HACE1, RAC1, and what else in the pathogenesis of SPPRS?

Han-Xiang Deng, MD, PhD

Neurol Genet 2019;5:e326. doi:10.1212/NXG.0000000000000326

Correspondence

Dr. Deng
h-deng@northwestern.edu

RELATED ARTICLE

HACE1 deficiency leads to structural and functional neurodevelopmental defects

[Page e330](#)

Spastic paraplegia and psychomotor retardation with or without seizures (SPPRS) is a complex neurodevelopmental disorder with an autosomal recessive inheritance. SPPRS typically shows an infantile onset, starting with hypotonia either at birth or by age 3–4 months, followed by severely impaired global development and delayed early motor milestones.¹ All patients with SPPRS develop slowly progressive bilateral lower limb spasticity, leaving them wheelchair bound and bed bound by their 20s. In some cases, patients may never walk. Most patients develop seizures in childhood and have a speech delay. Other variable features include ocular abnormalities, sensorineural hearing loss, skeletal abnormalities, obesity, and double incontinence. Some male patients have hypoplastic genitalia. Brain imaging may show generalized cerebral atrophy, ventricular dilatation, hypoplasia of the corpus callosum, and decreased white matter.¹

By using family-based and unbiased genotype-driven whole-exome sequencing approaches, Hollstein et al. and Akawi et al. identified mutations of *HACE1* in several patients with SPPRS.^{1,2} *HACE1* encodes a HECT domain and ankyrin repeat-containing ubiquitin ligase (*HACE1*), which is involved in specific tagging of target proteins, leading to their subcellular localization or proteasomal degradation. Most *HACE1* mutations in patients with SPPRS lead to a premature stop codon, suggesting that loss of *HACE1* function causes SPPRS. However, the pathogenic mechanism remains largely unknown.

In this issue, Nagy et al. provide important information for understanding the pathogenic mechanism underlying SPPRS.³ They identified 2 novel homozygous truncating mutations in *HACE1* in 3 patients from 2 families. More importantly, they performed detailed molecular and phenotypic analyses of *Hace1* knockout mice and SPPRS patient fibroblasts. They showed several clinical features in the *Hace1* knockout mice, which are similar to those observed in patients with SPPRS, including deficiencies in locomotion and learning/memory, enlarged ventricles, and hypoplastic corpus callosum. Pathologic and neurophysiologic studies demonstrated a reduced number of synaptic puncta and altered hippocampal synaptic transmission. The authors observed increased levels of active Rac1 in the *Hace1* knockout mouse brain and SPPRS patient–derived fibroblasts. RAC1 is a small GTPase with diverse roles in signaling, and *HACE1* targets RAC1 to the ubiquitin/proteasome system for degradation.⁴ Therefore, the authors hypothesize that upregulation of the RAC1 pathway may underlie the pathogenesis of SPPRS because of defective degradation of RAC1 by *HACE1* deficiency. This is the first in vivo study to show a molecular pathway underlying SPPRS.

A total of 11 mutations in 17 SPPRS cases have been reported to date.^{1,2,5} Except for a single amino acid deletion (p.Leu832del), all the others are truncation mutations. Although these truncation mutations presumably have almost identical functional consequences, great variations of clinical symptoms and disease severity were observed in these patients with SPPRS, suggesting that other genetic and environmental modifiers influence phenotype expression. It is known that the ankyrin repeats of *HACE1* are responsible for substrate recognition, whereas the HECT domain is essential for ubiquitinylation. The p.Leu832del mutation is located in the

From the Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

HECT domain, suggesting that the loss of ubiquitylation activity, rather than the loss of the entire HACE1 protein, is critical for development of SPPRS.

Loss of HACE1 was initially noted in human malignancies, and *Hace1* knockout mice were shown to develop spontaneous, late-onset multiple tumors after age 1 year.⁶ The tumor incidence was almost tenfold higher in the *Hace1* knockout homozygotes than the heterozygotes in 2-year-old mice (12% vs 1.3%). Loss of *Hace1* also rendered mice susceptible to second environmental and genetic hits for the development of multiple cancers. This led to the hypothesis that *HACE1* is a tumor suppressor gene, which prevents tumorigenesis by suppressing cyclin D levels and reactive oxygen species generation.^{6,7} However, the neurodevelopmental phenotype and pathology in the *Hace1* knockout mice have not been comprehensively investigated until the present study.

The hypothesis that upregulation of the RAC1 pathway underlies the pathogenesis of SPPRS is compatible with the previous data. It is well known that RAC1 plays an essential role in development and structural plasticity of dendrites and dendritic spines.^{8,9} Transgenic mice overexpressing constitutively active RAC1 in Purkinje neurons lead to ataxia and reduced Purkinje neuron axon terminals and smaller but increased number of dendritic spines.⁸ Recently, heterozygous missense mutations in *RAC1* were identified in developmental disorders with diverse phenotypes.¹⁰ Among 7 *RAC1* mutations, p.Tyr64Asp appears to be constitutively active. The patient with this mutation showed some clinical features overlapping with those in SPPRS, including severely impaired global development and delayed early motor milestones, hypoplastic corpus callosum and genitalia, ocular abnormalities, and sensorineural hearing loss. However, marked differences were also observed. Notably, the patient with p.Tyr64Asp showed hypotonia soon after birth, but he did not seem to develop progressive spasticity, a specific feature in SPPRS, even by age 12 years.¹⁰ This may suggest that upregulation of RAC1 is one of the multiple pathways affected by the HACE1 deficiency in SPPRS.

