Published in final edited form as:

Am J Med Genet. 2001 December 15; 104(4): 267–276.

Dominant Paternal Transmission of Cornelia de Lange Syndrome: A New Case and Review of 25 Previously Reported Familial Recurrences

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Abstract

The Cornelia de Lange syndrome (CdLS) is an autosomal dominant multisystem disorder characterized by somatic and cognitive retardation, characteristic facial features, limb abnormalities, hearing loss, and other organ system involvement. The vast majority of cases (99%) are sporadic, with rare familial occurrences having been reported. Most individuals with CdLS do not reproduce as a result of the severity of the disorder. Maternal transmission has been well documented, as have several cases of multiple-affected children being born to apparently unaffected parents. Paternal transmission has rarely been reported. A case is reported here of a father with classic features of CdLS with a similarly affected daughter. A review of the reported familial cases of CdLS is summarized.

Keywords

Cornelia de Lange syndrome; CdLS; familial occurrences; paternal transmission

INTRODUCTION

The Cornelia de Lange syndrome (CdLS), also termed the Brachmann-de Lange syndrome (BDLS) (OMIM# 122470) is a multisystem developmental disorder. The phenotype consists of growth and neurodevelopmental delay, characteristic facial features (including synophrys, long eyelashes, depressed nasal bridge with an upturned tip of the nose and anteverted nares, small widely spaced teeth, small head, and low-set ears), hirsutism, abnormalities of the upper extremities ranging from subtle changes in the phalanges and metacarpal bones to oligodactyly and phocomelia, and gastroesophageal dysfunction. Other frequent findings include ptosis, myopia, cryptorchidism, hypospadias, pyloric stenosis, congenital diaphragmatic hernias, cardiac septal defects, seizures, and hearing loss [Jackson et al.,

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1993; Ireland et al., 1993]. The prevalence of this syndrome has been estimated to be as high as 1 in 10,000 [Opitz, 1985].

Although CdLS was formally described nearly 70 years ago [de Lange, 1933], several aspects of this disorder still are not clearly defined. The wide variability of expression has been well documented for many years; however, it has only recently been addressed for diagnostic consideration [Pashayan et al., 1969; Leroy et al., 1993; Selicorni et al., 1993; Van Allen et al., 1993; Allanson et al., 1997]. The full range of clinical expression will not be fully characterized until a molecular marker is identified to confirm the milder phenotypes. Confounding the search for such a molecular marker is the failure to identify any consistent chromosomal abnormalities in individuals with CdLS as well as the paucity of families with multiple-affected individuals with which linkage analysis could be undertaken. Chromosome 3q has been suggested as a candidate region for the CdLS gene based on phenotypic overlap between individuals with CdLS and individuals with duplication of 3q [Ireland et al., 1995]. This hypothesis was supported by the identification of a child with classic features of CdLS who was found to have a de novo, apparently balanced t(3;17)(q26.3;q23.1) [Ireland et al., 1991]. The breakpoint on chromosome 3q in this patient is within a previously defined dup3q critical region [Aqua et al., 1995]. Studies have recently been initiated to perform linkage analysis in familial cases [Krantz et al., 2000]. Although in this study linkage to 3q26 was not demonstrated in all familial cases studied, the power of these studies is suboptimal because of the small size and number of available families to study and the possibility of locus heterogeneity.

The rarity of familial cases has led to some confusion as to the inheritance pattern of this disorder. Increasing evidence points toward CdLS being an autosomal dominant disorder, with the vast majority of cases (> 99%) being sporadic. The low probability of a severely affected CdLS individual to reproduce clearly contributes to a lack of familial cases. With the recognition of the milder CdLS phenotype [Greenberg and Robinson, 1989; Moeschler and Graham, 1993; Allanson et al., 1997], it is possible that a greater number of familial cases will be ascertained. It is unclear whether the mild and severe phenotypes are caused by defects in the same gene, although several reported cases seem to indicate that both forms can be present in the same family [Robinson et al., 1985; Kozma, 1996].

This report describes a familial case of classic CdLS, transmitted from father to daughter, and adds support for an autosomal dominant mode of transmission. Based on a review of all reported familial CdLS cases, the possible modes of inheritance will be discussed.

CLINICAL REPORT

Patient 1 (Proband)

The pregnancy was uncomplicated. There were no medications used during the pregnancy and no exposure to cigarettes, alcohol, or drugs. The pregnancy was approximately 36 weeks in gestation. Delivery was spontaneous and vaginal. Birth weight was 2.2 kg (10th–25th centile); birth length was 45 cm (10th–25th centile). There were no immediate problems in the newborn period. The proband was discharged home with the mother at 3 days of age.

