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Chapter 1

Review of the Literature

Clinical features.

Velocardiofacial syndrome (VCFS) is a congenital malformation disorder that was first described in 1968 by William Strong, M.D. Robert Shprintzen, Ph.D. later delineated the syndrome in 1978, when he described a similar pattern of symptoms in 12 patients (Arnold et al., 2001). VCFS is a syndrome of multiple anomalies that occur to varying degrees and frequency, and some features even appear to change according to age. The phenotypic features present in these patients consist primarily of distinct facial features, hypernasal speech, cleft palate, cardiac malformations, short stature, learning difficulties or mental retardation, delayed language development and social skills deficits. Due to the significant contributions made by Shprintzen et al., this congenital malformation also has been called Shprintzen syndrome.

Currently, there exists a broad phenotypic spectrum for this syndrome, and often diagnosis of this syndrome is difficult to make due to the various degrees of expression of the many anomalies. However, the name of this syndrome describes the main features involved. The term “syndrome” indicates that there is a pattern of features occurring together. Specific to VCFS, this pattern of features occurs over three areas. “Velo” is a derivative of the Latin word velum, which refers to the palate and the back of the throat. Typically it refers to either a cleft palate (which may be complete, incomplete, or submucous) or to the tone of the pharyngeal muscles, which may be poor (Lipson, 2000). In
the original report of the newly recognized congenital malformation syndrome, Shprintzen et al. (1978) determined that 50% of the patients had submucous clefts. Often, a cleft palate results in hypernasal speech. According to Goldberg et al. (1993) approximately 8% of all individuals with a cleft palate, but without an accompanying cleft lip, fit the diagnosis of VCFS.

"Cardio" refers to the heart malformations that may be seen within this syndrome. Predominant anomalies (Tetralogy of Fallot, ventricular septal defect, and right-sided aortic arch) can vary in severity and may necessitate various degrees of intervention. It is important to note, however, that approximately two-thirds of children with VCFS do not exhibit any heart abnormalities (Lipson, 2000).

Lastly, "facial" refers to the similar pattern of facial features that are typically demonstrated in children with VCFS. Typical features include hypotonia (low facial muscle tone), a long and prominent nasal bridge, small jaw, flat cheek bones, narrow palpebral (eyelid) fissures, an overall long appearance to the face, and microcephaly (smallness of the head) (Lipson, 2000). These facial features may not be obvious in the early years of life, but usually increase in prominence over time.

In addition to these primary physical symptoms, other features such as short stature, immune deficiencies, hypocalcaemia, hypothyroidism, long tapered fingers, hearing and vision problems, abundant hair scalp, and undescended testes, may also be present (Lipson, 2000). As aforementioned, these features may not be strikingly obviously in the early years of life. However, some infants with VCFS experience immediate difficulties such as postnatal failure to thrive. It is believed that this is likely due to heart abnormalities, as well as problems with feeding, which often accompany
VCFS during infancy (Carneol, Marks, & Weik, 1999; Lipson et al., 1991). In such cases, a diagnosis is more likely to be confirmed at an earlier age.

VCFS is one of the most common genetic disorders in humans (Scambler, 2000). Estimates vary across research studies, but the general consensus is that VCFS has a prevalence of approximately 1 in 4,000 live births (Murphy et al., 1998; Scambler, 2000). However, due to the fact that the spectrum of symptoms is quite broad, VCFS is still under-recognized and under-diagnosed and the precise prevalence is unknown (Thomas & Graham, 1997). Murphy et al. (1998) suggest that it is possible that VCFS is under-diagnosed due to a lack of genetic screening conducted in clinical populations functioning at a high intellectual level. Advances in human genetics have aided in the determination that VCFS is generally caused by an abnormality in chromosome 22, and more specifically to a deletion in band q11. The most accurate procedure employed by geneticists in testing for this deletion is the Fluorescent in Situ Hybridization (FISH) method (Eliez et al., 2000).

Approximately 82% of all cases of VCFS have a deletion within chromosome 22q11 (Scambler, 1992). Such a deletion is present from conception (Lipson, 2000). The chromosome 22q11 deletion can occur out of familial origin, meaning that it can be inherited in an autosomal dominant fashion, or it can occur as the result of a de novo deletion, meaning there is no family history. Only 10-15% of the cases of VCFS in children are inherited from a parent with VCFS, but there is a 50/50 chance of transmission with every pregnancy when one parent has the syndrome (Lipson, 2000). It is believed that the severity of the phenotypic expression of the syndrome is related to the origin of the deletion, those of familial origin typically being more severe than those of
de novo origin (Swillen et al., 1997). Initial speculation regarding this chromosomal deletion was that there was a connection between the size of the deletion and the severity of the symptoms. However, this speculation has not been substantiated and it still remains a mystery why affected individuals within the same family, with the same deletion, may exhibit very different problems (Scambler, 1992).

This 22q11 deletion has also been associated with DiGeorge syndrome and conotruncal anomalies face syndrome. Essentially, this deletion is responsible for a spectrum of related disorders. This spectrum of disorders related to the 22q11 deletion has been more recently coined as CATCH 22 syndrome (Thomas & Graham, 1997). Because these syndromes share a similar molecular genetic basis, it can be difficult for clearly delineated distinctions to be made, which has further contributed to difficulties with research in this area. According to Scambler (1992) DiGeorge sequence is usually diagnosed when heart defects and immune system problems are particularly severe. DiGeorge syndrome can be conceptualized as falling at the severe end of the spectrum of VCFS.

Cognitive implications.

Perhaps the most recognized, but under-investigated, symptoms of VCFS are mental retardation (MR) and learning disabilities. According to Swillen et al. (1997), a wide variability in intelligence in VCFS patients exists. Although this is the case, these authors cite that learning difficulties are reported in 82% to 100% of the patients with VCFS. However, much of the previous research is unclear in regard to how learning disabilities and/or mental retardation are operationally defined and measured. It is evident that there is not a universal understanding among professionals across various fields as to
how learning disability is defined. Several previous studies, especially within the medical literature, describe a learning disability as the attainment of below average IQ scores. In contrast, Public Law 94-142 describes a learning disability as, "The failure, on the part of a child who has adequate intelligence, maturational level, cultural background and educational experiences, to learn a scholastic skill" (Sattler, 1992, p.598). However, this definition is not met with universal acceptance. It is felt by some professionals that neither the requirement of "adequate intelligence", nor the presence of a discrepancy between ability and achievement test scores are truly necessary conditions. However, Public Law 94-142 indicates:

A designation of a specific learning disability should be applied only to children who have a severe discrepancy between achievement and intellectual ability in one or more expressive or receptive skills, such as written expression, listening and reading comprehension, or mathematics (Sattler, 1992, p.598).

Critics opposed to this criterion believe that the term "severe discrepancy" is ambiguous and misleading.

Furthermore, some research pertaining to VCFS identifies a discrepancy between Verbal IQ (VIQ) and Performance IQ (PIQ) as an indication of a specific learning disability. According to Sattler (1992), a VIQ-PIQ discrepancy should not be used as the only means of classifying an individual as learning disabled because it does not take into account achievement in school tasks. These ambiguities in past research regarding VCFS have made the understanding of phenotypic expression within the cognitive realm more challenging to delineate.
Ambiguity also exists around the definition of mental retardation, but the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (American Psychiatric Association, 2000) attempts to clarify it by stating:

The essential feature of mental retardation is significantly subaverage general intellectual functioning that is accompanied by significant limitations in adaptive functioning in at least two of the following skill areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health and safety (p.41).

The critical part of this statement is the idea that significantly low performance on a test of general intellectual ability is a necessary, but not sufficient, component of a diagnosis of mental retardation. Without an assessment of adaptive behavior, the diagnosis of mental retardation should not be made.

Wang et al. (1998) found that children with 22q11 deletions are likely to exhibit a cognitive profile similar to that seen in nonverbal learning disabilities (NLD). Within such a profile, VIQ is greater than PIQ and reading and spelling achievement are typically greater than math achievement. This is a somewhat surprising pattern considering the difficulties that some of these children possess with speech and language development. Swillen et al. (1997) determined for a group of 37 children and adolescents diagnosed with VCFS that a statistically significant difference existed between the average VIQ and PIQ for the total group. However, when looking more specifically within age groups for this study, it is apparent that the youngest children in the study demonstrated an overall higher mean VIQ than PIQ on the WPPSI-R, but that this was not statistically significant. The older children in the study (who were evaluated using the
WISC-R) demonstrated a larger mean difference between VIQ and PIQ that was indeed significant. Moss et al. (1999) also found a significant difference between Verbal and Performance scores, with VIQ scores being significantly higher than PIQ. There is some controversy within the literature about the VIQ and PIQ discrepancy and the consistency of this occurrence in the cognitive profiles of children with VCFS. Although it is more typical that patients exhibit a discrepancy characterized by VIQ > PIQ, individuals with VCFS may also demonstrate PIQ > VIQ (Henry et al., 2002). Perhaps the most important issue demonstrated here is that the cognitive profiles of these patients may include a significant difference between these two domains.

The VIQ and PIQ discrepancy, together with greater reading and spelling achievement than mathematic achievement, is often similar to the profile seen in persons with a Nonverbal Learning Disability (NLD) syndrome (Rourke, 1989). According to Rourke (1995) potential areas of deficit for individuals with this syndrome can be grouped into three major areas: neuropsychological deficits, academic deficits, and social-emotional/adaptational deficits. The neuropsychological deficits include visual perception, psychomotor coordination, nonverbal memory, reasoning, some executive functions, and aspects of speech and language. Primary academic concerns for persons with NLD include deficits in math calculations and reasoning, reading comprehension, and certain aspects of written language. Lastly, children with NLD are at an increased risk of having social deficits that include the manner in which they perceive social situations and in which they interact with others. Additionally, children with NLD often exhibit internalized forms of psychopathology, such as anxiety and depression. The general overall profile of individuals with NLD, which consists of the VIQ-PIQ
discrepancy, academic difficulties, internalized forms of psychopathology, and social skills deficits, is strikingly similar to those with VCFS. Thus, some research in this area parallels these two groups of individuals (Moss, 1999).

Learning disabilities and/or some degree of cognitive disabilities occur in approximately 99% of the VCFS patient population (Goldberg et al., 1993). However, this must be interpreted cautiously, keeping in mind the previously discussed differences among professionals as to how such entities are defined. Shprintzen (1990) reported that 40% of VCFS patients had mild intellectual disability (IQ<70) with particular deficiency in the areas of mathematics and reading comprehension. A study conducted by Eliez et al. (2000) found that three out of their four participants exhibited intellectual functioning in the borderline to mildly mentally retarded range. In contrast, Golding-Kushner, Weller, & Shprintzen (1985) determined that children under the age of six tested within the average range of intellectual ability. However, a follow-up study on several of the participants showed that children over the age of six did not progress beyond a concrete level of cognitive development and therefore experienced significant declines in their IQ scores. This decrease occurs because ability tests generally require more abstract thinking as age increases. When the ability to reason abstractly is limited, there is a decline in IQ scores is reflected. This indicates that even if a child with VCFS appears to be of average intelligence in early childhood, learning difficulties and cognitive deficits may appear at a later time.

Results obtained by Gerdes et al. (1999) are somewhat contradictory to the previously mentioned study. These investigators evaluated 40 preschool children and determined that the mean scores for this age group fell in the borderline range of
intelligence. Moreover, 44% of the children had a statistically significant difference between PIQ and VIQ (i.e., greater than nine points).

Swillen et al. (1997) found that 55% of the 17 children in their VCFS sample had either average or borderline IQ, and 45% scored in the mentally retarded range with IQs less than 70. The majority (N=14) had scores in the mild range of MR, two fell in the moderate MR range, and one was within the severe range. Further investigation into the participants with these MR scores revealed that the incidence of familial 22q11 deletion was much greater than that in de novo cases. This finding may suggest that a familial deletion can have more pronounced implications.

*Speech and language implications.*

Pervasive language/speech difficulties and developmental delays are also typically experienced with VCFS (Shprintzen, 1981). In fact, Scherer, D’Antonio, and Kalbfleisch (1999) state that speech-language impairment is one of the most common clinical features in VCFS and that most children with VCFS emerge from a critical speech and language learning period with severe limitations in their communicative abilities.

Language deficits are commonly seen across both receptive and expressive domains, although 31% of the patients in a study by Gerdes et al. (1999) demonstrated more pronounced impairments and delays in expressive language. Gerdes et al. (1999) also found language abilities that ranged from average to severely delayed. It is not uncommon for children with VCFS to be non-oral (no sounds) the first years of life. Gerdes et al. found that more than ¼ of the sample were non-oral communicators at 2 years of age. According to Marks (2001) children with VCFS who also have
Preschoolers with VCFS may have limited receptive language skills. This is likely evidenced through their ability to only comprehend single words and follow simple verbal directions. Although language skills are often delayed and impaired, the impairment is typically more pronounced in the expressive domain, indicating that children with VCFS generally have better-developed receptive language than overall speech production and expressive language abilities (Scherer et al., 1999, Gothelf & Lombroso, 2001). However, Marks (2001) indicates that other children with VCFS function very close to average in the receptive language domain. It appears as though the research in this area is still somewhat inconclusive. Specifically, Marks states that there exists a great degree of variability in the performance of 3- to 6-year-olds on language measures. When examining language deficits in children with VCFS, it is imperative that one remember that the syndrome may affect the hearing of these children and therefore this must be evaluated to make sure that this is not what is contributing to the language deficit. Moreover, Marks states that cognitive abilities and processing speed also have an impact on language comprehension and could alter receptive language.

Gerdes et al. (1999) also investigated the possibility of a link between the presence of cardiac anomalies and more pronounced language delays. They determined that there was no significant difference in language outcome in those patients with cardiac disease and those without cardiac abnormalities. It is noteworthy, however, that all participants in this study were delayed in the emergence of language skills.

Behaviors, emotional, and social implications.

