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Down Syndrome in Diverse Populations

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Down syndrome is the most common cause of cognitive impairment and presents clinically with universally recognizable signs and symptoms. In this study, we focus on exam findings and digital facial analysis technology in individuals with Down syndrome in diverse populations. Photos and clinical information were collected on 65 individuals from 13 countries, 56.9% were male and the average age was 6.6 years (range 1 month to 26 years; SD = 6.6 years). Subjective

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findings showed that clinical features were different across ethnicities (Africans, Asians, and Latin Americans), including brachycephaly, ear anomalies, clinodactyly, sandal gap, and abundant neck skin, which were all significantly less frequent in Africans ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.05$, and $P < 0.05$, respectively). Evaluation using a digital facial analysis technology of a larger diverse cohort of newborns to adults (n = 129 cases; n = 132 controls) was able to diagnose Down syndrome with a sensitivity of 0.961, specificity of 0.924, and accuracy of 0.943. Only the angles at medial canthus and ala of the nose were common significant findings amongst different ethnicities (Caucasians, Africans, and Asians) when compared to ethnically matched controls. The Asian group had the least number of significant digital facial biometrics at 4, compared to Caucasians at 8 and Africans at 7. In conclusion, this study displays the wide variety of findings across different geographic populations in Down syndrome and demonstrates the accuracy and promise of digital facial analysis technology in the diagnosis of Down syndrome internationally. © 2016 Wiley Periodicals, Inc.

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Key words: down syndrome; trisomy 21; diverse populations; facial analysis technology

INTRODUCTION

Down syndrome (DS), the most common cause for intellectual disability and congenital heart disease, is a well-known disorder caused by an extra chromosome 21. DS was first described by John Langdon Down in 1866 [Down, 1866] and nearly a century later in 1959, Jerome Lejeune associated DS with trisomy 21 [Lejeune et al., 1959]. The original papers characterizing DS focused on individuals of European descent [Hall, 1964] and it would be almost a hundred years from Langdon Down's original paper that DS was recognized in African populations [Parker, 1950; Luder and Musoke, 1955]. Some investigators in the 20th century believed that DS was uncommon in Africans [Jelliffe, 1954; Luder and Musoke, 1955] even after Parker reported an incidence of 1.16 per 1,000 in a study of 25,026 African American live births [Parker, 1950]. In 1982, Adeyokunnu documented in a Nigerian study that the incidence of DS in Africans was similar to other populations at 1.16 per 1,000 [Adeyokunnu, 1982], which matched Parker's 1950 estimate in African Americans [Parker, 1950]. The incidence of DS in Asian and Latin American countries has been found to approximate Caucasian and African populations [Verma and Singh, 1975; Kuroki et al., 1977; Carothers et al., 1999; Hook et al., 1999; Carothers et al., 2001; Forrester and Merz, 2003; Jackson et al., 2014]. With the purpose of focusing on DS in non-European populations, this present study focuses on the phenotype of DS in diverse populations around the world.

Infants with DS have characteristic facial features, allowing for a diagnosis to be made in the neonatal period; however, the clinical diagnosis of DS by a clinician before cytogenetic testing is only predicted to be 64% accurate [Sivakumar and Larkins, 2004]. The use of antenatal screening is not widespread in developing countries and diagnosis is often made after birth. In one large study in India, 90% of individuals with DS were referred after one month of age [Kava et al., 2004]. Early diagnosis of DS is crucial in order to address life threatening congenital medical problems such as atrioventricular septal defect (AVSD), which is 1,000-fold higher in incidence in DS compared to non-DS, the most common structural heart malformation in DS and leading contributor to infant mortality [Kruszka, 2015]. Advances in cardiac surgery have greatly improved survival over the last 70 years from a median of 12 years to now 60 years [Bittles et al., 2007; Weijerman et al., 2008].

Complicating early diagnosis, the medical literature is filled with examples of physical exam findings that differ amongst ethnicities. In one African report, one third of DS diagnoses in neonates were missed by medical practitioners [Christianson, 1996]. Differences between African DS newborns and African healthy newborns were significantly less prominent than in newborns of European descent [Luder and Musoke, 1955; Christianson et al., 1995]. Christianson et al. [1995] noted that the flat facial profile typically noted in DS infants was present in 64% of healthy African newborns, the flat nasal bridge typical of DS infants was present in 68% of healthy African newborns, and epicanthal folds, oblique palpebral fissures, protruding tongues, and excess nuchal skin were significantly more common in African newborns compared to infants of European background. Further obscuring the diagnosis of DS in Africans is the less frequent findings of brachycephaly and flat occiput in children with DS [Luder and Musoke, 1955; Christianson et al., 1995]. There have also been reports of difficult diagnosis of DS in Asian patients [Lee et al., 1961; Conen et al., 1962]. In addition to physical exam findings, it is important to point out other differences in clinical presentation as Freeman et al. [2008] found that African Americans were twice as likely to have AVSDs as Caucasians (odds ratio,

TABLE I. Summary of Exam Findings of Individuals With Down Syndrome From Diverse Backgrounds in Present Study and From Medical Literature