There was a history of gastroesophageal reflux with some nasal regurgitation, poor weight gain, and some constipation. There had been no hospitalizations.

The proband is the only child of her parents together. There is a 2-year-old female half-sibling through the mother with another partner who is healthy. The proband's father's history and examination is described later herein. The father has two brothers and one sister of normal stature, development, and health. Based on photographs, the father is significantly shorter and has facial features that are different from his parents and siblings. The paternal grandmother is 50 years of age, healthy, and 165 cm tall. The paternal grandfather is taller than the maternal grandmother and is 55 years of age and healthy. He has a history of unilateral hearing loss. He has a 21-year-old daughter through another partner who is healthy. The father's family is of Puerto Rican ancestry. The mother is 25 years of age and is healthy. She had a history of behavioral problems in school and did not complete high school. She has an 18- and a 21-year-old brother who are healthy, and a 26-year-old brother who has a history of psychiatric problems. The maternal grandfather is in his 50s and healthy; the maternal grandmother is 49 and healthy. The mother's family is of Puerto Rican ancestry. There is no history of consanguinity.

Developmental history—At 4 months of age, the proband had a head lag, was not rolling, and had minimal vocalizations.

Physical examination—On initial examination at 4 months of age, the proband was active and attentive (Fig. 1). Her length was 51 cm (less than 5th centile; 50th centile for a newborn; 50th centile on the CdLS growth charts), weight was 4 kg (less than the 5th

centile; 50th centile for $1\frac{1}{2}$ months; 75th centile on the CdLS growth charts), and head

circumference was 36 cm (less than the 3rd centile; 50th centile for $1\frac{1}{2}$ months; 75th centile on the CdLS growth charts). Her anterior fontanel was open. Her head appeared microbrachycephalic. She had synophrys and arched eyebrows. The inner canthal distance was 2.25 cm and the outer canthal distance was 6.5 cm, with a calculated interpupillary distance of 4.2 cm (50th centile). The ears appeared slightly cupped with no pits or tags. The nose had an upward slanted tip with anteverted nares. The mouth showed a thin upper lip with a “cupid’s bow” appearance and a pronounced descent of the midline portion below the lateral aspects (“drip”), made more prominent by the long philtrum. There was a high palate and a normal uvula. The neck was within normal limits. The chest showed no evidence of pectus with two clavicles palpated. The chest circumference was 36 cm; the internipple distance was 8.75 cm with a ratio of 0.24 (75th centile). The nipples were small. The abdomen was within normal limits with no organomegaly. The umbilicus was somewhat small. The extremities showed limited supination as well as limited extension at the elbows. The hands appeared small with a proximally placed thumb. The right palm measured 3.25 cm (less than the 3rd centile and less than 50th centile for a newborn). The middle finger measured 1.5 cm (less than the 3rd centile and less than the 50th centile for a full-term newborn). The dermatoglyphics were as shown in Table I.

There was no clinodactyly. The feet showed 2–3 syndactyly bilaterally and measured 7.5 cm (less than the 3rd centile; 50th centile for 37-week gestational age). Genitalia were normal female with a normal anus. There was some mild hypertonicity. The spine was within normal limits with no evidence of sacral dimpling.

On follow-up examination at 1 year of age (Fig. 1b), the physical findings were unchanged from those described above. Her head circumference at 1 year measured 41.5 cm (less than the 5th centile and 50th centile for a 4-month-old; 75th–98th centile on the CdLS growth charts), length was 62 cm (5th centile and 50th centile for 4 months; 50th–75th centile on the CdLS growth charts), weight was 6.32 kg (less than the 5th centile and 50th centile for 4.5 months; 95th centile on the CdLS growth charts). She was sitting by 9 months, and could crawl and pull to stand at the time of examination. She had persistent reflux that was being medically treated.

Radiologic studies of her arms and hands demonstrated bilateral radioulnar synostosis and short first metacarpals (Fig. 2).

Patient 2 (Father of Proband)

The proband's father (Fig. 3) was 30 years of age at the time of examination. He has a history of bilateral hearing loss requiring amplification. He described his walking and talking and other milestones as having been $1\frac{1}{2}$ years delayed. He also has a history of gastroesophageal reflux. He finished high school at 18 years of age and undertook $1\frac{1}{2}$ years of college (with support). He presently is not working and he is taking medications for depression and stress.