Recent studies also suggest relatively high rates of psychopathology in persons with VCFS (Arnold, 2001; Chow et al., 1998). This area of investigation is gaining more
recognition and attention, but links between VCFS and psychopathology have been suspected for some time. According to a study conducted by Goldberg et al. (1993), a large number of patients demonstrated psychiatric symptoms that necessitated referral for psychiatric treatment and drug therapy. The most common symptoms among these patients were mood disturbances and poor concentration and processing speed, often captured by the diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD). Other studies have found similar results with large numbers of patients meeting diagnostic criteria for ADHD and having pronounced behavioral profiles including blunted affect, impulsivity, disinhibition, proneness to temper tantrums and oppositional behavior, anxiety, phobic behavior, and social withdrawal (Gothelf & Lombroso, 2001; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2002). Golding-Kushner et al. (1985) suggested that VCFS is likely associated with extremes of behavior, as evidenced by individuals with either disinhibited and impulsive behavior or shyness and seriousness.

More recently, links have been made between VCFS and the development of bipolar disorder and schizophrenia. Gothelf and Lombroso (2001) report that the prevalence of schizophrenia in individuals with VCFS is 25 times that of the general population, and that nearly ¼ of individuals with VCFS develop psychotic symptoms. VCFS has even been identified as one of the highest risk factors for the development of schizophrenia aside from being a child of parents with schizophrenia or a monozygotic twin of an individual affected by the syndrome (Murphy, 2002). Moreover, these authors suggest that the diagnosis of schizophrenia is often made in adolescence, and that in general both patients with VCFS, with or without schizophrenia, score higher on a scale measuring schizotypal personality. Usiskin et al. (1999) determined that the rate of 22q11
deletions in childhood-onset schizophrenia is higher than in the general population and suggests that the earlier age of onset may be mediated by neurodevelopmental disruption.

Lachman et al. (1997) determined that a deletion on chromosome 22, near the region of deletion for VCFS, may be a possible locus for bipolar disorder among the general population. Although statistical significance was not reached in this study, these results approached significance and are consistent with previous hypotheses about such a link, thus warranting further investigation. Feinstein, Eliez, Blasey, and Reiss (2002) determined that although the frequency of DSM-IV psychiatric disorders was high in children and adolescents with VCFS, the prevalence was not significantly higher than a matched comparison group of children with developmental delays. These authors suggest that although difficulties with attention, anxiety, and mood exist in persons with VCFS at rates higher than in the general population, there is no evidence that the psychopathology is qualitatively or quantitatively different from persons with developmental delay. Moreover, the behavior problems exhibited by children with VCFS did not provide a unique psychiatric profile that could serve as a phenotypic indicator of vulnerability to schizophrenia. Additional research has also indicated that there is no existing strong or specific association between schizophrenia or bipolar illness and cleft palate as a marker of VCFS (Christensen & Mortensen, 2002). It is evident that conflicting results exist related to the psychopathological profile of individuals with VCFS, and that continued research is needed in order to reach more definitive conclusions. Murphy (2002) suggests that many studies examining the VCFS and schizophrenia connection have failed to utilize appropriate sample sizes and sound methodological approaches, producing conflicting results and a continued need for replication.
Additionally, a general lack of developed social skills and extreme shyness are frequently noticed in individuals with VCFS. Wang et al. (1998) suggest that social skills deficits, related to the clinical anxiety and depression that these children often exhibit, are frequently reported by parents. Several of the phenotypic characteristics of VCFS may contribute to the difficulties that these individuals face with social interactions. A combination of factors such as limited facial expression, monotone voice, and blunted or inappropriate affect are thought to exacerbate other difficulties related to interaction with others (Golding-Kushner et al., 1985; Usiskin et al., 1999).

Swillen et al. (1997) report that the “Social Problems” and “Attentional Problems” clusters on the Child Behavior Checklist (CBCL) for patients with VCFS, ages 4-18 years, were significantly higher than any of the other clusters of problem behavior for this instrument, except the cluster “Withdrawn”. These authors believe that the social withdrawal may be in part explained by the difficulties that these children have with communication with others, as well as neuropsychological deficits being partly responsible for poorer social interaction skills (i.e., problems perceiving new situations).

Although the phenotypic expression of this complicated syndrome varies from child to child, most individuals experience difficulties related to cognitive functioning, language development, and emotional and social functioning. It is imperative that parents, educators, and other professionals are aware of the multitude of challenges that children with VCFS encounter so that a better understanding of each child’s functioning can be obtained in order to inform treatment decisions and interventions. Further research is needed across age levels to determine the “typical” profiles that are exhibited as children with VCFS develop. One specific area that is lacking information is that of the
preschool age. It is critical that research is continued in this area so that early interventions can be tailored to the needs of these children.
Chapter II
Rationale and Hypotheses

The current literature assessing cognitive and language abilities and social skills of children with VCFS is limited, especially when considering the lack of investigation at the preschool age level. The current body of research has allowed several conclusions to be made about these three areas. Some children with VCFS have been found to function cognitively within the average range, but it is more common that these children will exhibit functioning characteristic of the borderline or mental retardation ranges. Although not unanimous, previous research has indicated that children with VCFS often exhibit differences between verbal and nonverbal abilities, with verbal skills typically being better developed. Moreover, there is quite a great deal of ambiguity in regards to previous studies that have assessed learning disabilities and mental retardation in children with VCFS. As previously mentioned, the operational definitions of these terms have been unclear in much of the research and thus it is difficult to distinguish what was actually being assessed. Previous research has also indicated that language abilities are often affected and that the typical language profile for these children can be described by receptive language being better developed than expressive language. However, research regarding this matter is not uniform in its conclusions. Significant proportions of children with VCFS also experience difficulties with the development of appropriate social skills and sometimes exhibit more problem behaviors. Children with VCFS are often shy and
Preschoolers with VCFS withdraw from others, have difficulty sustaining friendships, and have difficulties with reading social cues and relating in certain social situations.

Due to the limited accessibility of patients with VCFS, many of the previous studies have relatively small sample sizes. It is imperative that findings are replicated when dealing with small sample sizes in order to place significant emphasis upon the results. There are many questions that are still unanswered in regards to the prognosis and development of these affected children, and it is imperative that research in this area is continued so that parents, educators, psychologists, and other medical professionals can implement services as early as possible. Research on the cognitive abilities, language, behavior and social skills of children with VCFS is likely to provide substantial practical significance by contributing greatly to the public's understanding of a very complicated syndrome. Although several studies have examined the aforementioned areas, the research on the preschool age range is scant. Information regarding these topics would be useful as it would ultimately contribute to the preexisting knowledge base of a typical profile for a preschooler with VCFS. This present study attempts to assess the cognitive functioning, language development, and social skills of preschoolers with VCFS.

The hypotheses for this study are stated in the null and are as follows:

$H_0 1$: Children with VCFS will not statistically significantly differ on FSIQ scores from the normative mean on the FSIQ score of the Wechsler Preschool and Primary Scale of Intelligence-Third Edition.

$H_0 2$: Children with VCFS will not demonstrate a statistically significant difference between receptive language skills and expressive language skills as measured by the Preschool Language Scale-Fourth Edition.
$H_3$: Children with VCFS will not statistically significantly differ from the normative mean on social skills scores on the Preschool and Kindergarten Behavior Scales.

$H_4$: Children with VCFS will not demonstrate statistically significant differences from the normative mean on problem behavior scores on the Preschool and Kindergarten Behavior Scales.
Chapter III

Method

Participants

A minimum of 26 preschool age children between 4 years, 0 months to 6 years, 11 months will participate in this study. The sample size will depend on availability of individuals with VCFS who fit the chronological age criteria. Participation in this study will be obtained through letters that will be mailed by the principal investigator to the parents of individuals who meet the criteria for this study. These individuals will be accessed through the Division of Human Genetics at Cincinnati Children’s Hospital Medical Center (CCHMC), Cincinnati, OH. All participants will maintain the diagnosis of VCFS and will already have been identified as having a chromosome 22q11.2 deletion. Confirmation of the deletion will previously have been accomplished through FISH analysis at the aforementioned site.

The sample size necessary for .80 power to detect effects at the .05 level of significance for the difference between independent means is 26 (Cohen, 1992). This means that with a large estimated effect size and an estimated sample size of 26 participants, the power will be .80, indicating that there is an 80% chance of detecting a significant difference between the performance of the participants in this study and the normative data provided for the assessment measures. There is a 20% chance of Type II error, or failing to reject the null hypothesis when it is false. A large effect size has been
Preschoolers with VCFS

demonstrated in previous research and therefore the same expectation is assumed for this study (Golding-Kushner et al., 1985; Meier, 2002).

Measures

_Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) (Wechsler, 2002)._

The WPPSI-III has been recently updated to better represent the variability of development in young children and the author has thus divided the age range of the test into two age bands, ages 2:6-3:11 and ages 4:0-7:3, with different subtest batteries (Wechsler, 2002). For the age range of participants in this study, the WPPSI-III yields four composite scores and an optional fifth composite score, each of which has a mean of 100 and a standard deviation of 15. The five scores are as follows: Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), Processing Speed Quotient (PSQ), and General Language Composite (GLC). The subtests that comprise the GLC are typically only given to individuals between the ages of 2 years, 6 months and 3 years, 11 months. However, these subtests can be given to older individuals as optional subtests. This composite score was primarily designed to provide general language ability (including expressive and receptive aspects of language development for the aforementioned ages, but may be useful as a measure of language ability for older children suspected of having language delays (Wechsler, 2002). One of the strengths of this cognitive measure is that it has been newly revised to reduce emphasis on verbal expression thereby reducing the confounding effects of expressive language development on the examination of verbal cognitive abilities (Wechsler, 2002). This is an important consideration for this study.
considering that the majority of participants are likely to have expressive language deficits.

Although the age range for this instrument overlaps with the Wechsler Intelligence Scale for Children-III (WISC-III), the WPPSI-III is predictably better for low-functioning 6-year-olds and the WISC-III is better for gifted 6-year-olds. It is believed that the WPPSI-III is the more appropriate measure for a participant in this study that falls within these overlapping age ranges. For children suspected of below average cognitive ability, the WPPSI-III should be administered due to its lower floor at this age range. Also, children with limited English proficiency, language impairments, or verbal or expressive difficulties should be given the WPPSI-III to reduce the confounding effects of language or verbal expression on composite scores. Children who have difficulty completing a lengthier assessment may benefit from use of the WPPSI-III (Wechsler, 2002).

It is believed that the WPPSI-III is the more appropriate measure for a participant in this study due to the cognitive functioning of children with VCFS, as evidenced by past studies in this area, as well as the high incidence of language difficulties for this population.

The normative data for the WPPSI-III is based on national standardized samples representative of the U.S. population of children ages 2:6-7:3. The data gathered by this census provided the basis for stratification for the following variables: age, sex, race, parent education level, and geographic region. A total of 1,700 children were divided into nine age groups, each composed of 200 children except for the oldest age group that was comprised of 100 children. Each of these age groups was comprised of equal numbers of
males and females and the proportion of racial groups was proportional to the U.S. population according to the 2000 Census data (Wechsler, 2002).

The reliability coefficients for the WPPSI-III subtests have improved substantially over the WPPSI-R. For the overall standardized sample, the reliability coefficients of the WPPSI-III subtests range from .83 to .95. These coefficients are even greater for the composite scales, ranging from .89 to .96. The WPPSI-III also possesses impressive interrater reliability. Due to rather objective and simple scoring criteria for the majority of the subtests, the WPPSI-III has very high interscorer agreement ranging from .98 to .99 (Wechsler, 2002).

Validity for the WPPSI-III has been demonstrated in various ways. Content validity was examined by means of expert reviews and comprehensive literature reviews. The WPPSI-III also appears to correlate well with the WPPSI-R as evidenced by correlation coefficients of .86, .70, and .85 for VIQ, PIQ, and FSIQ respectively. The lowest subtest correlations occurred for several performance tasks such as Object Assembly and Block Design, which underwent significant changes to enhance their age appropriateness. Validity coefficients were also obtained for other instruments including the WISC-III, BSID-II, DAS, WIAT-II, and CMS, which all demonstrated sufficient evidence of convergent validity (Wechsler, 2002).


The participants in this study will also be administered the Preschool Language Scale-Fourth Edition (PLS-4) to assess auditory comprehension (receptive language skills) and expressive language. The PLS-4 also contains three supplemental assessments
that are optional to administer: the Language Sample Checklist, the Articulation Screener, and the Caregiver Questionnaire. The PLS-4 is typically administered to identify children who have a language disorder or delay (Zimmerman, Steiner, & Pond, 2002). Although the language abilities of the participants in this study will be screened through the GLC on the WPPSI-III, it was felt that the PLS-4 should also be administered in order to provide the best assessment of language and comprehensive understanding of the child’s language abilities. None of the supplemental assessments will be given during this study due to irrelevance or age criteria that are not applicable to this sample.

The PLS-4 yields norm-referenced test scores (standard scores, percentile ranks, and age equivalents) for the Auditory Comprehension (AC) and Expressive Communication (EC) subscales, as well as for the Total Language Score. These scores are available at 3-month intervals for birth through 11 months, and at 6-month intervals for ages 1 year through 6 years, 11 months. The PLS-4 uses census figures from 2000 in the standardized data that were collected in 2001 and reflect the increasingly diversifying population. The standard scores on the PLS-4 have a mean of 100 and a standard deviation of 15. Both the standard scores and the percentile ranks can be used to determine the severity of the child’s delay. The standard scores of the AC and EC will be examined to determine whether any subscale differences that may exist are atypical when compared to the subscale differences in the general population. If the subscale differences occur for 10% or less of the standardization population, then the difference in the AC and EC score is meaningful. However, the authors of this measure recommend that the best practice is for clinicians to compare the AC and EC confidence bands rather than comparing the AC and EC scores. The authors suggest that differences in scores may be
caused by measurement error and that certain differences occur by chance. Confidence bands provide a basis for evaluating the significance of any special difference. The authors of the PLS-4 suggest that one can consider the scores to be different only when there is no overlap in the confidence bands (Zimmerman, et al., 2002).

The PLS-4 is designed to be used with children who exhibit mild developmental delays as well as with children who exhibit severe impairments. It is recommended by the authors of this instrument that if the examiner suspects that a child has a mild or moderate impairment, that the examiner begins the test at 1 year below his or her chronological age (Zimmerman, 2002).

Evidence for reliability of the PLS-4 appears to be strong, as evidenced by test-retest stability coefficients ranging between .82 and .95 for the subscale scores and .90 to .97 for the Total Language Score. Internal consistency reliability coefficients for the PLS-4 are broken down by age ranges. The AC subscale coefficients range from .66 to .94, the EC subscale coefficients range from .73 to .95, and for the total language scale, coefficients range from .81 to .97. When determining evidence of reliability for an assessment instrument, it is imperative that one examines the standard error of measurement (SEM), which indicates the variability expected in obtained scores around the “true” score. The SEM for the PLS-4 is reported in terms of standard scores and ranges from 2.72 to 6.52 for the total language composite. The evidence for inter-rater reliability is very strong for the PLS-4. The majority of the PLS-4 tasks are objectively scored, but some of the EC tasks are subject to the examiner’s interpretation. Therefore, this was evaluated during the standardization phase of the test development, resulting in a 99% agreement between scorers. Since the correlation between EC scores was .99, it can

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be stated with confidence that this subscale maintains a high level of inter-rater reliability which suggests that the scoring criteria are well-developed and allow for consistency in scoring by various examiners (Zimmerman et al., 2002).

According to Zimmerman et al. (2002), the validity of the PLS-4 has been carefully researched resulting in the following conclusions:

1) the PLS-4 offers a thorough and balanced sample of language behaviors 2) the PLS-4 measures the processes it is intended to measure, i.e., language skills 3) the PLS-4 demonstrates the inter-relatedness of constructs related to assessing language 4) PLS-4 scores are highly correlated with scores obtained from other valid measures of language ability and the test consistently differentiates children who are language disordered from children who are not 5) PLS-4 has no known negative consequences of testing (pp. 190-191).

Literature reviews, user surveys, and content, bias, and task reviews were all conducted to verify breadth and appropriateness of task and item coverage. This information was used to determine that the PLS-4 has requisite content coverage and content relevance (Zimmerman et al., 2002).

Validity evidence based on internal structure is provided by examining the correlation between the two subscales AC and EC. These two scales should have a fairly strong correlation because they measure language, but this correlation should not be too strong because they measure different aspects of language. The correlation of PLS-4 subscale standard scores across ages was .80, indicating that although these two scales have similarities they also measure unique abilities (Zimmerman et al., 2002).
Convergent evidence of validity also exists as evidenced by the relationship between the PLS-4 and the language strand of the Denver II. All participants were typically developing children who, in the study, earned a “normal” rating on the Denver II and scored within 1 standard deviation of the mean on the PLS-4. This demonstrates a high level of agreement, which the authors of the PLS-4 hypothesized. A study of the relationship between the PLS-4 and the PLS-3 was also conducted. The standard scores for the PLS-4 AC and EC produced correlations with the PLS-3 of .65 and .79 respectively (Zimmerman et al., 2002).

During test development, a study was also conducted to determine the extent to which each of the PLS-4 scores differentiated between children who had previously been diagnosed as having a language disorder and children with typically developing language. The criterion for a language disorder on the PLS-4 is a standard score of 85 or less, which is equivalent to 1 standard deviation below the mean. The mean scores for children with typically developing language were as follows: AC=99.0, EC=99.7, and Total Composite=99.4. The mean scores for children with previously diagnosed language disorders were as follows: AC=74.6, EC=74.3, and Total Composite=72.0 (Zimmerman et al., 2002).

*Preschool and Kindergarten Behavior Scale-Second Edition (PKBS-2) (Merrell, 2002).*

The Preschool and Kindergarten Behavior Scale-Second Edition (PKBS-2) is a behavior rating scale designed for use in evaluating social skills and problem behaviors of preschool and kindergarten-age children, ages 3 through 6 years (Merrell, 2002). The PKBS-2 is comprised of two scales (Social Skills and Problem Behavior) that were
normed using the same nationwide standardization population. The PKBS-2 contains a summary/response form that is completed by home-based raters and/or school-based raters (Appendix A). The manual provides separate normative information and score conversion tables for the two types of raters. This instrument was developed specifically as a screening tool for identifying preschool and kindergarten-age children who exhibit at-risk behaviors and who may benefit from early intervention.

In a review of 13 third-party instruments that assess preschool behavior and social-emotional functioning, the PKBS was evaluated upon psychometric qualities and technical adequacy. It proved to be representative of the national norms and consistently met reliability criterion. Overall, the PKBS was cited as demonstrating several of the best technical characteristics of the 13 instruments that were evaluated (Bracken, Keith, & Walker, 1998). Although this was an earlier version of the instrument, many of these characteristics apply to the PKBS-2.

The author recommends use of the PKBS-2 as one component of a multi-method, multi-source assessment design (Merrell, 2002). This is the intent behind including the PKBS-2 in the current study, as part of a multi-source assessment. According to Sattler (1992), behavior rating scales can provide data on low frequency but important behaviors that might not be seen in direct observation sessions. These scales often capture judgments and observations of those that are most familiar with the child's behavior. Additionally, behavior rating scales offer objectivity that an unstructured interview or projective-expressive technique does not offer (Merrell, 2002).

Although behavior rating scales generally provide several advantages, they are not without potential problems. The problems associated with use of behavior rating
scales can typically be classified as the following: bias of response and error variance (Merrell, 2002).

The Social Skills Scale is comprised of 34 items that describe adaptive or positive behaviors that are likely to contribute to positive personal and social outcomes. The items on this scale are rated on a 4-point continuum as follows: 0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often. Within the Social Skills Scale, there exist three empirically derived subscales: Social Cooperation, Social Interaction, and Social Independence.

The Problem Behavior Scale is comprised of 42 items that describe problem behaviors commonly seen in the early childhood/preschool population. The same 4-point scale described above is used to rate these items. Within the Problem Behavior Scale there are two empirically derived subscales. The first of these subscales is the Externalizing Problems subscale, which is composed of 27 items that address acting out and disruptive behavior. The Internalizing Problems subscale includes 15 items that describe over-controlled emotional and behavioral problems (Merrell, 2002).

Once scores are obtained from the two scales of the instrument, the results can be interpreted to aid in understanding the child’s observed patterns of social skills and problem behavior to assist in making decisions regarding educational program placement and intervention planning (Merrell, 2002). Merrell suggests using a three-level approach to interpreting PKBS-2 scores. The first level entails interpreting the standard scores and percentile ranks in relation to other scores from the PKBS-2 normative sample. All standard scores are based on a distribution with a mean of 100 and a standard deviation of 15.
The second level of interpretation involves interpreting the risk level of the child. It is important to evaluate whether any risk levels are indicted and what implications the presence of risk levels might have. The PKBS-2 provides two risk levels (High Risk and Moderate Risk) that were devised to reflect common ranges of scores that may reflect varying levels of social-behavioral problems and deficits. Merrell (2002) states:

The High Risk level includes the most problematic 5% of scores. These scores include the lowest 5% in the Social Skills area, and in the highest 5% in the Problem Behavior area. Scores in the High Risk level typically range 2 or more standard deviations in the least desirable direction from the normative mean (p.23).

A child that scores within this range of scores warrants further examination and attention, as he/she is likely to benefit from intervention services. For scores falling within the Moderate Risk level, Merrell (2002) indicates the following:

The Moderate Risk level includes the most problematic 5% to 15% range of scores. This risk level includes scores ranging from the $5^{th}$ percentile to the $15^{th}$ percentile for the Social Skills Scale, and from the $85^{th}$ percentile to the $95^{th}$ percentile for the Problem Behavior Scale. Scores that are at the Moderate Risk level are typically from 1 to 2 standard deviations in the least desirable direction from the normative mean. PKBS-2 scores that are at the Moderate Risk level are not necessarily indicative of significant social skills deficits or significant problem behaviors. However, the risk of such problems or deficits and the possibility of additional screening or assessment procedures should be considered (p.23).
The third level of analysis of results recommended by Merrell (2002) is a qualitative inspection of individual items. Merrell suggests performing an item-level inspection to identify specific behavioral concerns and commonalities among the identified items. Moreover, individual items can be used on the Social Skills Scale to determine the strengths of a child.

The standardized sample used in the development of the PKBS-2 is very similar to that of the general U.S. population in terms of gender, race and ethnicity, and special education eligibility. The only two areas in which the normative sample is not virtually identical to the general U.S. population are geographic representation and parent occupational categories. According to Merrell (2002) these two factors appear to have no meaningful effect on the generalizability of the PKBS-2 scores.

The reliability studies conducted on the PKBS-2 are consistent with or superior to the results of similar studies that have been conducted with other behavior rating scales designed for use with young children. Cronbach’s coefficient alpha method and the Spearman-Brown split-half reliability formula were used to assess internal consistency reliability. The alpha and split-half coefficients for the PKBS-2 total scores range from .90 to .97 across three samples. The alpha and split-half coefficients for the PKBS-2 Social Skills and Problem Behavior subscales are all in the .80s and .90s, at or above the minimum levels of acceptability. The standard error of measurements (SEMs) for the PKBS-2 scores are relatively small, indicating that the range of error that surrounds obtained scores is minimal. The stability of PKBS-2 scores over short periods of time is strong, but also suggests that for the preschool population, behaviors relating to social competence may be slightly less stable over time than problem behaviors. Test-retest
Preschoolers with VCFS

reliability produced stability coefficients for Social Skills of .58 (3-week retest) and .69 (3-month retest) and stability coefficients for Problem Behavior of .86 (3-week retest) and .78 (3-month retest).

In order to measure alternate form reliability, the author of the PKBS-2 used scores of the English- and Spanish-language forms of the instrument, stating that the two versions should be considered parallel forms of the same instrument. The correlations from this comparison are very strong, indicating exceptional score comparability between these two versions of the PKBS-2. The range of correlation coefficients for the subscales is .88 to .96, and coefficients for the two total scores are .93 for the Social Skills Scale and .94 for the Problem Behavior Scale (Merrell, 2002).

Lastly, interrater reliability of the PKBS-2 across raters in the same settings has been moderate to moderately strong (.36 to .61 for Social Skills & .46 to .63 for Problem Behavior), but the reliability of scores from different raters in different settings is low to moderate (.20 to .57 for Social Skills & .13 to .42 for Problem Behavior). The author of this instrument believes that this is consistent with previous research on cross-informant assessment of child behavior (Merrell, 2002).

Validity of the PKBS-2 has been demonstrated in several ways. Content validity was ensured through careful and thorough item and scale development. Published research was investigated before the initial development of a large pool of initial items. A 16-person panel of expert judges was then used to narrow the item pool. Content validity was also demonstrated through a careful analysis of how well individual items fit within the domains in which they were placed. Item and Total Score correlations were calculated to further provide evidence that the contents of the PKBS-2 sample
theoretically and statistically cohesive traits and constructs. The correlation coefficients for the Social Skills Scale range from .32 to .70, with the majority of coefficients falling in the .60 to .70 range. The coefficients for the Problem Behavior Scale range from .40 to .75 (Merrell, 2002).

Convergent and discriminant construct validity were also examined during the development of the PKBS-2. A total of seven sets of comparisons were conducted between the PKBS-2 and other child behavior rating scales, which resulted in substantial evidence for the validity of the instrument for both social skills and problem behaviors. The PKBS-2 Social Skills Scores were consistently and strongly associated with other established measures of social skills such as the School Social Behavior Scales, Social Skills Rating System, and the Walker-McConnell Scale of Social Competence and School Adjustment. Additionally, the PKBS-2 Problem Behavior scores demonstrated a consistently strong association with established measures of problem behavior, such as the Conners' Teacher Rating Scale-39, Teacher's Report Form, and Adjustment Scales for Children and Adolescents. Discriminant validity was exhibited as PKBS-2 Social Skills scores were inversely associated with measures of problem behavior and the PKBS-2 Problem Behavior scores were inversely associated with the measures of social skills and pro-social behavior. Moreover, the PKBS-2 scores had very weak relationships with scores from measures that were conceptually different (Merrell, 2002).

Procedure

Upon approval by the CCHMC IRB and the Xavier University IRB, the parent(s)/legal guardian of all eligible participants will be initially contacted via mail by the principal investigator, at which time their child’s participation in the current study
Preschoolers with VCFS will be requested. The initial contact letter will describe the investigator’s connection to the Division of Human Genetics and the Craniofacial Center at CCHMC. The letter will provide a detailed description of the current study as well as the purpose of the investigation. It will further communicate to the recipient that his/her child with VCFS falls within the age range being investigated. Follow-up phone contact will be initiated by the principal investigator to obtain participants after the letters are received. Informed consent will be obtained from the parent or legal guardian.

Each participant will be evaluated at Xavier University using the WPPSI-III in order to assess cognitive abilities. All fourteen subtests across both the verbal and performance domains will be administered. This includes two optional subtests that comprise the GLC that typically is only given to the younger age range but that are appropriate to administer for this population. The participants will also be administered the PLS-4. These assessments will be conducted by the investigator, who is a doctoral trainee in clinical psychology and who has been appropriately trained in psychological assessment. The order of test administration will be counterbalanced to avoid any extraneous effects such as fatigue. The investigator will be supervised by her dissertation advisor and clinical director of the department of psychology at Xavier University, Cincinnati, OH. Each participant’s parent(s) or legal guardian will be asked to complete the PKBS-2 while the examiner is administering the WPPSI-III and PLS-4 to the participant.
Chapter IV

Proposed Analyses

Design

This study is designed to examine cognitive functioning, language skills, and behavior and social functioning of preschoolers with VCFS in comparison to established normative data for assessments across these three areas. The examiner will be comparing obtained mean scores of the participants to established means for these three measures. The examiner designed this study using well-normed instruments that are valid and reliable, as well as newly revised. No control group is implemented in the design of this study, in part due to the limitations this could potentially pose for recruitment of participants.

