



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, microcephaly, 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, seizures, cardiac and genito-urinary problems. Gastro-intestinal disorders are particularly problematic in CdLS, with up to 80% of individuals with CdLS experiencing Gastro-Esophageal Reflux Disease (GERD) (Macchini et al., 2010; Mariani et al., 2016).

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-injurious behaviour may also be more likely in those with lower levels of intellectual ability, low levels of communication, high levels of impulsivity and the NIPBL gene variant (Selicorni *et al.*, 2021).

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 repetitive behaviours within the syndrome, including repetitive movements and compulsive like behaviours such as tidying up and lining up (Hyman *et al.*, 2002; Moss *et al.* 2009; Srivastava *et al.*, 2021) also indicates that individuals with CdLS may be at risk for difficulties with behaviour regulation. Repetitive behaviours in CdLS are clinically impactful, as they are associated with distress (Srivastava *et al.*, 2021).

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 including greater social anxiety, fewer sensory differences and better use of eye contact and gestures (Groves *et al.*, 2021; 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, generalised anxiety and specific phobias (Crawford, Waite & Oliver, 2017; Groves *et al.*, 2022; Johnson, 2015). Low mood has also been reported in individuals with CdLS with specific difficulties 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, adolescence and early adulthood may be a period of increased difficulty (Goodban, 1993; Groves *et al.*, 2019; Groves *et al.*, 2021; 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 has demonstrated impairments in executive function including verbal fluency and cognitive functioning. Some work suggests that inhibition and working memory are relative strengths (Johnson, 2015), whereas other work suggests impairments across all areas of executive functioning including inhibition and working memory, as well as shifting, emotional control, and planning/organisation (Perry et al., 2021). Research suggests that impairments in executive function are not linked to adaptive ability but are associated with increased age, indicating that impairments in executive function may worsen with age in CdLS (Perry et al., 2021; Reid et al., 2017).

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/>

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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.

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The information contained in these syndrome sheets is aimed at clinicians, is for guidance only, and does not constitute a diagnostic tool. Many syndromes manifest in varying degrees of severity, and this information is not intended to inform patients of a specific prognosis.

The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation