Clinical Features and Follow-Up in Patients with 22q11.2 Deletion Syndrome

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Objective To investigate the clinical manifestations at diagnosis and during follow-up in patients with 22q11.2 deletion syndrome to better define the natural history of the disease.

Study design A retrospective and prospective multicenter study was conducted with 228 patients in the context of the Italian Network for Primary Immunodeficiencies. Clinical diagnosis was confirmed by cytogenetic or molecular analysis.

Results The cohort consisted of 112 males and 116 females; median age at diagnosis was 4 months (range 0 to 36 years 10 months). The diagnosis was made before 2 years of age in 71% of patients, predominantly related to the presence of heart anomalies and neonatal hypocalcemia. In patients diagnosed after 2 years of age, clinical features such as speech and language impairment, developmental delay, minor cardiac defects, recurrent infections, and facial features were the main elements leading to diagnosis. During follow-up (available for 172 patients), the frequency of autoimmune manifestations ($P = .015$) and speech disorders ($P = .002$) increased. After a median follow-up of 43 months, the survival probability was 0.92 at 15 years from diagnosis.

Conclusions Our data show a delay in the diagnosis of 22q11.2 deletion syndrome with noncardiac symptoms. This study provides guidelines for pediatricians and specialists for early identification of cases that can be confirmed by genetic testing, which would permit the provision of appropriate clinical management. *(J Pediatr 2014;164:1475-80)*.

Chromosome 22q11.2 deletion syndrome (22q11DS) (Mendelian Inheritance in Man [MIM] No. 611867), also known as velo-cardio-facial syndrome (MIM No. 192430), is one of the most common genetic syndromes with a prevalence of 1:4000 to 1:6000,[1,2] and possibly as high as 1:2000.[3] The syndrome has variously been labeled as DiGeorge syndrome (MIM No. 188400), velo-cardio-facial syndrome, cono-truncal-anomaly-face syndrome, Sedlačková syndrome, and, less frequently, Cayler cardiofacial syndrome.[4-8]

Microdeletions of the long arm of chromosome 22 at the q11.2 band are detected by fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, or array-based comparative genomic hybridization.

As is true for all microdeletion syndromes, inheritance is autosomal dominant, but most cases have a de novo 22 deletion.[9-11] The phenotypic spectrum is widely variable, with >190 features reported, including congenital heart disease, velo-

22q11DS	22q11.2 deletion syndrome
AIEOP	Italian Association of Pediatric Haematology and Oncology
MIM	Mendelian Inheritance in Man

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pharyngeal insufficiency and cleft palate, immune disorders, feeding difficulties, and hypocalcemia secondary to hypoparathyroidism.[3,12] The most common cardiac defects are conotruncal anomalies, including tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch.[13,14]

Despite the phenotypic variability, children with 22q11DS share a combination of features and have characteristic mild dysmorphic features, minor physical anomalies, or typical facial appearance (hypertelorism, hooded eyelids, tubular nose, broad nose tip, small mouth, and mild ear abnormalities). The main presenting features vary depending on the patient's age.[15,16]

The broad phenotypic spectrum of this syndrome requires multidisciplinary management of these patients.[17] However, there is limited information on the natural history of the disease and long-term outcome due to the lack of follow-up studies. Furthermore, clinical problems change over time and require different specialists, who might not always understand the complexity of the disorder. Here, we describe the results of an investigation of the presenting phenotype at diagnosis and follow-up of patients over time to better define the natural history of this 22q11DS.

Methods

In May 2005, Italian Network for Primary Immunodeficiencies and the Working Group of the Italian Association of Pediatric Haematology and Oncology (AIEOP) issued guidelines for management of patients with 22q11DS and invited through a questionnaire to register clinical data of patients in a secure database, compliant to International Conference on Harmonisation for Good Clinical Practice guidelines and European regulations. The AIEOP database registry is approved by the Ethical Committee of the reference center "Ospedale S. Orsola-Malpighi." From 2006 to 2012, 16 Italian centers from 10 of the 20 Italian regions have collected clinical retrospective end prospective data on 228 cases of 22q11DS and registered them in the database.

