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Turner syndrome in diverse populations

Paul Kruszka[1] | Yonit A. Addissie[1] | Cedrik Tekendo-Ngongang[1] | Kelly L. Jones[2] | Sarah K. Savage[3] | Neerja Gupta[4] | Nirmala D. Sirisena[5] | Vajira H. W. Dissanayake[5] | C. Sampath Paththinige[5] | Teresa Aravena[6] | Sheela Nampoothiri[7] | Dhanya Yesodharan[7] | Katta M. Girisha[8] | Siddaramappa Jagdish Patil[9] | Saumya Shekhar Jamuar[10,11,12] | Jasmine Chew-Yin Goh[13] | Agustini Utari[14] | Nydia Sihombing[14] | Rupesh Mishra[15] | Neer Shoba Chitrakar[15] | Brenda C. Iriele[1] | Ezana Lulseged[1] | Andre Megarbane[16] | Annette Uwineza[17] | Elizabeth Eberechi Oyenusi[18] | Oluwarotimi Bolaji Olopade[19] | Olufemi Adetola Fasanmade[19] | Milagros M. Duenas-Roque[20] | Meow-Keong Thong[21] | Joanna Y. L. Tung[22] | Gary T. K. Mok[22] | Nicole Fleischer[3] | Godfrey M. Rwegerera[23] | María Beatriz de Herreros[24] | Johnathan Watts[25] | Karen Fieggen[25] | Victoria Huckstadt[26] | Angélica Moresco[26] | María Gabriela Obregon[26] | Dalia Farouk Hussen[27] | Neveen A. Ashaat[28] | Engy A. Ashaat[29] | Brian H. Y. Chung[30] | Eben Badoe[31] | Sultana M. H. Faradz[12] | Mona O. El Ruby[29] | Vorasuk Shotelersuk[32] | Ambroise Wonkam[25] | Ekanem Nsikak Ekure[18] | Shubha R. Phadke[33] | Antonio Richieri-Costa[34] | Maximilian Muenke[1]

[1]Medical Genetics Branch, National Human Genome Research Institute, The National Institutes of Health, Bethesda, Maryland

[2]Division of Medical Genetics and Metabolism, Children's Hospital of The King's Daughters, Norfolk, Virginia

[3]FDNA Inc., Boston, Massachusetts

[4]Department of Paediatrics, All India Institute of Medical Sciences, New Delhi, India

[5]Human Genetics Unit, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

[6]Departamento de Medicina, Hospital Clínico de la Universidad de Chile, Santiago, Chile

[7]Department of Pediatric Genetics, Amrita Institute of Medical Sciences and Research Centre, Kerala, India

[8]Department of Medical Genetics, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India

[9]Mazumdar Shaw Medical Center, Narayana Hrudayalaya Hospital, Bangalore, India

[10]Genetics service, KK Women's and Children's Hospital, Singapore, Singapore

[11]Paediatrics Academic Clinical Programme, SingHealth Duke-NUS Medical School, Singapore, Singapore

[12]Paediatrics Academic Clinical Programme, SingHealth Duke-NUS Genomic Medicine Centre, Singapore, Singapore

[13]Division of Nursing - Nursing Specialist Services, KK Women's and Children's Hospital, Singapore, Singapore

[14]Division of Human Genetics, Center for Biomedical Research, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

[15]Division of Human Genetics, Civil Service Hospital, Kathmandu, Nepal

[16]Institut Jérôme Lejeune, Paris, France

[17]College of Medicine and Pharmacy, School of Medicine and Pharmacy, Center of Human Genetics, University of Rwanda, Kigali, Rwanda

[18]Department of Pediatrics, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria

[19]Department of Medicine, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria

[20]Servicio de Genética, Hospital Nacional Edgardo Rebagliati Martins, EsSalud, Lima, Peru

[21]Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[22]Department of Paediatrics, Hong Kong Children's Hospital, Hong Kong, China

[23]Department of Internal Medicine, University of Botswana, Gaborone, Botswana

[24]National Secretariat for the Rights of People with Disabilities (SENADIS), Fernando de la Mora, Paraguay

[25]Division of Human Genetics, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

[26]Servicio de Genética, Hospital de Pediatría Garrahan, Buenos Aires, Argentina

[27]Department of Human Cytogenetics, The National Research Centre, Cairo, Egypt

[28]Faculty of Women for Science, Ain Shams University, Cairo, Egypt

[29]Clinical Genetics Department, The National Research Centre, Cairo, Egypt

[30]Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, Hong Kong, China

[31]Department of Child Health, University of Ghana Medical School, Accra, Ghana

[32]Center of Excellence for Medical Genomics, Medical Genomics Cluster, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[33]Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

[34]Hospital for the Rehabilitation of Craniofacial Anomalies, São Paulo University, Bauru, Brazil

Correspondence
Paul Kruszka, Medical Genetics Branch, National Human Genome Research Institute, The National Institutes of Health, Bethesda, MD.
Email: paul.kruszka@nih.gov

Funding information
National Human Genome Research Institute

Abstract

Turner syndrome (TS) is a common multiple congenital anomaly syndrome resulting from complete or partial absence of the second X chromosome. In this study, we explore the phenotype of TS in diverse populations using clinical examination and facial analysis technology. Clinical data from 78 individuals and images from 108 individuals with TS from 19 different countries were analyzed. Individuals were grouped into categories of African descent (African), Asian, Latin American, Caucasian (European descent), and Middle Eastern. The most common phenotype features across all population groups were short stature (86%), cubitus valgus (76%), and low posterior hairline 70%. Two facial analysis technology experiments were conducted: TS versus general population and TS versus Noonan syndrome. Across all ethnicities, facial analysis was accurate in diagnosing TS from frontal facial images as measured by the area under the curve (AUC). An AUC of 0.903 ($p < .001$) was found for TS versus general population controls and 0.925 ($p < .001$) for TS versus individuals with Noonan syndrome. In summary, we present consistent clinical findings from global populations with TS and additionally demonstrate that facial analysis technology can accurately distinguish TS from the general population and Noonan syndrome.

