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Facial Diagnosis of Mild and Variant CdLS: Insights From a Dysmorphologist Survey

Sarika Rohatgi[1], **Dinah Clark**[1], **Antonie D. Kline**[2], **Laird G. Jackson**[3], **Juan Pie**[4], **Victoria Siu**[5], **Feliciano J. Ramos**[4], **Ian D. Krantz**[1,6], and **Matthew A. Deardorff**[1,6,*]

[1]Division of Genetics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania [2]Harvey Institute of Human Genetics, Baltimore, Maryland [3]Division of Obstetrics and Gynecology, Drexel University School of Medicine, Philadelphia, Pennsylvania [4]Unidad de Genética Clínica y Genómica Funcional, Departamentos de Fisiología y de Pediatría, Facultad de Medicina, Universidad de Zaragoza, Servicio de Pediatría, Hospital Clínico Universitario, Zaragoza, Spain [5]Children's Hospital of Western Ontario, London, Ontario, Canada [6]Department of Pediatrics, The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Abstract

Cornelia de Lange syndrome (CdLS) is a dominant disorder with classic severe forms and milder atypical variants. Central to making the diagnosis is identification of diagnostic facial features. With the recognition that patients with *SMC1A* and *SMC3* mutations have milder, atypical features, we surveyed 65 dysmorphologists using facial photographs from 32 CdLS patients with the goals of (1) Illustrating examples of milder patients with *SMC1A* mutations and (2) Obtaining objective data to determine which facial features were useful and misleading in making a diagnosis of CdLS. Clinicians were surveyed whether the patient had CdLS or another diagnosis, the certainty of response and the clinical features used to support each response. Using only facial photographs, an average of 24 cases (75%) were accurately diagnosed per clinician. Correct diagnoses were made in 90% of classic CdLS and 87% of non-CdLS cases, however, only 54% of mild or variant CdLS were correctly diagnosed by respondents. We confirmed that CdLS is most accurately diagnosed in childhood and the diagnosis becomes increasingly difficult with age. This survey demonstrated that emphasis is placed on the eyebrows, nasal features, prominent upper lip and micrognathia. In addition, the presence of fuller, atypical eyebrows, a prominent nasal bridge and significant prognathism with age dissuaded survey takers from arriving at a diagnosis of CdLS in individuals with mild *NIPBL* and *SMC1A* mutations. This work underscores the difficulty in diagnosing patients with mild and variant CdLS and serves to objectively classify both useful and misleading features in the diagnosis of CdLS.

*Correspondence to: Matthew A. Deardorff, M.D., Ph.D., 1002B Abramson Research Center, 3615 Civic Center Blvd, Philadelphia, PA 19104. deardorff@email.chop.edu.

Keywords

Cornelia de Lange syndrome; Brachmann–de Lange syndrome; facial features; facies; *NIPBL*; *SMC1*; *SMC1A*; *SMC1L1*; *SMC3*; mild; severe; survey; dysmorphology

INTRODUCTION

Cornelia de Lange syndrome (CdLS, OMIM #122470, #300590, and #610759), also known as Brachmann–de Lange syndrome, is a multi-system malformation syndrome including characteristic facial dysmorphia, hirsutism, upper-extremity malformations, proportionate small stature, growth and cognitive retardation as well as cardiac, musculoskeletal and gastrointestinal abnormalities. This syndrome has a broad spectrum of clinical involvement with increasing recognition of a milder phenotype that is often difficult to ascertain [Ireland, 1996; Allanson et al., 1997; Musio et al., 2006; Deardorff et al., 2007].

The characteristic craniofacial features of CdLS are central to the diagnosis of CdLS. A review of 31 previously diagnosed cases [Ireland et al., 1993] concluded that the facial findings of greatest diagnostic value were the characteristic eyebrows (well-defined, penciled and arched with synophrys), long philtrum, thin lips, and crescent-shaped mouth [Ireland and Burn, 1993; Ireland et al., 1993]. In identifying mild cases, it has been noted that useful features also include long thick curved eyelashes, depressed nasal bridge with anteverted nares, maxillary prognathism or mandibular retrognathism/micrognathia, “carp” mouth, small widely spaced teeth, highly arched or cleft palate, microbrachycephaly, low anterior and posterior hairline, low-set ears with malformed pinnae, and short neck [Preus and Rex, 1983; Van Allen et al., 1993; Allanson et al., 1997; Kline et al., 2007].

Based on the clinical variability in CdLS, a classification system has been proposed that divides CdLS into three sub-groups [Van Allen et al., 1993]. Type I, or classic CdLS has characteristic facial and skeletal changes, severe prenatal growth deficiency, moderate-to-profound psychomotor retardation, and major malformations. Type II, or mild CdLS, has similar facial features but minor skeletal and systemic malformations, which develop with time or are only partially expressed. They typically present with mild-to-borderline psychomotor retardation and less severe pre- and postnatal growth deficiency. Type III, or “phenocopy CdLS” includes patients who have phenotypic manifestations of CdLS that are presumably related to chromosomal aneuploidies or teratogenic exposures.

Mutations in NIPBL, which encodes a sister chromatid cohesion regulatory protein, account for 60% of clinically well-defined CdLS cases [Gillis et al., 2004; Krantz et al., 2004; Rollins et al., 2004; Tonkin et al., 2004; Bhuiyan et al., 2005; Musio et al., 2006; Yan et al., 2006; Selicorni et al., 2007]. Our experience is that *NIPBL* mutations account for nearly 80% of classic severe CdLS (Type I), while milder cases (Type II) have *NIPBL* mutations in ~25% (unpublished data). Other mutations causing CdLS include those in the *SMC1A* and *SMC3* genes, both of which encode core components of the Cohesin complex [Nasmyth and Haering, 2005; Musio et al., 2006; Borck et al., 2007; Deardorff et al., 2007]. *SMC1A* mutations contribute to 5% of CdLS cases and result in consistently milder phenotypes with absence of major structural anomalies associated with severe CdLS. Furthermore, we have

observed that mild patients with *NIPBL* mutations (often missense) have more typical but milder facies, whereas those with *SMC1A* mutations have mild, but less typical facies.

Since the "Cohesinopathies" may represent a wide spectrum of developmental disorders, classical CdLS may comprise a only small fraction of the spectrum. Due to extremely subtle and near-normal features in the mild CdLS cases, we hypothesize that they are often underdiagnosed, even by experienced dysmorphologists. To help increase awareness of these phenotypes, to clarify the subtle facial features that can be used to diagnose these mild and variant forms of CdLS, to define the most commonly used facial features for accurate diagnosis of CdLS and to identify the misleading features which may result in an incorrect diagnosis, we conducted a survey of a large group of experienced dysmorphologists using only facial photographs of selected individuals with CdLS.

Here we present the results of this survey that: (1) Indicate this is a useful approach to understand the clinical features used to arrive at a diagnosis, (2) Clarify the useful and misleading facial features of CdLS, (3) Confirm that the facial features of CdLS change with age and can be misleading, and (4) Demonstrate that the *SMC1A* and *NIPBL* patients have subtly different but distinguishable features.

MATERIALS AND METHODS

Subjects

All CdLS patients were enrolled in an IRB-approved protocol with informed photo consent and all non-CdLS individuals were consented for publication of facial photographs at the Children's Hospital of Philadelphia.

Survey Design

Facial photographs of 32 patients (23 patients with CdLS and 9 with other diagnoses) with symmetric growth retardation and varying degrees of mental retardation, most with facial features overlapping those of CdLS, were used. We weighted the survey with patients for whom the diagnosis of CdLS was more difficult. Each patient was presented with a frontal and lateral facial profile photos only (Fig. 1). The approximate ages of these patients were 0–2 years for patients #1–8, 3–6 years for patients #9–16, 7–12 years for patients #17–24 and ≥13 years for patients #25–32. An accompanying cover sheet explained that each patient had varying degrees of growth and mental retardation but the behavioral and non-facial physical features were not disclosed (see Supplementary Methods). A scoring sheet was given to indicate "Classic," "Mild" or "Non-CdLS" as well as the certainty (1–10) of the answer. The useful diagnostic facial features used for determining the diagnosis were also requested. The respondent experience level was requested but not required (see Supplementary Methods). This survey was distributed to ~150 dysmorphologists attending the 2006 David W. Smith Workshop on Malformations and Morphogenesis, Lake Arrowhead, CA. Although no signed consent was obtained from these clinicians, participation and identity were optional and we inferred consent to participate with the return of a completed survey. Clinicians were given the molecular diagnosis for each case at the conclusion of the meeting after all surveys were returned.

Data Analysis

In our assessment of "correct" answers, we disregarded a distinction between mild versus severe CdLS and either answer was scored as "CdLS." A response that accurately identified a case as "non-CdLS" was scored as "correct" whether or not an alternative diagnosis was provided. Results were analyzed on both respondent and patient bases for those respondents who returned the survey answer sheets. The comments were further evaluated and grouped into useful and misleading features. SPSS 17.0 (IBM, Chicago, IL) and Prism 5.0 (GraphPad Software, La Jolla, CA) were used for the statistical analysis to determine frequency, average values and *P*-values using chi-square and unpaired *t*-tests.

RESULTS

Competence of Cohort and Accuracy of Responses

Of the 150 surveys, 65 (43%) were returned. The composition of respondents included 16% trainees, 20% junior faculty, and 64% tenured faculty (including 47% full professors or chairs), indicating a very experienced test group.

The number of correct answers per respondent ranged from 18/ 32 (56%) to 30/32 (94%) with an average of 24 (75%). Dysmorphologist scores were distributed with 26% (17/65) scoring below 70% correct, 43% (28/65) from 70% to 80% correct, 23% (15/65) from 80% to 90% correct and 7% (5/65) with ≥90% correct. Furthermore, a bell-shaped curve is obtained when comparing the number of respondents with a given number of accurate responses (Fig. 2A) and suggests an informative data set from which to analyze the reported useful and misleading facial features.

Identification of Useful and Misleading Features

To identify the informative cases that were difficult to diagnose, we analyzed the data on a patient-by-patient basis. The breakdown of accurate diagnoses by group is shown in Table I. As an indicator of the high level of experience of the clinicians surveyed, the nine non-CdLS patients were correctly identified 87% of the time and frequently, the actual diagnosis was given. Of the 32 total patients, 19 were misdiagnosed by more than 10% of respondents, 17 of which had CdLS. Only 6 of 23 CdLS cases, all severe, were correctly diagnosed by >90% of respondents. Notably, a large majority of mild CdLS cases were under-diagnosed. In fact, compared with 87% of non-CdLS and 90% of classic CdLS cases accurately diagnosed by the respondents, only 54% of mild or variant CdLS were accurately diagnosed (Fig. 2B).

Although numbers are small, analysis of age subgroups confirms that CdLS is most easily diagnosed at an early age and the diagnosis becomes more difficult with age (Fig. 3). This is most clear when comparing accurate diagnosis by >90% respondents of classical CdLS cases for four of five patients in the 0–2 years group versus only one of five patients in the ≥13 years group. This data also supported our suspicion that mild CdLS cases were less well diagnosed in all age groups. Additionally, the level of difficulty (e.g., the percentage incorrect for each case) correlated with a lower average certainty (Fig. 3).

Useful diagnostic features were reported by 55 respondents (85%), with an average of 28 responding clinicians per patient, with comments ranging from a single word to multiple features for each patient. In performing the analysis, we made special note of these reported features in both correctly diagnosed cases (Supporting Features) and misdiagnosed cases (Misleading Features). After filtering for similar comments, including a significant degree of our interpretation as to the respondent meaning, the responses are summarized in Table II.

Although not collected in a manner that allowed effective quantitative evaluation, in reviewing these responses we noted a number of features often used in accurately making the diagnosis of CdLS. These included: penciled and arched eyebrows, high set/short anteverted nose, a long flat philtrum, thin upper lip, downturned corners of the mouth and micrognathia. Several less common, but insightful features included a round face and typical ears [Hunter et al., 2009]. Reduced facial movement, minimal smile, or “grimace”-like smile was a noted feature that correlated well with the accurate diagnoses in the moderate or severe cases, but was also misleading in the very mild cases. Finally, full or flat brows, a prominent nasal bridge or bulbous tip and/or a normal or prominent chin were all features that proved to be both frequently misleading. These same features also tended to correlate with accurate diagnoses in the older classic CdLS patients or those with *SMC1A* mutations.

