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Extracardiac features predicting 22q11.2 Deletion Syndrome in adult congenital heart disease

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Abstract

Background and objectives—22q11.2 Deletion Syndrome (22q11.2DS) is an important genetic syndrome to cardiologists yet remains under-recognized in adults. There is no evidence-based guideline for genetic testing referrals. Feasibility issues in many jurisdictions preclude testing for 22q11.2 deletions in every congenital cardiac patient. We aimed to determine an optimal combination of extracardiac features that could be clinically helpful in identifying adults with tetralogy of Fallot (TOF) and related conotruncal anomalies at highest risk for 22q11.2DS.

Methods—Adults (n=103) at a congenital cardiac clinic (86 with TOF) had a brief clinical screening assessment and genetic testing for 22q11.2 deletions using standard fluorescence in-situ hybridization; 31 had a 22q11.2 deletion. Discriminant ability (DA), defined as (sensitivity +specificity)/2, was used to measure performance of 18 (17 clinical and one demographic) features in predicting 22q11.2DS (DA>80%=a good screening test).

Results—Combining two features was required for a good test: a global impression of 22q11.2DS dysmorphic facies, with either learning difficulties (DA=82.4%) or voice abnormalities such as hypernasality (DA=81.6%). A four-feature combination (suggestive dysmorphic facies, voice abnormalities, learning difficulties and age <30 years) yielded maximal sensitivity (100%) and DA>85% at a cut-off of three features. Neither rates of right aortic arch or cardiac surgery differed between patients with and without 22q11.2 deletions.

Conclusions—Clinicians who consider as few as two extracardiac features readily detectable in a brief clinical encounter could help identify those with 22q11.2DS among adults with congenital heart disease. Diagnosis of 22q11.2DS is important for optimizing management of these complex patients.

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Keywords

Genetics; 22q11.2 Deletion Syndrome; Velocardiofacial syndrome; DiGeorge syndrome; Adult congenital heart disease; Discriminant ability

1. Introduction

22q11.2 Deletion Syndrome (22q11.2DS) (OMIM #188400/#192430) is one of the most important genetic syndromes in cardiology due to its high prevalence in conotruncal and other cardiac anomalies — especially those of the cardiac outflow tract [1,2]. The phenotype encompasses several clinical genetic syndromes, including velocardiofacial syndrome, DiGeorge syndrome, and conotruncal anomaly face syndrome [3,4]. Paediatric estimates indicate that about 15% of patients with tetralogy of Fallot (TOF) have 22q11.2 deletions [5]. At the same time, TOF has consistently been reported as the most commonly associated cardiac anomaly among patients with 22q11.2DS [4,6–8]. 22q11.2DS is also found in 20–50% of patients with pulmonary atresia/ventricular septal defect [9,10]. It may also be found in patients with truncus arteriosus, transposition of the great vessels, ventricular septal defect alone, and many other defects [8,11–13]. Ancillary cardiovascular features, e.g., right aortic arch, are common [1,8,12,14]. Common extracardiac features include dysmorphic facial features, hypernasal speech, learning and behavioural difficulties, as well as other congenital anomalies. The importance of later onset manifestations such as schizophrenia and endocrine disorders, and management implications for adults are increasingly recognized [15].

Timely diagnosis of 22q11.2DS is important for optimizing clinical care and for genetic counseling [3,15,16]. Some centres therefore screen all newborns with conotruncal anomalies using the gold standard clinical test: fluorescence in-situ hybridization (FISH) using a probe from the commonly deleted region [3]. While some may argue that this testing should ideally be conducted for every congenital cardiac clinic patient, this is infeasible in many jurisdictions, given practical and economic constraints.

Thanks to advances in paediatric cardiology and cardiac surgery, 90% of infants with TOF live past 30 years of age [17–19]. A recent North American study showed that there are nearly equal numbers of adults and children with severe congenital heart diseases [20]. However, testing for the 22q11.2 deletion has only been available in clinical laboratories since 1993–94. As such, even at centres performing newborn screening, millions of adolescent and adult patients with congenital heart disease [19] would not have had this testing. Also, the syndrome is known to be under-recognized, especially in adults [15,21,22]. We believe therefore that it is important to have a clinical protocol to help diagnose adults with a 22q11.2 deletion.

