REPORT

Mutations in Cohesin Complex Members SMC3 and SMC1A Cause a Mild Variant of Cornelia de Lange Syndrome with Predominant Mental Retardation

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Mutations in the cohesin regulators NIPBL and ESCO2 are causative of the Cornelia de Lange syndrome (CdLS) and Roberts or SC phocomelia syndrome, respectively. Recently, mutations in the cohesin complex structural component SMC1A have been identified in two probands with features of CdLS. Here, we report the identification of a mutation in the gene encoding the complementary subunit of the cohesin heterodimer, *SMC3,* and 14 additional *SMC1A* mutations. All mutations are predicted to retain an open reading frame, and no truncating mutations were identified. Structural analysis of the mutant SMC3 and SMC1A proteins indicate that all are likely to produce functional cohesin complexes, but we posit that they may alter their chromosome binding dynamics. Our data indicate that *SMC3* and *SMC1A* mutations (1) contribute to ~5% of cases of CdLS, (2) result in a consistently mild phenotype with absence of major structural anomalies typically associated with CdLS, and (3) in some instances, result in a phenotype that approaches that of apparently nonsyndromic mental retardation.

The cohesin proteins compose an evolutionarily conserved complex whose fundamental role in chromosome cohesion and coordinated segregation of sister chromatids has been well characterized across species.[1,2] Recently, regulators of cohesin and a structural component of the complex have surprisingly been found to cause phenotypically specific human developmental disorders when mutated. Mutations in NIPBL, the vertebrate homolog of the yeast Sister chromatid cohesion 2 (Scc2) protein, a regulator of cohesin loading and unloading, are responsible for ~50% of cases of Cornelia de Lange syndrome (CdLS [MIM #122470 and #300590]).[3–5] Mutations in another cohesin regulator, ESCO2, have been found to result in Roberts syndrome and SC phocomelia.[6,7] Two mutations in the cohesin structural component SMC1A (for structural maintenance of chromosomes 1A based on revised HUGO nomenclature; also called "SMC1L1") were recently found to result in an X-linked form of CdLS.[8] The conserved developmental perturbations seen in these disorders are likely the result of disruption of the cohesin complex's role in facilitating long-range enhancer promoter interactions and subsequent transcriptional dysregulation.[9,10]

CdLS is a dominantly inherited genetic multisystem developmental disorder. The clinical features consist of craniofacial dysmorphia, hirsutism, malformations of the upper extremities, gastroesophageal dysfunction, growth retardation, neurodevelopmental delay, and other structural anomalies (see facies and limbs of patient 1P in fig. 1).[11,12] The mental retardation seen in CdLS, although typically moderate to severe, displays a wide range of variability.[12]

The facial features of an individual with classical CdLS are unique, are easily recognizable, and may be among the most useful diagnostic signs. A milder CdLS phenotype has been reported consistently,[11,13–15] characterized by less significant psychomotor and growth retardation, a lower incidence of major malformations, and milder limb anomalies[15] and accounting for ~20%–30% of the CdLS population.[15]

Mutations in *NIPBL* account for ~50% of CdLS cases and have been shown to cause both mild and severe forms.[3,16,17] The recent discovery that mutations in the X-linked *SMC1A* gene also result in a variant of CdLS[8] suggests that other cohesin complex members may contribute to the etiology of CdLS and related disorders. Here, we report the screening of 115 *NIPBL*-mutation–negative in-