DISCUSSION

Although making a diagnosis of CdLS often incorporates growth, cognitive and limb findings, identifying key or suggestive facial features is often pivotal in making the diagnosis. This becomes especially relevant in mild cases with fewer structural abnormalities and cases with variant facial features. Previous work on the facial features in CdLS primarily utilized expert opinion and experience of a few CdLS-specialized clinicians to define relevant features [Jackson et al., 1993; Allanson et al., 1997; Kline et al., 2007]. After the recent recognition of a consistently mild and variant phenotype in the *SMC1A*- and *SMC3*-mutated CdLS patients, we wished to assess which features assist or detract clinicians while diagnosing both typical and variant CdLS. Our study used a relatively novel survey strategy of a large number of experienced dysmorphologists to help define these features.

This study suggests four major findings:

1. This survey approach is very useful to determine features that are *frequently and functionally* used by clinicians in making the diagnosis of CdLS.
2. The changing facial features of CdLS over time, specifically the coarsening of the eyebrows and eyes and prognathism increase the difficulty of a diagnosis in older individuals.
3. There is a considerable degree of difficulty in recognizing the facial features in mild and variant CdLS.
4. The presence of a more prominent nose and nasal bridge and/or thicker eyebrows, in the setting of otherwise milder features of CdLS is suggestive of a mutation in *SMC1A* or *SMC3*.

Use of a Survey Approach to Identify Dysmorphic Facial Features Used in Diagnosis

Although we are aware of several surveys of this nature being performed, few have been published regarding the utility of the approach and the results. This study approach attempts to objectively identify common and subjectively identify novel facial features used in making a diagnosis of CdLS and how they may be useful or misleading.

This approach has several intrinsic limitations. Most notably, it relies on the collective experience as well as time investment by survey takers. We were very fortunate to receive many very thorough responses. Secondly, the use of only facial features disregards many of the other features (structural, behavioral, and cognitive), which are often used to arrive at and support a diagnosis. Thirdly, this survey included some more "typical" facies but due to our intended educational goal, was somewhat intentionally biased and weighted to include those with more difficult and possibly instructional features. Underdiagnosis of the milder cases is also likely due to the fact that fewer *NIPBL* mutation-positive patients, which have more subtle but typical features, were included relative to the less typical *SMC1A* mutation-positive patients.

In addition, the use of open-ended responses to get the maximum range of answers resulted in what we presume to be similar responses with different wording (e.g., high set vs. short nose and prominent philtrum vs. long upper lip). Interpretation of these brief and often cryptic responses relied on our judgment of "intended" meaning, which also carries intrinsic bias. In addition, the use of open-ended responses effectively eliminated the use of a quantitative evaluation of these features. Furthermore, this study was limited by relatively small numbers of patients, especially in each age group. Finally, this study was not sufficient to adequately detect features used to over-diagnose CdLS (e.g., synophrys and hirsutism), since most non-CdLS cases were identified correctly.

Changing Facies of CdLS With Age

Our data serves to reinforce the difficulty associated with diagnosis as CdLS facies transform with age (Fig. 4) [Allanson et al., 1997] carefully analyzed and described the average changes that occur during aging in CdLS. They noted that with age, both in classical and mild CdLS phenotypes, there is an increase in the facial length, upper and lower facial widths, as well as nasal height, width and protrusion. They also emphasized that the eyebrows become fuller and bushy. The philtrum appears less long and the upper lip more full, although the downturned corners of the mouth remain, and the jaw often obtains a more squared or prognathic appearance [Ireland et al., 1993].

Interestingly, these specific features were less appreciated by this large group of dysmorphologists, who presumably do not focus on CdLS. In fact, in this survey, the presence of full eyebrows, squared or large jaw was often used to exclude a diagnosis of CdLS in older patients (Table II). Respondents often missed the diagnosis of patients with "classic" forms (#27, #29, #30, and #31) due to "coarse features," "thick bushy eyebrows," a "well-developed nasal bridge," "no upturned nose," and "mandibular prognathism." This may be due to reduced exposure of dysmorphologists to older patients with CdLS, either due to mortality or care of these patients by other specialties. These features may also result

from variable alteration of facial features due to self-injurious behavior. Furthermore, this underscores the importance of reviewing childhood photographs especially while considering the diagnosis in teenage and older individuals. This is illustrated in Figure 4, which demonstrates the changing facial feature of *SMC1A*-mutated Patient #26 and another mild *NIBPL*-mutated patient.

Difficulty in Diagnosing Mild and Variant CdLS

Allanson et al. [1997] also concluded that, in mild phenotypes, the characteristic facial appearance may not appear until 2–3 years of age. They also concluded that the typical appearance in milder phenotype is more recognizable in childhood,and tends to gradually deflect towards normal as they age, becoming less striking after age 9.

As expected, this is also appreciated in this survey, and is demonstrated by comments such as “too normal” (#11, #23, #25, #26), “too happy” (#25), “couldn’t have a mutation” (#20) and “no dysmorphia” (#11, #26). This is likely due to less deviation from normal features in the mild patients (i.e., shorter, less prominent philtrum, no ptosis, fuller upper lip, less micrognathia) as well as the presence of features seen in the variant cases not typically seen in normal individuals or typical CdLS patients (i.e., thick bushy eyebrows, prominent nasal bridge, prominent jaw, large ears).

Facial Features That Distinguish Patients With *NIPBL* Mutations From Those With *SMC1A* Mutations

Responses in this survey confirm that there are appreciable differences between mild patients that may be able to be used to distinguish genotypes. The mild *NIPBL*-mutated patients (#9, #23, #25, and #28) were consistently described by the respondents to have more typical features including penciled arched eyebrows, synophrys, long eyelashes, and thin upper lip, although in older patients, respondents were distracted by the prominent nasal bridge and/or chin.