Statistics

Z-test statistics will be conducted to determine if differences exist between the mean obtained standard scores of the participants in this sample and the normative data for the assessment measures used in this study. A z-test statistic will be used to test for a significant difference between the obtained mean FSIQ score of participants and the mean FSIQ for the WPPSI-III. The same procedure will also be conducted for both the participants' mean obtained Social Skills scores and Problem Behavior scores on the PKBS-2 in comparison to the normative data. Lastly, a paired samples t-test statistic will also be used to examine significant differences between mean obtained receptive and expressive scores of the participants on the PLS-4. Since all three assessment
measurements used in this study have a mean of 100 and a standard deviation of 15, direct comparisons can easily be made. The probability level of .05 or smaller will be used to indicate statistical significance.
References


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Preschoolers with VCFS

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microdeletion. *Genetics in Medicine, 3* (1), 34-39.

Appendix A

Due to copyright protection, the Preschool and Kindergarten Behavior Scales – Second Edition (Merrell, 2002) could not be included here, but is available through PRO-ED, Inc.
DATE: March 10, 2004

TO: Howard M. Saal, M.D.
Division, Human Genetics
Cincinnati Children's Hospital Medical Center
MLC #4006

FROM: Irwin Light, M.D., Chairman
Institutional Review Board
Cincinnati Children's Hospital Medical Center
MLC #5020

RE: ASSESSMENT OF INTELLIGENCE, LANGUAGE AND SOCIAL SKILLS IN PRESCHOOLERS WITH VELOCARDIOFACIAL SYNDROME (CHMC #03-12-52)

The investigator has provided item-by-item responses to the comments previously noted by the Institutional Review Board, including the revised consent form and a copy of the Dear Parent recruitment letter.

Approval is granted for the research protocol, revised consent form and recruitment letter for the study noted above.

Please, be certain to record the approval date on the revised consent form in order to identify the current version that will be used to enroll subjects on this study.
CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER INSTITUTIONAL REVIEW BOARD
NOTIFICATION OF FINAL APPROVAL

PRINCIPAL INVESTIGATOR: Saal, Howard M.D. CHMC PROTOCOL: 03-12-52

TITLE OF STUDY: ASSESSMENT OF INTELLIGENCE, LANGUAGE AND SOCIAL SKILLS IN PRESCHOOLERS WITH VELOCARDIOFACIAL SYNDROME

(✓) Full Review ( ) Expedited Review

The protocol and consent form for this study have been approved by the Children's Hospital Medical Center Institutional Review Board.

Approval Date: January 20, 2004  Termination Date: January 19, 2005

The IRB has determined that this is a minimal risk study without potential direct benefit.
(✓) Assent must be obtained from participating subjects 11 years of age and over, if clinically appropriate.
(✓) Assent need not be obtained from participants.
(✓) For this study, one parent must give permission for inclusion of the child (unless the parent is dead, incompetent, unknown, not reasonably available, or if only one has legal responsibility) if the subject is under 18 years of age.
5. ( ) Both parents must give permission for inclusion in this study.
6. ( ) Consent must be obtained from participants 18 years and older.
7. (✓) Consent must be obtained by investigators at the local sites.
8. (✓) Waiver of requirement for informed consent.

This approval is granted with the following requirements:
1. The investigator is responsible for reporting adverse events to the Children's Hospital Medical Center Institutional Review Board:
   a). Deaths and life-threatening problems must be reported to the Children's Hospital Medical Center Institutional Review Board within two working days (48 hours) and documented in writing within 10 working days.
   b). All serious or unanticipated significant adverse events must be reported in writing within 10 working days.
   c). Minor adverse events can be reported in summary form at the time of submission of the continuing review (Progress Report) or upon completion of the study, whichever comes first.
   d). The investigator may also be responsible for reporting to the sponsor, other agencies, and the Children's Hospital Medical Center Pharmacy and Therapeutics Committee.
2. The investigator is responsible for submitting a Progress Report for continuing review by the IRB
   a). This must be submitted prior to the termination date as long as the study is active or
   b). Upon termination of the study
3. There may be no change or additions to the protocol or consent form, without prior approval of the IRB.
4. Approval by the IRB does not indicate approval by other committees of the Medical Center, (e.g., CRC Scientific Advisory Committee, Radiation Safety Committee, College of Medicine Institutional Review Board).
5. It is the responsibility of the investigator to keep copies of the approved protocol, consent form and all correspondence and all changes pertaining to the study or consent form.

DHHS Assurance #FWA00002988

IRB No. 01

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April 22, 2004

Kristy Fritz, M.A.
2903 Linwood Ave., Apt. #22
Cincinnati, OH 45208

Dear Ms. Fritz:

The Xavier University IRB received your Protocol #0287-3, Assessment of Intelligence, Language, and Social Skills in Preschoolers with Velocardiofacial Syndrome, on April 5. Your protocol has been reviewed by the IRB. The committee felt the need for further consultation about the statement in the last paragraph of page 9 regarding the sharing of results with schools, teachers, or psychologists at the parents' request but not sharing results with parents. After further consultation, the IRB has decided to approve your protocol as presented in the Expedited category.

This approval expires 4/22/05. A progress report must be filed with XU's IRB by the expiration date either indicating that your research has been completed or that you request an extension of IRB approval. A form is enclosed for your convenience in future reporting. The form is also available at www.xu.edu/IRB/IRBforms.htm.

If there are any adverse events or modifications to the research, please notify the IRB immediately.

We wish you every success with your research.

Sincerely,

Robert C. Baumiller, S.J.
IRB Chair and Administrator

RCB:sm

cc: Dr. Janet Schultz, ML 6511

Enclosures: Progress Report
Approved Informed Consent
Appendix D

CINCINNATI CHILDREN’S HOSPITAL MEDICAL CENTER
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: Assessment of Cognitive Functioning, Language and Social Skills in Preschoolers with Velocardiofacial Syndrome

CCHMC IRB # 03-12-52 _______________ IRB Approval Date: 1-20-04

INVESTIGATOR INFORMATION:

Principal Investigator Name: Howard M. Saal, M.D. Telephone Number: 513 636-7837
24 hr Emergency Contact: 513 636-4200

Subject Name: ___________________________ Date of Birth: _______________

Throughout this document, references to “You” may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION:

You have been asked to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available and the right to withdraw from the study at any time. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty.
**WHY IS THIS RESEARCH BEING DONE?**

The purpose of this research study is to improve understanding of the intelligence, learning, language abilities and social skills of preschool children with velocardiofacial syndrome (deletion 22q11 syndrome).

**WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?**

You are being asked to take part in this research study because your child has been diagnosed with velocardiofacial syndrome (also called deletion 22q11 syndrome or DiGeorge syndrome).

**WHO SHOULD NOT BE IN THE RESEARCH STUDY?**

This study will include children who have been confirmed as having velocardiofacial syndrome by laboratory studies. Children who are not between the ages of 4 years, 0 months and 6 years 11 months will not be included in this study.

**HOW LONG WILL YOU BE IN THE RESEARCH STUDY?**

You will be in the research study for approximately 12 months. Your actual involvement, including the testing will take place over a single session lasting approximately 3 hours. No follow up testing will be required. This consent, unless you choose to withdraw it, shall remain in effect until the end of the study.

The researcher may decide to take you off this research study at any time.

**WHO IS CONDUCTING THE RESEARCH STUDY?**

The study is conducted by Kristy M. Fritz, M.A., a Doctoral student in the Department of Psychology at Xavier University. The testing will be done by Ms. Fritz at Xavier University. She will be supervised by Janet R. Schultz, Ph.D. and Howard M. Saal M.D.

**HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?**

About 26 people will take part in this study at Xavier University and Cincinnati Children’s Hospital Medical Center.
WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you take part in this study, your child will have the following tests performed in order to assess learning, language skills and social skills

- **Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III)** is a test of cognitive abilities that is designed to identify strengths and weaknesses related to cognition in young children. This test measures verbal and non-verbal reasoning abilities, receptive versus expressive vocabulary, and processing speed. Average testing time is 45-60 minutes. Because of the nature of this test and its interpretation, it should not be repeated for one year after it has been administered (i.e. it should not be given again if the child is tested in the schools or by a psychologist for one year).

- **Preschool Language Scale-Fourth Edition (PLS-4)** provides a picture of a child's overall total language skills, as well as receptive and expressive language abilities. It is an interactive instrument with activities that target attention, vocal/gestural behaviors, interaction, early literacy, and phonological awareness. Average testing time is 20-45 minutes.

- The parent will be asked to complete the **Preschool and Kindergarten Behavior Scale-Second Edition (PKBS-2)** to evaluate social skills and problem behaviors. This is a behavior rating scale designed for use in evaluating social skills and problem behaviors of preschool and kindergarten-age children, ages 3 through 6 years. The form usually takes parents between 8 and 12 minutes to complete.

- There will be no blood testing or other testing performed as part of this study.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

The only foreseeable risk in this study is that of boredom or inattention of children who are participating in this study. In the rare event that the child becomes upset, it may be necessary to reschedule the testing.

There may be unknown or unforeseen risks associated with study participation.

ARE THERE DIRECT BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

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If you agree to take part in this research study, there is not a direct medical benefit for you. The study investigators feel that it is not appropriate to share the results of each child's individual testing with the parents/guardians, since the context of this testing is to improve the understanding of learning, language and social skills for preschool children with velocardiofacial syndrome, but not to identify specific related issues for each child. The investigator will share the results of the testing with schools, teachers, or psychologists if requested by parents.

**WHAT OTHER CHOICES FOR CARE ARE THERE?**

You and your child have the option not to participate in this study. By not participating in this study, your child's health care and management will not be in any way affected.

**HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?**

Every effort will be made to maintain the confidentiality of your medical and research information ("Protected Health Information" or "PHI"), consisting of the identification of your child as having velocardiofacial syndrome and any medical complications which have occurred, including congenital heart defect, cleft palate, speech disorders, and any other medical problems. After this information and the information obtained from testing are recorded, these will be analyzed anonymously without any information which could link this information to your child or your family.

Protected Health Information is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered in a computer), that identifies you as an individual or offers a reasonable basis to believe that the information could be used to identify you.

By signing this consent form you are giving permission for representatives of the Cincinnati Children's Hospital Medical Center ("CCHMC"), the Investigator and CCHMC employees involved with the research study including the Institutional Review Board and the Office for Research Compliance, and any sponsoring company or their appointed agent to be allowed to inspect sections of your medical and research records related to this study.

The information from the research study may be published; however, you will not be identified in such publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant without your authorization.

Cincinnati Children's Hospital Medical Center and/or the Investigator will take the following precautionary measures to protect your privacy and confidentiality of
your research and/or medical records. All records will be coded with a non-identifiable assigned coded number. Any records containing protected health information will be stored in a locked cabinet available only to the study investigators. In any publications or reports resulting from the study, there will be no individual identifiers used.

**USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION**

The Protected Health Information described in the section above will be used/disclosed for the purpose of research by CCHMC to the other persons or entities identified above.

"Use" of an individual's health information is defined as the sharing, examination or analysis (break down) of the information that is collected and maintained for the length of the research study.

"Disclosure" of an individual's health information is defined as the release, transfer, providing access to, or to reveal in any other manner, the information outside the persons or entity holding the information as described in the section "How Will Information About You Be Kept Private And Confidential" in this consent form.

Once your Protected Health Information is disclosed, the information may be subject to re-disclosure and may no longer be protected by the federal privacy regulations.

**AVAILIBILITY OF INFORMATION?**

No information regarding your child obtained from this study will be made available to the study subjects, families, personal physicians, or teachers, unless a request is made by the parents to share testing results with schools, teachers, or psychologists.

**WHAT ARE YOUR COSTS TO BE IN THIS STUDY?**

There will be no costs to you for participating in this study.

**WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?**

There is no payment or reimbursement for participation in this study.

**WHAT ARE YOUR RIGHTS AS A PARTICIPANT?**

Your participation in this study is completely voluntary. You may choose either to take part or not to take part in this research study. Your decision whether or
not to participate will not result in any penalty or loss of benefits to you and the standard medical care for your condition will remain available to you.

If you decide to take part in the research study, you are free to withdraw your consent and discontinue participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

You may revoke (choose to withdraw) this Authorization as provided under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) at any time after you have signed it by providing Howard Saal, M.D. with a written statement that you wish to withdraw this Authorization. Your withdrawal of this Authorization will be effective immediately and your Protected Health Information can no longer be used/disclosed for research purposes by CCHMC and the other persons or entities that are identified in the "Use or Disclosure of Your Protected Health Information" section of this consent, except to the extent that CCHMC and/or the other persons or entities identified above have already taken action in reliance upon your consent. In addition, your Protected Health Information may continue to be used/disclosed to preserve the integrity of this research study.

The investigators will tell you about significant new findings developed during the course of the research and new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

For further information about your rights, please see CCHMC Notice of Privacy Practices.

**ABILITY TO CONDITION TREATMENT ON PARTICIPATION IN THIS STUDY**

You have a right to refuse to sign this consent to use/disclose your Protected Health Information for research purposes.

If you refuse to sign this consent, your rights concerning treatment, payment for services, enrollment in a health plan or eligibility for benefits will not be affected.

**WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?**
For questions about this research study or to report a research-related injury, you can contact the researcher, Howard M. Saal, M.D. at 513 636-4760 and the Division of Human Genetics at Cincinnati Children's Hospital. Researchers are available to answer any questions you may have about the research at any time."

If you have general questions about your rights as a research participant in this research study, you can call the Cincinnati Children's Hospital Medical Center Institutional Review Board at 513-636-8039.

**WITNESSING AND SIGNATURES**

I have read the information given above. The investigator or his/her designee have personally discussed with me the research study and have answered my questions. I am aware that, like in any research, the investigators cannot always predict what may happen or possibly go wrong. I have been given sufficient time to consider if I (or my child) should participate in this study. I hereby consent for myself (or my child) to take part in this study as a research study subject.

Check box if verbal assent is obtained from the child who is the research subject □

Subject's signature indicating consent or assent

Parent/Legal Guardian (Signature)

Parent/Legal Guardian (Signature)

I have witnessed the voluntary signing of this document by the research subject, or the legally authorized representative of the research subject.

