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Williams–Beuren syndrome in diverse populations

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Williams–Beuren syndrome (WBS) is a common microdeletion syndrome characterized by a 1.5Mb deletion in 7q11.23. The phenotype of WBS has been well described in populations of European descent with not as much attention given to other ethnicities. In this study, individuals with WBS from diverse populations were assessed clinically and by facial analysis technology. Clinical data and images from 137 individuals with WBS were found in 19 countries with an average age of 11 years and female gender of 45%. The most common clinical phenotype elements were periorbital fullness and intellectual disability which were present in greater than 90% of our cohort. Additionally, 75% or greater of all individuals with WBS had malar flattening, long philtrum, wide mouth, and small jaw. Using facial analysis technology, we compared 286 Asian, African, Caucasian, and Latin American individuals with WBS with 286 gender and age matched controls and found that the accuracy to discriminate between WBS and controls was 0.90 when the entire cohort was evaluated concurrently. The test accuracy of the facial recognition technology increased significantly when the cohort was analyzed by specific ethnic population (P-value < 0.001 for all comparisons), with accuracies for Caucasian, African, Asian, and Latin American groups of 0.92, 0.96, 0.92, and 0.93, respectively. In summary, we present consistent clinical findings from global populations with WBS and demonstrate how facial analysis technology can support clinicians in making accurate WBS diagnoses.

KEYWORDS
Africa, Asia, diverse populations, facial analysis technology, Latin America, Middle East, syndrome, Williams, Williams–Beuren

1 | INTRODUCTION

Williams-Beuren syndrome (WBS) was first characterized as a syndrome with dysmorphic facial features, supravalvar aortic stenosis, and cognitive impairment in the early 1960's (Beuren, Apitz, & Harmjanz, 1962; Williams, Barratt-Boyes, & Lowe, 1961). WBS is one of the common microdeletion syndromes occurring in roughly 1:7500 (Stromme, Bjornstad, & Ramstad, 2002) and caused by a 1.5 Mb deletion in 7q11.23 which includes 26–28 genes. Individuals with WBS present with intellectual disability, hypersocial behavior, distinctive facies, cardiovascular disease (supravalvar aortic stenosis and peripheral pulmonary stenosis), short stature, connective tissue anomalies, and endocrine abnormalities such as hypercalcemia (Morris, 1993, 2010; Sindhar et al., 2016). Facial characteristics include broad forehead, bitemporal narrowing, periorbital fullness, a stellate iris appearance, short nose, malar flattening, long philtrum, thick upper and lower lip vermillion, wide mouth, and large ear lobes (Morris, 1993, 2010).

The diagnosis of WBS is made based on dysmorphic features and intellectual and behavioral findings. Diagnosis is confirmed with molecular testing. Most studies have focused on Caucasians, which can be explained by a concentration of clinical geneticists in developed countries (Limwongse, 2017) and the absence of genetics services in areas such as sub-Saharan Africa (Tekendo-Ngongang et al., 2014). The American Academy of Pediatrics has outlined clinical diagnostic criteria (Committee on Genetics, 2001), which places emphasis on both facial features and echocardiography; however, these criteria may be difficult to apply to diverse populations such as sub-Saharan patients given the variation in facial features and difficulty obtaining echocardiograms (Tekendo-Ngongang et al., 2014). A few small studies have been conducted in diverse populations. Tekendo-Ngongang et al. presented three individuals with WBS from Cameroon in sub-Saharan Africa and noted that the facial features were not different from many unaffected sub-Saharan African individuals (Tekendo-Ngongang et al., 2014). Additionally, Lumaka et al. reported one case of WBS in a resource limited area of central Africa and these authors remind us that most cases in sub-Saharan Africa are undiagnosed based on insufficient training in the field of dysmorphology and scarcity of genetic resources (Lumaka et al., 2016).

