

# Mutations and Variants in the Cohesion Factor Genes *NIPBL*, *SMC1A*, and *SMC3* in a Cohort of 30 Unrelated Patients With Cornelia de Lange Syndrome

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**Cornelia de Lange syndrome (CdLS) manifests facial dysmorphic features, growth and cognitive impairment, and limb malformations. Mutations in three genes (*NIPBL*, *SMC1A*, and *SMC3*) of the cohesin complex and its regulators have been found in affected patients. Here, we present clinical and molecular characterization of 30 unrelated patients with CdLS. Eleven patients had mutations in *NIPBL* (37%) and three patients had mutations in *SMC1A* (10%), giving an overall rate of mutations of 47%. Several patients shared the same mutation in *NIPBL* (p.R827GfsX2) but had variable phenotypes, indicating the influence of modifiers in CdLS. Patients with *NIPBL* mutations had a more severe phenotype than those with mutations in *SMC1A* or those without identified mutations. However, a high**

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incidence of palate defects was noted in patients with *SMC1A* mutations. In addition, we observed a similar phenotype in both male and female patients with *SMC1A* mutations. Finally, we report the first patient with an *SMC1A* mutation and the Sandifer complex. © 2010 Wiley-Liss, Inc.

**Key words:** Cornelia de Lange syndrome (CdLS); *NIPBL*; *SMC1A*; *SMC3*; genes; mutations

## INTRODUCTION

Mutations in *NIPBL*, a regulator of the cohesin complex, were the first demonstrated cause of Cornelia de Lange syndrome (CDLS1, MIM 122470) [Krantz et al., 2004; Tonkin et al., 2004]. This disorder is characterized by distinctive dysmorphic facial features, impairment of growth and cognitive development, limb malformations, and additional organ system involvement with variable expressivity [Ireland et al., 1993]. Most patients with CdLS have unaffected parents but familial cases have been reported [Russell et al., 2001]. Recently, mutations in the cohesin structural components *SMC1A* and *SMC3* were found in patients with atypical CdLS (CDLS2, MIM 300590 and CDLS3, MIM 610759) [Musio et al., 2006; Borck et al., 2007; Deardorff et al., 2007]. Eleven different *SMC1A* mutations in 14 unrelated patients have been reported. All patients had a mild-to-moderate CdLS phenotype [Musio et al., 2006; Borck et al., 2007; Deardorff et al., 2007]. Only a single mildly affected patient has been identified with a mutation in *SMC3* [Deardorff et al., 2007].

Here, we report the identification of 14 additional mutations of the cohesin complex genes *NIPBL* (11) and *SMC1A* (3) and discuss genotype–phenotype correlations in a cohort of 30 unrelated patients with CdLS.

## MATERIALS AND METHODS

### Clinical Evaluation

Patients were enrolled in this study under an IRB-approved protocol. The evaluation included clinical and family history, physical examination, and psychological evaluation. Proband was classified following the criteria proposed by Gillis et al. [2004]. Genotype–phenotype correlations were established using SPSS v14.0 program for Windows. We used the  $\chi^2$  test of independence for the comparison between clinical findings and the presence of mutations in *NIPBL* and *SMC1A*. Post hoc analyses of the contingency table cells were based on adjusted residuals of Haberman. This is equivalent to a situation of multiple testing; therefore, Bonferroni corrections were calculated for the *P*-values of the cells.

### Variant Allele Analysis

Genomic DNA was isolated from peripheral blood lymphocytes or cultured chorionic villi by standard protocols. The coding region and flanking intronic sequences of *NIPBL* (exons 2–47), *SMC1A* (exons 1–25), and *SMC3* (exons 1–29) were screened for mutations by PCR amplification and bidirectional direct sequencing. Parental

genotypes and 50 ethnically matched population controls were screened to assess whether each variant was de novo. Reference sequences used for *SMC1A*, *SMC3*, and *NIPBL* were RefSeq NM\_006306, NM\_005445, and NM\_133433, respectively. When mRNA analysis was feasible, the Invitrogen (Paisley, UK). RT-PCR kit was used. RT-PCR products were confirmed by sequencing. Details of the primers used and PCR conditions for *NIPBL*, *SMC1A*, and *SMC3* amplification are available upon request. Protein subsequence motifs for human *NIPBL* were analyzed using data from Uniprot [Wu et al., 2006] and Pfam [Finn et al., 2006] databases.

