Supplementary material

Supplementary Table 1. Participants with photographs in Figures 2-5 from 10 countries.
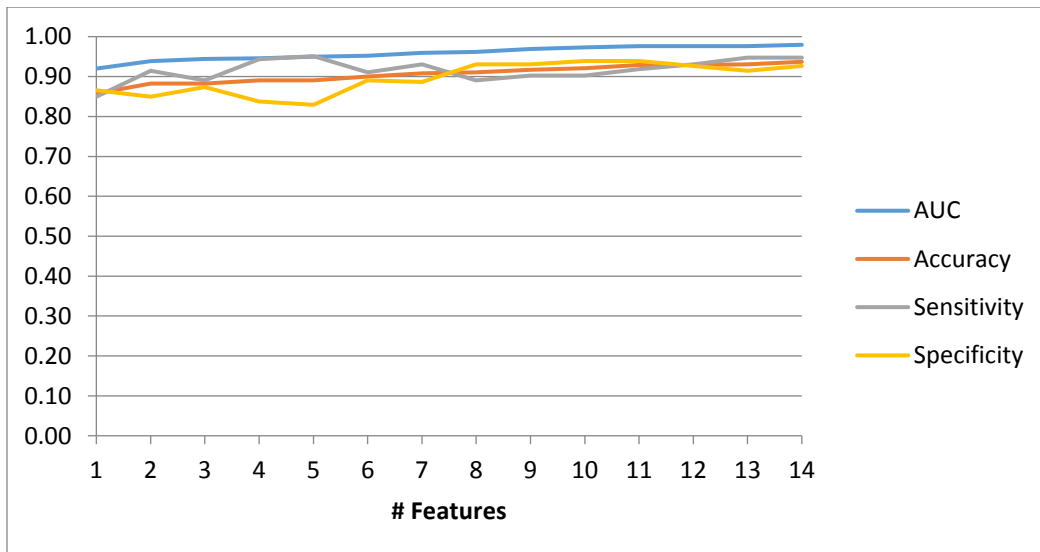
Patient	Country	Gene	Variant	Age	Gender
1	USA	NIPBL	p. Arg1789Gly	8 mo	Male
2	USA	NIPBL	p.Gly2081Val	2 yo	Female
3	USA	NIPBL	7789delC:L2597CfxX13	7 mo	Female
4	USA	NIPBL	p. Gln200X	8 mo	Male
5	USA	NIPBL	4529dupA:S1511TfxX79	9 yo	Female
6	USA	NIPBL	p.Arg2407X	2 yo	Female
7	USA	SMC1A	c.1736_1748del13	8 mo	Female
8	Ghana	Clinical dx by E.B.	NA	2 mo	Female
9	Ghana	Clinical dx by E.B.	NA	2 mo	Female
10	Ghana	Clinical dx by E.B.	NA	2 wo	Female
11	Rwanda	Clinical dx by A.U.	NA	10 mo	Male
12	Rwanda	Clinical dx by L.M.	NA	6 mo	Female
13	South Africa	Clinical dx by E.H.	NA	5 yo	Male
14	South Africa	Clinical dx by E.H.	NA	2 wo	Male
15	USA	NIPBL	p.Gln298Leu	4 yo	Female
16	USA	NIPBL	p.Val1800Asp	5 yo	Male
17	USA	NIPBL	40288-2>T	1 mo	Female
18	USA	NIPBL	64+1G>A	12 yo	Male
19	USA	NIPBL	180_183delTTTG:N60KfsX17	1 mo	Male
20	India	NIPBL	c.7301A>T	5 yo	Female
21	India	NIPBL	c.231-1G>T	7 yo	Male
22	USA	HDAC8	p.His42Pro	1 mo	Male
23	USA	HDAC8	1006-2A>G	4 yo	Female
24	India	Clinical dx by N.G.	NA	4 mo	Male
25	India	Clinical dx by N.G.	NA	10 yo	Male
26	India	Clinical dx by N.G.	NA	5 mo	Female
27	India	Clinical dx by N.G.	NA	4 mo	Male
28	India	Clinical dx by N.G.	NA	2 mo	Male
29	Thailand	Clinical dx by V.S.	NA	6 mo	Male
30	Malaysia	Clinical dx by M.T.	NA	4 yo	Female
31	India	Clinical dx by S.P.	NA	10 yo	Male
32	India	Clinical dx by S.P.	NA	8 yo	Female
33	India	Clinical dx by S.P.	NA	2 wo	Female
34	India	Clinical dx by S.P.	NA	9 yo	Female
35	Malaysia	Clinical dx by M.T.	NA	10 yo	Female
36	Thailand	Clinical dx by V.S.	NA	1 yo	Female
37	Sri Lanka	Clinical dx by N.S.	NA	9 yo	Female
38	USA	NIPBL	p.Val2147Gly	1 mo	Male
39	USA	NIPBL	p.Arg1789Leu	1 yo	Male
40	USA	NIPBL	p.Val1975Phe	3 yo	Female
41	USA	NIPBL	Phe1948Ser	37 yo	Male