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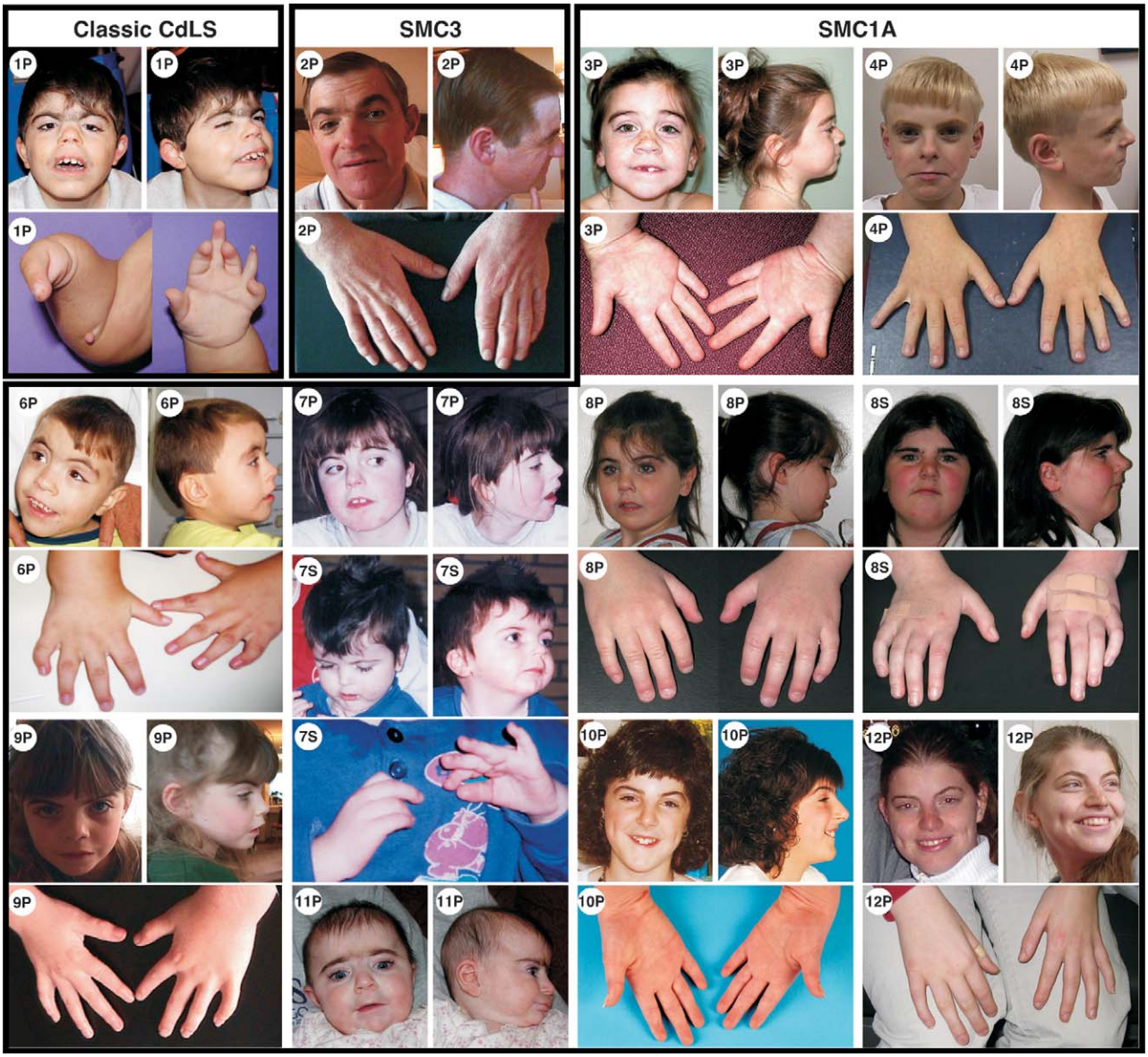

Figure 1. Facies and hands of classic CdLS in *SMC3*- and *SMC1A*-mutation–positive individuals. Proband numbers are indicated. A "P" following the number indicates proband, and an "S" indicates an affected sister. Facial features and upper extremities are shown for 1P, a patient with classic CdLS and a truncating NIPBL mutation; 2P, a male with a sporadic SMC3 E488del mutation; 3P, a female with a sporadic V58-R62del mutation; 4P, a male with a sporadic F133V mutation; 6P, a male with a sporadic R496C mutation; 7P and 7S, two sisters of family 2 with the R496H mutation and mosaicism in the unaffected parent; 8P and 8S, two sisters of family 1 who share a R496H mutation; 9P, a female with a sporadic R496H mutation; 10P, a male with a sporadic R711W mutation; 11P, a female with a sporadic R790Q mutation; and 12P, a female with a sporadic F1122L mutation.

dividuals with sporadic and familial CdLS and probands with CdLS-variant phenotypes for mutations in the cohesin complex components SMC3 and SMC1A.

Mutation analysis.—All probands were suspected to have CdLS or CdLS variant phenotypes by clinical geneticists experienced in the diagnosis of CdLS, and all were enrolled under an institutional review board–approved protocol of informed consent. All were prescreened for mutations in the 46 coding exons of *NIPBL* by use of conformation-sensitive gel electrophoresis and/or direct sequencing, as reported elsewhere.[3] No *NIPBL* mutations were previously identified in these 115 probands. *SMC3* and *SMC1A* (GenBank accession numbers NM_005445 and NM_006306) were analyzed by PCR amplification and direct sequencing of coding exons 1–29 and 2–25, respectively. Oligonucleotide primer sequences and PCR conditions for *SMC3* and *SMC1A* are available on request.

