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Cornelia de Lange Syndrome in Diverse Populations

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Abstract

Cornelia de Lange syndrome (CdLS) is a dominant multisystemic malformation syndrome due to mutations in 5 genes – *NIPBL*, *SMC1A*, *HDAC8*, *SMC3*, and *RAD21*. The characteristic facial dysmorphisms include microcephaly, arched eyebrows, synophrys, short nose with depressed bridge and anteverted nares, long philtrum, thin lips, micrognathia, and hypertrichosis. Most affected individuals have intellectual disability, growth deficiency, and upper limb anomalies. This study looked at individuals from diverse populations with both clinical and molecularly confirmed diagnoses of CdLS by facial analysis technology. Clinical data and images from 246 individuals with CdLS were obtained from 15 countries. This cohort included 49% female patients and ages ranged from infancy to 37 years. Individuals were grouped into ancestry categories of African descent, Asian, Latin American, Middle Eastern, and Caucasian. Across these populations, 14 features showed a statistically significant difference. The most common facial features found in all ancestry groups included synophrys, short nose with anteverted nares, and a long philtrum with thin vermillion of the upper lip. Using facial analysis technology we compared 246 individuals with CdLS to 246 gender/age matched controls and found that sensitivity was equal or greater than 95% for all groups. Specificity was equal or greater than 91%. In conclusion, we present consistent clinical findings from global populations with CdLS while demonstrating how facial analysis technology can be a tool to support accurate diagnoses in the clinical setting. This work, along with prior studies in this arena, will assist in earlier detection, recognition, and treatment of CdLS worldwide.

Keywords

Cornelia de lange syndrome; CdLS; diverse populations; underrepresented minorities; facial analysis technology; NIPBL; SMC1A; HDAC8; SMC3; RAD21; Asia; Africa; Latin America; Middle East

INTRODUCTION

Cornelia de Lange syndrome (CdLS) is a dominant multisystemic malformation syndrome with an estimated incidence of 1:10,000 to 1:30,000 live births [Mannini et al, 2013]. The characteristic facial dysmorphisms, critical in establishing a clinical diagnosis, include microcephaly, arched eyebrows, synophrys, short nose with depressed bridge and anteverted nares, long philtrum, thin vermillion of the upper lip, micrognathia, and hypertrichosis.

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While wide phenotypic variability exists within the CdLS spectrum, ranging from mild to severe, most patients have growth deficiency, intellectual disability, and facial dysmorphism [Kline et al, 2007a; Mehta et al, 2016]. There are 5 identified genes known to cause CdLS when mutated – *NIPBL*, *SMC1A*, *HDAC8*, *SMC3*, and *RAD21* [Krantz et al, 2004]. Because there is variability between clinical presentation based on causative gene and mutation type, evaluating the CdLS phenotype in patients of diverse descent or mixed-ancestry can make diagnosis difficult. Early diagnosis of CdLS is imperative to address life threatening medical issues such as malrotation and seizures [Deardorff et al, 2016; Kline et al, 2007b].

CdLS is a well-recognized condition; however, clinical descriptions of patients with CdLS from diverse ancestral backgrounds in the available medical literature is limited. There are a few case reports with African, Korean, Indian, Iranian, and Malaysian individuals with CdLS [Familant, 1968; Kim et al, 2005; Bhuiyan et al, 2006; Badoe, 2006; Tayebi, 2008; Reddy et al, 2013; Shenoy et al, 2014]. There are, however, numerous case reports of Caucasian individuals [Russell et al, 2001; DeScipio et al, 2005]. Larger studies have come out of Europe including patients from Italy, Canada, the United Kingdom, and the United States of America [Musio et al, 2006; Kline et al, 2007b; Olioso et al, 2009; Rohatgi et al, 2010; Deardorff, 2012; Pehlivan et al, 2012; Huisman et al, 2017].

