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22q11.2 deletion syndrome in diverse populations

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22q11.2 deletion syndrome (22q11.2 DS) is the most common microdeletion syndrome and is underdiagnosed in diverse populations. This syndrome has a variable phenotype and affects multiple systems, making early recognition imperative. In this study, individuals from diverse populations with 22q11.2 DS were evaluated clinically and by facial analysis technology. Clinical information from 106 individuals and images from 101 were collected from individuals with 22q11.2 DS from 11 countries; average age was 11.7 and 47% were male. Individuals were grouped into categories of African descent (African), Asian, and Latin American. We found that the phenotype of 22q11.2 DS varied across population groups. Only two findings, congenital heart disease and learning problems, were found in greater than 50% of participants. When comparing the clinical features of 22q11.2 DS in each population, the proportion of individuals within each clinical category was statistically different except for learning problems and ear anomalies ($P < 0.05$). However, when Africans were removed from analysis, six additional clinical features were found to be independent of ethnicity ($P \geq 0.05$). Using facial analysis technology, we compared 156 Caucasians, Africans, Asians, and Latin American individuals with 22q11.2 DS with 156 age and gender matched controls and found that sensitivity and specificity were greater than 96% for all populations. In summary, we present the varied findings from global populations with 22q11.2 DS and demonstrate how facial analysis technology can assist clinicians in making accurate 22q11.2 DS diagnoses. This work will assist in earlier detection and in increasing recognition of 22q11.2 DS throughout the world.

KEYWORDS
22q11.2 Deletion syndrome, DiGeorge syndrome, diverse populations, facial analysis technology, Velocardiofacial Syndrome

1 | INTRODUCTION

22q11.2 deletion syndrome is the most common microdeletion syndrome with an estimated prevalence of 1:3000 to 1:6000 children and 1:1000 unselected fetuses (Botto et al., 2003; Grati et al., 2015; McDonald-McGinn et al., 2015; Wapner et al., 2012). This condition is characterized by congenital heart disease (especially conotruncal defects), immunodeficiency, hypoparathyroidism, palatal, gastrointestinal, skeletal and renal abnormalities, characteristic facial features, developmental and speech delay, and an increased risk for psychiatric illness; early recognition is imperative (McDonald-McGinn, Emanuel, & Zackai, 1993; Oskarsdottir, Persson, Eriksson, & Fasth, 2005). Clinical presentation varies by age and is often due to clinical suspicion based on multiple findings; however, the phenotype is variable and different ethnicities may make the diagnosis more difficult (McDonald-McGinn et al., 2015).

Most studies to date have focused on individuals of European descent and investigators have found the diagnosis more difficult in diverse populations (Liu et al., 2014; McDonald-McGinn et al., 2005; Veerapandiyan et al., 2011). Two groups have found the craniofacial dysmorphisms in African Americans to be different than the standard recognized anomalies found in Caucasians (McDonald-McGinn et al., 2005; Veerapandiyan et al., 2011). In a large Chinese adult population with conotruncal defects, facial features of individuals with 22q11.2 DS were under-recognized and 22q11.2 DS was under-diagnosed (Liu et al., 2014). Liu et al. (2014) found that in every 10 adult patients with conotruncal anomalies, 1 previously unrecognized diagnosis of 22q11.2 DS was present. Another group studying Chinese individuals found that all 43 of their study participants with 22q11.2 DS had typical facial findings consisting of a vertically long face, narrow palpebral fissures, fleshy nose with a broad nasal root, flattened malar region, retrognathia, and overfolded helix; however, this was not a prospective study and it is difficult to determine if these findings would have been made without knowing the molecular diagnosis (Wu et al., 2013). Clinical descriptions of Latin Americans is scarce; one large study of 208 patients described multi-systemic anomalies in a Chilean population but did not include facial features (Repetto et al., 2009).

Here we compare the physical exam findings of individuals from different populations with 22q11.2 DS and we demonstrate how facial analysis technology can assist clinicians in making accurate 22q11.2 DS diagnoses across diverse populations.

2 | METHODS

2.1 | Review of medical literature

Studies that characterize 22q11.2 deletion Syndrome (22q11.2 DS) from diverse populations were found in a Medline search. The search terms used included: 22q11.2 deletion Syndrome, DiGeorge

Syndrome, Velocardiofacial Syndrome, diverse populations, and facial analysis technology. Further studies were ascertained using reference lists of papers pertaining to 22q11.2 DS. After obtaining journal permissions, photos of 22q11.2 DS patients were used to supplement study participants described below (De Decker et al., 2016; Grassi et al., 2014; Liu et al., 2014; Uwineza et al., 2014; Veerapandiyan et al., 2011).

2.2 | Patients

One hundred and six individuals with 22q11.2 DS were evaluated from 11 countries. All participants (Supplementary Table S1) had 22q11.2 DS confirmed by various forms of molecular testing including fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA) or chromosomal microarray. For this study's purpose, patients were grouped by geographic area of origin or ethnicity (African and African American, Asian, Latin American) with the understanding that phenotypes may vary considerably in similar geographic regions and ethnicities. Local clinical geneticists examined patients for a number of clinical features found in 22q11.2 DS including characteristic facial features, congenital heart disease, palatal abnormalities, immune deficiency, skeletal anomalies, renal anomalies, endocrine abnormalities, and learning problems (McDonald-McGinn et al., 1993).

Consent was obtained by local institutional review boards and the Personalized Genomics protocol at the National Institutes of Health (11-HG-0093). Exam findings from the current study and those from the medical literature were compiled in a table for review (Table 1).

