been made in describing the cognitive and behavioural characteristics associated with VCFS, which have been grouped into a 'behavioural phenotype' (for a review, see Shprintzen 2000; Murphy 2004).

About 10 years ago, we have reported some of the first systematic data on intelligence in children with

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VCFS, showing that these children have intellectual abilities ranging from borderline intelligence to moderate learning disability (Swillen *et al.* 1997). Their average Full-Scale IQ (FSIQ) was about 75 and the intellectual profile was often characterized by a discrepancy between Verbal IQ (VIQ) and Performance IQ (PIQ), favouring the VIQ. These data have been replicated by several other research groups (Moss *et al.* 1999; Niklasson *et al.* 2001; Woodin *et al.* 2001).

These initial studies were important first steps towards a thorough understanding of the cognitive phenotype in VCFS, and also suggested marked within syndrome variability in cognitive performance, similar to the variability in the VCFS physical phenotype (Ryan *et al.* 1997). One contributing factor to the variability in cognition in VCFS is the mode of inheritance of the deletion: *Familial* deletions show a more severely affected cognitive phenotype than *de novo* deletions (Swillen *et al.* 1997; Gerdes *et al.* 1999) and this might be explained by the lower education level of affected vs. unaffected parents (Swillen *et al.* 1997). Recently, Antshel *et al.* (2005) reported sex differences in cognitive function in VCFS, indicating that boys may be more cognitively affected than girls. Cardiac defects, which are common in VCFS (Ryan *et al.* 1997), are also known to affect cognitive performance and neurological development – e.g. due to intraoperative and postoperative factors, like circulatory arrest (Mahle 2001) – although earlier reports did not find an association between intellectual ability and the presence of cardiac malformations (Swillen *et al.* 1997; Gerdes *et al.* 1999).

It should be noted that the reported studies on IQ in children with VCFS were limited by small sample sizes and ascertainment biases. Therefore, the purpose of this study is to provide an update of our earlier findings on intelligence in VCFS and to examine intellectual ability in a large sample of children with VCFS, the largest study of its kind to date. This large sample also allows us to extend previous work by studying factors that might contribute to intellectual variability in VCFS, such as the mode of inheritance of the deletion, sex and the presence of a congenital heart defect (CHD). Because the psychiatric conditions of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have been frequently

reported in children with VCFS (Niklasson *et al.* 2001; Gothelf *et al.* 2004; Fine *et al.* 2005), we also explored the effect of these disorders on the cognitive profile in VCFS.

## Method

The original data of Swillen *et al.* (1997) ( $n = 37$ ) were extended with 66 children, which resulted in a final sample of 103 children with VCFS (56 males, 47 females). Participants were recruited from a group of patients followed at the VCFS clinic at the University Hospital of Leuven, which is the referral centre for patients with VCFS in Flanders (Belgium). In all children, diagnosis of VCFS was confirmed by FISH, using probe LSI Tuplet1 (Vysis, Downers Grove, IL, USA). The mean chronological age at the time of testing was 7 years and 9 months ( $SD = 3;1$ ; Range = 4–17 years). IQ was measured in all children by means of age-appropriate Wechsler Intelligence Scales (WPSSI-R and WISC-III) by the final author (A.S.). Psychiatric diagnosis was carried out by an experienced child psychiatrist (A.V.) and patients were diagnosed according to the standard DSM-IV criteria (American Psychiatric Association 1994). Twenty-seven children had a diagnosis of ADHD. Nineteen children met criteria for ASD. No other psychiatric diagnoses were made.

As the educational attainment level of the parents might explain why *familial* deletions show a more severely affected cognitive phenotype than *de novo* deletions, we asked all parents of the children who participated in the study to report their educational attainment level. Based on these data, mothers and fathers were classified into six categories (ranging from 0 = preprimary education to 5 = higher education) according to the International Standard Classification of Education system, developed by the UNESCO (OECD 1999). Because educational attainment level of the mother was highly related to that of the father ( $r = 0.83$ ,  $P < 0.0001$ ), we used the median of both values as an index of parental educational attainment in our analyses. Educational attainment level in the present sample ranged from category 0 to 5; 51% of the parents completed higher education or category 5 (= mode).