	Present Study					Taiwan	Malaysia	Korea	India	India	Isreal	Britain	Sweden	Sub-Saharan Africa	Sub-Saharan Africa	Brazil	Pakistan
	Global	African	Asian	Latin American	*P*- values**	Emanuel et al. [1968]	Azman et al. [2007]	Kim et al. [2002]	Kava et al. [2004]	Sureshbabu et al. [2011]	Fried et al. [1980]	Hindley & Medakkar [2002]	Hall [1964]	Christianson [1995]	Mgone [1983]	Pavarino Bertelli et al. [2009]	Ahmed et al. [2005]
						Newborns/ Children	Infants/ children	Infants/ children	Newborns/ Children	Infants/ Adults	Newborns	Newborns	Newborns	Newborns	Children	Children	Newborns/ Children
	n=65 [%]	n=25 [%]	n=31 [%]	n=9 [%]		n=56 [%]	n = 149 [%]	n=123 [%]	n = 524 [%]	n=95 [%]	n=30 [%]	n=72 [%]	n=58 [%]	n=40 [%]	n=50 [%]	n=62 [%]	n=295 [%]
Upslanting palpebral fissures	83	72	90	89	0.16	61	89	63	84	83		100	81	83	100	94	83
Epicanthal folds	65	44	71	78	0.23	46	18	61	57	94	76		70	83	98	79	63
Flat facial profile	89	79	93	100	0.14	91	65		51		96		89	95		98	
Flat nasal bridge	71	46	76	67	0.23	91				84		57	79	95	100	94	61
Ear anomalies	44	10	56	78	<0.001	57	56		67		72	89	62*	55	40	69	
Protruding tongue	43	32	43	67	0.19	21	19		30	53	64	24	68		84	34	
Flat occiput/ Brachycephaly	53	21	84	78	<0.001	59						29	23	30	48	84	40
Transverse palmar crease	65	67	58	75	0.69	36			33	61		99	54	50		84	65
Clinodactyly	60	24	82	100	<0.001	54	19		36	78				33	64	41	25
Brachydactyly	91	94	84	100	0.65	63	25		11						78	81	24
Sandal Gap	40	62	88	83	<0.05	55	33		46	81	60	80		55	66	65	46
Abundant neck skin	38	0	44	56	0.02	69**	12		37	61	100	47	81	48	46		

*Multiple forms of early anomalies were observed. Small ears were the most frequently recorded ear anomaly.
χ^2 test comparison of present study of African, Asian, and Latin American groups.

2.06; 95% confidence interval, 1.32–3.21) and Latin Americans were half as likely to have AVSDs as those of European descent (odds ratio, 0.48; 95% confidence interval, 0.30–0.77).

Down syndrome is a well-researched condition with thousands of journal articles written. However, very few have focused on diverse populations such as Africans [Christianson, 1997] and many clinicians have been trained with clinical genetic resources that used patients of northern European descent as the standard of reference [Muenke et al., 2016]. The first aim of this study is to examine the differences and similarities in DS populations from around the world. We accomplish this goal by comparing physician exam findings and digital facial analysis technology. The second objective of this study is to provide a spectrum of facial and extremity images of DS in diverse populations. Although the ethical complexities of examining patients from diverse populations is not a goal of this study, we acknowledge that questions derived from the historical complexity of medicine, race, and ethnicity may surface and that these concerns are thoroughly discussed by Koretzky et al. [2016].

METHODS

Review of Medical Literature

A Medline search was conducted to find studies that characterize DS in diverse populations. The key words and search terms used included: Down syndrome, trisomy 21, African, African-American, Asian, Latin American, Hispanic, Indian, and diverse populations. Additionally, reference lists of studies were reviewed.

Patients in Present Study

Sixty-five patients with DS confirmed by cytogenic testing (karyotype and/or chromosomal microarray) were evaluated from 13

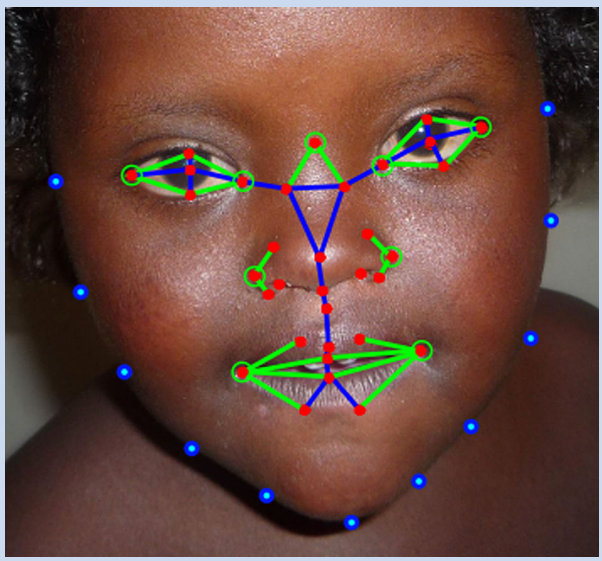

FIG. 1. Facial landmarks on a down syndrome patient. Inner facial landmarks are represented in red, while external landmarks are represented in blue. Blue lines indicate the calculate distances. Green circles represent the corners of the calculated angles. Texture features are extracted only from the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

FIG. 2. Frontal and lateral facial profiles of individuals of African descent with Down syndrome. Gender, age, and country of origin found in Supplementary Table I.

countries. For this study's purpose, patients were grouped by geographic area of origin (African, Asian, Latin American), knowing that these types of categories can be imprecise and that significant phenotypical variation exists between populations from similar areas of the world. Patients were examined by local clinical geneticists for a number of clinical criteria that have been applied to the diagnosis of DS including upslanting palpebral fissures, epicanthal folds, flat facial profile, and nasal bridge, ear anomalies, protruding tongue, flat occiput, brachycephaly, transverse palmar crease, clinodactyly, brachydactyly, sandal gap, and abundant neck skin [Hall, 1964; Fried, 1980; Jones et al., 2013].

