Phenotype of Adults With the 22q11 Deletion Syndrome: A Review

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Abstract

22q11 deletion syndrome (22qDS) is due to microdeletions of chromosome region 22q11.2. Little is known about the phenotype of adults. We reviewed available case reports of adults (age 18 years) with 22qDS and compared the prevalence of key findings to those reported in a large European survey of 22qDS (497 children and 61 adults) [Ryan et al., 1997: *J. Med. Genet.* 34:798–804]. Fifty-five studies reported on 126 adults (83 women, 40 men, 3 unknown sex), mean age 29.6 years ($SD = 8.7$ years). Compared with the European survey, adults with 22qDS reviewed had a lower rate of CHD, 30% versus 75%; $\chi^2 = 88.65$, $df = 1$, $P < 0.0001$, but higher rates of identified palate anomalies, 88% versus 15%; $\chi^2 = 37.45$, $df = 1$, $P < 0.0001$, and learning difficulties, 94% versus 79%; $\chi^2 = 12.13$, $df = 1$, $P = < 0.0008$. The most common finding reported was minor facial anomalies. Few reports provided details of minor physical anomalies. Psychiatric conditions were more prevalent, 36% versus 18%; $\chi^2 = 5.71$, $df = 1$, $P < 0.02$, than in the survey: 60% of reviewed adults were transmitting parents (72% mothers) ascertained following diagnosis of affected offspring. They had lower rates of CHD, cleft palate, and psychiatric disorders but similar rates of learning disabilities, and other palate and facial anomalies compared with adults ascertained by other methods. The results suggest that learning disabilities and facial and palate anomalies may be key findings in 22qDS adults, but that ascertainment is a key factor in the observed phenotype. Comprehensive studies of adults with 22qDS identified independently of familial transmission are necessary to further delineate the phenotype of adults and to determine the natural history of the syndrome.

Keywords

22q11 deletion syndrome; velocardiofacial syndrome; adults; phenotype; ascertainment; outcome

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INTRODUCTION

Chromosome 22q11 deletion syndrome (22qDS) encompasses velocardiofacial syndrome (VCFS), Di-George syndrome (DGS), and conotruncal anomaly face syndrome (CTAFS) [Thomas and Graham, 1997], all due to 22q11.2 microdeletions, which usually occur de novo, but may be inherited in 10 to 25% of cases [Demczuk and Aurias, 1995; Leana-Cox et al., 1996]. A large number of clinical findings have been reported in affected patients, including cardiac defects, palate anomalies, learning difficulties (LD), mental retardation (MR), athymia, and characteristic physiognomy [Goldberg et al., 1993]. The phenotype of 22qDS patients varies between families and even among members of the same family [Motzkin et al., 1993; Ravnan et al., 1996]. The prevalence of 22q11 deletions was estimated to be approximately 1/4,500 [Du Montcel et al., 1996; Devriendt et al., 1998]. However, because the phenotype is variable and includes mildly affected individuals, 22qDS is likely to be underdiagnosed [Motzkin et al., 1993; Du Montcel et al., 1996; Murphy et al., 1998]. To date, most phenotypic studies of 22qDS have involved populations of children ascertained through craniofacial or congenital heart clinics [Bassett et al., 1998].

In recent years, reports of later-onset illnesses associated with 22q11 deletions have appeared. The most important among these are psychiatric illnesses such as schizophrenia [Shprintzen et al., 1992; Chow et al., 1994; Karayiorgou et al., 1995; Bassett et al., 1998] and bipolar disorder [Papolos et al., 1996]. Shprintzen et al. [1992] were the first to report 4 of 13 (31%) adult VCFS patients with schizophrenia or schizoaffective disorder. In a recent study of 40 adults with 22q11.2 microdeletions, 28% fulfilled a *DSM-IV* (Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition) [American Psychiatric Association, 1994] diagnosis of a psychotic illness (schizophrenia, schizoaffective disorder, or bipolar disorder), and 13% had severe depression [Murphy et al., 1997]. Other later-onset conditions have also been reported in 22qDS including hypocalcemia [Maaswinkel-Mooij et al., 1989; Cuneo et al., 1997] thrombocytopenia [Carlson et al., 1997; Levy et al., 1997; Ryan et al., 1997], hypothyroidism [Bassett et al., 1998; Ryan and Wilson, 1998], and various neurological complications [Lynch et al., 1995; Gripp et al., 1997; Bassett et al., 1998; Vataja and Elomaa, 1998]. The morbidity due to many of the later-onset manifestations of 22qDS calls for a systematic investigation of the phenotype of adults.