In the *SMC1A*-mutated patients, clinicians also appreciated mild synophrys, long eyelashes, slightly short, high-set nose with mild anteversion, thin upper lip and downturned corners of the mouth. However, the prevalence of straight heavy eyebrows, a broad nasal bridge or tip, more developed or shorter philtrum and larger ears often distracted diagnosticians from a CdLS diagnosis, especially in the younger individuals. This echoes our experience in that the eyebrows are consistently fuller and the nose is more “box-like” than triangular in many of these *SMC1A* patients. These are often accompanied by more normal growth parameters at birth, less severe pre- and postnatal growth retardation and fewer major malformations [Musio et al., 2006; Borck et al., 2007; Deardorff et al., 2007]. Interestingly, alternative diagnoses provided for three different *SMC1A*-mutated patients included VCFS/22q11.2 deletion, which often demonstrates mild cognitive delay and a broad, “bulbous” or “tubular” nose. In the context of considering a diagnosis of CdLS, the variant nose and full or unarched eyebrows are very useful in suggesting the *SMC1A* subtype.

CONCLUSIONS

This survey was useful in both increasing awareness of mild phenotypes as well as assessing the degree of under-diagnosed cases. While these assessments were made in the absence of detailed information on cognition and non-facial anomalies, the results of our survey confirmed that the diagnosis of mild CdLS is especially difficult and often missed even by experienced dysmorphologists. By reviewing the diagnostic features used by respondents, we were able to confirm commonly used features used to make the diagnosis as well as identify a number of features considered inconsistent with CdLS that lead to under-diagnosis. As suggested by Kline et al. [2007], the significant progress in the clinical and molecular delineation of CdLS necessitates a modification of the diagnostic criteria that is more inclusive of the milder cases. Our data reinforces this need.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIG. 1.

Facies of patients used in this study. The number circled in white overlaps the frontal and profile image for each patient. [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

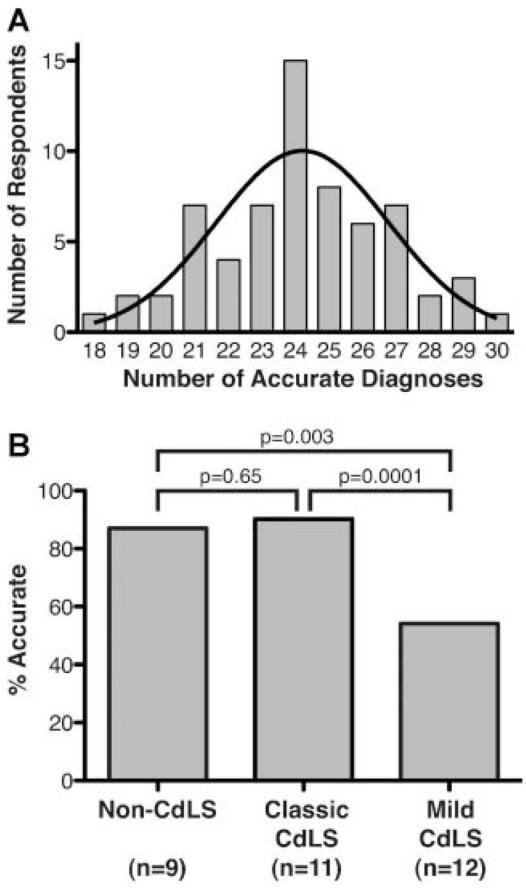

FIG. 2.

Overall results from CdLS facial feature survey. A: Distribution of number of accurate diagnoses of CdLS by respondents. Number of correct answers per respondent are indicated on the x-axis. The number of respondents with each number correct are plotted on the *y*-axis. A non-linear Gaussian curve fit to the results is overlayed. B: Differences in ability to diagnose classic versus mild CdLS. Unpaired *t*-test *P* values calculated using the total number of responses for the number (n) patients in each category indicated the statistical difficulty in diagnosing mild CdLS.

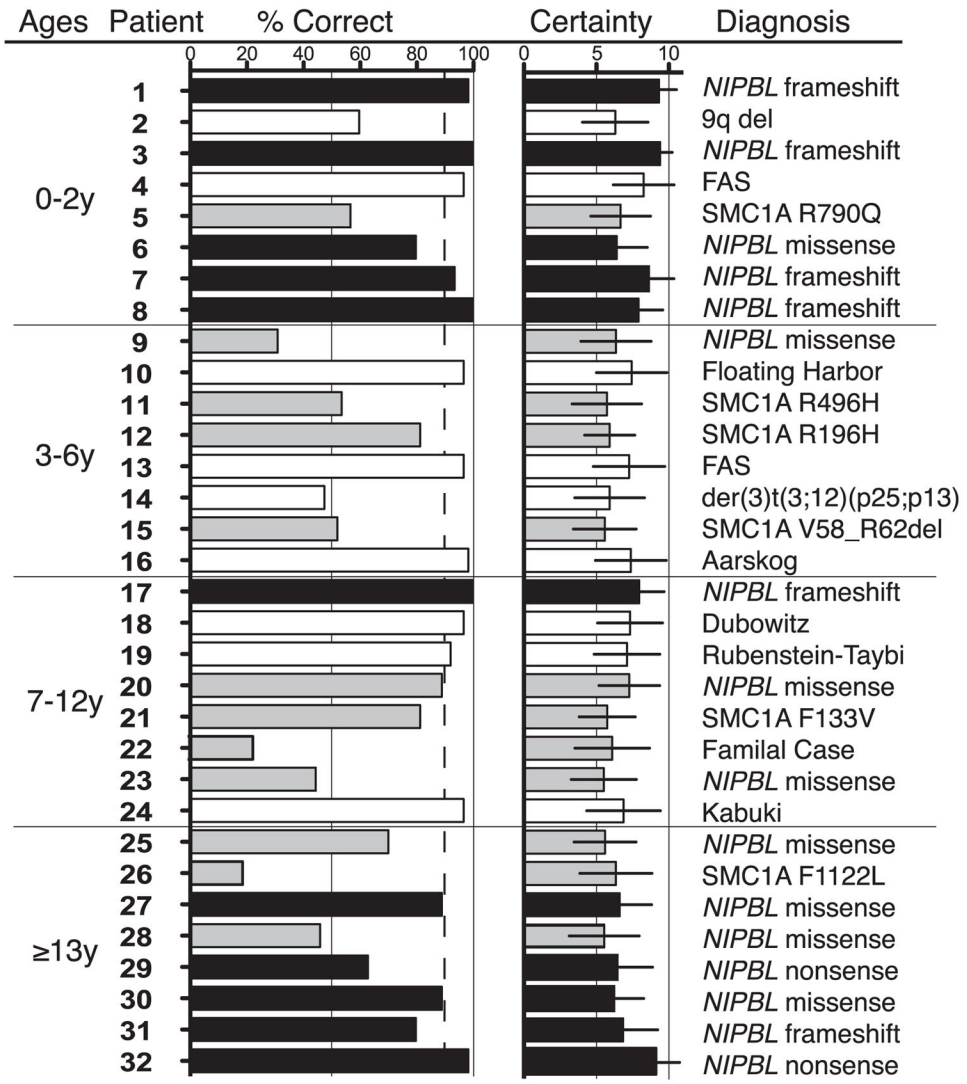

FIG. 3.

