Williams-Beuren Syndrome in Diverse Populations

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ABSTRACT

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.

KEY WORDS

Williams-Beuren; Williams; syndrome; diverse populations; Asia; Africa; Latin America; Middle East; facial analysis technology

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 1.5Mb 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, 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. Tekeno-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 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, Addissie, et al., 2017; Kruszka, Porras, Sobering, et al., 2017; Muenke, Adeyemo, & Kruszka, 2016).

METHODS

Review of Medical Literature

A Medline search was conducted with the following terms: Williams-Beuren syndrome, 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).

Patients

Individuals with Williams-Beuren syndrome were evaluated from 19 countries. All participants (Supplementary Table I) had Williams-Beuren syndrome 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, 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 I.

Facial Analysis Technology

As described in our previous studies (Kruszka, Addissie, et al., 2017; Kruszka, Porras, Addissie, et al., 2017; Kruszka, Porras, Sobering, et al., 2017), digital facial analysis technology (Cerrolaza et al., 2016; Zhao, Okada, et al., 2014; Zhao et al., 2013; 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, Okada, et al., 2014; Zhao et al., 2013; Zhao, Werghi, et al., 2014). The 286 individuals with WBS used for facial analysis technology included individuals from Supplementary Table I 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 II, we show ages, gender, and ethnicity of the facial analysis technology cohort.

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; Supplementary 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.

RESULTS

Clinical information (Table I) was collected on 137 individuals and images (Figure II-V; Supplementary Table I) on 128 individuals (17 individuals were obtained from the medical literature). The participants were from 19 countries, average age was 11.0 years (range newborn to 42 years), and 45% were females (Table I). 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 I does not show individuals from Middle East due to insufficient clinical information.

From the medical literature in Table I, 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 I). 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 I). In all studies in Table I, 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 Pérez Jurado et. al).

As seen in Table I, 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 ($P<0.05$; 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 III. . 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 (Table III). Supplementary Tables II-VI 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.

DISCUSSION

Williams-Beuren syndrome is a common microdeletion syndrome that has recognizable facial characteristics, intellectual disability, a characteristic friendly personality, and often cardiovascular disease. Given the well characterized phenotype of WBS, there is still a paucity of cases of Williams-Beuren syndrome 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 I 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 75% or more of all groups, including periorbital fullness, wide mouth, malar flattening, small jaw, long philtrum, and intellectual disability (Table I). In addition to this study, we have also made a publically available database that shows images of individuals with WBS and syndromes in diverse populations (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 III). 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; 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 (Supplementary Tables II-VI). 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 I. 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.

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 Williams-Beuren syndrome 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, Addissie, et al., 2017; Kruszka, Porras, Sobering, et al., 2017) and our recently created website, 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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LEGENDS

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.

Figure 2. Frontal and lateral facial profiles of individuals of African descent with WBS. Gender, age, and country of origin are presented in Supplementary Table I.

Figure 3. Frontal and lateral facial profiles of Asian individuals with WBS. Gender, age, and country of origin are presented in Supplementary Table I.

Figure 4. Frontal and lateral facial profiles of Latin Americans with WBS. Gender, age, and country of origin are presented in Supplementary Table I.

Figure 5. Frontal and lateral facial profiles of individuals from the Middle East with WBS. Gender, age, and country of origin are presented in Supplementary Table I

Table I. Summary of clinical exam findings of individuals with Williams-Beuren syndrome from diverse backgrounds