There are no consensus criteria guiding referrals for genetic testing for 22q11.2DS. The challenge at most centres is to identify patients with sufficiently high *a priori* probability of 22q11.2DS who warrant clinical genetic testing [12,22,23]. Optimal information for deciding whether to test for a 22q11.2 deletion in adults would include a comprehensive lifetime medical history and detailed physical examination for associated dysmorphic

features [24] — not feasible in a brief clinical encounter. A simple set of clinical criteria with high predictability of 22q11.2DS would be valuable to guide referral for genetic testing [25]. To identify adults at elevated risk for 22q11.2DS, our group has proposed clinical screening criteria [21], however their performance (e.g. specificity, sensitivity) has not been assessed.

While ancillary cardiovascular features are common in 22q11.2DS, they are also frequent in TOF and other congenital heart diseases [16] and therefore may not help in identifying high-risk individuals. Some ancillary anomalies have been reported to be more prevalent among children with TOF and 22q11.2DS but the predictive power of such anomalies in detecting 22q11.2DS among TOF patients has not been determined [26,27]. Given the absence of evidence-based guidelines for genetic testing referral, clinicians often select patients for genetic testing of 22q11.2 deletion based on features that are currently known to suggest high *a priori* probability of 22q11.2DS. However, the performance of such practices has not been objectively evaluated. The current study was designed to address this question by mimicking a real-world clinical practice setting in an adult congenital cardiac clinic — where patients were selected for genetic testing based on various features that have been suggested to be associated with 22q11.2DS. This is the first study of its kind. The study aimed to determine the performance of various clinical criteria in predicting 22q11.2 deletions. Our goal was to delineate a simple combination of extracardiac features that can be feasibly assessed in a brief clinical encounter with adult congenital cardiac clinic patients and which would be helpful for guiding referrals for 22q11.2 deletion genetic testing.

2. Materials and methods

2.1. Study sample

The study sample comprised 103 patients assessed at the University of Toronto Congenital Cardiac Centre for Adults from November 1998 to March 2005 who were clinically tested by karyotyping and FISH using a standard probe (TUPLE1 or N25) for 22q11.2 deletions. Ethics approval for the study was obtained from the University of Toronto and affiliated teaching hospitals. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. After obtaining written informed consent from each patient, trained research staff (research assistants, genetic counsellors, research fellows) carried out a brief screening assessment including demographics, selected medical history (e.g. thyroid and calcium abnormalities, birth defects, hearing problems), cognitive/developmental (e.g. learning difficulties, speech problems), behavioural and psychiatric history, and a limited physical examination. Dysmorphic facial features were rated both globally (some or no 22q11.2DS features) and on five areas: dysmorphisms in eyes (e.g. narrow palpebral fissures), ears (e.g. low set ears), nose (e.g. bulbous tip), mouth (e.g. retruded chin) and face (e.g. long, narrow face). Hand dysmorphisms (e.g. slender, tapered fingers) were separately assessed. In addition, patients were also observed for voice abnormalities (especially hypernasal speech) and behavioural abnormalities during the assessment. All patients were offered genetic counselling, and patients found to have 22q11.2 deletions have been followed by a clinical service for adults with 22q11.2DS [15].

The 103 study patients came from a source population of 509 patients (377 with TOF; 74.1%) who underwent clinical screening. The patients were sent for genetic testing by clinic cardiologists (GDW, MAG and others) and/or the research team for clinical features (n=100) or planned pregnancy (n=3). Eighty-six of the subjects (83.5%) had TOF, three had pulmonary atresia/ventricular septal defect, eight had ventricular septal defect alone, five had transposition of the great vessels (including one with double outlet right ventricle), and one had pulmonary atresia, atrial septal defect, patent ductus arteriosus and hypoplastic right ventricle (with intact ventricular septum).