42	USA	NIPBL	p.Arg841GlyfsX6	3 yo	Male
43	USA	NIPBL	p.Arg1789X	3 mo	Female
44	USA	NIPBL	p.Ser535X	17 yo	Male
45	USA	NIPBL	Del exons 2-17	4 yo	Female
46	USA	NIPBL	623+2T>G	1 do	Male
47	USA	NIPBL	7411-15del8ins10	7 mo	Female
48	USA	NIPBL	64+1G>A	3 yo	Male
49	USA	NIPBL	64+1G>A	6 yo	Female
50	USA	NIPBL	65-5A>G	7 yo	Female
51	USA	NIPBL	6108+4A>C	13 yo	Female
52	USA	NIPBL	868+1G>A	13 yo	Male
53	USA	NIPBL	p.Gln1499*	3 yo	Male
54	USA	NIPBL	2701_2704del4	10 yo	Male
55	USA	HDAC8	p.Thr311Met	1 do	Female
56	USA	HDAC8	p.His180Arg	3 yo	Female
57	USA	HDAC8	p.Gln236X	7 yo	Female
58	USA	HDAC8	717_719del	3 yo	Female
59	USA	SMC1A	p.Asp543Asn	11 yo	Male
60	USA	SMC3	p.Asn477Lys	2 yo	Male
61	Peru	Clinical dx by H.A.	NA	5 mo	Male
62	Peru	Clinical dx by H.A.	NA	3 mo	Male
63	Peru	Clinical dx by H.A.	NA	1 mo	Male
64	Peru	Clinical dx by H.A.	NA	6 yo	Male
65	Peru	Clinical dx by H.A.	NA	2 mo	Male
66	Peru	Clinical dx by H.A.	NA	2 mo	Male
67	Peru	Clinical dx by H.A.	NA	1 mo	Female
68	Peru	Clinical dx by H.A.	NA	2 yo	Female
69	USA	NIPBL	p.Ala2390Thr	6 yo	Female
70	USA	NIPBL	4002_4005del4	4 mo	Male
71	USA	NIPBL	249-250ins16:Gly84fsX8	1 yo	Male
72	USA	HDAC8	p.Gly320Arg	8 yo	Male
73	USA	SMC1A	p.Arg586Trp	5 mo	Female
74	Iran	Clinical dx by N.T.	NA	3 mo	Male
75	Lebanon	Clinical dx by A.M.	NA	6 mo	Male
76	Lebanon	Clinical dx by A.M.	NA	4 yo	Female

Supplementary Table 2. Geometric and texture feature comparison of Global (combined African descent, Asian, Latin American, Caucasian) CdLS individuals with normal controls using digital facial analysis technology. The ranges of the geometric linear features were normalized by the ear-to-ear distance. 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 CdLS.