Very few publications have focused on diverse populations such as Africans, Asians, and Latin Americans. As a result, many clinicians are trained with clinical genetic resources where only patients of European descent serve as the standard of reference [Muenke et al, 2016]. Here we compare physical exam findings of patients from underrepresented minority groups with CdLS and demonstrate how facial analysis technology can be a useful clinical tool in diagnosis of individuals from diverse ancestral backgrounds.

MATERIALS AND METHODS

Review of Medical Literature

A Medline search was performed to find studies that characterize CdLS in diverse populations. The key words and search terms included: Cornelia de Lange syndrome, NIPBL, SMC1A, HDAC8, SMC3, RAD21, diverse populations, underrepresented minorities, Africa, African-American, Asia, Latin America, Hispanic, Indian, Middle East, and facial analysis technology. Review of the references in papers pertaining to CdLS was also conducted.

Patients

We evaluated the dysmorphologic features in a large cohort of individuals with a clinical diagnosis of CdLS, and limited our analyses to patients with both clinical diagnoses and available clinical images. The average age was 4.2 years (range from birth to 37 years), the median age was 3 years, and 49% were females (Supplementary Table 1). We evaluated individuals with CdLS from 15 countries and identified 246 individuals belonging to the following ancestry groups – Caucasian (n=183), African and African American (n=14), Asian (n=23), Latin American (n=22), and Middle Eastern (n= 8). These groupings were made based on self-identification, with the understanding that phenotypes may vary considerably even within the same ancestry group. All patients had been consented and

evaluated by a trained clinical geneticist for features consistent with a diagnosis of CdLS, many of whom also had confirmed molecular diagnoses. Exam findings from our current study and those from the medical literature are recorded for review (Table 1).

Facial Analysis Technology

As described previously [Kruszka et al., 2017a; Kruszka et al., 2017b, Kruszka et al., 2017c], digital facial analysis technology was used to evaluate the frontal photos of individuals with CdLS from underrepresented minority backgrounds in our study [Zhao et al., 2013; Zhao et al., 2014a; Zhao et al., 2014b; Cerrolaza et al., 2016]. Both the underrepresented minority patients in our study and Caucasian controls with CdLS were matched by age and gender to unaffected individuals. The distribution of the dataset is presented in Table 2.

Using only facial images of our study participants, analysis was performed with our algorithms. Output consisted of feature extraction, selection, and classification. As in our previous studies, after facial detection and landmark positioning, a set of 126 facial features were extracted from a set of 44 landmarks placed on the frontal face images. This included both geometric and texture biomarkers. The geometric biomarkers consisted of a set of distances and angles calculated between the different inner facial landmarks as represented in Figure 1. As markers of monotonic illumination changes, local binary patterns were calculated at each of the 33 inner facial landmarks to quantify texture information. From the collection of geometric and texture features, those with the most significance were selected by methods previously described [Cai et al., 2010]. For each feature set, a support vector machine classifier [Cortes and Vapnik, 1995] was trained using a leave-one-out strategy cross-validation [Elisseef and Pontil, 2003]. The optimal number of features was selected as the one which maximized the classification of accuracy. Supplementary Figures 1–5 graphically demonstrate how the addition of features improves sensitivity, specificity, and accuracy within each ancestry group. Additionally, as an estimator of the individual discriminant power of each selected feature, the significance (p-value) was estimated using the Student’s t-test. Significance between methods used to detect CdLS was assessed using the Fisher’s exact test.

RESULTS

Clinical information and photos were collected on 246 patients with confirmed molecular diagnoses of CdLS, coming from diverse ancestral categories from 15 countries. Figures 2–5 show facial features of individuals of African descent (n=14), Asian descent (n=23), Latin American descent (n=31), and Middle Eastern descent (n=8) respectively. Figure 6 shows an age progression in some of the patients. Table 1 demonstrates physical exam variations in our CdLS population (Table 1). The participants with photographs used for Figures 1–6 are listed in Supplementary Table 1.

The cardinal signs of CdLS are listed in Table 1, and include synophrys, arched eyebrows, thick eyelashes, short nose with anteverted nares, long philtrum with thin upper lip and downturned mouth, hypertrichosis, and upper extremity anomalies. Features that varied across ancestry groups included palate anomalies, reflux, and hearing loss.