KEYWORDS

diverse populations, facial analysis technology, health disparities, Turner syndrome

1 | INTRODUCTION

Turner syndrome (TS) is caused by complete or partial deletion of the second X chromosome and affects 1 in 2,000 females in a European population (Stochholm, Juul, Juel, Naeraa, & Gravholt, 2006). In a study from Nigeria, the incidence of live births was found to be similar at 1 in 2,745 (Adeyokunnu, 1982). Mosaicism is common in TS; in a large study of 902 individuals with TS, 31% had mosaic karyotypes (Hook & Warburton, 1983). A high index of suspicion is necessary for diagnosing TS when associated phenotypes are encountered by clinicians. The phenotype characteristics of TS are short stature, characteristic physical exam findings, infertility secondary to ovarian

TABLE 1 Clinical findings

	Present study					Yesilkaya et al. (2015)	Ferguson-Smith (1965)		
	African (*n* = 19)	Asian (*n* = 32)	Latin American (*n* = 15)	Middle East (*n* = 12)	All (*n* = 78)	(*n* = 842)	45,X (*n* = 117)	45,X/46,XX (*n* = 38)	Combined (*n* = 155)
Average age (years)	19	13	5	11	13				
Karyotype	89% (17/19)	90% (29/32)	100% (15/15)	100% (12/12)	70% (73/78)				
45,X	53% (9/17)	65% (19/29)	47% (7/15)	33% (4/12)	53% (39/73)	427 (50.7%)			
Isochromosome	18% (3/17)	21% (6/29)	13% (2/15)	25% (3/12)	19% (14/73)	169 (20.1%)			
Mosaic	29% (5/17)	17% (5/29)	27% (4/15)	67% (8/12)	30% (22/73)	114 (21.2%)			
46,X,+mar	12% (3/17)	0	7% (1/15)	0	4% (4/5)	10 (1.2%)			
Height < 3rd centile	89% (17/19)	92% (25/27)	60% (9/15)	100% (12/12)	86% (63/73)	84% (708/842)	100% (105/105)	80% (29/36)	95% (134/141)
Congenital heart disease	38% (5/13)	41% (9/22)	21% (3/14)	41% (5/12)	36% (22/60)	25% (180/719)	21% (18/87)	7% (2/29)	17% (20/116)
Bicuspid aortic valve	11% (2/19)	14% (3/22)	14% (2/14)	0	11% (7/61)	8.6% (61/719)			
Coarctation (aorta)	16% (3/19)	14% (3/22)	14% (2/14)	33% (4/12)	20% (12/61)	6.5% (46/719)			
Aortic stenosis	0	14% (3/22)	0	0	5% (3/61)	5.4% (38/719)			
Growth hormone history[d]	22% (4/18)	17% (5/28)	14% (1/7)	60% (6/10)	25% (16/63)				
Estrogen replacement history[e]	30% (3/10)	37% (7/19)	100% (1/1)	87% (7/8)	47% (18/38)				
History of spontaneous menstruation	22% (2/9)[a]	17% (1/6)[b]	50% (2/4)[c]	0% (0/8)	19% (5/27)		8% (7/83)	21% (7/34)	12% (14/117)
Pregnancy history	0% (0/9)	0% (0/8)	None	0% (0/8)	0% (0/25)				
Narrow maxilla (palate)	43% (7/16)	33% (7/21)	86% (13/15)	25% (3/12)	46% (30/64)				
Small mandible	43% (7/16)	52% (13/25)	93% (14/15)	36% (4/11)	56% (38/67)				
Inner canthal folds	31% (5/16)	26% (7/26)	66% (10/15)	27% (3/11)	36% (25/68)				
Low posterior hairline	63% (12/19)	65% (19/29)	80% (12/15)	83% (10/12)	70% (53/75)				
Webbed posterior neck	47% (9/19)	50% (15/30)	66% (10/15)	80% (8/10)	56% (42/74)		54% (63/117)	16% (6/37)	45% (69/155)
Cubitus valgus or other elbow anomaly	73% (11/15)	74% (20/27)	66% (10/15)	100% (12/12)	76% (53/69)				
Short fourth metacarpal	26% (4/15)	28% (6/21)	73% (11/15)	91% (11/12)	50% (32/63)		58% (34/59)	44% (11/25)	54% (45/84)
Short fourth metatarsal	28% (4/14)	40% (9/22)	40% (6/15)	36% (4/11)	37% (23/62)				
Congenital lymphedema	30% (4/13)	8% (2/25)	53% (8/15)	54% (6/11)	31% (20/64)		39% (37/94)	12% (3/25)	34% (40/119)
Type of renal anomaly (i.e., horseshoe kidney)	11% (2/17)	15% (3/19)	26% (4/15)	8% (1/12)	15% (10/63)	16.3% (117/714)			
Excessive pigmented nevi	11% (2/17)	34% (9/26)	26% (4/15)	75% (9/12)	34% (24/70)		52% (32/62)	37% (11/30)	47% (43/92)
Narrow, hyperconvex, deep set nails, or hypoplastic	66% (10/15)	36% (9/25)	93% (14/15)	9% (1/11)	51% (34/66)		77% (20/26)	55% (10/18)	68% (30/44)
Hearing loss	13% (2/15)	16% (4/24)	46% (7/15)	9% (1/11)	21% (14/65)	10% (54/539)			

