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Please use this reference when citing this work:

Moss, J., Oliver, C., Berg, K., Kaur, G., Jephcott, L and Cornish, K. (2008). Prevalence of autism spectrum phenomenology in Cornelia de Lange and Cri du Chat syndromes. *American Journal of Mental Retardation*, 113, 278-291.

Prevalence of Autism Spectrum Phenomenology in Cornelia de Lange and Cri du Chat Syndromes

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Abstract

Autism spectrum disorder characteristics have not been evaluated in Cornelia de Lange and Cri du Chat syndromes using robust assessments. The Autism Diagnostic Observation Schedule and Social Communication Questionnaire were administered to 34 participants with Cornelia de Lange syndrome and a comparison group of 23 participants with Cri du Chat syndrome (M ages 12.4 [$SD = 3.8$] and 10.3 years [$SD = 3.6$], respectively). Twenty-one participants with Cornelia de Lange syndrome (61.8%) scored above the autism cut-off on the Autism Diagnostic Observation Schedule compared to 9 with Cri du chat syndrome (39.2%). Prevalence of autism spectrum disorder characteristics is heightened in Cornelia de Lange syndrome. The profile of characteristics is atypical to that of idiopathic autism.

Autism spectrum phenomenology has been described in a growing list of genetically determined syndromes, including tuberous sclerosis, fragile X, Rett, Cohen, Williams, Down, and Angelman syndromes (Bailey et al., 1998; Cornish, Turk, & Levitas, 2007; Howlin, Karpf, & Turk, 2005; Kent, Evans, Paul, & Sharp, 1999; Mount, Charman, Hastings, Reilly, & Cass 2003; Trillingsgaard & Østergaard, 2004). Although the identification of autism spectrum disorder in individuals with genetic syndromes is clearly important, the value of this diagnosis alongside the identification of a genetic syndrome is contentious. (The term *autism spectrum disorder* is employed throughout the text to refer to all conditions classified by the *Diagnostic and Statistical Manual of Mental Disorders—DSM-IV-R* [American Psychiatric Association; 2006] within the category of pervasive developmental disorder. When referring to diagnostic cut-off scores in the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire, the terms *autism* and *autism spectrum disorder* will be used as appropriate.) Overlap between autism spectrum phenomenology and the impairments and behaviors associated with intellectual disability make it difficult to differentiate the precise etiology of these phenomena. The picture is further complicated by the fact that many genetic syndromes evidence a range of complex communication, behavioral, emotional, and physical difficulties that may mask or emulate aspects of autism spectrum disorder or may give rise to an atypical presentation of the triad of impairments. As a result of these difficulties, it is often the case that any specific autistic-like characteristics observed within a given syndrome group are considered to be part and parcel of the syndrome itself and the possibility of a dual diagnosis is not always considered, even

when it may be beneficial to the individual concerned to receive some additional specialist intervention.

We argue that from a pragmatic perspective, it is not necessarily the etiology of these characteristics that is important (i.e., whether they are determined by the presence of an additional autism spectrum disorder-like condition or one result of a specific genetic disorder), rather, it is the recognition that an individual may share characteristics with those who have autism spectrum disorder and, therefore, may benefit from similar educational and other interventions that is of importance. Thus, it is important to identify those syndromes in which a heightened probability of autistic-like impairments and behaviors is evident.

One syndrome in which a heightened prevalence of autism spectrum disorder characteristics has been indicated is Cornelia de Lange syndrome, which is caused by a deletion in the NIPBL gene on chromosome 5 (locus 5p13) in 20% to 50% of cases (Gillis et al., 2004; Krantz et al., 2004; Miyake et al., 2005; Tonkin, Wang, Lisgo, Bamshad, & Strachan, 2004). Additional mutations on the SMC3 gene on chromosome 10 (Deardorff et al., 2007) and X linked SMC1 gene (Musio et al., 2006) are reported to account for 5% of cases. Cornelia de Lange syndrome is characterized by developmental delay, delayed growth, distinctive facial features, and limb abnormalities (Jackson, Kline, Barr, & Koch, 1993). A number of behavioral characteristics are also considered to be associated with Cornelia de Lange syndrome, including self-injurious and compulsive behaviors, aggression, hyperactivity, and an expressive–receptive language discrepancy (Arron et al., 2005; Berney, Ireland, & Burn, 1999; Gaultieri, 1991; Goodban, 1993; Hyman, Oliver, & Hall, 2002).

Early studies of Cornelia de Lange syndrome largely focused on describing self-injurious behavior. However, the association between Cornelia de Lange syndrome and autism spectrum disorder has recently received more attention. Berney et al. (1999) reported that 53% of 49 individuals with Cornelia de Lange syndrome demonstrated the triad of impairments diagnostic of autism spectrum disorder. For 37% of individuals, this triad was "pronounced." In a recent study by Oliver et al. (2005), those with Cornelia de Lange syndrome were found to score significantly higher on the Autism Screening Questionnaire (Berument, Rutter, Lord, Pickles, & Bailey) than did individuals with Cri du Chat and Prader-Willi syndromes. Also notable was the finding that the mean score of individuals with Cornelia de Lange syndrome was comparable with that of a group of individuals with fragile X syndrome.