Facial analysis technology was utilized for a more objective approach to phenotypic analysis. Table 2 shows the age and ancestry of cases and their Caucasian controls studied. A total of 63 minorities with CdLS, 183 Caucasians with CdLS, and 246 healthy controls were evaluated. When using both geometric and texture measures across the global population, sensitivity was 0.95, specificity was 0.93, and accuracy was 0.94 (Table 3). Accuracy was defined as the percentage of correct classifications in the cohort. All five population groups (African American, Asian, Middle Eastern, Latin American, and Caucasian) had improved sensitivity and accuracy when combining both geometric features and texture measures ($p < 0.001$ for all groups, Table 3). Supplementary Figures 1–5 graphically demonstrate how the addition of features improves these measures respectively. Supplementary Tables 2–6 present the relevant features for diagnosis of CdLS for each ancestry group as selected by the digital facial analysis technology.

DISCUSSION

CdLS is a rare condition that has multisystemic phenotypic variability within the general population. It is most commonly the recognition of the classically reported facial and limb anomalies that leads to clinical suspicion of the diagnosis and subsequent testing (when available and accessible) of the multiple genes known to be implicated in CdLS. These characteristic features have been typically recognized and predominantly reported in individuals of Caucasian/European ancestry and may be missed in patients from diverse populations. While molecular diagnostics is becoming more widely accessible and allows for an unbiased diagnosis, this is not the case in developing countries where clinical features are relied upon. Here, we present individuals with CdLS from diverse backgrounds. This study characterizes CdLS subjectively with images of facial findings, objectively through digital facial analysis technology, and collectively by organizing clinical exam findings from the medical literature. Facial analysis technology has been reported for the diagnosis of CdLS cohorts in the past, but have not looked specifically across diverse ancestry groups [Basel-Vanagaite et al, 2016]. The goal of this study is to give providers a baseline reference to help make a clinical diagnosis of CdLS in patients from underrepresented minorities. Earlier diagnosis can lead to screening for life threatening complications, thus leading to better care and preventative measures. This also facilitates discussion of prognosis, recurrence risk, and genetic counseling with patients and their families.

This study has found differences between phenotypic findings across various ancestry groups in individuals with CdLS. When looking at the 23 clinical characteristics, the only elements with statistical significance were long eyelashes, ptosis, hearing loss, palate anomalies, micromelia, reflux, malrotation, and growth deficiency (Table 1, $p<0.05$; χ^2 test). The clinical characteristics in our study present in over 80% of individuals were synophrys, arched eyebrows, full lashes, short nose with anteverted nares, long philtrum with thin upper lip, growth deficiency, and intellectual disability. Congenital heart disease was identified in 40% of the patients in our study – which falls within expected reports based on prior characterization studies ranging from 14–70% [Chatfield et al, 2012].

For many patients with *NIPBL* mutations, the severity of their features makes their clinical diagnosis easily recognizable. However, we do know that there are more subtle features

appreciable depending on gene involved and mutation type (Figures 2–6), and this diagnosis can potentially be missed [Deardorff et al, 2013; Gil-Rodriguez et al, 2015; Gillis et al, 2004]. Facial analysis technology can complement the elements of dysmorphologic examination, especially where molecular diagnosis may not be readily available. The study showed that the technology was able to diagnose patients from all ancestry groups with a sensitivity of 95% and a specificity of 93%. When evaluating within ancestry groups by the facial analysis algorithm, sensitivity and accuracy both increased to greater than or equal to 95% for all groups (Table 3). The technology identified quantitative facial biometrics specific to CdLS for each ancestry group. As expected, the analysis found lip width, distance between nose root and apex, and distance between medial canthi as significant features in all population groups (Supplementary tables 2–6).