## RESULTS

### Clinical Phenotypes

Thirty unrelated probands were studied. Twenty-seven were from Spain, two from Romania (patients C2 and C27), and one from Morocco (patient C18) (Table I). Additional molecular and clinical data of the 14 patients with identified mutations are included in supporting information Table I (supporting information Table I may be found in the online version of this article) and photographs are shown in Figure 1.

### Variant Alleles

***NIPBL*.** Thirty-eight variant alleles of *NIPBL* were identified in 30 unrelated probands (supporting information Tables I–III which may be found in the online version of this article). Four prenatal diagnoses were normal. Eleven of the variants were apparently de novo mutations, nine of which had not been previously reported, giving a prevalence of 37% in this cohort (supporting information Table I and supporting information Fig. 1A which may be found in the online version of this article). Of these new mutations, two were nonsense: c.2146C → T (p.Q716X) and c.6880C → T (p.Q2294X), three were splice site: c.230 + 1G → A (p.L22QfsX3), c.4320 + 5G → C (p.V1414\_A1440del), and c.4321G → T (p.F1442KfsX3/p.V1441L), three were missense: c.6242G → C (p.G2081A), c.6269G → T (p.S2090I), and c.6449T → C (p.L2150P), and one was an in-frame deletion: c.5689\_5691delAAT (p.N1897del). We also found two frameshift deletions that had been previously reported: c.2479\_2480delAG (p.R827GfsX2) in seven unrelated patients [Gillis et al., 2004; Kaur et al., 2005; Bhuiyan et al., 2006; Selicorni et al., 2007] and c.7438\_7439delAG (p.R2480KfsX5), which had been reported in one patient [Yan et al., 2006] (supporting information Table I may be found in the online version of this article). The mutation c.230 + 1G → A generated an alternative transcript with skipping of exon 3 to predict a truncated protein. The other intronic mutation (c.4320 + 5G → C) produced a variant without exon 19 to predict an in-frame deletion of 27 amino acid residues. However, the mutation c.4321G → T affected the first base of exon 20 and generated an alternative splicing with two transcripts, one bearing an exon 20 deletion to predict a truncated protein and another normal-sized transcript predicted to yield p.V1441L protein (supporting information Figs. 1A and 2 which may be found in the online version of this article). Multiple sequence analysis in the neighborhood of mutated residues V1441, N1897, G2081, S2090I, and L2150 was conserved across species (rat, chicken, zebrafish) (supporting information

TABLE I. Genotypes and Phenotypes of 30 Patients With Cornelia de Lange Syndrome

Clinical feature	Mutation negative, n (adjusted residuals)	Mutation positive		Total patients
		<i>NIPBL</i> , n (adjusted residuals)	<i>SMC1A</i> , n (adjusted residuals)	
Sex	11M/19F	2M/1F	4M/7F	30
IUGR (adjusted residuals)	6 [−2.5]	10 [2.5]**	2 [0.2]	18
Growth retardation				
Mild (>75%)	13 [2.8]**	2 [−3.8]	3 [1.4]	18
Moderate (25–75%)	2 [−2.8]	9 [3.8]***	0 [−1.4]	11
Limb abnormalities				
Mild (no reduction)	15 [1.6]	7 [−2.2]	3 [0.8]	25
Moderate (>2 fingers)	1 [−0.1]	1 [0.4]	0 [−0.5]	2
Severe (≤2 fingers)	0 [−2.0]	3 [2.4]*	0 [−0.6]	3
Developmental delay				
Mild (<2 years delayed)	7 [1.3]	3 [−0.2]	0 [−1.7]	10
Moderate (>2 years delayed)	5 [−0.9]	3 [−0.5]	3 [1.9]	11
Severe (profound delayed)	0 [−1.1]	1 [1.5]	0 [−0.4]	1
Other clinical findings				
Microcephaly	8 [−1.6]	9 [1.6]	2 [0.1]	19
Hirsutism	7 [−0.7]	7 [1.1]	1 [−0.6]	15
Cardiac defect	8 [−0.2]	5 [−0.1]	2 [0.5]	15
Gastroesophageal reflux	5 [−1.0]	5 [0.5]	2 [1.0]	12
Deafness	3 [−2.1]	7 [2.2]*	1 [−0.2]	11
Genitourinary anomalies	4 [−1.4]	6 [1.5]	1 [−0.1]	11
Ophthalmological anomalies	7 [0.9]	3 [−0.8]	1 [−0.1]	11
Palate anomalies	5 [−1.4]	5 [0.2]	3 [2.1]*	13

Evaluation of clinical findings in patients with CdLS with and without mutation in *NIPBL* or *SMC1A*. Growth curves are per CdLS curves. \*Significant between  $0.1 < P < 0.05$ , \*\*significant at  $P < 0.05$ , \*\*\*significant at  $P < 0.01$ , Bonferroni corrected  $P$ -value.