Using the Diagnostic Interview for Social and Communication Disorders (Wing, Leekman, Libby, Gould, & Larcombe, 2002), Bhyuian et al. (2006) reported that 66.6% of 36 individuals with Cornelia de Lange syndrome scored above cut-off for a diagnosis of autism. Furthermore, 61.1% of participants scored above the diagnostic cut-off for autism on the Autism-Algorithm Scale of the Developmental Behavior Checklist (Einfeld & Tonge, 1995). Similar prevalence figures are reported by Basile, Villa, Selicorni, and Molteni (2007). Using the Childhood Autism Rating Scale (Schopler & Renner, 1988), Basile et al. reported that 28 out of 56 participants with Cornelia de Lange syndrome (50%) showed a combination of impaired sociability, communication deficits, and repetitive behaviors, although this profile was only demonstrated for those individuals with moderate to profound intellectual disability, suggesting that degree of disability may play a role. However, Oliver, Arron, Sloneem, and Hall (2007) reported that 32.1% of 54 individuals with Cornelia

de Lange syndrome scored within the severe autism category of the Childhood Autism Rating Scale compared to only 7.1% of a matched control group of individuals with intellectual disability due to other causes, suggesting that the relationship between Cornelia de Lange syndrome and autism spectrum disorder is not solely accounted for by associated degree of disability. Further detailed study of early social interaction skills has demonstrated that poor social relatedness may be highly characteristic of Cornelia de Lange syndrome, although some heterogeneity may be present. Specifically, poor eye contact in the first year of life was found to be predictive of social relatedness in later years (Sarimski, 2007).

In all of the studies described above, the evidence points towards a strong association between autism spectrum disorder-like characteristics and Cornelia de Lange syndrome. However, it is important to note that, to date, the relationship between these two disorders has largely been considered at the diagnostic level. Lessons from the fragile X and Rett syndromes literature highlight the need to be cautious when basing conclusions of the status of this relationship purely on diagnostic level data. In both of these groups, the prevalence of autism spectrum disorder was initially considered to be high, whereas subsequent study has revealed a somewhat milder and atypical profile of behaviors and impairments than that which is characteristic of idiopathic autism spectrum disorder. Furthermore, this detailed level of analysis has enabled identification of other associated behavioral characteristics that may be important in understanding the syndromes and the relationship with autism spectrum disorder; for example, the presence of social anxiety in fragile X syndrome (see Dykens, Hodapp, & Finucane, 2000; Volkmar, Lord, Bailey, Schultz, & Klin, 2004). Investigation at the behavioral level is of utmost importance to provide a more valid interpretation, given the notion of a spectrum for

autism. Additionally, the use of standardized autism-specific assessments and appropriate comparison groups are needed to provide greater insight into this relationship.

According to Hodapp and Dykens (2001), making comparisons across syndrome groups provides the opportunity for a more detailed understanding of behavioral phenotypes and is far more insightful than single group study. Individuals who have Cri du Chat syndrome share several characteristics with Cornelia de Lange syndrome in regard to associated degree of disability, level of receptive and expressive language skills, and expressive–receptive discrepancies (Cornish & Bramble, 2002; Cornish, Bramble, Munir, & Pigram 1999; Cornish & Munir, 1998; Neibhur, 1978). The range of shared characteristics between these two syndromes make them well-suited for comparison, as has shown in an earlier study (Sarimski, 1999).

Cri du Chat syndrome is caused by a deletion on the short arm of chromosome 5 (5p15; Goddhart et al., 1994; Neibhur, 1978; Overhauser et al., 1994). Occurring in approximately 1 in 50,000 births, this syndrome is associated with severe and profound intellectual disability (Cornish et al., 1999) and characterized by significant impairments in expressive language skills, with receptive language being less impaired (Cornish & Munir, 1998; Cornish et al., 1999). Behavioral characteristics associated with the syndrome include hyperactivity and self-injurious, aggressive, and stereotyped behavior (Collins & Cornish, 2002). In particular, attachment to objects and sensitivity to sensory stimuli are highly prevalent (Cornish & Pigram, 1996; Moss et al., 2005). Verbal communication skills are delayed (Cornish & Munir, 1998; Cornish et al., 1999), which is thought to be accounted for by congenital abnormalities of the larynx and poor motor skills

(Neihbur, 1979; Sohner & Mitchell, 1991). Nonverbal communication skills and social interaction skills are reported to be a relative strength associated with this syndrome (Cornish & Pigram, 1996; Cornish et al., 1998; Dykens et al., 2000; Sarimski, 2002). To date, there are no published studies in which researchers have specifically investigated the prevalence of autism spectrum disorder characteristics in Cri du Chat syndrome. However, the behavioral profile associated with this syndrome does not suggest that autism spectrum disorder characteristics are likely to be particularly prominent.

In this study we employed two standardized assessments of autism spectrum disorder characteristics with two groups: individuals with Cornelia de Lange syndrome and a comparison group of individuals with Cri du Chat syndrome. The Autism Diagnostic Observation Schedule (Lord, Rutter, DiLavore, & Risi, 2000) allows for direct observation of autism spectrum disorder characteristics; the Social Communication Questionnaire (Rutter et al., 2003) is an informant measure of autism spectrum disorder. By using two standardized autism specific assessments and a well-matched comparison group, our aim was to establish the prevalence and phenomenology of autism spectrum disorder in Cornelia de Lange syndrome in comparison with that seen in an appropriately matched group.