Distribution and accuracy of CdLS diagnoses. Patient numbers correlate with Figure 1. Percent correct for each patient is indicated by a horizontal bar graph, with the scale from 0% to 100% indicated above. The dashed line indicates the 10% incorrect threshold, below which, individuals were analyzed by further analysis. The average certainty of diagnosis for each patient is indicated as a horizontal bar graph, with below the scale of 0 (least certain) to 10 (most certain). Horizontal black bars at the right side of the column indicate the standard deviation for the diagnosis certainty of each patient. Diagnosis of each patient and/ or CdLS molecular confirmation is indicated at the right. Solid black columns indicate patients with "classical" CdLS, solid gray bars indicate those with "mild CdLS" and open columns indicate patients with other diagnoses. Fine horizontal lines divide the age groups as indicated in the text.

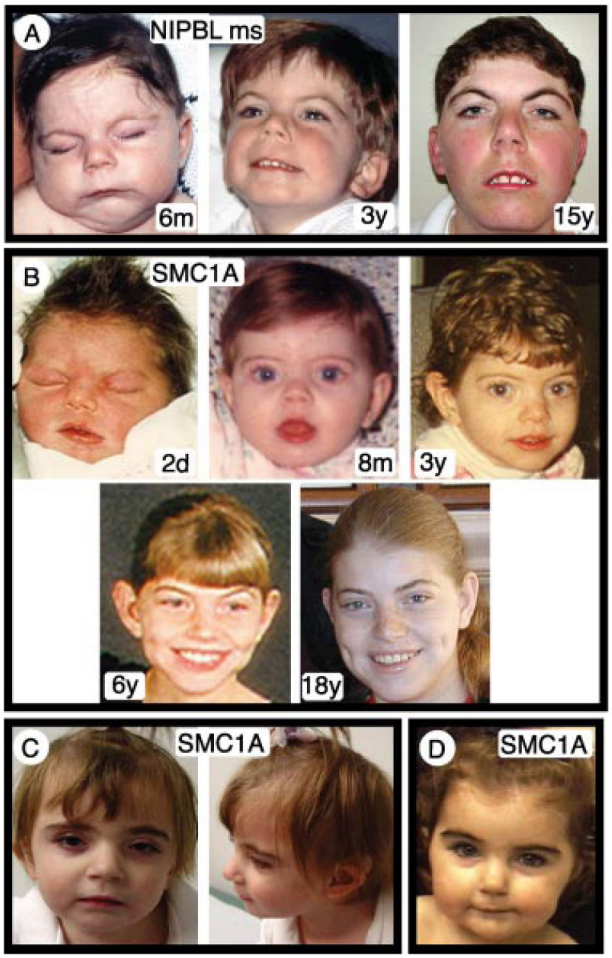

FIG. 4.

Representative facies in mild *NIPBL* and *SMC1A*-mutated CdLS patients. Facial images are illustrated indicating if an *NIBPL* or *SMC1A* mutation was identified. Ages are indicated using (d)ays, (m)onths and (y)ears. A: *NIPBL* c. 6893G>A, p. R2298H, (B) *SMC1A* c. 3364T>C, p. F1122L (patient #26 in survey), (C) *SMC1A* c. 2077C>G, p.R693G, and (D) *SMC1A* c.802_804del, p.K268del. Note in (A) and (B) the increased ease of diagnosis in early childhood. Note in (C) and (D) the flatter fuller eyebrows, the more prominent and bulbous nasal tip and the overall less distinctive facial features. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I

Distribution of Patients and Overall Accuracy of Diagnosis

Category	n (%)
Total patients	32 (100)
Actual diagnoses	
CdLS	23 (72)
Non-CdLS	9 (28)
Patients with >10% error	19 (59)
Undiagnosed CdLS	17 (53)
Over-diagnosed CdLS	2 (6)
Patients with <10% error	13 (41)
CdLS diagnosed correctly	6 (19)
Non-CdLS diagnosed correctly	7 (22)