Patients were consented by local institutional review boards and the Personalized Genomics protocol at the National Institutes of Health (11-HG-0093). Physical exam findings from the medical literature and from this study where compiled in a table for review (Table I).

Facial Analysis Technology

Digital facial analysis technology previously described [Zhao et al., 2013, 2014a,b; Cerrolaza et al., 2016] was applied to the sixty-five individuals with DS from this study and 64 cases and 132 healthy ethnically matched controls from our previously described database [Zhao et al., 2013, 2014a]. This technology analyzed the frontal facial images.

Using these individuals, we ran our algorithms for feature extraction, feature selection and classification. A total of 126 facial features were extracted from a set of 44 facial landmarks, represented in Figure 1. The features included both geometric and texture biomarkers. The geometric measurements are a set of distances and angles measured from the 33 inner facial landmarks, as shown in Figure 1. To quantify texture information, local binary patterns [Ojala et al., 1996], which are robust markers of monotonic illumination changes, were calculated at each of the inner facial landmarks, thus capturing the local face structure. Each local binary pattern constitutes a histogram of the contrast information centered at one landmark, which quantifies information such as shadows and lines on the faces. From the set of geometric and texture features, the most significant ones were selected using the method proposed by Cai et al. [2010]. For each feature set selected, a support vector machine [Cortes and Vapnik, 1995] classifier was trained using

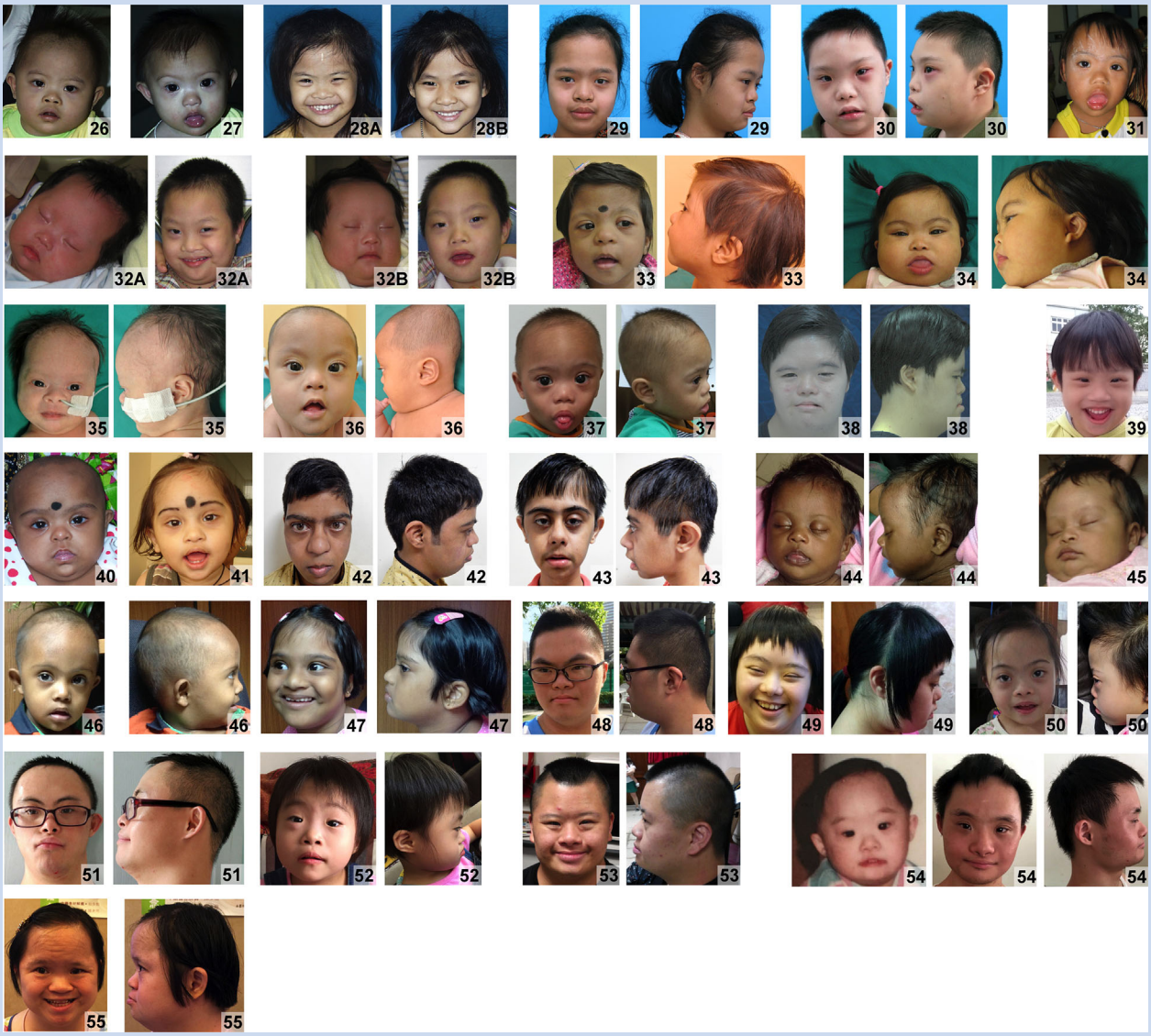

FIG. 3. Frontal and lateral facial profiles of Asian individuals with Down syndrome. Gender, age, and country of origin found in Supplementary Table I.

leave-one-out strategy cross-validation [Elisseeff and Pontil, 2003]. The optimal number of features for each classification was selected as the one that maximized the classification accuracy. In addition, we also calculated the significance (*P*-value) as an estimator of its individual discriminant power.