Although we know of at least one comparison of different ethnicities and WBS, where Zitzer-Comfort et al. compared global sociability

TABLE 1 Summary of clinical exam findings of individuals with Williams–Beuren syndrome from diverse backgrounds

	Present study				Perez Jurado et al. (1996)	Patil et al. (2012)
	Latin American $n = 105$	Asian $n = 24$	African $n = 8$	p values	African American, Asian, Caucasian, Latin American $n = 65$	Indian $n = 27$
Average age (years)	11.9	8.1	7.7			5.5
Male gender	55%	50%	75%			74%
Molecular diagnosis	100%	96%	75%		94% (56/59)	100%
Cardiovascular disease	73%	71%	88%	.64	50% (24/48)[a]	63%[a]
Wide mouth	91%	78% (18/23)	88%	<.001		100%
Short nose	74%	75%	88%	.71	90% (37/41)	100%
Periorbital fullness	95%	92%	100%	.62	96% (42/44)	100%
Malar flattening	99%	75%	100%	.001	100% (43/43)	85%
Small jaw	82%	75%	75%	.69	na	85%
Long philtrum	93%	79%	88%	.10	83% (35/42)	85%
Epicanthic folds	73%	63%	13%	.001	71% (27/38)	52%
Malocclusion	59% (55/94)	47% (8/17)	38%	.39	81% (25/31)	44%
Widely spaced teeth	47% (35/74)	93% (15/16)	71% (5/7)	.002		41%
Broad eyebrow	63%	58%	63%	.92	67% (22/33)[b]	37%
Stellate iris	85% (82/97)	12% (2/16)	14% (1/7)	<.001		15%
Strabismus	57% (59/104)	6% (1/17)	25%	<.001		11%
Intellectual disability	100% (103/103)	95% (18/19)	100% (7/7)	.05	91% (42/46)[c]	
Growth abnormalities	91% (93/102)	53% (9/17)	25%	<.001	18% (8/44)[d]	

[a]Supraventricular aortic stenosis.
[b]Described as medial eyebrow flare in Perez Jurado et al. (1996).
[c]IQ $\leq$ 75.
[d]Weight < 3rd centile.

between Japanese and United States individuals with WBS (Zitzer-Comfort, Doyle, Masataka, Korenberg, & Bellugi, 2007), we are unaware of a dysmorphology and diagnostic comparison. In line with other publications on genetic syndromes in diverse populations, we explore the phenotype of WBS in different ancestral populations using both clinical exam and facial analysis technology (Kruszka, Addissie, et al., 2017; Kruszka, Porras, et al., 2017; Kruszka, Porras, Sobering, et al., 2017; Muenke, Adeyemo, & Kruszka, 2016).

2 | METHODS

2.1 | Review of medical literature

A Medline search was conducted with the following terms: WBS, Africa, Asia, Latin America, Middle East, diverse populations, and facial analysis technology. Reference lists of journal studies were used to find further relevant journal articles. After obtaining journal permissions, photos of individuals with WBS were used to supplement study participants described below (Delgado et al., 2013; Honjo et al., 2015; Jiang & Liu, 2015; Lumaka et al., 2016; Mazumdar, Sarkar, Badveli, & Majumder, 2016; Morris, 1993, 2010; Patil, Madhusudhan, Shah, & Suresh, 2012; Sakhuja, Whyte, Kamath, Martin, & Chitayat, 2015; Smoot, Zhang, Klaiman, Schultz, & Pober, 2005; Tekendo-Ngongang et al., 2014; van Kogelenberg et al., 2010; Wu et al., 2002).

2.2 | Patients

Individuals with WBS were evaluated from 19 countries. All participants (Supporting Information Table 1) had WBS diagnosed by both clinical evaluation and/or molecular diagnosis. In a few cases molecular diagnosis was not done secondary to resource limitations. Geographic area of origin or ethnicity (African and African American, Asian, Latin American, and Middle Eastern) was used to categorize patients. Local clinical geneticists examined patients for established clinical features found in WBS (Committee on Genetics, 2001).

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 (Patil et al., 2012; Perez Jurado, Peoples, Kaplan, Hamel, & Francke, 1996) are recorded in Table 1.

2.3 | Facial analysis technology

As described in our previous studies (Kruszka, Addissie, et al., 2017; Kruszka, Porras, et al., 2017; Kruszka, Porras, Sobering, 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) evaluated 286 frontal images of individuals with WBS, and 286 healthy controls (matched for ethnicity, gender, and age) from our previously described database (Zhao et al., 2013; Zhao, Okada, et al., 2014; Zhao, Werghi, et al., 2014). The 286 individuals with WBS used for facial analysis technology included individuals from Supporting Information Table 1 and additional archival images of individuals with WBS. A Caucasian ethnic group was identified in addition to African, Asian, and Latin American groups for the purpose of facial analysis. In Table 2, we show ages, gender, and ethnicity of the facial analysis technology cohort.

