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Clinical characterization of 72 patients with del(22)(q11.2q11.2) from different ethnic backgrounds

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Abstract

Background: DiGeorge syndrome (DGS), caused by a deletion del(22)(q11.2q11.2), is the most frequently observed microdeletion syndrome. There is a vast clinical heterogeneity in DGS, and several studies suggested also heterogeneity of clinical signs and phenotypic appearance to be related to ethnic differences. Here, clinical characteristics of 72 patients with molecular diagnosed deletion del(22)(q11.2q11.2) derived from different countries from Europe, America, Africa, and Asia are summarized and compared.

Results: Unless ethnic differences, the expected major clinical signs were present in all cases. Frequent clinical manifestations found in this study were congenital heart disease with 68% (49/72), followed by dysmorphic features found in 61% (44/72); neurodevelopmental disorders were present in 43% (31/72) and thymus hypoplasia/aplasia in 32% (23/72). However, clinical features of the patients appeared/were recognized at different times during their lives. Within the group, under 2 years predominated heart disease, dysmorphic features, and hypocalcemia and/or hypoparathyroidism. In the group older than 2 years, the following combination of clinical findings was most frequent: dysmorphic features, congenital heart disease, intellectual disability, and immunological disorders. In the eight cases detected prenatally, abnormal sonographic findings were the major clinical signs (cardiovascular malformations and renal malformations).

Conclusions: Despite the heterogeneous nature of the sample analyzed, a number of clinical findings could be highlighted to be useful for the clinical delineation of this DGS. Interestingly, diagnostic indicators may vary depending on the age at diagnosis. Finally, apparent differences in DGS patients from different regions seem to be rather due to applied test systems than to real differences in patients from different ethnicities.

Keywords: DiGeorge syndrome (DGS), del(22)(q11.2q11.2), Clinical features, Molecular diagnosis

Introduction

Besides chromosomal aneuploidies, submicroscopic copy number variations are a major cause of intellectual disability and syndromic malformations; the latter are normally referred to as microdeletion and microduplication syndromes (=MDDs) [1, 2]. Among those, DiGeorge syndrome (DGS), caused by a deletion del(22)(q11.2q11.2), is the most frequently observed MDD [2–4]. It is suggested that DGS and other MDDs primarily form due to the presence of low copy repeat sequence (LCR) propagating non-allelic homologous recombination events during meiosis [5, 6]. DGS (OMIM #188,400,

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#192,430, #611,867) has an estimated frequency of 1 in 3000 to 6000 live births [4, 7, 8].

Not all deletions within the DGS-critical region are of identical length; they can vary between 0.7 and 3 Mb. There is a vast clinical heterogeneity in DGS, with a variety of craniofacial dysmorphic features, an involvement of cardiovascular, immune, endocrine, gastrointestinal, and genitourinary systems, as well as brain function impairment (developmental delay, cognitive deficits, and neuropsychiatric diseases) [5]. At the same time, there can be a tremendous inter-individual variability (even within families with identical deletion size); additionally, clinical signs may vary with age. However, there are classic clinical findings such as neurodevelopmental disorders, conotruncal cardiac anomalies, palatal defects, hypernasal speech, cellular immunodeficiency, hypocalcemia, and facial features, which can be useful for clinical diagnosis of this genetic condition [5, 6].

Interestingly, several studies suggested also heterogeneity of clinical signs and phenotypic appearance to be related to ethnic differences [9–12].

In developing countries, there are two main problems for the diagnosis of DGS patients: (i) access to centers where molecular diagnosis of DGS is offered, and (ii) optimization of available resources, which means, that at best the most suitable test should be offered to those patients, which have a high chance to obtain the corresponding diagnoses when taking the test. Thus, here clinical characteristics of patients with molecular diagnosis of DGS with deletion del(22)(q11.2q11.2) and different ethnic origins (like Cuban, Indian, North African, and European) are summarized and compared. The question of survival chances and possible complications of DGS patients was not part of this survey.