2.2. Statistical analysis

Analyses were performed using STATA version 7.0. We first compared the prevalence of demographic variables (age and sex), and each of the 17 clinical screening features (three based on general observation, six based on more detailed observation, eight based on history), and the average number of clinical features per subject, between subjects with and without 22q11.2 deletions using chi-square and two-sample Wilcoxon rank-sum (Mann–Whitney) tests. We then calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each of the features.

To provide a single ‘performance index’ for each feature as a predictor of 22q11.2 deletions, we used ‘discriminant ability’ (DA), defined as (sensitivity+specificity)/2 [28]. DA corresponds directly to the Area under the Receiver Operating Characteristics Curve, an index of performance for tests involving continuous predictor variables (e.g., DA 80% corresponds to an area of 0.8) [28]. An index that can perfectly distinguish between two groups has DA 100%; one in which groups overlap completely has DA 50% [29].

To achieve DA>80%, generally considered as the cut-off for a ‘good’ predictive test [29], we needed to combine individual clinical features. To select candidate variables for the combination that would yield a high DA and still be feasible in a brief clinical encounter, the 17 history and physical variables, together with ‘age <30 years’ and sex, were put into a multiple regression model as independent variables, with 22q11.2 deletion status as the dependent variable. The continuous variable ‘age of subjects at screening’ was transformed into multiple dichotomous variables, with DA calculated for each of these variables. ‘Age <30 years’ yielded the highest DA and was therefore selected for use in the multiple regression. Beginning with the full model (all variables), variables were eliminated using backward stepwise selection — where variables with P-value of >0.2 were removed from the model at each step. Eliminated variables were considered for re-entry to the model at each step if they had a P-value <0.1. Five variables were identified. As a confirmatory measure, variables were selected for the multiple regression modelling using forward stepwise selection — with all candidate variables. Beginning with an empty model, variables with P-value <0.1 were included in the model. At each step, variables already included in the model would be eliminated if P-values were >0.2. Four variables were identified, all of which were in the model developed through backward stepwise selection. All possible combinations of the five variables identified in the final model through backward stepwise selection, ranging from two to all five variables at a time, were studied in detail. For each of these 26

combinations, the sensitivity, specificity and DA values for the different possible cut-off points were calculated, and the cut-off point giving the highest DA value was determined.

3. Results

Of the 103 study subjects, 49 (47.6%) were male. Mean age of the sample was 28.4 years (SD=9.7; range: 17–62 years), with no significant difference between males (29.0; SD=10.0 years) and females (27.8; SD=9.5 years; t=0.62, df=101, P=0.54). Thirty-one patients (30.1%) (12 males, 19 females) had a clinically detectable 22q11.2 deletion: 25 (29.1%) with TOF, and 6 (54.5%) with ventricular septal defect. There were no significant differences in the proportion of males (χ^2 =1.40, df=1, P=0.24) or subjects with TOF (χ^2 =0.26, df=1, P=0.61) between those with and without a deletion. However, patients with a 22q11.2 deletion had a significantly younger mean age (23.1, SD=5.0 years) than those with no deletion (30.6, SD=10.4 years; t=3.84, df=101, P=0.0002). The proportion of patients with right aortic arch was not significantly different between those with (11/31) and without (23/72) a deletion (χ^2 =0.12, df=1, P=0.73). All patients with no deletion and 29 of those with a 22q11.2 deletion had had palliative and/or corrective cardiac surgery (Fisher's exact test, P=0.09). Three subjects without deletions had karyotypic abnormalities: a 22 year old woman with a known chromosome 18 hemizygous deletion (46, XX, del 18q22), a 25 year old man recently diagnosed with Klinefelter syndrome (47, XXY), and a 31 year old woman with psychosis who was found to have Triple X syndrome (47, XXX).

The number and proportion of subjects possessing the 17 clinical screening features and age variable are shown in Table 1. The prevalence of features ranged from 11.0% (history of hypocalcaemia) to 70.0% (history of learning difficulties). Eleven of these features were significantly more common in adults with 22q11.2DS than those without a clinically detectable 22q11.2 deletion, although two of these (mouth and ear dysmorphisms) would overlap with global dysmorphic facial pattern. Also, the significant difference in hand dysmorphism would not survive Bonferroni correction for multiple testing. Examining 83 subjects with complete data on 12 features (i.e., excluding detailed dysmorphic features) showed that subjects with 22q11.2 deletions (n=23) had significantly more features than those with no deletion (median: 7 vs. 4; range: 4–10 vs. 0–10; z=4.87, P<0.0001). Results were similar analyzing data from all 103 subjects.