Though molecular technologies are becoming more widespread and readily available, they are not as ubiquitous as the internet and social media. Throughout the world CdLS is still primarily diagnosed or suspected based on clinical exam features alone. Facial analysis technology for CdLS detection has proven to be both sensitive and specific, and can serve as a mobile, portable tool to aid in diagnosis. Presently, there are programs utilizing facial recognition technology that are widely available at no cost. Based on the authors' collective experiences, mobile device availability is widespread amongst providers in developing countries. The availability of this technology for recognizable malformation syndromes in developing countries has the potential to greatly inform providers in making diagnoses.

Study limitations include the ascertainment bias that exists when looking at individuals with clinical diagnosis that present with the most severe phenotypes which require medical attention; milder phenotypes are likely being missed. Inherent to studies looking at genetic syndromes across diverse populations comes the fact that many participating countries have limited resources and barriers to accessing medical care, let alone molecular testing in many instances. Thus, we accepted patients for inclusion in this study that were diagnosed clinically by a trained medical geneticist. The majority of our cohort, greater than 90%, had confirmed molecular diagnoses.

We understand that while ancestral subpopulations are unique, grouping individuals into broad categories is arbitrary. We also acknowledge that racial admixture exists across global populations as well. Future studies will allow us to account for genotype-phenotype correlations between mutation type and gene involvement. Also, facial analysis technology can be a tool to aid the clinician in supporting a diagnosis, but should not serve as a substitute for an evaluation by a geneticist.

In conclusion, we have assembled a catalog of ethnically diverse individuals with CdLS, summarized the limited medical literature pertaining to CdLS and diverse populations, and conducted objective evaluation with digital facial analysis technology to demonstrate differences in facial features between ancestral groups. Based on our study and similar reports (Kruszka et al., 2015; Kruszka et al., 2017a; Kruszka et al., 2017b), we predict that digital facial analysis technologies have applicability to individuals from widespread and diverse ancestral backgrounds – for both CdLS and other syndromes with distinct and recognizable dysmorphology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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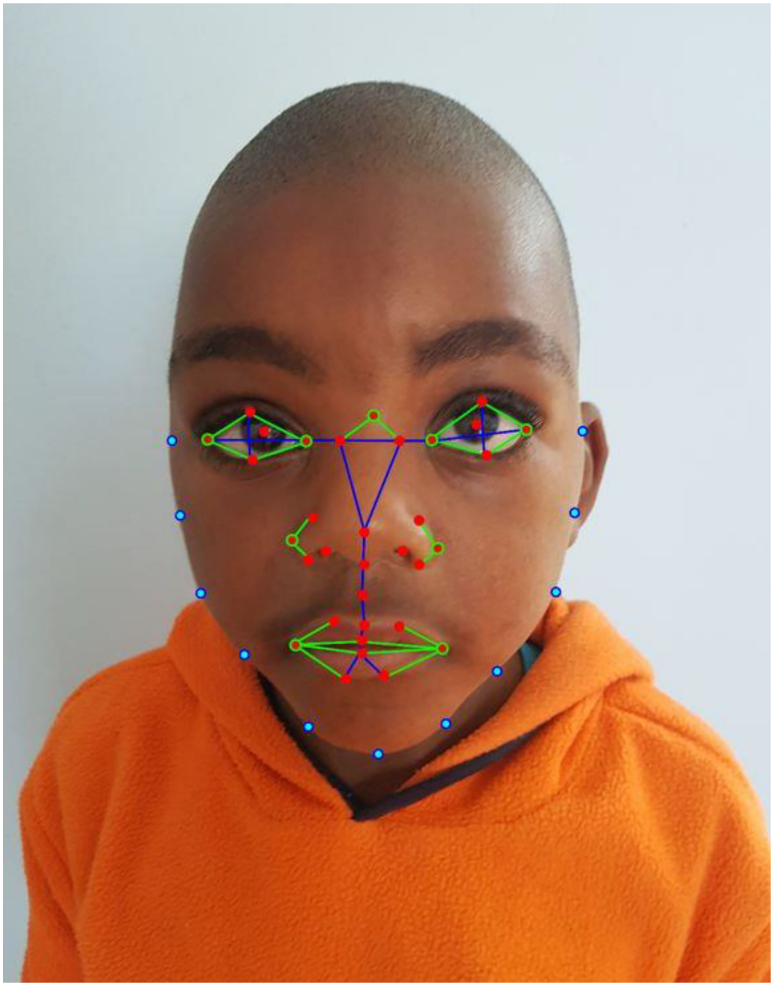

Figure 1.