<--heading 1-->**Method**<!--end heading 1-->

<!--heading 2 -->*Participants*<!--end heading 2-->

We contacted 86 individuals with Cornelia de Lange syndrome who had been involved in previous studies. We asked the Cri du Chat Syndrome Support Group in the United Kingdom to help us recruit individuals with Cri du Chat syndrome. Families attending one of three national conferences held by either the Cri du Chat Syndrome

Support Group or the Cornelia de Lange Syndrome Foundation (United Kingdom and Ireland) were also invited to participate. Criteria for inclusion were as follows:

individuals were between 5 and 19 years of age, had a confirmed diagnosis from a pediatrician or clinical geneticist, had no other known genetic abnormality, and lived within traveling distance from the research base. All individuals received a cover letter and an information sheet. Further information, a consent form, and questionnaire pack were sent to those who expressed interest in the study.

Of those contacted, 35 (40.7%) individuals with Cornelia de Lange syndrome and 25 (46.3%) with Cri du Chat syndrome agreed to participate. Three participants (1 with Cornelia de Lange syndrome, 2 with Cri du Chat syndrome) were later excluded from the analyses due to additional or questionable diagnoses. Table 1 presents the characteristics of the remaining participants. Statistical comparison of the groups showed that the Cornelia de Lange syndrome group were significantly older than the Cri du Chat syndrome group, $t(55) = 2.2, p = .04$. No other significant differences were identified. However, the difference in *SDs* on age equivalence scores of the Vineland Adaptive Behavior Scale indicates that although not significantly different, the two groups do differ with regard to degree of disability. In particular, there is far more heterogeneity of degree of disability within the Cornelia de Lange syndrome group. This heterogeneity in degree of difficulty was, therefore, taken into consideration during analyses.

+++++++ Insert table 1 about here+++++++

<!--heading 2 -->*Measures*<!--end heading 2-->

Demographic questionnaire. The demographic questionnaire provided information regarding chronological age (CA), gender, mobility (able to walk unaided), verbal ability (more than 30 signs/words) and diagnostic status (the precise diagnosis made, when and by whom it was given).

Autism Diagnostic Observation Schedule. The Autism Diagnostic Observation Schedule (Lord et al., 2000) is a semi-structured, standardized observational assessment of communication and social interaction skills, play and imaginative skills, and repetitive behavior. The assessment is suitable for individuals with a range of developmental abilities, CAs, and expressive language skills. The assessment incorporates the use of clear, planned social "presses" (social demands) that provide the optimum opportunity for the participant to display certain behaviors or responses. The presence/absence and nature of these behaviors and responses are recorded. The assessment consists of four modules, each of which can be administered in 20 to 40 minutes. Selection of a particular module is based on the individual's expressive language skills. Module 1 is selected for individuals with no speech or simple phrases only; Module 2, for individuals with flexible three-word phrases; Module 3, for young children/adolescents who are verbally fluent; and Module 4, for adolescents or adults who are verbally fluent. Although each module has its own protocol, scores on individual items in all of them range from 0 to 3, where a higher score indicates a greater level of impairment. For diagnostic purposes, we converted scores of 3 to 2 for the domain and algorithm scores. Each module provides four domain scores: Communication, Social Interaction, Imaginative Play/Imagination/Creativity, and Repetitive Behavior. Only the Communication and Social Interaction domains are included in the diagnostic algorithm. These two domains are combined to create a total algorithm score. Although not considered to

be the most optimum measure of repetitive behavior, We also assessed scores on the Repetitive Behavior domain because repetitive behaviors are a core diagnostic characteristic. On Modules 1 and 2, the total possible score on the Communication, Social Interaction, and Repetitive Behavior domains is 10, 14, and 6, respectively. For Modules 3 and 4, the total possible score on the Communication, Social Interaction, and Repetitive Behavior domains is 8, 14, and 8.

Sensitivity, specificity, and interrater reliability are reported to be robust (Lord et al., 2000). Concurrent validity between the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview and between the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire is good, $r_s = .57$ and $.55$, respectively, $p_s = .001$, is good (Howlin & Karpf, 2004; Rutter et al., 2003).

Social and Communication Questionnaire. The Social Communication Questionnaire (Rutter et al., 2003) is a 40-item informant assessment that screens for the behaviors and characteristics associated with autism spectrum disorder. There are three subscales: Social Interaction, Communication, and Repetitive Behavior. The current version of this questionnaire is completed with reference to the individual's behavior during the preceding 3-month period. All items require a yes/no response. A score of 1 is given for the presence of abnormal behavior and 0 for its absence. Total scores range from 0 to 39 (the item on current language level is not included in the summary score); the maximum possible score on the Communication, Social Interaction, and Repetitive Behavior domains are 12, 15, and 8, respectively. Rutter et al. suggested a cut-off of 15 for autism spectrum disorder and 22 for autism. Sensitivity and specificity are reported to be good for both scores (Berument et al., 1999). Concurrent validity with the Autism Diagnostic Interview–Revised (Rutter, LeCouteur, & Lord, 2003) is good for domain score (Bishop & Norbury, 2002).