	Present Study				Pérez Jurado et al. (1996)	Patil et al. (2012)
	Latin American	Asian	African	*P-values*	African-American, Asian, Caucasian, Latin American	Indian
	n=105	n=24	n=8		n=65	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%	*P*=0.64	50% (24/48)*	63%*
Wide mouth	91%	78% (18/23)	88%	*P*<0.001		100%
Short nose	74%	75%	88%	*P*=0.71	90% (37/41)	100%
Periorbital fullness	95%	92%	100%	P=0.62	96% (42/44)	100%
Malar flattening	99%	75%	100%	*P*<0.001	100% (43/43)	85%
Small jaw	82%	75%	75%	P=0.69	na	85%
Long philtrum	93%	79%	88%	P=0.10	83% (35/42)	85%
Epicanthic folds	73%	63%	13%	P=0.001	71% (27/38)	52%
Malocclusion	59% (55/94)	47% (8/17)	38%	P=0.39	81% (25/31)	44%
Widely spaced teeth	47% (35/74)	93% (15/16)	71% (5/7)	P=0.002		41%
Broad eyebrow	63%	58%	63%	P=0.92	67% (22/33)**	37%
Stellate iris	85% (82/97)	12% (2/16)	14% (1/7)	*P*<0.001		15%
Strabismus	57% (59/104)	6% (1/17)	25%	*P*<0.001		11%
Intellectual disability	100% (103/103)	95% (18/19)	100% (7/7)	P=0.05	91% (42/46)***	
Growth abnormalities	91% (93/102)	53% (9/17)	25%	*P*<0.001	18% (8/44)****	

*supraventricular aortic stenosis

**described as medial eyebrow flare in Perez Jurado et al. 1996

***IQ $\leq$ 75

****weight < 3rd centile

Table II. Population data used in facial analysis technology, which includes 286 individuals with Williams-Beuren syndrome.

	Williams-Beuren		**Controls**	
Age	**Number**	**%**	**Number**	**%**
< 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	**Number**	**%**	**Number**	**%**
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	**Number**	**%**	**Number**	**%**
Male	150	52%	150	52%
Female	136	48%	136	48%
Total	**286**		**286**	

Table III

	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

Figure 1. Facial landmarks on three patients with Williams-Beuren syndrome. 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.

316x159mm (300 x 300 DPI)

Figure 2. Frontal and lateral facial profiles of individuals of African descent with WBS. Gender, age, and country of origin are presented in Supplementary Table I.

334x90mm (300 x 300 DPI)

Figure 3. Frontal and lateral facial profiles of Asian individuals with WBS. Gender, age, and country of origin are presented in Supplementary Table I.

279x174mm (300 x 300 DPI)

Figure 4. Frontal and lateral facial profiles of Latin Americans with WBS. Gender, age, and country of origin are presented in Supplementary Table I.

328x161mm (300 x 300 DPI)

Figure 5. Frontal and lateral facial profiles of individuals from the Middle East with WBS. Gender, age, and country of origin are presented in Supplementary Table I

245x69mm (300 x 300 DPI)

Supplementary Table I. Participants with photographs in Figures 2-5. Participants are from 19 countries and diagnosed with Williams-Beuren syndrome (WBS).

Patient ID	Country	Diagnosis	Age	Gender	Comment
1	Ghana	clinical diagnosis by E.B.	6 mo	male	
2	Ghana	clinical diagnosis by E.B.	8 yo	female	
3	South Africa	FISH	7 yo	male	
4	South Africa	FISH	9 yr and 6 mo	male	
5	South Africa	MLPA	10 yo	male	
6	South Africa	FISH	17 yo	female	
7	USA	FISH	1.6 yo	female	
8	USA	FISH	2.75 yo	male	
9	USA	FISH	3.5 yo	female	
10	USA	FISH	5.5 yo	female	
11	USA	FISH	5.5 yo	female	
12	USA	FISH	5.6 yo	female	
13	USA	FISH	6 yo	female	
14	USA	FISH	7 yo	male	
15	USA	FISH	8 yo	female	
16	USA	FISH	8 yo	male	
17	USA	FISH	11 yo	male	
18	USA	FISH	12.8 yo	male	
19	USA	FISH	13 yo	female	
20	USA	microarray	13 yo	male	
21	USA	FISH	15 yo	female	
22	USA	FISH	35 yo	female	
23[a]	Bahrain	microarray	4 mo	male	
24[b]	Demoratic Republic of Congo	FISH and microarray	8.5 yo	Male	
25[c]	Cameroon	FISH and microarray	19 mo	Female	
26[c]	Cameroon	FISH and microarray	13 yo	Female	
27[c]	Cameroon	FISH and microarray	14 yo	Male	
28[d]	USA	not specified	11 mo	female	
29	Canada	FISH	38 yo	female	(Chinese decent)
30a	China	FISH	6 mo	male	
30b	China	FISH	31mo	male	
31a	China	MLPA	1 yr and 2 mo	female	
31b	China	MLPA	4 yo	male	
32	China	FISH/MLPA	5 yo	female	
33	China	FISH	6 yr and 10 mo	male	
34	India	FISH	5 mo	male	

