Current Opinion in Psychiatry

Behaviour across the lifespan in Cornelia de Lange syndrome

--Manuscript Draft--

Manuscript Number:	
Full Title:	Behaviour across the lifespan in Cornelia de Lange syndrome
Article Type:	Review Article
Corresponding Author:	Joanna F Moss University of Surrey Guildford, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Surrey
Corresponding Author's Secondary Institution:	
First Author:	Laura Groves
First Author Secondary Information:	
Order of Authors:	Laura Groves
	Chris Oliver
	Joanna F Moss
Order of Authors Secondary Information:	

Title: Behaviour across the lifespan in Cornelia de Lange syndrome

Laura Groves¹, Chris Oliver¹ and Joanna Moss²

¹ School of Psychology, University of Birmingham

² School of Psychology, University of Surrey

Corresponding Author:

Dr Joanna Moss

School of Psychology

University of Surrey

Guildford

GU2 7 XH

Email: j.moss@surrey.ac.uk

Abstract

Purpose of review

Whilst previous reviews have extended descriptions of the behavioural phenotype of Cornelia de Lange syndrome (CdLS) significantly, potential changes with age across the lifespan have been neglected. Age-related difference in the behavioural phenotype constitutes preliminary evidence of change with age. Documenting and understanding the developmental trajectories of behaviours is informative as it enables identification of risk periods for behavioural challenges and compromised mental health.

Recent findings

Recent cross sectional, longitudinal and mixed design studies report differing presentations of the behavioural phenotype across the lifespan. Of particular interest are autistic characteristics and behaviours consistent with compromised mental health, particularly anxiety and negative affect, which are reported to be more common and severe in older individuals. Preliminary evidence for identified causal pathways with consideration of biological, cognitive and environmental factors are discussed.

Summary

Older individuals with CdLS appear to be at greater risk of poorer psychological wellbeing than younger peers with significant implications for risk informed preventative and early interventions. Further work is required to document the behavioural phenotype across the lifespan with consideration of multiple factors that may influence the trajectory and extent of negative outcomes

Keywords: Cornelia de Lange syndrome, autism, anxiety, mood, age, executive function

Introduction

Cornelia de Lange syndrome (CdLS) is a rare genetic disorder (estimated prevalence of 1:10,000-1:30,000 live births) [1*] associated with mild to profound intellectual disability [2-4]. Approximately 70% of people with CdLS will evidence a mutation in the NIPBL gene with mutations in SMC1A, SMC3, HDAC8, BRD4, ANKRD11 and RAD21 genes also identified [1*, 5-10]. Mosaicism is reported in approximately 23% of people [11]. A broad range of behaviours are characteristic of individuals with CdLS including self-injury, anxiety, negative affect, autistic characteristics, atypical sensory processing, impulsivity, and sleep problems [1*, 4, 13-16).

Emerging evidence suggests that aspects of the behavioural, emotional and cognitive phenotype in CdLS change with chronological age. Documenting and understanding the developmental trajectory of these characteristics within a given syndrome is useful for understanding what may be ‘typical’ (i.e. parallel with and increasing at the same rate seen in typical development), ‘deviant’ (i.e. the trajectory is not parallel) or ‘delayed’ (i.e. the trajectory is broadly parallel but slower) [17]. Doing so enables identification of critical risk periods of onset or emergence of behaviours and compromised mental health detrimental to wellbeing, enabling targeted preventative and early intervention. In CdLS the developmental trajectory of a range of characteristics appears to be atypical [1*, 14, 18-22*], with a critical period of change spanning adolescence and early adulthood (i.e. approximately 15-22 years old) described by some studies [21, 23]. Interestingly, changes appear to plateau after this period, indicating that behaviour may stabilise later in adulthood. Reported change includes autistic characteristics, and negative affect and anxiety, with cross-sectional and longitudinal research identifying greater frequency and/or severity in older cohorts [4, 19*-21, 24-26]. However, this pattern has not always been replicated across studies [18, 24; 27-30]. The causal

mechanisms underlying these reported changes are not well understood but it is likely that a combination of biological, environmental and cognitive factors underpin this trajectory in CdLS.

In this review we outline evidence which documents the differing profiles of behavioural and cognitive characteristics across the lifespan of individuals with CdLS. The causal mechanisms hypothesised to underlie age associated phenotypes are discussed.

Autistic characteristics and Insistence on Sameness

Autistic characteristics are highly prevalent in CdLS, with between 51% and 67% of individuals meeting clinical diagnostic cut-off scores [13, 14, 24, 27-29, 31-33]. An atypical presentation of autistic characteristics has been described in CdLS, in which greater social anxiety is reported in contrast to individuals with non-syndromic autism alongside fewer sensory interests and less impaired use of eye contact and gestures [26, 34]. As for autistic individuals [35], intolerance of uncertainty is common in CdLS and an important mediating factor between autistic characteristics and anxiety [36]. Several cross-sectional studies have reported greater social withdrawal and social isolation in older than younger individuals with CdLS [4, 18, 37]. Increased severity of autism related social impairments has also been described in a seven-year longitudinal follow up study using observational assessments [38*], although this change was not apparent over a shorter, two-year follow up period [18].

Individuals with CdLS are reported to have a strong preference for sameness and routine [26, 39]. Insistence on sameness refers to a set of rigid, routinised, and ritualistic behaviours commonly observed in autism. Such behaviours are also observed in young typically developing children, arguably serving as an adaptive regulation strategy to manage situations

with high cognitive load before being replaced by more sophisticated strategies [40]. However, in autistic individuals and those with CdLS, insistence on sameness and preference for routines are also reported frequently across the lifespan [20, 41], indicative of a deviant developmental trajectory [17]. Additionally, Moss and colleagues [20] report insistence on sameness was positively associated with chronological age in individuals with NIPBL genetic variants of CdLS.

Negative affect

Negative affect is a broad term encompassing both *mood* and *interest and pleasure* which are considered behavioural markers of depression and anhedonia [42, 43]. Between 11% and 50% of individuals with CdLS are reported to show behaviour indicative of depression or negative affect [4, 24 37]. Associations with age are identified such that older individuals show greater negative affect, with adolescence or early adulthood reported to be critical periods [20, 21, 24, 44]. Generally, negative affect is assessed as a composite construct, both in the ID and CdLS literature, with mood, and interest and pleasure rarely assessed separately. Those studies that have evaluated mood, and interest and pleasure as distinct constructs have provided preliminary evidence that their developmental trajectories are divergent in CdLS [19*-21]. Specifically, interest and pleasure are lower in older individuals, whereas mood is reported to be stable across the lifespan [19*-21]. Additionally, this association with age may only be the case for individuals with the NIPBL genetic variant [20].

Anxiety

Anxiety is reported to be highly prevalent in individuals with CdLS [1*, 4, 45], with social anxiety and selective mutism particularly characteristic. More recent literature has suggested that individuals with CdLS show behaviour consistent with generalised anxiety, separation

anxiety and agoraphobia [4, 26, 32, 37, 45-47]. Additionally, increased cognitive demands and, anecdotally, changes to routine, are described as anxiety triggers [25, 48]. Evidence points towards intolerance of uncertainty as an important mediating factor in the onset of anxiety in CdLS [36]. Preliminary evidence suggests that older individuals with CdLS may show higher levels of anxiety than younger peers [4, 25, 26]. However, some studies report no associations with age [25, 30]. Variability in reported associations with age may be due to the type of anxiety being assessed, methodological differences such as the range of ages included in the study population or the statistical analysis strategy. However, critically, no study reports lower rates of anxiety in older individuals compared to younger cohorts suggesting that anxiety either persists or worsens and as such represents a significant area of concern in CdLS.

Cognitive abilities

Individuals with CdLS present with an uneven cognitive profile showing specific executive functioning deficits, beyond that expected given degree of intellectual disability [22*]. Specifically, deficits are observed in verbal memory and attention shifting [22*, 48]. Reid and colleagues [22*] also report a negative correlation between verbal working memory and chronological age such that older individuals show poorer performance compared to younger peers. This may be preliminary evidence of decline in cognitive functioning, underpinned by functional or structural impairment to the prefrontal cortex. Interestingly, a seven-year follow up of 30 individuals with CdLS demonstrated that broad adaptive abilities were stable over time, while receptive language skills improved [38*]. This suggests that the changes observed in CdLS are unlikely to be accounted for by decline in broad level cognitive functioning and that any changes observed are likely to be highly specific to executive functioning.