Clinical diagnosis was confirmed by fluorescence in situ hybridization 22 or molecular methods (multiplex ligation-dependent probe amplification 22 or comparative genomic hybridization microarray for 22q11.2 microdeletion) in all cases who presented with at least 2 of the following clinical features: congenital heart disease, palatal anomalies, neonatal hypocalcemia, recurrent infections/immunodeficiency and/or autoimmune disease, and characteristic facial features. Unavailability or lack of clinical features occurred for some specific variables depending on the sites reporting. Detailed information, consisting of personal data, family history, date of diagnosis, clinical manifestations, and treatment data, were collected in a structured questionnaire filled in at each center at the time of enrollment and on a yearly basis until 2012. All data have been stored in a central database at the AIEOP Operation Office and sent to the North-Eastern Italian Interuniversity Computing Center in Bologna.

Statistical Analyses

Participating centers were required to register all consecutive cases of 22q11DS, using a web-based database implemented at the North-Eastern Italian Interuniversity Computing Center in Bologna. Data were stored in a central database located at the AIEOP Operation Office.[18]

Standard statistical descriptions of variables were used to characterize the data (mean, median, and range). The Fisher exact test was used to compare differences in percentages for categorical variables, whereas the Student *t* test was adopted to compare means for continuous variables. Overall survival probability (±SE) was calculated both from the date of birth and from the date of diagnosis to the date of death due to any cause or of last contact, using the Kaplan-Meier method.[19] All *P* values were 2-sided and calculated among the same cohort of 172 patients. *P* values <.05 were considered statistically significant. Statistical analysis was performed using STATA (StataCorp, College Station, Texas).[20]

Results

Two hundred twenty-eight patients (112 males and 116 females) with a diagnosis of 22q11DS were included in the present study. The median age at diagnosis was 4 months (range 0-36 years 10 months, mean age 24 months). Prenatal diagnosis was made in 3 cases.

In 71% of patients (162/228), the diagnosis was made before 2 years of age: cardiac defects and neonatal hypocalcemia were the most relevant clinical features (**Table I**). The remaining 29% of patients (66/228) were diagnosed after 2 years of age (28% between 2 and 5 years, 36% between 5 and 10 years, 23% between 10 and 15 years, and 13% older than 15 years), and the clinical manifestations raising the suspicion of 22q11DS were speech and language impairment, development delay, and recurrent infections, associated with characteristic facial features (**Table I**). In 177 of 195 families (91%), neither parent was affected. The deletion was inherited from a parent in 18 of 195 families (9%); the mother had the deletion in 13 of 18 cases (72%) and the father in the remaining 5 (28%).

A congenital cardiovascular defect was confirmed in 172 of 219 subjects with 22q11DS (79%). In 103 of 186, cardiac defects led to diagnosis of the syndrome, and in most cases, this was established within the first years of life, except for 13 patients affected by minor cardiac anomalies (**Table I**). The most common major cardiac defect was tetralogy of Fallot in 37 of 172 cases (22%), followed by interrupted aortic arch type B, persistent truncus arteriosus, and aortic arch anomalies. Other cardiac anomalies were found in 109 cases and are described in **Table II** (available at www.jpeds.com).

Neonatal hypocalcemia was reported in 74 of 174 cases (43%), often associated with heart anomalies, although in 54 cases, information about possible neonatal hypocalcemia was not available. Hypocalcemia later in life and hypoparathyroidism were reported in 63 of 178 (35%) and 30 of 159 (19%) cases, respectively.

Table I. Clinical features suggesting the diagnosis of the 22q11.2DS in 127 infants and in 59 children ≥2 years old

	<2 y old		≥2 y old		Total	
	n	%	n	%	N	%
Patients evaluable	127		59		186	
Clinical features						
Cardiac defects	90	71	13	22	103	55
Neonatal hypocalcemia	29	23	8	14	37	20
Infections	12	9	10	17	22	12
Autoimmune manifestations	0	0	4	7	4	2
Otorhinolaryngologic manifestations	4	3	6	10	10	5
Neuropsychological manifestations	5	4	17	29	22	12
Typical features	12	9	19	32	31	17
Not known	35		7		42	

The thymus was evaluated during cardiac surgery in 76 of 127 patients (60%) or by radiological investigation in 47 of 127 patients (37%). Presence of the thymus was reported as normal in 41 of 127 patients (32%), and thymic aplasia or hypoplasia was reported in 35 and 51 of 127 patients (28% and 40%), respectively.

Characteristic facial features associated with 22q11DS were described in all patients evaluated (n = 212), the most frequent being small mouth, tubular nose, and minor ear anomalies (**Table II**).

A total of 109 of 217 cases had otorhinolaryngologic manifestations; the most common was velopharyngeal insufficiency, in 61 of 109 children. Hearing loss and palate abnormalities were both reported in 10% (**Table II**). Nineteen cases had surgical management of the palate defect.