TABLE II

Supporting and Misleading Diagnostic Features

Pt No.	Clinical/molecular diagnosis	% correct response	Number of clinicians commenting	Reported supporting features (n)	Reported misleading features
1	Classic CdLS, *NIPBL*, p.R1335LfsX1357	98	35	Microcephaly (1), hirsutism (1), ears (3), synophrys (12), arched brows (14)[a], penciled brows (1), bushy/long lashes (7), high set/short nose (10)[a], upturned nose (6), long philtrum (15)[a], prominent upper lip (4), thin upper lip (11), downturned mouth (6), micrognathia (8)[a], gestalt (5), limbs (2), nevus flameus (1)	Severe micrognathia (1), Rubinstein–Taybi? (1)
2	Not CdLS, 9q del	60	40	High hairline/square forehead (4), thin/sparse hair (5), small ears (1), upslanted palpebral fissures (1), hypertelorism (2), short nose (4), flat midface (1), normal/short philtrum (6), broad/prominent mandible/ prognathism (10)[a], thick/full lips (18)[a], gestalt/overall facies (2), coarse facies (5), Ka- buki? (1), Pallister–Killian? (1), Coffin–Siris? (1), 3q11del? (1), MPS? (1), Trisomy 21-like (4)	Thickened ear helices (1), synophrys (2)[a], arched brows (4)[a], long/up- turned lashes (5), short nose (3), upturned/anteverted nose (2), prominent maxilla (1), thin upper lip (1), downturned mouth (2), African-American difficult (2)[a]
3	Classic CdLS, *NIPBL* p.D817GfsX819	100	26	Micro/brachycephaly/round face (5), hirsutism (4), ears (2), synophrys (11)[a], arched brows (16)[a], penciled brows (7), long lashes (5), high set/short nose (11)[a], upturned/ anteverted nose (10)[a], long philtrum (14)[a], thin upper lip (17)[a], downturned mouth (5), micrognathia (6), gestalt/ overall facies (2), limbs (2)	
4	Not CdLS, fetal alcohol syndrome	97	30	No micro/brachycephaly (2), frontal bossing/tall forehead (10)[a], low set ears (1), sparse hair/brows (2), full eyebrows (1), no synophrys (2), short palpebral fissures (1), broad nose (5)[a], tented upper lip (2), short philtrum (3), prominent philtral groove (2), full lips (5)[a], no facial gestalt (7), FAS? (1), chromosomal anomaly? (1), Sotos? (1), Simpson–Golabi–Behmel? (1)	Upturned nose (1), downturned mouth (2)[a]
5	Mild CdLS, *SMC1A*, p.R790Q	57	30	Brachycephaly (1), hirsutism (1), ears (1), syn- ophrys (7)[a], full/prominent brows (4), long lashes (5), eye/nose junction (1), high set/short nose (7)[a], triangular nose (2), upturned/anteverted nose (2), long philtrum (11)[a], thin upper lip (8)[a], micrognathia (1), partial gestalt/facies (1)	No brachycephaly (1), large/normal ears (1)[b], flat/ straight brows (15)[b], full/bushy brows (2)[b], prominent/normal nasal bridge (8)[b], broad nose (2)[b], no anteverted nose (1), full cheeks (1), thin upper and lower lips (1), 1p36del? (4)[a], dup 3? (1), 9q34del? (1)
6	Classic CdLS, *NIPBL*, p.R1789G	80	34	Ears/low set ears (4), synophrys (2), brows (8)[a], arched brows (1), penciled brows (1), long lashes (17), ptosis (1), high set/short nose (15)[a], upturned/anteverted nose (3), long philtrum (11)[a], thin upper lip (1), downturned mouth (6), chin (1), gestalt/overall facies (1)	No synophrys (1), flat/wrong/bushy brows (6)[a], full nose (1), full lips (8)[a], wrong gestalt (1), African descent difficult (6)[a], BPES? (1)

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Pt No.	Clinical/molecular diagnosis	% correct response	Number of clinicians commenting	Reported supporting features (n)	Reported misleading features
7	Classic CdLS, *NIPBL*, c. 3048delATTA	94	29	Brachycephaly (3), synophrys (10)[a], arched/penciled brows (9)[a], long lashes (6), high set/short nose (7), upturned/anteverted nose (4), long philtrum (11)[a], thin upper lip (9), downturned mouth (5), micro/retrognathia (3), gestalt/overall facies (2), small hand (2), nevus flameus (1)	Severe brachycephaly (1), high hairline (1), wrong ears/thick helices (1), flat midface (1), wrong nose (1), chin too large (1), atypical/mild gestalt (2), Down syndrome? (4), chromosomal anomaly? (1), Smith–Magenis? (1)
8	Classic CdLS, *NIPBL*, c. 3048delATTA	100	31	Micro/brachycephaly/round face (1), synophrys (10), arched/penciled brows (13)[a], long lashes (4), high set/ short nose (5)[a], upturned/anteverted nose (6), long philtrum (13)[a], thin/prominent upper lip (14)[a], downturned mouth (7)[a], micro/retrognathia (4), gestalt/ overall facies (3)	Less brachycephaly (1), less brow arch (3), fine/ less coarse brow (2), obese/healthier (2), blond (1), 9q34del? (1)
9	Mild CdLS, *NIPBL*, p.Q1973P	31	30	Round face (1), ears (1), synophrys (3), arched/ penciled brows (8)[a], long lashes (5)[a], nose (1), thin upper lip (6), mouth (2)	Large head (2), normal ears (1), normal brows (3), flat/straight brows (4)[a], no midface hypoplasia (1), normal nose (4)[a], no nose upturn (1), normal philtrum (6), no downturned mouth (1), normal lips (5), prominent chin (1), overall gestalt/ nondysmorphic (7)[a], 1p36? (1), 22q11 del? (1)
10	Not CdLS, floating harbor	97	27	No brachycephaly (1), no synophrys (1), upslanted eyes (1), no midface hypoplasia (2), high nasal bridge/large nose (4), downturned nasal tip/wrong nose (7)[a], short philtrum (1), prominent chin (1), smiling/too happy (2), nondysmorphic (1), overall gestalt (3), “pixie” face, Rubinstein–Taybi? (6)[a], Kabuki if flatter nose (1)	Thin lips (2), micrognathia (1)
11	Mild CdLS, *SMC1A*, p.R496H	54	30	Round face (1), eyes (2), synophrys (2), arched brows (2)[a], brows (3)[a], heavy/full brows (3)[a], nose (6)[a], nasal root (1), high set/short nose (5)[a], upturned/anteverted nose (2), long philtrum (5)[a], thin upper lip (4), mouth (3), downturned mouth (1)	Face shape/no brachycephaly (2), eyes (1), no synophrys (1), thick brows (2)[b], no midface hypoplasia/ high nasal bridge (2), nose, odd/ VCFS-like/pinched/not triangular (5)[b], mouth (1), normal philtrum (5), lips too thick (1), no retrognathia (2), hair obscures (2), normal/ nondysmorphic (3), dup 3q? (1), 22q11 del? (1)
12	Mild CdLS, *SMC1A*, p.R196H	82	30	Low ears (1), eyes (2), synophrys (4), brows (2), arched brows (6)[a], penciled brows (1)[a], long lashes (1), nose (4)[a], upturned/anteverted nose (1), philtrum (6)[a], thin upper lip (8), mouth (4), downturned mouth (2), gestalt/ overall facies (2), skeletal films? (1)	Broad face (1), normal ears (1), long palpebral fissures (1), brows broad (2)/different (2)/ interrupted (1)[b], nose broad (1)/not high set (1)[b], short philtrum (1), FAS? (2)[a], chromosomal anomaly? (1), Kabuki? (1)