Facial landmarks on a CdLS patient. Inner facial landmarks are represented in red, external landmarks 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.

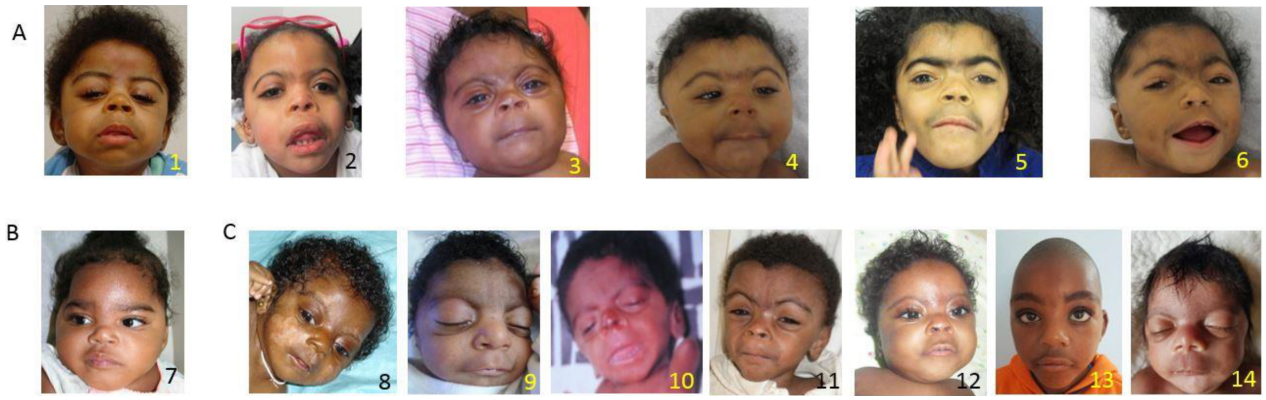

Figure 2.

Frontal profiles of individuals of African descent with CdLS. A) *NIPBL* mutations, B) *SMC1A* mutation, C) Clinical diagnosis only. Gender, age, and country of origin found in Supplementary Table 1.

