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Preventable Forms of Autism?

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Abstract

Inborn errors of metabolism underlying some cases of autism present possibilities for prevention and treatment

Autism has attracted enormous attention in recent years primarily because of the high incidence and the impact it has on patients' lives and their families, given its medical, social, financial, and emotional burdens (1, 2). There is growing acceptance that the incidence and prevalence of autism have dramatically increased over the past 20 years (3), although some of the increase relates to changing diagnostic terminology and criteria. The use of DNA microarrays and exome sequencing to detect pathological copy number variants (CNVs) and point mutations, respectively, is making progress in identifying genetic causes of autism. The recent confirmation that paternal age is a risk factor for autism relates to the occurrence of de novo point mutations that can now be discovered through next-generation sequencing (4). However, for virtually all of the pathological CNVs and point mutations causing autism, there is no definitive or curative therapy, although CNVs can be detected using invasive prenatal diagnosis. On page 394 of this issue, Novarino *et al.* (5) use exome sequencing in consanguineous families to discover an inborn metabolic error associated with autism, epilepsy, and intellectual disability, in which the clinical manifestations are likely to be treatable or, even better, preventable.

Empirical results reveal that the more severe and complex the autistic phenotype, the greater the likelihood that a causative mutation can be found. Most of the patients at the more severe end of the spectrum also have intellectual disability, and there is substantial overlap in the etiology for this group compared to that for intellectual disability in general. It has emerged from recent genetic studies that the number of different CNV loci and individual genes that —when mutated—can cause autism ranges into the hundreds, reflecting extreme genetic heterogeneity (6) (https://gene.sfari.org/). Another recurring observation is that the same genotype, whether CNV or point mutation, can give rise to a broad spectrum of phenotypes including autism, intellectual disability, schizophrenia, bipolar disorder, and epilepsy with various combinations of these being present in a single patient (variable expressivity), but with complete lack of penetrance (no symptoms) also occurring with such genotypes (7).

Novarino *et al.* identified a point mutation in a gene encoding the branched-chain keto acid dehydrogenase kinase (BCKDK). BCKDK inactivates an enzyme complex that converts branched-chain amino acids to the corresponding keto acids. Thus, defective BCKDK results in unchecked degradation and depletion of branched-chain amino acids. This is effectively the reverse of the metabolic problem present in maple syrup urine disease, where

deficiency of the same enzyme complex leads to toxic accumulation of branched-chain amino acids and their metabolites. In a mouse model of BCKDK deficiency, similar metabolic and neurobehavioral abnormalities are found, and the animals improve upon dietary supplementation with branched-chain amino acids.

Assuming that it would be desirable to prevent rather than reverse symptoms of BCKDK deficiency, newborn screening could be explored. Over 50 inborn errors of metabolism are detectable by newborn screening, and its use in treatable disorders is particularly beneficial. it is not clear whether BCKDK deficiency would be easily detected by newborn screening. It could involve measuring the plasma ratio of branched-chain amino acids to other amino acids or perhaps the ratio of branched-chain amino acids to their respective keto acids. If necessary, sequence analysis could be used. At this time, it is assumed that BCKDK deficiency will be quite rare, but newborn screening might prove to the contrary, and milder forms of the disorder may exist. Another rapidly evolving genetic strategy is universal carrier detection for autosomal recessive or X-linked mutations (8). Using universal carrier testing, couples might be alerted to their one-in-four risk of having an affected child even before conception. Then, they could consider preimplantation genetic diagnosis whereby only unaffected embryos would be implanted as an additional option.

BCKDK deficiency is not the first inborn error of metabolism to be linked with autism. Deficiency of carnitine biosynthesis was also reported recently as a likely risk factor for autism (9). The *TMLHE* (trimethyllysine hydroxylase, epsilon) gene maps to the X chromosome and encodes the first enzyme in the pathway for the biosynthesis of carnitine. Carnitine is an amino acid derivative necessary for transport of fatty acids from the cytoplasm into mitochondria. About 1 in 350 healthy males of European descent are deficient for *TMLHE*, and the penetrance for autism on a British or American diet would be only 2 to 4%, making replication studies essential to confirm the link to autism. In this case, toxic accumulation of trimethyllysine—or, more likely, neuronal camitine deficiency—might cause the autism. Thus, carnitine supplementation might be useful for treatment or prevention. For *TMLHE* deficiency, newborn screening is straight-forward, based on increased concentrations of trimethyllysine and reductions of other metabolites, although most infants identified would be expected to become normal adults even without intervention. The authors suggest that abnormalities of carnitine metabolism including intake, loss, transport, or synthesis may be important in a larger fraction of nondysmorphic autism cases.