Pt No.	Clinical/molecular diagnosis	% correct response	Number of clinicians commenting	Reported supporting features (n)	Reported misleading features
13	Not CdLS, fetal alcohol syndrome	97	34	Head shape (3), no brachycephaly/large/long face (3), prominent forehead (2), no lowset ears (1), brows (6), no synophrys (5), eyes (1), periorbital fullness (1), short palpebral fissures (2), hypertelorism (1), nose (2)/broad (1)/high bridge (2), short philtrum (1), full upper lip (1), no CdLS gestalt (4)/nondysmorphic (2), FAS? (13), fragile X? (1), 22q11 del? (2), Sotos? (1)/Williams? (1)/ Kabuki? (1)	Arched brow (2), nose (2), depressed nasal bridge (1), midface (2), mouth (3)[a], thin upper lip (3)[a]
14	Not CdLS, 46,XY, der(3)t(3;12) (p25.3;p13.3)	48	36	Head (1), no brachycephaly (1), long face (2), high hairline, forehead (2), thin hair (1), increased facial movement (1)[a], hypertelorism (1), brows (4), thin medially (2)[a], nose (4), mouth (5), wide (4)[a], chin (1), prognathism (1), no gestalt (1), too atypical for CdLS (2), Kabuki-like? (6), Angelman-like (2), Borjeson–Forssman–Lehmann? (1), FAS? (1), Coffin–Siris? (1)	Synophrys (4), arched brows (9)[a], lashes (3), nasal bridge depressed (1), short (3), anteverted nares (7)[a], thin lips (6), philtrum (1), long (1), CdLS gestalt (4)
15	Mild CdLS, *SMC1A* p.V58_R62del	52	27	Brachycephaly (1), round face (1), profile (3), posterior hairline (1), lowset ears (1), synophrys (4), arched brows (1), penciled brows (1), flat midface (1), low nasal root (1), nose (2), high set (1), short nose (2)[a], upturned, anteverted nose (1)[a], long philtrum (1), lip (2), prominent upper lip (5), thin lips (4)[a], mouth (2), downturned (2)[a], micro, retrognathia (1), gestalt (1)	No synophrys seen (2), brows (1), less arched (1), thin medially (2), prominent (1)[b], eyes (2), nose (1), mid nose (1), tip nose (1)[b], short philtrum (1), full cheeks (1), smile (1), too normal (1), no CdLS gestalt (1), Kabuki? (1)
16	Not CdLS, Aarskog syndrome	98	23	Large head (1), forehead (1), ear (1), eyes (2), hooded (1), no synophrys (1), normal brows (5), lashes (1), narrow palpebral fissures (1), nose (2), broad (2), no flat midface (1), short philtrum (3), mouth (2), cheeks full (1), normal facial movement (1), normal, no CdLS gestalt (11), Noonan? (1), Williams? (1), 22q11del? (1)	Thin upper lip (1), feeding issues (2)
17	Classic CdLS, *NIPBL* c. 6407insA	100	27	Round face (3), low frontal hairline (1), hirsutism (1), ears (1), brows (11), arched (3), penciled (1)[a], synophrys (9)[a], eyes (1), long lashes (1), nose (7), high set or short (2), anteverted (2)[a], philtrum (4), long (6), smooth (1), prominent (1)[a], mouth (2), downturned (6)[a], lips (5), thin upper lip (8)[a], chin (2), micro, retrognathia (1), gestalt, overall facies (6)	Nares not anteverted (1), less coarse (1)
18	Not CdLS, Dubowitz syndrome	97	30	Forehead (2), prominent (1), tall (2), no synophrys (1), brows (5), thick/bushy (3), no arch (1)[a], eyes (3), downslanted (1), epicanthal folds (1), blepharophimosis (4), nose (2), broad (1), long (2), prominent root (1), no upturn (1), short philtrum (2), full lips (2), normal mouth (3), no CdLS gestalt (4), FAS? (8), FG? (1), 22q11del? (1), Mowat- –Wilson? (1)	CdLS ears (1)
19	Not CdLS, Rubinstein–Taybi syndrome	92	33	No round face (1), eyebrows not seen (4), brows (2), small ears (1), nose (7), long (4), beaked (3), prominent (3), long columella (1), short philtrum (3), mouth not	