On physical examination, the proband's father had a height of 160 cm (less than the 5th centile; 50th centile for 13 years of age); his head circumference was 51 cm (less than the 3rd centile; and 50th centile for $3\frac{1}{2}$ years of age). The head appeared microbrachycephalic. The inner canthal distance measured 3.25 cm; the outer canthal distance measured 10 cm; the interpupillary distance measured 6.2 cm (75th centile). The eyebrows were high arched with synophrys. The nose showed an upturned tip with anteverted nares bilaterally. The mouth showed a thin upper lip with a midline "drip." There was a high palate and normal uvula. The ears appeared somewhat cupped with no pits or tags. There was a low anterior hairline. The hands appeared small. The right palm measured 9.5 cm (less than 3rd centile; 50th centile for a 12-year-old); the middle finger measured 6.5 cm (less than the 3rd centile; 50th centile for a 10-year-old). The right hand showed a single palmar crease with no clinodactyly. The left hand showed two creases with no clinodactyly. The feet showed evidence of mild 2–3 syndactyly and measured 22.5 cm (less than the 3rd centile and 50th centile for 11 years of age).

The proband's mother was also examined. She had a height of 155 cm (25th centile) and a head circumference of 54.5 cm (50th centile). She was nondysmorphic and did not show evidence of synophrys or arching of the eyebrows. Her palm measured 10 cm (3rd to 25th

centile), and the middle finger measured 7 cm (less than the 3rd centile and 50th centile for 11.5 years of age). She had two palmar creases bilaterally and her feet appeared within normal limits with no evidence of syndactyly.

CYTOGENETIC STUDIES

A karyotype at the 550-band level of resolution was 46,XX, normal female in the proband. Telomere testing (Cytocell, Ltd.) was also normal in the proband.

DISCUSSION

CdLS is one of the most well-recognized dysmorphic syndromes. Although characterized by Dr. de Lange more than 60 years ago, the underlying cause of CdLS remains elusive. The difficulty in identifying the genetic cause of CdLS results from a lack of any consistent chromosomal abnormalities associated with the phenotype as well as the paucity of informative families that can be used for linkage studies. Because of the small number of clearly documented families with CdLS, even the exact mode of inheritance of this condition has been difficult to ascertain. Variability in the expression pattern of CdLS has been well documented [Allanson et al., 1997]. This variability complicates ascertainment of familial cases because individuals with the most severe manifestations of CdLS do not reproduce, and in individuals with a milder presentation, as is often the case in multigenerational pedigrees, the diagnosis may be disputed or tentative (Fig. 4, Table II). Familial cases with multiple affected children with the severe manifestations born to unaffected parents may be caused by recessive inheritance, or germline mosaicism. Until a diagnostic marker becomes available, it will be difficult to definitively determine the extent of clinical variability within this diagnosis or the pattern(s) of inheritance.

Twenty-five familial cases of CdLS have been reported (Fig. 4A and B). Fifteen of these cases (60%) appear to demonstrate a dominant mode of transmission of the phenotype (Fig. 4A), whereas 10 (40%) may be consistent with recessive inheritance, or do not directly corroborate a dominant pattern (Fig. 4B). In addition to these cases, a recently published report by Krantz et al. [2000] describe nine previously unreported families of which four support dominant inheritance, four suggest recessive inheritance, and one is inconclusive. The clinical features described in the previously reported cases are summarized in Table II. It is difficult, based on clinical descriptions and the photographs provided in several of the published familial cases, to determine whether or not the diagnosis of CdLS is accurate. For the purpose of this review, all families reported as CdLS are included. Although there is considerable clinical variability between the reported families, this may be reflective of the phenotypic variability of CdLS rather than errors in diagnosis.

Ptacek et al. [1963] addressed the issue of inheritance patterns in CdLS. These authors suggested a dominant mutation as the possible mode of inheritance, although they pointed out that it would be difficult to prove as none of the CdLS patients reported at that time had reproduced. They raised the possibility of “gonadal mosaicism” as a mechanism in those families with recurrences among sibships. They went on to state that “several findings speak against the assumption that the Cornelia de Lange syndrome is produced by the homozygous