Materials and methods

We conducted a descriptive observational multicenter study that finally included 72 patients with molecular diagnosis of DGS with deletion del(22)(q11.2q11.2) and associated clinical features. The distribution of patients by the laboratory was as follows:

- 22 cases from Cuba
- 12 cases from South Asia, i.e., India (one of them without clinical information)
- 24 cases from Morocco
- 15 cases from Europe (Germany and Russia).

A questionnaire was prepared to ask the participating laboratories for the clinical features of their DGS patients, previously diagnosed by molecular methods. The molecular methods used were fluorescence in situ hybridization (FISH) (62 cases), using commercially available probes from Vysis (LSI TUPLE1 and/or LSI NP-25; Abbott Molecular, Il, USA), or molecular karyotyping (11 cases) by SNP array analysis (Affymetrix CytoScan HD, Nimblegene, USA).

In one case, two genetic conditions coincided: in addition to DGS a Kaufman Syndrome (oculocerebrofacial) syndrome (OMIM #244,450) was diagnosed, which is caused by a *UBE3B* gene mutation in chromosome 12q24. This case has several features of DGS as multiple ventricular septal defects, spinal dysraphism, hemivertebra, and learning disability.

Results

The clinical characteristics of 72 patients with DGS with deletion del(22)(q11.2q11.2) from 4 different geographical regions were analyzed (Table 1). Unless the ethnic differences, the expected major clinical signs were present in all cases. As most frequent clinical manifestations found in this study, congenital heart disease (CHD) was most prevalent with 68% (49/72), followed by dysmorphic features found in 61% (44/72) of the patients; neurodevelopmental disorders (learning disability/mental disability and developmental delay) were present in 43% (31/72) and thymus hypoplasia/ aplasia in 32% (23/72). The studied population was stratified into different age groups (Table 2): the group under 2 years of age predominated with 62.5% (45 cases) of the patients. In this group, heart disease was found in 67% of the cases, including five prenatal and 25 postnatal. In the group older than 2 years (27 cases), mental disabilities were more frequent with 93% (25/27). As for the diagnosis of facial dysmorphic features, there were no differences in these two age groups: 14 cases in children older than 2 years and 17 cases in children younger than 2 years.

In 8 of the 72 cases in which the diagnosis was prenatal, the main reason for molecular studies was abnormal findings detected in the fetal ultrasound. In four of these cases, it was known that one parent was a carrier of deletion del(22)(q11.2q11.2) (Table 3).

For clinical findings, congenital heart defects were mainly ventricular septal defect (VSD) isolated or associated with other cardiopathies, and tetralogy of Fallot (Table 4).

In the phenotypic analysis of the postnatal patients (64 cases), there were recurrent combinations of phenotypic features (Table 5). The largest group with the same combination of clinical findings was dysmorphic features + CHD + intellectual disability + immunological disorders with 19 patients. The second group of matches in phenotypic findings included those with dysmorphic features + CHD (11 cases)—further combinations are given in Table 5.

Table 1 Clinical findings observed in patients with DGS with deletion del(22)(q11.2q11.2) in the different countries

	Cuba	India	Morocco	Europe	Overall
Number of patients	22	11	24	15	72
Ethnic group	15 Caucasian 7 multiracial	11 Gujaratis	24 North African	15 Caucasian	72
Clinical findings					
Dysmorphic features	14 (63%)	3 (28%)	19 (79%)	8n (53%)	44 (61%)
Multiple congenital anomalies		1(9%)		3 (20%)	4 (6%)
Learning disability/ mental retardation/ developmental delay	10 (45%)	3 (27%)	12 (50%)	6 (40%)	31 (43%)
Cardiovascular (conotruncal/other)	14 (64%)	7 (64%)	20 (83%) *	8 (53%)	49 (68%)
Hypernasal speech (crying) and/or nasal regurgitation	4 (18%)			1 (6%)	5 (7%)
T cells low and/or impaired function. Timus hypoplasia/ aplasia	13 (59%)	2 (18%)	8 (33%)		23 (32%)
Hypocalcemia and/or hypoparathyroidism	2 (9%)	3 (28%)	12 (50%)	1 (6%)	18 (25%)
Gastroesophageal reflux	2 (9%)			1 (6%)	3 (4%)
Structural urinary tract anomaly	1 (4%)		2 (8%)	1 (6%)	4 (6%)
Recurrent seizures	2 (9%)	1 (9%)	6 (25%)	3 (20%)	11 (15%)
Failure to thrive	2 (9%)	2 (18%)			4 (6%)
Childhood disorders (e.g., attention deficit, autism spectrum disorders)				1 (6%)	1 (1%)
Other rare features	Choledochal cysts	Deformed thumb, spinal dysraphism hemivertebra sandal gap between 1st and 2nd toe	Flat foot, bilateral valgus, dental caries, extrophy of left eye with strong myopia and astigmatism	Short stature	

