Howard Hughes Medical Institute
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Media Advisory

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GENETIC DISCOVERY PROVIDES INSIGHT INTO HUMAN COGNITION

Media work

Las Vegas important
~~Salt Lake City~~--Researchers have discovered a gene ~~that causes~~ in human
~~impaired~~ cognitive development~~ in humans~~. Scientists report that deletion of a specific gene, *Lim-kinase*, encoding an intracellular signaling molecule causes impaired spatial cognition. The findings are the first to uncover the molecular basis for a specific human cognitive trait.

The collaborators include

This discovery will be published in the July 12 issue of the journal, *Cell*. Mark Keating, M.D., a molecular geneticist at the Howard Hughes Medical Institute (HHMI) at the University of Utah, ~~led the team in collaboration with~~ Colleen A. Morris, M.D., a medical ~~human~~ geneticist at the University of Nevada, School of Medicine Las Vegas, and Carolyn Mervis, Ph.D., a cognitive neuroscientist at Emory University, Atlanta.

The research was performed with individuals who have ~~a disorder known as~~ Williams syndrome. People with this disorder have great difficulty visualizing an object as a set of parts and constructing a

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replica of the object with those parts. In normal individuals, this cognitive ability is known as visuospatial constructive cognition, but in people with Williams syndrome spatial cognition is so impaired that they ~~cannot~~ have difficulty in construct even simple objects like a checkerboard consisting of four cubes. As a result, individuals with Williams syndrome have difficulty with tasks like building a model, assembling a piece of furniture, or following a simple bus route.

One of the remarkable features of Williams syndrome is the dichotomy between cognitive abilities and disabilities. Although individuals with Williams syndrome ~~suffer from~~ have mental retardation, they usually demonstrate strength in language and auditory memory, and some are musically gifted. People with Williams syndrome are also extremely friendly and loquacious, and have personality traits and abilities that belie their other cognitive deficits.

One of the keys to the discovery was identifying individuals who had some, but not all, the features of Williams syndrome. Researchers found that these individuals have smaller deletions on chromosome 7 than those with the complete syndrome. Molecular geneticists discovered that the loss of one copy of a gene known as *Lim-kinase* leads to impaired cognition in Williams syndrome; *Lim-kinase* was the only gene absent from this region. Studies also demonstrated that this gene is switched on in cells that are precursors for neurons in the brain essential for cognitive development.

This group previously discovered that loss of one copy of a gene known as elastin on chromosome 7 was responsible for heart disease and some unusual facial features in Williams syndrome. Elastin encodes a protein that provides elasticity to tissues like blood vessels and skin. Researchers hypothesized that elastin mutations could not account for the cognitive deficit in Williams syndrome. Instead, they speculated that a gene adjacent to elastin must also be involved in the deletion that causes this disorder. This research led to the discovery of *Lim-kinase*.

The research is supported by the Howard Hughes Medical Institute and the National Institutes of Health, and William Syndrome Association.

Citation:

Frangiskakis, JM, Ewart, AK, Morris, CA, Mervis, CB, Bertrand, J, Robinson, BF, Klein, BP, Ensing, GJ, Everett, LA, Green, ED, Proschel, C, Gutowski, N, Noble, M, Atkinson, DL, Odelberg, SJ, Keating, MT: *LIM-kinase1* hemizygosity in impaired visuospatial constructive cognition, *Cell*, in press, 1996.

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GENETIC DISCOVERY PROVIDES INSIGHT INTO HUMAN COGNITION

in lay terms

Las Vegas: Researchers have discovered that a deleted gene can cause impaired cognitive development in humans. Scientists report that deletion of one copy of the gene Lim-kinase 1, encoding an intracellular signaling molecule, causes impaired spatial cognition. The findings are the first to uncover a molecular basis for a specific human cognitive trait.

This discovery will be published in the July 12 issue of the journal, Cell. The research team included Colleen A. Morris, M.D. a medical geneticist at the University of Nevada School of Medicine, Las Vegas; Carolyn Mervis, Ph.D., a cognitive neuropsychologist at Emory University in Atlanta, GA; and Mark Keating, M.D., a molecular geneticist at the Howard Hughes Medical Institute (HHMI) at the University of Utah.

The deletion was discovered in individuals who have a disorder known as Williams syndrome. People with this disorder have great difficulty visualizing an object as a set of parts and constructing a replica of the object with those parts. This cognitive ability is known as visuospatial constructive cognition. In people with Williams syndrome, ~~spatial cognition~~ This ability is so impaired that they cannot copy even simple patterns like a checkerboard consisting of four cubes. As a result, most individuals with Williams syndrome

have difficulty with tasks like building a model or assembling a piece of furniture.

A remarkable feature of Williams syndrome is a unique profile of cognitive strengths and weaknesses. Most people with Williams syndrome have mild or moderate mental retardation along with extremely impaired ~~visuospatial constructive~~ spatial cognition. In contrast, their auditory short term memory ability is often in the normal range and the language abilities are relatively good. Most older children and adults with Williams syndrome speak in grammatical, well-formed sentences, and many have good vocabularies. This Williams syndrome is also associated with a unique personality profile. ~~They~~ These people are loquacious, overly friendly to strangers and acquaintances, ~~loquacious,~~ and overly sensitive to other people's feelings. The good auditory rote memory abilities and fluent language, combined with their overfriendliness, often lead to an overestimate of their capabilities.

One of the keys to the discovery was identifying individuals who had some, but not all, the features of Williams syndrome. Researchers found that these individuals have smaller deletions on chromosome 7 than those with the complete syndrome. The research team discovered that the loss of one copy of ~~a~~ The gene ~~known as~~ Lim-kinase 1 leads to ~~impaired visuospatial constructive cognition~~ the impairments described in Williams syndrome. Studies also demonstrated that this gene is switched on in cells that are precursors for neurons in the brain essential for cognitive development.

This ~~group~~ team previously discovered that loss of one copy of a gene known as elastin on chromosome 7 was responsible for heart disease and some unusual facial features in Williams syndrome. Elastin encodes a protein that provides elasticity to tissues like blood vessels and skin. Researchers hypothesized that elastin mutations could not account for the cognitive deficit in Williams syndrome. Instead, they speculated that other genes adjacent to elastin must also be involved in the deletion that causes this disorder. This research led to the discovery of the role of Lim-kinase 1 in human cognition.

Dr. Morris, University of Nevada School of Medicine Associate Professor of Pediatrics, said "Individuals with Williams syndrome have many diverse symptoms. The discovery that a small segment of chromosome 7 was missing was the first step in determining the cause of their problems. Now we are finding genes in the missing region responsible for specific characteristics. This discovery is particularly exciting because this gene is important in the function and development of the brain."

The research is supported by the Howard Hughes Medical Institute, National Institutes of Health, and the Williams Syndrome Association.

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