2.3 | Facial analysis technology

As previously described (Kruszka et al., 2017), digital facial analysis technology (Cerrolaza et al., 2016; Zhao et al., 2013; Zhao, Okada, et al., 2014; Zhao, Werghi, et al., 2014) was used to evaluate the 156 individuals with 22q11.2 DS from this study. Additionally, we used healthy controls from our previously described database (Zhao, Okada, et al., 2014; Zhao et al., 2013). Cases and controls were matched by ethnicity, age, and gender. Only frontal images were analyzed by this technology.

Using the images of our study participants as input to our algorithms, output consisted of feature extraction, feature selection, and classification. After face detection and landmark positioning, as explained in Zhao, Okada, et al., (2014), a set of 126 facial features, including both geometric and texture biomarkers, were extracted. The geometric biomarkers consisted of a set of distances and angles calculated between the different inner facial landmarks, as represented in Figure 1. As robust markers of monotonic illumination changes, local binary patterns (Ojala, Pietikäinen, & Harwood, 1996) were calculated at each of the 33 inner facial landmarks to quantify texture information (Figure 1). Texture is a quantitative measurement of the spatial arrangement of intensities in a selected region of an image. Every local binary pattern represents a histogram of the contrast information centered at one landmark, which quantifies information such as shadows and lines on the faces. Using a 2-dimensional extension of linear discriminant analysis (Ye, Janardan, & Li, 2004), the texture information was used to create optimal landmark-specific texture features, as presented in Cerrolaza et al. (2016). From the collection of geometric and texture features, the most significant ones were selected using the method proposed previously (Cai, Zhang, & He, 2010). For each feature set, a support vector machine classifier (Cortes & Vapnik, 1995) was trained using a leave-one-out cross-validation strategy (Elisseeff & Pontil, 2003). The optimal number of features was selected as the one that maximized the classification accuracy. As an estimator of the individual discriminant power of each feature selected, the *P*-value of each feature was also estimated using the Student's *t*-test. Significance between methods used to detect 22q11.2 DS was assessed using Fisher's exact test.

3 | RESULTS

Clinical information was collected on 106 individuals and photo images were collected from 101 individuals with 22q11.2 DS from 11 countries; average age was 11.7 years (range newborn to 43 years; SD = 10.1 years) and 47% were male (Supplementary Table S1); 10 of these individuals had been published previously (Liu et al., 2014; Uwineza et al., 2014). Additionally, 26 images from the medical literature were added to make a total of 127 images (Figures 2–4). Figures 2–4 demonstrate facial features in individuals of African ($n = 60$), Asian ($n = 27$), and Latin American ($n = 40$) heritage, respectively. Figure 5 focuses on hand findings and Figure 6 shows lower extremity findings. Table 1 shows exam findings in our study and the medical literature stratified by population. The clinical features of 22q11.2 DS described previously (McDonald-McGinn et al., 1993; Oskarsdottir, Holmberg, Fasth, & Stromland, 2008; Oskarsdottir et al., 2005) are listed in Table 1.

In both this study and the medical literature, clinical findings are varied. Only two findings in the present study, congenital heart disease and learning problems, were found in greater than 60% of participants. In the medical literature, most but not all studies reported a majority of participants with congenital heart disease (Table 1). Using the χ^2 and the null hypothesis that the phenotype of 22q11.2 DS is independent of ethnicity of geographical origin for this study, we found that only two features of this syndrome were independent of the population sampled ($P \geq 0.05$): learning problems and ear anomalies (Table 1). These differences in phenotype are largely due to the interpretation of individuals of African descent. If Africans are taken out of the analysis, eight of the clinical features of 22q11.2 DS for this study are found independent of ethnicity ($P \geq 0.05$; χ^2 test) including learning problems, developmental delay, palatal abnormalities, narrow palpebral fissures, nose anomalies, hooded eyelids, psychiatric illness, and ear anomalies. Compared to our study, the findings in the medical literature (Table 1) are difficult to interpret as different studies concentrate on different aspects of the phenotype of 22q11.2 DS.

Subjective exam facial findings are highlighted here as characteristic features that have been classically noted in individuals of northern European heritage (McDonald-McGinn et al., 2005). Nasal anomalies in the present study were found in 89% of Asian individuals and 80% of

TABLE 1 Summary of exam findings of individuals with 22q11.2 deletion syndrome from diverse backgrounds

