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Change in adolescence and adulthood in Cornelia de Lange syndrome

Cornelia de Lange syndrome is a neurodevelopmental condition or disorder. This means that due to delayed and or different development of the brain, intellectual ability and adaptive behaviours may not develop at the same rate or in the same way as they do for people who do not have the syndrome. The available research shows that in the early teenage years and into young adulthood, there appear to be changes in some types of behaviour only. There is an increase in some autistic like characteristics, such as insistence on sameness, a decrease in sociability and interest and pleasure on a day to day basis, and an increase in anxiety, particularly social anxiety that can lead to reluctance to speak in social settings [1-10]. Research has not identified any other significant changes during this period. Additionally, during this time adaptive behaviour does not change and receptive language skills continue to improve [3]. Those who experience these changes do not show more change in adaptive behaviour than other people. Limited research also shows that there might be some changes in some specific types of cognitive ability, such as short-term or working memory [11]. However, cognitive abilities are very hard to assess accurately in people with more severe intellectual ability so studies need to be conducted to check these results. Risk and patterns of change are highly variable across individuals [5, 9]. Notably changes in behaviour seem to stabilise in adult life.

It should be noted that studies to date have: 1) used groups of people with a clinical (i.e. not genetically confirmed) diagnosis, 2) used groups likely to include people with different genetic causes of CdLS and 3) reported group results (so there is significant individual variability within the group). This means that is not clear whether people with different genetic causes of CdLS will experience change in the same way or at all.

The causes of these changes are unclear. The most likely explanations are that anxiety plays a critical role and/or that as the brain develops in the teenage years the structure and connections in the frontal lobes in the brain do not form or develop as they would in someone without the syndrome. Researchers have speculated that there might be more widespread, ongoing change in the brain but this is highly unlikely given that behavioural change does not continue, adaptive behaviour is not changing, receptive language continues to develop and change is occurring in some areas of behaviour only. Any statements in research papers about the cause of change during this period are speculative or hypothetical and are identified as such.

At present the most effective interventions for this period of change are managing the environmental demands and unpredictability that are experienced by people with CdLS, together with anxiety reduction and management strategies. These interventions are part of the International Guidelines published in Nature Reviews Genetics written by the World Federation Cornelia de Lange Syndrome Scientific Advisory Committee [12]. The goal of intervention at present is to prevent any change from impinging on the quality of life of people with Cornelia de Lange syndrome and their families.

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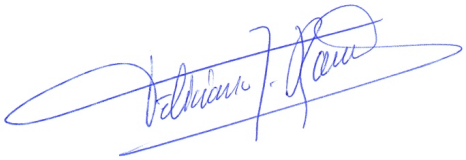

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References

1. Basile, E., Villa, L., Selicorni, A., & Molteni, M. The behavioural phenotype of Cornelia de Lange syndrome: A study of 56 individuals. *Journal of Intellectual Disability Research*, 2007; 51, 671–681.
2. 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. *American Journal of Medical Genetics Part C.*, 2015; 169(2): 188-97
3. Cochran, L., Welham, A., Oliver, C., Arshad, A. & Moss, J. Age-related Behavioural Change in Cornelia de Lange and Cri du Chat Syndromes: A Seven Year Follow-up Study. *J Autism Dev Disord* 49, 2019; 2476–2487. https://doi.org/10.1007/s10803-019-03966-6
4. Crawford, H., Waite, J., & Oliver, C. Diverse Profiles of Anxiety Related Disorders in Fragile X, Cornelia de Lange and Rubinstein-Taybi Syndromes. *Journal of Autism and Developmental Disorders*; 2017; 47(12), 3728-3740
5. Groves, L., Moss, J., Crawford, H., Nelson, L., Stinton, C., Singla, G., & Oliver, C. Lifespan trajectory of affect in Cornelia de Lange syndrome: Towards a neurobiological hypothesis. *Journal of Neurodevelopmental Disorders.* 2019. 11(6). doi.10.1186/s11689-019-9269-x
6. Kline, A. D., Krantz, I. D., Sommer, A., Kliewer, M., Jackson, L. G., FitzPatrick, D. R., … Selicorni, A. (2007). Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance*. American Journal of Medical Genetics Part A*, 2007. 143A(12), 1287–1296.doi:10.1002/ajmg.a.31757
7. Moss, J., Oliver, C., Nelson, L., Richards, C., & Hall, S. Delineating the profile of autism spectrum disorder characteristics in Cornelia de Lange and Fragile X syndromes. *American Journal on Intellectual and Developmental Disabilities*, 2013; 118(1), 55-73. doi:10.1352/1944-7558-118.1.55
8. Moss, J., Nelson, L., Powis, L., Waite, J., Richards, C., & Oliver, C. A Comparative Study of Sociability in Angelman, Cornelia de Lange, Fragile X, Down and Rubinstein Taybi Syndromes and Autism Spectrum Disorder. *American Journal on Intellectual and Developmental Disabilities*, 2016; 121(6), 465-486. doi:10.1352/1944-7558-121.6.465
9. Moss, J., Fitzpatrick, D., Welham, A., Penhallow, J., & Oliver, C. Genotype-phenotype correlations in Cornelia de Lange syndrome: Behavioral characteristics and changes with age. *American Journal of Medical Genetics*; 2017; 173A: 1566-1574.
10. Nelson, L., Moss, J., & Oliver, C. A longitudinal follow-up study of affect in children and adults with Cornelia de Lange syndrome. *American Journal on Intellectual and Developmental Disabilities*; 2014; 119(3): 235-252.
11. Reid, D., Moss, J., Nelson, L., Groves, L., & Oliver, C. Executive functioning in Cornelia de Lange syndrome: domain asynchrony and age related performance. *Journal of Neurodevelopmental Disorders*; 2017; 9 (1): 29 doi:10.1186/s11689-017-9208-7
12. Kline, A. D., Moss, J., Selicorni, A., Bisgaard, A-M., Deardorff, M., Gillett., P,… Hennekam, R. Diagnosis and management in Cornelia de Lange Syndrome: First international consensus statement. *Nature Reviews Genetics.* 2018; 19(10), 649-666.doi:10.1038/s41576-018-0031-0