*A patient presented tetralogy of Fallot and interventricular communication

Table 2 Age of patients studied here with molecular and clinical diagnosis

Age (years)	Number of patients	%
Prenatal	8	10
≤ 1	27	39
1–2	10	14
3–12	15	21
13–21	6	9
≥ 21	6	7
Overall	72	100

Hypocalcemia and/or hypoparathyroidism were combined with different phenotypic signs being relatively frequent (18 cases). Their detection is reported more frequently in children under 2 years of age (13 cases).

Besides, there were eight postnatal DGS patients who could not be included in these combinations.

- 1 patient with complex CHD and failure to thrive,
- 3 patients with conotruncal heart disease as the only feature,
- 1 patient with heart disease and hypocalcemia,
- 1 patient with primary hypoparathyroidism,
- 1 patient with CHD associated with velopharyngeal insufficiency, gastroesophageal reflux, structural urinary tract anomaly, recurrent seizures, and short stature, and
- 1 patient with recurrent seizures and learning disorders.

As visible in Fig. 1, there are nonetheless country-/region-specific differences in DGS phenotypes: dysmorphic features are diagnosed on average in 60% of the cases while those are reported in < 30% of Indian and almost 80% of Marocain DGS cases. Learning deficits are seen on average in slightly > 40% of the cases, in India these are reported for < 30% of the cases. Cardiovascular defects are the major finding in all here studies DGS cases (almost 70%), but in Morocco these are diagnosed in > 80% of the cases. Low T cells or impaired thymus function is generally reported in ~ 30% of the cases, but for Cuba in almost 60% and for India in only less than 20% of the cases. Hypercalcemia is seen in general in ~ 25% of the cases but in Morocco in 50% of the cases.

Table 3 Findings in and indication for prenatally diagnosed patients

Country of origin	Indication for prenatal study	Sonographic findings	Other data of interest
Cuba	Mother carrier of del(22)	Choledochal cysts and bilateral renal pyelectasis	Mother with dysmorphic features, without heart disease
Cuba	Mother carrier of del(22)	Right aortic arch and thymic hypoplasia	Mother with dysmorphic features and learning disability
India	Mother carrier of del(22)	Cardiac anomaly with thymic aplasia	Mother with 22q11.2DS phenotype
Germany	Father carrier of del(22)	Not reported	Father with mental disorders and DGS phenotype
India	Malformation detected by ultrasound	Multiple congenital anomalies. Cardiovascular malformation	
Germany	Malformation detected by ultrasound	VSD, pulmonary valve stenosis, right aortic arch, riding aorta	
Germany	Malformation detected by ultrasound	VSD + interrupted aortic arch	
Germany	Malformation detected by ultrasound	Renal agenesis	

VSD ventricular septal defect

Table 4 Heart defects observed in patients with 22q11 deletion; abbreviations: CHD—congenital heart disease, VSD—ventricular septum defect

CHD	Cuba	India	Morocco	Europe	Total
VSD isolated or associated other malformations *	8	3	6	5	22
Tetralogy of Fallot	2		7		9
Interrupted aortic arch type B	1	1			2
Open septum pulmonary atresia			4		4
Transposition of large vessels	1				1
Bicuspid aortic valve	1				1
Truncus arteriosus			3	2	5
Pentalogy of Fallot	1				1
Others		3		1	4
Total (%)	14	7	19 **	1	49

*Ventricular septal defect was found associated to several other malformations as: levocardia, small auricular septal defect, pulmonary arterial hypertension, pulmonic stenosis, double aortic arch, communication inter auricular, vascular ring, interrupted aortic arch, pulmonary valve stenosis, pulmonary atresia

**A patient presented tetralogy of Fallot and interventricular communication

These results are compared with those obtained in the study by Poirsier et al. [13], who analyzed more than 700 cases from different laboratories in France.