Internal consistency and concurrent validity with the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview are also good (Howlin & Karpf, 2004).

Vineland Adaptive Behavior Scale–Survey Form. The survey form of the VABS (Sparrow, Balla, & Cicchetti, 1984) is a semi-structured interview designed to assess adaptive behavior for use with individuals up to the age of 18 years. The interview is conducted using open-ended questions regarding what the individual "usually" does. Items comprise four domains: Communication Skills, Daily Living Skills, Socialization Skills, and Motor Skills, and there is an overall Adaptive Behavior Composite (ABC). Standard scores and age equivalence scores, derived from a sample 3,000 children, can be calculated for each domain and ABC score. A severity classification (borderline, mild, moderate, severe, and profound) can be determined from the ABC score. Interrater, test–retest reliability, construct validity, content validity, and criterion-related validity are robust.

British Picture Vocabulary Scale–2nd ed. The BPVS (Dunn, Dunn, Whetton, & Burley, 1997) is used to assess receptive vocabulary for Standard English. Each item has four simple black and white pictures. The participant is asked to select the picture considered to illustrate the best meaning of a stimulus word presented orally by the examiner. Split-half reliability and internal consistency are good.

<!--heading 2 -->*Procedure*<!--end heading 2-->

The VABS was administered to the primary caregiver either by telephone interview or face to face. Following this interview, we visited the participant at their school/ day center. Three participants were visited at home because of the constraints of school holidays. One participant was visited at home due to absence from school or college. All data were collected within a 12-week window of

completion of the questionnaires. All Autism Diagnostic Observation Schedule assessments were conducted in a quiet, distraction-free room and were videorecorded with a Sony TRV-48E video camera. We scored assessments immediately after administration of the measure, using a combination of live and videorecorded observations.

<!--heading 2 -->Reliability and Validity<!--end heading 2-->

Interrater reliability. Using video recordings of the assessments, we established interrater reliability for the Autism Diagnostic Observation Schedule standard codes for 16 (28.07%) randomly selected participants using video recordings of the assessments. Two trained raters coded the videorecorded assessments independently. Intraclass correlations between raters ranged from .61 to .80 for domain and total score of the assessment. Kappa coefficients for diagnostic cut-off scores for autism on the social interaction domain and total score were adequate (.56 and .50, respectively) but low for the communication domain cut-off score (.26), suggesting that caution should be exercised when interpreting the diagnostic cut-off data.

Concurrent validity. Concurrent validity between the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire was established for the total sample at total and domain/subscale scores and diagnostic cut-off levels. Intraclass correlation coefficients ranged from .37 to .53. Kappa coefficients for diagnostic cut-off scores for autism and autism spectrum disorder on total score were .27 and .24, respectively. Twenty-two participants (38.6%) scored above the cut-off for autism on the Autism Diagnostic Observation Schedule but did not reach cut-off on the Social Communication Questionnaire. Twenty-four participants (42.1%)

scored above the cut-off for autism spectrum disorder on the Autism Diagnostic Observation Schedule but did not reach cut-off on the Social Communication Questionnaire. This is consistent with previous studies in which researchers employed both the Social Communication Questionnaire and the Autism Diagnostic Observation Schedule (Howlin et al., 2005; Howlin & Karpf, 2002), suggesting that the threshold for diagnosis on the Autism Diagnostic Observation Schedule is lower than that on the Social Communication Questionnaire.

<!--heading 2 -->*Data Analysis*<!--end heading 2-->

We conducted data analysis of autism phenomenology at three levels: algorithm cut-off score, domain and total score levels of the Autism Diagnostic Observation Schedule, and the Social Communication Questionnaire. We employed a between-groups approach to identify differences regarding scores at each level of analysis. Although the Repetitive Behavior domain of the Autism Diagnostic Observation Schedule does not contribute to the algorithm, the presence of repetitive behavior is a key diagnostic characteristic of autism spectrum disorder. Thus, scores on this domain were included in the analyses.

We conducted chi-square tests (or Fisher's Exact where appropriate) where data were categorical and *t* tests to assess the difference between the Cornelia de Lange syndrome and Cri du Chat syndrome groups on domain/subscale and total scores on the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire. Where significant differences were identified, we employed two strategies to investigate the role of degree of disability on the identified difference. First, one-way ANOVAs were conducted controlling for ABC age equivalence scores. (The participants in the Cornelia de Lange syndrome group were

significantly older than those in the Cri du Chat syndrome group; CA was not employed as a covariate in this analysis because this variable was not significantly related to scores on the Social Communication Questionnaire and Autism Diagnostic Observation Schedule domain/subscale and total score levels: Pearson correlation coefficients ranged from $-.07$ to $.25$.) Second, we repeated t tests excluding participants with profound intellectual disability from the samples.

Bonferroni corrected alpha levels were employed for comparisons at domain/subscale level, $p < .025$. For comparisons at total score level and for post hoc analyses, we considered a p value of less than $.05$ as significant.