The purpose of this study was to review the phenotype features of reported adults with 22q11.2 deletions and to compare them with those reported in a large 22qDS sample comprised primarily of children [Ryan et al., 1997]. We hypothesized that adults with 22qDS would have a milder phenotype. We also hypothesized that most reported adults would have been ascertained as parents of affected offspring and that these transmitting parents would have a milder physical and behavior phenotype than adults with 22qDS ascertained by other methods.

MATERIALS AND METHODS

A MEDLINE (1966–July, 1998) search was carried out for English language articles with any of the keywords “22q11,” “22q11.2,” “velocardiofacial,” “velo-cardio-facial,” “DiGeorge,” or “conotruncal anomaly face” in the title or abstract. We reviewed reports of

adults (18 years old) recording the presence or absence of at least three major phenotypic findings of 22qDS (typical facial anomalies, congenital heart defects, palatal anomalies, learning difficulties/mental retardation, psychiatric diagnoses, hypocalcemia, or athymia). We included only participants with a 22q11.2 deletion detected by fluorescent in-situ hybridization (FISH) or molecular testing, or before clinical testing was available, parents who had at least three major manifestations of 22qDS and an affected offspring were assumed to have transmitted a 22q11.2 deletion. Demographic and major clinical findings (facial characteristics, medical problems, and cognitive and psychiatric data) of cases meeting inclusion criteria were collected and the mode of ascertainment noted. Cardiac anomalies were studied by methods including physical examination, echocardiography, and cardiac catheterization; therefore, only cardiac defects that usually require surgery (e.g., tetralogy of Fallot, ventricular septal defect, atrial septal defect, pulmonary valve atresia) as defined in a European survey [Ryan et al., 1997] were included. Anomalies that were inconsistently documented, including asymptomatic isolated right aortic arch, bicuspid aortic valve, and abnormal subclavian artery, were not considered in this review. Every effort was made to determine cases reported several times and to include these only once. Rates of major findings were compared using chi-square statistics to those reported in a European survey of 558 patients with 22q11.2 deletions, 89% ($n = 497$) of whom were children [Ryan et al., 1997].

RESULTS

One hundred twenty-six adults with 22qDS reported in 55 articles met inclusion criteria. There were significantly more women ($n = 83$) than men ($n = 40$) participants, ($\chi^2 = 7.02$, $df = 1$, $P < 0.01$; sex was not recorded in 3 subjects. The mean age was 29.6 years ($SD = 8.7$ years; range = 18 to 69 years); only 1 subject was older than 50 years [Bassett et al., 1998].

Transmitting Parents

Most subjects (76/126, 60%) were transmitting parents of affected offspring (one 22qDS adult subject reported per study unless otherwise indicated) [Strong, 1968; Young et al., 1980 ($n = 3$); Greenberg et al., 1984; Rohn et al., 1984; Williams et al., 1985; Wraith et al., 1985; Meinecke et al., 1986; Keppen et al., 1988; Maaswinkel-Mooij et al., 1989; Stevens et al., 1990; Scambler et al., 1991 (same subject as in Keppen et al., 1988); Wilson et al., 1991; Driscoll et al., 1992; Wilson et al., 1992 (same subject as in De Silva et al., 1995); Desmaze et al., 1993, ($n = 4$); Driscoll et al., 1993 (same subject as in Driscoll et al., 1992); Holder et al., 1993; McLean et al., 1993; De Silva et al., 1995 ($n = 2$); Lindsay et al., 1995b ($n = 2$); McDonald-McGinn et al., 1995; Morrow et al., 1995; Van Hemel et al., 1995; Leana-Cox et al., 1996 ($n = 5$); Ravnan et al., 1996 ($n = 4$); Shalev et al., 1996; Cuneo et al., 1997, ($n = 4$); Devriendt et al., 1997a; Devriendt et al., 1997b; Digilio et al., 1997 ($n = 7$); Levy et al., 1997 ($n = 2$); Mehraein et al., 1997 ($n = 2$); Bassett et al., 1998; Marble et al., 1998; Matsouka et al., 1998 ($n = 19$); McCandless et al., 1998]. Eleven (14%) of these parents were assumed to have transmitted a deletion although no FISH or molecular testing was reported.