Causal mechanisms of age-related change in CdLS:

This review has described an emergent literature evidencing changes with chronological age in specific behavioural and cognitive characteristics in individuals with CdLS. In the following sections we explore the possible mechanisms underlying the atypical trajectory of development in CdLS. Whilst understanding of these mechanisms is limited at present, we present hypothesised biological, cognitive and environmental levels of explanation and consider how these might interact.

Biological factors contributing to age-related change in CdLS:

The genetic mutations associated with CdLS all contribute to the cohesion complex, making CdLS a cohesinopathy [1*]. Abnormalities of the cohesin complex are associated with downregulation of proteins implicated in neural growth, maintenance and repair [49]. Additionally, increased apoptosis (programmed cell death) has been identified in zebra fish models for NIPBL, SMC3, SMC1A and RAD21 variants [50]. Furthermore, Gimigliano et al. [51] found cell lines associated with mutations of the SMC1A and SMC3 genes in CdLS showed increased global oxidative stress due to dysregulated protein expression, which has been noted to be similar to the presentation of neurodegenerative disorders [52-53*]. Whilst CdLS is not understood or described as a neurodegenerative disorder, such mechanisms may provide some degree of explanation for the specific behavioural changes with age reported in CdLS.

Cognitive factors contributing to age-related change in CdLS:

As discussed previously, there is evidence suggesting that some older individuals with CdLS may have greater executive functioning deficits than younger individuals, specifically in verbal memory [22*]. Interestingly, some studies document associations between executive

functioning profiles and behavioural characteristics. For example, reduced verbalisations in social situations, which may be indicative of difficulties with sociability and social anxiety, has been associated with poor working memory and planning ability [23]. This may be because individuals with compromised planning and working memory find keeping pace with and following the flow of social interactions challenging. Therefore, further reduction of verbal memory capacity with age may underlie increases in autism-like difficulties and anxiety in social situations. Additionally, a high preference for routine and insistence on sameness is reported in CdLS [26, 39] which is hypothesised to be a coping strategy in typically developing and autistic individuals as it lessens the cognitive load on executive functioning in daily life [40]. Thus, any changes in executive functioning with age, such as those identified by Reid and colleagues [22*], may lead to increased use of such coping strategies. This may result in greater insistence on sameness and ultimately withdrawal from activities, which could underlie lower interest and pleasure in older individuals with CdLS described previously [19*, 21]. Additionally, there may be a reduced tolerance of novel situations as these present a large quantity of new incoming information, increasing the cognitive load on executive functioning skills. This tendency for intolerance of uncertainty may lead to increased anxiety in response to divergence from predictable structure or routines.

Thus, compromised cognitive functioning, and associated age-related changes, may underlie differences in behaviour profiles across the lifespan in CdLS. However, this change is not ubiquitous, not every individual shows evidence of this, and global changes in all aspects of behaviour and functioning are not reported; as evidenced by Cochran and colleagues [38*]. Therefore, manifestation of behavioural difficulties may be dependent on additional factors, such as the environment.

Environmental factors contributing to age-related change in CdLS:

Evidence suggests that changes in mood and behaviour in individuals with CdLS are most likely in late adolescence or early adulthood [4, 24, 44, 54]. The period between 15 and 22 years has been highlighted as a particularly critical period following which a period of improvement is evident and stability returns [21, 23]. It is notable that the age at which this critical period has been evidenced, coincides with the significant period of transition for individuals and their families with transition from child to adult health services and the end of school-based education. It is well established that this transition period can be particularly challenging for individuals with intellectual disability and those with complex needs [55, 56]. This may be because transitions from school-based education mark an end to or a loss of predictable structure and routine, which has been in place for many years. Transitions from school-based education to college or adult learning facilities and from child to adult professional/clinical services introduce a great deal of unpredictability and uncertainty into the young person's life, and often greater environmental and social, and hence cognitive, demands. Anecdotal reports of incomplete or delayed transitions or transition to placements that do not meet the individual's needs are not uncommon in individuals with CdLS [57]. The high rates of autistic characteristics in CdLS, coupled with low levels of recognition and diagnosis of autism in genetic syndrome populations [58], is likely to significantly exacerbate such challenges. These negative transitional experiences, within the context of a syndrome in which there is increased risk of anxiety, autistic characteristics and executive dysfunction might result in significantly reduced capacity to cope under such circumstances and thus provide some explanation of the changes reported in individuals with CdLS. For example, under such circumstances it might be anticipated that increased adherence to routine and insistence on sameness become adaptive coping strategies for some individuals with CdLS to deal with the anxiety generated by an increasingly unpredictable environment and the person experiencing

understandably showing less interest and pleasure in such an environment. In recognition of this, the recently published international consensus statement concerning the management of CdLS [1*] highlights the need for additional support during adolescence and adulthood and transitional care periods in order to ‘mitigate mental health issues and problematic behaviour’.