<--heading 1-->**Results**<!--end heading 1-->

<!--heading 2 -->*Diagnostic Cut-Off Score Analysis*<!--end heading 2-->

Table 2 shows the percentage and number of participants scoring above the cut-off for autism and autism spectrum disorder at domain and total score levels on the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire. A significantly greater proportion of participants with Cornelia de Lange syndrome scored above the cut-off score for autism and autism spectrum disorder on the Social Communication Questionnaire compared to the Cri du Chat syndrome group. No significant differences between the two groups were identified on the domain or total algorithm cut-off scores of the Autism Diagnostic Observation Schedule. However, the difference on the Communication domain approached significance, $p = .05$.

+++++++Insert Table 2 about here:+++++++

<!--heading 2 -->Domain/Subscale and Total Score Analysis<!--end heading 2-->

Autism Diagnostic Observation Schedule. Figure 1 presents the mean scores, SDs, and *t* test analyses at domain and total score levels on the Autism Diagnostic Observation Schedule. The Cornelia de Lange syndrome group scored significantly higher than the Cri du Chat syndrome group on the Communication domain, $t(1, 55) = 2.59$; $p = .012$. This difference remained significant when ABC age equivalence was employed as a covariate, $F(1, 54) = 10.52$, $p = .001$, and when individuals with profound intellectual disability were removed from the analysis, $t(1, 43) = 2.26$, $p = .029$. No other significant differences were found.

There is a possibility that differences in the way in which items contribute to the algorithm scores across different Autism Diagnostic Observation Schedule modules could affect these findings. In particular, the fact that the total possible score available on Modules 1 and 2 is different than that in Modules 3 and 4 is problematic. Consequently, we repeated comparisons between the Cornelia de Lange syndrome and Cri du Chat syndrome groups on domain and total scores of the Autism Diagnostic Observation Schedule, removing those participants that had taken part in either a Module 3 or a Module 4 assessment from the sample. Using this subsample, we found that the Cornelia de Lange syndrome group scored significantly higher on the Communication domain, $t(1, 46) = 3.38$, $p = .001$, and on the total score, $t(1, 46) = 2.53$, $p = .015$.

<!--heading 2 -->Social Communication Questionnaire<!--end heading 2-->

Figure 2 presents the mean scores and SDs at subscale and total score levels. The Cornelia de Lange syndrome group scored significantly higher than the Cri du Chat syndrome group on the total score, $t(1, 55) = 2.46$, $p = .017$,

Communication subscale, $t(1, 55) = 3.65, p = .001$, and Social Interaction subscale, $t(1, 55) = 2.44, p = .018$. The difference identified on the Communication subscale remained significant when ABC age equivalence was employed as a covariate, $F(1, 54) = 16.42, p < .001$, and when participants with profound intellectual disability were excluded from the analysis, $t(1, 43) = 2.97, p = .005$. The differences identified on the Social Interaction subscale and total score remained significant when ABC age equivalence was employed as a covariate, $F_s(1, 54) = 15.97$ and 13.78 , respectively, $p_s < .001$. These differences did not remain significant when participants with profound intellectual disability were excluded from the analyses.

<--heading 1-->**Discussion**<!--end heading 1-->

In this study, we detail the results of the first assessment of the prevalence and phenomenology of autism spectrum disorder characteristics in Cornelia de Lange and Cri du Chat syndromes using two standardized assessments; the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire. Initial comparisons indicated that the two participant groups did not differ with regard to gender, ABC, and receptive language age equivalence scores. Individuals in the Cornelia de Lange syndrome group were significantly older than those in the Cri du Chat syndrome group, although this was only a difference of 2 years.

<--heading 1-->*Prevalence of Autism Spectrum Disorder in Cornelia de Lange and Cri du Chat Syndromes*<!--end heading 2-->

A significantly greater number of individuals with Cornelia de Lange syndrome met criteria for autism according to the Social Communication Questionnaire. Eight participants (23.5%) with Cornelia de Lange syndrome scored above the cut-off for

autism whereas none of the Cri du Chat syndrome participants scored at this level on this assessment. Fourteen participants with Cornelia de Lange syndrome scored above the cut-off for autism spectrum disorder on the Social Communication Questionnaire compared with only 2 participants with Cri du Chat syndrome. On the Autism Diagnostic Observation Schedule, 21 participants (61.8%) with Cornelia de Lange syndrome scored above the algorithm cut-off for autism compared with 9 (39.2%) participants with Cri du Chat syndrome. Twenty-five (73.5%) participants with Cornelia de Lange syndrome scored above the less conservative cut-off for autism spectrum disorder on this assessment compared to 14 (60.8%) participants with Cri du Chat syndrome. These differences did not reach significance. As discussed above, there is a possibility that differences in the way in which items contribute to the algorithm scores across the different Autism Diagnostic Observation Schedule modules could affect these findings. No differences were identified on the Social Interaction domain or the Repetitive Behavior domain. However, comparison of domain scores excluding individuals assessed on Modules 3 or 4 largely reflected the results reported for the group as whole (inclusive of Modules 3 and 4). The difference identified in the Communication domain was enhanced with the removal of Modules 3 and 4, and although the difference on the total score was not identified when these modules were included in the analysis, this discrepancy is likely to be accounted for by the enhanced difference on the Communication domain. Given these findings, it is clear that the capacity for a participant to achieve a higher or lower score on a given module is unlikely to account for the differences in scores on the Autism Diagnostic Observation Schedule observed between the groups in the present study.