(Continues)

TABLE 1 (Continued)

	Present study					Yesilkaya et al. (2015)	Ferguson-Smith (1965)		
	African (*n* = 19)	Asian (*n* = 32)	Latin American (*n* = 15)	Middle East (*n* = 12)	All (*n* = 78)	(*n* = 842)	45,X (*n* = 117)	45,X/46,XX (*n* = 38)	Combined (*n* = 155)
Learning disorder	50% (8/16)	19% (5/26)	66% (6/9)	70% (7/10)	42% (26/61)	16.1% (47/291)			
Visual-spatial organization deficits	30% (3/10)	6% (1/15)	0% (0/7)	0% (0/10)	9% (4/42)				
Social cognition deficits (i.e., failure to appreciate subtle social cues)	25% (2/8)	0% (0/13)	62% (5/8)	50% (5/10)	30% (12/39)				
Math problems	64% (9/14)	31% (5/16)	50% (4/8)	90% (9/10)	56% (27/48)				
Type of mental health illness (i.e., depression or anxiety)	45% (5/11)	0% (0/10)	0% (0/4)	66% (6/9)	32% (11/34)				

[a]One individual was mosaic and the other karyotype was unknown.
[b]This individual is mosaic 45 X(63)/46XX(10).
[c]One individual is a short-arm deletion on the X chromosome: 46,X,del(X) (p21.1) [20]; the other is mosaic: 45,X [27]/46,XX [3].
[d]Individual was considered eligible for growth hormone therapy if greater than 5 years.
[e]Individual was considered eligible for if greater than 11 years.
Abbreviation: ERT, estrogen replacement therapy.

dysgenesis, congenital heart disease, autoimmune disease and endocrine disorders, and a specific neurocognitive profile (Gravholt, Viuff, Brun, Stochholm, & Andersen, 2019). Traditional reported facial features of TS include narrow maxilla, small mandible, and inner canthal folds (Jones, Jones, & Campo, 2013). Although general intelligence is normal for individuals with TS, there is a higher prevalence of specific learning disabilities including visual-spatial and/or visual-perceptual abilities (Pavlidis, McCauley, & Sybert, 1995). Treatment begins in early childhood and includes multiple therapies such as growth hormone at ages 4–6 years and estrogen replacement at ages 11–12 (Gravholt et al., 2017). This therapeutic regimen will continue to change with scientific advances (Kruszka & Silberbach, 2019). Unfortunately, the average diagnosis is 15 years of age in a European population which can delay recommended treatments (Berglund et al., 2019; Gravholt et al., 2019), and the age of diagnosis is most likely later in economically developing countries. In a study of 11 participants with TS in Cameroon, 10 were diagnosed due to late puberty and one due to short stature and the average age of diagnosis was 18.4 ± 2.8 years (*SD*) (Wonkam et al., 2015).

Few studies have been done in underserved areas of the world such as sub-Saharan Africa (Rivera & Rwegerera, 2016; Wonkam et al., 2015). The ability to make early diagnoses in developing countries is important for counseling and treatment of girls with TS (Wonkam et al., 2015).

In previous studies, we have investigated genetic syndromes in diverse populations (Dowsett et al., 2019; Kruszka et al., 2017; Kruszka et al., 2017; Kruszka et al., 2017; Kruszka et al., 2018; Kruszka, Tekendo-Ngongang, & Muenke, 2019). In this study, we compare clinical characteristics of girls and women with TS across diverse populations with respect to clinical characteristics and facial analysis technology.

2 | METHODS

2.1 | Patients

Individuals with TS were evaluated from 19 countries. All participants (Supplementary Table S1) had TS diagnosed by both clinical evaluation and/or cytogenetic and molecular diagnosis. The patients were grouped by geographic area of origin or ethnicity (African and African American, Asian, Latin American, and the Middle East). Local clinical geneticists or pediatricians examined patients for established clinical features found in TS.

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 are recorded in Table 1.

2.2 | Facial analysis technology

Facial analysis was performed using technology developed by the Face2Gene Research application (FDNA Inc., Boston, MA) as previously

FIGURE 1 Hands of individuals with Turner syndrome. See Supplementary Table S1 for age, country of origin, and karyotype. Note shortened fourth metacarpals [Color figure can be viewed at wileyonlinelibrary.com]