Discussion

Differences in clinical features found among countries

The differences in the clinical features found in the patients in the different regions analyzed are due more to the mode and method used for the clinical evaluation than to the patients themselves. For example:

- *The medical profile of the institution where the clinical analysis of patients is performed* In Cuba, the pediatric referral hospital to which these children are referred is attached to a pediatric heart disease center; this may be the reason why in Cuba cases with deletion in 22q11.2 are showing higher rates of heart disease than in other studies. By contrast, in Russia, the selected patients come from a research center for mental illnesses, and cardiopathies are almost nonexistent, very mild and maybe not tested that intensely, but neurodevelopmental disorders are abundant. In one of the referral hospitals in Morocco, there is an infectious disease service. These diseases could cause fever and seizures. When apyretic seizures are detected, hypocalcemia/hypoparathyroidism studies are performed, if positive, then a direct referral is made to look for the deletion in 22q11.2.
- *The medical profile of the referring physician to the laboratory* The recording of clinical features of a disease is different if we compare pediatricians, cardiologists, general clinicians, etc., with the subject matter expertise of a specialist in medical genetics. For example, in one of the laboratories in Morocco, all children from different parts of the country with heart disease (mainly CHD) are referred by non-geneticist physicians directly for molecular studies, and hence the high incidence of heart disease was detected. At the same time, there will also be many patients with cardiovascular malformations without the DGS-typical deletion tested. In India, there were no medical geneticists to make a clinical delineation of dysmorphic features and such prevailing clinical findings were only detected by ultrasound.
- *A correct algorithm for the study of these patients*, designed by geneticists, seems to be preferable in DGS diagnostics. Hereby, priority is given to the clini-

Table 5 Different combinations of clinical features that contributed to the disease molecular diagnosis. The eight prenatal cases were excluded here

	Cuba	India	Morocco	Europe	Total
Patients analyzed	20	9	24	11	64
Clinical findings					
Dysmorphic features + CHD	6	1	3	1	11
Dysmorphic features + Thymus hypoplasia/ aplasia	2				2
Dysmorphic features + CHD + mental disability + immune disorders	6	2	10	1	19
Dysmorphic features + CHD + thymus hypoplasia/ aplasia	2	1	2		5
Dysmorphic features + immune disorders + mental disability	1		4	5	10
CHD + thymus / aplasia + immune disorders	3	3	3		9
Total number of cases sharing all of the above characteristics	20	7	22	7	56 (87.5%)
Hypocalcemia and/or hypoparathyroidism in combination with different clinical features	2	3	12	1	18