On the basis of examination, clinical information, and/

Table 1. Characteristics of *NIPBL*-Mutation–Negative Probands with CdLS

Feature and Subcategory	*SMC3*-Mutation Positive	*SMC1A*-Mutation Positive	Percentage *SMC1A*-Mutation Positive
Facies:			
Typical	0/50	6/52	12
Atypical[a]	1/46	3/49	6
Sex:			
Male	1/43	3/54	6
Female	0/53	7/54	13
Severity[b]:			
Mild:	1/51	9/60	15
Males	1/20	2/23	9
Females	0/31	7/37	19
Moderate	0/27	0/27	0
Severe	0/18	0/14	0
Limb deficiencies:			
Present	0/13	0/11	0
Absent	1/83	9/90	10
Familial cases	0/15	3/20	15

NOTE.—Clinical information was not available from all patients, so all feature categories do not sum to 115. The denominator in each cell indicates the number screened within each subcategory.

[a] Atypical facies usually consisted of a more prominent nose with less upturn, lack of synophrys or arched eyebrows, and/or no micrognathia.

[b] Severity was determined as by Gillis et al.[3]

or photographs, patients for whom detailed information was available were categorized as indicated in table 1, which also shows the percentage of *SMC3* and *SMC1A* mutations in each subgroup. A single mutation was identified in *SMC3* in 1 of the 96 probands screened. Eight unique *SMC1A* mutations were identified in 10 of 115 probands, giving a prevalence of 9% among this cohort of *NIPBL*-mutation–negative probands and an overall prevalence of ~5% among unscreened patients with CdLS.

One male (2P) (fig. 1 and tables 2 and 3) was found to have a unique *SMC3* mutation that comprised a 3-nt deletion (c.1464_1466delAGA) and that resulted in the deletion of a single amino acid (p.E488del). Paternity was confirmed, and neither parent carried the mutation, which indicates a de novo event. Furthermore, this change was not observed in >350 control alleles.

Nine probands had missense mutations in SMC1A, and one had an in-frame deletion of 5 aa. One amino acid residue (R496) was mutated in 4 unrelated probands, 2 of which involved familial cases, to account for 7 of the 14 mutation-positive patients. One R496H familial case (involving patients 8P and 8S) (fig. 1 and tables 2 and 3) resulted from germline mosaicism, and the other (involving patients 7P and 7S) resulted from a somatic and germline mosaic parent with no clinical features of CdLS. The mother in the third family (5P) was found to carry the SMC1A mutation (R496C) and is thought to have mild mental retardation and small hands. A mutation-positive, mentally retarded, affected half-brother developed speech but is institutionalized. All other mutations (V58_R62del, F133V, R196H, R711W, R790Q, and F1122L) were de novo and were identified in patients with unaffected parents who were negative for mutations. In addition, all mutations were absent in >220 normal control alleles. Analysis of protein sequences for human, *Fugu, Saccharomyces cerevisiae,* and *Thermotoga maritime,* aligned by the ClustalW method[18] (MacVector [Accelrys]), demonstrated that all mutated residues affect evolutionarily conserved amino acids (fig. 2).

SMC3 and SMC1A mutations result in a mild variant of CdLS.—Tables 2 and 3 list the mutations and clinical characteristics of all probands and available affected family members. Notably, the *SMC3*- and *SMC1A*-mutation–positive patients demonstrated very mild facial features, no absence or reduction of limbs or digits, and no other major structural anomalies. This is in contrast to classical CdLS (see patient 1P in fig. 1), as summarized in table 4. As noted for the patients studied by Musio et al.,[8] several of our patients had a more prominent nasal bridge (4P, 8S, 10P, and 12P) (fig. 1) than is typically seen in CdLS. It should be emphasized that, unlike in classic CdLS, in this cohort (1) 80% had birth weights that were normal, and several probands (6P, 9P, and 12P) had growth and head circumferences within the normal range; (2) all individuals walked, and all but one acquired speech; and (3) all had cognitive delays—however, some participated in mainstream classes (3P and 4P), and one was employed in a supervised position in a greenhouse (2P). Of six individuals with the R496H and R496C mutations, considerable variability was noted for growth and development, although all were considered to have mild CdLS. Polymorphisms identified in this work are shown in table 5.