Overall, and in line with previous studies, the findings suggest that the prevalence of autism spectrum disorder characteristics is heightened in Cornelia de Lange syndrome (Basile et al., 2007; Berney et al., 1999; Bhuyian et al., 2006; Oliver et al., 2007). Although this is the first study in which prevalence of autism spectrum disorder in Cri du Chat syndrome was formally assessed, the findings are consistent with descriptions in the literature indicating that an autism spectrum disorder-like profile is unlikely to be associated with the syndrome. However, the question of prevalence of autism spectrum disorder in a given syndrome may be far more complex than can be considered using algorithm cut-off scores. Our own reliability analyses identified only moderate to poor reliability at this level of classification (see *Reliability* section above). Furthermore, the discrepancy between the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire with regard to the number of participants reaching autism spectrum disorder and autism cut-off scores suggests that these may not provide a valid indication of the number of individuals with Cornelia de Lange and Cri du Chat syndromes who meet autism spectrum disorder criteria. The use of the Autism Diagnostic Observation Schedule and Social Communication Questionnaire alone cannot replace expert clinical diagnosis of autism spectrum disorder and, therefore, cannot be relied upon to provide clear-cut diagnostic information. Identifying the nature and profile of autism spectrum disorder phenomenology at a more detailed level may prove to be more insightful of the relationship between autism spectrum disorder and Cornelia de Lange and Cri du Chat syndromes.

The importance of conducting fine-grained analysis of autism spectrum disorder characteristics beyond the level of algorithm classification in genetic syndrome groups has been well illustrated in the fragile X and Rett syndromes

literature. These examples are reminders of the need to remain cautious about interpreting data at the level of algorithm cut-off scores and of the importance of considering autism spectrum disorder phenomenology in greater detail prior to drawing conclusions regarding the significance of this relationship within a given syndrome group.

<!--heading 2 -->*Phenomenology of Autism Spectrum Characteristics in Cornelia de Lange and Cri du Chat Syndromes*<!--end heading 2-->

Analyses at domain/subscale level on both the Autism Diagnostic Observation Schedule and the Social Communication Questionnaire demonstrated that autism spectrum disorder-like impairments in communication skills were far more prominent in the Cornelia de Lange syndrome group than in the Cri du Chat syndrome group. Moreover, this difference remained significant when degree of disability and adaptive behavior skills were accounted for. These findings indicate that it is unlikely that degree of disability and adaptive behavior skills alone are unlikely to explain the heightened prevalence of autism spectrum disorder phenomenology in Cornelia de Lange syndrome.

Communication difficulties have been reported in the literature on both syndromes considered in this study. Individuals with both conditions have been reported to evidence delayed development and discrepant receptive and expressive language skills (Cornish & Munir, 1998; Cornish et al., 1999; Goodban, 1993). The fact that there are clearly some global deficits in communication that are common to both groups adds weight to the argument that the impairments identified in the Cornelia de Lange syndrome group are likely to be autism spectrum disorder-related characteristics that occur over and above these global deficits. A comparison of the

nature of communication impairments in Cornelia de Lange syndrome and individuals with autism spectrum disorder of similar intellectual ability would be helpful in further establishing the specific areas of similarity and difference in this area.

With regard to impairments in social interaction, the findings are less clear-cut. One should consider that the subscales on the Social Communication Questionnaire are not as well-defined as those on the Autism Diagnostic Observation Schedule. The Cornelia de Lange syndrome group scored significantly higher than the Cri du Chat syndrome group on the Social Interaction subscale of the Social Communication Questionnaire. Although this difference remained significant when adaptive behavior skills were accounted for, it was not replicated in scores on the Autism Diagnostic Observation Schedule nor was it identified when individuals classified as having profound intellectual disability were removed from the analyses. It may be the case that the apparent discrepancy between the two assessments reflects differences in the sensitivity of the assessments to distinguish autism spectrum disorder characteristics at this level of disability. However, it is important to note that 24 individuals with Cornelia de Lange syndrome (70.6%) scored above the algorithm cut-off for autism on the Social Interaction domain of the Autism Diagnostic Observation Schedule compared to only 11 individuals (47.8%) with Cri du Chat syndrome. Although not reaching statistical significance, the difference between the two groups is substantial, indicating that social interaction is likely to be impaired to a greater degree in individuals with Cornelia de Lange syndrome.

Anecdotal evidence also supports this finding. Four out of 34 participants with Cornelia de Lange syndrome did not produce any spoken language throughout the assessment session, despite the fact that they were reportedly able to use at least three-word phrase language. Interestingly, one of these individuals did use Makaton

signs in place of spoken language. An additional 3 participants with Cornelia de Lange syndrome produced comparatively less spoken language than they were reportedly capable of and were extremely shy and reluctant to use their communication skills. These participants did not produce any spontaneous offering of information and produced spoken language only in response to the communicative demands made by examiner. Furthermore, the examiner was required to prompt the participants several times before a response was forthcoming. Finally, 2 additional participants were extremely shy and reluctant to use spoken language in the initial stages of the assessment, but this became less evident towards the end of the session. These observations are consistent with reports that individuals with Cornelia de Lange syndrome are shy, quiet, and reluctant to use their communication skills for social interaction (Goodban, 1993; Johnson, Ekman, Freisen, Nyhan, & Shear, 1976). This description bears some similarity to the profile of social anxiety and extreme shyness described in fragile X syndrome (Dykens & Volkmar, 1997). Thus, although social interaction skills are impaired in Cornelia de Lange syndrome, these impairments may not be typical of the social impairments observed in idiopathic autism spectrum disorder.