35	India	FISH	3 yr	male	
36	India	FISH	7 yo	female	
37	India	FISH	9 yr	male	
38	India	FISH	10 yr	female	
39	Malaysia	FISH	2 yr and 1 mo	Female	
40	Malaysia	FISH	2 yr and 9 mo	Female	
41	Malaysia	FISH	6 yr and 7 mo	Male	
42	Singapore	FISH	10 years old	Male	
43	SIngapore	FISH	19 years old	Male	
44	Sri Lanka	FISH	3 yr and 9mo	Female	
45	Sri Lanka	FISH	6 yr and 9 mo	Female	
46	Taiwan	MLPA	1 yr and 1 mo	Male	
47	Thailand	FISH	3 yo	Female	
48	Thailand	FISH	4 yo	Female	
49	United States	FISH and array	7 yo	female	Latin American
50	Thailand	FISH	14 yo	Male	
51	Thailand	FISH	22 yo	male	
52	USA	FISH	4.5 yo	male	
53	USA	FISH	11 yo	female	
54	USA	FISH	12 yo	male	(Hawaii)
55	USA	FISH	17 yo	male	
56[e]	China	microarray	8 mo	male	
57[f]	India	FISH	12 yo	male	
58[g]	New Zealand	FISH	11 yo	Male	
59[h]	USA	FISH	19 months	female	
60[i]	USA	not specified	42 months	female	
61[j]	India	FISH	2 yo	female	
62[j]	India	FISH	4 yo	male	
63[j]	India	FISH	7 yo	female	
64[j]	India	FISH	9 yo	male	
65	Argentina	clinical diagnosis	11 mo	male	
66	Argentina	clinical diagnosis	1.8 yo	female	
67	Argentina	clinical diagnosis	2 yo	male	
68	Brazil	FISH	10 mo	female	
69	Brazil	FISH	1.4 yo	male	
70	Brazil	FISH	1 yr and 10 mo	male	
71	Brazil	FISH	1 yr an d 11 mo	male	
72	Brazil	FISH	2 yr and 7 mo	female	
73	Brazil	FISH	3 yo	female	
74	Brazil	FISH	4 yo	male	
75	Brazil	FISH	4 yr and 5 mo	female	
76	Brazil	FISH	5 yo	female	

77	Brazil	FISH	6 yo	female	
78	Brazil	FISH	7 yo	female	
79	Brazil	FISH	8 yo	male	
80	Brazil	FISH	9 yo	male	
81	Brazil	FISH	10 yo	female	
82	Brazil	FISH	11 yo	male	
83	Brazil	FISH	12 yo	male	
84	Brazil	FISH	14 yo	female	
85	Brazil	FISH	15 yo	male	
86	Brazil	FISH	16 yo	female	
87	Brazil	FISH	17 yo	female	
88	Brazil	FISH	18 yo	male	
89	Costa Rica	FISH	6 yo	female	
90	Costa Rica	FISH	14 yo	female	
91	Costa Rica	FISH	11 yo	male	
92	Paraguay	FISH	4yr and 3mo	female	
93	Paraguay	FISH	5yr and 11mo	female	
94	Peru	microarray	1.5 mo	female	
95	Peru	microarray	2 mo	male	
96	Peru	microarray	4 mo	female	
97	Peru	microarray	11 mo	male	
98	Peru	microarray	2 yo	female	
99	Peru	microarray	9 yo	female	
100	USA	FISH	2 yo	female	
101	USA	FISH	2.25 yo	male	
102	USA	FISH	3 yo	female	
103	USA	FISH	3.5 yo	female	
104	USA	FISH	4 yo	female	
105	USA	FISH	5 yo	male	
106	USA	FISH	5.5 yo	male	
107	USA	FISH	6 yo	female	
108	USA	FISH	8.5 yo	female	
109	USA	FISH	9 yo	male	
110	USA	FISH	10 yo	male	
111	USA	FISH	11 yo	female	
112[k]	Argentina	qPCR	4 mo	female	
113[l]	Brazil	MLPA	5.5 yo	male	
114	Canada	microarray	17 yo	Male	(Syrian decent)
115	Egypt	FISH	2 months	Female	
116	Egypt	FISH	9 months	male	
117	Egypt	FISH	1 yr and 2 mo	Male	
118	Egypt	FISH	5.9 yo	female	