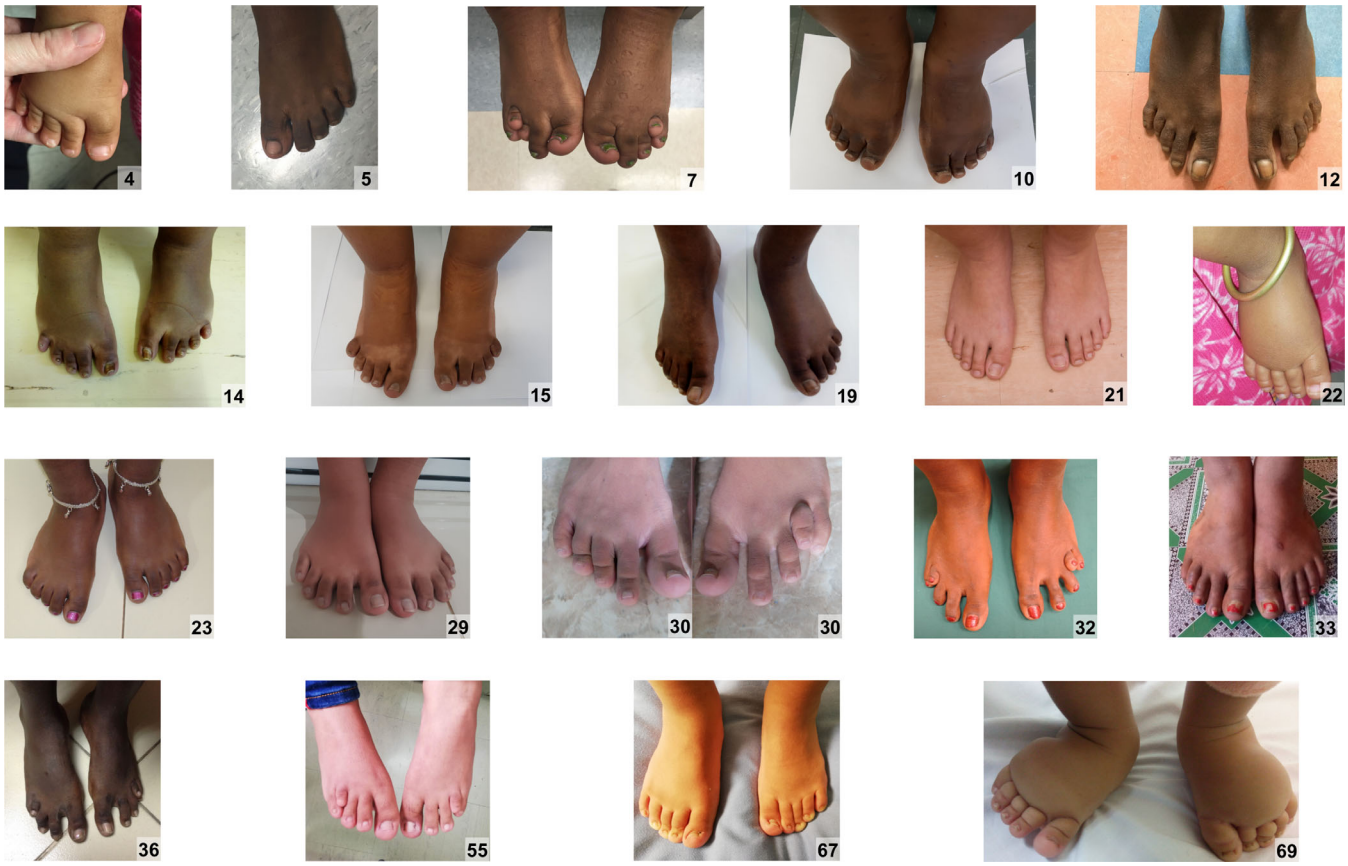

FIGURE 2 Feet of individuals with Turner syndrome. See Supplementary Table S1 for age, country of origin, and karyotype. Note shortened fourth metatarsals and lymphedema [Color figure can be viewed at wileyonlinelibrary.com]

described (Gurovich et al., 2019; Kruszka et al., 2019). Facial images were collected from girls and women with TS and the medical literature (Supplementary Table S2 lists source of images). A control group with Noonan syndrome, previously described by Kruszka, Porras, Addissie, et al., 2017), and another unaffected control group was used for comparisons. Noonan syndrome was used as a control group due to the similarity in phenotypes between Noonan syndrome and TS. Controls were matched for age, gender, and ethnicity. Two binary classification experiments were performed (Gurovich et al., 2019). All facial images were fully deidentified through the use of the DeepGestalt facial analysis (Gurovich et al., 2019).

3 | RESULTS

3.1 | Clinical results

Table 1 summarizes the phenotype of the present study and two large prior comparison studies from the medical literature (Ferguson-Smith, 1965; Yesilkaya et al., 2015). A total of 78 individuals had phenotype information available. The average age was 13 years with the Latin American cohort being the youngest at 5 years. The most common finding was short stature, defined by stature below third centile using Centers for Disease Control graphs (https://www.cdc.gov/growthcharts/clinical_charts.htm), which was found in 86% (63/73) of individuals of all ethnicities (Table 1). Short stature was least prevalent in the Latin American group, most likely due to the average age of only 5 years. The next most frequent exam finding was cubitus valgus 76% (53/69) followed by low posterior hairline 70% (53/75). Other phenotype features found in over half included posterior webbed neck (56%), small mandible (56%), narrow hyperconvex and deep set fingernails (51%), and short fourth metacarpals (50%). Figures 1 and 2 demonstrate hand and foot anomalies, respectively, in the present cohort. Congenital heart disease was found in 36% of the cohort which was similar to previous reports (Yesilkaya et al., 2015).

There were no pregnancies and only 19% of the cohort over the age of 16 years had history of spontaneous menstruation, three of five of these individuals were mosaic, and none were 45,X. Of the individuals eligible for estrogen replacement therapy (ERT), 47% (18/38) received this therapy, and the African group was least likely to receive ERT, 30% (3/10). Growth hormone was given to 25% of individuals greater than 5 years of age; however, if the Middle Eastern group is removed and only the African, Latin American, and Asian groups are considered, only 19% (10/53) received growth hormone therapy.

With regards to cognitive and mental health issues, 56% reported difficulty in math, 32% reported anxiety and/or depression, 30% reported social cognition deficits, and 9% reported visual-spatial deficits (Table 1).

