Summary of 'The neurodevelopmental spectrum of CASK-related disorder'

by J. Martin, A. Mavrogalou-Foti, J. Eck, L. Hattersley and K. Baker.

The *CASK* gene is important for brain development, and *CASK* gene differences (known as variants or mutations) lead to neurodevelopmental difficulties. Some people with *CASK* gene differences have mild learning difficulties, whilst others have severe learning difficulties and brain structure differences, such as microcephaly (a smaller head) and pontocerebellar hypoplasia – when parts of the brain that control movement and coordination are smaller or less well developed (known collectively as MICPCH). However, beyond learning and brain structure differences, there is limited information about other neurodevelopmental difficulties, such as social, emotional, and behavioural challenges.

Understanding the type and range of neurodevelopmental difficulties in *CASK*-related disorder is increasingly important as the number of people diagnosed is rising. Knowing how different factors interact – for example, brain structure difference and developmental delay – is also important, and may help identify key areas for future interventions.

What did we do? In this study, we explored neurodevelopmental difficulties in people with *CASK*-related disorder by examining information from two sources:

1) published reports of 151 people with *CASK* gene differences from previous studies; and

2) new assessments of 31 children and young people with *CASK* gene differences from the BINGO study, a UK-based research project that focuses on brain function and behaviour in people with rare genetic conditions.

By comparing the new (BINGO) group to earlier reports, we were able to examine whether the same types of neurodevelopmental difficulties appeared in both and how common they were. In the BINGO group, we also explored whether certain problems, such as epilepsy or brain structure differences, were linked to poorer adaptive function – greater challenges with daily life skills, communication, and social abilities.

What did we find? The types of neurodevelopmental difficulties reported in the BINGO group were similar to those described in earlier studies, though severe learning difficulties, brain structure differences and visual problems were less common. We also found that cerebral visual impairment (CVI) – when the brain, rather than the eyes, has problems processing visual information – and sleeping difficulties were common in the BINGO group, even though these hadn't been reported in previous research. The presence of epilepsy, but not brain structure differences, was also linked to poorer adaptive function in the BINGO group.

Why this matters? / How can this research help? Understanding the full spectrum of *CASK*-related neurodevelopmental difference can help families, clinicians and researchers identify areas for monitoring and intervention. This study highlights additional areas to monitor, such as CVI and sleep, which may not have been previously recognised. Additionally, preliminary findings suggest that epilepsy might be linked to developmental ability.

Limitations and future directions: The BINGO group included a limited number of participants, and we did not include a comparison group in this study. Assessments of brain structure differences and epilepsy were limited, so these findings should be interpreted with caution. More research is needed on how brain structure, epilepsy and behaviour are linked in people with *CASK* gene differences.

Conclusion: This study provides an up-to-date description of *CASK*-related disorder and is a useful step toward understanding the spectrum of neurodevelopmental difficulties linked to *CASK* gene differences.