Gastrointestinal manifestations were reported in 90 of 220 patients (41%). Some children had a history of feeding difficulties during infancy reported to be frequently associated with emesis and nasal regurgitation in 41 cases. Gastrointestinal malformations such as anorectal malformations and esophageal atresia were reported in 11 and 2 patients of 218, respectively (**Table II**).

Neuropsychological manifestations were described in 141 of 202 patients; psychomotor and speech/language developmental delay were reported in 48% (96/202) and 53% (81/153) of cases, respectively (**Table II**). These manifestations often led to diagnosis in subjects older than 2 years (**Table I**).

Orthopedic abnormalities were observed in 78 of 217 patients, mainly scoliosis and congenital clubfoot. Structural or functional urogenital abnormalities, such as vesicoureteral reflux, pyelectasis, hydronephrosis, cryptorchidism, and phimosis, were reported in 36 of 183 patients. Eighty-four percent of patients (172/204) received ≥1 treatments at diagnosis (**Table II**).

Infections were often present in our patient cohort, but they were rarely the only symptom leading to diagnosis (**Table I**). One hundred twenty-three of 218 patients with 22q11DS showed recurrent infections, mainly of the respiratory tract, whereas 16 of 216 patients (7%) had a history of sepsis (**Table II**). One child was diagnosed when language impairment occurred after adenotonsillectomy was performed to reduce recurrent otitis.

Thirty-three of 199 subjects (17%) received daily prophylactic broad-spectrum antibiotics due to severe or recurrent infections. Only 6 of 205 patients (3%) who presented with hypogammaglobulinemia and severe infections required intravenous immunoglobulin treatment every 4 weeks.

Of note, 24 of 217 patients (11%) displayed autoimmune manifestations, with autoimmune thrombocytopenia being present in 30% of cases. The median thrombocyte count was 221 000/mm^3 (range 90 000-693 000/mm^3, n = 184). A significant proportion of the patients (24/184) showed mildly decreased platelet values (<150 000 mm^3), probably not associated with an autoimmune pathogenesis. Other relevant manifestations included autoimmune hemolytic anemia and thyroiditis, both reported in 4 cases. One subject presented with a lymphoproliferative syndrome secondary to chronic Epstein-Barr virus infection associated with autoimmune thrombocytopenia, anemia, and hepatitis; 22q11DS was diagnosed 2 years later.

With a median follow-up of 43 months, the survival probability was 0.92 (SE 0.02) at 15 years after diagnosis (**Figure 1**; available at www.jpeds.com). Eleven patients died of cardiovascular complications, 10 within the second year of life and 1 at 4 years of age. Two subjects without cardiac defects at diagnosis died during follow-up. The first died at 16 months of age of severe autoimmune anemia and thrombocytopenia that did not respond to steroid treatment. The second case had a previous diagnosis of lymphoproliferative disorder in the first year of life with subsequent diagnosis of 22q11DS. She died at 10 years of age due to cardiac insufficiency secondary to cardiac hypertrophy during growth hormone treatment.

One hundred seventy-two subjects (range 0-27 years, mean age 29 months, median age 5 months) were evaluated at diagnosis and during follow-up (range 5 months-34 years, mean age 8.5 years, median age 7 years).

An increase in neuropsychological manifestations was reported during follow-up ($P = .0001$). In particular, speech and language delay, observed in 115 of 164 cases (70%), became a significantly more frequent symptom in patients with 22q11DS ($P = .002$). Also, autoimmune manifestations were more frequent at follow-up ($P = .015$), with a specific increase in the frequency of thyroiditis ($P = .018$) and thrombocytopenia ($P = .002$). Conversely, we observed decreased gastrointestinal manifestations ($P = .001$), with a significant improvement of gastroesophageal reflux ($P = .001$). Although the total frequency of infections increased slightly during follow-up, severe infections, such as sepsis, decreased significantly ($P = .003$) (**Table III**).