Other Ascertainment

Of the 50 adult cases ascertained not as transmitting parents, 21 (42%) were from studies of patients from a group of collaborative researchers with multiple ascertainment sources, including craniofacial, cardiology, genetics, and psychiatric services [Driscoll et al., 1992; Scambler et al., 1992; Driscoll et al., 1993; Lindsay et al., 1993; Pulver et al., 1994; Karayiorgou et al., 1995; Morrow et al., 1995; Papolos et al., 1996; Carlson et al., 1997]. The proportion of these subjects ascertained as transmitting parents of affected offspring was not reported, and all subjects were assumed to be non-transmitting adults. The remaining 29 subjects were ascertained from the following sources: 12 from psychiatric sources [Gothelf et al., 1997 (n = 2); Bassett et al., 1998 (n = 8); Chow et al., 1998; Vataja et al., 1998], 4 from genetics clinics [Chow et al., 1994 (same subject as in Bassett et al., 1998); Fryer, 1996 (n = 2); Bassett et al., 1998 (n = 2)], 4 from endocrinology clinics [Scire et al., 1994; Adachi et al., 1998 (n = 3)], 3 on the basis of learning disabilities [Kozma, 1998; Murphy et al., 1998 (n = 2)], 3 from cardiology [Winter et al., 1984; Burn et al., 1993; Matsuoka et al., 1998], 2 from computer database crossmatches of cleft palate and other manifestations of the 22q11 deletion syndrome [Brøndum-Nielsen and Christensen, 1996; Gothelf et al., 1997], and 1 (same subject) from neurology [Lynch et al., 1995; Gripp et al., 1997].

Major Clinical Findings

Table I summarizes the frequency of specific clinical findings of 22qDS recorded in reported adults compared with that in the European survey [Ryan et al., 1997]. Comparatively, a higher percentage of reviewed cases reported on the sex of subjects and the frequency of cognitive problems (LD/MR). Adults reviewed had significantly lower rates of major cardiac anomalies ($P < 0.0001$) but significantly higher rates of a wide range of palate anomalies ($P < 0.0001$), cognitive difficulties ($P < 0.0008$), and psychiatric conditions ($P < 0.02$). There were no significant differences between males and females in the frequency of any of the clinical anomalies examined in the adult subjects reviewed. Ninety-nine percent (120/121) of the adults were described to have minor facial anomalies although specific findings were rarely noted.

Psychiatric Conditions

Most (63%) reviewed cases did not report on behavior or psychiatric problems. Reports of psychiatric conditions with 22qDS were limited primarily to studies in which psychiatric morbidity was directly investigated or was the mode of ascertainment. Of the 45 subjects with psychiatric problems, 12 (27%) were given more than one psychiatric diagnosis. Thirty-three subjects (73%) had evidence of a psychotic illness, (schizophrenia, schizoaffective disorder, auditory hallucinations, paranoid/grandiose delusions), including 4 cases (9%) in which characteristics of both psychotic and mood disorders were present. Five subjects (11%) were diagnosed with a mood disorder (depression or bipolar disorder without psychosis) and 7 (16%) were reported to have other psychiatric diagnoses or an unspecified behavior problem only. One subject was reported to have a normal behavior pattern. Assuming that the 80 cases with no data reported had no psychiatric disorder, the rate of psychiatric disorders was still significantly higher, $P < 0.02$, in the reviewed cases than that

reported for the 61 adults in the European survey [Ryan et al., 1997] (see Table I). Most cases reviewed did not provide details on learning disabilities nor results of formal neuropsychological assessments (e.g., IQ) making it impossible to determine rates for borderline, mild, and more severe forms of mental retardation.

Other Phenotypic Findings

Other medical findings that were noted in 2 of the 126 adults included: 19 (15%) with hypocalcemia occurring at varying ages at onset (neonatal—33 years) and severity, 14 (12%) with thrombocytopenia or recurrent epistaxis, 10 (8%) with recurrent infections or low T-lymphocyte count, 4 (3%) with inguinal hernias, 3 (2%) with cataracts, 3 (2%) with a laryngeal, pharyngeal, or subglottic web, and 2 reports (1%) each of ptosis, hypothyroidism and cleft lip. Similar rates were reported in the European survey [Ryan et al., 1997] for laryngeal web, cleft lip, and recurrent infections; rates for thrombocytopenia, hernias, cataracts, ptosis, and hypothyroidism were not reported in the survey [Ryan et al., 1997]. The rate of hypocalcemia in reviewed adults approximated the 18% rate for unresolved hypocalcemia in adulthood but was much lower than the overall rate (60%) reported in the survey [Ryan et al., 1997]. There were insufficient data on renal anomalies in adults reviewed to compare with the 36% rate (49/136) reported in the survey [Ryan et al., 1997].