The observations of social anxiety related behaviors and extreme shyness in Cornelia de Lange syndrome were not identified empirically in either the Autism Diagnostic Observation Schedule or the Social Communication Questionnaire. Perhaps these assessments were not sensitive enough to identify these subtle social impairments in Cornelia de Lange syndrome. Alternatively, some of these deficits may have been recorded/evaluated within the Communication domain of the Autism Diagnostic Observation Schedule. Thus, difficulties relating to social anxiety and shyness might be scored within the Communication domains of these two

assessments. For example, an individual with social anxiety or selective mutism is likely to score poorly on items such as "amount of social overtures/maintenance of attention" and "conversation," both of which fall within the Communication domain of the Autism Diagnostic Observation Schedule and, thus, be misreported as communication difficulties when the underlying problem relates to social functioning. Consequently, some of these social difficulties may be masked.

We found that repetitive behavior did not differ between the two participant groups. However, this domain is not considered to be a particularly valid indicator of repetitive behavior in individuals with autism spectrum disorder and, thus, was not included in the algorithm for this reason. In previous studies researchers who used a more fine-grained approach to repetitive behavior within Cornelia de Lange syndrome have identified compulsive-like behaviors to be particularly prevalent. Lining up and tidying up behavior are the most frequent behaviors observed in this group (Hyman et al., 2002; Moss et al., 2005). Although not identified in the current study, these previous findings suggest that repetitive behaviors similar to those described in individuals with autism spectrum disorder (Turner, 1999) are characteristic of the syndrome.

In summary, we have considered the relationship between autism spectrum disorder and Cornelia de Lange syndrome and Cri du Chat syndrome in two ways. In the first, a somewhat crude assessment of this association, we considered the data at the level of algorithm cut-off scores. In the second, a more detailed approach, we used subscale level scores to determine the specific profile of autism spectrum disorder phenomenology in this group. The analysis at the algorithm level identified a greater number of individuals with Cornelia de Lange syndrome scoring above the cut-off for autism spectrum disorder on both the Social Communication Questionnaire

and Autism Diagnostic Observation Schedule in comparison to the Cri du Chat syndrome group, suggesting that a diagnosis of autism spectrum disorder may be relevant for at least some individuals with the syndrome. However, analysis at the subscale level revealed a somewhat atypical profile of autism spectrum disorder phenomenology. Impairments in communication were accompanied by difficulties in social interaction that are somewhat different to those observed in idiopathic autism, suggesting that the profile of autistic characteristics may be atypical within this group.

The presence of an atypical profile is not uncommon in genetic and medical disorders. Rutter, Bailey, Bolton, and LeCouteur (1994) noted that when autistic characteristics are observed in such populations, the profile is almost invariably slightly different to that identified in idiopathic autism (e.g., PKU, Cohen syndrome, fragile X syndrome, rubella). Moreover, according to Charman and Swettenham (2001), atypical profiles are also observed within the autism spectrum disorder population, particularly in those individuals who fall at the more extreme or broader end of the autism spectrum. Indeed, within both the *DSM-IV* (American Psychiatric Association, 1994) and *International Classification of Diseases--ICD-10* (World Health Organization, 1992) classification manuals, there is a separate diagnostic category for atypical autism. It is also well-established that the diagnostic characteristics of autism spectrum disorder change and develop with age, so that an individual who met full diagnostic criteria at 4 years of age may not demonstrate all diagnostic characteristics when they are 15 (Seltzer et al., 2003). The fact that the profile of autism phenomenology is so heterogeneous across different genetic syndromes, medical disorders, and indeed across *and* within individuals who fall within the autism spectrum, raises questions regarding how robust the concept of the

triad of impairments is and has implications regarding the etiology of these core characteristics (Happé, Ronald, & Plomin, 2006).

It is clear that the presence of atypical profiles of autism spectrum disorder characteristics is not uncommon in any way, particularly within the genetic syndrome population. However, the interpretation of these profiles remains difficult. If an individual does not meet all of the diagnostic criteria, then can he or she be considered to fall within the autism spectrum? If the answer to this question is no, how, then, do we account for the overlap in phenomenology? At a clinical level, we would argue that the answer to this question may not be important but, rather, as is suggested by Rutter et al. (1994), it is the recognition of shared characteristics that should be considered and, in particular, that similar, specialist intervention may be beneficial to this group. Although it is important to avoid over-inclusive use of the term *autism*, the significance of recognizing the shared needs between a given syndrome and autism spectrum disorder for learning, development, and quality of life is highlighted in case study reports within the literature (e.g., Howlin, Wing, & Gould 1995). The fact that education on and intervention for autism spectrum disorder is far better developed than education about other genetic syndromes may also be extremely beneficial to individuals who share such characteristics.

