

ORIGINAL ARTICLE

Turner syndrome in diverse populations

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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				Ferguson-Smith (1965)	
	African (n = 19)	Asian (n = 32)	Latin American (n = 15)	Middle East (n = 12)	All (n = 78)	Yesilkaya et al. (2015) (n = 842)
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)
Congenital heart disease	38% (5/13)	41% (9/22)	21% (3/14)	41% (5/12)	36% (22/60)	25% (180/719)
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)
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)
Cubitus valgus or other elbow anomaly	73% (11/15)	74% (20/27)	66% (10/15)	100% (12/12)	76% (53/69)	16% (6/37)
Short fourth metacarpal	26% (4/15)	28% (6/21)	73% (11/15)	91% (11/12)	50% (32/63)	58% (34/59)
Short fourth metatarsal	28% (4/14)	40% (9/22)	40% (6/15)	36% (4/11)	37% (23/62)	44% (11/25)
Congenital lymphedema	30% (4/13)	8% (2/25)	53% (8/15)	54% (6/11)	31% (20/64)	39% (37/94)
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)
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)
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)				

^aOne individual was mosaic and the other karyotype was unknown.

^bThis individual is mosaic 45 X(63)/46XX(10).

^cOne 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].

^dIndividual was considered eligible for growth hormone therapy if greater than 5 years.

^eIndividual 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
Average age	TS (n = 17) vs. unaffected (n = 19) 13 years	TS (n = 33) vs. unaffected (n = 34) 12.3 years	TS (n = 35) vs. unaffected (n = 35) 5.3 years	TS (n = 23) vs. unaffected (n = 21) 10.5 years	TS (n = 108) vs. unaffected (n = 111) 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)	0.97 (0.02)	0.89 (0.06)	0.93 (0.05)	0.91 (0.01)
Aggregated AUC (p-value)	0.72 (0.13)	0.96 (0.001)	0.90 (0.04)	0.89 (0.05)	0.93 (0.01)
Face2Gene rank: TS diagnoses: percent in top five diagnoses (%)	0.74 (.14)	0.97 (0.005)	0.89 (<.001)	0.92 (.002)	0.903 (<.001)
	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 indiscriminate 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, Williamson, 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 physical 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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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