We obtained results using only geometric features, and then using both geometric and texture features for all the patient groups. Significance was assessed using Fisher's exact test.

RESULTS

Photo images and clinical information were collected on 65 individuals with DS from 13 countries, average age was 6.6 years (range 1 month to 26 years; SD = 6.6 years) and 56.9% were male (Supplementary Table SI). Figures 2–4 show facial features in individuals of African (n = 25), Asian (n = 31), and Latin American (n = 9) heritage, respectively. Figure 5 focuses on hand findings and Figure 6 shows lower extremity findings. Figure 7 is an age progression in some of the participants, showing the variability in features at different stages in life. Table I demonstrates physical exam variations in our study population and in the medical literature in individuals with DS from different geographic locations. The exam findings for the cardinal signs of DS described above [Hall, 1964; Fried, 1980; Jones et al., 2013] are listed in Table I. For the present study, subjective findings (Table I) showed that clinical features differed across ethnicities (Africans, Asians, and

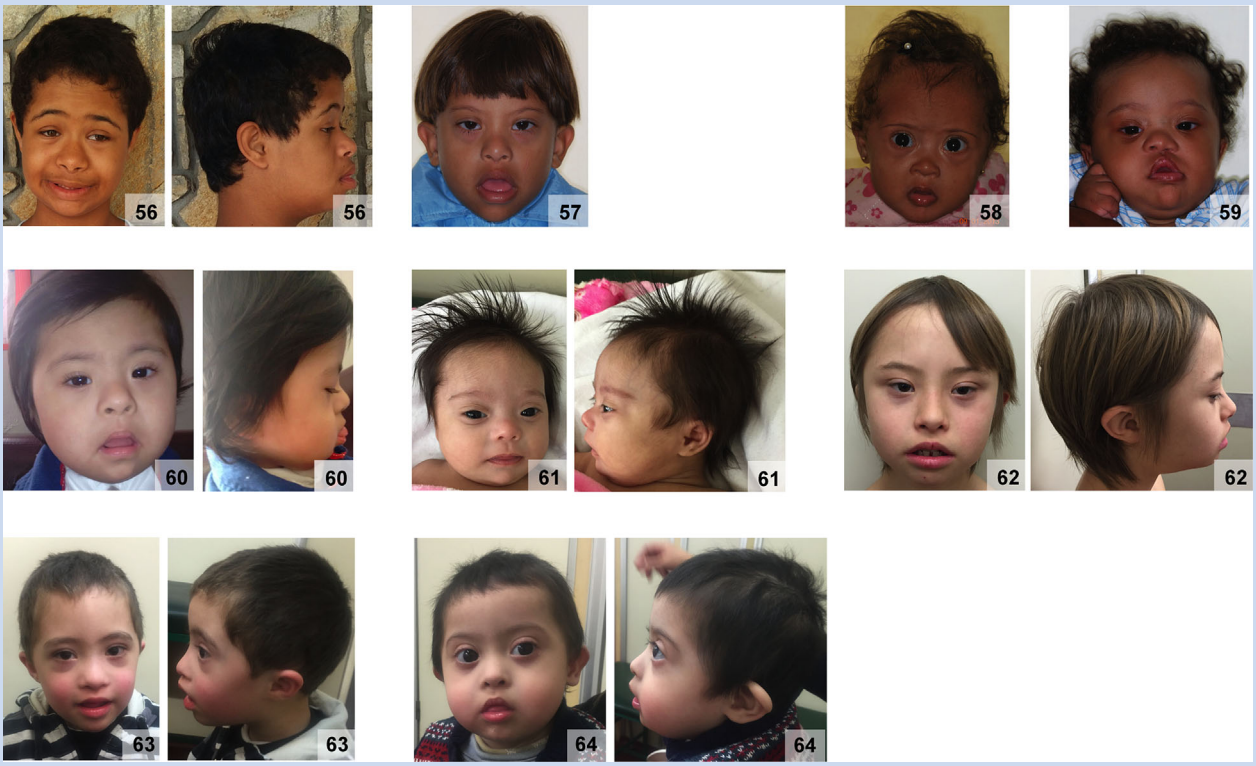

FIG. 4. Frontal and lateral facial profiles of Latin Americans with Down syndrome. Gender, age, and country of origin found in Supplementary Table I.

Latin Americans) including brachycephaly, ear anomalies, clinodactyly, sandal gap, and abundant neck skin, which were all significantly less frequent in Africans ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.05$, and $P < 0.05$, respectively). The most common features found in the present study and previous studies, and the only two findings found in over half of participants (Table I) were upslanting palpebral fissures and flat facial profile with minimum prevalences of 61% and 51%, respectively. However, there was large variation in facial findings between all studies, even within the same ethnic groups (Table I). For example, epicanthal folds in Asians were found in 71% of the present study and range from 18% in a Malaysian study of 149 [Azman et al., 2007] to 61% in a Korean study of 123 participants [Kim et al., 2002]. Limb findings in our cohort and the medical literature were varied with transverse palmar creases ranging from 33% to 99%, clinodactyly 19% to 100%, brachydactyly 11% to 100%, and sandal gap 33% to 88%.