One patient, who presented with a cardiac defect, severe neonatal hypocalcemia, and a picture of severe combined immunodeficiency with total absence of T cells, underwent thymus transplantation at the age of 7 months. After transplantation, she was treated with immunosuppressive drugs and presented with several complications during follow-up (ie, autoimmune thrombocytopenia, anemia, and hepatitis probably triggered by a human herpesvirus 6 and parvovirus

Table III. Comparison of the clinical manifestation in 172 patients with 22q11.2DS and at diagnosis and follow-up

	Diagnosis		Follow-up		*P*
	n/N	%	n/N	%	significance
Otorhinolaryngologic manifestations	79/172	46	62/172	36	-
Hearing loss	16/150	11	26/159	16	
Neurosensorial deafness	1/148	1	6/160	4	
Other	37/170	22	54/165	33	
Gastrointestinal manifestations	76/172	44	46/172	27	.001
Gastroesophageal reflux	37/160	23	15/164	9	.001
Esophageal atresia	2/169	1	1/162	1	
Chronic constipation	10/158	6	11/164	7	
Others	48/171	28	34/166	18	
Neuropsychological manifestations	110/172	64	143/172	83	.0001
Speech and language delay	59/115	51	115/164	70	.002
Psychomotor developmental delay	47/114	40	87/163	53	
Learning difficulties	75/155	48	99/152	65	
Behavioral abnormalities	4/79	5	14/114	11	
Psychiatric disorders	2/78	3	8/123	7	
Infections	97/172	56	98/172	57	-
Otitis	36/165	22	31/166	19	
Sinusitis	6/168	6	6/167	4	
Bronchopneumonia	33/168	20	14/167	8	
Bronchiolitis	17/168	10	3/167	2	
Bronchitis	25/125	20	23/139	17	
Pharyngotonsillitis	20/124	16	35/138	25	
Meningitis	1/168	1	0	0	
Sepsis	14/168	8	2/167	1	.003
Gastroenteritis	13/167	8	11/167	7	
Other	53/170	31	46/165	28	
Autoimmune manifestations	21/172	12	39/172	23	.015
Thrombocytopenia	6/165	4	12/167	7	.002
Hemolytic anemia	3/165	2	2/167	2	
Thyroiditis	2/166	1	16/166	10	.001
Arthritides	0/167	0	5/167	3	
Hepatitides	1/167	1	1/167	1	
Other	16/170	9	10/166	6	
Urogenital abnormalities	30/146	21	20/147	14	

B19 coinfection). At the last follow-up (at 6 years of age), she still had a T-cell defect.

Eighty-two percent of patients (143/172) had received at least 1 treatment at follow-up.

During follow-up, more patients increased speech therapy and motor rehabilitation, and a few decreased calcium and vitamin D therapy supplementation. Interestingly, a reduction in antibiotic prophylaxis ($P = .006$) was reported (**Table IV**; available at www.jpeds.com).

Discussion

Our results confirm that congenital cardiac defects associated with neonatal hypocalcemia are the most frequent features leading to diagnosis in the first months of life,[12] thus strongly suggesting that newborns with typical cardiac defects associated with facial features should be investigated for 22q11.2 microdeletions.

Conotruncal and aortic arch defects were the most typical cardiac malformations associated with 22q11DS, in agreement with previous reports.[14] Importantly, although cardiac problems improved after surgical treatment in the majority of patients, cardiovascular complications were the main cause of death within the first year after the diagnosis of 22q11DS. In our series, minor cardiac problems, such as isolated atrial and ventricular septal defects, are quite frequent. In 29% of patients without classic presentation, other symptoms, such as developmental delay, learning difficulties, and minor cardiac defects, frequently associated with typical facial features led to diagnosis later in life. Therefore, cases without a well-known phenotype might be missed, and the real prevalence could be underestimated. These facial features, associated with other symptoms, suggested diagnosis in only 17% of patients (**Table I**), although typical features are reported in all cases after the evaluation by a clinical geneticist. Because recognition of common features of the syndrome would help in the clinical diagnostic process, increasing pediatricians' and specialists' knowledge of these features could contribute to an earlier identification of children with 22q11DS.

Inheritance of 22q11DS occurred in 9% of cases, from 13 mothers and 5 fathers, suggesting a preferential maternal transmission, as observed in previous reports.[4,15] Decreased fertility of males with the deletion, preferential transmission of the deletion from females, or different reproductive behavior could account for this phenomenon. Thus, we recommend that all parents be assessed for clinical features and 22q11.2 deletion because affected parents might have a milder phenotype. Interestingly, the presence of 22q11.2 deletion was observed in 2 cousins, although their parents were negative for the deletion (**Figure 2**; available at www.jpeds.com). This could be explained by genetic predisposition to deletions in some families or the presence of germline mosaicism, although independent de novo events in the same family cannot be excluded.[21-23]

Neonatal hypocalcemia caused by hypoparathyroidism is one of the cardinal symptoms of 22q11DS. In our series, it was reported in only 43% of cases but may have been underestimated because blood calcium levels were tested only in symptomatic patients. The frequency of hypocalcemia was reduced during follow-up, as could be expected due to the implementation of calcium therapy. However, mild or transient hypocalcemia may be frequently missed. Three children with recurrent leg and abdominal pain were found to have a mild hypocalcemia that improved on calcium therapy with regression of symptoms. As suggested by the recent guidelines, we therefore recommend systematic screening and monitoring of all affected individuals, if necessary with computed x-ray absorptiometry, starting at the preadolescent/adolescent age[24] to prevent any significant reduction in bone mass.