119	Lebanon	FISH	3.5 mo	male
120	Lebanon	FISH	6 mo	female
121	Lebanon	FISH	1 yo	male
122	Lebanon	FISH	2 yo	female
123	Lebanon	FISH	2.5 yo	male
124	Lebanon	FISH	3 yo	male
125	Lebanon	FISH	11.5 yo	female
126	Lebanon	FISH	13 yo	female
127	Morocco	FISH	8 yo	male
128	Morocco	FISH	12 yo	female

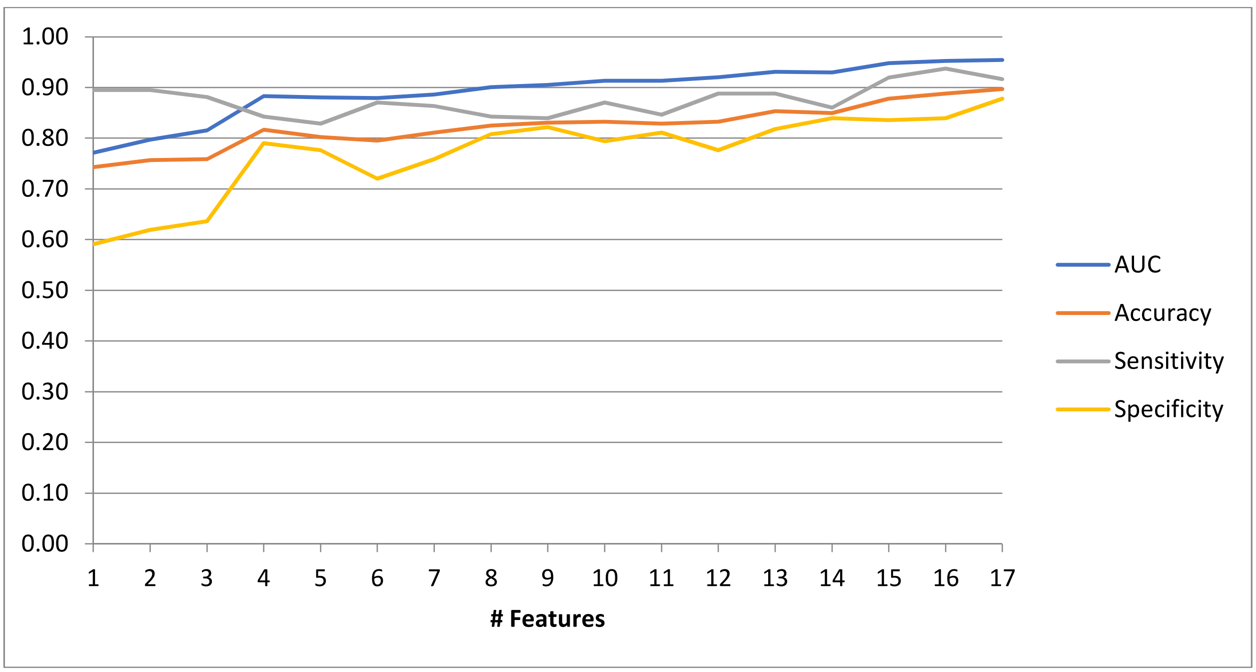
[a](Sakhuja, Whyte, Kamath, Martin, & Chitayat, 2015)
[b](Lumaka et al., 2016)
[c](Tekendo-Ngongang et al., 2014)
[d](Smoot, Zhang, Klaiman, Schultz, & Pober, 2005)
[e](Jiang & Liu, 2015)
[f](Mazumdar, Sarkar, Badveli, & Majumder, 2016)
[g](van Kogelenberg et al., 2010)
[h](Morris, 2010)
[i](Morris, 1993)
[i](Patil, Madhusudhan, Shah, & Suresh, 2012)
[k](Delgado et al., 2013)
[l](Honjo et al., 2015)