Fig. 1 which may be found in the online version of this article). These changes were not detected in their respective parents or in 100 control alleles.

**SMC1A.** Among the 19 *NIPBL*-negative patients, we identified three mutations in *SMC1A*, giving a prevalence of 10% among the 30 patients reported here. We found an in-frame deletion c.802\_804delAAG (p.K268del) in one woman and a missense mutation c.2132G → A (p.R711Q) in one male (supporting information Table I which may be found in the online version of this article, Fig. 1, and supporting information Fig. 3A which may be found in the online version of this article). These residues were conserved (supporting information Fig. 3B,C which may be found in the online version of this article) and were not detected in parents or in 100 control alleles, suggesting de novo events. The other mutation, a c.587G → A (p.R196H) was previously reported [Deardorff et al., 2007], but the patient developed new clinical symptoms, which we describe in this report (supporting information Table I and supporting information Fig. 3A which may be found in the online version of this article). Two novel and two previously reported *SMC1A* polymorphisms or variants of unknown significance were also observed [Deardorff et al., 2007] (supporting information Tables II and III which may be found in the online version of this article).

**SMC3.** Twenty-nine sequence variants in *SMC3* that may represent neutral polymorphisms were observed in 16 *NIPBL*-negative probands (supporting information Tables II and III which may be found in the online version of this article).

## DISCUSSION

In this study of 30 patients with CdLS, we identified mutations in *NIPBL* (37%) or *SMC1A* (10%) (47% overall). Our *NIPBL* and *SMC1A* mutation rates were similar to prior reports [Gillis et al., 2004; Bhuiyan et al., 2006; Musio et al., 2006; Yan et al., 2006; Borck et al., 2007; Deardorff et al., 2007; Selicorni et al., 2007]. To carry out accurate genotype–phenotype correlations in this cohort, the *NIPBL*-positive probands were classified into three groups: truncating mutations, splice-site mutations, and missense or in-frame deletion mutations. Truncating mutations presumably result in haploinsufficiency and, as expected, led to more severe phenotypes. Interestingly, patient 20, who had severe bilateral limb defects, carried the mutation p.R827GfsX2, which had been previously identified in seven patients of distinct ethnic origins. This is currently the most frequent CdLS-causing mutation worldwide [Gillis et al., 2004; Kaur et al., 2005; Bhuiyan et al., 2006; Selicorni et al., 2007]. In addition, phenotypes associated with this mutation



FIG. 1. Phenotypes of patients with CdLS and mutations in *NIPBL* and *SMC1A*. Individuals C5, C8, C10, C14, C18, C20, C21, C25, C26, C28, and C29 have mutations in *NIPBL*. Individuals C13 and C30 have mutations in *SMC1A*. Phenotype of individual C2 has been published elsewhere [Deardorff et al., 2007]. Patients with *NIPBL* mutations are surrounded by a solid line, and patients with *SMC1A* mutations are surrounded by a dashed line.

are quite variable, with limb defects ranging from mild to severe. This indicates the influence of modifiers in the expressivity of CdLS [Gillis et al., 2004].

As in a previous report we noted a splice-site mutation with a variable phenotype [Selicorni et al., 2007]. Patient C10, who had a mild phenotype, had the mutation p.L22QfsX3, which generates both a normal transcript and a predominant aberrant alternatively spliced transcript with an exon 3 deletion. The pathogenic effect of this mutation, in addition to the early truncation of the protein, may be explained by disruption of NIPBL interaction with mau-2 in the cohesin complex [Seitan et al., 2006]. Another interesting splice-site mutation is p.V1414\_A1440del (c.4320 + 5G → C), which generated an aberrant spliced transcript with deletion of exon 19. This small exon codifies 27 amino acids located within the more preserved carboxy terminal half of the protein, although it has not been associated with any functional domain. Loss of exon 19 in patient C28 led to severe limb defects. To date, only one other single mutation, p.V1414\_A1440del (c.4320 + 2T → A), which deleted exon 19 and was associated with severe limb malformations, has been reported [Schoumans et al., 2007]. The finding of another splice-site mutation, p.F1442KfsX3/p.V1441L (c.4321G → T), which caused the deletion of exon 20 and mild symptoms, suggests that this domain of the protein is important in limb formation.