In our cohort, psychomotor development and speech and language delay are among the most common manifestations of 22q11DS, and specialists in these areas should be made aware of this and consider 22q11DS in their differential diagnoses. Of note, speech and language delay in particular increases during follow-up because it becomes more apparent over time. In addition to developmental delay, phonation

defect and hearing difficulties influence language acquisition in most patients.

It is interesting to note that in our series, 50% of subjects had reported palate anomalies,[4,12] but the frequency is reported as higher in other studies,[25,26] probably because most of the cases in our cohort came from immunohematology centers. The lower frequency could be attributed to the difficulty for a nonspecialist to identify these defects without state-of-the-art diagnostic procedures for submucous cleft palate and occult submucous cleft palate. A complete otorhinolaryngologic and early audiometric evaluation by a specialized team to diagnose these problems is required, to detect and correct palate defects if necessary. Specific speech therapy should be started early. The speech problems and velopharyngeal insufficiency that became apparent with increasing age in the present series assessed by immunologists would probably have been detected earlier by an otorhinolaryngologist.[17]

Although the rate of behavioral and psychiatric disorders in 22q11DS is higher than in the general population,[27] we observed a lower frequency of these disorders than found in other reports[4,12,28,29] because of the young age of the population enrolled. Psychiatrists should be made aware of the fact that psychosis and behavioral alterations can be the symptoms of 22q11DS, and this could be the reason for some patients not responding to conventional psychiatric treatments.

Forty-one percent of our cohort had a history of gastrointestinal problems that decreased over time. Other studies have also reported an improvement with age, but they also reported a higher percentage (75%) of gastrointestinal problems in the first years of life.[12] This discrepancy could be due to incomplete anamnestic data. Although feeding difficulties are frequent in these patients, only a few of them required gastrostomy. We observed a decrease in severe infections during follow-up. Several factors, such as immunologic alterations, atopic manifestations, anatomic defects, cardiac diseases, gastroesophageal reflux, and poor nutrition, could contribute to a higher risk of infections, particularly during the first years of life. Many of these factors improved with increased age. In agreement with previous reports, we found variable alterations in T-cell counts (data not shown), and >30% of patients had an antibody defect, which could contribute to an increased risk of recurrent infections.[30] A high frequency (23%) of autoimmune manifestations was reported during the follow-up in comparison with the other series.[31-38] Hematologists and rheumatologists should be alerted to the fact that thrombocytopenia, anemia, and arthritis were the most frequent manifestations. In these diseases, the use of immunosuppressive therapy, including steroids, might mask typical facial features. Of note, 2 patients developed severe autoimmune diseases and complications of Epstein-Barr virus–induced lymphoproliferative syndrome, respectively. Other authors have observed an increased risk of severe infections and autoimmune and lymphoproliferative complications in a specific immunologic subgroup of infants with 22q11DS.[39] Specific studies are needed to identify immunologic markers predictive of a higher risk for severe infections and autoimmune manifestations in patients with 22q11DS.

This study shows that diagnosis was delayed in children with 22q11DS without characteristic symptoms, suggesting that many patients could still be undiagnosed. An interdisciplinary team of experts is essential to address the high complexity of this condition and for correct management during the long-term follow-up. The diffusion of diagnostic and therapeutic guidelines should be encouraged to increase the knowledge of this disease among pediatricians and specialists and thus reduce the delay in diagnosis and guarantee optimal care. ■