state of a recessive mutation,” including 1) the absence of consanguinity in the parents, and 2) the high proportion of sporadic cases. In 1964, Opitz et al. reversed their initial impression on the Ptacek et al. article [1963] and determined that the most likely inheritance pattern for CdLS was postulated as being autosomal recessive. The rationale for this suggestion was given as follows: “1. Multiple anomaly syndromes... are seldom inherited as dominant mutations, either autosomal or X-linked, 2. To date no evidence has been advanced for an environmental cause, 3. The overwhelming number of cases analyzed cytogenetically... have not revealed a chromosomal aberration.” Again Opitz tackled the inheritance issue in a comprehensive review of the syndrome in 1985. In this article referring to CdLS, he states that “the condition is complex enough and biologically of the right type to be due to aneuploidy ...the rarity and inconsistency of the reported chromosomal abnormalities makes it unlikely that they are the cause...”. Based on cases reported since his earlier suggestion of autosomal recessive inheritance [Robinson et al., 1985], Opitz considered the possibility of CdLS being caused by autosomal dominant inheritance. He goes on to postulate that those cases of familial recurrence without apparently affected parents may be caused by incomplete penetrance or highly variable expressivity (although he also admits that they could be secondary to a heterozygous state of a recessive disorder), and that the low recurrence risk may also be consistent with a dominant mutation (although he points out that this may also be secondary to prenatal mortality of homozygotes).

In our review of the previously reported cases, the only case with documented consanguinity is that of Naguib et al. [1987] in a family of Arabic background (Fig. 4B). The parents of the two affected siblings are first cousins. Because the rate of consanguineous marriages is high among this ethnic group, the significance of this finding is unclear. Although a familial recurrence of a child with CdLS born to parents who were first cousins has been reported [Borghi et al., 1954], another affected individual identified in the same pedigree makes a dominant pattern of inheritance more likely (Fig. 4A). Several dominant pedigrees with convincing CdLS phenotypes have been reported [Kozma, 1996; Robinson et al., 1985; Leavitt et al., 1985; Bankier et al., 1986]. However, these pedigrees cannot definitively exclude X-linked or mitochondrial inheritance. The apparent preponderance of maternal transmission of the trait suggested a possible imprinting effect; however, this has not held up because both paternal and maternal transmission has since been documented, and molecular studies have not supported the postulate [Shaffer et al., 1993; De Marchi et al., 1994]. Similarly, mitochondrial inheritance seems unlikely, although there has been a single report of a child with CdLS with multiple mitochondrial DNA deletions [Melegh et al., 1996]. The case reported by Kozma [1996] is particularly fascinating in demonstrating the variable expressivity within a family with the mother having typical facial features, small hands, mild mental retardation, and normal stature, whereas her male child had striking facial features, severe limb involvement, and growth and mental retardation.

In this report we describe a rare case of paternal transmission of CdLS. Of the 25 previously reported cases of CdLS, only 3 have suggested paternal inheritance [Halal and Silver, 1992; Chodirker and Chudley, 1994; McKenney et al., 1996]. In a recent publication, Krantz et al. [2000] describe an unaffected father with two daughters with CdLS through separate partners. The case reported by Halal et al. describes three sibs (two boys and one girl) and their father with microcephaly, facial features of CdLS, and mild developmental delays. In

the report by McKenney et al., two half siblings (a boy and a girl) are described with characteristic facial features, growth failure, other dysmorphic features, and the developmental profile of CdLS. The father of these two children is described as having facial features of, and other minor differences associated with, CdLS, although he is of normal stature and completed grade 10 without special assistance. Chodirker and Chudley [1994] reported a father and son with mild manifestations of CdLS. The son was described as having growth failure, developmental delay, and facial features consistent with CdLS. The father was of normal stature with microcephaly and developmental and learning disabilities and facial features similar to his son's. Metacarpophalangeal profiling using methods described by Halal and Preus [1979] was consistent with a diagnosis of CdLS.

The family reported here demonstrates dominant transmission of the CdLS phenotype and lends support to the hypothesis that CdLS is an autosomal dominant disorder. Although genetic heterogeneity cannot be ruled out, the majority of reported cases are consistent with a dominant pattern of inheritance, and cases of male-to-male transmission suggest that inheritance is autosomal. It is unknown if the families that appear to demonstrate a recessive pattern of inheritance represent a genetically distinct group. Most individuals in this group have a more severe phenotypic presentation. In keeping with a dominant hypothesis, it is possible that these families represent cases of germline mosaicism or a lack of phenotypic expression (nonpenetrance) in one of the parents. Arguments against a recessive mode of inheritance for CdLS include 1) rare familial recurrences with most cases seemingly sporadic (which would be more consistent with a new dominant mutation), 2) the lack of identification of ethnic populations with a higher prevalence of CdLS, 3) the paucity of reported cases of parental consanguinity in CdLS sibships, and 4) documented cases of vertical transmission as well as recurrence among half-siblings with unaffected parents.

Definitive establishment of the mode of inheritance and the clinical spectrum depends on identification of a genetic marker to objectively establish the diagnosis. Based on the family reported here and our review of reported familial cases, autosomal dominant inheritance is the most likely mode of transmission in CdLS, with the vast majority of cases arising from spontaneous mutations.