3.2 | Facial analysis technology

We used facial analysis technology to test the hypothesis that an objective single syndrome classifier developed by Face2Gene

TABLE 2 Facial analysis technology results

	African		Asian		Latin American		Caucasian		Combined	
	TS (n = 17) vs. unaffected (n = 19)	TS (n = 17) vs. NS (n = 16)	TS (n = 33) vs. unaffected (n = 34)	TS (n = 33) vs. NS (n = 17)	TS (n = 35) vs. unaffected (n = 35)	TS (n = 35) vs. NS (n = 21)	TS (n = 23) vs. unaffected	TS (n = 23) vs. NS (n = 21)	TS (n = 108) vs. unaffected (n = 111)	TS (n = 108) vs. NS (n = 75)
Average age	13 years		12.3 years		5.3 years		10.5 years		9.8 years	
Age range	0.8–52 years		0.5–24 years		2 days, 15 years		2 days, 35 years		2 days, 52 years	
Mean AUC (STD)	0.81 (0.07)	0.72 (0.13)	0.97 (0.02)	0.97 (0.02)	0.89 (0.06)	0.90 (0.04)	0.93 (0.05)	0.89 (0.05)	0.91 (0.01)	0.93 (0.01)
Aggregated AUC (p-value)	0.78 (.03)	0.74 (.14)	0.96 (.001)	0.97 (.005)	0.89 (<.001)	0.89 (.008)	0.92 (.002)	0.87 (.01)	0.903 (<.001)	0.925 (<.001)
Face2Gene rank: TS diagnoses: percent in top five diagnoses (%)	68		85		66		61		72	

Abbreviations: AUC, area under the curve; TS, Turner syndrome.

FIGURE 3 Individuals of African descent with Turner syndrome. See Supplementary Table S1 for age, country of origin, and karyotype [Color figure can be viewed at wileyonlinelibrary.com]

(Gurovich et al., 2019) could discriminate between TS and individuals without TS, regardless of ethnicity or country of origin. Two different experiments were run, the first experiment compared TS to an unaffected female population and the second experiment compared TS to individuals with Noonan syndrome. The discrimination ability of this facial analysis technology was measured using the area under the curve (AUC) of the receiver operating characteristic curve. An AUC of 1 represents perfect separation between individuals with TS and controls and an AUC of 0.5 represents the worst separation, in other words, a random and indiscriminative test.

We collected 108 images of individuals with TS; average age was 9.8 years with a range of 2 days to 54 years (Table 2). Images with permissions to publish are shown in Figures 3–5 for the African, Asian, and Latin American cohorts, respectively. The images used for facial analysis technology for the Caucasian cohort came from the medical literature (Atton et al., 2015; Cassidy & Allanson, 2010; Chaput et al., 2013; Doswell, Visootsak, Brady, & Graham Jr., 2006; Gamstorp, 1985; Hall, Sybert, Willamson, Fisher, & Reed, 1982; Hennekam, Gorlin, Allanson, & Krantz, 2010; Jones et al., 2013; Kunze, 2010; Loscalzo, 2008; Mazzocco & Ross, 2007; Muenke, Adeyemo, & Kruszka, 2016; Nabhan & Eugster, 2006; Nebesio & Eugster, 2007; Russell, 2001; Thiesen, Ilha, Borges, & Freitas, 2015) and the TS Research Registry (Prakash et al., 2019).

Comparing the features of all ethnicities of 108 individuals with TS with 111 age and ethnic matched controls resulted in an AUC of 0.903 ($p < .001$) (Supplementary Figure S1), showing excellent ability to classify TS (Table 2). Similarly, when comparing TS with Noonan syndrome, excellent discrimination was seen with an AUC of 0.925 ($p < .001$) (Supplementary Figure S2).

When performing the same discrimination testing on distinct populations, our results were varied. The Asian group had the best separation between cases and controls (Table 2). For Asian individuals with TS versus unaffected, the AUC was 0.96 ($p = .001$) and for TS versus Noonan syndrome in Asians, the AUC was 0.97 ($p = .005$). The facial analysis technology performed worse on the African American group (Table 2). When comparing TS versus unaffected in individuals of African descent, the AUC was 0.78 ($p = .03$) and the AUC for TS versus Noonan syndrome was 0.74 ($p = .14$). This may partly be explained by the number of participants used to train the algorithm, 33 in the Asian TS cohort and 17 in the African cohort. It should be noted that the Latin American cohort ($n = 35$) was larger than the Asian cohort and the Asian cohort still had more favorable AUCs.

When the Face2Gene application ranked the participants against 301 (version 19.1.5) other genetic syndromes, TS was ranked in top five diagnoses (Table 2) for 72% of the total participants. After TS, the four other most common diagnoses in the differential diagnosis of the Face2Gene application were Kabuki syndrome, neurofibromatosis Type 1, Noonan syndrome, and Stickler syndrome, in order of decreasing frequency. There was no

FIGURE 4 Individuals of Asian descent with Turner syndrome. See Supplementary Table S1 for age, country of origin, and karyotype [Color figure can be viewed at wileyonlinelibrary.com]

significant different between ethnic groups for top five rankings (p = .2; χ^2 test). Supplementary Figures S1 and S2 show the Face2Gene technology composites of individuals with TS and the control groups.

4 | DISCUSSION

In this study, we present 78 clinical examinations and of individuals from diverse populations affected by TS. We demonstrate that regardless of their ethnicity or country of origin, individuals with TS have a distinct phenotype consisting of short stature, amenorrhea, infertility, congenital heart disease and clinical exam findings that include cubitus valgus, low posterior hairline, webbing of the neck, and short fourth metacarpals (Table 1). Our findings are consistent with other large phenotype studies (Ferguson-Smith, 1965; Yesilkaya et al., 2015).