Mapping of mutations to the cohesin crystal structure.—To understand the molecular implications of *SMC3* and

Table 2. Dysmorphia and Minor Anomalies of *SMC3*- and *SMC1A*-Mutation–Positive Patients with CdLS

Characteristic	Patient												
	2P	3P	4P	5P	6P	7P	7S	8P	8S	9P	10P	11P	12P
Sex	M	F	M	M	M	F	F	F	F	F	F	F	F
Gene mutated	*SMC3*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*
cDNA mutation	1464_1466delAGA	173del15	397T→G	587G→A	1486C→T	1487G→A	1487G→A	1487G→A	1487G→A	1487G→A	2131C→T	2369G→A	3364T→C
Protein effect	E488del	V58_R62del	F133V	R196H	R496C	R496H	R496H	R496H	R496H	R496H	R711W	R790Q	F1122L
Brachycephaly	−	−	−	+	+	−	−	−	−	−	−	+	+
Low anterior hairline	−	−	−	+	+	+	+	−	−	−	+	+	−
Arched eyebrows	+	+	+	−	Full	+	+	+	+	+	+	+	+
Synophrys	+	+	+	+	+	+	−	+	+	+	+	+	Mild
Long eyelashes	+	+	+	+	+	+	+	+	+	+	+	+	+
Palpebrae	Normal	Normal	Normal	Normal	Mild ptosis	Lacrimal duct stenosis	Ptosis, lacrimal duct stenosis	Normal	Lacrimal duct stenosis	Ptosis	Lacrimal duct stenosis	Lacrimal duct obstruction	Mild ptosis
Myopia	+	+	Astigmatism	−	−	+	+			−		++	−
Nasal bridge	High	Low	High	High	Normal	Low	Low	Low	Low	Low	High	Low	High
Anteverted nostrils	−	+	+	Mild	−	+	+	+	+	+	Mild	+	−
Long/featureless philtrum	−	+	+	+	−	+	+	−	−	+	+	+	−
Thin lips	+	+	+	+	−	+	+	+	+	+	+	+	+
Downturned corners of the mouth	−	+	+	+	−	+	+	+	+	+	−	+	−
Palate	High	−	Normal	Normal	High	−	−	Posterior cleft	High	Normal	Mild cleft		−
Micrognathia	−	−	−	+	+	+	+	+	+	+	−	+	−
Hearing loss	−	+	−	−	−	+	−	+	−	−	−	+	−
Cutis marmorata	−	+	+		+	+	+	+	+	+		+	+
Small hands	+	+	+	+	+	+	+	+	−	+	+	+	+
Small feet	+	+	+	+	+	+	+		+	+	+	+	+
Proximally set thumbs	+	+	−	−	+	+	+	+	+	+	+	−	+
Clinodactyly of 5th finger	+	+	−	−	+	+	+	+	+	+	+	+	+
Restriction of elbow movements	+		+	−	−	−	+			−	−	−	−
Hirsutism	+	+		+	+	+	+	−	−	+	−		−

NOTE.—Blank cells indicate that information was unavailable.

Table 3. Growth and Development of *SMC3*- and *SMC1A*-Mutation–Positive Patients with CdLS

Characteristic	Patient												
	2P	3P	4P	5P	6P	7P	7S	8P	8S	9P	10P	11P	12P
Sex	M	F	M	M	M	F	F	F	F	F	F	F	F
Gene mutated	*SMC3*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*	*SMC1A*
cDNA mutation	1464_1466delAGA	173del15	397T→G	587G→A	1486C→T	1487G→A	1487G→A	1487G→A	1487G→A	1487G→A	2131C→T	2369G→A	3364T→C
Protein effect	E488del	V58_R62del	F133V	R196H	R496C	R496H	R496H	R496H	R496H	R496H	R711W	R790Q	F1122L
Birth weight, percentile	<3	8	75	10	8	<3	<3	23	11		40	15	
Length at birth, percentile	25	16			35	29	<3	37			35	5	
HC at birth, percentile		<3				7	3	54			4		
APGAR score[a]		8/9		9/10								8/9	
Feeding problems in infancy	+	−	+	−	+			+			−	+	+
Weight at time of study, percentile	<3	12		<3	53	18	<3	3	<3	44	4	<3	25
Height at time of study, percentile	<3	<3	14	<3	86	<3	<3	<3	<3	73	6		25
HC at time of study, percentile		<3	3	<3	75	<3	<3	<3	<3	10	<3	<3	25
Psychomotor delay	+	+	+	+	+ Nonverbal	+	+	+	+	+	+		+
Mental retardation	+	Mainstream 2nd grade			Autistic-like behavior	++	++	+ DQV = 36; DQM = 68	+ DQV = 35; DQM = 45		+		IQ = 59
Major malformations	−	Mild PS	−	ASD		−	−	−	−	−	−	PS	−
CNS anomalies	−		Normal CT scan			−	−				−		
GER	+	+	+	−		+	+	+	+	−	+	+	+
Seizures	−			−	Single	In the past	In the past	+			−		
Other medical problems	Small hiatal hernia	Intubated with pneumonia, VU reflux	Anxiety		History of encephalitis, now hemiparetic	Pulmonic stenosis					Intention tremor		Recurrent sinusitis

NOTE.—Growth percentages were estimated from Centers for Disease Control and Prevention growth charts.[19] ASD = atrial septal defect; DQM = developmental quotient, motor; DQV = developmental quotient, verbal; GER = gastroesophageal reflux; HC = head circumference; PS = pulmonic stenosis; VU = vesicoureteral. Blank cells indicate that information was unknown.