Using a more objective approach with facial recognition technology, Table II shows the age and geographic origin of cases and controls studied, consisting of Caucasians, Africans or African American, and Asians. A total of 129 individuals with DS and 132 healthy controls were evaluated (Table II). Using previously described methods for feature extraction and analysis [Zhao et al., 2014a], the three groups (Caucasian, Asian, and African) only shared two biomarkers that were significantly different from controls: the angles at the medial canthus and ala of the nose (Supplementary Tables SII–IV). Latin American patients were not included in this analysis due to the small sample size. The Asian group had the least number of significant geometric features at four compared to Caucasians at eight and African at seven (Supplementary Tables SII and SIV). Caucasians and Africans shared the most significant anatomical features at six geometric measures (Supplementary Tables SII and SIV), including the upslanting of the palpebral fissures, the length of the nose and the distance between the medial canthi. The African and Asian groups shared three significant features, including the angle at the nose root. The Asian and Caucasian groups also shared three features, including the distance between the oral commissures. Interestingly, the upslanting of the palpebral fissures was not a discriminative features of DS in the Asian group.

Sensitivity, specificity, and diagnostic accuracy were 0.853, 0.856, and 0.854, respectively for a combined analysis of the entire cohort ($n = 129$ cases; $n = 132$ controls) using only geometric features (Table III). When using both geometric and texture measures, sensitivity increased to 0.961, specificity to 0.924, and accuracy to 0.943 ($P < 0.001$, see Table III). All three population groups (Caucasian, African, and Asian) improved in sensitivity, specificity, and accuracy when combining geometric and texture features for distinct groups ($P < 0.001$ for all, see Table III). Supplementary Figures S1–3 graphically demonstrate how the addition of features improves the measures of sensitivity,

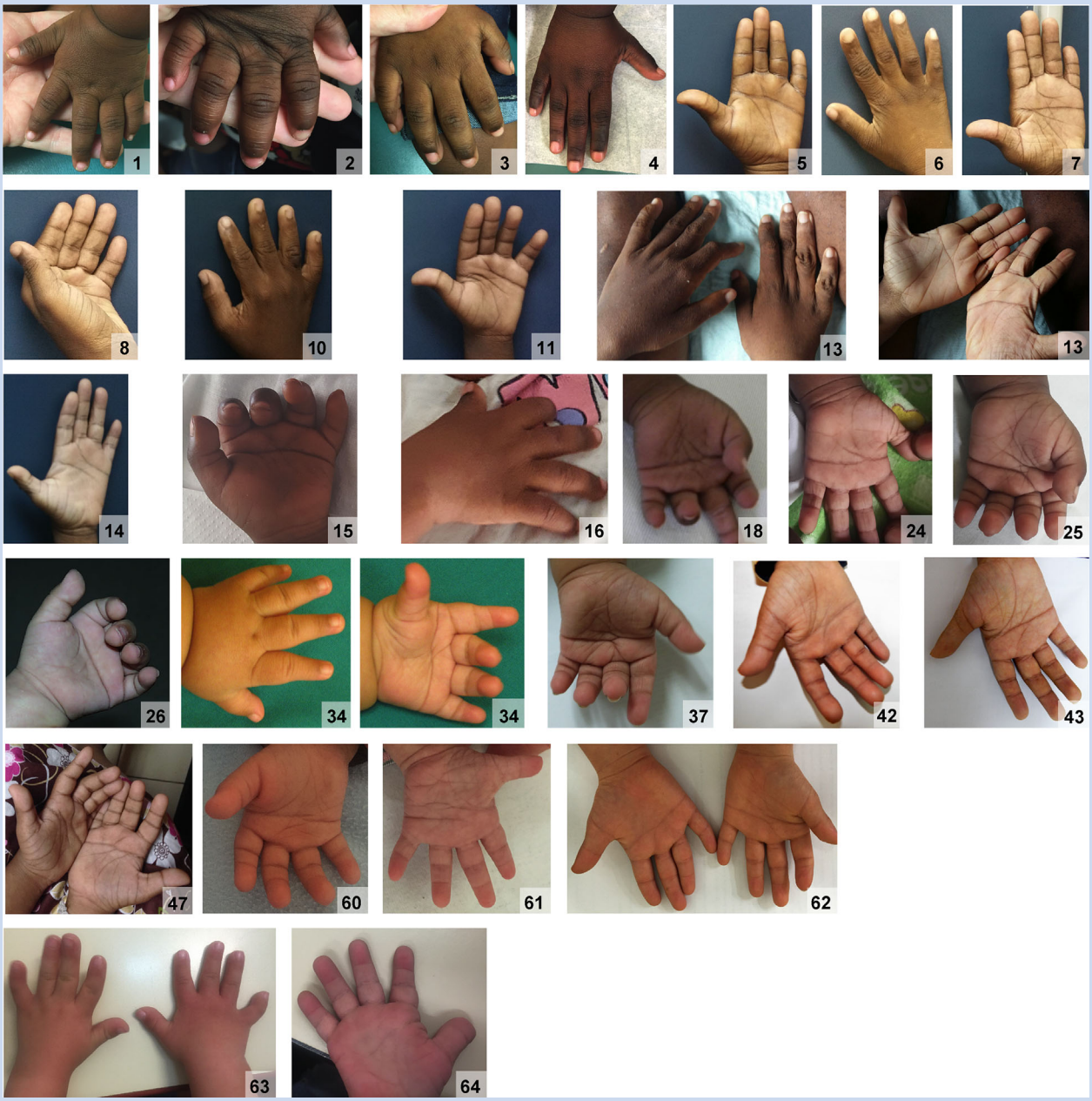

FIG. 5. Hand findings. Image numbers correspond with Supplementary Table I.

specificity, and accuracy. Supplementary Tables SII–IV presented the relevant features for the diagnosis of DS for each population, as selected by the digital facial analysis technology.