TABLE 2 Population data used in facial analysis technology, which includes 286 individuals with Williams–Beuren syndrome

	Williams–Beuren		Controls	
	Number	%	Number	%
Age				
<30 days	0	0	0	0
1–24 months	49	17	49	17
25–60 months	47	16	47	16
5–12 years	71	25	71	25
13–18 years	28	10	28	10
>18 years	91	32	91	32
Total	**286**		**286**	
Ethnicity				
African Descent	28	10	28	10
Asian	26	9	26	9
Caucasian	121	42	121	42
Latino	111	39	111	39
Total	**286**		**286**	
Gender				
Male	150	52	150	52
Female	136	48	136	48
Total	**286**		**286**	

With feature extraction, feature selection, and classification as output variables, our algorithms analyzed study participants' images. From a set of 44 landmarks placed on the frontal face images, a total of 126 facial features, including both geometric and texture biomarkers, were isolated. Figure 1 shows the landmark locations and the geometric features extracted. The geometric biomarkers are distances and angles calculated between the different inner facial landmarks. Texture patterns (Cerrolaza et al., 2016) were calculated at each of the 33 inner facial landmarks to quantify texture information (Figure 1). Using the method proposed previously (Cai, Zhang, & He, 2010), from the collection of geometric and texture features, the most significant ones were selected. 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 minimum number for which the classification accuracy converged to its maximum; Supporting Information Figures 1–5 graphically demonstrate how the addition of features improves the measures of sensitivity, specificity, and accuracy. The p value of each feature was also estimated using the Student's t-test as an estimator of the individual discriminant power of each feature selected. We evaluated the improvements of using classification models trained specifically for each ethnicity to detect WBS compared to using one single classification model trained using all the cases available from all ethnicities. The statistical significance of their differences was assessed using Fisher's exact test.

3 | RESULTS

Clinical information (Table 1) was collected on 137 individuals and images (Figures 2–5; Supporting Information Table 1) on 128 individuals (17 individuals were obtained from the medical literature). The

FIGURE 1 Facial landmarks on three patients with WBS. 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. [Color figure can be viewed at wileyonlinelibrary.com]

participants were from 19 countries, average age was 11.0 years (range newborn to 42 years), and 45% were females (Table 1). Individuals of African descent are shown in Figure 2, Asian in Figure 3, Latin American in Figure 4, and Middle Eastern patients in Figure 5. Table 1 does not show individuals from Middle East due to insufficient clinical information.

From the medical literature in Table 1, we show facial and other phenotype elements from two studies that each evaluated over 25 participants from diverse backgrounds (Patil et al., 2012; Perez Jurado et al., 1996). We compared unpublished patients from the present study with the above-mentioned studies from the medical literature (Table 1). The most common phenotype element in both the present study and the medical literature was periorbital fullness and intellectual disability which was present in greater than 90% of our cohort (Table 1). In all studies in Table 1, 75% or greater of all individuals with WBS had malar flattening, long philtrum, wide mouth, and small jaw (wide mouth and small jaw not reported in Perez Jurado et al., 1996).

As seen in Table 1, the majority of clinical exam findings in the present study were consistent between the different population groups with the following exam elements differing statistically amongst groups: wide mouth, malar flattening, epicanthal folds, widely spaced teeth, stellate iris, strabismus, and growth abnormalities ($p < .05$; χ^2 test).

As a more objective measure of phenotype, facial analysis technology was applied to 286 individuals (Caucasian, African, Asian, and Latin American) with results shown in Table 3. The accuracy to discriminate between WBS and controls was 0.90 when the entire cohort was evaluated concurrently. The test accuracy of the facial recognition technology increased significantly when the cohort was analyzed by specific ethnic population (p value $< .001$ for all comparisons), with accuracies for Caucasian, African, Asian, and Latin American groups of 0.92, 0.96, 0.92, and 0.93, respectively (Table 3). Supporting Information Tables 2–6 show the geometric and texture feature comparisons between individuals with WBS and unaffected individuals. Interestingly, the angle at the nose root is the most significant geographic discriminator between WBS and controls across all ethnicities.