	Present study					Repetto et al. (2009)	Grassi et al. (2014)	Matsuoka et al. (1998)	Wu et al. (2013)	Liu et al. (2014)	Veerapandiyan et al. (2011)	McDonald-McGinn et al. (2005)		
	Global	African	Asian	Latin American		Chile	Brazil	Japan	China	Hong Kong	U.S.A. (African American)	U.S.A. (African American)	U.S.A. (Hispanic)	U.S.A. (Caucasian)
Number of participants	106	55	27	24		208	60	180	43	18	50	33	11	204
Age range (years)	Infant-43	1-44	Infant-43	1-39		NB-39	NB-20	NB-35	2-21	18-46	NB-62	NB-52		
Males	50/106 (47%)	26/55 (44%)	12/27 (44%)	12/24 (50%)		101 (49%)	34 (57%)	90 (50%)	22 (51%)	4		52%		
CHD	78/104 (75%)	40/55 (73%)	24/25 (96%)	14/24 (58%)	$P < 0.01$	124 (60%)		157 (87%)	10 (23%)	18	26 (52%)			
Learning problems	67/100 (67%)	31/54 (57%)	18/22 (82%)	18/24 (75%)	$P = 0.08$									
Developmental delay	39/79 (49%)	20/50 (40%)	9/11 (82%)	10/18 (56%)	$P < 0.05$						29 (58%)			
Short stature	21/86 (24%)	9/53 (17%)	7/9 (78%)	5/24 (21%)	$P < 0.001$	87 (42%)				3				
Palatal anomalies	46/95 (48%)	13/53 (25%)	14/18 (78%)	19/24 (79%)	$P < 0.001$	165 (79%)	15 (25%)		43 (100%)	8	19 (38%)			
Nasal anomalies[a]	40/83 (48%)	16/54 (30%)	8/9 (89%)	16/20 (80%)	$P < 0.001$		32 (53%)			2	20 (40%)	5 (15%)	9 (82%)	127 (62%)
Narrow palpebral fissures	33/94 (35%)	5/55 (9%)	11/16 (69%)	17/23 (74%)	$P < 0.001$		30 (50%)				11 (22%)			
Hooded eyelids	39/88 (44%)	10/54 (19%)	9/10 (90%)	20/24 (83%)	$P < 0.001$						6 (12%)	2 (6%)	4 (36%)	52 (26%)
Long face	20/90 (22%)	4/55 (7%)	8/11 (73%)	8/24 (33%)	$P < 0.001$		36 (60%)			2				
microcephaly	9/81 (11%)	3/54 (6%)	5/7 (71%)	1/20 (5%)	$P < 0.001$									
Ear anomalies	53/90 (59%)	28/55 (51%)	8/11 (73%)	17/24 (71%)	$P = 0.15$		29 (48%)				32 (64%)	26 (79%)	10 (91%)	170 (83%)
Skeletal anomalies	27/48 (56%)	2/4 (50%)	6/20 (30%)	19/24 (79%)	NA	65 (31%)		13 (7%)			32 (64%)			
Psychiatric illness	16/100 (16%)	5/54 (9%)	8/22 (36%)	3/24 (13%)	$P < 0.05$			6 (3%)						
Renal anomalies	6/42 (14%)	Not examined	3/18 (17%)	3/24 (13%)	NA	16/126 (11%)		3 (2%)						
Immune deficiency	21/42 (50%)	Not examined	8/18 (44%)	13/24 (54%)	NA			28 (16%)	24 (56%)					
Hypocalcemia/ hypoparathyroidism	14/41 (34%)	Not examined	6/18 (33%)	8/23 (35%)	NA									

[a]Nose anomalies included bulbous nasal tip, prominent nasal root, wide nasal bridge; most frequent anomaly reported.

Repetto et al. (2009); Grassi et al. (2014); Matsuoka et al. (1998); Wu et al. (2013); Liu et al. (2014); Veerapandiyan et al. (2011); McDonald-McGinn et al. (2005).

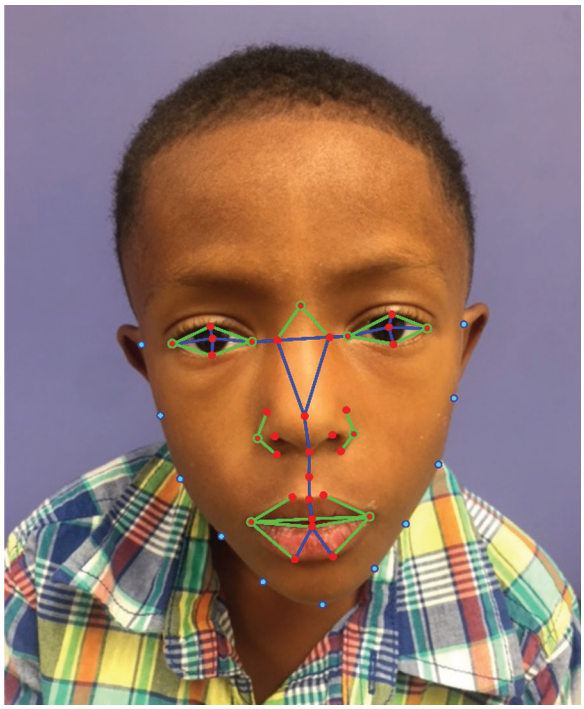

FIGURE 1 Facial landmarks on a 22q11.2 deletion syndrome patient. Inner facial landmarks are represented in red, while external landmarks are represented in blue. Blue lines indicate the calculated distances. Green circles represent the corners of the calculated angles. Texture features are extracted only from the inner facial landmarks.

Latin Americans, but only in 30% of individuals of African descent ($P < 0.001$). In the medical literature, McDonald-McGinn et al. (2005) found that only 15% of African Americans had a characteristic nasal difference and Veerapandiyan et al. (2011) found nasal anomalies in 40% of African Americans; however, other populations range from 53% to 100% (Table 1). Hooded eyelids in the present study were found in 90% of Asians and 83% of Latin Americans, but only 19% of Africans and African Americans. Similarly in the medical literature, hooded eyelids ranged from 36% to 100% except for McDonald-McGinn et al. (2005) group finding of 6% in African Americans and Veerapandiyan et al. (2011) finding of 12% of their African American cohort. Narrow palpebral fissures in our study were reported in only 9% of individuals of African descent, but in 69% of Asians and 74% of Latin Americans; in the medical literature, Veerapandiyan et al. (2011) found 22% of African Americans to have narrow palpebral fissures. Independent of population studied ($P = 0.15$), ear anomalies were common in our cohort and other studies examined in Table 1 with anomalies ranging from 64% to 91% except for the Grassi et al. (2014) study that found only 48% of their Brazilian cohort to have ear findings.