DISCUSSION

Down syndrome is often diagnosed prenatally in developed countries by ultrasound and/or genetic testing from amniocytes or chorionic villus samples. When these resources are not used, especially in developing countries, diagnosis is made by clinical observation of morphologic findings. Here, we present individuals with DS from multiple geographies, with a majority ascertained from developing nations. This study characterizes DS subjectively with images of facial and limb findings, objectively with facial analysis technology, and collectively by organizing clinical exam findings from the medical literature. The goal of this work is to give providers a baseline reference to make the diagnosis of DS in diverse populations, as an earlier diagnosis allows for appropriate

TABLE II. Data From Diverse Populations Used by Facial Analysis Technology

	Down syndrome (N = 129)		Healthy controls (N = 132)	
Age	Number	%	Number	%
Newborn	2	2	8	6
Infant	66	51	86	65
Toddler	37	29	30	23
Child	14	11	7	5
Adolescent	8	6	1	1
Adult	2	2	0	0
Total	129		132	
Ethnicity	Number	%	Number	%
Caucasian	75	58	84	64
African and African American	22	17	26	20
Asian	32	25	22	17
Total	129		132	
Gender	Number	%	Number	%
Male	60	47	68	52
Female	69	53	64	48
Total	129		132	

preventive measures, early recognition of complications such as congenital heart disease, and genetic counseling and recurrence risk discussions with parents.

This study and previous studies have found differences between different ethnicities in individuals with DS. Subjective analysis of our study group showed statistically significant differences when all groups were compared together (Table I) in five classic exam findings (brachycephaly, ear anomalies, clinodactyly, sandal gap, and abundant neck skin) due to decreased findings in African patients. To further explore these differences, we employed objective facial analysis technology in 129 cases with DS and 132 controls. Interestingly, the Asian cohort in our digital facial recognition group had the least amount of significant different morphological (here called geometric) characteristics compared to a healthy control group (Supplementary Table SIV). Differences with morphological appearances in healthy individuals between ethnicities must also be considered and how these differences are related to DS. For example, Christianson et al. [1995] reported that in African neonates with DS, craniofacial findings approximate healthy African neonates more than is the case with Caucasians,

TABLE III. Results of the Detection of Down Syndrome from Diverse Populations Using the Objective Facial Analysis Technology

	No. of features	AUC	Accuracy	Sensitivity	Specificity
Global					
Geometric	11	0.905	0.854	0.853	0.856
Geometric + texture	29	0.978	0.943	0.961	0.924
Caucasian					
Geometric	16	0.916	0.849	0.800	0.893
Geometric + texture	30	0.976	0.956	0.933	0.976
African and African American					
Geometric	12	0.946	0.917	0.909	0.923
Geometric + texture	14	0.962	0.979	1.000	0.962
Asian					
Geometric	12	0.899	0.889	0.844	0.864
Geometric + texture	21	1.000	1.000	1.000	1.000

AUC, area under the receiver operating characteristic curve.

