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Investigation of Autistic Features Among Individuals With Mild to Moderate Cornelia de Lange Syndrome

Mariko Nakanishi^{1,*}, Matthew A. Deardorff², Dinah Clark², Susan E. Levy^{1,3}, Ian Krantz^{2,3}, and Mary Pipan^{1,3}

¹Division of Child Development, Rehabilitation, and Metabolic Disease, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

²Division of Human Genetics and Molecular Biology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

³University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Abstract

Cornelia de Lange syndrome (CdLS) is a congenital disorder characterized by distinctive facial features, growth retardation, limb abnormalities, intellectual disability, and behavioral problems. Autism has been reported to occur frequently in CdLS, but the frequency of autism in individuals with the milder CdLS phenotype is not well studied. We investigated autistic features by using a screening tool and a diagnostic interview in 49 individuals with the mild to moderate phenotype from a CdLS research database at the Children's Hospital of Philadelphia. The Social Communication Questionnaire (SCQ), a screening instrument for autistic disorder, was completed for all individuals. For individuals who screened positive and a subset of those that screened negative, the Autism Diagnostic Interview-Revised (ADI-R) was administered. Autistic symptom severity was not significantly different by gender, age groups, and genotypes. There was a significant correlation between higher levels of adaptive functioning and lower scores of autistic symptoms. The estimated prevalence of significant autistic features by ADI-R criteria was 43% in our cohort of individuals with the mild to moderate CdLS phenotype, which suggests that prevalence of autistic disorder may be higher than previously described among individuals with mild to moderate phenotype of CdLS. Clinicians who take care of individuals with CdLS should have a high index of suspicion for autistic features, and refer for further evaluation when these features are present in order to expedite appropriate intervention.

Keywords

Cornelia de Lange syndrome (CdLS); autism; behavioral phenotype; *NIPBL*; *SMC1A*; *SMC3*

INTRODUCTION

Cornelia de Lange syndrome (CdLS) is a multisystem genetic disorder characterized by facial dysmorphism, upper extremity malformations, growth and cognitive delays, and gastrointestinal abnormalities. Facial features include bushy arched eyebrows and synophrys, long, curly eyelashes, depressed nasal bridge with anteverted nares, thin upper lip with down turned corners of the mouth, and micrognathia. Since the identification of the

genetic etiology of CdLS, it has been appreciated that there is a wide range of severity in phenotypic features. The milder phenotype is characterized by a lower prevalence of major malformations, less distinctive facial features, and less significant psychomotor and growth delays [Ireland et al., 1993; Kline et al., 1993; Moeschler and Graham, 1993; Saul et al., 1993; Allanson et al., 1997; Selicorni et al., 2005].

The behavioral profile of CdLS includes self-injury, aggression, hyperactivity, hand posturing, and autistic behaviors [Barr et al., 1971; Johnson et al., 1976; Beck, 1987; Jackson et al., 1993]. Studies have estimated that autistic disorder occurs in 32–67% of individuals with CdLS, without differentiation of the severity of the CdLS phenotype [Bhuiyan et al., 2006; Basile et al., 2007; Oliver et al., 2008; Moss et al., 2008]. A few small studies of individuals with the mild to moderate CdLS phenotype suggest that autistic disorder may be less frequent in this group. For example, Berney et al. [1999] described behavioral characteristics using questionnaires in 9 individuals with CdLS who had borderline to mild intellectual disability (ID) and 40 individuals with moderate to profound ID. Autism was diagnosed in 11% of individuals in the borderline to mild ID group, and 42% in the severe ID group [Berney et al., 1999]. Bhuiyan et al. [2006] conducted diagnostic interviews to investigate autism diagnoses in 23 individuals with classic and 7 individuals with mild phenotype, and reported that 87% of individuals with the classic, and 14% of mild type met criteria for autism. Basile et al. studied 36 individuals with classic CdLS and 20 individuals with mild CdLS by direct observation of behavior using a behavioral rating scale. Autism was diagnosed in 36% of individuals with moderate to profound ID, and none with the normal to mild ID [Basile et al., 2007]. These studies are limited by the small sample of individuals with the mild to moderate phenotype.