A more objective evaluation using facial analysis technology, Table 2 shows the age and geographic origin of cases and controls studied, consisting of Caucasians, Africans or African Americans, Asians, and Latin Americans. A total of 156 participants with 22q11.2 DS and 156 healthy controls from our previous database (Zhao et al., 2013; Zhao, Okada, et al., 2014) were evaluated (Table 2). Using the previously described method for feature extraction and analysis (Cerrolaza et al., 2016; Kruszka et al., 2017;

FIGURE 2 Frontal and lateral facial profiles of individuals of African descent with 22q11.2 deletion syndrome. Gender, age, and country of origin found in Supplementary Table S1. [a]Individual previously published in Uwineza et al. (2014); [b]Reprinted from De Decker et al. (2016); [c]Veerapandiyan et al. (2011).

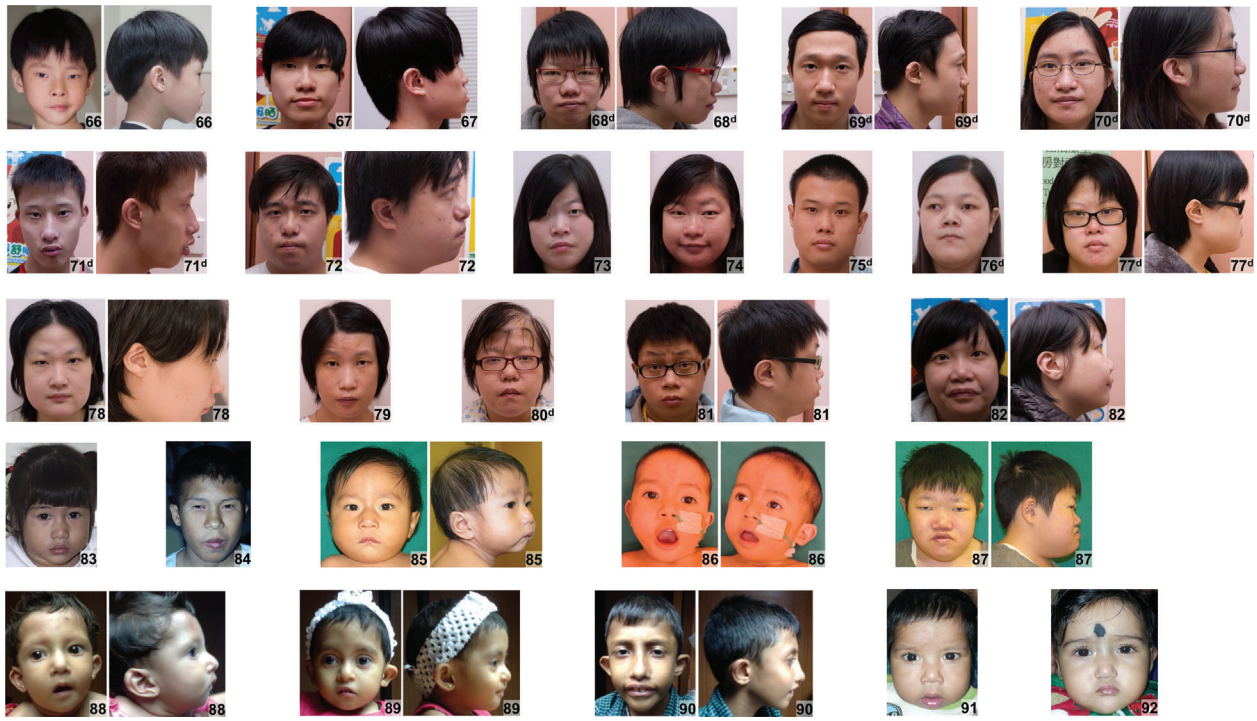

FIGURE 3 Frontal and lateral facial profiles of Asian individuals with 22q11.2 deletion syndrome. Gender, age, and country of origin found in Supplementary Table S1. [d]Individual previously published in Liu et al. (2014).

Zhao, Okada, et al., 2014), the four ethnic groups (Caucasian, African, Asian, and Latin American) only shared two geometric biomarkers that were significantly different from ethnically matched controls: increased distance between medial canthi (telecanthus) and decreased distance between medial and lateral canthi, also known as short palpebral fissures (Supplementary Tables S2–5). The Caucasian group had the least number of significant geometric features at five compared to the African group

