RESEARCH LETTER

No Association Between SRGAP3/MEGAP Haploinsufficiency and Mental Retardation

Mental retardation (MR) affects 2% to 3% of children and is defined by the presence of significant limitations in cognitive and adaptive behavior.\(^1\) A classic neuropathological feature of patients with MR is altered dendritic spine morphology and/or density. These structural abnormalities reflect impaired cytoskeleton remodeling and are associated with synaptic dysfunction.\(^2\) Members of the Rho family of guanine triphosphatases (Rho GTPases) regulate cytoskeletal remodeling in the context of dendritic structures and synaptic plasticity. Mutations in several genes of the Rho-GTPase signaling pathway have been reported in MR.\(^3\) One example of such genes is SRGAP3/MEGAP, which encodes a Rho-GTPase activator (RhoGAP) that regulates actin remodeling.\(^4,5\) The SRGAP3 gene was disrupted by a de novo balanced translocation in a patient with facial dysmorphism, hypotonia, and severe MR, features characteristic of 3p\(−\) microdeletion syndrome.\(^6\) The breakpoint was located between exons 3 and 4 of SRGAP3, and the translocation did not seem to be associated with copy number changes. SRGAP3 was also found to be among the genes deleted in some patients with 3p\(−\) microdeletion syndrome.\(^4\) Together, these observations suggest that SRGAP3 haploinsufficiency causes MR.

As part of the Synapse-to-Disease project aimed at performing large-scale mutation analysis of genes affecting the synapse in neurodevelopmental diseases, we sequenced SRGAP3 in patients with idiopathic MR (n = 95) or autism spectrum disorders (ASD; n = 142). Our findings suggest that heterozygous disruption of SRGAP3 is not associated with MR.

Methods. Cohorts of 95 sporadic cases of MR (without growth abnormalities or dysmorphic features), 142 patients with ASD, and 285 healthy ethnically matched individuals were recruited. Most individuals with MR or ASD and control individuals were French Canadian. After approval by the institutional ethics committees, blood samples were collected from all individuals and from their parents for genomic DNA extraction (Puregene DNA kit; Qiagen, Mississauga, Ontario, Canada). Paternity and maternity of all families were confirmed using 6 microsatellite markers. Twenty-two coding exons and their intronic flanking regions from SRGAP3 (chr3:8997278-9266311; RefSeq NM_014850) were amplified by polymerase chain reaction from genomic DNA and directly sequenced. Mutations were confirmed by reamplification and resequencing of the proband and the parents in both directions.

Results. We identified the following 5 heterozygous missense mutations in SRGAP3: p.E394V (c.1181A>T; ASD: 1/142), p.F511L (c.1531T>C; ASD: 2/142), p.I628V (c.1882A>G; MR: 1/95; ASD: 1/142; dbSNP: rs2271207), p.V799I (c.2395G>A; MR: 1/95), and p.G942C (c.2824G>T; ASD: 1/142) (Figure). These mutations are predicted not to affect protein function\(^6\) and are unlikely to be pathogenic, as they are transmitted from healthy parents. We also identified one heterozygous nonsense mutation (c.1162C>T; p.Q388X) in a different patient with MR. This mutation lies in exon 8, before the alternatively spliced exon 12, and is predicted to truncate SRGAP3 upstream of its RhoGAP domain; thus, it is expected to abolish SRGAP3 function (Figure). The proband with p.Q388X is an 18-year-old French Canadian woman with mild nonsyndromic MR. The heterozygous p.Q388X was also found in the DNA of the proband’s mother, maternal uncle, and maternal grandfather, who are all healthy and display no cognitive deficits. This mutation was absent from the proband’s healthy father and brother, from her sister who also shows mild nonsyndromic MR, and from 285 ethnically matched controls.

Comment. Here we describe a heterozygous SRGAP3-truncating mutation in 3 healthy individuals and 1 pa-
tient with MR, all from the same family. This finding and the fact that p.Q388X was found only in 1 of 2 sisters sharing a similar MR phenotype argue against the notion that heterozygous disruption of SRGAP3 causes MR. The previously described association between SRGAP3 and MR mainly relied on the observation of a balanced translocation disrupting this gene in a patient with MR.4 Balanced translocations are complex rearrangements that can cause disease through gain- and/or loss-of-function mechanisms. It remains unknown whether this translocation is coincidental in this patient, whether it causes MR by disrupting the expression of another gene, or whether it induces a gain-of-function effect that could involve SRGAP3.

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COMMENTS AND OPINIONS

D. Carleton Gajdusek, MD (1923-2008)

I first learned of the groundbreaking work with kuru by D. Carleton Gajdusek, MD, when I was a neurology resident in the early 1960s. Fascinated by geographical isolates myself, I went on to read of his investigations of other isolates: the muscular dystrophy in New Britain, Papua New Guinea; the Vilyuiiskencephalitis in Siberia; the genetic diseases of Australia. When I went to Guam in the 1990s to study the amytrophic lateral sclerosis-parkinsonism-dementia disease there, which Gajdusek had investigated a decade earlier, I wrote to him to ask for his papers on the subject.

This started a correspondence and a friendship that lasted until his death. I first met him in person in 1997, when I visited him during his incarceration in a minimum-security prison outside Baltimore, Maryland, after his tragic conviction for child abuse. I brought food, but he said he was not allowed to accept this—and that in any case, his real need was for intellectual food. He was not allowed to receive bound books or anything with staples in prison, but he would be allowed, he said, photocopies of books and papers. For the remainder of his 18-month sentence, I sent him weekly parcels of photocopied books and articles. Often he would write to request certain titles; more frequently I would send him whatever I had enjoyed reading recently. His intellectual appetite was limitless, and I could be sure he would devour almost anything—essays, poetry, biographies, literature—and then send me long letters about these. He was especially taken by a biography of Alexander von Humboldt that I sent to him (Douglas Botting’s Humboldt and the Cosmos)—I think he identified to some extent with Humboldt.

Later, I visited Gajdusek in Paris, France, Amsterdam, the Netherlands, and Tromso, Norway, where he spent much of the year. He would talk torrentially, sometimes for hours on end, and on every subject imaginable, from his latest thoughts on protein folding to his admiration of Chinese art and literature (he usually went to China for several months every year to travel and lecture).

Although he was overweight and in poor health (“I should have died 20 years ago,” he sometimes said), his creative energy and extraordinary mental powers were with him to the last and he always looked forward to the fu-