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Prenatal diagnosis for Joubert syndrome?

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The identification of a gene that causes a common form of Joubert syndrome might elucidate the neurological pathways involved in this and related brain disorders. It is hoped that this discovery will enable clinicians to better diagnose birth defects of the cerebellum within the next five years.

Joubert syndrome

Originally described in 1968 based on clinical features that include unusual breathing and eye movements, Joubert syndrome is diagnosed today by its magnetic resonance imaging (MRI) phenotype: the absence of the cerebellar vermis and the 'molar tooth sign,' abnormally shaped superior cerebellar peduncles [1,2]. Individuals affected with this autosomal recessive brain disorder typically suffer from motor abnormalities, in some cases an inability to walk due to severe clumsiness and mirror movements, as well as cognitive difficulties and autistic behaviors.

Joubert syndrome is rare, with an estimated incidence of 1 in 10,000. However, it and other birth defects of the cerebellum are identified as a fluid cyst behind the fetal brain at a much higher rate in prenatal ultrasounds. Although the outcome of these children varies greatly, it isn't possible to distinguish between Joubert syndrome, Dandy-Walker malformation and the other cerebellar birth defects at this stage of development.

Further, Joubert syndrome itself has significant clinical and genetic heterogeneity. 'It's a group of syndromes with variable features,' says William B. Dobyns, Professor of Human Genetics, Neurology and Pediatrics at The University of Chicago (www.uchicago.edu). 'We believe there are going to be a number of different genetic causes.'

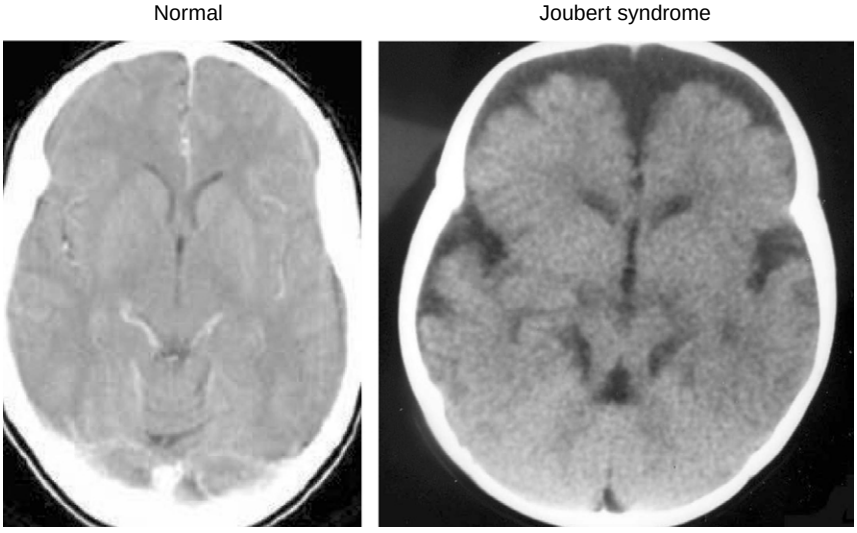

Figure 1. Excessive folding in the cerebral cortex of a patient with Joubert syndrome. Image courtesy of J. Gleeson of the University of California, San Diego.

Middle Eastern population

After trying unsuccessfully to identify a gene within the US, researchers turned to the Middle East where patterns of intermarriage increase the ease of genetic linkage studies. Using homozygosity mapping, two groups of scientists independently identified the *AHI1* gene in patients with a form of Joubert syndrome that affects the brain but not the kidney or retina [2,3]. The patients studied by Joseph Gleeson, Assistant Professor of Neurosciences, University of California, San Diego (http://medicine.ucsd.edu/neurosci/) and Children's Hospital San Diego (http://www.chsd.org/), and his colleagues also exhibited cortical polymicrogyria or increased folds within the cerebral cortex (Figure 1).

A preliminary analysis of the *AHI1* gene suggests that it codes for a cytoplasmic adaptor protein involved in neuronal signaling. 'By understanding this gene and its effects, we might be able to identify other proteins involved in Joubert syndrome,' says Russ Ferland, Instructor in Neurology at Harvard Medical School (http://hms.harvard.edu/hms).

It also appears as though the *AHI1* gene, which evolved differently in the human lineage, might 'have a critical role in controlling the direction in which axons cross through the brain,' says Christopher A. Walsh, Howard Hughes Medical Institute Investigator (http://www.hhmi.org) and Neurology Professor at Harvard Medical School.