4 | DISCUSSION

WBS is a common microdeletion syndrome that has recognizable facial characteristics, intellectual disability, a characteristic friendly personality,

FIGURE 2 Frontal and lateral facial profiles of individuals of African descent with WBS. Gender, age, and country of origin are presented in Supporting Information Table 1. [Color figure can be viewed at wileyonlinelibrary.com]

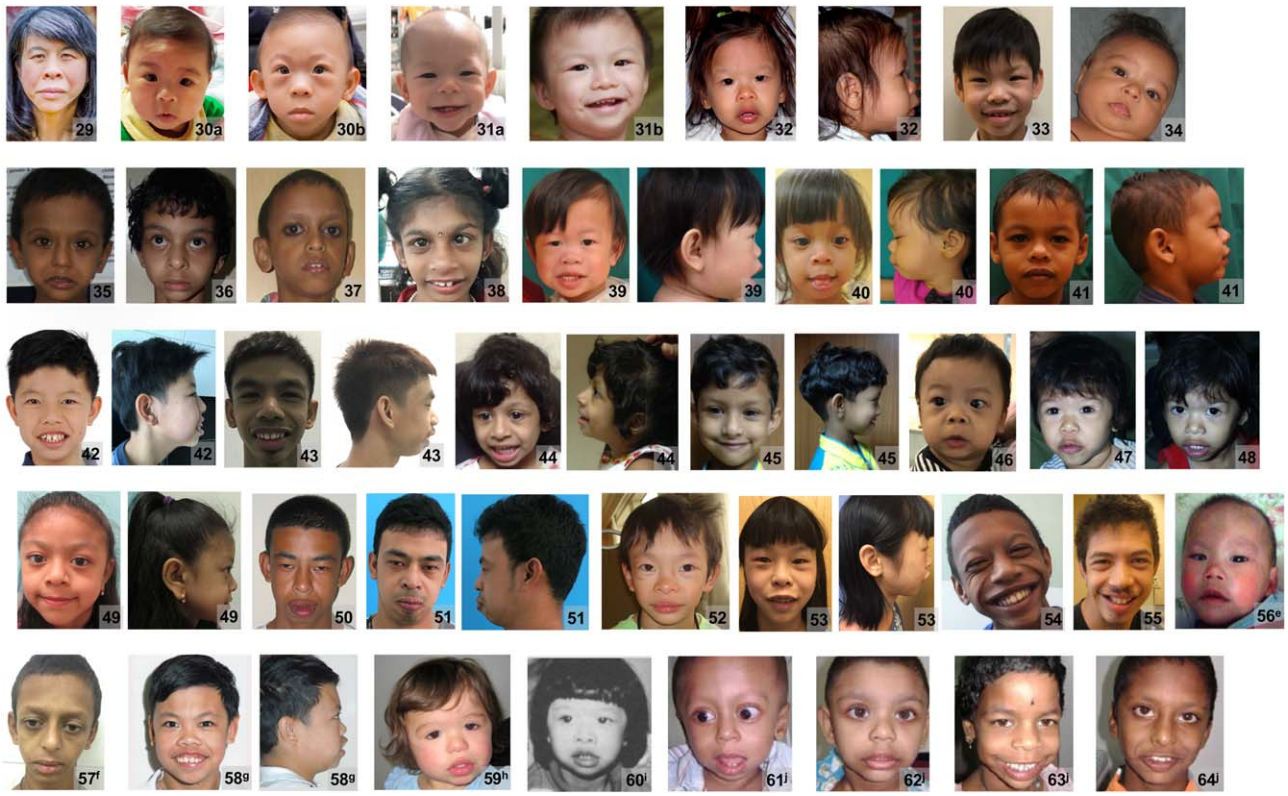

FIGURE 3 Frontal and lateral facial profiles of Asian individuals with WBS. Gender, age, and country of origin are presented in Supporting Information Table 1. [Color figure can be viewed at wileyonlinelibrary.com]

and often cardiovascular disease. Given the well characterized phenotype of WBS, there is still a paucity of cases of WBS from developing countries in the medical literature (Lumaka et al., 2016; Tekendo-Ngongang et al., 2014). The first goal of this study was to assemble and characterize a cohort of individuals with WBS from diverse populations. Table 1 lists the clinical phenotype of 137 individuals from Latin American, Asian, and African ancestry and Figures 2–5 show 128 facial images of individuals from diverse populations. Although there are some statistically significant differences in phenotype elements across population groups, there are multiple well-known characteristics that are present in