Table II summarizes the phenotype of subjects ascertained as transmitting parents of affected offspring compared to the phenotype of adults ascertained independently of transmission of 22qDS. In both subgroups, there were significantly more females than males. However, when the 21 (14 females, 7 males) subjects with unreported transmission status were excluded from the non-transmitting subgroup, the proportion of females in the remaining 29 subjects was 53.8%, not significantly different from the expected 50% ($\chi^2 = 0.3623$, $df = 1$, $P = 0.274$). As hypothesized, rates of major cardiac anomalies and cleft palate were significantly lower in adults ascertained through familial transmission of 22qDS (see Table II). Overall rates of minor facial anomalies, palate anomalies, and learning difficulties were similar between the two subgroups. However, there were fewer reports of psychiatric disorders in the transmitting parent subgroup than for adults ascertained by other methods. The rate (20/38, 53%) of psychiatric disorders in the non-transmitting parents whose mode of ascertainment was from non-psychiatric sources or was unknown was significantly higher than that described in the European survey [Ryan et al., 1997].

DISCUSSION

The results of this review indicate that reported adults with 22qDS have much lower rates of congenital heart defects but higher rates of palate anomalies and learning disabilities/mental retardation than a large survey of predominantly pediatric patients. Ascertainment biases and age required to identify manifestations not obvious at birth (such as learning disabilities and minor palatal anomalies) likely explain these differences. Comparisons between adult and child 22qDS phenotype have previously been confined to parent–offspring pairs with most reports indicating a less severe phenotype in transmitting parents [Leana-Cox et al., 1996; Ryan et al., 1997], particularly regarding rates of cardiac anomalies and developmental/learning problems. Results from this review were consistent with transmitting parents having

particularly low rates of cardiac anomalies. However, transmitting parents in this review also had lower rates of cleft palate and reported psychiatric conditions than other adults with 22qDS in the literature.

The expected sex ratio for an autosomal dominant condition is 1:1, but more female than male 22qDS participants were found in this review. Given the high proportion of transmitting parents in our participants, preferential maternal transmission of 22q11.2 deletions, which has been reported by some investigators [Shprintzen et al., 1981; Desmaze et al., 1993; McLean et al., 1993; Wilson et al., 1993; Leana-Cox et al., 1996], although not all [Morrow et al., 1995; Ryan et al., 1997], may explain the overall female excess in the reviewed cases. Proposed explanations for maternal excess of 22qDS transmission include ascertainment bias due to sociological factors, and decreased reproductive fitness of affected males [Leana-Cox et al., 1996; Ravnan et al., 1996]. In the cases ascertained independently of transmission, the reason for the high frequency of females found is less apparent. The female excess may have been due to uncertainty of the mode of ascertainment in a substantial subset of cases ($n = 21$), some of whom may have been transmitting mothers. In fact, when these 21 subjects were excluded, the proportion of females in the remaining participants was not significantly elevated. However, chance or decreased survival of males with 22qDS into adulthood are alternate explanations for the observed high frequency of females.

A lower rate of cardiac anomalies in adults may in part be due to infant mortality associated with severe cardiac anomalies. However, survival rates of surgical corrections are high [Karr et al., 1992; Nollert et al., 1997], and the European survey reported 5% of patients with 22qDS dying with a known cardiac cause [Ryan et al., 1997]. Ascertainment bias in pediatric reports of 22qDS is another likely factor. The higher rate of cardiac defects in the non-transmitting subjects compared to the transmitting parents may be explained by an association between increased severity of phenotype and decreased reproductive fitness. However, there may also be an ascertainment bias arising from the relatively small subgroup of non-transmitting adults, many of whom were diagnosed with 22qDS as children with cardiac defects, and then followed into adulthood [Shprintzen et al., 1992; Goldberg et al., 1993; Lindsay et al., 1995a].