Acknowledgments

Grant sponsor: The Joshua Ackels Fund (I.D.K.); Grant sponsor: National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases) (I.D.K.); Grant number: 5 KO8 DK02541-02. We acknowledge the support of the family described here as well as The Joshua Ackles Fund for supporting our ongoing research into the underlying cause of CdLS.

REFERENCES

- Allanson JE, Hennekam RCM, Ireland M. De Lange syndrome: subjective and objective comparison of the classical and mild phenotypes. *J Med Genet.* 1997; 34:645–650. [PubMed: 9279756]
- Aqua MS, Rizzu P, Lindsay EA, Shaffer LG, Zackai EH, Overhauser J, Baldini A. Duplication 3q syndrome: molecular delineation of the critical region. *Am J Med Genet.* 1995; 55:33–37. [PubMed: 7702094]
- Bankier A, Haan E, Birrell R. Letter to the editor: familial occurrence of Brachmann-de Lange syndrome. *Am J Med Genet.* 1986; 25:163–165. [PubMed: 3799716]

- Beck B. Familial occurrence of Cornelia de Lange's syndrome. *Acta Paediatr Scand.* 1974; 63:225–231. [PubMed: 4820586]
- Beer S, Wallis K, Czerniak P. Two cases of de Lange's syndrome (typus degenerativus Amstelodamensis). *J Ment Defic Res.* 1967; 12:128–137. [PubMed: 5663939]
- Beratis NG, Hsu LY, Hirschhorn K. Familial de Lange syndrome: report of three cases in a sibship. *Clin Genet.* 1971; 2:170–176. [PubMed: 5124937]
- Borghi A, Giusti G, Bigozzi U. Nanismo degenerativo tipo di Amsterdam (typus Amstelodamensis - malattia di Cornelia de Lange). Presentazione di un caso e considerazioni di ordine genetico. *Acta Genet Med Gemell.* 1954; 3:365.
- Breslau EJ, Distèche C, Hall JG, Thuline H, Cooper P. Prometaphase chromosomes in five patients with Brachmann-de Lange syndrome. *Am J Med Genet.* 1981; 10:179–186. [PubMed: 7315874]
- Chodirker BN, Chudley AE. Male-to-male transmission of mild Brachmann-de Lange syndrome. *Am J Med Genet.* 1994; 52:331–333. [PubMed: 7528973]
- de Die-Smulders C, Schrander-Stumpel C, Fryns JP, Theunissen P. Exclusively maternal transmission of autosomal dominant Brachmann-de Lange syndrome. *Am J Med Genet.* 1994; 52:363. [PubMed: 7810572]
- de Lange C. Sur un type nouveau de dégénération (typus Amstelodamensis). *Arch Med Enfants.* 1933; 36:713–719.
- De Marchi N, Antonarakis SE, Jackson L. No uniparental disomy for chromosome 3 in Brachmann-de Lange syndrome. *Am J Med Genet.* 1994; 49:133–135. [PubMed: 8172242]
- Feingold M, Lin AE. Familial Brachmann-de Lange syndrome: further evidence for autosomal dominant inheritance and review of the literature. *Am J Med Genet.* 1993; 47:1064–1067. [PubMed: 8291524]
- Fryns JP, Dereymaeker AM, Hoefnagels M, D'Hondt F, Mertens G, van den Berghe H. The Brachmann-de Lange syndrome in two siblings of normal parents. *Clin Genet.* 1987; 31:413–415. [PubMed: 3621646]
- Greenberg F, Robinson LK. Mild Brachmann-de Lange syndrome: changes of phenotype with age. *Am J Med Genet.* 1989; 32:90–92. [PubMed: 2705489]
- Halal F, Preus M. The hand profile in de Lange syndrome: diagnostic criteria. *Am J Med Genet.* 1979; 3:317–323. [PubMed: 474631]
- Halal F, Silver K. Syndrome of microcephaly, Brachmann-de Lange-like facial changes, severe metatarsus adductus, and developmental delay: mild Brachmann-de Lange syndrome? *Am J Med Genet.* 1992; 42:381–386. [PubMed: 1536185]
- Ireland M, English C, Cross I, Houlsby WT, Burn J. A de novo translocation t(3;17)(q26.3;q23.1) in a child with Cornelia de Lange syndrome. *J Med Genet.* 1991; 28:639–640. [PubMed: 1956066]
- Ireland M, English C, Cross I, Lindsay S, Strachan T. Partial trisomy 3q and the mild Cornelia de Lange syndrome phenotype. *J Med Genet.* 1995; 32:837–838. [PubMed: 8558571]
- Jackson L, Kline AD, Barr MA, Koch S. de Lange syndrome: a clinical review of 310 individuals. *Am J Med Genet.* 1993; 47:940–946. [PubMed: 8291537]
- Kousseff BG, Newkirk P, Root AW. Brachmann-de Lange syndrome. *Arch Pediatr Adolesc Med.* 1994; 148:749–755. [PubMed: 8019632]
- Kozma C. Autosomal dominant inheritance of Brachmann-de Lange syndrome. *Am J Med Genet.* 1996; 66:445–448. [PubMed: 8989465]
- Krajewska-Walasek M, Chrzanowska K, Tylki-Szymanska A, Bialecka M. A further report of Brachmann-de Lange syndrome in two sibs with normal parents. *Clin Genet.* 1995; 47:324–327. [PubMed: 7554368]
- Krantz ID, Tonkin E, Smith M, Devoto M, Bottanu A, Simpson C, Hofreiter M, Abraham V, Jukofsky L, Conti BP, Strachan T, Jackson L. Exclusion of linkage to the CDL1 Gene region on chromosome 3q26.3 in some familial cases of Cornelia de Lange syndrome. *Am J Med Genet.* 2000; 101:120–129. [PubMed: 11391654]
- Kumar D, Blank CE, Griffiths BL. Cornelia de Lange syndrome in several members of the same family. *J Med Genet.* 1985; 22:296–300. [PubMed: 4045958]