3.1. Predicting 22q11.2 deletions

Table 2 lists the performance characteristics for each clinical feature; DA values ranged from 50.6% to 76.1%. Global dysmorphic facial pattern characteristic of 22q11.2DS yielded the highest sensitivity (100%), NPV (100%) and DA (76.1%), but modest specificity (52.2%) and PPV (47.6%). In contrast, history of hypocalcaemia yielded the highest specificity (95.7%) and PPV (72.7%), but showed poor sensitivity (25.8%) and modest DA (60.7%) and NPV (74.1%). No single item yielded a DA higher than 80%.

Using backwards stepwise selection in multiple regression, five variables remained in the final model: age <30 years, global dysmorphic facies, voice abnormalities, hypocalcaemia and history of learning difficulties. To achieve DA>80%, these five clinical features were combined. Table 3 shows the performance characteristics of the combinations yielding the

highest DAs at each combination of 2, 3, 4 or 5 clinical features at a time, with the corresponding optimal cut-off number of features. The 4-item combination of global dysmorphic facies, history of learning difficulties, history of hypocalcaemia, and age <30 years, yielded the highest DA value, 85.6% (95%CI: 78.3%–92.2%) at a cut-off of 3 items. Substituting voice abnormalities in place of hypocalcaemia yielded a comparable DA (85.4%) at a cut-off of 3 out of 4 items, with a higher sensitivity (100%) and lower specificity (70.8%). For all analyses presented, similar results were obtained for the subgroup of 86 subjects with TOF (data not shown).

As global dysmorphic facial patterns characteristic of 22q11.2DS might not be readily recognized by clinicians who have had limited exposure to patients with 22q11.2DS, we calculated the performance characteristics with this item excluded. Combining the remaining four features (history of learning difficulties, history of hypocalcaemia, voice abnormalities, age <30 years) yielded a DA value of 82.8% (95% CI: 74.1%–91.4%) at a cut-off of 3 items, with corresponding sensitivity 76.7%, specificity 88.9%, PPV 76.7%, and NPV 88.9%.

4. Discussion

The results showed that just two extracardiac features, such as global dysmorphic facies and history of learning difficulties, were sufficient to act as a good (DA>80%) predictor of 22q11.2DS in adults with TOF and other congenital heart disease referred for genetic testing. The combination of any three of global dysmorphic facies, voice abnormalities, history of learning difficulties, and age <30 years may represent optimal (sensitivity 100%, DA>85%) screening criteria for 22q11.2DS in similar clinical settings. To some extent these differ from the extracardiac congenital anomalies (e.g. athymus) commonly associated with detecting 22q11.2DS in infants [12,15,30]. Although subjects with 22q11.2 deletions had more features on average, the pattern of features is usually more important in syndrome recognition [31,32]. The results would likely apply to patients with conotruncal anomalies and other congenital heart disease where index of suspicion for 22q11.2DS is elevated [12]. The findings are also likely to be generalizable to adolescents, where features such as hypernasality and history of learning difficulties are discernible. Even in adults, making a diagnosis of 22q11.2DS is important to patients, their families, and their clinicians. The genetic diagnosis provides an explanation for their multi-system condition, anticipatory care that can improve prognosis and genetic counselling specific to this autosomal dominant syndrome that usually arises as a spontaneous mutation but is transmitted at a rate of 50% [3,15,30].