Group comparisons were done by means of Student's *t*-test and ANOVAS. Wilcoxon two-sample

tests were used in case of non-normally distributed variables.

## Results

Full-scale IQ ranged from 50 to 109. It was normally distributed around a mean of 73.48 (SD = 11.73), which is about 2 SD lower than the mean FSIQ (Mean = 100; SD = 15) in normally developing subjects. In our sample, 15/103 children showed normal intellectual development (FSIQ > 85). Forty-seven children showed borderline intellectual functioning (FSIQ between 70 and 85). Mild intellectual disability (FSIQ between 55 and 70) was present in 37 children. Four children showed a moderate intellectual disability (FSIQ < 55).

VIQ (Mean = 78.66; SD = 14.01) was higher than PIQ (Mean = 72.64; SD = 10.89) and this discrepancy was statistically significant [ $t(102) = 5.69$ ,  $P < 0.01$ ]. At the subject level, 75/103 children showed a VIQ > PIQ intellectual profile, whereas 27/103 showed the reverse pattern. A clinically significant discrepancy of more than 15 scaled score

points was found in 23 children: 18 of them showed a VIQ > PIQ profile and 5 had a PIQ > VIQ discrepancy.

Table 1 provides an overview of the investigated variables that might influence variability in IQ in VCFS. Inheritance of the deletion affected cognitive performance in VCFS, with children with familial deletions having significant lower FSIQ than children with a *de novo* deletion [ $t(101) = 2.61$ ,  $P = 0.01$ ]. We further examined whether this difference in FSIQ between both groups could be explained by the educational attainment level of the parents. Parents of children with *de novo* deletions had higher educational levels than parents of children with familial deletions (Wilcoxon two-sample test,  $W = 231.5$ ,  $P < 0.01$ ). We further ran an ANOVA, with inheritance of the deletion and educational attainment level of the parents as between-subject factors and FSIQ as dependent variable. There was an effect of educational attainment level of the parents on FSIQ ( $F_{4,97} = 5.25$ ,  $P < 0.01$ ) and group differences in FSIQ between children with *de novo* and *familial* deletions disappeared ( $F_{1,97} = 0.26$ ,

Table 1 Group means (SD)

			P
Deletion	<i>De novo</i> (n = 92)	Familial (n = 11)	
FSIQ	74.50 (11.69)	65.00 (8.45)	0.01
VIQ	79.79 (13.91)	69.27 (11.53)	0.02
PIQ	73.42 (10.89)	66.09 (8.84)	0.03
Sex	Female (n = 47)	Male (n = 56)	
FSIQ	73.19 (10.40)	73.73 (12.84)	0.82
VIQ	78.87 (12.27)	78.50 (15.43)	0.89
PIQ	72.28 (10.38)	72.95 (11.39)	0.76
CHD	Yes (n = 55)	No (n = 48)	
FSIQ	74.38 (11.84)	72.46 (11.65)	0.41
VIQ	79.05 (14.23)	78.23 (13.89)	0.77
PIQ	73.56 (10.77)	71.58 (11.05)	0.36
Psychiatric	Non-ADHD (n = 76)	ADHD (n = 27)	
FSIQ	73.32 (12.32)	73.96 (10.10)	0.81
VIQ	78.30 (14.78)	79.70 (11.76)	0.66
PIQ	72.97 (11.18)	71.70 (10.19)	0.61
	Non-ASD (n = 84)	ASD (n = 19)	
FSIQ	74.56 (11.83)	68.74 (10.26)	0.05
VIQ	79.32 (14.51)	75.79 (11.43)	0.32
PIQ	73.71 (10.90)	67.89 (9.78)	0.03

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CHD, congenital heart defect; FSIQ, full-scale IQ; PIQ, performance IQ; SD, standard deviation; VIQ, verbal IQ.