[a] APGAR scores are indicated by score at 1 min/score at 5 min.

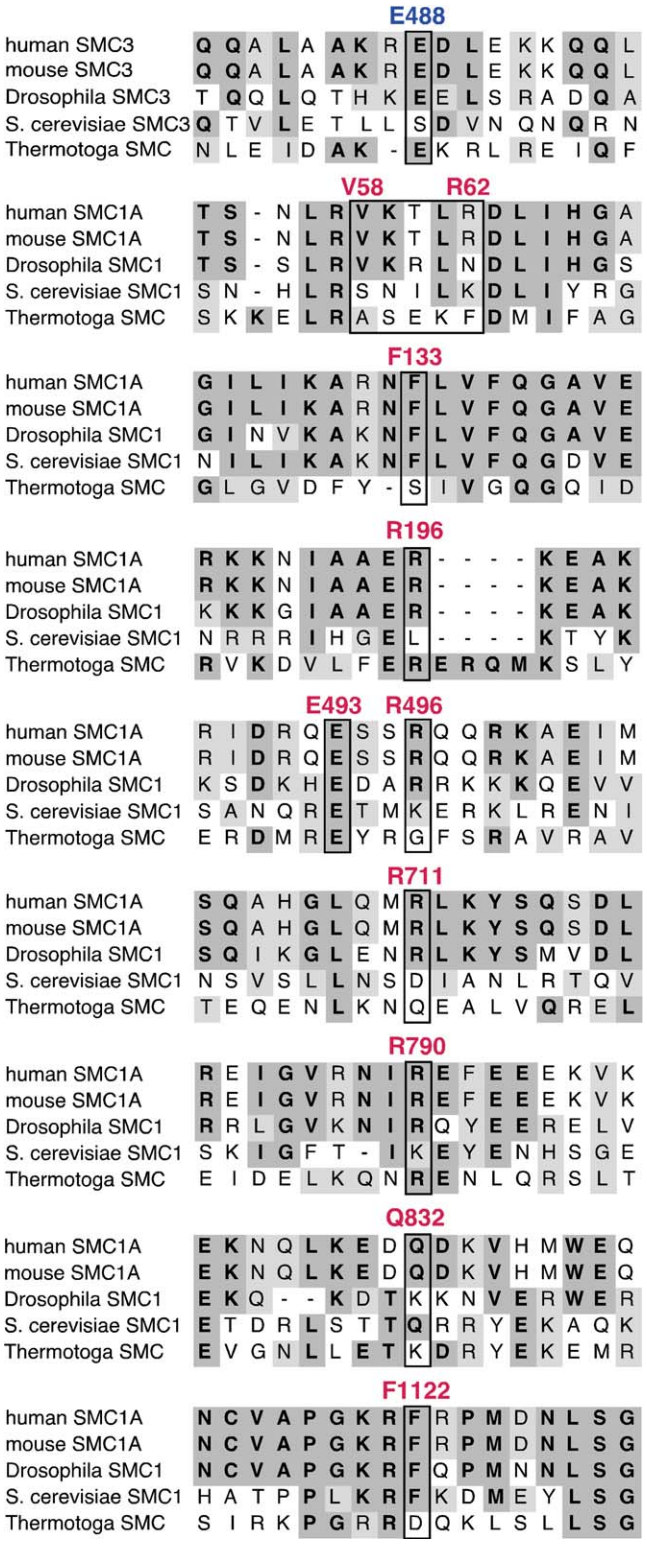

Figure 2. Conservation of SMC3 and SMC1A and location of mutations. Alignment of human, mouse, *Drosophila melanogaster, S. cerevisiae,* and *T. maritima* SMC3- and SMC1-related sequences. Identical residues are indicated in bold with dark shading. Similar residues are indicated in normal font with light shading. Amino acids for which human mutations have been identified are outlined by boxes, with the position indicated above.