The single best predictor of 22q11.2DS was ‘global dysmorphic facial pattern’ including ‘at least some features of 22q11.2DS’ (DA 76.1%, regarded as a fair test). Notably, this feature figured in all predictive combinations and had 100% sensitivity and 100% NPV. The fact that most raters had limited experience with 22q11.2DS suggests that the ability to recognize a facial gestalt of 22q11.2DS can be readily acquired. Other studies indicate that in-person clinical encounters are likely to be more useful in identifying patients than photographs [22,25], and our experience supports this. Optimal training of clinicians would therefore include meeting adults with 22q11.2DS in addition to reviewing pictures of patients [22,31]. Fig. 1 shows photographs of adults with 22q11.2DS.

Individual facial features yielded lower DA values, suggesting that they would be less helpful in predicting the presence of 22q11.2DS than a general impression of '22q11.2DS' facies. Despite a 23-fold greater prevalence of schizophrenia in 22q11.2DS than in the general population [15], psychiatric history did not help to identify patients with a 22q11.2 deletion. This may be due to the high prevalence of depression and anxiety in the general population and difficulty assessing psychiatric history in a brief encounter. Consistent with previous reports [8,12,14,33], rates of right aortic arch and history of cardiac surgery were similar in patients with and without 22q11.2 deletions.

Although good predictive values for 22q11.2 deletions could be achieved without an age criterion, age <30 years was a predictive feature in our analyses. This may be because other features are easier to distinguish in younger adults. Also, older patients with 22q11.2DS may attend clinic less or have reduced longevity [34]. These possibilities would be consistent with the lower (3.8%) prevalence of 22q11.2DS reported in one study of 77 TOF patients with mean age 40 years [22], compared to paediatric TOF samples (8–23%) [12,14,35,36]. Age effects on likelihood of diagnosis of 22q11.2DS in adults could change as more patients benefiting from improved surgical techniques get older [16,20], may vary across centres and would vary with paediatric detection rates of 22q11.2DS.

In addition to detecting 22q11.2 deletions, genetic testing also identified one patient with a previously undetected abnormality Triple X syndrome (47, XXX). This demonstrates the value of karyotyping as part of standard clinical testing protocols for 22q11.2 deletions and provides further support for the value of an increased index of suspicion for syndromic features.

We emphasize that the purpose of our study was to document the performance of various clinical criteria — and their combinations — in predicting 22q11.2DS among patients selected for genetic testing based on an elevated *a priori* probability of 22q11.2DS. This mimics the real-world clinical settings of many cardiologists where selected, but not all, congenital cardiac patients may be referred for genetic testing for 22q11.2 deletions. Our study was not designed to determine the prevalence of 22q11.2DS. Our cardiologists and screeners chose patients for testing based on clinical features consistent with a genetic syndrome; most had several features. Patients selected in this manner would be expected to have a higher *a priori* probability of 22q11.2DS than those not selected for testing. Thus we found 30.1% of 103 patients selected for testing had clinically detectable 22q11.2 deletions. The true rate of 22q11.2 deletions in the overall population of adults at our clinic remains unknown, pending molecular screening on a research basis. However, if we consider the 377 patients with TOF screened, we have already detected 22q11.2 deletions in 6.6% (n=25), nearly twice the rate of a study testing all TOF adults presenting to a U.S. clinic [22]. Applying the predictive features identified in this study to the 406 patients with clinical screening data but no FISH testing, we can predict that three of these patients may have a 22q11.2 deletion. However, this would not significantly change the proportion with 22q11.2DS in the overall population screened, even if they were all in the TOF group (28/377; 7.4%).

Our study has several limitations. More detailed information on history or physical examination could have increased the ability to differentiate individuals with 22q11.2DS. However, our screening instrument was designed to assess features in a brief encounter. Also, our results suggest that detailed features were less helpful in predicting the presence of 22q11.2DS than the presence of several features or global facial features, likely because most are individually prevalent in non-deleted patients (Table 1). The extracardiac features assessed are common in most syndromes and individually are not specific to 22q11.2DS, as illustrated by karyotypic detection of a previously undiagnosed sex chromosome anomaly. It is possible that a minority of patients with no genetic anomaly detected may have atypical 22q11.2 deletions not detectable using clinical FISH probes [37], or other anomalies that in the future could be revealed with new higher resolution techniques [38].

