Cornelia de Lange Syndrome

First description and alternative names

Cornelia de Lange Syndrome is named after a Dutch paediatrician who first described the syndrome in 1933. The disorder is occasionally referred to as Brachmann de Lange Syndrome after a German doctor who is also thought to have described a patient with the syndrome in 1916.

Incidence/prevalence

CdLS has an estimated prevalence of 1 in 10,000 to 30,000 live births (Kline et al., 2018), although this is thought to be an underestimate, with more mildly affected individuals increasingly being identified.

Genetics

CdLS is caused by a deletion on the *NIPBL* gene on chromosome 5 (locus 5p13) in up to 80% of cases (Gillis *et al.*, 2004; Krantz *et al.*, 2004; Miyake *et al.,* 2005; Tonkin *et al.*, 2004, Huisman et al., 2013). Mosaicism for *NIPBL* mutations is identified in 23% of individuals [Huisman et al., 2013]. Additional mutations in *SMC3* on chromosome 10 (Deardorff *et al.*, 2007), X linked *SMC1a* and *HDAC8* genes (Deardorff et al*.,* 2012a; Musio et al*.,* 2006) and more recently identified *RAD21*, *ANKRD11* and *BRD4* mutations (Deardorff et al., 2012b; Kline et al., 2018) are reported to account for a smaller proportion of cases. All genes are involved in the structure and regulation of the cohesin complex which is crucial for neural maintenance and repair (Deardorff et al., 2012b; Liu & Krantz 2009). It is probable that there are further unidentified mutations relevant to the cause of CdLS.

The *NIPBL* gene is expressed in the developing skeleton and soft tissue of the limbs, hands, spinal column, face and head including the ear canal, the atrial and ventricular areas of the heart, oesophagus, trachea and lungs (Tonkin *et al.* 2004). Individuals with *NIPBL* mutations show large variability in presentation but a larger proportion of these individuals appear to be more severely affected by the syndrome with more severe intellectual disability and limb abnormalities (Gillis *et al.* 2004; Bhuiyan *et al.* 2006; Huisman et al., 2017). In contrast, mutations in *SMC1a* and *SMC3* have currently been found to result in a milder presentation of the CdLS phenotype with less severe intellectual disability and fewer physical abnormalities (Deardorff *et al.* 2007; Huisman et al., 2017).

Physical features and natural history

Individuals with CdLS typically have a low birth weight, small stature, upper limb abnormalities (25%) and hirsutism, although those with a milder presentation seem less affected by these problems (Deardorff *et al.* 2007; Kline *et al.* 2007). Distinctive facial features, including: synophrys, long, thick eyelashes, a long and prominent philtrum, a thin upper lip; and a downturned mouth appear characteristic of most individuals with the syndrome (Kline *et al.* 2007). CdLS is associated with many health problems (for overview see Kline et al., 2018). Some of the most commonly occurring problems include: gastro-intestinal disorders, hearing and eye abnormalities, cardiac and genito- urinary problems. Gastro-intestinal disorders are particularly problematic in CdLS.

Little is known about the life expectancy of individuals with CdLS, although recent research studies have included participants aged 40 to 50 years and above (Cochran et al., 2015; Groves et al., 2018; Moss *et al.,* 2009; Nelson et al., 2014; Oliver *et al.,* 2011). Gastro-intestinal disorders associated with CdLS create an increased risk of early mortality due to aspiration, leading to pneumonia in

some cases. Early assessment and intervention of gastro- intestinal difficulties is of utmost importance in individuals with CdLS.

Behavioural characteristics

Self-injurious behaviour is generally thought to be more common in people with CdLS than in the general intellectual disability population (Sloneem *et al.* 2009) and reported to be influenced by anxiety, sleep problems and social reinforcement for some individuals (Arron *et al*., 2006; Huisman et al., 2018; Kline et al., 2018). There is a notable association between self-injurious behaviour and associated medical conditions, particularly gastrointestinal reflux (Huisman et al., 2018; Luzzani *et al*., 2003).