Findings that appear after infancy may not be reported as often in pediatric cases of 22qDS. For instance, the low rate of palate anomalies in the European survey [Ryan et al., 1997] may be partly due to the fact that over half of the surveyed subjects were under age 6. Hypernasal speech is difficult to identify until speech develops and speech delay is common in 22qDS [Golding-Kushner et al., 1985]. However, this would not explain the higher rate of cleft palate in adults reviewed than in the survey. Rates of palatal anomalies comparable to those found in reviewed adults have been reported in other reviews of 22qDS [Lipson et al., 1991; Burn et al., 1993; Goldberg et al., 1993; Lindsay et al., 1995B].

One of the most striking findings from this review was the relative paucity of detailed information on the adult phenotype of 22qDS, with the exception of major malformations such as congenital heart and palate defects. Although the rate of minor facial anomalies in adults reviewed was similar to the 100% (38/38) rate reported in an Australian study of

children with 22qDS [Lipson et al., 1991], detailed descriptions of the face were generally absent. Details on facial appearance of adults may be important because some manifestations, for example, bulbous nasal tip, may become more apparent with age [Lipson et al., 1991; Kitano et al., 1997], whereas others may become less “typical” in adulthood [Burn et al., 1993]. A comprehensive phenotype analysis of 22qDS adults would help to clarify if there are differences in “typical” 22qDS facial anomalies in adults compared with those reported for infants and children, and could also clarify possible racial differences [Kitano et al., 1997]. Another area lacking detailed descriptions was that of learning difficulties and cognitive functioning. This is similar to the pediatric literature where there are relatively few reports and sample sizes are small [Golding-Kushner et al., 1985; Kok and Solman, 1995; Swillen et al., 1997; Wang et al., 1998]. Developmental delays in infancy may be outgrown and milder learning difficulties may not become apparent until later childhood or adolescence. It would be important to learn more about the neurocognitive profile in 22qDS adults, and to examine for differences from that in 22qDS children. Other later occurring phenomena, such as psychiatric illnesses, are most likely to develop in adolescence or adulthood. Estimates of prevalence for later-onset disorders in 22qDS will therefore need to take age of the sample into account. These key data were lacking from the large European survey [Ryan et al., 1997]. There is still no consensus as to the precise prevalence of individual diagnoses, such as schizophrenia, in 22qDS, although preliminary reports suggest rates of psychiatric (and particularly psychotic) illness that are much higher than in the general population [Shprintzen et al., 1992; Pulver et al., 1994; Murphy et al., 1998].

Limitations

In this study, we included only cases with description of the presence or absence of three or more major findings of 22qDS. Although this inclusion criterion obviously excluded cases with limited data, it helped ensure that adequate clinical descriptions were being used for comparisons. A second limitation involved the assumption that 11 (14%) of the 76 adults ascertained as transmitting parents had 22qDS, although they had neither cytogenetic nor molecular evidence of 22q11.2 deletions. Since approximately 80% of syndromal patients tested are found to have 22q11.2 deletions [Carlson et al., 1997], one can estimate that 9 of the 11 patients would have had deletions. Including an estimated 2 patients without deletions would likely not have affected results of the review. The European collaborative survey [Ryan et al., 1997] included 61 adults, some of whom may have been reported in other publications and thus could have overlapped with adult cases in our review. However, examining the author lists showed only 6 possible overlapping patients, representing 5% of adults reviewed, whose inclusion would not have affected results significantly. Another potential limitation was that a high frequency (12/50) of non-transmitting adults with known ascertainment was from psychiatric sources. Although this may have led to an overestimate of the prevalence of psychiatric illness in 22qDS adults, the limited data on the presence of psychiatric conditions in most participants (80/126) would favor an underestimate of rates of psychiatric illness. The high rates of psychiatric disorders noted even after excluding the 12 psychiatrically ascertained subjects indicates that the frequency of psychiatric illness in 22qDS adults is significant. Finally, the difficulty in determining the precise nature of ascertainment for a subgroup of the patients may have interfered with the ability to detect

phenotypic differences between transmitting parents and adults with other ascertainment. The high proportion of females in this subgroup suggests that several of these patients may have had mixed ascertainment, likely including transmitting parents.