In this article we report our findings on autistic features with data gathered through autism screening and diagnostic interview in the largest sample of individuals with mild to moderate CdLS examined to date. We also investigated whether the autistic symptoms were different among gender, age groups, levels of ID as measured by adaptive functioning, and known gene mutations causing CdLS (*NIPBL*, *SMC1A*, and *SMC3*) in individuals with an identified mutation.

Autistic features evaluated by the ADI-R include qualitative abnormalities in reciprocal social interaction, qualitative abnormalities in communication, and restricted, repetitive and stereotyped patterns of behavior. In order for an individual to meet ADI-R diagnostic criteria for autistic disorder, cut-off scores must be met in all three areas. Social and communication skills are foundational to learning, and thus when deficits are identified, they need to be specifically addressed in the child's educational programming.

METHODS

Subjects

Patients were identified from an existing cohort of patients and families enrolled in The CdLS Research Study. The CdLS Research Study enrolls sporadic and familial cases of CdLS referred to the Division of Human Genetics and Molecular Biology at The Children's Hospital of Philadelphia, and maintains the CdLS database of clinical and molecular information. The CdLS Foundation USA is a major source of referral to the CdLS Research Study. All subjects in the CdLS database were evaluated by geneticists experienced in the diagnosis and management of CdLS. The diagnosis of CdLS was confirmed clinically. Individuals were also included in the database if molecular testing revealed a mutation in one of the genes known to be associated with CdLS. Individuals were identified as having the mild or moderate CdLS phenotype based on the phenotypic classification proposed by Gillis et al. [2004]. Specifically the moderate phenotype was defined as individuals with not

more than two digits reduction on each hand, delays in initial motor developmental milestones more than 2 years, limited speech and communication, and growth 25th–75th centile on the standard growth curves for CdLS. Mild phenotype was defined as individuals with no limb reduction, less than 2 years delayed in initial motor developmental milestones, speech and communication present, and growth more than 75th centile on the standard growth curves for CdLS.

Mutation analyses were performed for consented individuals in the lab within the Division of Human Genetics and Molecular Biology at The Children's Hospital of Philadelphia. Genomic DNA was isolated from peripheral blood lymphocytes. All were screened for mutations in the 46 coding exons of *NIPBL*, as reported elsewhere [Gillis et al., 2004]. If no *NIPBL* mutations were identified, *SMC3* and *SMC1A* were analyzed by PCR amplification and direct sequencing of coding exons. Details of analyses were reported elsewhere [Deardorff et al., 2007].

One hundred twenty-two patients in the database were identified as having a mild to moderate CdLS phenotype and being at least 4 years of age. The CdLS Foundation USA provided updates of contact information of identified individuals. The families of potential subjects were invited to participate in the study by mail and 76 families consented to participation. All individuals enrolled in the study were enrolled under a protocol of informed consent approved by the Institutional Review Board of The Children's Hospital of Philadelphia.

Sixty-six families completed all three questionnaires. Thirteen individuals were excluded from further study because their adaptive skills were below 2 years of age. Four individuals who resided outside the United States or Canada were also excluded from further analysis for autism spectrum disorder. Table I summarizes age, gender, disability levels, and genotype of total and the evaluated participants.

Study Measures

Families of the individuals whose parents or caregivers consented to participation filled out the Vineland Adaptive Behavior Scales (VABS) to screen for adaptive functioning, and the Social Communication Questionnaire (SCQ) to screen for features of Autism Spectrum Disorder. The Vineland Adaptive Behavior Scales, Second Edition-Parent/Caregiver Rating Form (VABS) [Sparrow et al., 2005] was used to determine global adaptive abilities reported as the Adaptive Behavior Composite (ABC) Standard Score. Based on the ABC Standard Scores, individuals were classified as borderline/normal adaptive functioning, mild deficit, moderate deficit, severe deficit, and profound deficit. Individuals whose age equivalence on the Daily Living Skills domain of the VABS was less than 24 months old were not assessed further because the Social Communication Questionnaire (SCQ) and the Autism Diagnostic Interview are not considered valid for individuals functioning at less than a 2-year level.