Self-restraint behaviours are common (Hyman *et al*., 2002) and this has led to suggestions that individuals with CdLS may be at risk for self-injurious behaviour to become difficult to regulate. The increased frequency of compulsive like behaviours within the syndrome such as tidying up and lining up behaviours (Hyman *et al*., 2002; Moss *et al.* 2009) also indicates that individuals with CdLS may be at risk for difficulties with behaviour regulation.

An association between CdLS and autism characteristics has been consistently reported (Basile *et al.,* 2007; Berney *et al*., 1999; Bhuiyan *et al*., 2006; Moss *et al*., 2008; Nakanishi et al., 2012; Oliver et al., 2011; Srivastava et al., 2014). It is estimated 43% of individuals with CdLS may show autism characteristics (Richards et al., 2015). This association with autism is not solely accounted for by associated intellectual disability (Moss *et al*., 2008), although the profile of autism characteristics appears to be different to that of non-syndromic autism (Moss et al., 2012; Moss et al, 2013). Extreme shyness and social anxiety are characteristic of many individuals with CdLS and an unusually high number of individuals with CdLS are reported to show characteristics of selective mutism (Crawford et al., in review; Moss et al., 2016).

In addition to social anxiety, other types of anxiety have been reported in individuals with CdLS including demand related anxiety, separation anxiety and generalised anxiety (Crawford, Waite & Oliver, 2017; Johnson, 2015). Low mood has also been reported in individuals with CdLS with specific diffiuclties for low interest and pleasure described (Groves et al., 2019); Nelson et al., 2014; Moss et al., 2017). These difficulties may become more prominent with age (Goodban, 1993; Groves et al., 2019); Nelson et al., 2014; Moss et al., 2017; Richards et al., 2009).

Neuropsychological characteristics

Degree of intellectual disability (ID) is variable in CdLS but most individuals show a severe or profound level of disability (30.43% severe level of ID; 45.6% profound level of ID) with notably poor expressive communication, primarily evidenced by limited or absent speech (Sarimski 1997; Berney *et al.* 1999; Kline et al., 2018).The degree of ID and level of communication skills seem dependent on the phenotype; those with a milder presentation generally have a less severe degree of ID and appear more likely to acquire speech (Bhuiyan *et al.* 2006; Deardorff *et al.* 2007; Huisman et al., 2017).

Recent research by Reid et al. (2017) and Johnson (2015) demonstrated impairments in aspects of executive function including impairment on tasks requiring generativity (verbal fluency), cogntive flexibility but with inhibition and working memory representing relative strengths. Reid et al. (2017) also demonstrated that verbal working memory (backwards digit span) and verbal fluency skills were significantly negatively correlated with chronological age in CdLS but not a contrast group of individuals with DS, indicating increased deficits in these areas with age.

Age related change

There is emerging evidence indicating broad age-related changes in CdLS including increased anxiety, low interest and pleasure, social withdrawal, self-injurious behaviour and verbal working memory difficulties (Berney et al., 1999; Cochran et al., 2015; Groves et al., 2019; Kline et al., 2018; Moss et al., 2017; Nelson et al., 2014; Oliver et al., 2011; Reid et al., 2017; Sarimski, 1997) alongside the early onset of physical signs of ageing (Kline et al., 2007). Biological processes that occur downstream from the genetic mutations responsible for CdLS have been implicated in these reported changes with age (Gimigliano et al., 2012; Kline et al., 2007).

Available guidelines for behavioural assessment / treatment / management

Kline, A., Moss, J., Selicorni, A., Bisgaard, A-M., Deardorff, M., Gillett., P, et al. (2019). Diagnosis and management in Cornelia de Lange Syndrome: First international consensus statement. *Nature Reviews Genetics*. 19(10), 649-666.

Summary available from: https://www.cdlsworld.org/xwiki/bin/view/cdlsPublications/consensus/

Kline AD, Krantz ID, Sommer A, Kliewer M, Jackson LG, FitzPatrick DR, Levin AV, Selicorni A. (2007) Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance. *Am J Med Gen, Part A 143A*:1287–1296.