SMC1A mutations, we capitalized on extensive previous SMC protein biochemistry, electron microscopy, and x-ray crystallography.[1,2] SMC proteins consist of globular N- and C-terminal domains that contain ATP-binding Walker A and Walker B motifs, respectively. These motifs are juxtaposed in the globular head domain of SMCs as a result of an intramolecular antiparallel coiled coil (figs. 3 and 4). A central domain of SMC1 (SMC1A in humans) forms a globular hinge domain that interacts with a similar motif of SMC3 to form a heterodimer. The C-terminal domains of SMC1 and SMC3 also contain ATP binding cassette (ABC) signature (or C) motifs. In addition to their interactions at the hinge domain, the globular head domains of SMC1 and SMC3 interact to complete two tripartite ATP-binding pockets formed by the Walker A and B motifs of one molecule and the signature/C motif of the other (figs. 3 and 4). It has been shown that ATP binding promotes association of the two intermolecular heads and that ATP hydrolysis drives them apart[22]; both events facilitate the ability of cohesin to encircle chromatin.

In figure 3, SMC3 and SMC1A mutations are mapped onto crystal data derived from the *Thermotoga* SMC hinge domain dimer[23] and a yeast Smc1 head domain dimer[24] (NCBI Protein Database). The SMC3 E488del and the SMC1A R496H, R496C, and E493A[8] mutations all map to the junction of the N-terminal coiled-coil and the hinge (fig. 3*A*). This region is remarkably conserved from bacteria to humans (fig. 2).

The process of loading the cohesin onto DNA is dependent on factors that include NIPBL (also known as "Scc2")[25,26] and the hydrolysis of ATP.[26,27] It has been shown that mutations of the *Bacillus* SMC hinge domain

Table 4. Features of *SMC3*- and *SMC1A*-Mutation–Positive Patients Compared with Classic CdLS

Time and Feature	Patients Positive for Mutation in		Percentage of Patients with Classic CdLS
	SMC1A	*SMC3*	
At birth:			
Normal weight	8/10	0/1	32
Normal length	6/7	0/1	50
Normal HC	3/6	NA	15
At later timepoint:			
Normal weight	6/12	0/1	15
Normal height	5/11	0/1	5
Normal HC	3/12	NA	<5
Prominent nose	5/12	1/1	NA
Limb deficiencies/reductions	0/13	0/1	33
Small hands	11/12	1/1	93
MR and/or developmental delay	12/12	1/1	100
Acquired speech	11/12	1/1	35

NOTE.—Complete clinical information was not available from all mutation-positive patients. The denominator in each cell indicates the number assessed for each feature. CdLS data on a 310-member cohort is taken from Kline et al.[20] and Jackson et al.[12] Growth percentages were determined from Centers for Disease Control and Prevention growth charts.[19] Normal growth parameters are defined as >3rd percentile for age and sex. HC = head circumference; MR = mental retardation; NA = not available.

Table 5. *SMC3* and *SMC1A* Polymorphisms Identified

Gene and Nucleotide Change	Amino Acid	Location	dbSNP	Alleles Identified[a]	Allele Frequency
SMC3:					
c.−99C→A	…	5′ UTR	…	5/192	.03
c.15+89_90insA	…	Intron 1	…	1/20	.05
c.91+67C→G	…	Intron 2	*rs11195194*	192/192	1.00
c.255A→G	p.S85S	Exon 5	…	2/192	.02
c.350+21T→A	…	Intron 6	*rs11195194*	21/192	.11
c.350+30T→G	…	Intron 6	*rs7914351*	11/192	.06
c.351−9T→C	…	Intron 6	…	14/192	.07
c.548−45A→C	…	Intron 8	*rs2275570*	28/192	.15
c.548−4_3insAA	…	Intron 8	…	20/192	.10
c.547+92A→G	…	Intron 8	*rs7911129*	3/20	.15
c.724−5_6insT	…	Intron 9	*rs11380915*	10/192	.05
c.724−206_201delTTGTAG	…	Intron 9	…	3/20	.15
c.805−26A→G	…	Intron 10	*rs11815960*	2/20	.10
c.969+23A→G	…	Intron 11	…	3/192	.02
c.970−8G→A	…	Intron 11	*rs11195199*	28/192	.15
c.1092−18T→C	…	Intron 12	*rs11195200*	22/190	.12
c.1306−81A→G	…	Intron 13	…	1/20	.05
c.1365T→C	p.Y455Y	Exon 14	…	11/192	.06
c.1409+6T→C	…	Intron 14	…	1/192	.01
c.1410−48T→C	…	Intron 14	*rs3737293*	14/192	.07
c.2116+23G→A	…	Intron 19	*rs7075340*	192/192	1.00
c.2428−92A→G	…	Intron 21	*rs3737292*	21/192	.11
c.2644+48A→G	…	Intron 23	*rs11195213*	25/192	.13
c.2892+23T→C	…	Intron 24	…	4/192	.02
c.3039A→G	p.S1013S	Exon 25	*rs17846396*	192/192	1.00
c.3582+51G→A	…	Intron 28	…	8/192	.04
c.3973G→A	…	3′ UTR	…	1/192	.01
SMC1A:					
c.−19C→T	…	5′ UTR	*rs1264011*	96/150	.64
c.1338−32A→C	…	Intron 8	*rs1264008*	7/145	.05

NOTE.—Numbering is based on *SMC3* and *SMC1A* cDNA sequences (RefSeq accession numbers NM_005445 and NM_006306, respectively), starting from the first nucleotide of the ORF. Nomenclature is according to den Dunnen and Antonarakis[21] and the Human Genome Variation Society Mutation Nomenclature Recommendations.