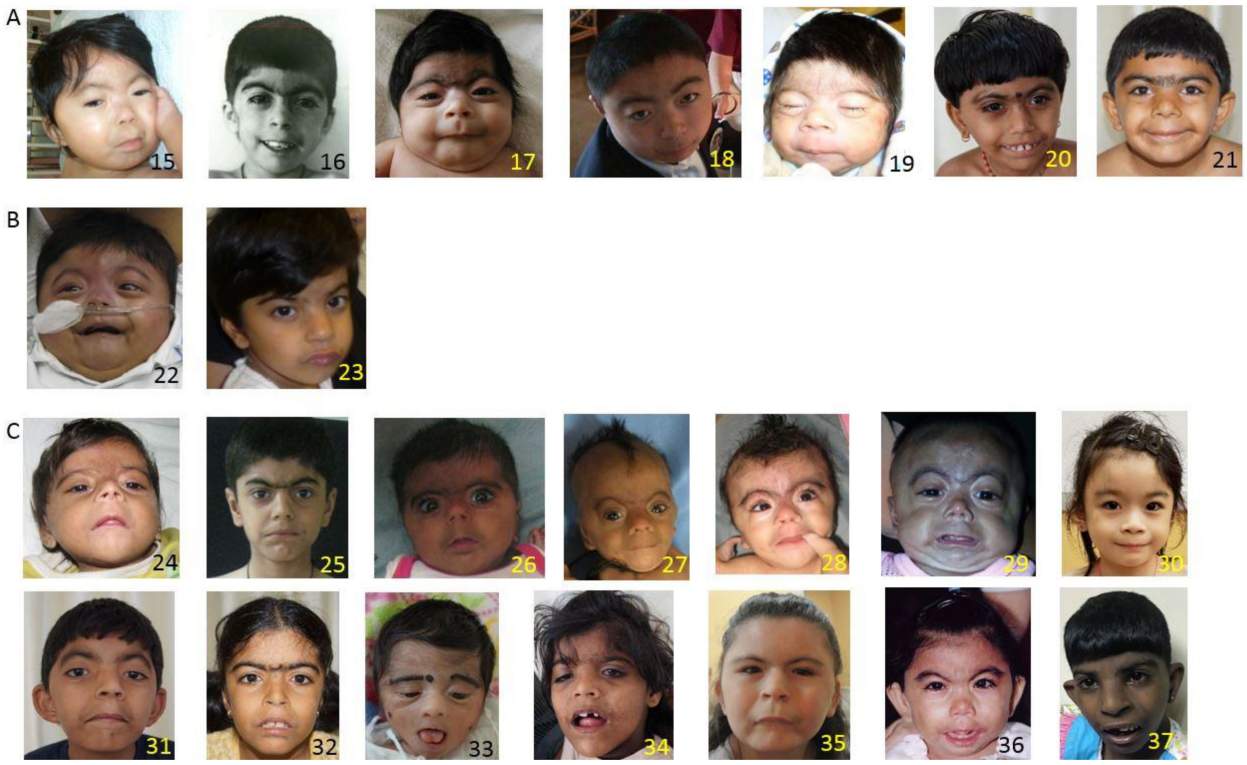

Figure 3.

Frontal profiles of individuals of Asian descent with CdLS. A) *NIPBL* mutations, B) *HDAC8* mutations, C) Clinical diagnosis only. Gender, age, and country of origin found in Supplementary Table 1.