Pt No.	Clinical/molecular diagnosis	% correct response	Number of clinicians commenting	Reported supporting features (n)	Reported misleading features
				downturned (1), not CdLS (1), no CdLS gestalt (2), Rubinstein–Taybi? (12)	
				downturned (1), not CdLS (1), no CdLS gestalt (2), Rubinstein–Taybi? (12) postsurgical Treacher-Collins? (1), floating harbor? (1)	
20	Mild CdLS, *NIPBL*, p.R2298H	89	27	Round face (1), eyes (2), brows (7), synophrys (4), arched (6), thin, penciled (4), high (1)[a], lashes (1), nose (9), high set (1), short (2), upturned/anteverted (5)[a], mouth (4), small (2), downturned (2), philtrum (5), long (8), smooth (1)[a], lips (2), thin upper (9)[a], micro/retrognathia (2), gestalt/overall facies (2)	Ears not quite right (1), full cheeks (2)[a], nose atypical (2)
21	Mild CdLS, *SMC1A*, p.F133V	82	32	Face shape (1), lower face (2), eyes (2), brows (1), arched (1), synophrys (2), nose (2), short (1), anteverted (1), tip (1)[a], mouth (6), downturned (7)[a], philtrum (1), long (2), lips (1), prominent upper (4), thin upper (4)[a], mouth (6), downturned (7)[a], micro/retrognathia (1), gestalt/overall facies (1)	Normal ears (1), eyes (1), heavy/ bushy brows (2)[b], low brows (1)[b], nose, normal (1), long (1)[b], no midface hypoplasia (1)[b], blond difficult (1), Alagille? (1), 9q34? (1)
22	Mild CdLS, Familal Case, cannot exclude 5p13	23	24	Lashes (1), brows (1), arched (1), upslanted eyes (1), nose (1), anteverted (1), gestalt/overall facies (2)	Uplifted ear lobes (1), brows (2), straight (3), nose (3), pointed (1), long root (2), phltrum (1), short (3), mouth (3), normal (1), chin (1), prominent (2), defined (1), normal facial movement/expression (2), no hirsutism (1), normal gestalt (3), Angelman? (1), RTS? (1)
23	Mild CdLS, *NIPBL*, p.Q1338R	45	27	Round face (1), brows (5), arched (3), synophrys (5)[a], long lashes (2), nose (1), philtrum (1), lips, thin upper (4)[a], gestalt/overall facies (1)	Eyes (1), hypertelorism (1), brows (2), thick (1), low (1), flat (1), nose (3), long (1), no anteversion (1), prominent root (2), small alae (2), low columella (2)[a], philtrum, short (5), mouth, no downturned corners (1), no micrognathia (1), no hirsutism (1), normal gestalt (3), Alagille? (2), 22q11del? (1), floating harbor? (1)
24	Not CdLS, Kabuki	97	24	Head, big (1), no brachycephaly (1), ear (2), brow (7), no arch (1), bushy (2), lashes, sparse (1), eyes, upslanted (1), hypertelorism (1), hooded (1), epicanthal folds (1), everted lower lids (1)[a], nose (3), round (1), bulbous (2), downturned (2)[a], philtrum (1), flat (1), mouth (2), small (1), lips (1), full upper (4)[a], fine features (1), overall gestalt not CdLS (3), Kabuki? (1), 22q11del? (2), Dubowitz? (1)	
25	Mild CdLS, *NIPBL*, p.D1830V	70	28	Brachycephaly (1), round face (3), low frontal hairline (1), hirsutism (1), ears (1), eyes (2), brows (10), arched (6), thin/penciled (1), synophrys (1)[a], long lashes (2), nose (2), high set/short (1), root (1)[a], philtrum (1), long (1), lips (3), thin upper (7)[a], chin (1), gestalt/overall facies (2), grimace smile (1)[a]	Ear (1), nose (2), short philtrum (1), mouth (2), square chin (1), no retrognathia (1), happy/smiling (2)[a], no gestalt (2), Cohen syndrome? (1)

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26	Mild CdLS, *SMC1A*, p.F1122L	19	23	Brows (4), slight arched (1)[a], midface (1),	Brows (2), eyes (1), eye contact (1), nose wrong (6)[b], upper lip (1), short philtrum (3), mouth (2), dimples (2), lips (1)[a], facial movement/good smile (2), well-defined chin (1), nondysmorphic (10)[a], wrong gestalt (3), 22q11del? (2)[b]
27	Classic CdLS, *NIPBL*, p.R2298C	89	23	Eyes (4), brows (8), arched (2), heavy (2), synophrys (5)[a], lashes (1), nose (3), high set (1), sharp (1), mouth (4), downturned (6), lips (2), thin upper (5), micro/ retrognathia (1), smile (1), gestalt/overall facies (6)	Thick brows (2)[a], nose (1), no anteversion (2)[a], short philtrum (6), upper lip (1)
28	Mild CdLS, *NIPBL*, p.Q1338R	46	24	Low ears (1), eyes, palpebral fissures (1), brows (6), arched (2), bushy (1), synophrys (4)[a], lashes (1), nose (1), philtrum (1), lips, thin upper (2), gestalt/ overall facies (2)	Ear (1), short palpebral fissures (1), raising brows (1), nose (3), high bridge (1), mouth (2), no downturn (1), short philtrum (2), lower face (1), chin (2), long (1), broad (4), prognathism (3), no micrognathia (1)[a], gestalt (1), happy (1), up-turned smile (1)[a], FAS? (1)
29	Classic CdLS, *NIPBL*, p.S235X	63	25	Microcephaly (1), head shape (1), thickened ear helices (1), eyes (2), brows (4), arched (1), heavy (1), synophrys (2), lashes (1), midface hypoplasia (2), nasal tip (1), mouth (1), downturned (2), philtrum (1), gestalt/overall facies (1)	No brachycephaly (1), ears (1), thick brows (1)[a], nose (1), built-up root (2), broad bridge (2)[a], lower face (1), short philtrum (1), broad jaw (1), prognathism (13), no retrognathia (1)[a], no thin upper lip (1), coarsening (3)[a], no gestalt (1), Coffin–Lowry? (1), Phelan- –McDermod? (1), ATRX? (1)[a]
30	Classic CdLS, *NIPBL*, p.R1895T	89	22	Eyes (1), brows (8), arched (2), long lashes (1), nose (2), short (1), upturned/anteverted (1), mouth (4), downturned (4)[a], philtrum (2), long (1), lips, prominent upper (1), thin upper (2), chin (1), gestalt/overall facies (3), lower face (1)[a], grimace- like smile (1)[a], small hands (1)	Short philtrum (2), alert (1), no gestalt (1), FAS? (1), cytogenetic abnormality (1)
31	Classic CdLS, *NIPBL* c. 7825insG	80	26	Thick hair (1), eyes (2), brows (6), arched (1), synophrys (5)[a], lashes (1), nose, high set/short (1), midface hypoplasia (1), mouth (4), down-turned (5)[a], philtrum, long (1), lips (1), prominent upper (1), thin upper (1), gestalt/overall facies (5)	Brows, thick (1), wide laterally (1), nose (5), depressed tip (2)[a], upper lip (1), lower face (1), chin (2), prognathism (1), Smith–Magenis? (1), Kabuki? (1)
32	Classic CdLS, NIPBL, p.R1536X	98	23	Hirsutism (1), eyes (3), downslanted (1), brows (6), arched (2), synophrys (9)[a], long lashes (2), nose (3), high set/short (2), anteverted (4)[a], mouth (6), downturned (4)[a], philtrum (4), long (1), lips (1), prominent upper (1), thin upper (6)[a], chin (1), micro/retrognathia (2), square (1), gestalt/overall facies (6), lower face (1)	Prominent nasal bridge (1)

Features described from top of head to chin and then overall impressions. del, deletion; dup, duplication.

[a]Distinguishing feature.

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[b] Variant feature characteristic in patients with *SMC1A* mutations.