- Leavitt A, Dinno N, Davis C. Cornelia de Lange syndrome in a mother and daughter. *Clin Genet*. 1985; 28:157–161. [PubMed: 4042398]
- Leroy JG, Persijn J, Van de Weghe V, Van Hecke R, Oostra A, De Bie S, Craen M. On the variability of the Brachmann-de Lange syndrome in seven patients. *Am J Med Genet*. 1993; 47:983–991. [PubMed: 8291541]
- Lieber E, Glaser JH, Jhaveri R. Brachmann-de Lange syndrome: report of two cases in a sibship. *Am J Dis Child*. 1973; 125:717–718. [PubMed: 4699505]
- McKenney RR, Elder FFB, Garcia J, Northrup H. Brachmann-de Lange syndrome: autosomal dominant inheritance and male-to-male transmission. *Am J Med Genet*. 1996; 66:449–452. [PubMed: 8989466]
- Melegh B, Bock I, Gati I, Mehes K. Multiple mitochondrial DNA deletions and persistent hyperthermia in a patient with Brachmann-de Lange phenotype. *Am J Med Genet*. 1996; 65:82–88. [PubMed: 8914746]
- Moeschler JB, Graham JM Jr. Mild Brachmann-de Lange syndrome. Phenotypic and developmental characteristics of mildly affected individuals. *Am J Med Genet*. 1993; 47:969–976. [PubMed: 7507295]
- Naguib KK, Teebi AS, Al-Awad SA, Marafie MJ. Brachmann-de Lange syndrome in sibs. *J Med Genet*. 1987; 24:627–631. [PubMed: 3681909]
- Opitz JM. Editorial comment: the Brachmann-de Lange syndrome. *Am J Med Genet*. 1985; 22:89–102. [PubMed: 3901753]
- Opitz JM, Segal AT, Lehrke R, Nadler H. Brachmann/De Lange syndrome. *Lancet*. 1964; 7:1019. [PubMed: 14201663]
- Pashayan H, Whelan D, Guttman S, Fraser FC. Variability of the de Lange syndrome: report of 3 cases and genetic analysis of 54 families. *J Pediatr*. 1969; 75:853–858. [PubMed: 5347434]
- Preus M, Rex AP. Definition and diagnosis of the Brachmann-de Lange syndrome. *Am J Med Genet*. 1983; 16:301–312. [PubMed: 6650570]
- Ptacek LJ, Opitz JM, Smith DW, Gerritsen T, Waisman HA. The Cornelia de Lange syndrome. *J Pediatr*. 1963; 63:1000–1020. [PubMed: 14071035]
- Reid CS, Edelman C, McDonald-McGinn D, Levitas A, Zackai E. Features of Brachmann-de Lange syndrome in three generations. *Proc Greenwood Genet Cent*. 1991; 11:132.
- Robinson LK, Wolfsberg E, Jones KL. Brachmann-de Lange syndrome: evidence for autosomal dominant inheritance. *Am J Med Genet*. 1985; 22:109–115. [PubMed: 4050846]
- Selicorni A, Lalatta F, Livini E, Briscioli V, Piguzzi T, Bagozzi DC, Mastroiacovo P, Zampino G, Gaeta G, Pugliese A, Cerutti- Mainaroli P, Guala A, Zelante L, Stabile M, Belli S, Franceschini P, Gianotti A, Scarano G. Variability of the Brachmann-de Lange syndrome. *Am J Med Genet*. 1993; 47:977–982. [PubMed: 8291540]
- Shaffer LG, Overhauser J, Jackson LG, Ledbetter DH. Genetic syndromes and uniparental disomy: a study of 16 cases of Brachmann-de Lange syndrome. *Am J Med Genet*. 1993; 47:383–386. [PubMed: 8135286]
- Van Allen MI, Filippi G, Siegel-Bartelt J, Yong SL, McGillivray B, Zuker RN, Smith CR, Magee JF, Ritchie S, Toi A, Reynolds JF. Clinical variability within Brachmann-de Lange syndrome: a proposed classification system. *Am J Med Genet*. 1993; 47:947–958. [PubMed: 8291538]

