

# Investigation of inherited mutations in autism spectrum disorder

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Autism spectrum disorder (ASD) is a set of conditions that affect a baby, toddler or preschooler's mental development. The signs can come on as early as 6 months, but usually, in India, diagnosis happens around 3-5 years. ASD is diagnosed as a problem in social communication-language, non-verbal signs of social interaction, and compulsive interests

or activities that the child insists on doing to the exclusion of everything else. Mental retardation, epilepsy, and attention deficit issues may also accompany ASD.

ASD is a very complex condition but has been recognised worldwide to have a very strong genetic basis. One verified theory is that children with ASD have more than usual disruptive [mutations](#) in their genome than unaffected children. These mutations can be of two types: inherited from parents, and some that are novel and crop up only in the child with ASD. Research of the past 10 years has focused on the novel mutations, with an acknowledgement that inherited mutations from parents may have some effect.

At the other end, in the past 20 years, after the release of the human genome, almost all diseases are under scrutiny for a genetic basis. Two kinds of mutations have also been found for ASD—one causal, that just by their presence can cause the disease—and the other an influencer, that doesn't cause the disease but changes response to medicines, the severity of symptoms, etc. As a practice, causal mutations are studied, but influencer mutations have gained importance with the advent of precision medicine and biomarker development.

Researchers at the Centre for Neurodevelopmental Synaptopathies (CNS), inStem, decided to pursue the inherited mutations in ASD databases in cellular pathways that control protein synthesis. Timely protein synthesis is a key requirement for proper brain development and function, as new proteins are made "on-demand" when we encode a memory or learn a new skill. The team, led by Dr. Aditi Bhattacharya, found a novel mutation in an important enzyme for protein synthesis called the p70 S6 Kinase 1 (S6K1). S6K1 not only helps proper brain function, but is also important for heart, pancreas and muscle function.

This mutation was found in the Simon Simplex Collection genetic

database of the SFARI foundation, which has sequenced more than 2700 families, called simplex or quads (meaning both parents' DNA is sequenced, and the family has only one child with ASD, or one normally developing child and one with ASD). The team found, in collaboration with Dr. Ivan Iossifov at Cold Spring Harbor and Prof. Eric Klann at New York University, that the S6K1 mutation, when occurring in children with ASD, and not their parents or unaffected siblings, changed certain cognitive abilities in the children.

The scientists then uncovered how the mutant S6k1 enzyme was hyperactive, in a series of biochemical tests in two different kinds of cells, and also found increased protein synthesis across the board. Furthermore, this mutant protein could not be targeted using an inhibitor molecule, which has important implications for patient response to drugs developed for S6k1 that are in clinical trial preparation.

Finally, the study showed that having this mutation in S6k1 changed the course of normal neural development when expressed in the stem cell line and also changed the structure of cultured neurons which would likely also change memory forming capacity. The mutation is present fairly commonly in the population and future steps would be to test how this altered S6K1 would change the function of pancreatic, cardiac and skeletal muscle cells.

Results of this work are early evidence that inherited mutations in neurological conditions may be a good place to look for mapping the variation in disease symptoms and treatment responses.

**More information:** Janani Priya Venkatasubramani et al, N-terminal variant Asp14Asn of the human p70 S6 Kinase 1 enhances translational signaling causing different effects in developing and mature neuronal cells, *Neurobiology of Learning and Memory* (2020). [DOI: 10.1016/j.nlm.2020.107203](https://doi.org/10.1016/j.nlm.2020.107203)

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