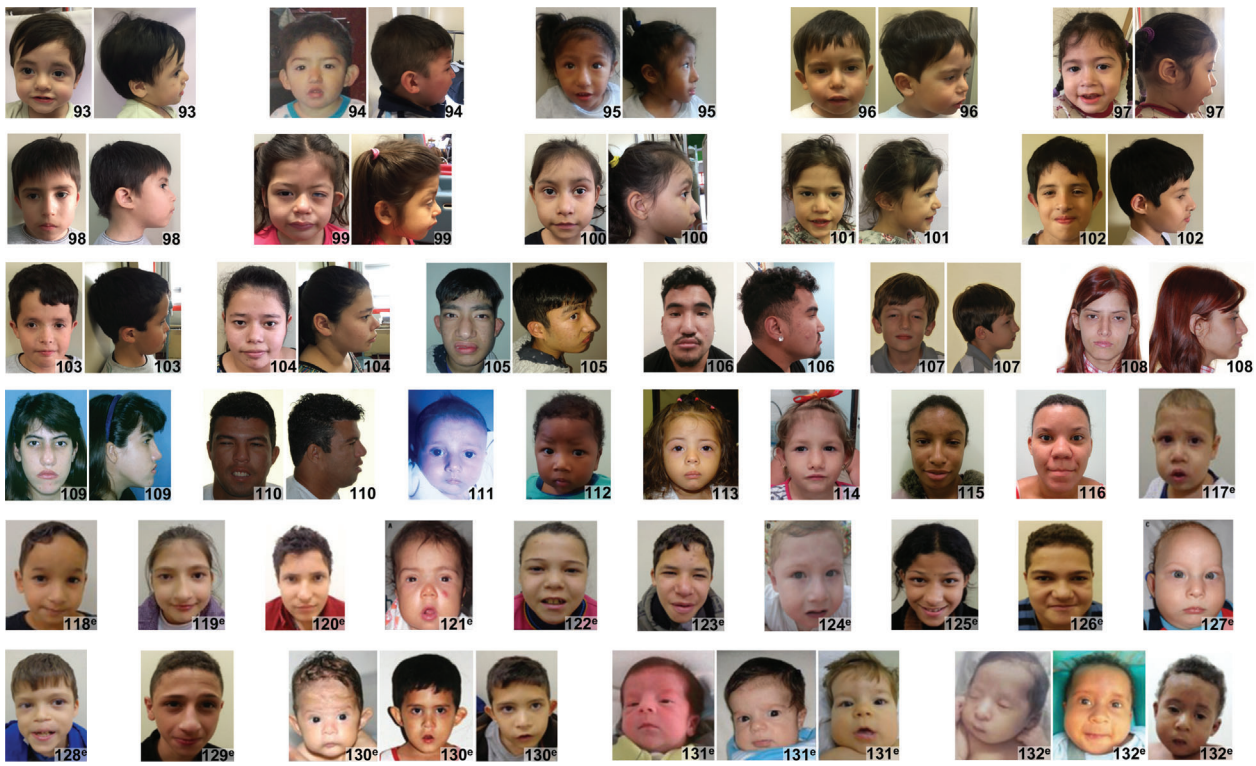

FIGURE 4 Frontal and lateral facial profiles of Latin Americans with 22q11.2 deletion syndrome. Gender, age, and country of origin found in Supplementary Table S1. [e]Reprinted from Grassi et al. (2014).

FIGURE 5 Hand findings. Image numbers correspond with Supplementary Table S1. [d]Individual previously published in Liu et al. (2014).

at seven and the Asian and Latin American groups each at 9 (Supplementary Tables S2 and S5). The African and Asian groups were most similar, sharing six significant geometric features that were different from their, respectively, matched controls including: telecanthus, short palpebral fissures, angle at nose root, increased upper lip width, increased angle of ala of the nose, and decreased distance between oral commissures (narrow mouth).

Sensitivity, specificity and diagnostic accuracy were 0.833, 0.859, and 0.846, respectively for a combined analysis of the entire cohort ($n = 156$ cases; $n = 156$ controls) using only geometric features (Table 3). However, when using both geometric and texture measures, sensitivity increased to 0.962, specificity to 0.936 and accuracy to 0.949 ($P \leq 0.001$ for all, Table 3). All four population groups (Caucasian, African, Asian, and Latin American)

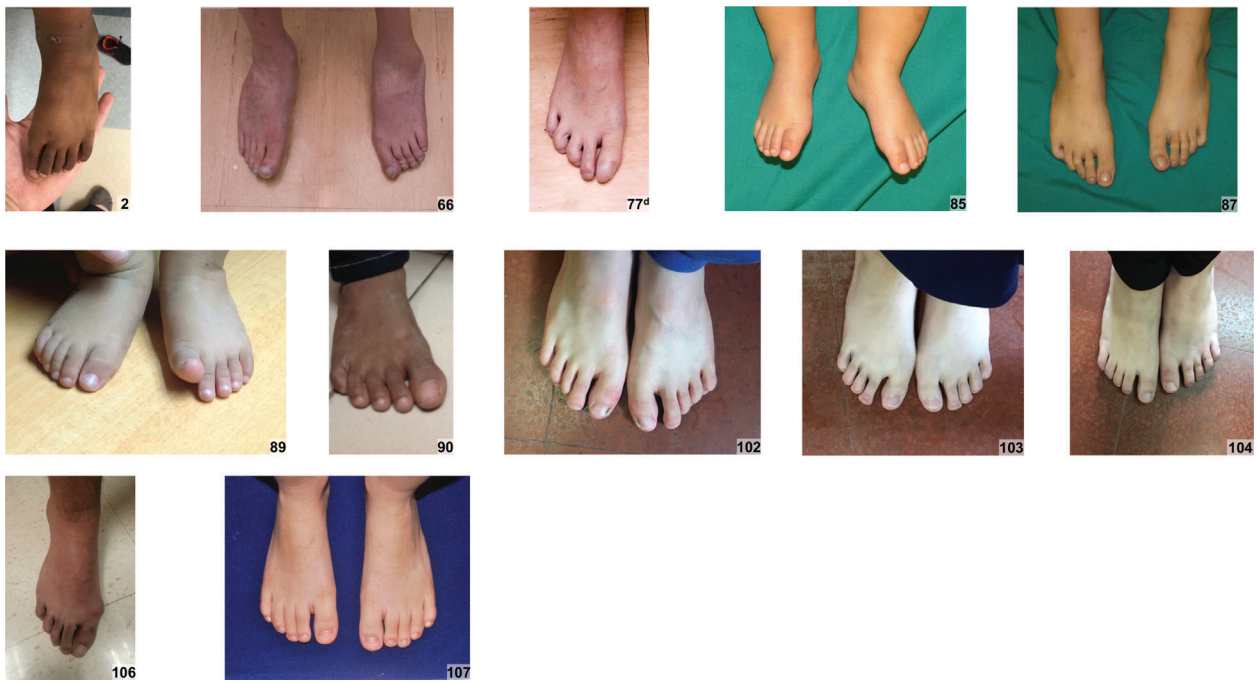

FIGURE 6 Foot findings. Image numbers correspond with Supplementary Table S1. [d]Individual previously published in Liu et al. (2014).