Supplementary Table II. Geometric and texture feature comparison of Global (combined Caucasian, Asian, African descent, Latin American) WBS individuals with normal controls using digital facial analysis technology. The ranges of the horizontal geometric linear features were normalized by the ear-to-ear distance, while the vertical distances were normalized by the distance between the eyes and the lower lip. Geometric angle features are presented in degrees. Texture features were computed at three scales (r1, r2, r3). Features are presented in order of their relevance for the diagnosis of WBS.

Feature	Normal	Syndromic	p-value
Angle at nose root	70.257 +/- 16.576	85.238 +/- 9.971	5.27309E-34
Distance between left side of nose root and nose apex	0.399 +/- 0.059	0.343 +/- 0.051	2.31168E-30
Distance between right side of nose root and nose apex	0.4 +/- 0.063	0.344 +/- 0.051	1.00668E-27
Texture at left lateral of nose root (r3)			4.40235E-19
Texture at left part of lower lip (r2)			4.75375E-18
Texture at right lateral of nose root (r2)			4.81703E-18
Angle of right side of the mouth	51.116 +/- 14.337	62.593 +/- 17.234	6.14376E-17

(measured from the outside of the lips)			
Texture at upper eyelid of right eye (r2)			3.80611E-15
Texture at top of right ala of the nose (r2)			1.44215E-14
Distance between oral commissures	0.388 +/- 0.074	0.434 +/- 0.077	6.28365E-13
Texture at left part of cupids bow (r3)			3.59229E-12
Distance between nose apex and columella	0.173 +/- 0.025	0.187 +/- 0.023	1.16009E-11
Texture at columella (r2)			3.7276E-09
Texture at lateral canthus of left eye (r3)			4.61505E-08
Upper lip width	0.068 +/- 0.025	0.078 +/- 0.026	4.5928E-06
Angle at lateral canthus (right eye)	41.228 +/- 8.35	44.008 +/- 10.468	0.000124189
Angle at medial canthus (left eye)	41.093 +/- 8.096	43.384 +/- 8.731	0.000750293

Supplementary Figure 1. Global population: Graph of area under the ROC curve (AUC), accuracy, sensitivity, and specificity versus the number of features selected.