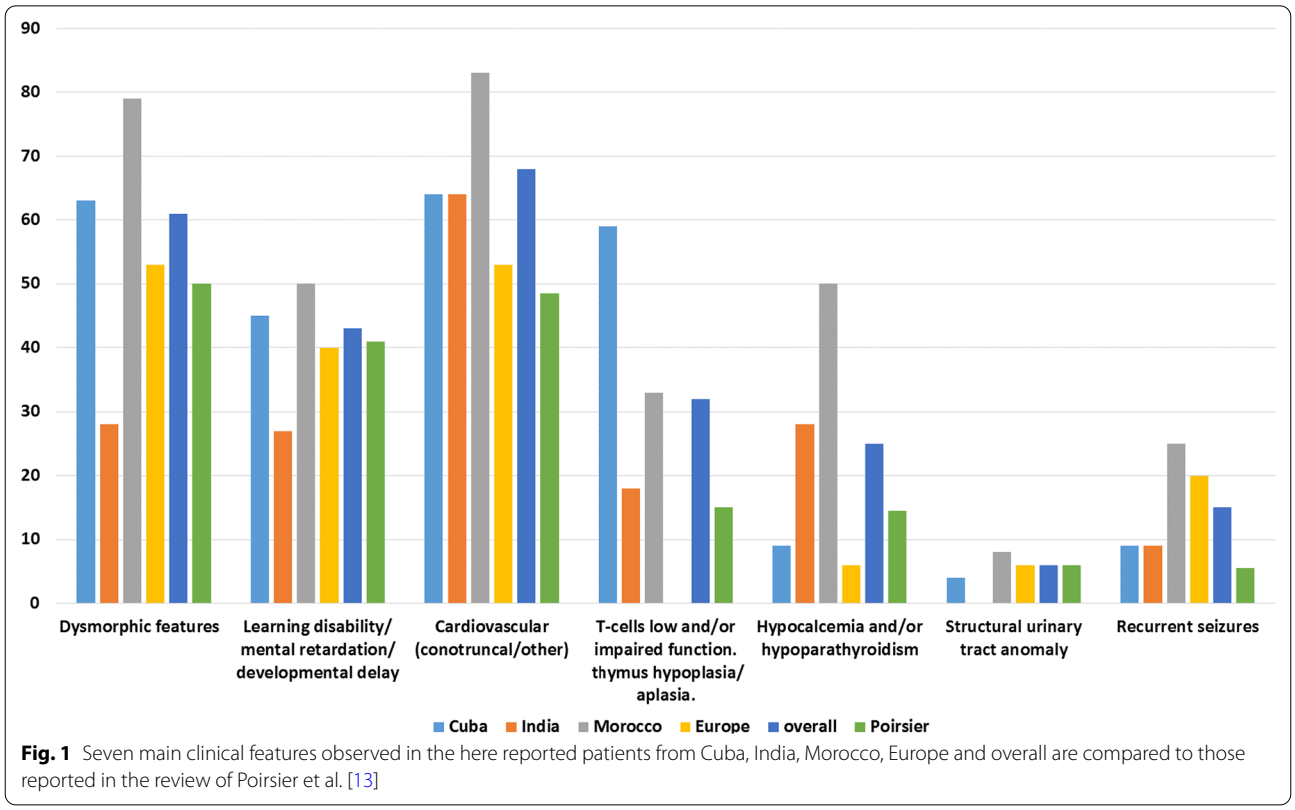

Fig. 1 Seven main clinical features observed in the here reported patients from Cuba, India, Morocco, Europe and overall are compared to those reported in the review of Poirsier et al. [13]

cal evaluation of the patient (seizures, suspected heart disease, facial dysmorphisms, neonatal sepsis) and complementary examinations (echocardiogram, thymus ultrasound, study of calcium levels, immunological studies) before a molecular test is performed. For example, in Cuba (where ecographic studies are prioritized because they are cheaper and more accessible to the population) as a way to alleviate the shortage of reagents for molecular studies of the deletion.

However, the great phenotypic heterogeneity present in the DGS syndrome makes a correct clinical delimitation difficult, which, together with the ethnic characteristics of each population, could potentially make the

recognition of dysmorphic traits in affected individuals more problematic, as well [9–13].

Craniofacial dysmorphic

In this study, a group of patients from different ethnic origins and geographic regions was gathered, identifying facial features of individuals with deletion del(22)(q11.2q11.2) in 68% of the patients despite the fact that several of them were at infant or prenatal stage. In order to make an early DGS syndrome identification, the clinical geneticist can rely on three fundamental pillars: endophenotype, facial findings, and functional disorders. The endophenotype is given by congenital defects present at birth including conotruncal cardiovascular, thymus hypoplasia, and palate defects. The facial findings most often can be associated besides with DGS, also with conotruncal anomaly face syndrome = Sedlackova syndrome (OMIM #217,095), autosomal dominant Opitz G/BBB syndrome (OMIM #300,000), and/or Cayler cardiofacial syndrome (OMIM %125,520) with a variety of signs. Considering facial features are variable and may not be present especially in persons of African/American heritage, still most important are ear dysplasia, nasal anomalies, asymmetric crying faces, micrognathia, a prominent nasal bridge, bulbous nose, and hypoplastic alae nasi. Functional disorders are associated with digestive system dysfunction (including palate), intellectual disability, behavior or mental disorders and also endocrine dysfunction of parathyroid and cellular CD3/CD4 immunologic presents in some cases even without thymes hypoplasia [5]. In comparison—taken from the literature—in Brazil, at least 72.06% of the individuals present concomitantly two or more recurrent clinical manifestations indicative of deletion del(22)(q11.2q112.); most frequently seen in that study are velopharyngeal alterations and CHD [14].