[a] The denominator indicates the total number of alleles screened.

disrupt both DNA binding[22] and ATP hydrolysis.[2] Thus, it is possible that SMC3 and SMC1A mutations at the boundary of the hinge domain disrupt DNA binding or ATP hydrolysis kinetics, leading to similar phenotypes as well as to those seen for some mutations in NIPBL. Three SMC1A mutations (V58_62del, F133V, and F1122L) occur in the head domain (fig. 3*B*) and are positioned near the Walker A, B, and signature/C motifs that could affect ATP binding, ATP hydrolysis, and/or SMC1/SMC3 head-domain dimerization, an ATP-dependent process.

The SMC1A mutations R196H, R711W, and R790Q and the familial D831_Q832delinsE mutation[8] all reside in the coiled-coil domain (fig. 4). By use of the Coils program,[28] which predicts the probability of a protein to form a coiled-coil, these mutations had a small likelihood of disrupting the coiled-coil arms. However, the alterations caused by these mutations may affect the angulation of the coiled-coil,[29] resulting in impaired intra- or intermolecular approximation of the SMC head domains, or disrupt binding of accessory proteins to the cohesin ring.

SMC1A mutations in females.—In contrast to previous work on *SMC1A*,[8] 10 of 14 total *SMC1A*-mutation–positive individuals were female. Furthermore, we describe similarly affected male and female probands, implying an X-linked dominant mode of expression. Interestingly, several males were rather mildly affected (4P and 6P) and no more severely affected than many of the *SMC1A*-mutation–positive females. Since *SMC1A* escapes X inactivation,[30] it is likely that the mechanism in affected females is due to a dominant negative effect of the altered protein and less likely that is is due to decreased protein levels[8] or skewed X inactivation. Consistent with this dominant negative effect on cohesin, the SMC3 mutation is also a single amino acid deletion.

The cohesin complex and mental retardation.—Of note, all the patients described here have disease in the mild-to-moderate range of CdLS and were ascertained as having mild facial features reminiscent of CdLS, but none has major structural anomalies typically seen in classic CdLS (table 4). However, without exception, all had varying degrees of mental retardation (fig. 1 and tables 3 and 4). Although the facial features in many of these individuals