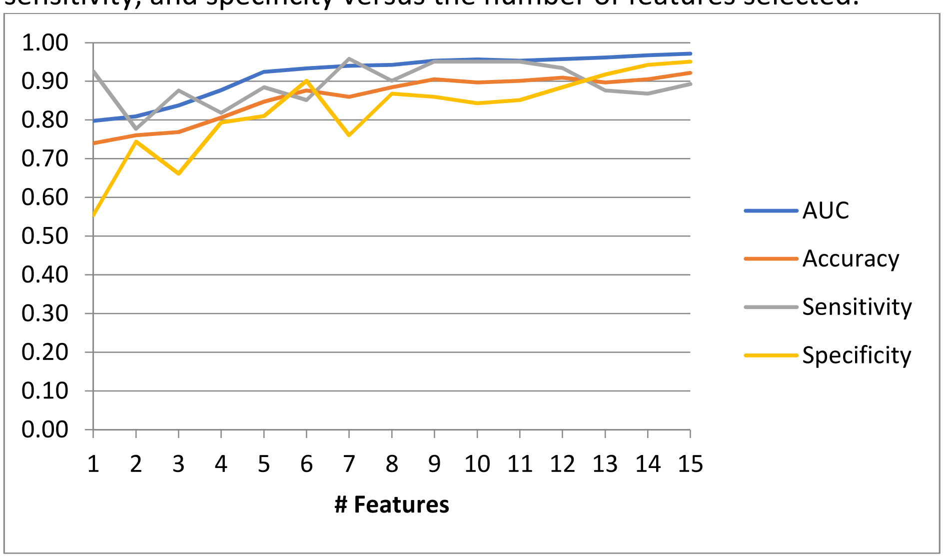


Supplementary Table III. Geometric and texture feature comparison of Caucasian WBS individuals with normal controls using digital facial analysis technology The ranges of the horizontal geometric linear features were normalized by the ear-to-ear distance, while the vertical distances were normalized by the distance between the eyes and the lower lip. Geometric angle features are presented in degrees. Texture features were computed at three scales (r1, r2, r3). Features are presented in order of their relevance for the diagnosis of WBS.

Feature	Normal	Syndromic	p-value

Angle at nose root	70.166 +/- 16.187	86.053 +/- 9.426	6.77962E-18
Distance between left side of nose root and nose apex	0.409 +/- 0.061	0.341 +/- 0.054	2.09375E-17
Texture at columella (r3)			1.25918E-11
Texture at lower eyelid of left eye (r3)			4.28087E-11
Texture at top of right ala of the nose (r1)			1.92217E-10
Texture at center of cupids bow (r3)			4.29519E-10
Texture at upper border of lower lip (r2)			1.88941E-09
Texture at top of left ala of the nose (r2)			2.14126E-09
Texture at lower eyelid of right eye (r2)			2.46039E-08
Distance between oral commissures	0.394 +/- 0.076	0.443 +/- 0.073	7.32473E-07
Texture at lateral canthus of right eye (r3)			8.00163E-07
Texture at upper border of lower lip (r3)			2.1651E-06
Texture at top of right ala of the nose (r3)			7.92805E-06
Upper lip width	0.059 +/- 0.021	0.072 +/- 0.023	2.05443E-05
Texture at upper eyelid of left eye (r1)			0.000134999

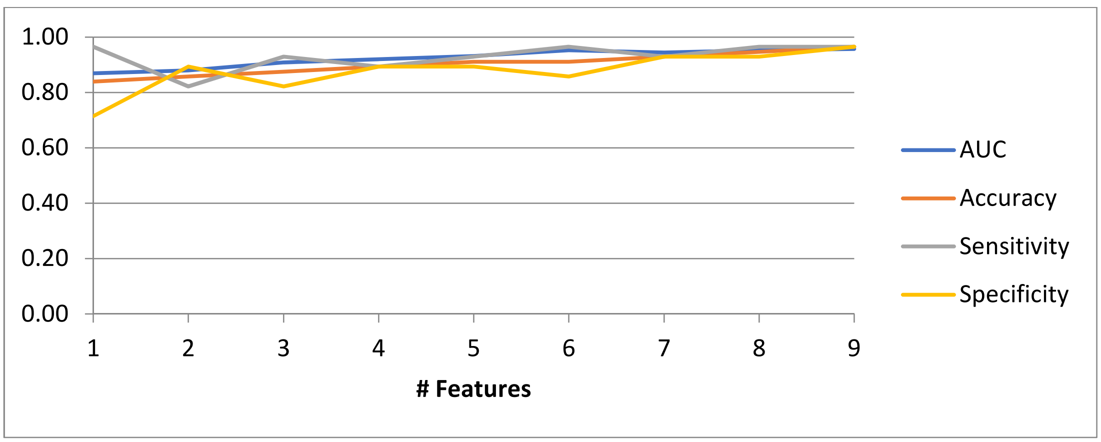
Supplementary Figure 2. Caucasians: Graph of area under the ROC curve (AUC), accuracy, sensitivity, and specificity versus the number of features selected.