Cardiovascular malformations

Another predominant clinical feature of DGS is cardiovascular malformations (conotruncal or other) present in 68% of patients. Goldmuntz [14] states that cardiopathies are present in DGS individuals in a range between 60 and 80%. In recent studies the prevalence of heart disease has varied according to the age of diagnosis of this pathology; for example, Cancrini et al. [15] found a prevalence of CHD of 71%, if diagnosed before 2 years of age and only 22% after this age.

On the other hand, Poirsier et al. [13] found different prevalences of heart disease according to age a diagnosis was done first: they vary between 84% in fetal stage, 79% in neonates, 63% in children between 1 month and 2 years and 30% in children between 3 and 6 years.

The different diagnoses for CHD fall, according to Campbell et al. [16], who studied 1400 DGS patients, into three major groups: VSD (23%), tetralogy of Fallot (18%) and aortic arch anomalies (14%). This is in concordance with the present study for VSD (42%) and tetralogy of Fallot (22%), while aortic arch anomalies were almost absent here. Similar results were obtained by Poirsier et al. [13] doing a large multicenter study in France where VSD predominated in 30.7% and tetralogy of Fallot was found in only 17% of these patients. Nevertheless, Rozas et al. [17] found tetralogy of Fallot (20%) to be more frequent than VSD (14.7%). Goldmuntz [14] reviewed all these findings as (i) the prevalence of each subtype of heart disease is possibly associated with the age of the patients at the time of molecular diagnosis.

Combination of the most frequent clinical characteristics by age

In this study, in children under 2 years of age, cardiopathies were present in 67% of the individuals (30/45) together with facial dysmorphies, both being most useful from the clinical point of view to suspect this syndrome in children under 2 years of age. These two features could be complemented by determining possible hypocalcemia and/or hypoparathyroidism, as suggested by our findings. Accordingly, we suggest that the triad cardiopathy + dysmorphic features + hypocalcemia and/or hypoparathyroidism may be of great importance for the early diagnosis of DGS syndrome.

In patients older than 2 years, the most frequent clinical features were dysmorphic features + CHD + mental impairment + immunological disorders, which may be used for pointing the way toward DGS diagnoses. In general, young children with del(22)(q11.2q11.2) have delay in reaching motor milestones and emergence of language with a prevalence of nonverbal language at 2–3 years. Mental disabilities are frequently diagnosed after this age and include attention deficit, anxiety, perseveration, and difficulties in social interactions. Autism/autism spectrum disorders are reported in approximately 20% of DGS individuals. Behavioral abnormalities may set up before the age of 10 years, they are rarely observed, but may provide an opportunity for early intervention [18]. Silva et al. [12] point out that psycho-pedagogical follow-up is a key aspect for recognition of individual school performance and psychosocial activities. Up to 40% of individuals with intellectual disability have a psychiatric disorder and these alterations manifest more frequently in adolescence, which make early diagnosis impossible if

this may be the most evident characteristic of DGS in an individual.

In addition, a group of patients older than 2 years was identified, in which cardiovascular malformations are absent and distinctive features there were: dysmorphic features + immune disorders + mental dysfunction (10 cases). Goldmuntz [14] suggests that this may depend on the consistency with which a cardiac diagnosis is sought, and its classification is made. Especially in CHDs diagnosed after the first years of life, due to the absence of earlier relevant clinical features, those may not be evaluated that rigorously using advanced imaging techniques to detect clinically less significant cardiac features, such as aortic arch anomalies. Overall, the true CHD prevalence of DGS is difficult.