Moss, J. and Oliver, C. (2012). Autism in genetic syndromes: implications for assessment and intervention. *Cerebra E-briefing.* Cerebra

Welham, A., Moss, J. and Oliver, C. (2012). Special Report: Growing up with CdLS: Changes in adolescence and young adulthood. *Special Issue Report for the Cornelia de Lange Syndrome Foundation.* March, S1-S16.

Useful websites/associations for more information

- CdLS Foundation UK and Ireland: www.cdls.org.uk
- CdLS World: www.cdlsworld.org
- FIND resources: www.findresources.co.uk
- Oliver C., Moss J., Petty J., Arron K., Sloneem J. & Hall S. (2003). *Self-injurious Behaviour in Cornelia de Lange Syndrome: A Guide for Parents and Carers*. Trident Communications Ltd.: Coventry. – Available from the CdLS Foundation UK and Ireland.
- CdLS Foundation UK and Ireland (2007). *Facing the Challenges: A Guide for Caregivers to People with the Cornelia de Lange Syndrome* – Book and DVD available from the CdLS Foundation UK and Ireland.
- Oliver, C., Moss, J., Petty, J., Tunnicliffe, P., Hastings, R., Howlin, P., Griffith, G., Bull, L., Villa, D. and Yip, M. (2009). *Understanding and Changing Challenging Behaviour in Cornelia de Lange Syndrome.* Aerocomm Ltd: Essex -Available from the CdLS Foundation UK and Ireland.

References

1. **Arron K., Oliver C., Hall S., Sloneem J., Forman D. & McClintock K. (2006)** Effects of social interaction on pragmatic communication and self-injurious behavior in Cornelia de Lange Syndrome. *Am J Mental Retard* 111, 184–92.
2. **Basile E., Villa L., Selicorni A., & Molteni M. (2007).** The behavioural phenotype of Cornelia de Lange syndrome: A study of 56 individuals. *J Intell Disabil Res* 51, 671–681.
3. **Berney T. P., Ireland M. & Burn J. (1999)** Behavioural phenotype of Cornelia de