5. Conclusions

At the present time, due to feasibility and economic constraints, patients in many congenital cardiac clinics worldwide are not universally screened for 22q11.2DS using molecular cytogenetic testing. In such clinical settings, cardiologists often select patients for 22q11.2 deletion genetic testing based on features that have been suggested in the literature to be associated with 22q11.2DS. This study is the first to document the performance of various clinical criteria — and their combinations — in predicting 22q11.2DS among patients who have been selected by clinicians for genetic testing based on higher *a priori* probability of 22q11.2DS than those not selected for testing. The results can help guide cardiologists in such practice settings to decide which clinical criteria to use in selecting adults with congenital heart disease for genetic testing referrals. We have demonstrated that the presence of 22q11.2DS in adults with TOF and related conotruncal anomalies could be well predicted by the presence of readily detectable features: 1) global dysmorphic facies; 2) voice abnormalities such as hypernasality; 3) history of learning difficulties; 4) relative youth. Cardiologists and other clinicians caring for similar patient populations should gain experience with recognizing 22q11.2DS and incorporate a routine check for relevant features in their clinical practice. Identifying 22q11.2DS can lead to significant changes in follow-up and genetic counselling that are helpful to the patient, their family, and their clinicians [15,18].

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Fig. 1.
Variable facial features of adults with 22q11.2 deletion syndrome.

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Table 1

Clinical features in 103 adults with congenital heart disease, with (n=31) and without (n=72) 22q11.2 deletion syndrome (22q11.2DS)

	All subjects			Analysis					
	Total number of observations recorded	Subjects with the feature		Subjects with 22q11.2DS who have the feature		Subjects without 22q11.2DS who have the feature		χ^2	*P*-value (*df*=1)
		n	%	*n*	%	*n*	%		
History/demographic features									
Learning/behavioural difficulties in school	100	70	70.0	30	96.8	40	58.0	15.3	**<0.001**
Age <30 years	103	62	60.2	27	87.1	35	48.6	13.4	**<0.001**
Childhood infections	100	54	54.0	23	79.3	31	43.7	10.5	**0.001**
Speech problems	102	47	46.1	22	71.0	25	35.2	11.1	**0.001**
Non-cardiac birth defects	95	43	45.3	13	50.0	30	43.5	0.32	0.569
Behavioural/psychiatric problems	102	42	41.2	13	41.9	29	40.8	0.01	0.918
Hearing problems	103	19	18.4	6	19.4	13	18.1	0.02	0.876
Thyroid abnormalities	101	13	12.9	5	16.1	8	11.4	0.42	0.515
Hypocalcaemia	100	11	11.0	8	25.8	3	4.3	10.1	**0.002**
Physical features									
Global dysmorphic facial pattern	99	63	63.6	30	100.0	33	47.8	24.6	**<0.001**
Eye dysmorphism [a]	89	62	69.7	21	84.0	41	64.1	3.38	0.066
Nose dysmorphism [a]	90	58	64.4	19	76.0	39	60.0	2.02	0.156
Facial shape dysmorphism [a]	89	48	53.9	16	61.5	32	50.8	0.86	0.355
Ear dysmorphism [a]	84	44	52.4	20	76.9	24	41.4	9.09	**0.003**
Mouth dysmorphism [a]	86	25	29.1	11	45.8	14	22.6	4.54	**0.033**
Hand dysmorphism	90	33	36.7	14	53.9	19	29.7	4.65	**0.031**
Voice abnormalities	99	52	52.5	26	86.7	26	37.7	20.1	**<0.001**
Behavioural abnormalities	99	45	45.5	16	53.3	29	42.0	1.08	0.299

[a] Detailed facial dysmorphic features (likely to overlap with Global dysmorphic facial pattern).

P-values <0.05 are shown in bold.

