



“Distinct cerebellar foliation anomalies in a *Chd7* haploinsufficient mouse model of CHARGE syndrome”

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AUTHORS AND THEIR CONNECTION TO THE CHARGE SYNDROME FOUNDATION:



Danielle Whittaker, BVetMed, PhD, is currently training to be a specialist in veterinary neurology and neurosurgery at the Royal Veterinary College, London.

She has a particular interest in the role of chromatin remodeling factors in neurodevelopment.



Albert Basson, PhD, is a reader in Developmental and Stem Cell Biology at the Centre for Craniofacial and Regenerative Biology and the MRC Centre for Neurodevelopmental Disorders, King's College London.

His research focuses on signaling pathways and chromatin remodeling factors implicated in neurodevelopmental disorders. Albert has presented at the CHARGE syndrome conferences and collaborates with many other CHARGE researchers.



The other authors comprise a team of individuals who have been involved in research or are training in neurodevelopment in animals and humans. One, however, deserves mention here because of his direct connection to the CHARGE Syndrome Foundation:

Alex Donovan (PhD candidate) attended the 2017 CHARGE conference as a Sandra Davenport CHARGE Fellow, where he got to meet other researchers and the families his research may eventually affect. See more about Alex in the [Spring 2018 CHARGE Accounts](#) newsletter.

SUMMARY OF THE PAPER:

Abstract: Mutations in the *CHD7* gene are the major cause of CHARGE syndrome (CS). Neurodevelopmental defects and a range of neurological signs have been identified in individuals with CS, including developmental delay, lack of coordination, intellectual disability, and autistic traits. We previously identified the brain findings of cerebellar vermis underdevelopment and abnormal cerebellar folding in individuals with CS. Here, we report mild cerebellar

underdevelopment and distinct cerebellar foliation changes in a *Chd7* mouse model. We describe specific alterations in the precise sequence of fissure formation during perinatal brain development responsible for these anomalies. The altered cerebellar foliation patterns in *Chd7* mice show some similarities to those reported in mice with altered expression of several other genes. We propose that changes in these genes may modify the cerebellar findings in CS. Our findings in a mouse model of CS indicate that a careful analysis of brain cerebellar foliation may be warranted in patients with CS syndrome, particularly in those with cerebellar hypoplasia and developmental delay.

Additional summary: This team used a mouse model of CS to more closely look at changes in the brain, particularly changes in the cerebellum, at the base of the brain. They compare changes seen in mice with those reported in humans and discuss how these changes may be related to the developmental issues seen in individuals with CS. The human and mouse genes are designated as “*CHD7*” and “*Chd7*” respectively.

The specific effects of *CHD7* on basic brain structure are not known. Children with CS sometimes have brain differences noticeable on MRI, but many of the differences described are subtle and have not been systematically investigated. This study looks very carefully at the brains of mice with *Chd7* (HET - heterozygotes) and compares them with unaffected littermates (WT – wild type). Detailed examination of MRI of the brains of all of the HET mice showed subtle and variable, but significant, changes. Figures include MRIs and diagrams of mouse brain WT type as compared with those with *Chd7* mutations (HET) and descriptions of the affected areas of the brains.

As in people, *Chd7* does not do the same thing to every individual mouse with the same mutation. Even littermates (siblings) did not always show the same degree of effect of identical *Chd7* variants. The authors discuss the interactions of *Chd7* with other genes and gene complexes. They note that the cerebellar vermis changes described in some humans with CS share some similarities with Dandy Walker malformation (DWM), the most frequent congenital cerebellar malformation in the human population. They also point out that vestibular dysfunction (absent semicircular canals in the inner ear) alone is not enough to fully explain gait (walking) abnormalities in children with CS. They believe further investigation of a potential cerebellar contribution to the balance issues in CS should be done.

WHAT DOES THIS MEAN TO FAMILY/PERSON WITH CHARGE?

Although it will not make a difference to everyday management, studies like this help explain the complexity of some of the developmental aspects of CS. Our ability to image the brain or otherwise get information that can be translated to explaining developmental issues or behavior is in its infancy. This fascinating study contributes to areas of research that may eventually help us understand not only CS development and behavior, but childhood development and behavior in general. This work will help us understand what we need to be paying attention to in brains – what to be looking at when brain imaging is done.

SHOULD I READ IT? SHOULD ONE OF MY DOCTORS READ IT?

It won't help your doctors take care of your child, but if you are interested in learning more about brain embryology, take a look, especially at the figures. Most people will be able to understand the abstract, introduction and conclusions. The figures showing mouse brain MRIs and colorful depictions of the changes in CHARGE mouse brains are very cool.

FULL CITATION:

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