Witness as to the voluntary nature of the Signatures noted above (Signature)

Investigator or specific individual who has been designated to obtain consent (Signature)

Investigator (Signature)

This research study and consent form have been reviewed and approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (telephone number 513-636-8039).
Chapter V: Dissertation

Abstract

This study investigated cognitive functioning, language abilities, behavior and social skills of preschool age children with velocardiofacial syndrome (VCFS) as compared to children with non-syndromal cleft lip and/or palate. Participants were administered the Wechsler Preschool and Primary Scale of Intelligence-Third Edition, the Preschool Language Scale-Fourth Edition, and the Preschool and Kindergarten Behavior Scales-Second Edition. Results indicated that children with VCFS demonstrated significantly lower Performance IQ and processing speed than a comparison group of children with non-syndromal cleft lip and/or palate. There was also a significant within group difference between Verbal IQ scores and Performance IQ scores for preschoolers with VCFS, with Verbal IQ being significantly higher. No significant discrepancy was found between the expressive and receptive language abilities of children with VCFS, though their expressive, receptive, and total language abilities were significantly lower than the comparison group. Parent ratings of social skills and problem behavior were not statistically different between the VCFS group and the comparison group.
Assessment of Cognitive Functioning, Language, Behavior and Social Skills in Preschoolers with Velocardiofacial Syndrome

Although velocardiofacial syndrome (VCFS) is one of the most common genetic conditions (1 in 4,000 live births), there exists comparatively little research and limited knowledge within the general public regarding this syndrome. Due to the fact that the spectrum of symptoms is quite broad, VCFS is still under-recognized and under-diagnosed (Thomas & Graham, 1997). One can only imagine the reaction that parents experience when receiving this diagnosis, particularly given the limited knowledge of this condition, even among medical professionals and educators.

VCFS (also referred to as 22q11.2 deletion syndrome) is a congenital malformation disorder that was first described in 1968 by William Strong, M.D. and later delineated by Robert Shprintzen, Ph.D. in 1978. VCFS is a syndrome of multiple anomalies that occur to varying degrees and frequency, with some features appearing to change with age. The phenotypic presentation of these patients consists primarily of distinct facial features, hypernasal speech, cleft palate, cardiac malformations, short stature, learning difficulties or mental retardation, delayed language development, behavioral problems and social skills deficits (Arnold et al., 2001).

Perhaps the most recognized, but under-investigated, symptoms of VCFS are mental retardation (MR) and learning disabilities. The research in the areas of cognitive functioning and learning disabilities is sometimes difficult to interpret, particularly
because medical professionals, psychologists, and educators often use the terms differently. Nonetheless, the areas of cognitive functioning and learning are important to examine due to the high rates of reported problems for individuals with VCFS. Swillen et al. (1997) found that although wide variability in intelligence in VCFS patients exists, learning difficulties were exhibited in 82% or greater of their patient sample with VCFS. Similarly, Goldberg et al. (1993) reported that learning disabilities and/or some degree of cognitive disabilities occur in approximately 99% of the patient population.

Studies specifically investigating cognitive functioning suggest that most children with VCFS fall within the Borderline to Mild Mental Retardation ranges of intellectual functioning. Shprintzen (1990) reported that 40% of VCFS patients had mild intellectual disability (IQ<70) with particular deficiency in the areas of mathematics and reading comprehension. Swillen et al. (1997) conducted a study of intelligence and found that 55% of the children in their sample had either average or borderline IQ scores, and 45% scored in the mentally retarded range with IQs less than 70. Of the 17 children in this study that scored below 70, 14 fell in the range of mild MR, two fell in the moderate MR range, and one was within the severe range. Further investigation indicated that the majority of the very low scores belonged to children with familial 22q11 deletion. A similar, but more recent, study of 33 patients with confirmed 22q11.2 deletion found that Full-Scale IQ scores ranged from the average to the moderately retarded range, with a mean score ($M = 71.2, SD = 12.8$) in the Borderline range (Moss et al., 1999).

Within the literature on cognitive functioning of children with the 22q11.2 deletion, few studies have exclusively examined cognitive abilities of preschool and kindergarten aged children. Golding-Kushner, Weller, & Shprintzen (1985) reported that
children under the age of six tested within the average range of intellectual ability. However, a follow-up study on several of the participants showed that children over the age of six did not progress beyond a concrete level of cognitive development and therefore experienced significant decline in their IQ scores upon reassessment. These results must be interpreted cautiously, as they are likely reflective of variations in psychometric properties and demands of the assessment measures rather than true decline in cognitive functioning. Results obtained by Gerdes et al. (1999) and Gerdes, Solot, Wang, McDonald-McGinn, and Zackai (2001) are somewhat contradictory to the previously mentioned study regarding young children with VCFS. Their original study and subsequent follow-up investigation were the first prospective multidisciplinary evaluations to focus solely on toddlers and preschool age children diagnosed with the 22q11.2 deletion. These investigators determined that the mean scores for this age group fell in the borderline range of intellectual functioning. Moreover, 44% of the children had a statistically significant difference between VIQ and PIQ (i.e., greater than nine points). These findings are similar to the aforementioned cognitive findings of older children with VCFS. Gerdes et al. (2001) further reported that preschool children with a 22q11.2 deletion are most commonly found to be developmentally and language delayed, which places them at higher risk for subsequently being diagnosed with mild or moderate mental retardation. It is important to note that none of the participants in this multidisciplinary study of preschoolers were found to have severe or profound retardation, and that several were functioning within the average range; however, even those with average cognitive scores obtained developmental scores in the low average range.
Wang et al. (1998) examined cognitive profiles and specifically reported that children with 22q11.2 deletions are likely to exhibit a cognitive profile similar to that seen in nonverbal learning disabilities (NLD). Within such a profile, the Verbal Intelligence Quotient (VIQ) is greater than the Performance Intelligence Quotient (PIQ) and reading and spelling achievement are typically greater than math achievement (Rourke, 1989). Swillen et al. (1997) determined for a group of 37 children and adolescents diagnosed with VCFS that a statistically significant difference existed between mean Verbal and Performance IQs for the group. This difference was also found by Moss et al. (1999) and Woodin et al. (2001), with VIQ scores being significantly higher than PIQ. There is some controversy within the literature about this VIQ and PIQ difference and the consistency of this occurrence in the cognitive profiles of children with VCFS. More typically, patients exhibit a difference characterized by VIQ > PIQ, though individuals with VCFS have also demonstrated PIQ > VIQ (Henry et al., 2002). It should be noted that this latter finding is less often substantiated in the literature. Perhaps the most important issue demonstrated here is that the cognitive profiles of these patients may include a significant difference between these two domains, which will likely impact overall learning style and may be indicative of a specific learning disability.

Bearden et al. (2001) concluded that patients with 22q11.2 deletion demonstrate a specific neurocognitive phenotype. These authors described patients as having select deficits in visual-spatial memory, which was consistent with their deficits in arithmetic and general visual-spatial cognition. Bearden et al. proposed that this particular region of chromosome 22q11 may actually harbor a gene or multiple genes responsible for the etiology of nonverbal learning deficits.
In addition to the frequent cognitive deficits, Scherer, D’Antonio, & Kalbfleisch (1999) identified speech-language impairment as one of the most common clinical features in VCFS. They reported that most children emerge from a critical speech and language learning period with severe limitations in their communicative abilities. Although language skills are often impaired across both expressive and receptive domains, the impairment is typically more pronounced in the expressive domain. Gerdes et al. (1999) reported language abilities that ranged from average to severely delayed, with 31% showing more severe delays in expressive language. A follow-up study by Gerdes et al. (2001) found 80% of 112 preschoolers with VCFS to be below average in language development. Additionally, Marks (2001) found that children with VCFS who have developmental and intellectual delays are at risk for having limited receptive language skills. This is evidenced in their limited ability to comprehend multiple words and complex verbal directions. As mentioned above, the overall language profile for children with VCFS can include deficits across both domains, though it is generally characterized by better developed receptive language than overall speech production and expressive language abilities (Gothelf & Lombroso, 2001; Scherer et al., 1999).

In addition to the medical, cognitive, and language sequela, Golding-Kushner et al. (1985) suggested that VCFS is likely associated with extremes of behavior, as evidenced by individuals with disinhibited/impulsive behavior or extreme shyness and seriousness. These extremes in behavior often warrant psychiatric diagnoses (such as Attention-Deficit/Hyperactivity Disorder, Oppositional Defiant Disorder, anxiety
Preschoolers with VCFS disorders, depressive disorders), particularly as children with VCFS mature and behavioral differences become more evident when compared to same-age peers.

Frequently accompanying this behavioral profile for children with the 22q11.2 deletion is a general presence of underdeveloped social skills. Social skills deficits are frequently reported by parents to be a result of the internalizing problems (i.e., anxiety, depression, withdrawal, somatic complaints) that these children often exhibit (Wang et al., 1998; Woodin et al., 2001). Several of the physical characteristics of VCFS may also contribute to the difficulties that these individuals face in social interactions. A combination of phenotypic characteristics such as limited facial expression, monotone voice, and blunted or inappropriate affect are thought to exacerbate other difficulties related to interaction with others (Golding-Kushner et al., 1985; Usiskin et al., 1999). As much as internalizing behaviors are detrimental to social skills development so, too, are externalizing behaviors. It is well documented within the ADHD literature that children with increased impulsivity and hyperactivity have more difficulty maintaining friendships and demonstrating appropriate social skills (Nixon, 2001). Since many children with VCFS exhibit behavioral characteristics similar to children with ADHD, they are at increased risk for problems with social relations.

Swillen et al. (1997) report that the “Social Problems” and the “Attentional Problems” clusters on the Child Behavior Checklist (CBCL) for patients with VCFS ages 4-18 years were significantly higher than any of the other clusters of problem behavior for this instrument, except the cluster “Withdrawn”. These authors believe that the social withdrawal may be explained, in part, by the difficulties that these children have communicating with others. Neuropsychological deficits are also felt to contribute to
poorer social interaction skills (i.e. problems perceiving new situations). Thus, it is not uncommon for some of these children to receive a diagnosis of pervasive developmental disorder or an autism spectrum disorder (Gerdes et al., 2001; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001).

Gerdes et al. (2001) described a pattern of observed behavior that was systematically documented in a study of preschoolers with 22q11.2 deletion. They reported a pattern of behavior seen in several of the children that maintained the following characteristics: Self-directed behavior, noncompliance, high activity, and poor social skills. These children preferred independent play and, though they would interact socially, they did not seem motivated by praise or other verbal reinforcement to the same extent as other children. Moreover, the parents of these children reported more often that their child exhibited a reluctance to follow adult directions. The unique aspect of this observation is that parents did not necessarily report defiant behavior, but rather an absence of compliance. Impulsivity and increased activity levels were noted in some but not all children within this study. There was also a general trend of delays in social skills development. The authors also felt that the limited variety of facial expressions employed by these children (sometimes due to hypotonia), language delays, and self-directed play style did not promote peer interactions.

Methods

Participants

Original proposed study.

The original aim for this project was to obtain the participation of 26 participants with VCFS for comparison to the national normative data for cognitive, language, and
behavioral rating measures. This sample size was necessary to achieve appropriate power and confidence in the obtained results. All patients were recruited through the Division of Genetics through Cincinnati Children’s Hospital Medical Center (CCHMC) in Cincinnati, OH. In order to qualify for participation in this study, participants were required to be within the age range of 4-years-0-months to 6-years-11-months and have a previously confirmed diagnosis of 22q11.2 chromosome deletion that had been established through fluorescence in situ hybridization (FISH) testing.

Recruitment letters were sent to a total of 32 patients who were identified through the patient database of the Department of Human Genetics at CCHMC as meeting study criteria. Several of the eligible patients were also reminded of this study and encouraged to participate during follow-up clinic appointments within the Division of Human Genetics, which appeared to be a more effective means of recruitment.

Various challenges with recruitment developed throughout the course of this study, preventing the desired sample size from being achieved. Preschool age children with VCFS often endure significant medical procedures, such as pharyngeal flap repair, during this developmental time. This impeded participation for some individuals who were interested but declined due to medical priorities. Additionally, this project did not have grant support, which made recruitment more challenging since no incentive was offered to families for participation.

Two of the 32 letters were returned as undeliverable. Follow-up phone contact revealed that five other families could not be reached due to phone numbers that had been changed or disconnected. Two additional children were unable to participate due to various family scheduling conflicts (i.e., move, work schedule) and their parents were
unable to identify future times that would be more convenient. The parents of three
patients declined participation upon follow-up phone contact. Two other patients were
scheduled for participation but had to cancel due to unexpected illness of extended family
members. Rescheduling attempts with these families were unsuccessful. Other attempts
were made to obtain participants, including contact with support groups in Ohio and
Michigan, and contact with other genetic divisions at multiple sites. These efforts did not
yield feasible methods for further recruitment.

Of the projected 26 participants, 10 children with confirmed 22q11.2 deletion
were ultimately recruited for participation in this study. The age range of the 10
participants with VCFS was 4-years-2-months to 5-years-11-months. The mean age of
participants was 4-years-10-months. The sample consisted of two females and eight
males, and included two monozygotic male twins. Eight of the participants were
Caucasian and two were bi-racial (African American/Caucasian and Asian
American/Caucasian). Seven of the participants were enrolled in a preschool program and
two attended early intervention programming. All participants were receiving speech and
language therapy services.

Revision to original proposed study.

Due to the limited success with initial recruitment efforts, it was decided that the
generalizability of the data was compromised. Therefore, it was determined that in order
to make a more scientific contribution to the literature, a comparison condition should be
added to the design of the originally approved study. A comparison group consisting of
patients with non-syndromal cleft lip and/or palate (CLP) was incorporated into the
design of this study. Recruitment methods for this group were similar to those outlined
above. Original hypotheses were maintained, as it was believed that the children with VCFS have a distinct cognitive, language, and social-behavioral profile that differentiates them from other children, including those with craniofacial anomalies not associated with this genetic condition. The change in original design of the study required the investigators to re-submit this study to the institutional review boards at both CCHMC and Xavier University for approval. Both institutions granted approval of the revisions to this study (see Appendices A and B for approval letters).