Lange Syndrome. A*rch Dis Child* 81, 333–6.
4. **Bhuiyan Z. A., Klein M., Hammond P., van Haeringen A., Mannens M.A.M., Van Berckelaer- Onnes I., & Hennekam R.C.M. (2006)** Genotype-phenotype correlations of 39 patients with Cornelia de Lange syndrome: The Dutch experience. *J Med Genet* 46, 568–575.
5. **Cochran, L., Moss, J., Nelson, L. and Oliver, C. (2015).** 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. *American Journal of Medical Genetics, Part C.* 169, 188-197
6. **Crawford, H., Waite, J. & Oliver, C. (2017)** Diverse profiles of anxiety related disorders in fragile X, Cornelia de Lange and Rubinstein-Taybi syndromes. *Journal of Autism and Developmental Disorders*. 47, 3728–3740
7. **Crawford, H., Moss, J., Groves, L., Dowlen, R., Nelson, L., Reid, D. & Oliver, C. (in review**). A Behavioural Assessment of Social Anxiety and Social Motivation in Fragile X, Cornelia de Lange and Rubinstein-Taybi Syndromes. *Journal of Autism and Developmental Disorders*.
8. **Deardorff M. A., Kaur M., Yaeger D., Rampuria A., Korolev S., Pie J. *et al*. (2007)** Mutations in cohesion complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange Syndrome with predominant mental retardation. *Am J Hum Gen* 80, 485–94.
9. **Deardorff, M.A., Bando, M., Nakato, R., Watrin, E., Itoh, T., Minamino, M. et al. (2012).** HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. *Nature, 489*, 313-317.
10. **Deardorff, MA, Wilde, JJ, Albrecht, M, Dickinson, E, Tennstedt, S, Braunholz, et al. (2012)**: RAD21 Mutations Cause a Human Cohesinopathy. *American Journal of Human Genetics,* 90, 1014-1027.
11. **Gillis L.A., McCallum J., Kaur M., DeScipio C., Yaeger D., Mariani A., Kline A.D., Li H., Devoto M., Jackson L.G., Krantz I.D. (2004)** NIPBL mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotype-phenotype correlations. *Am J Hum Gen* 75, 610-623.
12. **Gimigliano, A., Mannini, L., Bianchi, L., Puglia, M., Deardorff, M.A., Menga, S. et al. (2012).** Proteomic profile identifies dysregulated pathways in Cornelia de Lange syndrome cells with distinct mutations in SMCA1 and SMC3 genes. *Journal of Proteomic Research, 11*, 6111-6123.
13. **Groves, L., Crawford, H., Moss, J., Royston, R., Waite, J., Bradley, L., Thomas, A., Moss, K. & Oliver, C. (2018).** The Prevalence and Profile of Anxiety Disorders in Cornelia de Lange and Fragile X Syndromes. *Journal of Intellectual Disability Research* 62 (8), 667-667
14. **Groves, L., Moss, J., Crawford, H., Nelson, L., Stinton, C., Singla, G. & Oliver, C. (2019)**. Lifespan trajectory of affect in Cornelia de Lange syndrome: Towards a neurobiological hypothesis. *Journal of Neurodevelopmental Disorders.* 11:6, doi.org/10.1186/s11689-019-9269-x
15. **Goodban M.T. (1993)** Survey of speech and language skills with prognostic indicators in 116 patients with Cornelia de Lange syndrome. *Am J Med Gen* 47, 1059– 1063.
16. **Hyman P., Oliver C. & Hall S. (2002)** Self-injurious behavior, self-restraint, and compulsive behaviors in Cornelia de Lange Syndrome. *Am J Mental Retard* 107, 146–54.
17. **Huisman, S. A., Redeker, E. J. W., Maas, S. M., Mannens, M. M. & Hennekam, R. C. (2013)**. High rate of mosaicism in individuals with Cornelia de Lange syndrome. *Journal of Medical Genetics*. 50, 339–344
18. **Huisman, S. A. et al. (2017)** Phenotypes and genotypes in 51 individuals with SMC1A variants. *American Journal of Medical Genetics Part A.* 173A, 2108–2125.
19. **Huisman, S. A. et al. (2018).** Self-injurious behavior. *Neuroscience & Biobehavioral Reviews*. Rev. 84, 483–491.