Modelling the interaction between biological, cognitive and environmental factors contributing to age-related change in CdLS:

The evidence outlined above suggests that there may be specific biological and cognitive vulnerabilities that emerge with chronological age in CdLS. These factors may go some way to understanding the reported age-related changes in behaviour described in individuals with CdLS. Importantly, the fact that adaptive skills remain stable while receptive language shows continued improvement with chronological age [38*] suggests that the pattern of change described in CdLS is highly specific and not a global decline in ability. We propose that emergent biological and cognitive vulnerabilities, coupled with an increased risk for autism characteristics, intolerance of uncertainty and anxiety, which are often unrecognised and untreated in individuals with CdLS, leads to reducing capacities to cope with significant environmental change and/or unpredictable environments/situations as individuals with CdLS become older. This leaves adolescents and adults with CdLS particularly susceptible to experiencing negative behavioural and mental health outcomes during challenging transitional periods and when faced with unpredictable environments/situations.

Conclusions

In this review we have examined preliminary evidence of changes in the behavioural phenotype across the lifespan in individuals with CdLS. Prospective causal mechanisms for change with consideration of biological, cognitive and environmental factors have been discussed. The literature suggests there is evidence of increasing frequency or severity of autistic

characteristics, lower interest and pleasure, and increasing anxiety with age. This should be considered by professionals working with individuals with CdLS to provide prevention and early intervention strategies and support for those at risk of experiencing decline, consistent with recommendations made elsewhere [1*]. To corroborate hypotheses of causal pathways, longitudinal research is required with particular emphasis on inter-disciplinary studies that can concurrently evaluate biological, cognitive and environmental factors. Such research would inform the production and delivery of early interventions for individuals with CdLS, informed by risk.

Key points

- Studies identify differing profiles of behaviour across the CdLS lifespan which provide preliminary evidence of change. Of particular interest are autistic characteristics, negative affect and anxiety.
- Older individuals with CdLS are reported to show more autistic characteristics, such as more social impairment, greater insistence on sameness, and less interest and pleasure compared to younger individuals. Mood remains stable across the lifespan.
- Behaviours indicative of anxiety are reported consistently across the lifespan or at elevated levels in older individuals. Anxiety is a critical area of concern.
- Studies have described biological, cognitive and environmental factors which could underlie change in the CdLS behavioural phenotype with an interaction between these factors likely.
- Applied research should focus on risk driven preventative and early intervention.

Acknowledgements

The authors gratefully acknowledge the support of Cerebra and the Cornelia de Lange Syndrome Foundation, UK and Ireland via grant support for the work that enabled this review.

Financial support and sponsorship

None.

Conflicts of interest

None.

References

1. *Kline AD, Moss J, Selicorni A, *et al.* Diagnosis and management in Cornelia de Lange Syndrome: First international consensus statement. *Nat Rev Genet* 2018. 19(10), 649-666.doi:10.1038/s41576-018-0031-0

This article presents a systematic review of the CdLS literature and the first consensus statement of recommendations for clinical practice from an international panel of experts.

2. Ajmone PF, Rigamonti C, Dall'Ara F *et al.* Communication, cognitive development and behavior in children with Cornelia de Lange Syndrome (CdLS): preliminary results. *Am J Med Genet B* 2018; 165b(3), 223-229. doi:10.1002/ajmg.b.32224
3. Huisman S, Mulder P, Kuijk J, *et al.* Self-injurious behavior. *Neurosci Biobehav Rev* 2018; 84, 483–491. doi:10.1016/j.neubiorev.2017.02.027
4. Kline AD, Grados M, Sponseller P, *et al.* Natural history of aging in Cornelia de Lange syndrome. *Am J Med Genet C* 2007, 145c(3), 248-260. doi:10.1002/ajmg.c.30137
5. Krantz ID, McCallum J, DeScipio C, *et al.* Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of *Drosophila melanogaster* Nipped-B. *Nat Genet* 2004, 36(6), 631–635.doi:10.1038/ng1364
6. Yan J, Saifi GM, Wierzbica TH, *et al.* Mutational and genotype–phenotype correlation analyses in 28 Polish patients with Cornelia de Lange syndrome. *Am J Med Genet A* 2006; 140:1531–1541.
7. Deardorff MA, Bando M, Nakato R, *et al.* HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. *Nature* 2012; 489:313–7.
8. Deardorff MA, Kaur M, Yaeger D, *et al.* Mutations in cohesion complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange Syndrome with