For prenatal diagnosis such an important identifier as 'dysmorphic features' cannot be evaluated; still fetal ultrasound findings are very useful for the diagnosis of this pathology. In this small series studied prenatally here, in seven fetuses anatomical malformations were found, predominantly as CHDs in 57% (4/7) and renal malformations in 29% (2/7). On the other hand, in one fetus, no malformation was detected by prenatal ultrasound, but it was known that the father was a carrier of the DGS deletion. In multicenter prenatal studies, the prevalence of the DGS was 1 in 100, when fetal anatomical anomalies were found, with a prevalence of heart disease. On the contrary, in those fetuses in which no anomalies were detected by prenatal ultrasound, DGS prevalence was 1 in approximately 1000 pregnancies [19, 20]. When it is known that one of the parents is a del(22)(q11.2q11.2) carrier, the risk for the offspring is 50%, and prenatal diagnosis should be recommended. For example, in this study, all four parents carrying the deletion had affected children.

However, it is interesting to note the point of view of Atli et al. [21] who consider phenotypic differences in individuals as a part of the syndrome and propose that also atypical anomalies should be taken into account to test for DGS, like developmental delay and intellectual disability along with CHD. Besides, deviating phenotypes in a family when identical deletions are present different causes should be considered as parental imprinting, unbalanced regulatory effects, polymorphisms not masked by recessive mutations or hemizygosity, environmental factors, and/ or stochastic events during morphogenesis.

In some studies also differences in DGS-critical region deletion size and affected regions are discussed [22, 23]. However, in the present study at least, for those patients studied by microarray, there was no evidence for variant deletions in 22q11.2. Still eight cases of this study with a phenotype that does not match the most frequent clinical feature groups can either be due to an ascertainment bias, that the clinical information provided may not be complete, or variant deletion sizes may have appeared (as those cases where only studied by FISH).

As in developed countries, testing methodologies are constantly improving, there is a greater likelihood of accurate diagnosis. Especially, it is increasingly common to replace descriptive, clinical diagnoses by direct molecular diagnosis [24]. However, in developing countries, the traditional paradigm of genetic evaluation is maintained (the patient or tutor interrogation, the preparation of the genealogical tree, the clinical and dysmorphological examination, and the evaluation with complementary tests such as ultrasound and other laboratory tests) before performing costly genetic tests. Thus, genotype–phenotype correlations are more important for developing countries nowadays, than for industrial ones, even though saving costs in the health system is a topic in all societies.

Conclusions

Despite the heterogeneous nature of the sample analyzed, with respect to geographic distribution, a number of clinical findings could be highlighted to be useful for the clinical delineation of this DGS. Interestingly, diagnostic indicators may vary depending on the age at diagnosis. This study suggests that in early ages (less than 2 years) the combination of heart disease and dysmorphic features, together with hypocalcemia and/or hypoparathyroidism, offers the best option for an accurate diagnosis of the disease. In older individuals, the most frequently found combination was dysmorphic features + CHD + mental disability + immune disorders. In the case of diagnosed prenatally, the usefulness of fetal ultrasound is relevant, with findings of cardiovascular and/or renal malformations predominating.

Abbreviations

CHD: Congenital heart disease; DGS: DiGeorge syndrome; FISH: Fluorescence in situ hybridization (FISH); LCR: Low copy repeat sequence; MDDs: Microdeletion and microduplication syndromes; OMIM: Online Mendelian inheritance in man; VSD: Ventricular septal defect.

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Author contributions

LAMR and TL contributed to conception and design of the study; AAB, AG, AN, DH, FS, II, ML, NLO, OXK, SGV, and TL contributed to clinical analysis of the patients; AAB, DH, FS, II, LAMR, OXK, and SGV performed molecular diagnosis; AAB, AG, AN, DH, FS, II, LAMR, ML, NLO, OXK, SGV, and TL analyzed and interpreted the data; LAMR, NLO, and TL drafted the manuscript. All authors

agreed on the final version of the paper. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
In all laboratories, each patient was assigned a code in the database and anonymity was maintained during data processing. The data were acquired and used completely anonymized during routine diagnostics; thus, ethics approval is waived.

Consent for publication
As participants were completely anonymized, consent for publication is not necessary/applicable.

Competing interests
The authors declare that they have no competing interests.

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