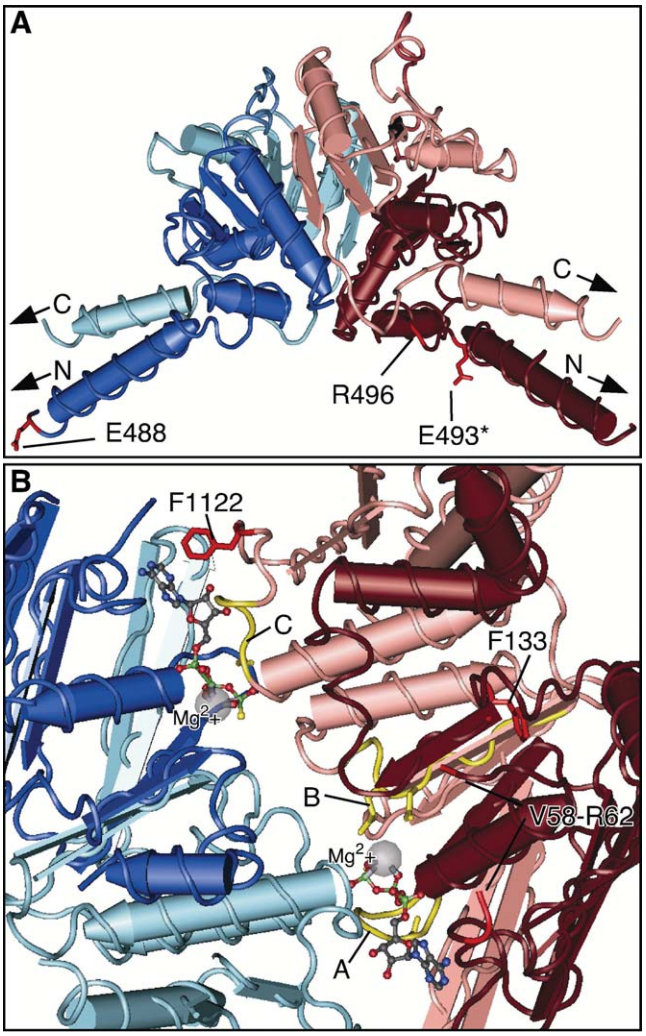

Figure 3. Mapping of SMC1A and SMC3 mutations to known SMC crystal structure data. *A,* Mutations in the hinge domain are represented on the *Thermotoga* SMC dimeric hinge crystal structure. Monomers are colored either red or blue. The darker red and blue regions indicate the N-terminal portions of each monomer. Arrows indicate the N- and C-termini, which are at the end of the coiled-coil domain nearest the hinge region. Mutated residues are shaded bright red. An asterisk (*) indicates the E493 altered residue reported by Musio et al.[8] The R496 residue in humans is a glycine in *Thermotoga* (see fig. 2). *B,* Mutations placed on the yeast SMC1 head domain dimer. These regions are key in the binding and hydrolysis of ATP, indicated by ball and stick molecules. Magnesium molecules at the active sites are indicated by gray balls. Three SMC1A mutations occur in the head domain—two in the N-terminus and one in the C-terminus. The V58_R62del overlaps a loop that is unstructured in the yeast SMC1 crystal structure but is positioned near the Walker A and B motifs (*yellow residues A and B*) and thus could affect ATP binding or hydrolysis. The F133V mutation is adjacent to the Walker B motif that contains a serine, which contacts ATP directly at the active site. The F1122L mutation is in the signature/C motif (*yellow residues C*) of the C-terminal head domain. It is positioned at the SMC1/SMC3 head-domain intermolecular interface adjoining the adenine ring of ATP. Structural analysis was performed with Cn3D (NCBI Structure Group).

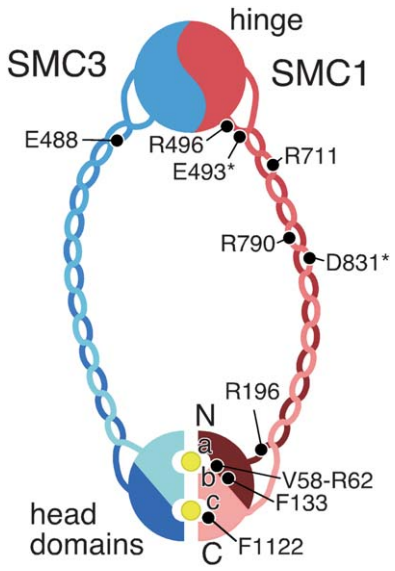

Figure 4. Schematic indicating the presumed organization of the SMC1/SMC3 heterodimer and the locations of SMC1A and SMC3 mutations on the cohesin ring. SMC1 is shaded red, and SMC3 is shaded blue, with darker red and blue regions indicating the N-terminal portions of each monomer. Yellow circles indicate ATP molecules bound in proximity to Walker A, B, and C motifs (a, b, and c, respectively). The N-and C-termini are indicated. Mutation locations are indicated by black circles. Altered residues reported by Musio et al.[8] are indicated by an asterisk (*).

may be appreciated by dysmorphologists experienced in this diagnosis, for the most part, they would present to clinical attention as individuals with mild-to-moderate mental retardation, often without the hallmark short stature and/or microcephaly of CdLS (table 4). This strongly suggests that brain development is the process most sensitive to perturbation of these proteins. The relatively small contribution of *SMC3* (~1%) and *SMC1A* (~5%) mutations in our study group may be the result of the selection bias of our study subjects, who were ascertained as having CdLS or CdLS-variant phenotypes. There may be a subset of individuals among the larger diagnostic category of mental retardation spectrum disorders with an apparently nonsyndromic etiology who may be carrying the bulk of mutations in cohesin pathway genes. Furthermore, additional "cohesinopathies" may result from perturbation of the >15 additional components of this complex that have yet to be associated with human disorders.

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Web Resources

Accession numbers and URLs for data presented herein are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for human SMC3 [accession number NM_005445] and human SMC1A [accession number NM_006306])

HUGO Gene Nomenclature Committee, http://www.gene.ucl.ac.uk/nomenclature/

Human Genome Variation Society Mutation Nomenclature Recommendations, http://www.hgvs.org/mutnomen/

NCBI Protein Database, http://www.ncbi.nlm.nih.gov/ (for struture coordinates for the *Thermotoga* SMC hinge domain [accession numbers 1GXLB and 1GXLA] and *S. cerevisiae* Smc1 head domain [accession numbers 1W1WA and 1W1WB])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CdLS)

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