Supplementary Table IV. Geometric and texture feature comparison of African and African American individuals with WBS with healthy controls using digital facial analysis technology. The ranges of the horizontal geometric linear features were normalized by the ear-to-ear distance, while the vertical distances were normalized by the distance between the eyes and the lower lip. Geometric angle features are presented in degrees. Texture features were computed at three scales (r1, r2, r3). Features are presented in order of their relevance for the diagnosis of WBS.

Feature	Normal	Syndromic	p-value
Angle at nose root	68.538 +/- 15.375	90.814 +/- 9.608	2.11124E-08
Angle at medial canthus (left eye)	39.385 +/- 9.425	47.215 +/- 8.191	0.001765581
Distance between lateral canthi	0.654 +/- 0.031	0.675 +/- 0.032	0.018077955
Texture at upper eyelid of right eye (r3)			0.023922328
Upper lip width	0.08 +/- 0.036	0.098 +/- 0.029	0.043702077
Texture at center of the right eye (r1)			0.10475625
Texture at upper border of lower lip (r1)			0.10533431
Texture at columella (r2)			0.11443245
Texture at center of left ala of the nose (r3)			0.134

Supplementary Figure 3. Africans and African Americans: Graph of area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, and specificity versus the number of features selected.

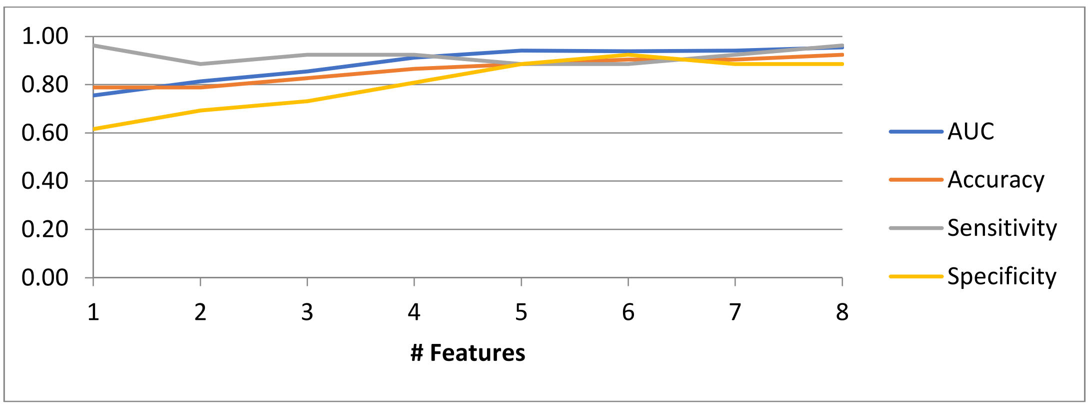


Supplementary Table V. Geometric and texture feature comparison of Asian WBS individuals with normal controls using digital facial analysis technology. The ranges of the horizontal geometric linear features were normalized by the ear-to-ear distance, while the vertical distances were normalized by the distance between the eyes and the lower lip. Geometric angle features are presented in degrees. Texture features were computed at three scales (r1, r2, r3). Features are presented in order of their relevance for the diagnosis of WBS.

Feature	Normal	Syndromic	p-value
Angle at nose root	66.276 +/- 18.235	82.611 +/- 7.463	1.25E-04
Palpebral slanting (left eye)	177.133 +/- 2.065	173.082 +/- 4.089	2.97E-04

Maximum distance between eyelids (left eye)	0.153 +/- 0.046	0.117 +/- 0.033	2.24E-03
Distance between oral commissures	0.337 +/- 0.066	0.397 +/- 0.079	0.004762157
Texture at columella (r3)			0.007999173
Distance between nose apex and columella	0.169 +/- 0.022	0.185 +/- 0.021	0.012007229
Angle of right side of the mouth (measured from the outside of the lips)	59.188 +/- 18.173	67.233 +/- 15.641	0.10583069
Palpebral slanting (right eye)	174.146 +/- 4.095	175.458 +/- 3.302	0.17602848

Supplementary Figure 4. Asians: Graph of area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, and specificity versus the number of features selected.