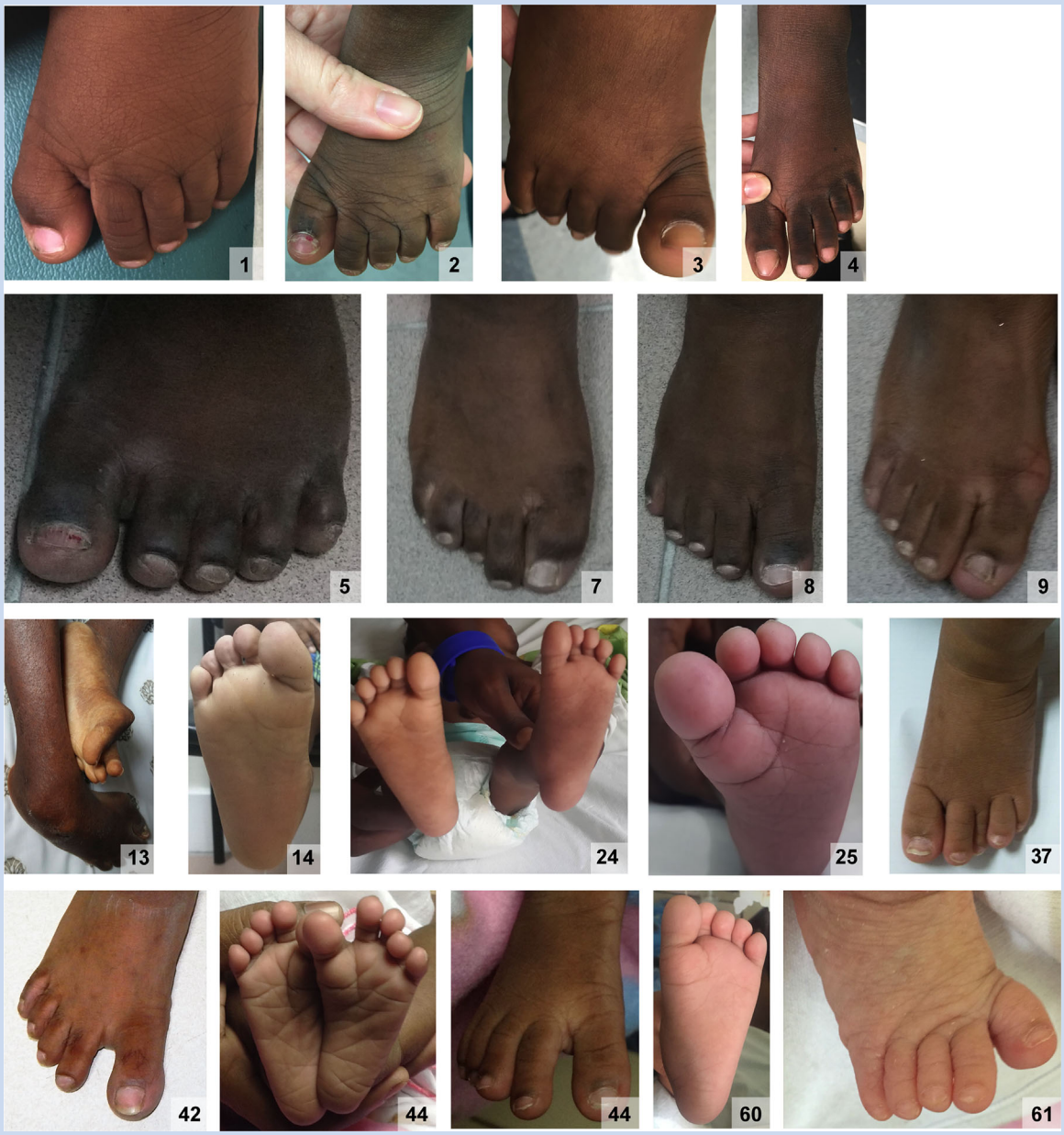

FIG. 6. Foot findings. Image numbers correspond with Supplementary Table I.

supporting our digital facial analysis data (Supplementary Tables SII–IV). The study by Christianson et al. was based on physician exam findings of 40 neonate cases and 50 healthy controls. The data obtained using facial analysis techniques, the subjective exam findings of this study, and the medical literature support differences in ethnicities and highlight some of the challenges in diagnosing DS with only physical exam.

However, throughout the world, as noted above, DS often is diagnosed with only physical exam findings. Facial analysis technology for DS detection has proven to be both sensitive and specific. When applied globally, we found the sensitivity to be 96.1% and specificity to be 92.4% (Table II). The accuracy of the technology increased significantly when applied to distinct population groups (African, Asian, and Caucasian). The accuracy of digital facial analysis technology is already well known [Zhao et al., 2013, 2014a; Cerrolaza et al., 2016], 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 syndrome 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

FIG. 7. Sequential photos of individuals with Down syndrome at different ages. Image numbers correspond with Supplementary Table I.

[Koretzky et al., 2016] and are considered beyond the scope of this study.

There are a number of potential limitations to this study. One challenge was studying individuals across a wide range of ages. Facial features change with age as shown by Figure 7, and many studies focus on a specific age range such as newborns. An inherent weakness of any study of this type will be capturing the many multitudes of different ethnicities and tribes 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 DS, summarized the medical literature pertaining to 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 DS, but to those from diverse populations with DS and other conditions with distinctive dysmorphic features.

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REFERENCES

Adeyokunnu AA. 1982. The incidence of Down syndrome in Nigeria. Med Genet 19:277–279.

Ahmed I, Ghafoor T, Samore NA, Chattha MN. 2005. Down syndrome: Clinical and cytogenetic analysis. J Coll Phys Surg Pak 15:426–429.

Azman BZ, Ankathil R, Siti Mariam I, Suhaida MA, Norhashimah M, Tarmizi AB, Nor Atifah MA, Kannan TP, Zilfalil BA. 2007. Cytogenetic and clinical profile of Down syndrome in northeast Malaysia. Singapore Med J 48:550–554.

Bittles AH, Bower C, Hussain R, Glasson EJ. 2007. The four ages of Down syndrome. Eur J Public Health 17:221–225.

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. 333–342.

Carothers AD, Hecht CA, Hook EB. 1999. International variation in reported live birth prevalence rates of Down syndrome, adjusted for maternal age. J Med Genet 36:386–393.

Carothers AD, Castilla EE, Dutra MG, Hook EB. 2001. Search for ethnic, geographic, and other factors in the epidemiology of Down syndrome in South America: Analysis of data from the ECLAMC project, 1967–1997. Am J Med Genet 103:149–156.

Cerrolaza JJ, Porras AR, Mansoor A, Zhao Q, Summar M, Linguraru MG. 2016. Identification of dysmorphic syndromes using landmark-specific local texture descriptors. IEEE Int Symp Biomed Imaging 1080–1083.

Christianson AL, Kromberg JG, Viljoen E. 1995. Clinical features of black African neonates with Down's syndrome. East Afr Med J 72:306–310.

Christianson AL. 1996. Down syndrome in sub-saharan Africa. J Med Genet 33:89–92.

Christianson AL. 1997. Down syndrome in black South African infants and children-clinical features and delayed diagnosis. S Afr Med J 87:992–995.

Conen PE, BelL AG, Rance CP. 1962. A review of chromosome studies in the diagnosis of mongolism. Case report of a Chinese infant. J Pediatr 60:533–539.

Cortes C, Vapnik V. 1995. Support-vector networks. Mach Learn 20:273–297.

Down JL. 1866. Observations on an ethnic classification of idiots. London Hospital Clinical Lectures and Reports 3:259–262.

Elisseeff A, Pontil M. 2003. Leave-one-out error and stability of learning algorithms with applications. In: Suykens J, Horvath G, Basu S, editors. Advances in learning theory: Methods, models and applications. Amsterdam: IOS Press. pp 111e129.

Emanuel I, Huang SW, Yeh EK. 1968. Physical features of Chinese children with Down's syndrome. Am J Dis Child 115:461–468.

Forrester MB, Merz RD. 2003. Maternal age-specific Down syndrome rates by maternal race/ethnicity, Hawaii, 1986–2000. Birth Defects Res A Clin Mol Teratol 67:625–629.