Upregulation of RAC1 in SPPRS suggests a potential therapeutic approach by using specific pharmacologic inhibition of RAC1.¹¹ However, caution should be taken because the development and function of the brain requires RAC1 to be finely tuned, as shown by the observations that either loss (or dominant-negative effect) or gain of RAC1 function led to developmental disorders in humans,¹⁰ and both depletion and overexpression of Rac1 resulted in abnormal phenotypes in *Xenopus laevis*.¹²

Upregulation of RAC1 may explain a part of the clinical symptoms in SPPRS, but it does not cover the full spectrum.

This suggests that HACE1 may have other substrates. Indeed, HACE1 also regulates other small GTPases, including RAB11a, RAB6a, and RAB8a.^{13,14} It has also been reported that HACE1 promotes the stability of Nrf2 and plays an important role in antioxidant response, and loss of *hace1* in a mouse model of Huntington disease accelerates motor deficits and exacerbates cognitive and psychiatric phenotypes.¹⁵

The molecular mechanism by which increased RAC1 leads to the abnormal structure and function of synapses and the pathogenic roles of other HACE1 regulated proteins in the pathogenesis of SPPRS are still not understood. These issues remain to be addressed in future studies.

Author contributions

H.-X. Deng: drafting/revising the manuscript.

Study funding

No targeted funding reported.

Disclosure

The author reports no disclosures. Full disclosures available: Neurology.org/NG.

References

1. Hollstein R, Parry DA, Nalbach L, et al. HACE1 deficiency causes an autosomal recessive neurodevelopmental syndrome. *J Med Genet* 2015;52:797–803.
2. Akawi N, McRae J, Ansari M, et al. Discovery of four recessive developmental disorders using probabilistic genotype and phenotype matching among 4,125 families. *Nat Genet* 2015;47:1363–1369.
3. Nagy V, Hollstein R, Pai T-P, et al. HACE1 deficiency leads to structural and functional neurodevelopmental defects. *Neurol Genet* 2019;5:e330. doi: 10.1212/NXG.0000000000000330.
4. Torrinio S, Visvikis O, Doye A, et al. The E3 ubiquitin-ligase HACE1 catalyzes the ubiquitylation of active Rac1. *Dev Cell* 2011;21:959–965.
5. Hariharan N, Ravi S, Pradeep BE, et al. A novel loss-of-function mutation in HACE1 is linked to a genetic disorder in a patient from India. *Hum Genome* 2018;5:17061.
6. Zhang L, Anglesio MS, O'Sullivan M, et al. The E3 ligase HACE1 is a critical chromosome 6q21 tumor suppressor involved in multiple cancers. *Nat Med* 2007;13:1060–1069.
7. Daugaard M, Nitsch R, Razaghi B, et al. HACE1 controls ROS generation of vertebrate Rac1-dependent NADPH oxidase complexes. *Nat Commun* 2013;4:2180.
8. Luo L, Hensch TK, Ackerman L, Barbel S, Jan LY, Jan YN. Differential effects of the Rac GTPase on Purkinje cell axons and dendritic trunks and spines. *Nature* 1996;379:837–840.
9. Bongmba OY, Martinez LA, Elhardt ME, Butler K, Tejada-Simon MV. Modulation of dendritic spines and synaptic function by Rac1: a possible link to Fragile X syndrome pathology. *Brain Res* 2011;1399:79–95.
10. Reijnders MRF, Ansors NM, Kousi M, et al. RAC1 missense mutations in developmental disorders with diverse phenotypes. *Am J Hum Genet* 2017;101:466–477.
11. Martinez LA, Tejada-Simon MV. Pharmacological inactivation of the small GTPase Rac1 impairs long-term plasticity in the mouse hippocampus. *Neuropharmacology* 2011;61:305–312.
12. Iimura A, Yamazaki F, Suzuki T, Endo T, Nishida E, Kusakabe M. The E3 ubiquitin ligase HACE1 is required for early embryonic development in *Xenopus laevis*. *BMC Dev Biol* 2016;16:31.
13. Lachance V, Degrandmaison J, Marois S, et al. Ubiquitylation and activation of a Rab GTPase is promoted by a beta(2)AR-HACE1 complex. *J Cell Sci* 2014;127:111–123.
14. Tang D, Xiang Y, De Renzi S, et al. The ubiquitin ligase HACE1 regulates Golgi membrane dynamics during the cell cycle. *Nat Commun* 2011;2:501.
15. Ehrnhoefer DE, Southwell AL, Sivasubramanian M, et al. HACE1 is essential for astrocyte mitochondrial function and influences Huntington disease phenotypes in vivo. *Hum Mol Genet* 2018;27:239–253.

Neurology[®] Genetics

HACE1, RAC1, and what else in the pathogenesis of SPPRS?

Han-Xiang Deng

Neurol Genet 2019;5;

DOI 10.1212/NXG.0000000000000326

This information is current as of April 30, 2019

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.. All rights reserved. Online ISSN: 2376-7839.

Updated Information & Services

including high resolution figures, can be found at:
<http://ng.neurology.org/content/5/3/e326.full.html>

References

This article cites 15 articles, 3 of which you can access for free at:
<http://ng.neurology.org/content/5/3/e326.full.html##ref-list-1>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

All Genetics

http://ng.neurology.org/cgi/collection/all_genetics

Gait disorders/ataxia

http://ng.neurology.org/cgi/collection/gait_disorders_ataxia

Intelligence

<http://ng.neurology.org/cgi/collection/intelligence>

Mental retardation

http://ng.neurology.org/cgi/collection/mental_retardation

Spastic paraplegia

http://ng.neurology.org/cgi/collection/spastic_paraplegia

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

<http://ng.neurology.org/misc/about.xhtml#permissions>

Reprints

Information about ordering reprints can be found online:

<http://ng.neurology.org/misc/addir.xhtml#reprintsus>

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.