The Social Communication Questionnaire—Lifetime Form (SCQ) consists of 40 items inquiring about socialization, communication, and atypical behaviors and it has been validated as a screening measure for ASD in individuals over age 4 years whose mental age exceeds 2.0 years. We used the recommended cut-off of 15, which has a sensitivity of 0.85 and a specificity of 0.75 for diagnosing ASD in individuals age 4–40 years [Berument et al., 1999; Eaves et al., 2006].

Individuals who screened positive for ASD by the SCQ and randomly selected individuals who screened negative were administered the Autism Diagnostic Interview-Revised (ADI-R). The ADI-R is a semi-structure interview designed to differentiate individuals with

autism from those without autism [Lord et al., 1994; Rutter et al., 2003]. It has been shown to have high sensitivity and specificity in identifying autism in varied groups including preschool children and children with developmental disabilities, although both sensitivity and specificity are lower in children with developmental ages less than 2 years [Lord et al., 1993, 1994; Cox et al., 1999; de Bildt et al., 2004; Ventola et al., 2006; Corsello et al., 2007; Gray et al., 2008; Papanikolaou et al., 2009]. The questions in the ADI-R focus on the three areas of behavior that are seen in autism spectrum disorders: qualitative impairments in social interaction, qualitative abnormalities in communication, and restricted, repetitive, and stereotyped patterns of behavior. Each question item is coded on a “0–3” scale, with “0” indicating the absence of the specific abnormality and “3” indicating an abnormality that interferes with daily life. Individuals are identified as qualifying for a diagnosis of autistic disorder based on the ADI-R criteria when scores are above the cut-off in all three domains of the diagnostic algorithm [Lord et al., 1994; Rutter et al., 2003].

Interviews were conducted by investigators trained in the administration and coding of the ADI-R, who were supervised by a psychologist who had established research reliability. Interviews were conducted either face to face or on the phone due to geographic constraints. All interviews were video or audio taped upon consent by individuals and families. Recorded materials from six interviews (17%) were reviewed and independently coded by another investigator, to assure valid administration of the ADI-R, and for inter-rater reliability. Inter-rater reliability was 89%. The percentage of individuals who met the ADI-R criteria of autistic disorder was calculated by totaling those in the sample who met the criteria for autism on the ADI-R. The ADI-R total scores were compared between genders, age groups, genotypes, and classification of adaptive functioning deficits by *T*-test. Correlation of ADI-R total scores to age and adaptive abilities was also calculated.

RESULTS

Table I summarizes gender, age, and genotype of the total participants, non-participants, and evaluated participants. There were no significant differences in gender, age, and genotype between participants and non-participants. Figure 1 summarizes the subject selection and the end results of those studied. Data from 49 of the 66 participants who completed questionnaires were screened and/or evaluated for autistic features.

Of the 49 evaluated participants, 24 individuals (49%) screened positive for autism with an SCQ score greater than 15. Caregivers of all 24 of these individuals were administered the ADI-R. The ADI-R scores were above cut-off diagnosis of autism in 17 of the 24 individuals (71%). Twenty-five of the 49 evaluated individuals (51%) screened negative for autism. Of these individuals, 12 were randomly selected to be administered the ADI-R and 4 of these 12 individuals (33%) met ADI-R criteria for autism. Thus, of the 49 individuals studied, 21 (43%) had ADI-R scores meeting criteria for a diagnosis of autism. The mean scores of the SCQ among screen negative individuals who received, and did not receive the ADI-R were 9.8 and 8.2 with a standard deviation of 3.2 and 3.5, respectively. Table II summarizes the mean ADI-R total scores by gender, age group, disability level, and genotypes. There was no significant difference in the percentages of individuals who met ADI-R cut-off for autistic disorder nor in ADI-R total scores between male and female genders. Pearson correlation analysis indicated no significant correlation between age and the ADI-R total scores ($r = 0.16$, $P = 0.364$; two-tailed). There was a statistically significant negative correlation between VABS ABC standard scores and the ADI-R total scores ($r = -0.43$, $P = 0.008$; two-tailed), indicating that individuals with lower adaptive functioning had higher autistic symptoms. Of the 10 individuals with the ABC standard scores above 70 (borderline to normal adaptive functioning), none met the ADI-R criteria of autism. In individuals with mild deficits in adaptive functioning (ABC standard score from 50 to 69),

50% met the ADI-R criteria of autistic disorder, which was not significantly different from 64% among those with moderate to severe range of impairment.