The age range of the ten comparison participants with non-syndromal CLP was 4-years-3-months to 6-years-4-months. The mean age of participants in this comparison group was 5-years-2-months. The comparison sample consisted of three females and seven males. Nine of the participants in this group were Caucasian and one was Asian. Seven of the participants in this comparison group were enrolled in preschool or other school programming and three participants in this group were receiving speech and language therapy services.

*Measures*

*Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III)*

*(Wechsler, 2002)*.

The Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) was used as a means of assessing cognitive abilities. For the age range of participants in this study, the WPPSI-III yields four composite scores and an optional fifth composite score, each of which has a mean of 100 and a standard deviation of 15. The five scores are: Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), Processing Speed Quotient (PSQ), and General Language Composite (GLC).
The subtests that comprise the GLC are typically only given to individuals between the ages of 2 years, 6 months and 3 years, 11 months. However, these subtests can be given to older individuals as optional subtests. This composite score was primarily designed to provide general language ability (including expressive and receptive aspects of language development for the aforementioned ages, but may be useful as a measure of language ability for older children suspected of having language delays (Wechsler, 2002). The subtests comprising this composite were administered to 7 of the 10 VCFS participants in this study. It was not administered to three children due to test fatigue and their difficulties with inattention and non-compliance. It was the examiner’s judgment that continuing with the assessments would have compromised the validity of the results. All children with CLP were administered this composite.

One of the strengths of the WPPSI-III is that it has been newly revised to reduce emphasis on verbal expression, thereby reducing the confounding effects of expressive language development on the examination of verbal cognitive abilities (Wechsler, 2002). This was an important consideration for this study in light of the prediction that participants with VCFS would have expressive language deficits.

The reliability coefficients of the WPPSI-III subtests range from .83 to .95 for the overall standardized sample. These coefficients are even greater for the composite scales, ranging from .89 to .96. The WPPSI-III also possesses impressive interrater reliability. Due to rather objective and simple scoring criteria for the majority of the subtests, the WPPSI-III has very high interscorer agreement ranging from .98 to .99 (Wechsler, 2002). Validity for the WPPSI-III has been demonstrated in various ways. Content
validity was examined by means of expert reviews and comprehensive literature reviews. The WPPSI-III also appears to correlate well with the WPPSI-R as evidenced by correlation coefficients of .86, .70, and .85 for VIQ, PIQ, and FSIQ respectively. The lowest subtest correlations occurred for several performance tasks such as Object Assembly and Block Design, which underwent significant changes to enhance their age appropriateness. Validity coefficients were also obtained for other instruments including the WISC-III, BSID-II, DAS, WIAT-II, and CMS, which all demonstrated sufficient evidence of convergent validity (Wechsler, 2002).

*Preschool Language Scale-Fourth Edition (PLS-4) (Zimmerman, Steiner, & Pond, 2002).*

Participants were administered the Preschool Language Scale-Fourth Edition (PLS-4) to assess receptive and expressive language. The PLS-4 is typically administered to identify children who have a language disorder or delay. It yields norm-referenced test scores (standard scores, percentile ranks, and age equivalents) for two subscales - Auditory Comprehension (receptive language) and Expressive Communication (expressive language). Additionally, it yields a Total Language Score that reflects the child's overall language abilities. All three standard scores on the PLS-4 have a mean of 100 and a standard deviation of 15.

Evidence for reliability of the PLS-4 appears to be strong, as evidenced by test-retest stability coefficients ranging between .82 and .95 for the subscale scores and .90 to .97 for the Total Language Score. Internal consistency reliability coefficients for the PLS-4 are broken down by age ranges. The AC subscale coefficients range from .66 to .94, the
EC subscale coefficients range from .73 to .95, and for the total language scale, coefficients range from .81 to .97.

Evidence of convergent validity exists, as evidenced by the relationship between the PLS-4 and the language strand of the Denver II. A study of the relationship between the PLS-4 and the PLS-3 was also conducted. The standard scores for the PLS-4 AC and EC produced correlations with the PLS-3 of .65 and .79 respectively (Zimmerman et al., 2002).

Nine of the 10 participants with VCFS were administered this measure. One of the participants was unable to complete the assessment due to non-compliance. All 10 children with CLP completed the language assessment.


The Preschool and Kindergarten Behavior Scale-Second Edition (PKBS-2) is a behavior rating scale designed for the evaluation of social skills and problem behaviors of preschool and kindergarten-age children, ages 3 through 6 years. All standard scores are based on a distribution with a mean of 100 and a standard deviation of 15.

The PKBS-2 is comprised of two scales: Social Skills and Problem Behavior. This instrument was developed specifically as a screening tool for identifying preschool and kindergarten-age children who exhibit at-risk behaviors and who may benefit from early intervention. The PKBS-2 contains a summary/response form that is completed by home-based raters and/or school-based raters. For purposes of this study, the PKBS-2 was completed at the evaluation by one parent.
The author of the PKBS-2 recommends its use as one component of a multi-method, multi-source assessment design (Merrell, 2002). This was the intent in including the PKBS-2 in the current study, as part of this multi-method, multi-source assessment. Behavior rating scales can provide data on low frequency, but important, behaviors that might not be seen in direct observation sessions (Sattler, 1992). These scales often capture judgments and observations of those who are most familiar with the child's behavior.

The Social Skills Scale is comprised of 34 items that describe adaptive or positive behaviors that are likely to contribute to positive personal and social outcomes. The items on this scale are rated on a 4-point continuum as follows: 0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often. Within the Social Skills Scale, there exist three empirically derived subscales: Social Cooperation, Social Interaction, and Social Independence. Overall, higher Social Skills scores indicate greater levels of social adjustment.

The Problem Behavior Scale is comprised of 42 items that describe problem behaviors commonly seen in the early childhood/preschool population. The same 4-point scale described above is used to rate these items. Within the Problem Behavior Scale there are two empirically derived subscales. The first of these subscales is the Externalizing Problems subscale, which is composed of 27 items that address acting-out and disruptive behavior. The Internalizing Problems subscale includes 15 items that describe over-controlled emotional and behavioral problems (Merrell, 2002). Higher overall Problem Behavior scores indicate greater levels of problem behavior.

The reliability studies conducted on the PKBS-2 are consistent with or superior to the results of similar studies that have been conducted with other behavior rating scales.
designated for use with young children. Cronbach's coefficient alpha method and the Spearman-Brown split-half reliability formula were used to assess internal consistency reliability. The alpha and split-half coefficients for the PKBS-2 total scores range from .90 to .97 across three samples. The alpha and split-half coefficients for the PKBS-2 Social Skills and Problem Behavior subscales are all in the .80s and .90s, at or above the minimum levels of acceptability. The standard error of measurements (SEMs) for the PKBS-2 scores are relatively small, indicating that the range of error that surrounds obtained scores is minimal.

Validity of the PKBS-2 has been demonstrated in several ways. The correlation coefficients for the Social Skills Scale range from .32 to .70, with the majority of coefficients falling in the .60 to .70 range. The coefficients for the Problem Behavior Scale range from .40 to .75 (Merrell, 2002). Additionally, the PKBS-2 Problem Behavior scores demonstrated a consistently strong association with established measures of problem behavior, such as the Conners' Teacher Rating Scale-39, Teacher's Report Form, and Adjustment Scales for Children and Adolescents. Discriminant validity was exhibited as PKBS-2 Social Skills scores were inversely associated with measures of problem behavior and the PKBS-2 Problem Behavior scores were inversely associated with the measures of social skills and pro-social behavior. Moreover, the PKBS-2 scores had very weak relationships with scores from measures that were conceptually different (Merrell, 2002).

Procedure

Identified patients with VCFS who met study criteria were contacted through an initial letter sent by the Division of Human Genetics at CCHMC. The letter provided the
rationale of the project and criteria for participation. Follow-up phone contact was made to the parent(s) of eligible participants after the initial recruitment letters had been mailed. Once assessment times and dates were arranged for willing participants, a confirmation letter was mailed to the families that included the appointment time, date, and directions to the established location. The psychological assessments were conducted by a psychology doctoral trainee during the summer of 2004 through the winter of 2005. There was no monetary compensation for participation, though small token prizes and edible reinforcers were granted to the participants to encourage cooperation and reinforce positive behavior during the assessment period. The order of administration of the WPPSI-III and PLS-IV was counterbalanced to minimize effects of fatigue.

Participants for the comparison condition were recruited through the Craniofacial Center at CCHMC. Eligible patients were identified through the patient database. Attempts were made to control for age, gender, and ethnicity, though it was virtually impossible to control entirely for all confounding variables across groups. This was complicated by the nature of the study, as participants were required to meet specific medical criteria (i.e., non-syndromal CLP). As described above, letters were sent to 29 eligible patients and follow-up phone contact was initiated to address questions regarding the study and to assess willingness to participate. In light of recruitment difficulty with the participants with VCFS, revision to the original study included the addition of a $25 gift card incentive for members of the comparison group. It was believed that this was a necessary addition, assuming that families in the comparison group would potentially be less motivated to participate given that the research would not have direct relevance to
them as it would for those in the VCFS sample. The order of administration of the
WPPSI-III and PLS-IV was counterbalanced to minimize the effects of fatigue on scores.

Statistical Analyses

Independent samples $t$ test statistics were conducted using SPSS (version 10.0) to
determine if the obtained means for the participants were significantly different from
those of the comparison group for each measure. Levene's Test for Equality of Variances
was computed for each independent samples $t$ test to ensure that the distributions of
scores from the means (variances) for the two groups were not significantly different. $T$
tests for the General Language Composite on the WPPSI-III and all language scores on
the PLS-IV were conducted based on unequal variances due to inequality of sample sizes
(Green, Salkind, & Akey, 2000). The paired sample $t$ test statistic was used to assess for
significant differences between VIQ-PIQ scores and receptive-expressive language
within the VCFS and comparison groups. An alpha level of .01 was used for all statistical
tests. This more conservative alpha level was used to help minimize the chance of family-
wise error, or error that can occur when computing multiple $t$ tests.

Results

The mean age of participants for the VCFS and comparison groups did not
statistically differ, $t (18) = -1.043, p = .311$ (two-tailed). Table 1 depicts the demographic
variables for both groups.

In the first hypothesis for this study, it was proposed that there would not be a
statistically significant difference in Full-Scale IQ (FSIQ) scores between preschool age
children with VCFS and children in the comparison group. Results of the statistical
analysis for the cognitive functioning of participants indicated that there was not an
overall significant difference between this sample and that of the comparison sample for the FSIQ at the .01 level of significance, $t(18) = -2.637, p = .017$ (two-tailed). Table 2 depicts this and all other analyses for this study. Notably, the sample mean for the VCFS group was $83.5 \pm 11.76$, which is in the low-average range of cognitive functioning, whereas the mean of the comparison sample of children with non-syndromal CLP was in the average range ($M = 103, SD = 20.21$). This difference is clinically meaningful, even if it is not statistically significant. Moreover, the effect size for this finding is large, $d = -1.179$. Figure 1 represents the distribution of FSIQ scores for the VCFS and comparison samples. Thirty percent of the VCFS sample obtained a FSIQ score in the average range of cognitive functioning, 30% fell within the low-average range, 30% obtained a score in the borderline range, and 10% were in the extremely low range of overall cognitive functioning. In comparison, 10% of the CLP sample obtained a FSIQ score in the very superior range, 10% obtained a score in the superior range, 30% scored in the high average range, 30% fell within the average range, 10% scored in the borderline range, and 10% scored in the extremely low range of overall cognitive functioning.

The overall mean Verbal IQ (VIQ) score for participants with VCFS was within the average range of functioning ($M = 92.5, SD = 14.33$) and did not differ statistically from the comparison group mean ($M = 108.4, SD = 20.20$), $t(18) = -2.030, p = .057$ (two-tailed), $d = -0.908$. Figure 2 represents the distribution of VIQ scores for the samples.

The overall mean Performance IQ (PIQ) for the VCFS sample ($M = 79.9, SD = 7.39$) was significantly lower compared to the average range for the comparison sample ($M = 98.20, SD = 16.99$), $t(18) = -3.124, p = .006$ (two-tailed), and fell within the upper end of the borderline range of functioning. The effect size for this finding is large, $d =$
-1.397. Figure 3 represents the PIQ scores for the VCFS and comparison groups.

There was a significant difference found between VIQ and PIQ scores of children with VCFS, $t(9) = 4.03, p = .003$ (two-tailed), $d = 1.28$, with the mean VIQ score greater than the mean PIQ score by a difference of 12.6 points. Figure 4 demonstrates this difference in scores. This degree of difference is statistically meaningful, as it only occurs in approximately 19.1% of the population (Wechsler, 2002). In comparison to the findings of Gerdes et al., (2001), which demonstrated that 44% of the preschool sample exhibited a VIQ-PIQ difference of greater than nine points, the present study found 80% of preschool age children to exhibit this degree of difference. There was a difference of 10.20 points between the mean VIQ and PIQ scores of children with CLP, though this was not statistically significant, $t(9) = 2.436, p = .038$ (two-tailed).

The preschoolers with VCFS also obtained an overall lower Processing Speed Quotient (PSQ) score ($M = 80.7, SD = 12.91$), $t(18) = -3.014, p = .007$ (two-tailed), $d = -1.348$, than preschoolers with CLP ($M = 101.5, SD = 17.60$). This sample of children with VCFS exhibited difficulty with visual-motor coordination and the ability to process visual information quickly and accurately. Figure 5 details the difference in scores between the VCFS and comparison groups.

Hypothesis two predicted that preschool age children with VCFS would not demonstrate a statistically significant difference between receptive and expressive language skills as measured by the Preschool Language Scale-Fourth Edition. It is important to note that only 9 of the 10 participants with VCFS were able to be evaluated for language abilities due to test fatigue and non-compliance. There was no observed discrepancy in scores between expressive and receptive language domains for the sample.
of children with VCFS, \( t(8) = 1.868, p = .099 \) (two-tailed). Figure 6 represents this comparison. Previous research findings have suggested that children with VCFS generally demonstrate more pronounced deficits in the expressive domain (Gerdes et al., 1999, 2001; Gothelf & Lombroso, 2001; Scherer, D’Antonio, & Kalbfleisch, 1999). The results of this study did not support a significant discrepancy between expressive and receptive domains within the sample of children with VCFS. There was also no significant discrepancy between these two domains for children in the CLP comparison group, \( t(9) = .111, p = .457 \) (two-tailed).