In 108 facial analysis technology evaluations, we show that facial analysis technology is accurate in discriminating individuals with TS from healthy controls and individuals with Noonan syndrome. The ability to discriminate TS from Noonan syndrome is particularly encouraging as TS and Noonan syndrome share phenotypic features and considering that the initial reports of Noonan syndrome used the terminology "TS" (Celermajer, Bowdler, & Cohen, 1968; Noonan, 1968; Nora & Sinha, 1968). The Face2Gene technology was most accurate in the Asian group (AUC 0.96 for TS vs. unaffected and 0.97 for TS vs. NS) and least accurate in the African American cohort (AUC 0.78 for TS vs. unaffected and 0.74 for TS vs. NS). Additionally, we show that the Face2Gene application ranks TS in the top 5 of over 300 syndromes for 72% of our study participants (Table 2).

One factor that may have influenced a decreased accuracy (AUC) in the African group is the smaller number of participants. Recruiting individuals of African descent was more difficult in this study and highlights the importance of studies such as the present study that

FIGURE 5 Latin American individuals with Turner syndrome. See Supplementary Table S1 for age, country of origin, and karyotype [Color figure can be viewed at wileyonlinelibrary.com]

focuses on diversity. In the medical literature, there are simply a near absence of studies describing TS in African populations (Wonkam et al., 2015). In a recent review on TS, Gravholt et al. reinforce this point with "there is a paucity of studies from Africa, Asia, and South America" (Gravholt et al., 2019).

A weakness of this study is ascertainment bias. Especially as many of the participants came from resource limited areas of the world, these individuals presented for medical attention secondary to significant medical problems such as structural heart disease. There is evidence from a previous study that incidentally prenatal diagnosed individuals (i.e., amniocentesis done for advance maternal age) had fewer phenotypic features, lower incidence of congenital heart disease, and more likely to be mosaic than clinically diagnosed individuals (Gunther et al., 2004). With the advent of noninvasive prenatal screening and possibly newborn screening in the future, more information on full phenotypic spectrum of TS will be available (Bianchi, 2019; Murdock et al., 2017).

In addition to the phenotypic and facial analysis data that this study presents, there is an evidence of treatment differences in the data. Given the relatively young age of this study with an average of 13 years, only 25% of individuals older than 5 years received growth hormone therapy which is recommended to start between ages 4 and 6. Only 47% received ERT which is recommended between ages 11 and 12 (Gravholt et al., 2017).

We are encouraged that more studies are being done in diverse populations, and that increased attention is being focused on earlier diagnosis and potentially early treatment (Kruszka, Addissie, McGinn, et al., 2017; Kruszka et al., 2018; Kruszka, Porras, Addissie, et al., 2017; Kruszka, Porras, Sobering, et al., 2017; Kruszka, Tekendo-Ngongang, & Muenke, 2019). Given that there is a paucity of clinical geneticists in many developing countries (Kruszka, Tekendo-Ngongang, & Muenke, 2019), we propose facial analysis technology as another tool in addition to history and physicial exam for primary care physicians and specialists when evaluating individuals with a clinical suspicion of TS due to typical signs (Gravholt et al., 2017). Currently, there is no clinical outcome data on the use of facial analysis in TS in diverse populations; however, evaluating the utility of this technology in a clinical setting will be the next research priority.

In summary, we provide a summary of the phenotype of TS in diverse populations and demonstrate that facial analysis technology using Face2Gene is accurate in discriminating TS from the general population and Noonan syndrome.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

P.K. wrote the original draft, coordinated data acquisition and interpretation, revised final draft, and is accountable for accuracy of the manuscript. Y.A.A., C.T., K.L.J., S.K.S., N.G., N.D.S., V.H.W.D., C.S.P., T.A., S.N., D.Y., K.M.G., S.J.P., S.S.J., J.C.G., A.U., N.S., R.M., N.S.C., B.C.I., E.L., A.M., A.U., E.E.O., O.B.O., O.A.F., M.M.D., M.K.T., J.Y.L.T., G.T.K.M., N.F., G.M.R., M.B.H., J.W., K.F., V.H., A.M., M.G.O., D.F.H., N.A.A., E.A.A, B.H.Y.C., E.B., S.M.H.F., M.O.E.R., V.S., A.W., E.N.E., S.R.P., A.R., and M.M. contributed to the acquisition and interpretation of data, manuscript revision, final approval of manuscript, and are accountable for accuracy of manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Paul Kruszka https://orcid.org/0000-0003-4949-0875
Kelly L. Jones https://orcid.org/0000-0002-5097-9865
Katta M. Girisha https://orcid.org/0000-0002-0139-8239
Siddaramappa Jagdish Patil https://orcid.org/0000-0001-7154-3449
Saumya Shekhar Jamuar https://orcid.org/0000-0003-2341-8349
Agustini Utari https://orcid.org/0000-0001-5965-1981
Andre Megarbane https://orcid.org/0000-0003-0714-2469
Neveen A. Ashaat https://orcid.org/0000-0002-7548-6143
Engy A. Ashaat https://orcid.org/0000-0002-2116-1570
Shubha R. Phadke https://orcid.org/0000-0002-6624-082X

REFERENCES

Adeyokunnu, A. A. (1982). The incidence of Turner's syndrome in Ibadan, Nigeria. *African Journal of Medicine and Medical Sciences*, *11*(3), 105–112 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/6307025