There was a trend of higher ADI-R total scores in individuals with a *NIPBL* mutation compared to individuals without an identified mutation, although it was not statistically significant. The adaptive functioning was significantly higher in the individuals without an identified mutation compared to individuals with a *NIPBL* mutation.

Findings of the ADI-R total and subscale scores in individuals with different mutation types are summarized in Table III. Scores of Individuals with *NIPBL* missense mutations, truncating mutations, *SMC1A* mutations, and no identified mutations were compared by one-way ANOVA. There were no significant differences in the ADI-R total and subscale scores between different genotypes. The individual with a mutation in *SMC3* was screened negative for autism by SCQ, and did not receive ADI-R.

DISCUSSION

The present study investigates the presence of autistic symptoms and their severity in relation to demographic factors, adaptive functioning, and genotype in 49 individuals with a mild to moderate clinical phenotype of CdLS. Our results suggest that in individuals with mild to moderate CdLS phenotype, and with mild to severe impairment in adaptive functioning, autistic disorder is likely to be a more common co-morbidity than previously recognized. This result in our cohort may be an underestimate due to the high false-negative rate of the SCQ screening in our study population. In a population with a high prevalence of autism, such as individuals with CdLS, screening tools such as the Social Communication Questionnaire may yield high false-negative results, and thus negative screening should not preclude further investigation for autism unless other examinations and observations are also negative for suspicion for autism. It is also important to reiterate that no individuals in our cohort with borderline to normal levels of functioning met the ADI-R criteria for autistic disorder.

There was no significant difference in severity of autistic behaviors measured as ADI-R total score between genders and age groups. There was a statistically significant negative correlation between VABS ABC standard scores and the ADI-R total, indicating that individuals with lower adaptive functioning had higher autistic symptoms. The trend of higher ADI-R total scores in individuals with *NIPBL* mutations compared to individuals without identified mutations could be explained by the significantly higher adaptive functioning levels in the latter population as indicated in Table II. Overall, we have found that autistic symptoms were not strictly related to genotype. However, it is notable that there was a higher incidence of individuals who met the ADI-R criteria for autistic disorder among individuals with missense *NIPBL* mutation as compared to individuals with truncating mutation as indicated in Table III. This should be tested further for statistical significance in a larger population.

A major limitation of our study was the use of the ADI-R without direct clinical assessment. Our study used the accepted ADI-R cut-off scores for autistic disorder as a guideline to determine clinical significance of autistic symptoms by caregiver's responses, and ADI-R total score to measure severity of autistic symptoms, but in order for formal diagnosis of autistic disorder to be made, additional direct clinical observation is necessary. The ADI-R is a diagnostic tool widely accepted in autism research, but does rely on parent report. There are a number of studies that have investigated the validity of the ADI-R. Sensitivity and specificity is good among individuals with mental ages greater than 2 years. Studies indicate that the ADI-R has sensitivity of 0.77–0.96, specificity of 0.63–0.92, positive predictive

value of 0.43–0.92, and negative predictive value of 0.69–0.96 in classifying autism or not autism [Lord et al., 1993, 1994, 1997; de Bildt et al., 2004; Corsello et al., 2007; Gray et al., 2008; Papanikolaou et al., 2009]. de Bildt et al. reported the lowest specificity and positive predictive value among individuals 5 years and above. In their study, specificity and positive predictive value was also low using the ADOS, and the ADI-R had better criterion-related validity compared with the clinical classification. Basile et al. performed a direct observation of the individual's behavior and used the Childhood Autism Rating Scale (CARS) as a diagnostic tool. Studies in young children indicate that the CARS is more inclusive in making a diagnosis of autism than the ADI-R [Lord, 1995; Saemundsen et al., 2003], and thus can result in a higher prevalence rate. Bhuiyan et al. used the Diagnostic Interview for Social and Communication Disorders schedule (DISCO). In one study, the agreement between the DISCO and the ADI-R was excellent, but the ADI-R diagnosed slightly more individuals than the DISCO [Nygren et al., 2009]. Future studies should consider using the ADI-R and a diagnostic observation tool such as the ADOS on all subjects.

