QnAs with Arthur Beaudet

Prashant Nair

Science Writer

In May 2012 Arthur Beaudet, a geneticist at Baylor College of Medicine, Houston, TX, and a member of the National Academy of Sciences, reported a preliminary link between the deficiency of a gene that helps cells synthesize a biomolecule called carnitine and the risk of autism in some boys. Beaudet's 2012 Inaugural Article (1) in PNAS raised the possibility that carnitine—a fatty acid-ferrying molecule that cells derive through diet or make anew—might influence the risk of autism. Beaudet's findings have yet to be independently validated, but they have opened an avenue of investigation that approaches autism as an inborn error of metabolism, suggesting that some forms of autism may turn out to be preventable. Beaudet has long been recognized for his contributions to the genetic diagnosis of developmental disorders, and here he discusses the implications of his work on autism with PNAS.

PNAS: How did you come to suspect a link between autism and carnitine deficiency?

Beaudet: We had previously published a study speculating that there may be de novo mutations or epigenetic effects that explain why most conventional genetic studies of autism, particularly genome-wide association studies, turned out to be negative. Over the last five years or so, autism-associated copy number variants and point mutations have been uncovered. These are all heterogeneous; no one gene accounts for more than a fraction of observed cases. We looked at copy number abnormalities for every exon (protein-coding DNA) in the genome of a patient with autism and discovered a deletion in exon 2 of a gene called TMLHE on the X chromosome. The deletion inactivates the gene, which encodes an enzyme involved in the first step of carnitine biosynthesis. We also found a number of healthy adult males—about 1 in 360—with the deletion. However, the results seemed to suggest that the absence of the enzyme conferred an increased risk of autism. So, we became fairly convinced that this enzyme deficiency is a risk factor for autism, although most people with the defect do not go on to develop autism. Males born with the deficiency have a 3% chance of being diagnosed with autism; that's about twofold higher than the general population's risk for males.

PNAS: What is your current thinking on how carnitine biosynthesis might be tied to autism?

Beaudet: Our current hypothesis is that carnitine deficiency might be a more general risk tied to autism than that attributed to TMLHE deficiency alone. We suspect that carnitine deficiency might underlie the clinical regression in social and language skills—such as the loss of word use and eye contact acquired during development—typically reported between 12 and 18 months of age in some autistic children. There may be other genes related to carnitine metabolism that might also be risk factors for autism. We are now studying two autistic patients who have had episodes of regression and carnitine deficiency at the time of regression.

PNAS: If the link between carnitine metabolism and autism bears out, will there be systematic attempts to study the preventive or therapeutic effects of dietary carnitine supplementation on autism?

Beaudet: We are trying to collaborate with a research group called the Baby Siblings Research Consortium, which involves about a dozen study sites that enroll and follow newborn siblings from families with an autistic child. The Consortium previously reported that 26% of male siblings born into such families ultimately developed a diagnosis of autism. If a family had two prior children with autism, the risk of a third child developing autism rose to 45% for a male sibling. We are trying to launch a preventive trial in partnership with the Consortium to test the effect of dietary carnitine supplementation on the baby-siblings. The idea that you can lower the risk of autism in healthy infants through dietary change merits testing.

PNAS: Can you comment on recent findings that reported a direct association between carnitine levels and the risk of heart disease and stroke?

Beaudet: There is a recent publication reporting that eating large amounts of red meat, which equates to high carnitine intake, can be associated with bacteria in the gut converting carnitine to trimethylamine-*N*-oxide (TMAO), and that higher blood concentrations of TMAO may be associated with increased risk of atherosclerosis. I don't know

Arthur Beaudet. Image courtesy of Baylor College of Medicine, Houston, TX.

if this study will be proven to be correct, but even if that is the case, a generous intake of carnitine in early infancy is unlikely to be a risk in this regard.

PNAS: You helped uncover the role of genomic imprinting on chromosome 15 in the onset of Angelman Syndrome and Prader-Willi Syndrome, and at Baylor College, you have long provided diagnostic services. As the cost of genome sequencing continues to plummet, do you think genetic tests of individual loci might lose some of their clinical relevance in the near future?

Beaudet: Tests of individual genes will continue to have relevance in cases where the genes tied to the conditions are clearly identified, such as cystic fibrosis or muscular dystrophy. In those cases, it wouldn't be necessary to sequence the entire genome. However, we are increasingly providing whole exome and genome sequencing for diagnosis for more general problems, such as birth defects, intellectual disability, and developmental delay. There aren't many laboratories offering these technically sophisticated diagnostic services, but there are no patent issues tied to these tests.

PNAS: Speaking of patents for genetic tests, what are your views on the patentability of genes, now that the issue of patents for the

BRCA genes in breast cancer screening has earned the coveted attention of the United States Supreme Court?

Beaudet: I am opposed to gene patents for diagnostic purposes. The investment of companies trying to corner this market is often minor compared with the publicly funded

groundwork (NIH and other taxpayer-derived sources) that made it possible to create the tests. Because taxpayers foot a large share of the cost toward developing the tests, which can be performed by other companies at competitive costs, I believe that patents for such diagnostic tests are

not warranted. On the other hand, the therapeutic use of a gene may warrant patent protection, depending on the circumstances.

1 Celestino-Soper PB, et al. (2012) A common X-linked inborn error of carnitine biosynthesis may be a risk factor for nondysmorphic autism. *Proc Natl Acad Sci USA* 109(21):7974–7981.