- predominant mental retardation. *Am J Hum Genet* 2017; 80(3), 485–494. doi:10.1086/511888
9. Deardorff MA, Wilde JJ, Albrecht M, *et al.* RAD21 mutations cause a human cohesinopathy. *Am J Hum Genet* 2012; 90:1014–27.
10. Dorsett D, Krantz ID. On the molecular etiology of Cornelia de Lange Syndrome. *Ann N Y Acad Sci* 2009; 1151(1), doi.org/10.1111/j.1749-6632.2008.03450.x
11. Huisman SA, Redeker EJW, Maas SM, *et al.* High rate of mosaicism in individuals with Cornelia de Lange syndrome. *J Med Genet* 2013, 50(5), 339–344. doi:10.1136/jmedgenet-2012-101477
12. Heald M, Adams D, Oliver C. Profiles of atypical sensory processing in Angelman, Cornelia de Lange and Fragile X syndromes. *J Intellect Disabil Res* 2019; 64 (2), doi: 10.1111/jir.12702
13. Mulder PA, Huisman SA, Henneham RC, *et al.* Behaviour in Cornelia de Lange syndrome: a systematic review. *Developmental Medicine & Child Neurology* 2017; 59 (4), doi:10.1111/dmcn.13361
14. Oliver C, Berg K, Moss J, Arron K, Burbidge C. Delineation of behavioural phenotypes in genetic syndromes. Comparison of autism spectrum disorder, affect and hyperactivity. *J Autism Dev Disord* 2011; 41: 1019-1032.
15. Srivastava S, Clark B, Landy-Schmitt C, *et al.* Repetitive and Self-injurious Behaviors in Children with Cornelia de Lange Syndrome. *J Autism Dev Disord* 2020. <https://doi.org/10.1007/s10803-020-04617-x>
16. Zambrelli E, Fossati C, Turner K, *et al.* Sleep disorders in Cornelia de Lange syndrome. *Am J Med Genet C Semin Med Genet* 2016; 172, (2), doi: 10.1002/ajmg.c.31497

17. Thomas MSC, Annaz D, Ansari D, *et al.* Using Developmental Trajectories to Understand Developmental Disorders. *J Speech Lang Hear Res* 2009, 52(2), 336. doi:10.1044/1092-4388(2009/07-0144)
18. Cochran L, Moss J, Nelson L, Oliver C. Contrasting age related changes in autism spectrum disorder phenomenology in Cornelia de Lange, Fragile X, and Cri du Chat syndromes: Results from a 2.5 year follow-up. *Am J Med Genet C* 2015; 169(2): 188-97
19. *Groves L, Moss J, Crawford H, *et al.* Lifespan trajectory of affect in Cornelia de Lange syndrome: Towards a neurobiological hypothesis. *J Neurodev Disord* 2019. 11(6). doi:10.1186/s11689-019-9269-x

This study presents a seven-year longitudinal study of negative affect in individuals with CdLS and a preliminary hypothesis of the biological and cognitive underpinnings of this.

20. Moss J, Penhallow J, Ansari M, *et al.* Genotype–phenotype correlations in Cornelia de Lange syndrome: Behavioral characteristics and changes with age. *Am J Med Genet A* 2017; 173(6):1566–1574. doi: 10.1002/ajmg.a.38228.
21. Nelson L, Moss J, Oliver C. A longitudinal follow-up study of affect in children and adults with Cornelia de Lange syndrome. *Am J Intellect Dev Disabil* 2014; 119(3), 235-252. doi:10.1352/1944-7558-119.3.235
22. *Reid D, Moss J, Nelson L, *et al.* Executive functioning in Cornelia de Lange syndrome: domain asynchrony and age related performance. *J Neurodev Disord* 2017; 9 (1): 29 doi:10.1186/s11689-017-9208-7

This is a cross sectional study of executive function abilities in CdLS compared to a matched contrast group of individuals with Down syndrome. The study presents

data regarding the association between chronological age and executive function skills.