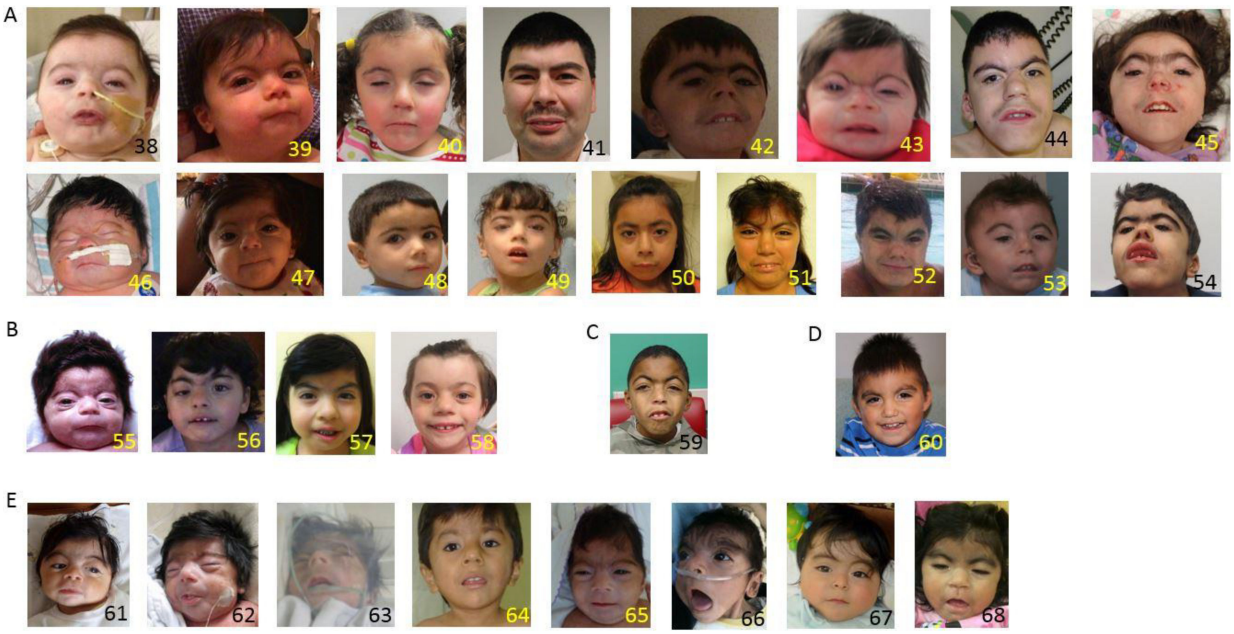

Figure 4.

Frontal profiles of individuals of Latin American descent with CdLS. A) *NIPBL* mutations, B) *HDAC8* mutations, C) *SMC1A* mutation, D) *SMC3* mutation, and E) Clinical diagnosis only. Gender, age, and country of origin found in Supplementary Table 1.

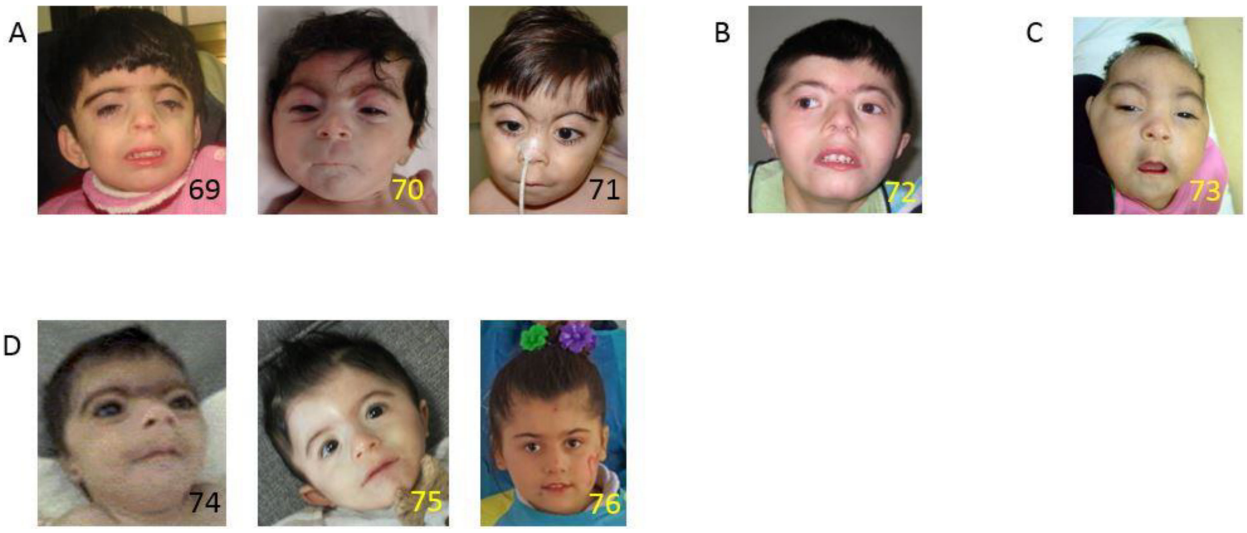

Figure 5.

Frontal profiles of individuals of Middle Eastern descent with CdLS. A) *NIPBL* mutations, B) *HDAC8* mutations, C) *SMC1A* mutation, D) Clinical diagnosis only. Gender, age, and country of origin found in Supplementary Table 1.

Figure 6.

Sequential photos of individuals of various descent with CdLS at different ages. Gender, age, and country of origin found in Supplementary Table 1.

Table 1.

Summary of exam findings of individuals with CdLS from diverse backgrounds including 67 individuals from the present study.