Fig. 1. Proband at 4 months (**a**) and at 1 year (**b**). The small hands with proximally placed thumbs are demonstrated in (**c**), and the small feet with mild 2–3 syndactyly in (**d**).

Fig. 2.
Radiographs of the proband's right and left forearms demonstrating bilateral short first metacarpals and radioulnar synostosis.

Fig. 3. Father of the proband. **A:** Facial features. **B:** Small hands with proximal thumbs and single palmar crease on the right. **C:** Small feet with mild 2–3 syndactyly.

Fig. 4.

Pedigrees of reported familial cases of Cornelia de Lange syndrome. **A:** Pedigrees demonstrating apparent dominant transmission of the phenotype. **B:** Pedigrees demonstrating apparent recessive transmission of the trait. Shaded circles and squares indicate affected individuals; hatched circles and squares indicate mildly affected individuals, or individuals with partial phenotypes (i.e., facial features).

TABLE I

Dermatoglyphics of Patient 1 (Probability) *

	1	2	3	4	5	Triradius	Creases
Right	CL	A	UL	UL	UL	Normal	Two
Left	CL	A	UL	UL	UL	Normal	Single

* CL, closed loop; A, arch; UL, ulnar loop.

TABLE II
Clinical Features of Individuals in Reported Familial Cases of Cornelia de Lange Syndrome (CdLS)

Reported	Affected individuals	Growth delay	Facial features	MR/DD	Limb anomaly	Other
Present case [2000]	Father	+	+	+	+	(Mild) Feeding problems as a child, bilateral hearing loss
	Daughter	+	+	+	+	(Mild) Gastroesophageal reflux
	Father	+	+	+	+	(Mild) Cryptorchidism
	Daughter	+	+	+	+	Hirsute
	Pat. grand-mother	?	+	?	+	(Mild)
Beer et al. [1968]	Distant male	+	+	+	?	Hirsute, seizures
	6 siblings					
	Male	+	+	+	+	(Mild) Hypothyroid
	Female	?	+	-	+	(Mild) (Authors state "not a typical case of CdL," mother, maternal uncles, cousin, maternal grandfather all with synophrys only)
	Female	?	+	-	+	Polydactyly
Beck [1974]	Female	?	+	-	+	Mild
	Female	?	-	-	+	Polydactyly
	Female	?	+	-	+	Mild
	Male	?	+	-	+	Mild
	2 siblings					
Kumar et al. [1985]	Male	+/-	+	+	+	(Mild) Hypospadias, undescended testes
	Female	+	+	(Severe) + (Severe)	+	(Mild) Another female sibling had facial characteristics, mild MR, seizures, normal growth. "Forme fruste" mother had IQ of 77, synophrys, long lashes, clinodactyly, and at least 3 SABs
	Mother	+	+	-	+	(Mild) Intermittent bilateral hearing loss, undescended testes (Son 1)
	Son 1	+	+	+	+	(Mild) Diagnosed by separate pediatrician and died at 3 months due to respiratory illness associated with congenital heart disease (Son 2)
	Son 2 (diff. father)	?	+	N/A	?	Niece had severe hearing loss and feeding problems