23. Nelson L, Crawford H, Reid D, *et al.* An experimental study of executive function and social impairment in Cornelia de Lange syndrome. *J Neurodev Disord* 2017; 9(1), 33. doi:10.1186/s11689-017-9213-x
24. Basile E, Villa L, Selicorni A, Molteni M. The behavioural phenotype of Cornelia de Lange syndrome: A study of 56 individuals. *J Intellect Disabil Res* 2007; 51, 671–681.
25. Crawford H, Waite J, Oliver C. Diverse Profiles of Anxiety Related Disorders in Fragile X, Cornelia de Lange and Rubinstein-Taybi Syndromes. *J Autism Dev Disord* 2017; 47(12), 3728-3740.
26. Moss J, Nelson L, Powis L, *et al.* A Comparative Study of Sociability in Angelman, Cornelia de Lange, Fragile X, Down and Rubinstein Taybi Syndromes and Autism Spectrum Disorder. *Am J Intellect Dev Disabil* 2016, 121(6), 465-486. doi:10.1352/1944-7558-121.6.465
27. Bhuiyan ZA, Klein M, Hammond P, *et al.* Genotype-phenotype correlations of 39 patients with Cornelia De Lange syndrome: the Dutch experience. *J Med Genet* 2006; 43(7), 568-575. doi:10.1136/jmg.2005.038240
28. Nakanishi M, Deardorff MA, Clark D, *et al.* Investigation of autistic features among individuals with mild to moderate Cornelia de Lange syndrome. *Am J Med Genet A* 2012, 158a(8), 1841-1847. doi:10.1002/ajmg.a.34014
29. Srivastava S, Landy-Schmitt C, Clark B, *et al.* Autism traits in children and adolescents with Cornelia de Lange syndrome. *Am J Med Genet A* 2014; 164a(6), 1400-1410. doi:10.1002/ajmg.a.36573
30. Wulffaert J, van Berckelaer-Onnes I, Kroonenberg P, *et al.* Simultaneous analysis of the behavioural phenotype, physical factors, and parenting stress in people with

- Cornelia de Lange syndrome. *J Intellect Disabil Res* 2009; 53(7), 604-619.
doi:10.1111/j.1365-2788.2009.01185.x
31. Oliver C, Arron K, Sloneem J, Hall S. Behavioural phenotype of Cornelia de Lange syndrome: case-control study. *Br J Psychiatry* 2008; 193(6), 466-470.
doi:10.1192/bjp.bp.107.044370
32. Moss JF, Oliver C, Berg K, *et al.* Prevalence of autism spectrum phenomenology in Cornelia de Lange and Cri du Chat syndromes. *Am J Ment Retard* 2008, 113(4), 278-291.
33. Richards C, Jones C, Groves L., *et al.* Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis. *Lancet Psychiatry* 2015; 2(10), 909–916.
34. Moss J, Howlin P, Magiati I, Oliver C. Characteristics of autism spectrum disorder in Cornelia de Lange syndrome. *J Child Psychol Psychiatry* 2012, 53(8), 883-891.
doi:10.1111/j.1469-7610.2012.02540.x
35. Rodgers J, Glod M., Connolly B, McConachie H. The relationship between anxiety and repetitive behaviours in autism spectrum disorder. *J Autism Dev Disord* 2012.; 42(11):2404-9
36. Johnson, V. *Predicting anxiety within atypical development*. University of Warwick, 2019.
37. Sarimski K. Communication, social-emotional development and parenting stress in Cornelia-de-Lange syndrome. *J Intellect Disabil Res* 1997; 41: 70–75
38. *Cochran L, Welham A, Oliver C, *et al.* Age-related Behavioural Change in Cornelia de Lange and Cri du Chat Syndromes: A Seven Year Follow-up Study. *J Autism Dev Disord* 2019; 49(6): 2488.

This study presents a seven-year longitudinal study of behaviour in individuals with CdLS.