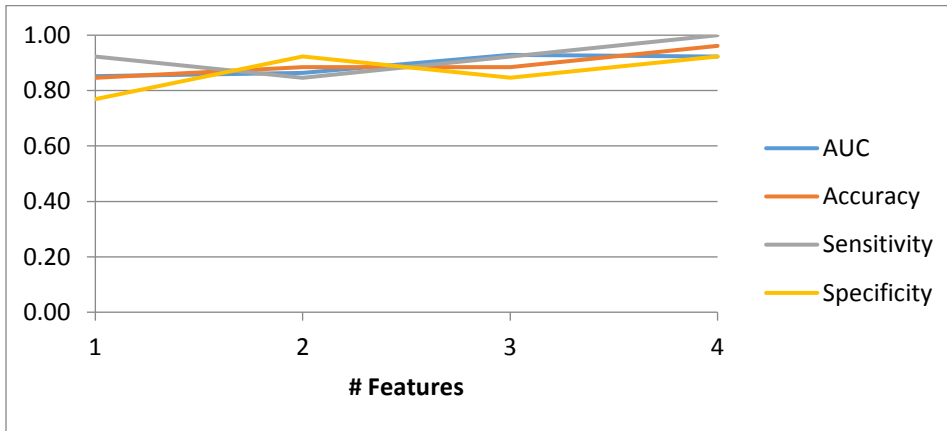| Feature	Normal	Syndromic	p-value
Angle at nose root	62.5533 ± 16.0870	96.6052 ± 18.0666	0
Distance between nose apex and columella	0.1747 ± 0.0239	0.2116 ± 0.0331	1.30E-38
Distance between medial canthi	0.2709 ± 0.0282	0.2969 ± 0.0279	1.45E-22
Distance between columella and cupids bow	0.2207 ± 0.0537	0.2769 ± 0.0691	8.51E-22
Texture at bottom of left ala of the nose (r2)			2.57E-17
Texture at lower border of upper lip (r3)			8.56E-15
Texture al philtrum (r2)			9.87E-15
Texture at lower eyelid of right eye (r3)			2.16E-14
Texture at top of right ala of the nose (r3)			3.20E-14
Texture at right nostril (r2)			5.47E-08
Texture at lower eyelid of right eye (r2)			3.21E-06
Texture at lateral canthus of left eye (r3)			3.57E-06
Angle of left ala of the nose	105.9474 ± 12.8005	110.6521 ± 12.7227	5.39E-05
Texture at upper eyelid of right eye (r1)			9.59E-03

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

Supplementary Table 3. Geometric and texture feature comparison of African descent CdLS individuals with normal controls using digital facial analysis technology. The ranges of the geometric linear features were normalized by the ear-to-ear distance. 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 CdLS.

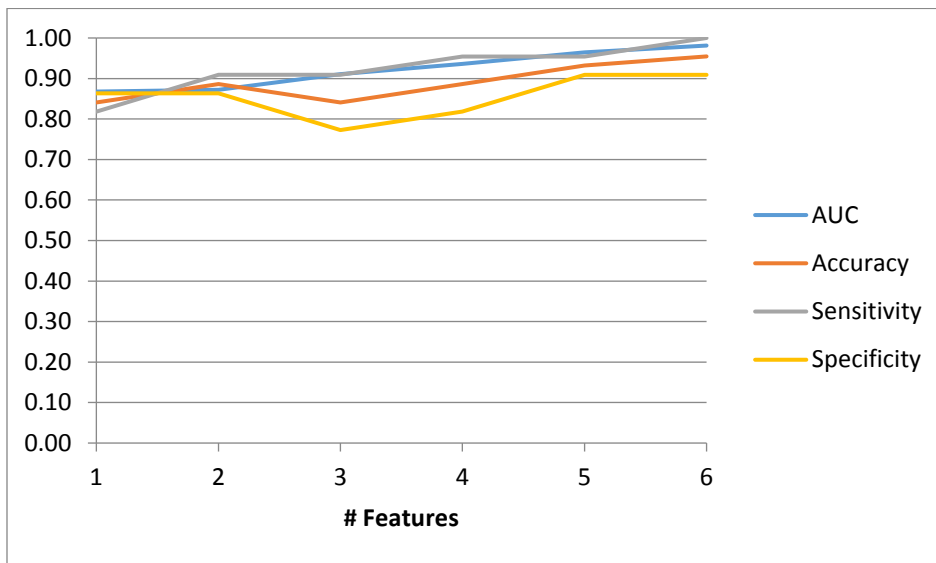| Feature	Normal	Syndromic	p-value
Lower lip width (measure on left side)	0.1912 ± 0.0343	0.1277 ± 0.0309	4.50E-05
Lower lip width (measure on right side)	0.1876 ± 0.0366	0.1214 ± 0.0391	1.63E-04
Distance between left side of nose root and nose apex	0.3419 ± 0.0393	0.2790 ± 0.0632	5.55E-03
Distance between medial canthi	0.2753 ± 0.0299	0.3102 ± 0.0291	5.89E-03

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

Supplementary Table 4. Geometric and texture feature comparison of Asian CdLS individuals with normal controls using digital facial analysis technology. The ranges of the geometric linear features were normalized by the ear-to-ear distance. 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 CdLS.