Conclusion

Delineating the adult phenotype of 22qDS independently of familial ascertainment would provide information that could help clinicians identify the syndrome in adults. 22qDS is important to diagnose in adults because they likely present a high-risk population for the development of treatable psychiatric and medical illnesses, such as hypocalcemia. Diagnosis of 22qDS could therefore allow therapy at an early stage of illness when the chance for improving long-term prognosis is greatest. Preliminary clinical screening methods have been proposed to help screen psychiatric patient populations for 22qDS [Gothelf et al., 1997; Bassett et al., 1998; Murphy et al., 1998; Bassett and Chow, in press], but they remain to be tested in large groups. Once validated, these methods may help a wide variety of clinicians including psychiatrists, endocrinologists, and hematologists identify 22qDS in adults. Furthermore, because most 22qDS adults described are relatively young, more studies of adults would help provide needed information on the life expectancy and long-term prognosis of 22qDS and on risks for late-onset medical and psychiatric conditions in this syndrome.

Acknowledgments

Contract grant sponsor: National Alliance for Research on Schizophrenia and Depression (NARSAD); Contract grant sponsor: Scottish Rite Schizophrenia Research Program.

The authors thank Stephanie Roberts, Susana Correia, and Laura E. Scutt for their assistance. Funding for Eyal Cohen was provided by the Dr. Harvey Moldofsky Scholarship.

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Sex and Major Clinical Findings of 22q11 Deletion Syndrome in 126 Adults Reported in the Literature Compared with a Large European Survey (maximum *N* = 558, 89% children) [Ryan et al., 1997]

TABLE I

Clinical findings	Cases reporting data on finding (presence/absence)					Cases with finding present				
	Adults reviewed		European survey [Ryan et al., 1997]			Adults reviewed		European survey [Ryan et al., 1997]		
	<i>N</i>	(%)	<i>N</i>	(%)	χ^2 [*] <i>p</i>	<i>N</i>	(%)	<i>N</i>	(%)	<i>p</i>
Female sex	123	(98)	399	(72)	38.02 <.0001	83	(67)	202	(51)	10.97 <.0015
CHD ^a	120	(95)	545	(98)	2.00 NS	36	(30)	409	(75)	88.65 <.0001
Palatal anomalies (all)	105	(83)	496	(89)	2.79 NS	92	(88)	233	(47)	56.95 <.0001
Cleft palate (overt or submucous)						43	(41)	72	(15)	37.45 <.0001
VPI or hypernasal speech						49	(47)	161	(32)	7.77 <.0004
Minor facial anomalies ^b	121	(96)	–	–	–	120	(99)	–	–	–
LD/MR ^c	111	(88)	338	(61)	34.84 <.0001	104	(94)	268	(79)	12.13 <.0008
Psychiatric disorders adults ^d	46	(37)	61 ^e	–	–	45	(36)	11 ^e	(18) ^e	5.71 <.02

^{*} *df* = 1.

^a CHD = congenital heart defects, major anomalies only (see text).

^b Not reported in [Ryan et al., 1997].

^c Includes any motor, language, or speech delay.

^d All cases assumed to have no psychiatric disorder unless otherwise specified.

^e The survey included 61 adults, 11 of which were specified as having at least one psychiatric disorder. The remaining 50 adults were assumed to have no psychiatric disorder.

N = number of subjects.

NS = non-significant.

VPI = velopharyngeal insufficiency.

LD/MR = learning difficulties or mental retardation.

TABLE II
Effect of Ascertainment on Adults with 22qDS: Transmitting Parents Versus Other Ascertainment

Clinical findings	Cases with finding present					χ^2 ^a	<i>p</i>
	Transmitting parents (<i>n</i> = 76)		Other ascertainment (<i>n</i> = 50)				
	N	(%)	N	(%)			
Female sex	55	(72)	28	(60)	1.80	NS	
CHD ^a	11	(15)	25	(56)	22.40	<.0001	
Palatal anomalies (all)	50	(83)	42	(93)	2.36	NS	
Cleft palate (overt or submucous)	18	(30)	25	(56)	7.89	<.005	
VPI or hypernasal speech	32	(53)	17	(38)	2.50	NS	
Minor facial anomalies	75	(100)	45	(98)	0.01	NS	
LD/MR ^b	58	(91)	46	(98)	2.49	NS	
Psychiatric disorders (adults) ^c	13	(17)	32	(64)	28.27	<.0001	

^a $df = 1$.

^a CHD = congenital heart defects, major anomalies only (see text).

^b Includes any motor, language, or speech delay.

^c All cases assumed to have no psychiatric disorder unless otherwise specified.

N = number.

NS = non-significant.

VPI = velopharyngeal insufficiency.

LD/MR = learning difficulties or mental retardation.