Another limitation of the study relates to study recruitment. The source of this study's recruitment, The CdLS Research Study database, recruits patients from those individuals referred to the Children's Hospital of Philadelphia for genetic assessment as well as through the CdLS Foundation, USA. Thus our study cannot be considered a population based study, and likely over-represents families who have the resources and motivation to participate in genetic study and/or be involved in a national support group. Although participation in this study was high (62% enrolled and 54% completed), we cannot assume that it truly represents the database population of mild to moderately affected individuals. Recruitment bias on this level could lead to an overestimation of the prevalence of autistic features if parents and caregivers who were concerned about autism were more likely to want to participate. Although the study was presented as a study of behavioral phenotype, the investigation for autism was emphasized in the consent form. Recruitment bias could also lead to an underestimate of the prevalence of autistic features if parents of children with an already established diagnosis of autism saw little reason to participate, if parents viewed the diagnosis of autistic disorder as an additional burden which they would rather avoid, or if parents did not see a reason to identify autism above and beyond the already known disabilities.

The third limitation concerns the identification of mild to moderate phenotype. The subjects in The CdLS Research Study database all underwent rigorous clinical evaluation, either in person by a clinician with expertise in CdLS (I.D.K. or M.A.D.), or through a careful review of medical records with images, and proband determination of the clinical diagnosis and classification were made following established guidelines by Gillis et al. We were not able to use the most recent Scoring System for Severity in CdLS that was proposed in 2007 [Kline et al., 2007], because data collection and severity classification of many of the participants of the CdLS Research Study was done prior to the publication of this new scoring system. If the classification system proposed by Kline et al. had been used, more individuals in the database might have been classified as severe rather than moderate. We did exclude individuals whose daily living skills were at less than age equivalent of 2 years, which did not preclude individuals with severe cognitive impairment from participating. Using the Gillis et al. guidelines, 78% of the participants in our study were clinically classified as mild CdLS phenotype and 22% were clinically classified as moderate phenotype. The VABS ABC standard scores among participants classified as mild and moderate clinical phenotype were 64.9 (SD $\pm$ 18.2) and 44.8 (SD $\pm$ 24.0), respectively. Definition of milder phenotype varies across studies as do the measures of adaptive or cognitive function. The level of functioning in our study population was higher than the population of Bhuiyan study, which also used VABS to measure functional deficits. Among

tested individuals with mild functional deficits on VABS, we found a considerably higher rate of individuals who met the criteria for autism compared to Bhuiyan's study.

Lastly, this study did not include a control group of individuals with a matched level of functional impairment, and the investigators were not blinded for the diagnosis of CdLS. Future studies should consider inclusion of a control group. Many syndromes have been reported to have high prevalence of autistic features [Moss and Howlin, 2009]. Further systematic evaluation of cognitive, adaptive, and social emotional functioning should be undertaken to determine to what degree autism is a co-morbidity related to the specific genotype versus related to the cognitive impairment itself. Such studies may lead to a better understanding of the relationship between impaired cognition and autism, and provide valuable insights into the underlying molecular pathogenesis of autism.

In summary, this study suggests that autistic disorder may be more common in individuals with the mild to moderate CdLS phenotype than previously reported. This is the largest study to date that has investigated autistic features in a well-defined cohort of individuals with mild to moderate phenotype using a research validated measure. These data suggest that all individuals with CdLS should receive close monitoring of their social and communication development, and early referral for diagnostic evaluation and intervention. Early identification and intervention for social and communication deficits is necessary because of the foundational nature of socialization and communication for learning. Appropriate intervention with autistic support programming may help individuals with CdLS maximize their potential for learning, and minimize the maladaptive behaviors and social communication deficits that are so frequently a part of CdLS.