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Appendix

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Table II. Clinical manifestations and therapy in 228 patients with 22q11.2DS evaluated at diagnosis

	n/N	%
Neonatal hypocalcemia	74/174	43
Cardiac defects	172/219	79
TOF	37/172	22
VSD+PA+MAPCAs	10/172	6
Interrupted aortic arch type B	27/172	16
Truncus arteriosus	25/172	15
Aortic arch anomalies	17/172	10
ASD	21/172	12
VSD isolated	16/172	9
Others	109/172	63
Typical features	212/212	100*
Hypertelorism	67/212	32
Tubular nose	103/212	49
High arch palate	43/212	20
Narrow palpebral fissures	72/212	34
Micrognathia	74/212	35
Hooded eyelids	35/212	17
Small mouth	111/212	52
Ear anomalies	99/212	47
Other	86/212	41
Otorhinolaryngologic manifestations	109/217	50
Velopharyngeal insufficiency	61/200	31
Palate (hard/soft), submucosal cleft	22/217	10
Hearing loss	20/195	10
Laryngomalacia	13/213	6
Neurosensorial deafness	2/194	1
Other	49/217	24
Gastrointestinal manifestations	90/220	41
Gastroesophageal reflux	41/207	20
Esophageal atresia	2/218	1
Anorectal malformations	11/218	5
Chronic constipation	10/205	5
Others	60/220	27
Neuropsychological manifestations	141/202	70
Speech and language delay	81/153	53
Psychomotor developmental delay	96/202	48
Learning difficulties	66/152	43
Behavioral abnormalities	7/107	7
Psychiatric disorders	5/100	5
Other	2/194	1
Infections	123/218	56
Otitis	47/211	22
Sinusitis	8/216	4
Bronchopneumonia	39/214	18
Bronchiolitis	20/215	9
Meningitis	1/215	0.5
Sepsis	16/216	7
Gastroenteritis	18/215	8
Other	67/218	31
Autoimmune manifestations	24/217	11
Thrombocytopenia	7/212	3
Hemolytic anemia	4/210	2
Thyroiditis	4/213	2
Arthritides	1/214	0.5
Hepatitides	1/214	0.5
Other	16/217	7
Orthopedic abnormalities	78/217	36
Urogenital abnormalities	63/183	34
Patients treated	172/204	84

ASD, atrial septal defect; *TOF*, Tetralogy of Fallot; *VSD+PA+MAPCAs*, ventricular septal defect/Pulmonary atresia/multiple aortic pulmonary collateral arteries.
*Patients evaluated by a clinical geneticist.

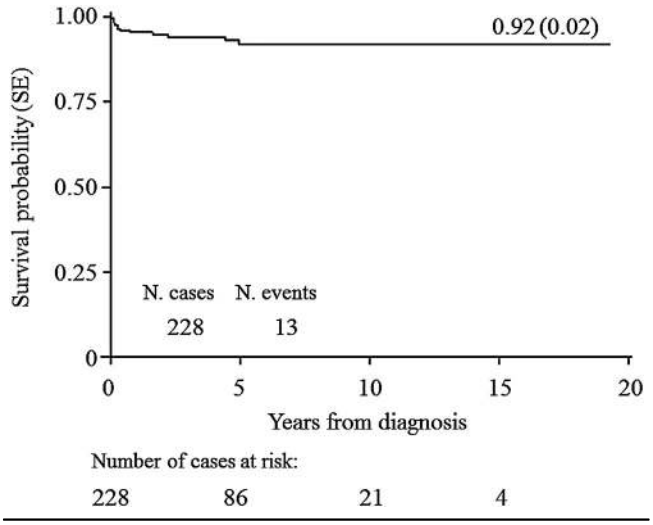

Figure 1. Kaplan-Meier estimates for survival of all patients with 22q11DS.

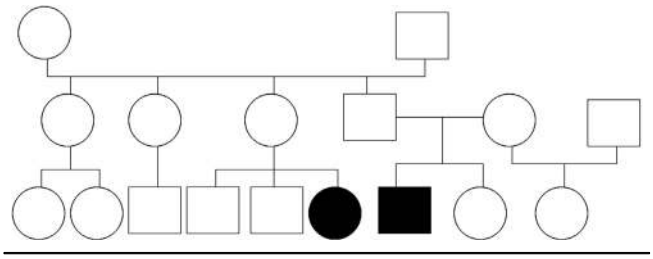

Figure 2. A family pedigree of 2 cousins affected by 22q11DS, with parents having negative testing.

Table IV. Treatments reported in 172 patients with 22q11.2 DS at diagnosis and at follow-up

	Diagnosis		Follow-up	
	n/N	%	n/N	%
Patients treated	150/172	87	141/172	82
Calcium supplementation	52/154	34	39/160	24
Vitamin D supplementation	47/153	31	39/161	24
Antibiotic prophylaxis	35/157	20	17/161	11
Intravenous immunoglobulin	6/162	4	5/159	3
Speech therapy	45/126	36	76/159	48
Motor rehabilitation	41/157	26	52/157	33
Others	63/163	39	55/164	34