TABLE 2 Population data used in facial analysis technology

	22q11.2 DS (*N* = 156)		Controls (*N* = 156)	
	Number	%	Number	%
Age				
Newborn	0	0%	0	0%
Infant	36	34%	36	34%
Toddler	30	28%	30	28%
Child	56	53%	56	53%
Adolescence	14	13%	14	13%
Adult	20	19%	20	19%
Total	156		156	
Ethnicity				
Caucasian	59	56%	59	56%
African Descent	54	51%	54	51%
Asian	27	25%	27	25%
Latin-American	16	15%	16	15%
Total	156		156	
Gender				
Male	83	78%	83	78%
Female	73	69%	73	69%
Total	156		156	

improved significantly in sensitivity, specificity, and accuracy when combining geometric and texture features for distinct ethnic groups ($P \leq 0.001$ for all, Table 3). Supplementary Figures 1–4 graphically demonstrate how the addition of features improves the measures of sensitivity, specificity, and accuracy. Supplementary Tables S2–5 presented the relevant features for the diagnosis of 22q11.2 DS for each population, as selected by the digital facial analysis technology.

4 | DISCUSSION

Based on the prenatal prevalence of 22q11.2 deletions identified in non-selected fetuses (~1:1,000), 22q11.2 DS syndrome is an underdiagnosed condition in the general population but even more so in developing countries and diverse populations. Many patients are ascertained secondary to congenital heart disease (75% in our cohort), leaving less severely affected individuals undiagnosed. The goal of this study was to characterize the similarities and differences in clinical findings of 22q11.2 DS in diverse populations and examine the ability of facial analysis technology to assist in diagnosis. We believe that studies like this (Kruszka et al., 2017) and our recently created website, www.genome.gov/atlas, (Atlas of Human Malformations in Diverse Populations, 2016) will assist providers in making a diagnosis/an earlier diagnosis and address known comorbidities of 22q11.2 DS such as the need for irradiated blood for cardiopulmonary bypass or blood transfusion, immunodeficiency and hypocalcemia, cascade testing of family members, and genetic counseling (Bassett et al., 2011; Fung et al., 2015; Kobrynski and Sullivan, 2007), especially when there is limited access to laboratory testing. In our diverse cohort of individuals with 22q11.2 DS, we were able to draw important conclusions from the findings for individuals with 22q11.2 DS in different populations.

Our first finding mirrors previous studies (De Decker et al., 2016; McDonald-McGinn et al., 2005; Veerapandiyan et al., 2011; Wichajam and Kampan, 2014) demonstrating that the clinical presentation is variable among different populations group, making the diagnosis potentially difficult. Our group of examiners for the present study and groups in the medical literature had the most difficulty diagnosing individuals of African descent with 22q11.2 DS. As noted above, only learning problems and ear anomalies were present in similar ratios ($P \geq 0.05$) across ethnicities when individuals were evaluated subjectively; however, when removing the African and African American

TABLE 3 Results of facial analysis technology applied to diverse populations of individuals with 22q11.2 DS

	Number of features	AUC	Accuracy	Sensitivity	Specificity
Global					
Geometric	18	0.899	0.846	0.833	0.859
Geometric + texture	29	0.987	0.949	0.962	0.936
Caucasian					
Geometric	27	0.832	0.788	0.661	0.915
Geometric + texture	25	0.978	0.966	0.966	0.966
African and African American					
Geometric	12	0.908	0.870	0.926	0.815
Geometric + texture	22	0.997	0.981	1.000	0.963
Asian					
Geometric	26	0.941	0.926	0.926	0.926
Geometric + texture	21	0.967	0.981	1.000	0.963
Latin American					
Geometric	4	0.906	0.906	0.875	0.938
Geometric + texture	26	1.000	1.000	1.000	1.000

*AUC—area under the receiver operating characteristic curve.

cohort, the number of clinical features that were present in similar ratios across ethnicities ($P \geq 0.05$) increased from two to eight.

Subjective exam findings such as those shown in Table 1 are difficult to compare due to differences in examiners and reported outcomes, making an objective strategy such as facial analysis technology more attractive. As our second conclusion, we found that digital facial technology also finds differences between population groups. Interestingly, the facial analysis data also recognized one population group that was different, but it was the Caucasian cohort. All four groups (Caucasian, African, Asian, and Latin American) only shared two common geographic facial analysis features: telecanthus and narrow palpebral fissures (Supplementary Tables S2–5). However, if the Caucasian cohort was removed, the other three groups shared four geographic features including telecanthus, short palpebral fissures, angle of the ala of the nose, and narrow mouth.