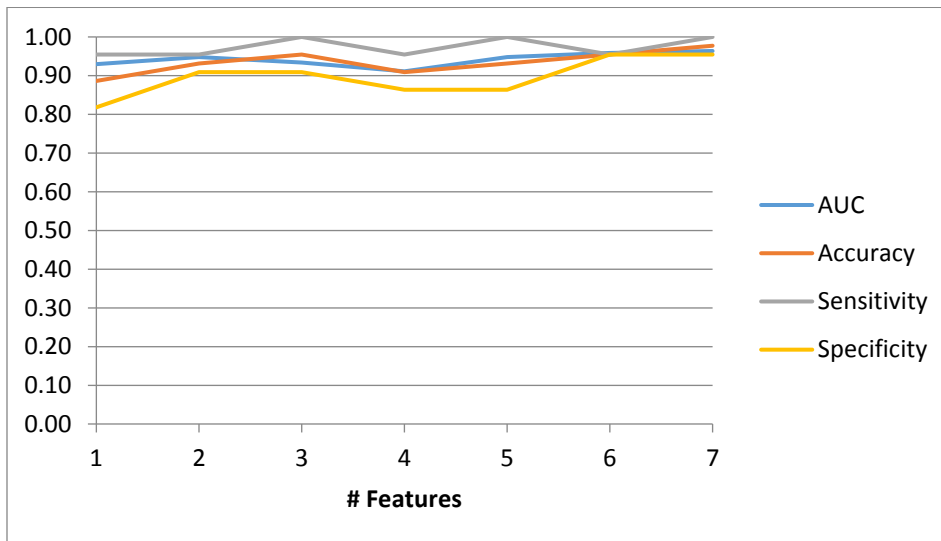| Feature	Normal	Syndromic	p-value
Angle at nose root	69.1136 ± 15.4606	97.0466 ± 16.6019	5.84E-07
Lower lip width (measure on right side)	0.1602 ± 0.0418	0.1184 ± 0.0184	1.03E-04
Distance between columella and cupids bow	0.2007 ± 0.0534	0.2772 ± 0.0720	2.49E-04
Distance between medial canthi	0.2759 ± 0.0250	0.3014 ± 0.0280	2.75E-03
Texture at medial canthus of right eye (r3)			8.24E-03
Distance between medial and lateral canthi (right eye)	0.1866 ± 0.0138	0.1737 ± 0.0199	1.68E-02

Supplementary Figure 3. Asian: Graph of area under the ROC curve (AUC), accuracy, sensitivity, and specificity versus the number of features selected.

Supplementary Table 5. Geometric and texture feature comparison of Latin American CdLS individuals with normal controls using digital facial analysis technology. The ranges of the geometric linear features were normalized by the ear-to-ear distance. 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 CdLS.

Feature	Normal	Syndromic	p-value
Angle at nose root	66.9714 ± 18.1570	104.2930 ± 14.3274	1.27E-09
Angle of left ala of the nose	98.7158 ± 11.3275	113.5985 ± 9.5663	2.90E-05
Distance between columella and cupids bow	0.2252 ± 0.0397	0.2961 ± 0.0800	5.86E-04
Texture at nose apex (r3)			5.97E-02
Texture at right lateral of nose root (r1)			6.62E-02
Texture at bottom of left ala of the nose (r3)			1.48E-01
Texture at medial canthus of left eye (r2)			3.03E-01

Supplementary Figure 4. Latin American: Graph of area under the ROC curve (AUC), accuracy, sensitivity, and specificity versus the number of features selected.

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Supplementary Table 6. Geometric and texture feature comparison of Caucasian CdLS individuals with normal controls using digital facial analysis technology. The ranges of the geometric linear features were normalized by the ear-to-ear distance. 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 CdLS.

Feature	Normal	Syndromic	p-value
Angle at nose root	59.8210 ± 14.5617	95.8101 ± 18.9321	0
Distance between nose apex and columella	0.1718 ± 0.0203	0.2133 ± 0.0334	2.46E-37
Texture at left lateral of nose root (r2)			1.18E-18
Distance between medial canthi	0.2684 ± 0.0282	0.2947 ± 0.0286	3.60E-17
Lower lip width (measure on left side)	0.1544 ± 0.0325	0.1277 ± 0.0258	1.15E-16
Distance between columella and cupids bow	0.2200 ± 0.0543	0.2721 ± 0.0664	3.63E-15
Texture at top of left ala of the nose (r2)			4.17E-12
Texture at left nostril (r1)			2.63E-11
Texture at top of right ala of the nose (r1)			4.51E-05
Texture at upper eyelid of right eye (r1)			2.10E-04
Texture at bottom of right ala of the nose (r1)			3.27E-03
Texture at lower eyelid of left eye (r2)			8.46E-03

Supplementary Figure 5. Caucasian: Graph of area under the ROC curve (AUC), accuracy, sensitivity, and specificity versus the number of features selected.