<--heading 1-->**Conclusion**<!--end heading 1-->

This is the first study in which the prevalence and phenomenology of autism spectrum disorder characteristics were investigated for Cornelia de Lange and Cri du Chat syndromes and standardized diagnostic assessments utilized. Analyses at the level of algorithm cut-off scores revealed that significantly more participants with Cornelia de Lange syndrome scored above the diagnostic cut-off on the Social

Communication Questionnaire than did those with Cri du Chat syndrome. Similar differences were identified using the Autism Diagnostic Observation Schedule, although these differences were not significant. Analyses at subscale level provided more detailed insight into the profile of autism spectrum phenomenology in Cornelia de Lange syndrome that were not identified at the diagnostic level. Participants with this syndrome demonstrated significantly more autism spectrum disorder-like impairments compared to those with Cri du Chat syndrome, despite shared difficulties in the area of language and communication. No significant differences were identified in the social interaction or repetitive behavior domains. However, anecdotal evidence suggests that individuals with Cornelia de Lange syndrome demonstrate difficulties with social interaction that may be related to social anxiety. Thus, the profile of phenomenology in this syndrome is likely to be atypical to that observed in individuals with idiopathic autism spectrum disorder.

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Received 9/28/06, accepted 9/14/07.

Editor-in-charge: Elisabeth Dykens

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Table 1, Means, SDs, Ranges, and Statistical Analyses of Demographic Characteristics by Group

Characteristic	Cornelia de Lange syndrome (n=34)	Cri du Chat syndrome (n=23)	t/ χ^2 (df)	p
Age (in years)				.04
Mean	12.39	10.26	2.12(55)	
(SD)	(3.82)	(3.60)		
Range	5.00–18.96	5.62 –18.61		
Gender (% male)	47.2	30.4	1.58(1)	.21
Speech (% verbal)	64.7	69.6	.146(1)	.70
Mobility (% mobile)	91.2	82.6	*	.42
Adaptive behavior ABC ^a age equivalence ^b			1.41(55)	.16
Mean	42.66	33.72		
(SD)	(29.43)	(18.30)		
Range	9.60–98.67	13.00–77.00		
ABC standard score			-.52(55)	.61
Mean	32.50	34.47		
(SD)	(12.97)	(15.85)		
Range	19.0–68.0	19.0–94.0		
Classification (n)				
Profound	9	3		
Severe	16	15		
Moderate	6	3		
Mild	3	1		
Borderline	0	1	*	.40
Receptive language age equivalence			.06	.95
Mean	50.53	50.09		
(SD)	(26.11)	(26.69)		
Range	28.00–104.00	28.00–116.00		
ADOS ^c module			4.99	.17
Module 1	15	17		
Module 2	12	4		
Module 3	4	1		
Module 4	3	1		

^aAdaptive Behavior Composite. ^bScores based on three domains of the Vineland Adaptive Behavior Scales–Survey Form. ^cBritish Picture Vocabulary Scales. ^cAutism Diagnostic Observation Schedule. *Fisher's Exact.

Table 2. Percentage of Participants by Syndrome Group Scoring Above the Suggested Cut-Off for Autism and Autism Spectrum Disorder on Domain and Total Level Scores

Measure	% scoring above autism cut-off (<i>n</i>)				χ^2 ^c	<i>p</i>	% scoring above autistic spectrum disorder cut-off (<i>n</i>)				χ^2 ^c	<i>p</i>
	CdLS ^a (<i>n</i> =34)		CdC ^b (<i>n</i> =23)				CdLS (<i>n</i> =34)		CdC (<i>n</i> =23)			
	%	<i>n</i>	%	<i>n</i>			%	<i>n</i>	%	<i>n</i>		
ADOS ^d												
Communication	61.8	21	34.8	8	4.08							
Social Interaction	70.6	24	47.8	11	3.08	.08	76.5	26	91.3	21	*	.18
Total score ^e	61.8	21	39.1	9	2.82	.09	73.5	25	60.9	14	1.02	.31
SCQ ^f												
Total score	23.5	8	0.0	0	*	.02	41.2	14	8.7	2	7.17	.01

^aCornelia de Lange syndrome. ^bCri du Chat syndrome. ^cAll *dfs* = 1. ^dAutism Diagnostic Observation Schedule. ^eTotal score on the ADOS refers to the combined score on the social interaction and communication domain scores. ^fSocial Communication Questionnaire. Total score on the SCQ refers to the summed total of Items 2–40. There are no subscale score diagnostic cut-off scores available for the SCQ. *Fischer's Exact employed when one or more cells had expected counts less than 5.

Figure Captions

Figure 1. Mean scores and *SDs* of the Communication, Social Interaction, and repetitive Behavior domains and Total score of the Autism Diagnostic Observation Schedule in individuals with Cornelia de Lange syndrome (CdLS) or Cri du Chat (CdCS) syndrome. Higher score indicates a greater impairment.

Figure 2. Mean scores, *SDs* of the Communication, Social Interaction, and Repetitive Behavior domains and the total score of the Social Communication Questionnaire (SCQ) in individuals with Cornelia de Lange syndrome (CdLS) OR Cri du Chat (CdCS) syndrome.

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