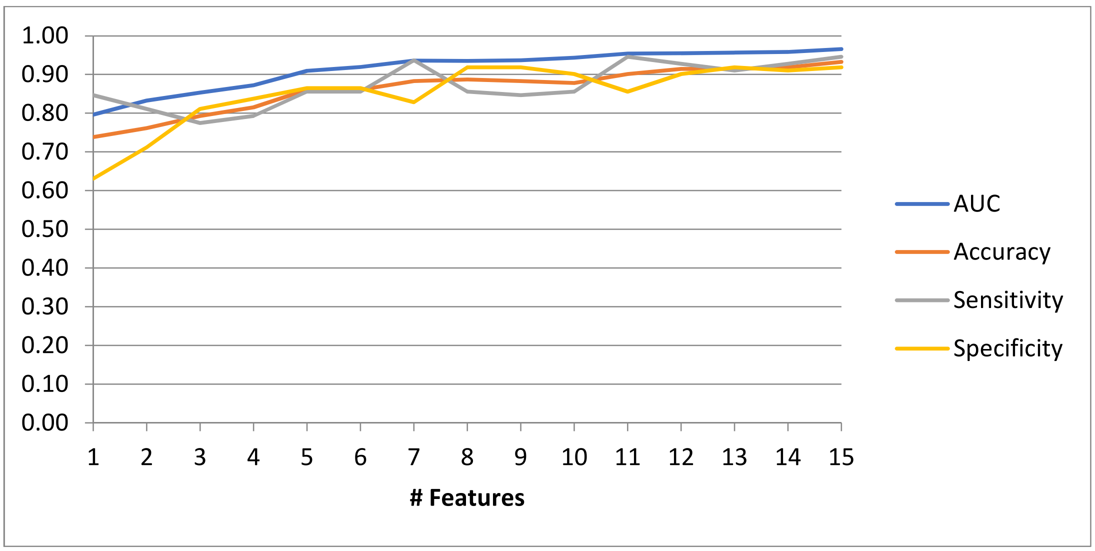


Supplementary Table VI. Geometric and texture feature comparison of Latin American WBS individuals with normal controls using digital facial analysis technology. The ranges of the horizontal geometric linear features were normalized by the ear-to-ear distance, while the vertical distances were normalized by the distance between the eyes and the lower lip. Geometric angle features are presented in degrees. Texture features were computed at three scales (r1, r2, r3). Features are presented in order of their relevance for the diagnosis of WBS.

Feature	Normal	Syndromic	p-value
Distance between right side of nose root and nose apex	0.405 +/- 0.054	0.342 +/- 0.051	3.27092E-16
Texture at left part of cupids bow (r2)			3.95193E-10
Angle at nose root	71.722 +/- 16.905	83.56 +/- 10.594	4.36518E-09
Angle of right side of the mouth (measured from the outside of the lips)	51.206 +/- 13.151	62.909 +/- 16.918	4.01331E-08
Texture at top of left ala of the nose (r2)			1.6398E-06

Texture at bottom of right ala of the nose (r1)			2.0606E-06
Texture at right part of lower lip (r3)			2.10672E-06
Texture at medial canthus of right eye (r2)			4.45863E-06
Distance between oral commissures	0.389 +/- 0.069	0.435 +/- 0.077	4.78453E-06
Distance between nose apex and columella	0.172 +/- 0.027	0.188 +/- 0.024	1.10052E-05
Texture at upper border of lower lip (r2)			4.34483E-05
Texture at left oral commissure (r2)			8.47653E-05
Angle at lateral canthus (right eye)	41.111 +/- 8.147	45.206 +/- 9.923	0.000493682
Palpebral slanting (left eye)	175.506 +/- 3.375	173.944 +/- 3.957	0.003714073
Angle at lateral canthus (left eye)	40.22 +/- 9.265	43.81 +/- 9.502	0.005189508

Supplementary Figure 5. Latin Americans: Graph of area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, and specificity versus the number of features selected.



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