39. Moss J, Oliver C, Arron K, *et al.* The prevalence and phenomenology of repetitive behavior in genetic syndromes. *J Autism Dev Disord* 2009, 39(4), 572-588. doi:10.1007/s10803-008-0655-6
40. Leekam SR, Tandos J, McConachie H, *et al.* Repetitive behaviors in typically developing 2-year-olds. *J Child Psychol Psychiatry*. 2007;48(11):1131–8.
41. Esbensen AJ, Seltzer MM, Lam KS, Bodfish JW. Age-related differences in restricted repetitive behaviors in autism spectrum disorders. *J Autism Dev Disord* 2009, 39, 57–66.
42. Deb S, Thomas M, Bright C. Mental disorder in adults with intellectual disability. I: Prevalence of functional psychiatric illness among a community-based population aged between 16 and 64 years. *J Intellect Disabil Res* 2001; 45: 495–505.
43. Ross E, Oliver C. Preliminary analysis of the psychometric properties of the Mood, Interest and Pleasure Questionnaire (MIPQ) for adults with severe and profound learning disabilities. *Br J Clin Psychol* 2013; 42: 81–93.
44. Berney TP, Ireland M, Burn J. Behavioural phenotype of Cornelia de Lange syndrome. *Arch Dis* 1999; 81(4), 333-336.
45. Crawford H, Moss J, Groves L, *et al.* A behavioural assessment of social anxiety and social motivation in Fragile X, Cornelia de Lange and Rubinstein-Taybi Syndromes. *J Autism Dev Disord* 2020; 50(1), 127-144. <https://doi.org/10.1007/s10803-019-04232-5>
46. Moss J, Howlin P, Hastings RP, *et al.* Social behavior and characteristics of autism spectrum disorder in Angelman, Cornelia de Lange, and Cri du Chat syndromes. *Am J Intellect Dev Disabil* 2013, 118(4), 262-283. doi:10.1352/1944-7558-118.4.262
47. Richards C, Moss J, O'Farrell L, *et al.* Social anxiety in Cornelia de Lange syndrome. *J Autism Dev Disord* 2009; 39(8), 1155-1162. doi:10.1007/s10803-009-0730-7

48. Johnson V. *Executive functioning and decision making in Cornelia de Lange syndrome*. University of Birmingham 2015
49. Vrouwe MG, Elghalbzouri-Maghrani E, Meijers M, *et al*. Increased DNA damage sensitivity of Cornelia de Lange syndrome cells: evidence for impaired recombinational repair. *Hum Mol Genet* 2007; 16(5): 1478-1487
50. Banerjz R, Skibbens RV, Iovine MK. How many roads lead to cohesinopathies? *Dev Dyn* 2017; 246(11):881-888.
51. Gimigliano A, Mannini L, Bianchi L, *et al*. Proteomic profile identifies dysregulated pathways in Cornelia de Lange Syndrome cells with distinct mutations in SMC1A and SMC3 genes. *J Proteome Res* 2012; 11(12): 6111-6123.
52. Cukrov D, Newman TAC, Leask M, *et al*. Antioxidant treatment ameliorates phenotypic features of SMC1A-mutated Cornelia de Lange syndrome in vitro and in vivo. *Hum Mol Genet* 2018; 27:3002–11.
53. *Sarogni P, Pallotta MM, Musio A. Cornelia de Lange syndrome: from molecular diagnosis to therapeutic approach. *J Med Genet* 2020;57:289–295.

This review describes the biological processes dysregulated in CdLS that occur downstream from CdLS causal mutations, including processes related to oxidative stress.

54. Collis L, Oliver C, Moss J. Low mood and social anxiety in Cornelia de Lange Syndrome. *J Intellect Disabil Res* 2006; 50, 792.
55. Brown M, Higgins A, MacArthur J. Transition from child to adult health services: A qualitative study of the views and experiences of families of young adults with intellectual disabilities, *J Clin Nurs* 2019; **29**, 1-2, 195-207

56. Solanke F, Colver A, McConachie H. Transition collaborative group. Are the health needs of young people with cerebral palsy met during transition from child to adult health care? *Child Care Health Dev* 2018; 44(3):355-363. doi:10.1111/cch.12549
57. Welham, Moss & Oliver, *Growing up with CdLS: Changes in adolescence and young adulthood*. Reaching Out 2012.
58. Moss J, Howlin P. Autism spectrum disorders in genetic syndromes: implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. *J Intellect Disabil Res* 2009; 53(10), 852–873. doi:10.1111/j.1365-2788.2009.01197.x