FIGURE 4 Frontal and lateral facial profiles of Latin Americans with WBS. Gender, age, and country of origin are presented in Supporting Information Table 1. [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 5 Frontal and lateral facial profiles of individuals from the Middle East with WBS. Gender, age, and country of origin are presented in Supporting Information Table 1. [Color figure can be viewed at wileyonlinelibrary.com]

75% or more of all groups, including periorbital fullness, wide mouth, malar flattening, small jaw, long philtrum, and intellectual disability (Table 1). In addition to this study, we have also made a publicly available database that shows images of individuals with WBS and syndromes in diverse populations (http://www.genome.gov/atlas) (Koretzky et al., 2016; Muenke et al., 2016).

The second goal of this study was to test whether a diagnosis was more difficult in different ethnicities as has been suggested (Patil et al., 2012; Tekendo-Ngongang et al., 2014). To answer this question, we used the objectivity of facial analysis technology. The facial analysis technology accurately discriminated between individuals with WBS and controls with accuracy above 92% in all population groups (Table 3). The test accuracy of the facial recognition technology increased significantly when the cohort was analyzed by specific ethnic population (p value $< .001$ for all comparisons; Fisher's test), in other words, when the computer was trained on an ethnic specific data set, the accuracy improved.

Some of the characteristic features of WBS in the global population determined by facial analysis technology are: wide mouth, short nose, and texture of eyelids/epicanthic folds, which were also noted in the clinical evaluation of most of the cases. We would like to make special mention of the angle of the nose root. As noted in the results, the angle at the nose root is the most significant geographic discriminator between WBS and controls across all ethnicities (Supporting Information Tables 2–6). The angle at the nose root is not typically measured by clinicians; however, the angle at the nose root increases for shorter noses, which is a well-known feature in patients with Williams syndrome as seen in Table 1. Interestingly, the only population group for which the width of the mouth was not depicted as a top feature of WBS by our technology was the African group.

TABLE 3 Measures of diagnostic accuracy for facial analysis technology that discriminate between Williams-Beuren syndrome and unaffected individuals, stratified by populations

	Number of features	AUC	Accuracy	Sensitivity	Specificity
Global	17	0.95	0.90	0.92	0.88
Caucasian	15	0.97	0.92	0.89	0.95
African and African American	9	0.96	0.96	0.96	0.96
Asian	8	0.95	0.92	0.96	0.88
Latin American	15	0.97	0.93	0.95	0.92

AUC = area under the receiver operating characteristic curve

The study has several limitations. We acknowledge that ascertainment bias exists with only the most severe phenotypes or those with severe congenital heart disease seeking medical attention. Thus, the milder cases of WBS are most likely missed. Due to relatively small sample sizes, this study grouped populations by large geographical areas. For example, individuals from India, Thailand, and China are grouped into the category "Asia." In the future, we plan to narrow this geographic constraint. Another limitation is that much of the clinical data is subjective and based on provider judgement. We have attempted to address this issue with the use of objective measurements using digital face analysis technology.

We conclude by acknowledging that WBS can be a difficult diagnosis to make (average age of diagnosis of WBS is 3.7–5.3 years in developed countries) (Ferrero et al., 2007; Huang, Sadler, O'Riordan, & Robin, 2002). This study and similar reports (Kruszka, Addissie, et al., 2017; Kruszka, Porras, et al., 2017; Kruszka, Porras, Sobering, et al., 2017) and our recently created website, http://www.genome.gov/atlas are designed to have widespread clinical significance for the diagnosis of individuals with WBS, especially in countries without access to genetic services or genetic testing where the simplicity of facial analysis technology may be a useful asset.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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