	Present Study					
	Africa n = 14	**Asia n = 23**	**Latin America n = 22**	**Middle East n = 8**	**p-values**	**Kline et al. (2007b)n = 49 *90% Caucasian descent**
Average Age (years)	1.4	4.3	6.5	2.6		17
Age Range	2w – 9y	2w – 12y	1d – 37y	3m – 8y		11–50y
NIPBL (%)	100% (6/6)	75% (6/8)	77%	60% (3/5)		93% (13/14)
HDAC8(%)	0	2/8 (25%)	18%	1/5 (20%)		0
SMC1A (%)	0	0	5%	1/5 (20%)		7% (1/14)
Synophrys	100%	91%	100%	88%	0.278	100%
Arched eyebrows	100%	91%	100%	100%	0.268	n/a
Long eyeashes	100%	100%	100%	75%	0.002	n/a
Ptosis	71%	39%	36%	0%	0.011	n/a
Short nose/anteverted nares	100%	83%	100%	88%	0.090	78%
Long philtrumThin vermillion border of upper lipDownturned corners of mouth	100%	100%	100%	100%	0.999	78%
Hearing loss	69% (9/13)	22% (4/18)	32%	60% (3/5)	0.037	65%
Micrognathia	85% (11/13)	56% (10/18)	59%	40% (2/5)	0.235	47%
Palate anomalies	23% (3/13)	11% (2/18)	27%	80% (4/5)	0.021	37%
Clinodactyly	92% (12/13)	56% (10/18)	45%	60% (3/5)	0.051	n/a
Micromelia	92% (12/13)	89% (16/18)	100%	60% (3/5)	0.037	74%
Crease anomalies	38% (5/13)	33% (6/18)	32%	20% (1/5)	0.903	n/a
Upper extremity anomaly	77% (10/13)	33% (6/18)	45%	60% (3/5)	0.722	33%
Hypertrichosis	85% (11/13)	67% (12/18)	68%	100% (5/5)	0.331	80%
Hypoplastic umbilicus/nipples	54% (7/13)	17% (3/18)	32%	20% (1/5)	0.159	n/a
Reflux	85% (11/13)	28% (5/18)	73%	40% (2/5)	0.004	82%
Malrotation	15% (2/13)	0%	0%	0%	0.038	10%
Renal anomalies	27% (4/13)	11% (2/18)	9%	20% (1/5)	0.342	4%
Congenital heart disease	28% (3/13)	22% (4/18)	41%	40% (2/5)	0.527	22%
Behavioral changes	38% (5/13)	17% (3/18)	23%	0%	0.514	80%
Neurologic abnormalities	8% (1/13)	6% (1/18)	5%	0%	0.885	26%
Intellectual disability (mod-severe)	85% (11/13)	100% (18/18)	100%	80% (4/5)	0.066	74%
Growth deficiency	100% (13/13)	100% (18/18)	100%	80% (4/5)	0.013	98% (43/44)

Table 2.

Population data used in facial analysis technology which includes 246 individuals with CdLS from Supplementary Table 1 and additional archival images of individuals with CdLS.

	CdLS (N=246)		Controls (N=246)	
Age	Number	%	Number	%
Newborn	6	2%	6	2%
Infant	67	27%	67	27%
Toddler	61	25%	61	25%
Child	66	27%	66	27%
Adolescent	19	8%	19	8%
Adult	27	11%	27	11%
Total	246		246	
Ancestry				
African descent	13	5%	13	5%
Asian	22	9%	22	9%
Latino	22	9%	22	9%
Middle Eastern	6	2%	6	2%
Caucasian	183	74%	183	74%
Total	246		246	
Gender				
Male	126	51%	126	51%
Female	120	49%	120	49%
Total	246		246	

Table 3.

Measures of diagnostic accuracy for facial analysis technology that discriminate between CdLS and unaffected individuals, stratified by ancestry group.

	Number of features	AUC	Accuracy	Sensitivity	Specificity
Global	14	0.98	0.94	0.95	0.93
African descent	4	0.92	0.96	1.00	0.92
Asian	6	0.98	0.95	1.00	0.91
Latin American	7	0.96	0.98	1.00	0.95
Caucasian	12	0.99	0.95	0.96	0.93

* AUC – area under the receiver operating characteristic curve