20. **Johnson, V. (2015).** *Executive function and decision making in Cornelia de Lange syndrome*. PhD thesis, University of Birmingham
21. **Kline A. D., Krantz I. D., Sommer A., Kliewer M., Jackson L. G., FitzPatrick D. R. *et al*. (2007)** Cornelia de Lange syndrome: clinical review, diagnostic and scoring systems, and anticipatory guidance. *Am J Med Gen* 143A, 1287–96.
22. **Kline, A., Moss, J., Selicorni, A., Bisgaard, A-M., Deardorff, M., Gillett., P, et al. (2019).** Diagnosis and management in Cornelia de Lange Syndrome: First international consensus statement. *Nature Reviews Genetics*. 19(10), 649-666
23. **Krantz I. D., McCallum J., DeScipio C., Kaur M., Gillis L. A., Yaeger D. *et al*. (2004)** Cornelia de Lange Syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. *Nat Gen* 36, 631–5.
24. **Liu, J & Krantz, ID (2009):** Cornelia de Lange syndrome, cohesion, and beyond. *Clinical Genetics*, 76: 303-314.
25. **Luzzani S., Macchini F., Valade A., Milani D. & Selicorni A. (2003)** Gastroesophageal reflux and Cornelia de Lange Syndrome: typical and atypical symptoms. *Am J Med Gen Part A* 119 (Suppl.3), 283–7.
26. **Miyake N., Visser R., Kinoshita A., Yoshiura K.I., Niikawa N., Kondoh T., Matsumoto N., Harada N., Okamoto N., Sonoda T., Naritomi K., Kaname T., Chinen Y., Tonoki H., & Kurosawa K. (2005)** Four novel NIPBL mutations in Japanese patients with Cornelia de Lange syndrome. *Am J Med Gen* 135*,* 103–105.
27. **Moss J., Oliver C., Wilkie L., Berg K., Kaur G., and Cornish K.** Prevalence of autism spectrum phenomenology in Cornelia de Lange and Cri du Chat syndromes.(2008). *Am J Mental Retard* 113, 278-291.
28. **Moss J., Oliver C., Arron K., Burbidge C. and Berg K. (2009)**.The prevalence and phenomenology of repetitive behaviour in genetic syndromes. *J Aut Dev Disord* 39, 572-588.
29. **Moss, J., Magiati, I., Howlin, P. & Oliver, C. (2012)**. Characteristics of autism spectrum disorder in Cornelia de Lange syndrome. *Journal of Child Psychology and Psychiatry,* 53, 883–891
30. **Moss, J. Howlin, P., Hastings, R. P., Beaumont, S., Griffith, G. M., Petty, J., Tunnicliffe, P., Yates, R., Villa, D. & Oliver, C. (2013)** Social behavior and characteristics of Autism Spectrum Disorder in Angelman, Cornelia de Lange and Cri du Chat syndromes. *American Journal on Intellectual and Developmental Disabilities,* 118, 262–283 (2013)
31. **Moss, J., Nelson, L., Powis, L., Waite, J., Rcihards, C. & Oliver C (2016)**. A comparative study of sociability and selective mutism in autism spectrum disorder, Angelman, Cornelia de Lange, Fragile X and Rubinstein-Taybi syndromes. *American Journal on Intellectual and Developmental Disabilities,* 121, 465–486.
32. **Moss, J., Fitzpatrick, D., Welham, A., Penhallow, J. & Oliver, C. (2017)** Genotype-phenotype correlations in Cornelia de Lange syndrome: behavioral characteristics and changes with age. *American Journal of Medical Genetics* 173A, 1566–1574.
33. **Musio A., Selicorni A., Focarelli M. L., Gervasini C., Milani D., Russo S. *et al*. (2006)** X-linked Cornelia de Lange Syndrome owing to SMC1L1 mutations. *Nat Gen* 38, 528–30.
34. **Nakanishi, M. et al. (2012)**. Investigation of autistic features among individuals with mild to moderate Cornelia de Lange syndrome. Am. J. Med. Genet. 158A, 1841–1847 (2002).
35. **Nelson, L., Moss, J. and Oliver, C. (2014)**. A longitudinal study of affect in children and adults with Cornelia de Lange syndrome. *American Journal on Intellectual and Developmental Disabilities,* 119, 235-252.
36. **Oliver, C., Berg, K., Moss, J., Arron K. and Burbidge, C. (2011)**. Delineation of behavioural phenotypes in genetic syndromes. Comparison of autism spectrum disorder, affect and hyperactivity. *Journal of Autism and Developmental Disorders, 41,* 1019-1032
37. **Reid, D., Moss, J., Nelson, L., Groves, L. & Oliver, C**. Executive functioning in Cornelia de Lange syndrome: domain asynchrony and age related performance. J.

Neurodev. Dis. 9, 29 (2017)
38. **Richards, C., Moss, J., O'Farrell, L., Kaur, G. & Oliver, C. (2009)**. Social anxiety in Cornelia de Lange syndrome. J. Autism Dev. Disord. 39, 1155–1162.
39. **Richards, C., Groves, L., Jones, C., Moss, J. & Oliver, C. (2015).** Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis. Lancet Psychiatry 2, 909–916.
40. **Sarimski K. (1997)** Communication, social-emotional development and parenting stress in Cornelia-de-Lange syndrome. *J Intell Disabil Res* 41, 70–5.
41. **Srivastava, S. et al.** Autism traits in children and adolescents with Cornelia de Lange syndrome. Am. J. Med. Genet. 164A, 1400–1410 (2014).
42. **Sloneem J., Oliver C., Hall S. & Arron K. (2009)**. Self-injurious behaviour in Cornelia de Lange syndrome: 2. association with environmental events. *J Intell Disabil Res* 53, 590-603.
43. **Tonkin E., Wang T. J., Lisgo S., Bamshad M. J. & Strachan T. (2004)** NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteisn and fly Nipped-B, is mutated in Cornelia de Lange Syndrome. *Nat Gen* 36, 636–41.

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