Atton, G., Gordon, K., Brice, G., Keeley, V., Riches, K., Ostergaard, P., … Mansour, S. (2015). The lymphatic phenotype in Turner syndrome: An evaluation of nineteen patients and literature review. *European Journal of Human Genetics*, *23*(12), 1634–1639. https://doi.org/10.1038/ejhg.2015.41

Berglund, A., Viuff, M. H., Skakkebaek, A., Chang, S., Stochholm, K., & Gravholt, C. H. (2019). Changes in the cohort composition of turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: A nationwide cohort study. *Orphanet Journal of Rare Diseases*, *14*(1), 16. https://doi.org/10.1186/s13023-018-0976-2

Bianchi, D. W. (2019). Turner syndrome: New insights from prenatal genomics and transcriptomics. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *181*, 29–33. https://doi.org/10.1002/ajmg.c.31675

Cassidy, S. B., & Allanson, J. E. (2010). *Management of genetic syndromes* (3rd ed.). Hoboken, NJ: Wiley-Blackwell.

Celermajer, J. M., Bowdler, J. D., & Cohen, D. H. (1968). Pulmonary stenosis in patients with the turner phenotype in the male. *American Journal of Diseases of Children*, *116*(4), 351–358. https://doi.org/10.1001/archpedi.1968.02100020355002

Chaput, B., Chavoin, J. P., Lopez, R., Meresse, T., Nadon, F., Herlin, C., … Grolleau, J. L. (2013). The "posterior cervical lift": A new approach to pterygium colli management. *Plastic and Reconstructive Surgery. Global Open*, *1*(6), e46. https://doi.org/10.1097/GOX.0b013e3182a8c597

Doswell, B. H., Visootsak, J., Brady, A. N., & Graham, J. M., Jr. (2006). Turner syndrome: An update and review for the primary pediatrician. *Clinical Pediatrics (Phila)*, *45*(4), 301–313. https://doi.org/10.1177/000992280604500402

Dowsett, L., Porras, A. R., Kruszka, P., Davis, B., Hu, T., Honey, E., … Krantz, I. D. (2019). Cornelia de Lange syndrome in diverse populations. *American Journal of Medical Genetics. Part A*, *179*(2), 150–158. https://doi.org/10.1002/ajmg.a.61033

Ferguson-Smith, M. A. (1965). Karyotype-phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. *Journal of Medical Genetics*, *2*(2), 142–155. https://doi.org/10.1136/jmg.2.2.142

Gamstorp, I. (1985). *Paediatric neurology* (2nd ed.). London, England: Butterworths.

Gravholt, C. H., Andersen, N. H., Conway, G. S., Dekkers, O. M., Geffner, M. E., Klein, K. O., … International Turner Syndrome Consensus Group. (2017). Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *European Journal of Endocrinology*, *177*(3), G1–G70. https://doi.org/10.1530/EJE-17-0430

Gravholt, C. H., Viuff, M. H., Brun, S., Stochholm, K., & Andersen, N. H. (2019). Turner syndrome: Mechanisms and management. *Nature Reviews. Endocrinology*, *15*(10), 601–614. https://doi.org/10.1038/s41574-019-0224-4

Gunther, D. F., Eugster, E., Zagar, A. J., Bryant, C. G., Davenport, M. L., & Quigley, C. A. (2004). Ascertainment bias in Turner syndrome: New insights from girls who were diagnosed incidentally in prenatal life. *Pediatrics*, *114*(3), 640–644. https://doi.org/10.1542/peds.2003-1122-L

Gurovich, Y., Hanani, Y., Bar, O., Nadav, G., Fleischer, N., Gelbman, D., … Gripp, K. W. (2019). Identifying facial phenotypes of genetic disorders using deep learning. *Nature Medicine*, *25*(1), 60–64. https://doi.org/10.1038/s41591-018-0279-0

Hall, J. G., Sybert, V. P., Willamson, R. A., Fisher, N. L., & Reed, S. D. (1982). Turner's syndrome. *The Western Journal of Medicine*, *137*, 32–44.

Hennekam, R. C. M., Gorlin, R. J., Allanson, J. E., & Krantz, I. D. (2010). *Gorlin's syndromes of the head and neck* (5th ed.). New York, NY: Oxford University Press.

Hook, E. B., & Warburton, D. (1983). The distribution of chromosomal genotypes associated with Turner's syndrome: Livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. *Human Genetics*, *64*(1), 24–27. https://doi.org/10.1007/bf00289473

Jones, K. L., Jones, M. C., & Campo, M. d. (2013). *Smith's recognizable patterns of human malformation* (7th ed.). Philadelphia, PA: Elsevier Saunders.

Kruszka, P., Addissie, Y. A., McGinn, D. E., Porras, A. R., Biggs, E., Share, M., … Muenke, M. (2017). 22q11.2 deletion syndrome in diverse populations. *American Journal of Medical Genetics. Part A*, *173*(4), 879–888. https://doi.org/10.1002/ajmg.a.38199

Kruszka, P., Hu, T., Hong, S., Signer, R., Cogne, B., Isidor, B., … Muenke, M. (2019). Phenotype delineation of ZNF462 related syndrome. *American*

Journal of Medical Genetics. Part A, *179*(10), 2075–2082. https://doi.org/10.1002/ajmg.a.61306

Kruszka, P., Porras, A. R., Addissie, Y. A., Moresco, A., Medrano, S., Mok, G. T. K., … Muenke, M. (2017). Noonan syndrome in diverse populations. *American Journal of Medical Genetics. Part A*, *173*(9), 2323–2334. https://doi.org/10.1002/ajmg.a.38362