However, the receptive, expressive, and total language abilities of preschoolers with VCFS, as measured by the Preschool Language Scale-Fourth Edition (PLS-IV), were all significantly less well developed than those of children with non-syndromal CLP. The mean score for children with VCFS on the receptive language composite of the PLS-IV, which was in the low average range (\( M = 86.22, SD = 14.09 \)), was significantly lower than the comparison mean (\( M = 108.40, SD = 18.63 \)), which was in the average range, \( t(16.55) = -2.944, p = .009 \) (two-tailed). The effect size for this finding was large, \( d = -1.332 \). Figure 7 represents the distribution of Auditory Comprehension (receptive language) scores for both samples.

Scores on the expressive language composite of the PLS-IV for preschoolers with VCFS (\( M = 82.22, SD = 18.79 \)) were also significantly lower than that of the comparison group (\( M = 105.5, SD = 15.15 \)), \( t(15.41) = -2.952, p = .010 \) (two-tailed), and met clinical criteria for a language disorder. The effect size for this finding was large, \( d = -1.373 \). Figure 8 represents the distribution of Expressive Communication scores.
The scores of the children with VCFS on the Total Language Composite \( (M = 82.44, SD = 18.10) \) was significantly lower than that of the comparison group \( (M = 108.10, SD = 17.77) \), \( t (16.72) = -3.111, p = .006 \) (two-tailed), and met clinical criteria for a language disorder. The effect size for this finding was large, \( d = -1.431 \). Figure 9 represents the distribution of Total Language Composite scores.

Preschoolers with VCFS did not score significantly lower \( (M = 91.86, SD = 8.63) \) than the comparison group \( (M = 103.2, SD = 11.75) \) on the General Language Composite (GLC) of the WPPSI-III, which also measured overall language abilities, \( t (14.92) = -2.294, p = .037 \) (two-tailed), \( d = -1.130 \). Figure 10 demonstrates GLC scores for both groups.

The third hypothesis of this study predicted that children with VCFS would not statistically differ from the comparison group on social skills ratings on the Preschool and Kindergarten Behavior Scales-Second Edition (PKBS-II). Sixty percent \( (n = 6) \) of the parental behavior ratings for preschoolers with VCFS yielded one or more clinical elevations across the Social Skills and/or Problem Behavior subscales, indicating risk for having or developing significant behavioral and/or emotional problems, whereas only 30\% \( (n = 3) \) of the parental behavior ratings for the CLP sample yielded one or more clinical elevations. However, the mean Social Skills score for the preschool age children with VCFS \( (M = 94.9, SD = 19.84) \) was not significantly different from the comparison group \( (M = 107.1, SD = 11.43) \), \( t (18) = -1.685, p = .109 \) (two-tailed). Figure 11 represents the distribution of scores on the Social Skills subscale.

Hypothesis four predicted that children with VCFS would not statistically differ from the comparison group on problem behavior, as measured by the PKBS-II. Similar to
findings within the social skills domain, the mean scores of the preschool age children with VCFS ($M = 108.8, SD = 16.53$) did not significantly differ from the comparison group ($M = 96.8, SD = 14.53$) in problem behavior scores on the PKBS-II, $t(18) = 1.724$, $p = .102$ (two-tailed). Figure 12 details the distribution of scores. The Problem Behavior subscale is divided into externalizing behaviors and internalizing behaviors. Of the six preschoolers with VCFS who obtained a clinical elevation on the Problem Behavior subscale, 67% obtained a clinically elevated score for externalizing behaviors and 33% for internalizing behaviors.

Discussion

The present study examined the cognitive functioning, language abilities, and social and behavioral functioning of preschool age children with VCFS. Obtained means for this sample on the WPPSI-III, PLS-IV, and PKBS-2 were compared to means of children with non-syndromal CLP to determine which characteristics were differentially associated with VCFS. The following discussion will address the limitations and implications of this study as well as future directions for research in this area.

Results of the current study regarding overall cognitive functioning indicate that the null hypothesis, which stated that there would be no significant difference between the VCFS and comparison group for mean Full Scale IQ (FSIQ), should not be rejected because there is not a significant difference between these two groups. However, the mean FSIQ score for the VCFS sample fell in the low average range of cognitive functioning, which although is slightly higher than that found by Gerdes et al. (2001), does not support previous findings by Golding-Kushner, Weller, and Shprintzen (1985).
which demonstrated that children under the age of six tested within the average range of intellectual ability.

Interestingly, this study, demonstrated Verbal IQ (VIQ) scores in average range. Though these scores were predicted to be higher than Performance IQ (PIQ), it was not thought that they would fall within the average range. This could potentially be a reflection of test artifact, as the WPPSI-III was designed to be less verbally demanding than previous versions of this measure which were used in previous studies.

Although results of language functioning did not demonstrate a difference between receptive and expressive abilities within the VCFS group, and hypothesis two could not be rejected, the preschoolers with VCFS demonstrated significantly lower language scores on the PLS-IV than the comparison group. This confirms that children with VCFS typically demonstrate language deficits that meet clinical criteria for language delay and warrant intervention services (Gerdes et al., 2001).

It is possible that a significant difference between receptive and expressive language abilities for the preschoolers with VCFS was less pronounced due to the fact that all participants in this group were receiving speech and language therapy. It is possible that deficits in expressive language functioning were identified early and targeted as primary goals of therapy, thus making the frequently cited receptive-expressive discrepancy less apparent in the children involved in this study.

It is important to address the failure to find differences for the preschoolers with VCFS on the General Language Composite (GLC) of the WPPSI-III. This finding does not support the general conclusions derived from their scores on the Preschool Language Scale-IV (PLS-IV), a well-normed language measure frequently cited in the literature. It
is most likely that this is due to the reduced sample size (n = 7) that was administered the GLC due to test fatigue and non-compliance. Moreover, evidence for convergent validity for the GLC is not well documented in the WPPSI-III technical manual, thus a reason why this composite was not used as a primary assessment of language in this study.

We were not able to reject the null hypotheses related to measures of social skills and problem behaviors. Although this may be attributed to the small sample size, the sole attainment of behavior ratings from parents may have been the reason why this study did not support previous research findings. It is important to consider that parental ratings have some element of bias. It was also previously reported that parents of children with craniofacial anomalies did not endorse social skills deficits that were observed in a research setting (Krueckeberg, Kapp-Simon, & Ribordy, 1993). It would have been beneficial to have multiple raters (teacher and parent) complete the PKBS-2, particularly knowing, in hindsight, the number of participants who were enrolled in preschool/early intervention programming. Teachers and parents observe different aspects of the child and therefore both sources should be utilized to obtain the most comprehensive clinical picture (Sattler, 1992, p.377). This is an important consideration for future projects with preschool age children and a behavioral rating component.

Another explanation for the lack of significant differences in social skills and problem behaviors between groups is that these are problematic for children with craniofacial anomalies, not just specifically children with VCFS. Previous research has suggested that psychosocial adjustment varies with cleft type (Millard & Richman, 2001). A recent systematic review of 64 studies revealed a general lack of uniformity and consistency required to adequately summarize the psychosocial problems resulting from
Preschoolers with VCFS (Hunt, Burden, Hepper, & Johnston, 2005). The authors indicated that there is some evidence suggesting that individuals with CLP may encounter psychosocial problems, though overall adjustment appears reasonably good. However, as mentioned above, the overall consistency across studies does not allow for generalizations to be made about this population.

An alternate explanation for the findings could be that of Krueckeberg et al. (1993), who determined that preschoolers with CLP tend to have good self-perceptions and are more similar to their peers, which initially serve as protective factors for children with craniofacial anomalies. It is proposed that these children start out with similar levels of social skills and later begin to encounter difficulties as they develop and become more aware of stigmatization and stressors that often accompany craniofacial anomalies. Moreover, children with craniofacial anomalies were found by Krueckeberg et al. to demonstrate poor facial encoding ability and less friendly responses to hypothetical situations, which are predictive factors of social skills and produce greater social inhibition over time. It is thought that the differences between children with craniofacial anomalies and their peers in social skills development become more pronounced as they age. Therefore, it is possible that the children in this study have not yet demonstrated problems in adjustment, but could appear less skilled than their peers over time. The reported degree of deficits in social skills that are seen in the literature for older children simply may not be readily apparent at this age.

Limitations of the Study

Admittedly, the major limitation of this study is the lack of statistical power due to the significantly reduced sample size. Although recruitment efforts were exhaustive, an
adequate sample size was not obtained. Therefore, the likelihood of Type II error for this investigation is high. However, it is believed that the obtained results are still beneficial in that they contribute to the scant body of literature regarding the profiles of preschoolers with VCFS. Previous studies have also included a limited number of subjects, and therefore continued replication of findings is needed.

Although the number of participants was less than planned, the effect sizes obtained in this study warrant careful consideration as they measure the magnitude of the differences in means and are independent of sample size. Effect sizes were large for findings in this study, which indicates that these findings were robust and are reflective of true differences in means that would likely be present with a larger sample. It is important to examine these obtained results in comparison to the first prospective multidisciplinary evaluation by Gerdes et al. (2001) that focused solely on 112 toddlers and preschool age children diagnosed with a 22q11.2 deletion. Several of the obtained mean scores of this present study reflect similar findings from the aforementioned study, which utilized similar methodology and assessment measures. The most consistent finding in this study is the mean PIQ ($M = 79.9, SD = 7.39$), which is very similar to results by Gerdes et al. ($M = 78.0, SD = 12$).

In addition to the above limitations, it is also important to consider recruitment bias when reviewing the results of this study. We know that many children did not participate due to conflicts with other medical appointments, arranged surgeries, etc., which may be associated with more severe anomalies or developmental delays. Moreover, one must consider the type of family that volunteers for a research project in which there is little incentive offered. One can assume that this impacts the decision to
participate, and potentially biases the sample regarding socio-economic status, access to resources, etc. This specific demographic information was not collected during this study, but may have been useful in better understanding who chose to participate. Another important question to pose is whether parents of children who are developmentally and behaviorally more “typical” are more inclined to participate in research. It is possible that parents whose children have more severe developmental delays or social-behavioral problems did not agree to participate in this study, which would result in a skewed sample. However, recruitment bias is not unique to this study and may be an issue in any research that relies on volunteers.

Lastly, testing young children can be a challenge due to their inherent immaturity, limited behavioral control, and limited ability to attend to tasks for extended periods of time. It is known, therefore, that there is less reliability in test scores of younger children and more room for error and variance in scores. The IQ scores of children do not remain static, and there is particular concern for stability in scores when the child is under the age of six (Sattler, 1992, p.3). Though information about preschool age children with VCFS is needed, the inherent nature of the preschool population presents a challenge to the design of any study incorporating this population.

*Implications for Intervention*

Though it is not uncommon for young children to manifest some degree of difference in abilities between the verbal and non-verbal domains on tests of cognitive functioning, the extent of the observed difference in this study is very large, and likely a valid reflection of unequally developed abilities. Although academic achievement was not assessed due to the age of these children and limited exposure to formal education,
the aforementioned finding is important when considering academic planning in the future. Many older children with VCFS demonstrate a learning profile and behavioral phenotype similar to that of a non-verbal learning disability (NLD) (Woodin et al., 2001). It is important to note that the VIQ-PIQ difference, one frequent finding within the NLD profile, was observed for the sample in this study. Although this difference is not exclusively diagnostic for the presence of a learning disability, it suggests a need for re-evaluation and continued monitoring of these children in the early school years to determine if a true learning disability exists. As part of early intervention for preschoolers with VCFS, specific strategies should target the non-verbal domain to bolster visual-spatial abilities of those identified to have a significant profile of VIQ>PIQ.

Another potential implication of this study is that the routine use of behavior rating scales could prove to be beneficial for young children with VCFS in identifying early stages of behavioral or emotional problems. The majority of such behavior rating scales take very little time to administer, score, and interpret and are designed to be used with the early childhood/preschool population. Use of these instruments could help medical providers and school personnel make more informed recommendations about social-behavioral problems warranting further attention, treatment, and intervention services. The purpose of screening for social-behavioral problems is usually for secondary prevention, which precludes the existing problem from becoming worse (Kauffman, 1997).

Conclusions

Though there are clear limitations to this study, most significantly the small sample size, there are meaningful conclusions that can be extracted from the data. Most
notably, the preschoolers with VCFS in this study demonstrated specific deficits in cognitive functioning and language abilities in comparison to children with non-syndromal CLP, suggesting a phenotypic profile that is associated with 22q11.2 deletion and not merely the presence of a craniofacial anomaly. These findings add to the limited research specific to these domains in preschool age children with VCFS. These findings support the idea that these deficits can be identified early and appropriate intervention strategies can be subsequently developed to target these specific concerns. This knowledge needs to be conveyed to the medical professionals and educators working with these children. It will be useful for parents to be provided with an overview of research findings for this population so that early intervention programming can be implemented, so that even the subtlest deficits can be identified and targeted. Children with the 22q11.2 deletion should routinely be followed and assessed knowing what this research and previous studies have identified as sequela of this syndrome beyond the medical complications.

Continued research efforts in this area are warranted, and the ability to provide more detailed feedback of individual performance, as well as monetary reimbursement for participation will likely increase the overall number of participants.

Future directions for research should focus on success of particular early intervention strategies for these children during the preschool years. There is a growing trend for cardiologists to routinely refer patients with conotruncal cardiac anomalies for genetic screening for the 22q11.2 deletion (Gerdes et al., 2001). This translates into more parents receiving news of the diagnosis earlier, which ultimately allows them to screen for other associated deficits and implement early intervention strategies accordingly.
Gerdes et al. propose that all children with the 22q11.2 deletion be eligible for monitoring and for additional services considering the high risk for developmental disabilities. These authors specifically recommended (a) physical therapy to address hypotonia; (b) preventative speech therapy, including the use of sign language, by one year of age; and (c) early introduction of social skills training. It is believed that a more proactive approach could reduce the severity of the associated developmental disabilities and improve the diagnoses and treatment of other social-behavioral sequela.