The final and possibly the most important conclusion of this study is the accuracy of digital facial technology which we propose as an alternative to cytogenetic/molecular testing in diverse populations when laboratory studies are not available. The sensitivity of facial analysis technology is equal to or greater than 96.6% for each diverse population, and specificity is equal to greater than 96.3% (Table 3). When using a scoring system designed from a European cohort (Oskarsdottir et al., 2005), De Decker et al. (2016) found the scoring system to only have a positive predictive value of 14% when applied to 125 South African individuals with congenital heart disease. Applying the prevalence of 22q11.2 DS cases in De Decker et al.'s South African study of 4.8%, our facial analysis technology application would give a positive predictive value of 55% using the sensitivity and specificity found in Table 3, a fourfold increase over the diagnostic criteria used in their study (De Decker et al., 2016). As noted above, Liu et al. (2014) found that one individual with 22q11.2 DS goes undiagnosed for every 10 individuals in their cohort of Chinese adults with conotruncal heart defects. Using the prevalence in Liu et al., (2014) cohort and the sensitivity and specificity in Table 3 for the Asian cohort, the positive predictive value of facial analysis technology would have been 78% and the high sensitivity of our assay would have picked up all cases of 22q11.2 DS in their study. The accuracy of digital facial analysis technology is already well known in Down syndrome (Kruszka et al., 2017; Zhao, Okada, et al., 2014), and with the wide spread availability of hand held devices throughout the world, this study proposes the use of this technology across diverse populations.

The ethical implications of associating genetic diagnoses with diverse populations are potentially a source of disconcert for some, especially when considering historical concerns about the association of biological classifications and racial and ethnic categories. These issues have been reviewed in depth (Koretzky et al., 2016) and are considered beyond the scope of this study.

There are several potential limitations to this study. One challenge was studying individuals across a wide range of ages. Clinical features of 22q11.2 DS change with age (McDonald-McGinn et al., 2015) and 22q11.2 DS is ideally diagnosed in the newborn period; however, the diagnosis is made in all ages. An inherent weakness of any study of this type will be capturing the multitude of varying ethnicities found throughout the world. Although this study encompasses many participants and countries, it only represents a small fraction of the global population. Additionally, much of the data of this study and others are subjective and based on examiner judgment; for this reason, we have employed digital facial analysis technology.

In conclusion, we have assembled a catalog of ethnically diverse individuals with 22q11.2 DS, summarized the medical literature pertaining to 22q11.2 DS and diverse populations, and conducted objective evaluation with digital facial analysis technology to demonstrate the differences in facial features. Based on our study, we propose and predict that digital facial analysis technologies will have widespread applicability to not just Caucasians with 22q11.2 DS, but to those from diverse populations with 22q11.2 DS and other conditions with distinctive dysmorphic features.

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REFERENCES

Atlas of Human Malformation Syndromes in Diverse Populations. https://www.genome.gov/atlas. Accessed December 27, 2016.

Bassett, A. S., McDonald-McGinn, D. M., Devriendt, K., Digilio, M. C., Goldenberg, P., Habel, A., ... Consortium International 22q11.2 Deletion, S. (2011). Practical guidelines for managing patients with 22q11.2 deletion syndrome. *Jornal de Pediatria*, *159*, 332–9e1.

Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S. A., ... Campbell, R. M. (2003). A population-based study of the 22q11.2 deletion: Phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics*, *112*, 101–107.

Cai, D., Zhang, C., & He, X. (2010). *Unsupervised Feature Selection for Multi-Cluster Data*. Proceedings of the 16th ACM SIGKDD international conference on knowledge discovery and data mining, New York, NY (pp. 333–342).

Cerrolaza, J. J., Porras, A. R., Mansoor, A., Zhao, Q., Summar, M., & Linguraru, M. G. (2016). *Identification of dysmorphic syndromes using landmark-specific local texture descriptors*. IEEE Int Symp Biomed Imaging, New York, NY (pp. 1080–1083).

Cortes, C., & Vapnik, V. (1995). Support-vector networks. *Machine Learning*, *20*, 273–297.

De Decker, R., Bruwer, Z., Hendricks, L., Schoeman, M., Schutte, G., & Lawrenson, J. (2016). Predicted v. real prevalence of the 22q11.2 deletion syndrome in children with congenital heart disease presenting to Red Cross War Memorial Childrens Hospital, South Africa: A prospective study. *South African Medical Journal*, *106*, S82–S86.

Elisseeff, A., & Pontil, M., (2003). Leave-one-out error and stability of learning algorithms with applications. In G. Horvath, J. Suykens, & S. Basu, (Eds.), *Advances in learing theory: Methods, models and applications*. Amsterdam: IOS Press.

Fung, W. L., Butcher, N. J., Costain, G., Andrade, D. M., Boot, E., Chow, E. W., … Bassett, A. S. (2015). Practical guidelines for managing adults with 22q11.2 deletion syndrome. *Genetics in Medicine*, *17*, 599–609.

Grassi, M. S., Jacob, C. M., Kulikowski, L. D., Pastorino, A. C., Dutra, R. L., Miura, N., … Carneiro-Sampaio, M. (2014). Congenital heart disease as a warning sign for the diagnosis of the 22q11.2 deletion. *Arquivos Brasileiros De Cardiologia*, *103*, 382–390.

Grati, F. R., Molina Gomes, D., Ferreira, J. C., Dupont, C., Alesi, V., Gouas, L., … Vialard, F. (2015). Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. *Prenatal Diagnosis*, *35*, 801–809.

Kobrynski, L. J., & Sullivan, K. E. (2007). Velocardiofacial syndrome, DiGeorge syndrome: The chromosome 22q11.2 deletion syndromes. *The Lancet*, *370*, 1443–1452.