Kruszka, P., Porras, A. R., de Souza, D. H., Moresco, A., Huckstadt, V., Gill, A. D., … Muenke, M. (2018). Williams-Beuren syndrome in diverse populations. *American Journal of Medical Genetics. Part A*, *176*(5), 1128–1136. https://doi.org/10.1002/ajmg.a.38672

Kruszka, P., Porras, A. R., Sobering, A. K., Ikolo, F. A., La Qua, S., Shotelersuk, V., … Muenke, M. (2017). Down syndrome in diverse populations. *American Journal of Medical Genetics. Part A*, *173*(1), 42–53. https://doi.org/10.1002/ajmg.a.38043

Kruszka, P., & Silberbach, M. (2019). The state of Turner syndrome science: Are we on the threshold of discovery? *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *181*(1), 4–6. https://doi.org/10.1002/ajmg.c.31688

Kruszka, P., Tekendo-Ngongang, C., & Muenke, M. (2019). Diversity and dysmorphology. *Current Opinion in Pediatrics*, *31*(6), 702–707. https://doi.org/10.1097/MOP.0000000000000816

Kunze, J. r. (2010). *Wiedemanns atlas klinischer syndrome: Phänomenologie, atiologie, differenzialdiagnose* (6th ed.). Stuttgart: Schattauer.

Loscalzo, M. L. (2008). Turner syndrome. *Pediatrics in Review*, *29*(7), 219–227. https://doi.org/10.1542/pir.29-7-219

Mazzocco, M. M. M., & Ross, J. L. (2007). *Neurogenetic developmental disorders: Variation of manifestation in childhood*. Cambridge, MA: MIT Press.

Muenke, M., Adeyemo, A., & Kruszka, P. (2016). An electronic atlas of human malformation syndromes in diverse populations. *Genetics in Medicine*, *18*(11), 1085–1087. https://doi.org/10.1038/gim.2016.3

Murdock, D. R., Donovan, F. X., Chandrasekharappa, S. C., Banks, N., Bondy, C., Muenke, M., & Kruszka, P. (2017). Whole-exome sequencing for diagnosis of Turner syndrome: Toward next-generation sequencing and newborn screening. *The Journal of Clinical Endocrinology and Metabolism*, *102*(5), 1529–1537. https://doi.org/10.1210/jc.2016-3414

Nabhan, Z. M., & Eugster, E. A. (2006). Monozygotic twins with Turner syndrome develop slipped capital femoral epiphysis on growth hormone therapy. *Pediatrics*, *118*(6), e1900–e1903. https://doi.org/10.1542/peds.2006-0955

Nebesio, T. D., & Eugster, E. A. (2007). Current concepts in normal and abnormal puberty. *Current Problems in Pediatric and Adolescent Health Care*, *37*(2), 50–72. https://doi.org/10.1016/j.cppeds.2006.10.005

Noonan, J. A. (1968). Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease. *American Journal of Diseases of Children*, *116*(4), 373–380. https://doi.org/10.1001/archpedi.1968.02100020377005

Nora, J. J., & Sinha, A. K. (1968). Direct familial transmission of the Turner phenotype. *American Journal of Diseases of Children*, *116*(4), 343–350. https://doi.org/10.1001/archpedi.1968.02100020347001

Pavlidis, K., McCauley, E., & Sybert, V. P. (1995). Psychosocial and sexual functioning in women with Turner syndrome. *Clinical Genetics*, *47*(2), 85–89. https://doi.org/10.1111/j.1399-0004.1995.tb03929.x

Prakash, S. K., Lugo-Ruiz, S., Rivera-Davila, M., Rubio, N., Jr., Shah, A. N., Knickmeyer, R. C., … Scientific Advisory Board of the TSRR. (2019). The Turner syndrome research registry: Creating equipoise between investigators and participants. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *181*(1), 135–140. https://doi.org/10.1002/ajmg.c.31689

Rivera, Y. P., & Rwegerera, G. M. (2016). A rare case of turner syndrome mosaicism in an African black woman. *Case Reports in Internal Medicine*, *3*(4), 44–49. https://doi.org/10.5430/crim.v3n4p44

Russell, K. A. (2001). Orthodontic treatment for patients with Turner syndrome. *American Journal of Orthodontics and Dentofacial Orthopedics*, *120*(3), 314–322. https://doi.org/10.1067/mod.2001.115719

Stochholm, K., Juul, S., Juel, K., Naeraa, R. W., & Gravholt, C. H. (2006). Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *91*(10), 3897–3902. https://doi.org/10.1210/jc.2006-0558

Thiesen, G., Ilha, M. C., Borges, T. S., & Freitas, M. P. M. (2015). Turner syndrome case report: A multidisciplinary approach. *Stoma*, *21*(40), 13–20.

Wonkam, A., Veigne, S. W., Abass, A., Ngo Um, S., Noubiap, J. J., Mbanya, J. C., & Sobngwi, E. (2015). Features of Turner syndrome among a group of Cameroonian patients. *International Journal of Gynaecology and Obstetrics*, *129*(3), 264–266. https://doi.org/10.1016/j.ijgo.2014.11.025

Yesilkaya, E., Bereket, A., Darendeliler, F., Bas, F., Poyrazoglu, S., Kucukemre Aydin, B., … Bondy, C. (2015). Turner syndrome and associated problems in Turkish children: A multicenter study. *Journal of Clinical Research in Pediatric Endocrinology*, *7*(1), 27–36. https://doi.org/10.4274/jcrpe.1771

SUPPORTING INFORMATION

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