Prenatal testing limited

Another gene, *NPHP1*, and two additional loci on chromosomes 9 and

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11 have been implicated in Joubert syndrome [4–6]. However, it's only with the identification of the *AHI1* gene that the potential for a prenatal genetic screen has been raised.

'Prenatal diagnosis could be offered with existing technology tomorrow, but only for the second child in an affected family,' says Dobyns. He estimates that the *AHI1* gene causes 10–20% of Joubert syndrome and, more broadly, that Joubert syndrome accounts for only about 10% of the cerebellar brain defects observed in prenatal ultrasounds.

As genes for other brain disorders are identified, such as *ZIC1* and *ZIC4* for Dandy-Walker malformation, a broader genetic screen will become feasible [7]. It's also possible that these genes might be involved in more common childhood brain and behavioral abnormalities, says Gleeson, who is currently working with the Cure Autism Now Foundation (http://www.canfoundation.org/) to screen their patient collection for changes in the *AHI1* gene.

References

1 Joubert, M. *et al.* (1968) Familial dysgenesis of the vermis: a syndrome of hyperventilation, abnormal eye movements and retardation. *Neurology* 18, 302c–303c

2 Ferland, R.J. *et al.* (2004) Abnormal cerebellar development and axonal decussation due to mutations in *AHI1* in Joubert syndrome. *Nat. Genet.* 36, 1008–1013

3 Dixon–Salazar, T. *et al.* (2004) Mutations in the *AHI1* gene, encoding Jouberin, cause Joubert syndrome with cortical polymicrogyria. *Am. J. Hum. Genet.* 75, 979–987

4 Parisi, M.A. *et al.* (2004) The *NPHP1* gene deletion associated with juvenile nephronophthisis is present in a subset of individuals of with Joubert syndrome. *Am. J. Hum. Genet.* 75, 82–91

5 Saar, K. *et al.* (1999) Homozygosity mapping in families with Joubert syndrome identifies a locus on chromosome 9q34.3 and evidence for genetic heterogeneity. *Am. J. Hum. Genet.* 65, 1666–1671

6 Keeler, L.C. *et al.* (2003) Linkage analysis in families with Joubert syndrome plus oculo–renal involvement identifies the CORS2 locus on chromosome 11p12–q13.3. *Am. J. Hum. Genet.* 73, 656–662

7 Grinberg, I. *et al.* (2004) Heterozygous deletion of the linked genes *ZIC1* and *ZIC4* is involved in Dandy–Walker malformation. *Nat. Genet.* 36, 1053–1055

Sugar directly triggers fat formation

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Consume too many carbohydrates in your diet and your liver will convert them into fatty acids for long-term energy storage, evidenced by our burgeoning waistlines. Processed carbohydrates are touted as enemy number one by popular diets, with insulin touted as the key player in the process. However, it's now clear that sugar can act alone in making us fat. Kosaku Uyeda and colleagues at the University of Texas Southwestern Medical Center in Dallas, TX, USA (http://www.utsouthwestern.edu) report that simple sugars can also directly trigger fat formation via the activation of several genes responsible for control of glucose metabolism, as well as fatty acid and triglyercide synthesis [1].

Lipogenesis

Carbohydrate response element-binding protein (ChREBP) is a transcription factor, first discovered by Uyeda's group in 2001, and is responsible for the glucose-induced transcription of the liver pyruvate kinase gene (*LPK*), a regulatory enzyme in the glycolytic pathway. Under low glucose

conditions, ChREBP remains in the cytosol of hepatocytes, and cannot bind to its DNA target due to phosphorylation of multiple sites. In the presence of high glucose, these sites are dephosphorylated and ChREBP can now bind to its targets, triggering fat formation without any help from insulin.

ChREBP promotes lipogenesis enzymes

In findings published earlier this year [2] Uyeda's group described their mouse model in which the *ChREBP* gene is knocked out. Mice unable to produce ChREBP showed a reduced ability to metabolize glucose and store fat, and accumulated excess glycogen in the liver.

Now their latest findings confirm those *in vivo* findings, ruling out indirect mechanisms that could have been involved. Using liver cells from wild-type and *ChREBP*-knockout mice, they show that ChREBP is responsible for glucose-dependent transcriptional activation of LPK and carbohydrate-responsive lipogenic enzyme genes, including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), both involved in fatty acid synthesis, among others.[1]

'Not only is it directing regulatory gene expression for LPK, but also these lipogenic enzyme genes, resulting in a

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