This study adds to the limited knowledge of cognitive, language, and social-behavioral functioning of preschool age children with VCFS. While this study has a fair number of limitations, it contributes significant findings that highlight the importance of early intervention for this vulnerable group of children.
References


Prentice-Hall, Inc.


York: Guilford Press.


Table 1

Demographic Variables for Participants

<table>
<thead>
<tr>
<th></th>
<th>VCFS (n = 10)</th>
<th>CLP (n = 10)</th>
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<td>Mean Age in Months</td>
<td>58.0 (SD = 8.29)</td>
<td>62.30 (SD = 10.05)</td>
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<tr>
<td>Ethnicity</td>
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<td>9 Caucasian, 1 Asian</td>
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<tr>
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<td>30% receiving services</td>
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<td>SD</td>
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<td><strong>Performance IQ</strong></td>
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<tr>
<td>VCFS</td>
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<td>CLP</td>
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<td>SD</td>
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<tr>
<td><strong>Total Language Score</strong></td>
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*Note.* *p ≤ .01
Figure 1. Boxplots for Full-Scale IQ scores on the WPPSI-III for VCFS and CLP groups.
Figure 2. Boxplots for Verbal IQ Scores on the WPPSI-III for VCFS and CLP groups.
Figure 3. Boxplots for Performance IQ Scores on the WPPSI-III for VCFS and CLP groups.

O = Outlier
Figure 4. Difference in Verbal IQ-Performance IQ scores for the VCFS group on the WPPSI-III.
Figure 5. Boxplots for Processing Speed Quotient scores on the WPPSI-III for VCFS and CLP groups.
Figure 6. Difference in receptive-expressive communication scores for the VCFS group on the PLS-IV.
Figure 7. Boxplots for Auditory Comprehension (receptive language) scores for the VCFS and CLP groups on the PLS-IV.
Figure 8. Boxplots for Expressive Communication (expressive language) scores for the VCFS and CLP groups on the PLS-IV.
Figure 9. Boxplots for Total Language scores for the VCFS and CLP groups on the PLS-IV.
Figure 10. Boxplots for General Language Composite scores for the VCFS and CLP groups on the WPPSI-III.
Figure 11. Boxplots for Social Skills scores for the VCFS and CLP groups on the PKBS-II.
Figure 12. Boxplots for Problem Behavior scores for the VCFS and CLP groups on the PKBS-II.
DATE: July 5, 2005

TO: Howard M. Saal, M.D.
Division, Human Genetics
Cincinnati Children's Hospital Medical Center
MLC 4006

RE: ASSESSMENT OF INTELLIGENCE, LANGUAGE AND SOCIAL SKILLS IN PRESCHOOLERS WITH VELOCARDIOFACIAL SYNDROME
(CHMC # 03-12-52)

FROM: Vivian M. Creutzinger, RN, BSN
Research Compliance Specialist
Institutional Review Board
MLC 5020

M. Douglas Ris, Ph.D., Co-Chairman
Institutional Review Board
MLC 5020

The Institutional Review Board has received a request for the following revisions:

- Revision to Currently Approved Protocol

  Change in design of the protocol from 26 subjects with Velocardiofacial Syndrome to 10 subjects with an added control group of 10 subjects with uncomplicated non-syndromic cleft lip or cleft palate.

  A new incentive of 25.00 gift certificate and snacks to families and children.

- Revision to Consent Form

  Revised to reflect the above changes.
☐ Other – (e.g., advertisement)

It has been determined that:

☐ This revision does not increase risks to participants enrolled in the study.

☐ This revision does increase risks to participants enrolled in the study.

☐ This requested revision to the consent form is approved.

☐ The requested protocol revision is approved.

☐ The requested revision is approved.

☐ The requested revision has not been approved. The following information is requested.

The amendment has been reviewed by full board review ☐

The amendment has been reviewed by expedited review ☑
June 2, 2005

Kristy Fritz, M.A.
1129 N. Center Street, #202
Royal Oak, MI 48067

Dear Ms. Fritz:

The Xavier University IRB received the changes to your revised Protocol #0287M-3, Assessment of Intelligence, Language, and Social Skills in Preschoolers with Velocardiofacial Syndrome, on June 1. Your revised protocol is approved in the Expedited category.

This approval expires 6/2/06. A progress report must be filed with XU’s IRB by the expiration date either indicating that your research has been completed or that you request an extension of IRB approval. A form is enclosed for your convenience in future reporting. The form is also available at www.xu.edu/IRB/IRBforms.htm.

If there are any adverse events or modifications to the research, please notify the IRB immediately.

We wish you every success with your research.

Sincerely,

Robert C. Baumiller, S.J.
IRB Chair and Administrator

RCB:nm

cc: Dr. Janet Schultz, ML 6511

Enclosures: Progress Report
           Approved Informed Consent

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 Appendix C

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: Assessment of Intelligence, Language and Social Skills in Preschoolers with Velocardiofacial Syndrome

CCHMC IRB # 03-12-52 IRB Approval Date: 01-20-04

INVESTIGATOR INFORMATION:

Principal Investigator Name: Howard M. Saal, M.D. Telephone Number: 513 636-7837
24 hr Emergency Contact: 513 636-4200

Subject Name: ___________________________ Date of Birth: _____/_____/_____

Throughout this document, references to “You” may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION:
You have been asked to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available and the right to withdraw from the study at any time. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty.

WHY IS THIS RESEARCH BEING DONE?
The purpose of this research study is to improve understanding of the intelligence, learning, language abilities and social skills of preschool children with velocardiofacial syndrome (deletion 22q11 syndrome).
WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because your child has either been diagnosed with velocardiofacial syndrome (also called deletion 22q11 syndrome or DiGeorge syndrome) or your child has an oral cleft and is being asked to participate as a member of the control group for this study.

WHO SHOULD NOT BE IN THE RESEARCH STUDY?

This study will include children who have been confirmed as having velocardiofacial syndrome by laboratory studies and a control group comprised of children with an oral cleft but no known genetic syndrome. The participants in the control group will be matched for age, gender, and ethnicity. Children who are not between the ages of 4 years, 0 months and 6 years 11 months will not be included in this study.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 12 months. Your actual involvement, including the testing will take place over a single session lasting approximately 3 hours. No follow up testing will be required. This consent, unless you choose to withdraw it, shall remain in effect until the end of the study.

The researcher may decide to take you off this research study at any time.

WHO IS CONDUCTING THE RESEARCH STUDY?

The study is conducted by Kristy M. Fritz, M.A., a Doctoral student in the Department of Psychology at Xavier University. The testing will be done by Ms. Fritz at Xavier University. She will be supervised by Janet R. Schultz, Ph.D. and Howard M. Saal M.D.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About 20 people will take part in this study at Xavier University and Cincinnati Children’s Hospital Medical Center.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you take part in this study, your child will have the following tests performed in order to assess learning, language skills and social skills:

- Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) is a test of cognitive abilities that is designed to identify strengths and weaknesses related to cognition in young children. This test measures verbal and non-verbal reasoning abilities, receptive versus expressive vocabulary, and processing speed. Average testing time is 45-60 minutes. Because of the nature of this test and its interpretation, it should not be repeated for one year after it has
been administered (i.e. it should not be given again if the child is tested in the schools or by a psychologist for one year).

- Preschool Language Scale-Fourth Edition (PLS-4) provides a picture of a child's overall total language skills, as well as receptive and expressive language abilities. It is an interactive instrument with activities that target attention, vocal/gestural behaviors, interaction, early literacy, and phonological awareness. Average testing time is 20-45 minutes.

- The parent will be asked to complete the Preschool and Kindergarten Behavior Scale-Second Edition (PKBS-2) to evaluate social skills and problem behaviors. This is a behavior rating scale designed for use in evaluating social skills and problem behaviors of preschool and kindergarten-age children, ages 3 through 6 years. The form usually takes parents between 8 and 12 minutes to complete.

- There will be no blood testing or other testing performed as part of this study.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

The only foreseeable risk in this study is that of boredom or inattention of children who are participating in this study. In the rare event that the child becomes upset, it may be necessary to reschedule the testing. There may be unknown or unforeseen risks associated with study participation.

ARE THERE DIRECT BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this research study, there is not a direct medical benefit for you. The study investigators feel that it is not appropriate to share the results of each child’s individual testing with the parents/guardians, since the context of this testing is to improve the understanding of learning, language and social skills for preschool children with velocardiofacial syndrome, but not to identify specific related issues for each child. The investigator will share the results of the testing with schools, teachers, or psychologists if requested by parents.

WHAT OTHER CHOICES FOR CARE ARE THERE?

You and your child have the option not to participate in this study. By not participating in this study, your child’s health care and management will not be in any way affected.
HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research information ("Protected Health Information" or "PHI"), consisting of the identification of your child as having velocardiofacial syndrome and any medical complications which have occurred, including congenital heart defect, cleft palate, speech disorders, and any other medical problems. After this information and the information obtained from testing are recorded, these will be analyzed anonymously without any information which could link this information to your child or your family.

Protected Health Information is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered in a computer), that identifies you as an individual or offers a reasonable basis to believe that the information could be used to identify you.

By signing this consent form you are giving permission for representatives of the Cincinnati Children’s Hospital Medical Center ("CCHMC"), the Investigator and CCHMC employees involved with the research study including the Institutional Review Board and the Office for Research Compliance, and any sponsoring company or their appointed agent to be allowed to inspect sections of your medical and research records related to this study.

The information from the research study may be published; however, you will not be identified in such publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant without your authorization.

Cincinnati Children’s Hospital Medical Center and/or the Investigator will take the following precautionary measures to protect your privacy and confidentiality of your research and/or medical records. All records will be coded with a non-identifiable assigned coded number. Any records containing protected health information will be stored in a locked cabinet available only to the study investigators. In any publications or reports resulting from the study, there will be no individual identifiers used.

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

The Protected Health Information described in the section above will be used /disclosed for the purpose of research by CCHMC to the other persons or entities identified above.

"Use" of an individual’s health information is defined as the sharing, examination or analysis (break down) of the information that is collected and maintained for the length of the research study.

"Disclosure" of an individual’s health information is defined as the release, transfer, providing access to, or to reveal in any other manner, the information outside the persons
or entity holding the information as described in the section “How Will Information About You Be Kept Private And Confidential” in this consent form.

Once your Protected Health Information is disclosed, the information may be subject to re-disclosure and may no longer be protected by the federal privacy regulations.

**AVAILIBILITY OF INFORMATION?**

No information regarding your child obtained from this study will be made available to the study subjects, families, personal physicians, or teachers, unless a request is made by the parents to share testing results with schools, teachers, or psychologists.

**WHAT ARE YOUR COSTS TO BE IN THIS STUDY?**

There will be no costs to you for participating in this study.

**WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?**

Participants will receive a $25 gift card to an area retail store as reimbursement for participation in this study. Snacks will also be provided to you and your child during the testing.

**WHAT ARE YOUR RIGHTS AS A PARTICIPANT?**

Your participation in this study is completely voluntary. You may choose either to take part or not to take part in this research study. Your decision whether or not to participate will not result in any penalty or loss of benefits to you and the standard medical care for your condition will remain available to you.

If you decide to take part in the research study, you are free to withdraw your consent and discontinue participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

You may revoke (choose to withdraw) this Authorization as provided under the Health Insurance Portability and Accountability Act of 1996 (HIPAA™) at any time after you have signed it by providing Howard Saal, M.D. with a written statement that you wish to withdraw this Authorization. Your withdrawal of this Authorization will be effective immediately and your Protected Health Information can no longer be used/disclosed for research purposes by CCHMC and the other persons or entities that are identified in the “Use or Disclosure of Your Protected Health Information” section of this consent, except to the extent that CCHMC and/or the other persons or entities identified above have already taken action in reliance upon your consent. In addition, your Protected Health Information may continue to be used/disclosed to preserve the integrity of this research study.
The investigators will tell you about significant new findings developed during the course of the research and new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

For further information about your rights, please see CCHMC Notice of Privacy Practices.

ABILITY TO CONDITION TREATMENT ON PARTICIPATION IN THIS STUDY

You have a right to refuse to sign this consent to use/disclose your Protected Health Information for research purposes.

If you refuse to sign this consent, your rights concerning treatment, payment for services, enrollment in a health plan or eligibility for benefits will not be affected.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions about this research study or to report a research-related injury, you can contact the researcher Howard M. Saal, M.D. at 513 636-4760 and the Division of Human Genetics at Cincinnati Children's Hospital. Researchers are available to answer any questions you may have about the research at any time.

If you have general questions about your rights as a research participant in this research study, you can call the Cincinnati Children's Hospital Medical Center Institutional Review Board at 513-636-8039 or the Xavier University Institutional Review Board at 513-745-2870.

WITNESSING AND SIGNATURES

I have read the information given above. The investigator or his/her designee have personally discussed with me the research study and have answered my questions. I am aware that, like in any research, the investigators cannot always predict what may happen or possibly go wrong. I have been given sufficient time to consider if I (or my child) should participate in this study. I hereby consent for myself (or my child) to take part in this study as a research study subject.

Check box if verbal assent is obtained from the child who is the research subject □
Subject's signature indicating consent or assent

Date: ______________

Parent/Legal Guardian (Signature)

Date: ______________

Parent/Legal Guardian (Signature)

Date: ______________

I have witnessed the voluntary signing of this document by the research subject, or the legally authorized representative of the research subject.

Witness as to the voluntary nature of the Signatures noted above (Signature)

Date: ______________

Investigator or specific individual who has been designated to obtain consent (Signature)

Date: ______________

Investigator (Signature)

Date: ______________

This research study and consent form have been reviewed and approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (telephone number 513-636-8039) and by the Xavier University Institutional Review Board.