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 to 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.

**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; Forrestor 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 atriointerventricular 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; Wiejerman 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,
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 cytogenetic testing (karyotype and/or chromosomal microarray) were evaluated from 13
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 were 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...
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...
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,
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
preemptive 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 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 | | |
| Asian | 32 | 25 | 22 | 17 |
| Total | 129 | 132 |
| **Gender** | **Number** | **%** | **Number** | **%** |
| Male | 60 | 47 | 68 | 52 |
| Female | 69 | 53 | 64 | 48 |
| Total | 129 | 132 |

| 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.
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 discomfort 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 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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