Koretzky, M., Bonham, V. L., Berkman, B. E., Kruszka, P., Adeyemo, A., Muenke, M., & Hull, S. C. (2016). Towards a more representative morphology: clinical and ethical considerations for including diverse populations in diagnostic genetic atlases. *Genetics in Medicine: Official Journal of the American College of Medical Genetics 18*, 1069–1074.

Kruszka, P., Porras, A. R., Sobering, A. K., Ikolo, F. A., La Qua, S., Shotelersuk, V., … Muenke, M. (2017). Down syndrome in diverse populations. *American Journal of Medical Genetics Part A*, *173*, 42–53.

Liu, A. P., Chow, P. C., Lee, P. P., Mok, G. T., Tang, W. F., Lau, E. T., … Chung, B. H. (2014). Under-recognition of 22q11.2 deletion in adult Chinese patients with conotruncal anomalies: Implications in transitional care. *European Journal of Medical Genetics*, *57*, 306–311.

Matsuoka, R., Kimura, M., Scambler, P. J., Morrow, B. E., Imamura, S., Minoshima, S., … Momma, K. (1998). Molecular and clinical study of 183 patients with conotruncal anomaly face syndrome. *Human Genetics*, *103*, 70–80.

McDonald-McGinn, D. M., Emanuel, B. S., & Zackai, E. H., (1993). 22q11.2 deletion syndrome. In R. A. Pagon, M. P. Adam, H. H. Ardinger, S. E. Wallace, A. Amemiya, L. J. H. Bean, T. D. Bird, C. T. Fong, H. C. Mefford, R. J. H. Smith, & K. Stephens, (Eds.), *GeneReviews(R)*. Seattle (WA): University of Washington.

McDonald-McGinn, D. M., Minugh-Purvis, N., Kirschner, R. E., Jawad, A., Tonnesen, M. K., Catanzaro, J. R., … Zackai, E. H. (2005). The 22q11.2 deletion in African-American patients: An underdiagnosed population?. *American Journal of Medical Genetics Part A*, *134*, 242–246.

McDonald-McGinn, D. M., Sullivan, K. E., Marino, B., Philip, N., Swillen, A., Vorstman, J. A., … Bassett, A. S. (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*, 15071.

Ojala, T., Pietikäinen, M., & Harwood, D. (1996). A comparative study of texture measures with classification based on featured distributions. *Pattern Recognition*, *29*, 51–59.

Oskarsdottir, S., Holmberg, E., Fasth, A., & Stromland, K. (2008). Facial features in children with the 22q11 deletion syndrome. *Acta Paediatrica*, *97*, 1113–1117.

Oskarsdottir, S., Persson, C., Eriksson, B. O., & Fasth, A. (2005). Presenting phenotype in 100 children with the 22q11 deletion syndrome. *European Journal of Pediatrics*, *164*, 146–153.

Repetto, G. M., Guzman, M. L., Puga, A., Calderon, J. F., Astete, C. P., Aracena, M., … Sanz, P. (2009). Clinical features of chromosome 22q11.2 microdeletion syndrome in 208 Chilean patients. *Clinical Genetics*, *76*, 465–470.

Uwineza, A., Caberg, J. H., Hitayezu, J., Hellin, A. C., Jamar, M., Dideberg, V., … Mutesa, L. (2014). Array-CGH analysis in Rwandan patients presenting development delay/intellectual disability with multiple congenital anomalies. *BMC Medical Genetics*, *15*, 79.

Veerapandiyan, A., Abdul-Rahman, O. A., Adam, M. P., Lyons, M. J., Manning, M., Coleman, K., … Shashi, V. (2011). Chromosome 22q11.2 deletion syndrome in African-American patients: A diagnostic challenge. *American Journal of Medical Genetics Part A*, *155A*, 2186–2195.

Wapner, R. J., Martin, C. L., Levy, B., Ballif, B. C., Eng, C. M., Zachary, J. M., … Jackson, L. (2012). Chromosomal microarray versus karyotyping for prenatal diagnosis. *New England Journal of Medicine*, *367*, 2175–2184.

Wichajam, K., & Kampan, J. (2014). Difference of clinical phenotypes and immunological features of 22q11.2 deletion syndrome in north-eastern Thai children compare to western countries. *Journal of the Medical Association of Thailand*, *97*(Suppl 10), S59–S66.

Wu, D., Chen, Y., Xu, C., Wang, K., Wang, H., Zheng, F., … Wang, G. (2013). Characteristic face: A key indicator for direct diagnosis of 22q11.2 deletions in Chinese velocardiofacial syndrome patients. *PLoS ONE*, *8*, e54404.

Ye, J., Janardan, R., & Li, Q. (2004). Two-dimensional linear discriminant analysis. *Advances in Neural Information Processing Systems*, *17*, 1569–1576.

Zhao, Q., Okada, K., Rosenbaum, K., Kehoe, L., Zand, D. J., Sze, R., … Linguraru, M. G. (2014). Digital facial dysmorphology for genetic screening: Hierarchical constrained local model using ICA. *Medical Image Analysis*, *18*, 699–710.

Zhao, Q., Okada, K., Rosenbaum, K., Zand, D. J., Sze, R., Summar, M., & Linguraru, M. G. (2013). Hierarchical constrained local model using ICA and its application to Down syndrome detection. *Medical Image Computing and Computer-Assisted Intervention*, *16*, 222–229.

Zhao, Q., Werghi, N., Okada, K., Rosenbaum, K., Summar, M., & Linguraru, M. G. (2014). Ensemble learning for the detection of facial dysmorphology. *Conference Proceedings IEEE Engineering in Medicine and Biology Society*, *2014*, 754–757.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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