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Team makes breakthrough in understanding Canavan disease

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UC Davis investigators have settled a long-standing controversy surrounding the molecular basis of an inherited disorder that historically affected Ashkenazi Jews from Eastern Europe but now also arises in other populations of Semitic descent, particularly families from Saudi Arabia.

Through a series of elegant experiments, the researchers uncovered the biochemical underpinnings of Canavan disease, a type of leukodystrophy that is an incurable and progressively fatal neurological condition. The UC Davis team identified an abnormally high buildup of the second most common molecule in the brain, N-acetylaspartate (NAA), as the culprit that causes the syndrome's destructive effect.

The findings, which are now available online, appear in the May 2015 issue of the journal *Annals of Neurology* in an article titled, "Ablating N-acetylaspartate prevents leukodystrophy in a Canavan disease model."

"By finally identifying the biochemical basis for this terrible disorder, we are hopeful that it can lead to an effective treatment," said David Pleasure, a UC Davis Distinguished Professor of neurology and pediatrics, and principal investigator of the study.

Leukodystrophies comprise a number of rare genetic disorders of the central nervous system that involve disrupted development of the myelin sheath that grows around neurons, which is essential for normal nerve conduction. Canavan disease usually becomes apparent in infancy with

poor muscle tone and abnormal head enlargement, and rapidly progresses to mental retardation, paralysis, blindness, hearing loss, and usually death by age 10. There is currently no treatment.

Canavan disease is inherited in an autosomal recessive pattern, meaning that if both parents carry the mutation, each child has a one in four chance of developing the condition. Although the disease occurs worldwide, the most frequent carriers of the mutation are Ashkenazi Jews from Eastern Europe. Because of widespread genetic counseling in that population, most cases of the disease now arise in families from other backgrounds, especially in Saudi Arabians.

It has been well understood for years that the critical mutation that leads to Canavan disease is of the gene that codes for an enzyme called aspartoacylase (ASPA), which breaks down NAA into acetate and aspartate. Without a working ASPA enzyme, NAA—which provides multiple important functions in the brain—builds up, resulting in a shortage of the two byproducts. Knowing this led to two hypotheses of what is responsible for the manifestation of Canavan disease—it might either be a problem of too much NAA or too little availability of the byproducts. Because acetate is an essential component of myelin synthesis, the "too little byproduct" hypothesis had a good theoretical basis and led to attempted treatments that stymied investigators because of their ineffectiveness.

Pleasure's group used mice engineered with specific genetic mutations to prove that the "too much NAA" theory is the correct one. Mice that were genetically unable to produce NAA exhibited normal myelination, indicating that not having acetate available from this pathway cannot be responsible for poor myelin development. Furthermore, these same mice, if also given the ASPA mutation of Canavan disease, did not develop signs of the syndrome.

It has been suggested that one of NAA's functions is to preserve the essential water and salt balance in the brain. It is this possible function that Pleasure believes is likely to be the primary problem in Canavan disease. Children with the disease have enlarged fluid-filled areas in the brain evident in magnetic resonance imaging studies, possible evidence of a water-salt imbalance. According to this theory, dysmyelination occurs secondarily to the problems caused by fluid imbalance.

Attempts to treat Canavan disease have taken several directions. Supplementing acetate has been unsuccessful, which according to the new findings is to be expected. Combating the mutation directly by implanting a working ASPA gene using a viral vector has worked well in mouse models of the disease but is technically unfeasible so far in humans.

This current research points to a new avenue of treatment: blocking the production of NAA. However, NAA, being such a common molecule in the brain, must have essential functions, according to Pleasure. Mice that are genetically engineered to be unable to synthesize NAA have been reported to have abnormal social interactions. One child has been identified in the literature who was unable to produce NAA because of a genetic mutation. The child had neurodevelopmental retardation.

"Reducing NAA without eliminating it completely may be the most promising direction of treatment," said Pleasure, whose laboratory is based in Sacramento at Shriners Hospitals for Children Northern California. "Our goal is to find a method to reverse the process in children with the disease - that will be the most useful to families with this heartbreaking condition."

Provided by UC Davis