Freeman SB, Bean LH, Allen EG, Tinker SW, Locke AE, Druschel C, Hobbs CA, Romitti PA, Royle MH, Torfs CP, Dooley KJ, Sherman SL. 2008. Ethnicity, sex, and the incidence of congenital heart defects: A report from the National Down syndrome project. Genet Med 10:173–180.

Fried K. 1980. A score based on eight signs in the diagnosis of Down syndrome in the newborn. J Ment Defic Res 24:181–185.

Hall B. 1964. Mongolism in newborns. Acta Paediatr Scand 154:1–95.

Hindley D, Medakkar S. 2002. Diagnosis of Down's syndrome in neonates. Arch Dis Child Fetal Neonatal Ed 87:F220–F221.

Hook EB, Carothers AD, Hecht CA. 1999. Elevated maternal age-specific rates of Down syndrome liveborn offspring of women of Mexican and Central American origin in California. Prenat Diagn 19:245–251.

Jackson JM, Crider KS, Cragan JD, Rasmussen SA, Olney RS. 2014. Frequency of prenatal cytogenetic diagnosis and pregnancy outcomes by maternal race-ethnicity, and the effect on the prevalence of trisomy 21, Metropolitan Atlanta, 1996–2005. Am J Med Genet A 164A:70–76.

Jelliffe DB. 1954. Mongolism in Jamaican children. West Indian Med J 3:164–165.

Jones LJ, Jones MC, Del Campo M. 2013. Smith's recognizable patterns of human malformation seventh edition. Philadelphia, PA: Elsevier Saunders.

Kava MP, Tullu MS, Muranjan MN, Girisha KM. 2004. Down syndrome: Clinical profile from India. Arch Med Res 35:31–35.

Kim JH, Hwang JM, Kim HJ, Yu YS. 2002. Characteristic ocular findings in Asian children with Down syndrome. Eye (Lond) 16:710–714.

Koretzky M, Bonham VL, Berkman BE, Kruszka P, Adeyemo A, Muenke M, Hull SC. 2016. Towards a more representative morphology: Clinical and ethical considerations for including diverse populations in diagnostic genetic atlases. Genet Med [Epub ahead of print].

Kruszka P. 2015. Down syndrome. In: Muenke M, Kruszka P, Sable C, Belmont J, editors. Congenital cardiovascular anomalies: Molecular genetics, principles of diagnosis and treatment, basel. Karger Publishing: Switzerland. pp 82–90.

Kuroki Y, Yamamoto Y, Matsui I, Kurita T. 1977. Down syndrome and maternal age in Japan, 1950–1973. Clin Genet 12:43–46.

Lee CH, Schmid W, Smith PM. 1961. Definitive diagnosis of mongolism in newborn infants by chromosome studies. JAMA 178:1030–1032.

Lejeune J, Gautier M, Turpin R. 1959. Etude des chromosomes somatiques de neuf enfants mongoliens. C R Hebd Seances Acad Sci 248:1721–1722.

Luder J, Musoke LK. 1955. Mongolism in Africans. Arch Dis Child 30:310–315.

Mgone CS. 1983. Physical features in African children with Down's syndrome. E Afr Med 60:314–318.

Muenke M, Adeyemo A, Kruszka P. 2016. An electronic atlas of human malformation syndromes in diverse populations. Genet Med [Epub ahead of print].

Ojala T, Pietikäinen M, Harwood D. 1996. A comparative study of texture measures with classification based on featured distributions. Pattern Recogn 29:51–59.

Parker GF. 1950. The incidence of mongoloid imbecility in the newborn infant: A 10 year study covering live births. J Pediat 36:493–494.

Pavarino Bertelli EC, Biselli JM, Bonfim D, Goloni-Bertollo EM. 2009. Clinical profile of children with Down syndrome treated in a genetics outpatient service in the southeast of Brazil. Rev Assoc Med Bras 55:547–552.

Sivakumar S, Larkins S. 2004. Accuracy of clinical diagnosis in Down's syndrome. Arch Dis Child 89:691–693.

Solomons G, Zellweger H, Jahnke PG. 1965. Four common eye signs in mongolism. Am J Dis Child 110:46–50.

Sureshbabu R, Kumari R, Ranugha S, Sathyamoorthy R, Udayashankar C, Oudeacoumar P. 2011. Phenotypic and dermatological manifestations in Down Syndrome. Dermatol Online J 17:3.

Torfs CP, Christianson RE. 1998. Anomalies in Down syndrome individuals in a large population-based registry. Am J Med Genet 77:431–438.

Verma IC, Singh M. 1975. Letter: Down syndrome in India. Lancet 1:1200.

Weijerman ME, van Furth AM, Vonk Noordegraaf A, van Wouwe JP, Broers CJ, Gemke RJ. 2008. Prevalence, neonatal characteristics, and first-year mortality of Down syndrome: A national study. J Pediatr 152:15–19.

Zhao Q, Okada K, Rosenbaum K, Zand DJ, Sze R, Summar M, Linguraru MG. 2013. Hierarchical constrained local model using ICA and its application to Down syndrome detection. Med Image Comput Comput Assist Interv 16:222–229.

Zhao Q, Werghi N, Okada K, Rosenbaum K, Summar M, Linguraru MG. 2014. Ensemble learning for the detection of facial dysmorphology. Conf Proc IEEE Eng Med Biol Soc 2014:754–757.

Zhao Q, Okada K, Rosenbaum K, Kehoe L, Zand DJ, Sze R, Summar M, Linguraru MG. 2014b. Digital facial dysmorphology for genetic screening: Hierarchical constrained local model using ICA. Med Image Anal 18:699–710.

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