As expected, patients with missense mutations or in-frame deletions (when compared to patients with nonsense or frameshift mutations) had milder clinical features, with one exception; patient C18, who had bilateral single-digit hypomelia and carried the mutation p.L2150P. The presence of severe phenotypes in patients carrying missense mutations suggests the involvement of functional domains of the protein. Among the 147 mutations previously reported in NIPBL, only two missense mutations have been associated with severe limb defects [Tonkin et al., 2004; Schoumans et al., 2007]. Surprisingly, one of them, p.T2146P, is located four amino acids away (in the 5' side) from the mutation p.L2150P mutation and lies in the protein interaction region HEAT repeat [Schoumans et al., 2007] (supporting information Fig. 1A,E which may be found in the online version of this article). The *Drosophila* (*Nipped-B*<sup>NC39</sup>) mutation *Nipped-BI1510* (equivalent to V2147 en NIPBL) produces an increase in the number of "nicks" in the wings. These alterations are currently considered equivalent to those seen in the human hands [Gause et al., 2008]. The mutated residue I1510 in *Nipped-B* is also conserved in NIPBL (V2147) and it is close (in the 3' direction) to mutation T2146 and to three amino acids (in the 5' direction) of the new mutation L2150 (supporting information Fig. 1A,E which may be found in the online version of this article). The similarities in the effects of the change in these residues indicate that they are part of an amino acid sequence involved in limb development.

More recently, it has been reported that in NIPBL the sequence between residues 1838 and 2000, included in the predicted region HEAT repeat interacts with histone deacetylases 1 and 3 [Jahnke et al., 2008]. The novel mutation p.N1897del is located in the middle of this sequence, two amino acids away from mutation p.R1895T, which affects that interaction [Jahnke et al., 2008]. The clinical findings associated with this mutation and with the four reported that affect that domain [Gillis et al., 2004;

Borck et al., 2007; Selicorni et al., 2007; Jahnke et al., 2008] include mild involvement of the limbs and suggest that the NIPBL–deacetylase interaction has a minor role in limb development.

The two new mutations identified in the *SMC1A* gene, one missense and one in-frame deletion, suggest that more severe mutations of the protein are incompatible with life [Liu and Krantz, 2008]. Both mutations are located in the predicted coiled-coil structure. The deletion of residue K268 (p.K268del) would cause a shift in the relative position of the accompanying residues, leading to displacement of corresponding residues of the two antiparallel helices that form the coiled coil. The missense mutation p.R711Q affects arginine R711, which was mutated in other patient previously reported (p.R711W) [Deardorff et al., 2007]. It is interesting that 5 out of 11 mutations in the *SMC1A* gene affect positively charged arginine residues, and it has been proposed that these residues may be involved in an interaction with DNA [White and Erickson, 2009].

In this series, we found no mutations in the *SMC3* gene. Instead, we found a large number of polymorphisms or variants of unknown significance.

The study of the clinical features of this cohort showed that the growth retardation, limb malformations, and even hearing loss are more likely to be present in patients carrying *NIPBL* mutations, compared to patients with *SMC1A* mutations. In contrast, patients with mutations in *SMC1A* had a higher incidence of high palate anomalies, a finding not previously reported. The remaining clinical manifestations in patients with mutations in *SMC1A* were usually moderate to mild, and similar to those of patients in whom no mutation was found (Table I). Of the three major clinical features of CdLS, mental retardation is the only one that is consistently present in the three groups of patients analyzed. This indicates that additional genes implicated in CdLS may produce mild or moderate phenotypes with mental retardation as the most relevant feature [Deardorff et al., 2007].

Another interesting finding is the presence of the Sandifer complex in a 3-year-old boy (C30) carrying a mutation in the *SMC1A* gene. Although the Sandifer complex has been previously reported in patients with CdLS [Sommer, 1993], we report the first patient with this manifestation and with an identified genetic mutation. Besides, this patient had recently developed epilepsy, for which he was being treated with an anticonvulsant. Finally, the female patient with *SMC1A* mutation did not appear to have milder clinical manifestations than the males carrying a mutation in the same gene, indicating that in our cohort of *SMC1A* mutated cases, gender is irrelevant to expressivity.

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