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Table 2

The ability of individual clinical features to distinguish adults with congenital heart disease who have 22q11.2 deletions

						Discriminant ability	
Clinical features	**Number of observations [a]**	**Sensitivity (%)**	**Specificity (%)**	**PPV [b] (%)**	**NPV [b] (%)**	**(%)**	**95% Confidence interval**
Global dysmorphic facial pattern	99	100.0	52.2	47.6	100.0	76.1	(70.2, 82.0)
Voice abnormalities (including hypernasal)	99	86.7	62.3	50.0	91.5	74.5	(66.0, 83.0)
Learning/behavioural difficulties in school	100	96.8	42.0	42.9	96.7	69.4	(62.7, 76.1)
Age <30 years	103	87.1	51.4	43.6	90.2	69.2	(60.9, 77.6)
Speech problems	102	71.0	64.8	46.8	83.6	67.9	(58.0, 77.7)
Childhood infections	100	79.3	56.3	42.6	87.0	67.8	(58.3, 77.3)
Ear dysmorphism	84	76.9	58.6	45.5	85.0	67.8	(57.3, 78.2)
Hand dysmorphism	90	53.9	70.3	42.4	79.0	62.1	(50.8, 73.4)
Mouth dysmorphism	86	45.8	77.4	44.0	78.7	61.6	(50.2, 73.1)
Hypocalcaemia (history)	100	25.8	95.7	72.7	74.1	60.7	(52.5, 68.9)
Eye dysmorphism	89	84.0	36.0	33.9	85.2	60.0	(50.5, 69.4)
Nose dysmorphism	90	76.0	40.0	32.8	81.3	58.0	(47.6, 68.4)
Behavioural abnormalities	99	53.3	58.0	35.6	74.1	55.7	(44.8, 66.5)
Facial shape dysmorphism	89	61.5	49.2	33.3	75.6	55.4	(44.0, 66.8)
Non-cardiac birth defects	95	50.0	56.5	30.2	75.0	53.3	(41.8, 64.7)
Thyroid abnormalities (history)	101	16.1	88.6	38.5	70.5	52.4	(44.8, 59.9)
Hearing problems	103	19.4	81.9	31.6	70.2	50.7	(42.3, 59.0)
Behavioural/psychiatric problems (history)	102	41.9	59.2	31.0	70.0	50.6	(40.0, 61.1)

[a] Where presence/absence of the feature was recorded.

[b] PPV: positive predictive value; NPV: negative predictive value.

Table 3

Combinations of clinical features meeting criteria for a good test (discriminant ability >80%) for detecting patients likely to have 22q11.2 deletion syndrome in 103 adults with congenital heart disease

Criteria [a] (2 to 5 items)	Optimal cut-off number of items	Number of observations [b] total (with, without 22q11.2DS)	Subjects with the feature		Sensitivity at cut-off (%)	Specificity at cut-off (%)	PPV[a] (%)	NPV[a] (%)	Discriminant ability at cut-off	
			With 22q11.2DS	No 22q11.2 deletion					%	95% Confidence interval
Dys, Voice	2 of 2	98 (30, 68)	26	16	86.7	76.5	61.9	92.9	81.6	(73.6, 89.6)
Dys, Lbd	2 of 2	96 (30, 66)	29	21	96.7	68.2	58.0	97.8	82.4	(75.9, 89.0)
Dys, Calcium, Age	2 of 3	97 (30, 67)	28	18	93.3	73.2	60.9	96.1	83.2	(76.2, 90.3)
Dys, Voice, Lbd	3 of 3	95 (30, 65)	25	11	83.3	83.1	69.4	91.5	83.2	(75.0, 91.4)
Dys, Voice, Lbd, Age	3 of 4	95 (30, 65)	30	19	100.0	70.8	61.2	100.0	85.4	(79.8, 91.0)
Dys, Lbd, Calcium, Age	3 of 4	94 (30, 64)	27	12	90.0	81.3	69.2	94.6	85.6	(78.3, 92.9)
Dys, Voice, Lbd, Calcium, Age	3 of 5	93 (30, 63)	30	19	100.0	69.8	61.2	100.0	84.9	(79.2, 90.6)

[a]Dys = global dysmorphic facial pattern characteristic of 22q11.2DS; Voice = voice abnormalities; Lbd = learning/behavioural difficulties history; Age = age <30 years; Calcium = hypocalcaemia history; PPV: positive predictive value; NPV: negative predictive value.

[b]Where presence or absence of the feature was recorded.