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ADI refers to the Autism Diagnostic Interview-Revised
 SCQ refers to the Social Communication Questionnaires score

FIG. 1.

Enrollment and results of the investigation for autism.

TABLE I

Summary of Total and Evaluated Participants

	Total participants (n = 66)	Evaluated participants (n = 49)	Non-participants (n = 56)
Gender			
Male	31 (47%)	23 (47%)	31 (55%)
Age			
Mean (range)	14.7 (4–44)	15.2 (4–44)	13.1 (4–39)
Genotype			
Total analyzed	53	38	46
<i>NIPBL</i>	30 (57%)	22 (58%)	29 (63%)
<i>SMC1A</i>	5 (9%)	3 (8%)	4 (9%)
<i>SMC3</i>	1 (2%)	1 (3%)	0
No mutation	17 (32%)	12 (32%)	13 (28%)
Not analyzed	13	11	10
VABS-ABC standard score			
Mean (range)	56 (20–101)	60 (20–101)	
Disability level			
71 or above	10 (15%)	10 (20%)	
51–70 (mild)	35 (53%)	28 (57%)	
36–50 (moderate)	9 (14%)	5 (10%)	
21–35 (severe)	3 (4.5%)	0 (0%)	
20 or less (profound)	9 (14%)	6 (12%)	

VABS-ABC, Vineland Adaptive Behavior Scale II Adaptive Behavior Composite.

TABLE II

The ADI-R and VABS Results in Stratified Groups

	n	ADI done	Autism (% of n)	ADI total, mean (SD)	P-value	VABS ABC, mean (SD)	P-value
Gender							
Male	23	15	11 (48%)	32 (12.5)	0.211	60 (18)	1.000
Female	26	21	10 (38%)	27 (11.0)		60 (21)	
Age							
4-12	26	23	11 (42%)	27 (11.2)	0.513	66 (8)	0.835
13-21	14	9	6 (43%)	31 (15.1)	0.862	67 (17)	0.000
22+	9	4	4 (44%)	32 (7.8)		32 (22)	
Disability level ^a							
Borderline/normal	10	6	0	17 (5.3)	0.023	82 (11)	
Mild	28	23	14 (50%)	29 (11.6)	0.125	64 (5)	
Moderate	4	3	3 (75%)	39 (10.6)	0.530	43 (3)	
Severe/profound	7	4	4 (57%)	34 (8.2)		20 (0)	
Genotype							
<i>NIPBL</i> mutation	22	14	10 (45%)	34 (12.3)	0.055	57 (18)	0.045
No mutation	12	9	4 (33%)	24 (8.8)		72 (21)	
<i>NIPBL</i> mutation type							
Missense	15	9	8 (53%)	35 (11.8)	0.558	58 (19)	0.881
Truncating	7	5	2 (29%)	31 (11.0)		57 (18)	

VABS-ABC, Vineland Adaptive Behavior Scale II Adaptive Behavior Composite; ADI, Autism Diagnostic Interview-Revised; SD, standard deviation.

^aDefinition of disability level as indicated in Table I.

Findings of the ADI-R by Mutation Types

TABLE III

Mutations	n	ADI-R scores, mean (SD)				ADI-R results		
		Total	Socialization	Communication	Stereotypic behavior	Autism	Not autism	Not done
<i>NIPBL</i>								
Missense	15	35 (12)	18 (8)	12 (5)	6 (2)	8	1	6
Truncating	7	31 (14)	14 (8)	13 (6)	4 (3)	2	3	2
<i>SMC1A</i>	3	29 (20)	15 (13)	9 (7)	4 (2)	2	1	0
<i>SMC3</i>	1	—	—	—	—	0	0	1
No mutations	12	24 (9)	12 (4)	9 (4)	3 (2)	4	5	3

ADI-R, Autism Diagnostic Interview-Revised; SD, standard deviation.