$P = 0.61$ ) when educational attainment level of the parents was taken into account.

There were no main effects of sex or CHD on IQ ( $P > 0.30$ ), and there was no effect of interaction between sex and CHD on IQ ( $P > 0.15$ ).

Children with ADHD did not differ in intellectual profile from children without ( $P > 0.80$ ). However, the presence of ASD seemed to affect cognitive performance in children with VCFS, as children with ASD tended to have a lower FSIQ than children without ASD [ $t(101) = -1.98$ ,  $P = 0.05$ ]. This difference was due to the fact that both groups differed significantly in PIQ [ $t(101) = -2.14$ ,  $P = 0.03$ ], but not in VIQ [ $t(101) = -0.99$ ,  $P = 0.32$ ].

## Discussion

The present report provides a replication of lowered IQ in a large sample of children with VCFS. About 60% of the children showed a borderline to normal intelligence (FSIQ  $> 70$ ), whereas an intellectual disability (FSIQ  $< 70$ ) was noted in 40%. At the group level, children with VCFS also showed a discrepancy between VIQ and PIQ, favouring verbal abilities. These data are in line with previous reports on children with VCFS (Swillen *et al.* 1997; Moss *et al.* 1999; Niklasson *et al.* 2001; Woodin *et al.* 2001).

Turning to the factors that might affect variability in IQ in patients with VCFS, we only found a significant effect of the mode of inheritance of the disorder: Cognitive function seems to be more severely affected in case of familial inherited deletions, which replicates the initial reports by Swillen *et al.* (1997) and Gerdes *et al.* (1999). The difference in FSIQ between children with *de novo* deletions and children with familial inherited deletions was due to a lower educational attainment level of the parents of children with familial inherited deletions. This might be explained by the lower educational level of the affected parents and by the condition of assortative mating, which results in a lower educational level in the unaffected parents, in familial inherited deletions (see also Swillen *et al.* 1997). In this respect, it is interesting to note that, educational attainment level of the parents had an overall effect on FSIQ in children of our sample, which indicates

both genetic (i.e. educational attainment level is largely determined by one's intellectual abilities) and environmental influences on intellectual variability in children with VCFS.

In contrast to findings of Antshel *et al.* (2005), sex does not seem to have an effect on cognitive function in VCFS. There is also no evidence for an association between the presence of cardiac malformations and cognitive functioning in children with VCFS. The latter indicates that variations in IQ cannot merely be explained by the physical anomalies associated with VCFS, but are probably due to the deletion 22q11 itself (Swillen *et al.* 1997).

What are the effects of psychiatric morbidity on intelligence in VCFS? The presence of ADHD did not have an effect on cognitive function in VCFS and this is similar to the findings of Gothelf *et al.* (2004). Children with VCFS and ASD tended to have lower intellectual abilities than children without ASD, but this difference was entirely due to a lowered PIQ in children with VCFS and ASD, with no differences in VIQ.

In recent years, progress has been made in determining the genetic variations that might explain cognitive variability in VCFS. For example, polymorphisms of genes within the 22q11 deleted region, like COMT and PRODH, seem to affect cognitive function in VCFS (Gothelf *et al.* 2005). The examination of the association between genetic variations and cognitive performance requires large sample sizes with sufficient numbers of subjects with each genetic variant. Time is now ripe to study such associations in our sample, and these analyses will be carried out in the near future. Rauch *et al.* (2005) suggested that size of the deletion may alter intellectual abilities in VCFS. However, smaller (atypical) deletions are relatively uncommon, which makes it difficult to perform within-group analyses with regard to cognitive performance. Carefully designed case studies with smaller or atypically deleted individuals might provide some useful clues to unravel genotype-phenotype associations.

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