

# Genetic analysis supports prediction that spontaneous rare mutations cause half of autism

September 22 2015

---



Quinn, an autistic boy, and the line of toys he made before falling asleep. Repeatedly stacking or lining up objects is a behavior commonly associated with autism. Credit: Wikipedia.

A team led by researchers at Cold Spring Harbor Laboratory (CSHL) this week publishes in *PNAS* a new analysis of data on the genetics of autism spectrum disorder (ASD). One commonly held theory is that

autism results from the chance combinations of commonly occurring gene mutations, which are otherwise harmless. But the authors' work provides support for a different theory.

They find, instead, further evidence to suggest that devastating "ultra-rare" mutations of genes that they classify as "vulnerable" play a causal role in roughly half of all ASD cases. The vulnerable genes to which they refer harbor what they call an LGD, or likely gene-disruption. These LGD mutations can occur "spontaneously" between generations, and when that happens they are found in the affected child but not found in either parent.

Although LGDs can impair the function of key genes, and in this way have a deleterious impact on health, this is not always the case. The study, whose first author is the quantitative biologist Ivan Iossifov, a CSHL assistant professor and on faculty at the New York Genome Center, finds that "[autism](#) genes" - i.e., those that, when mutated, may contribute to an ASD diagnosis - tend to have fewer mutations than most genes in the human gene pool.

This seems paradoxical, but only on the surface. Iossifov explains that genes with devastating de novo LGD mutations, when they occur in a child and give rise to autism, usually don't remain in the gene pool for more than one generation before they are, in evolutionary terms, purged. This is because those born with severe autism rarely reproduce.

The team's data helps the research community prioritize which genes with LGDs are most likely to play a causal role in ASD. The team pares down a list of about 500 likely causal genes to slightly more than 200 best "candidate" autism genes.

The current study also sheds new light on the transmission to children of LGDs that are carried by parents who harbor them but whose health is

nevertheless not severely affected. Such transmission events were observed and documented in the families used in the study, comprising the Simons Simplex Collection (SSC). When parents carry potentially devastating LGD mutations, these are more frequently found in the ASD-affected children than in their unaffected children, and most often come from the mother.

This result supports a theory first published in 2007 by senior author Michael Wigler, a CSHL professor, and Dr. Kenny Ye, a statistician at Albert Einstein College of Medicine. They predicted that unaffected mothers are "carriers" of devastating mutations that are preferentially transmitted to children affected with severe ASD. Females have an as yet unexplained factor that protects them from mutations which, when they occur in males, will be significantly more likely to cause ASD. It is well known that at least four times as many males as females have ASD.

Wigler's 2007 "unified theory" of sporadic autism causation predicted precisely this effect. "Devastating de novo mutations in autism genes should be under strong negative selection pressure," he explains. "And that is among the findings of the paper we're publishing today. Our analysis also revealed that a surprising proportion of rare devastating mutations transmitted by parents occurs in genes expressed in the embryonic brain." This finding tends to support theories suggesting that at least some of the gene [mutations](#) with the power to cause ASD occur in [genes](#) that are indispensable for normal brain development.

**More information:** "Low load for disruptive mutations in autism genes and their biased transmission" appears in the Early Edition of *Proceedings of the National Academy of Sciences* the week of September 21, 2015. [www.pnas.org/cgi/doi/10.1073/pnas.1516376112](http://www.pnas.org/cgi/doi/10.1073/pnas.1516376112)

Provided by Cold Spring Harbor Laboratory

Citation: Genetic analysis supports prediction that spontaneous rare mutations cause half of autism (2015, September 22) retrieved 27 April 2024 from <https://medicalxpress.com/news/2015-09-genetic-analysis-spontaneous-rare-mutations.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.