Reported	Affected individuals	Growth delay	Facial features	MR/DD	Limb anomaly	Other	
Leavitt et al. [1985]	Mother's niece	+	+	+	+	(Mild)	Possibly others mildly affected
	Mother	+	+(Mild)	+	+	+(Mild)	
	Daughter	+	+	+	+	+(Mild)	
	Mother	−	+	+	+	+/−	Hearing loss, feeding problems (mother has unaffected daughter)
Robinson et al. [1985]	Son	+	+	+	+	+(Mild)	
	Son	+	+	+	+	+(Mild)	
	Mother	−	+/−	+	−	−	Microcephaly
	Daughter	+	+	+	+	+(Mild)	
Bankier et al. [1986]	Son	+/−	+	+	+	+(Mild)	
	3-generation family						
	Mother	?	+	+(Mild)	+	Acromicria	Two of the mother's half-siblings died neonatally, one of whom had unspecified anomalies
	Daughter	+	+	+	+	Acromicria	
Reid et al. [1991]	Maternal aunt	?	+	+(Mild)	+	Acromicria	
	Maternal aunt	?	+	+(Mild)	+	Acromicria	
	Maternal grandmother	?	+	+	+	Acromicria	
	Father	+/−	+	+	+(Mild)	−	All had loss of chromosome 22p, including grandfather who was phenotypically normal
	Daughter	+	+	−	−	−	
	Son	+	+	+(Mild)	−	−	
	Son	+/−	+	+	+	−	
	Mother	+	+(Mild)	+	+	+(Mild)	
Feingold & Lin [1993]	Daughter	+	+(Mild)	+	+	+(Mild)	
	Father	−	+	+	?	?	No consanguinity, but both sides of family of Dutch/Mennonite descent
Chodirker & Chudley [1994]	Son	+	+	+	+	+(Mild)	
	Mother	−	+	−	?	?	Feeding problems as child (mother)
	Son	+	+	+	?	?	Severe feeding problems, hirsute, laryngomalacia (son)
De Die-Smulders et al. [1994]							Maternal grandmother and maternal aunt with facial features

Reported	Affected individuals	Growth delay	Facial features	MR/DD	Limb anomaly	Other
Kousseff et al. [1994]	Mother	+	+	+	+ Mild	
	Daughter	+	+	?	+/-	
	Mother	+/-	+	+	+	Low-frequency unilateral hearing loss, bony palatal prominence epispadias, died of respiratory complications at 6 years
Kozma [1996]	Son	-	+	+	+	Severe
	Father	-	+	+	+	Mild
	Daughter	+	+	+	+	Mild
Pacek et al. [1963]	Son (diff. mother)	+	+	+	+	Mild
	2 siblings					No information about parents
	Male	+	+	+	+	Severe
Beratis et al. [1971]	Female	+	+	+	+	Severe
	Female	+	+	+	+	Severe
	Male	+	+	+	+	Severe
Lieber et al. [1973]	2 siblings					Parents unaffected
	Female	+	+	+	+	Severe
	Male	+	+	+	+	Severe
Breslau et al. [1981]	2 siblings					Parents unaffected
	Female	+	+	+	+	Severe
	Female	+	+	+	+	Severe
Preus & Rex [1983]	2 Maternal first cousins					Article states: "One patient seen in Ottawa has a first cousin with a well-documented diagnosis of BDLS, the patients being related through their mothers"
	Pt. 1	?	+	?	?	
	Pt. 2	?	+	?	?	
Fryns et al. [1987]	2 siblings					
	Female	+	+	d.3 wks	+	Severe

Reported	Affected individuals	Growth delay	Facial features	MR/DD	Limb anomaly	Other
Naguib et al. [1987]	Male	+	+	d. 3 wks	+	(Severe)
	2 siblings					Parents were unaffected and first cousins
	Female	+	+	+	+	
Krajewska-Walasek et al. [1995]	Male	+	+	+	+	(Severe)
	2 siblings					Cryptorchidism, small penis
	Female	+	+	+	+	Another male sibling born with multiple congenital anomalies (not examined). 2 unaffected siblings
Van Allen et al. [1993]	Male	+	+	+	-	Hypospadias, cryptorchidism
	Siblings					Mother: arched brows, thin lip with beaking, normal IQ
	Female	+	+	+	+	Pierre Robin, severe feeding problems, hearing loss; ventricular septal defect, horseshoe kidneys, bicornuate uterus, trilobed lungs
	Female fetus	+	+	N/A	+	Severe
Opitz [1985]	3rd cousins					
	Male	?	?	?	?	Another distant male cousin possibly affected, not confirmed
	Male	?	?	?	?	

+, trait present; -, trait absent; ?, trait not reported; N/A, trait not applicable, +/-, + trait equivocal, SABs, spontaneous abortions; MR, mental retardation; DD, developmental disability; BDLs, Brachmann-de Lange syndrome.