EMAX HEALTH: Autism Genes Tied To Glitches In Early Learning

Some cases of **autism** may be a failure of the young brain to wire itself properly in response to a baby's social and physical surroundings, according to a new systematic analysis of disease genetics.

The newfound mutations may interfere with the brain's ability to create the connections normally sculpted by a child's early experiences, report HMS researchers and their international collaborators in the July 11 Science. The data correspond to the clinical onset and spectrum of autism symptoms, said co–first author Eric Morrow, HMS instructor in psychiatry at Massachusetts General Hospital. "Autism emerges in the first three years of life, during which time synapses mature in response to experience," Morrow said. "Autism is not a single disorder. At least a significant subset appears to be various disorders—dozens if not hundreds of distinct rare diseases that end up affecting a final common pathway."

The genetic basis of autism seems to be as varied as the severity of symptoms, which can range from oddities in social communication to severe mental retardation. The new study adds a handful of affected genes to the list and finds a common biological link among several of them.

Disconnection

Beginning around birth, the continuous dynamic give-and-take between a baby's neurons and experiences sparks a glut of synaptic connections. At about age 1, the evolving interactions guide the pruning and tailoring of the neural networks. On that foundation, more advanced cognitive, social, and emotional skills develop most profoundly through childhood and continue to progress through life. Without that foundation, further brain development can be impaired.

"These sorts of mutations may explain why some kids appear quite normal in the first year or two of life and develop trouble during cognitive development," said senior author Christopher A. Walsh, chief of genetics at Children's Hospital Boston. "The more we learn about autism, the more it seems to involve cellular processes of brain plasticity."

Three of the genes affected by the new mutations belong to a network of several hundred genes thought to be at the heart of the molecular program that orchestrates the response of synapses to life experiences, the researchers report. Of further significance, the five mutations identified in the latest study affect the predicted on–off switches of the genes, but not the genes themselves.

The possibility that genes are only disabled, not destroyed, reinforces the importance of early intervention programs, now the only treatment for autism, said developmental psychologist Janice Ware, a co-author, HMS assistant professor of psychology in the Department of Psychiatry, and associate director of the Developmental Medicine Center at Children's Hospital. Without intervention, autistic adults are indistinguishable from severely retarded people.

The findings also make researchers hopeful that further study will lead to effective drugs that can do as much or more than intensive early interventions to shore up essential neural networks. "We may not always be able to identify the specific gene, but we may be able to modulate the synaptic plasticity," said Walsh, also a Howard Hughes investigator at Beth Israel Deaconess Medical Center and the Bullard professor of neurology and pediatrics at HMS.

Family Structures

The wide spectrum of clinical symptoms and the many different genetic mutations have made it difficult for scientists to use genetic tools to probe the etiology of autism and pursue potential new therapies.

For this study, Morrow, co-first author Seung-Yun Yoo, and their colleagues extended an ongoing collaboration between the Walsh lab and clinician-researcher colleagues in the Middle East in genetic studies of other developmental brain disorders, such as mental retardation and microcephaly.

As did Charles Darwin and Albert Einstein, people in Middle Eastern families often have married their first cousins. Marriages between second cousins are also common and even better for such genetic studies, Walsh said. For such marriages, the risk of neurological birth defects doubles from about 1.5 percent to 3 percent—about the same extra risk, by a different mechanism, of having a child at age 40 instead of age 20—but most kids are healthy.

The structure of many families with recent shared ancestry provides statistical power to map rare, recessive genetic traits within individual pedigrees. Rare recessive genetic mutations can hide behind a good copy of a chromosome for generations and only surface in diseases when both copies of a family's signature mutation are passed along to a child.

In this first report from the international Homozygosity Mapping Collaborative for Autism, researchers recruited families with autistic children, traced the family trees, and compared DNA of family members with and without autism. Walsh's team later flew to sites in Turkey, Dubai, Kuwait, and Saudi Arabia to confirm the diagnoses. Of the 104 families analyzed in this study, 88 families had parents who were first or second cousins, and 19 of them had two or more cases of autism.

In five of the 88 families, the researchers found large deletions clearly linked to autism. In all, the technique identified five chromosome deletions affecting at least six identifiable genes (C3orf58, NHE9, PCDH10, contactin-3 [CNTN3],

RNF8, and genes encoding a cluster of cellular sodium channels). One of the genes, NHE9, was also mutated in autistic children with seizures in families having nonrelated parents from Europe and America. In six more families, the team found six more loci—a different one for each family—that they will be analyzing in more detail to find the specific mutations.

Meanwhile, co-author Michael Greenberg, director of the F.M. Kirby Neurobiology Center at Children's, had independently hypothesized that autism may arise from defects in the gene network his lab discovered that transforms environmental cues into changes in synaptic connections. At a meeting in London they both attended, Walsh and Greenberg decided to compare the genes identified in the autism study to Greenberg's list.

"We found that three of the genes identified in the autism study are on our list of genes that are controlled by experience," said Greenberg, professor and newly appointed chair of neurobiology at HMS (see page 3). "It's speculative, but it provides more evidence in support of autism as a disorder of experience-dependent synaptic development."

The authors caution that the findings need to be replicated and the predicted on–off switches for the affected genes need to be confirmed. The study continues to recruit and enroll families with autistic children in the Middle East, and the researchers are analyzing data from several hundred more families.

The results reinforce the importance of early treatment and intensive special education to teach crucial skills for optimal functioning later in life, said co-author Nahit Mukaddes, head of the **autism** clinic at Istanbul Medical School. The average age at referral of children with symptoms of autism has dropped from 5 years old a decade ago to two and a half years old, she said. "The influence of these programs in long-term outcome has not been well established yet, she said, but "the role of early and intensive intervention in the treatment of autistic symptoms is well known."

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