The role of carnitine might be relevant for explaining part of the male predominance of autism because there is an estrogen-inducible, X-linked carnitine transporter at the blood-brain barrier (10, 11). The sex ratio in autism is quite noteworthy. For the severe end of the spectrum, the male:female ratio is between 2 to 1 and 4 to 1, but at the milder end of the spectrum, including Asperger syndrome, the male:female ratio is often 8 to 1 or greater. One group found a sex ratio of 23 to 1 in patients with a normal physical examination and a normal MRI of the brain (12). Part or all of the sex ratio at the severe end of the spectrum may be explained by CNVs or point mutations affecting causative genes located on the X chromosome; but identification of causative mutations is rare for the milder end of the spectrum. The basis of the sex ratio and the etiology of the autism are both very enigmatic

for the milder end of the spectrum, but the sex ratio suggests that there may be a substantial group of at least 10 to 20% with a more homogeneous pathophysiology or etiology within the milder autism population that depends highly on the biological differences between males and females (see the table). Regression in behavioral or learning skills is common in autism, and there is evidence linking regression to transient milder macrocephaly (13). The putative increase in the incidence of autism is more prominent in children with higher levels of functioning (3).

There may be a common thread for both of these newly discovered inborn errors of metabolism. For both disorders, physical examinations are generally normal with no dysmorphic features described (as is true for most inborn errors of metabolism). Both could involve neuronal deficiency of essential nutrients. Malnutrition is widely accepted to contribute to intellectual disability, and perhaps specific nutritional deficiencies (e.g., of branched-chain amino acids or camitine) in the brain can lead to abnormal synaptic development. Maternal exposure to famine increases the risk of schizophrenia. At the time that solid foods are introduced into the diet, fruits, cereals, and vegetables are usually offered for several weeks and months. These foods are especially low in camitine and branched-chain amino acid content, and neuronal deficiency of any of these nutrients could provide a mechanism to explain the regression that can occur in autism. From this perspective, dietary intake, infection, other factors causing loss of nutrients, and altered transport across the blood-brain-barrier all become interesting variables. A recent study on twin pairs increased the evidence for a role of shared environmental factors in addition to genetic heritability in the etiology of autism (14). The level of metabolites in the cerebrospinal fluid would be of great interest for both disorders, but no data are yet available. Intensive metabolomic analyses of cerebrospinal fluid (15) in cases of autism would be very worthwhile and might uncover other treatable or preventable forms of autism.

References

1. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators Centers for Disease Control and Prevention. MMWR Surveill. Summ. 2007; 56:12. [PubMed: 17287715]
2. Karst JS, Van Hecke AV. Clin. Child Fam Psychol. Rev. 2012; 15:247. [PubMed: 22869324]
3. Keyes KM, et al. Int. J. Epidemiol. 2012; 41:495. [PubMed: 22253308]
4. Kong A, et al. Nature. 2012; 488:471. [PubMed: 22914163]
5. Novarino G, et al. Science. 2012; 338:394. [PubMed: 22956686]
6. Banerjee-Basu S, Packer A. Dis. Model. Mech. 2010; 3:133. [PubMed: 20212079]
7. Sebat J, Levy DL, McCarthy SE. Trends Genet. 2009; 25:528. [PubMed: 19883952]
8. Srinivasan BS, et al. Reprod. Biomed. Online. 2010; 21:537. [PubMed: 20729146]
9. Celestino-Soper PB, et al. Proc. Natl. Acad. Sci. U.S.A. 2012; 109:7974. [PubMed: 22566635]
10. Nakanishi T, et al. J. Physiol. 2001; 532:297. [PubMed: 11306651]
11. Karunakaran S, et al. J. Biol. Chem. 2011; 286:31830. [PubMed: 21771784]
12. Miles JH, Hillman RE. Am. J. Med. Genet. 2000; 91:245. [PubMed: 10766977]
13. Nordahl CW, et al. Proc. Natl. Acad. Sci. U.S.A. 2011; 108:20195. [PubMed: 22123952]
14. Hallmayer J, et al. Arch. Gen. Psychiatry. 2011; 68:1095. [PubMed: 21727249]
15. Mandal R, et al. Genome Med. 2012; 4:38. [PubMed: 22546835]

Hypothesis for an alternative subtype of autism

Characteristics of a proposed form of autism (right column) that is predominantly male and represents 10 to 20 % of all autism.

HYPOTHESIS FOR A MILDER, MORE HOMOGENEOUS FORM OF AUTISM	
Severe, complex, syndromic with genetic etiology	**Milder, sole autism with unknown etiology**
Lower mean IQ	Higher mean IQ
Mix of de novo and inherited mutations	Unkown genetic inheritance
CNVs and point mutations	Unknown genetic mutations
Extreme genetic heterogeneity	Possibly less heterogeneity
Environment less important	Environment more important
Paternal age relevant	Paternal age less relevant
Sex ratio 2–4 to 1	Sex ratio 4–8 to 1
Often dysmorphic/complex	Nondysmorphic
Microcephaly or extreme macrocephaly	Mild transient macrocephaly
Regression rare	Regression more common
Treatment of prevention difficult except prenatal diagnosis	Possible optimism for treatment or prevention