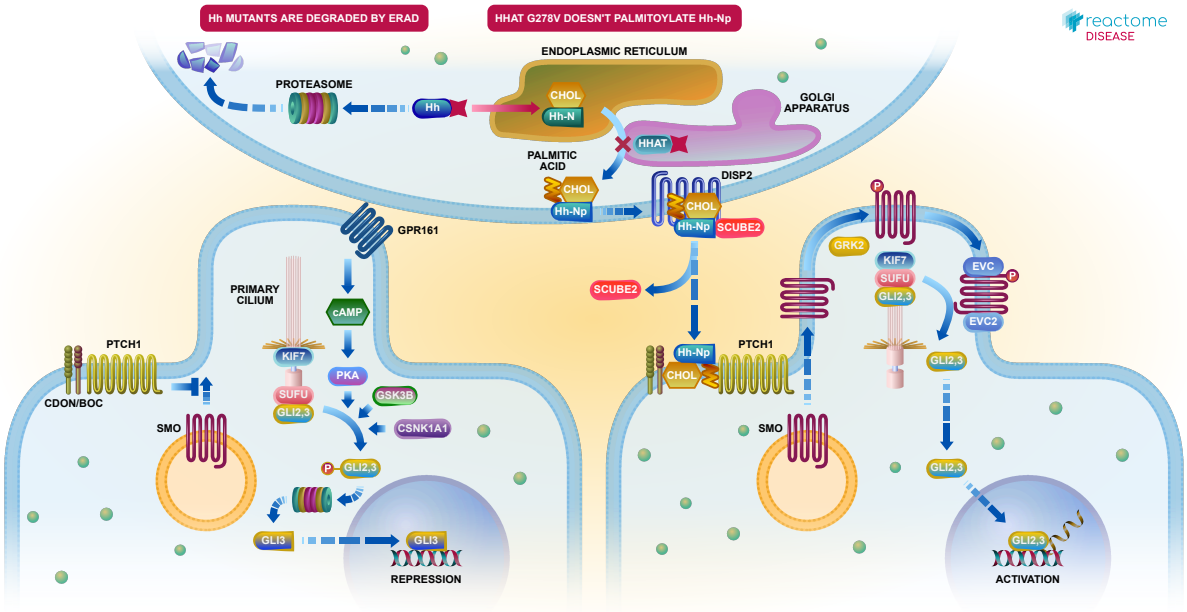
Hh mutants abrogate ligand secretion



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05/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

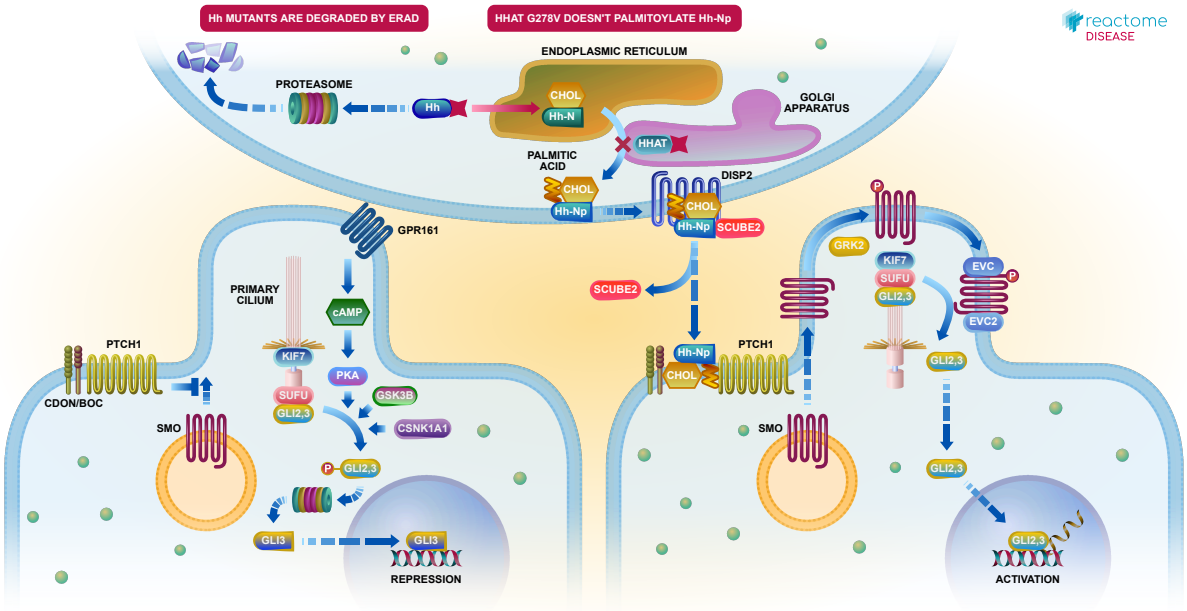
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Hh mutants abrogate ligand secretion ↗

Stable identifier: R-HSA-5387390

Diseases: holoprosencephaly



Hh signaling is required for a number of developmental processes, and mutations that disrupt the normal processing and biogenesis of Hh ligand can result in neonatal abnormalities. SHH is one of a number of genes that have been associated with the congenital disorder holoprosencephaly, which causes abnormalities in brain and craniofacial development (Roessler et al, 2009; reviewed in Roessler and Muenke, 2011). SHH variants associated with the condition affect the autocatalytic processing of the precursor and dramatically impair the production of the secreted active Hh-Np, abrogating signaling (reviewed in Pan et al, 2013). Aberrant Hh signaling is also associated with gondal dysgenesis syndromes in which palmitoylation of DHH is abrogated by mutation of the acyltransferase HHAT (Callier et al, 2014).

Literature references

Rolland, A., Bernard, P., Callier, P., Antonarakis, SE., Nef, S., Faivre, L. et al. (2014). Loss of Function Mutation in the Palmitoyl-Transferase HHAT Leads to Syndromic 46,XY Disorder of Sex Development by Impeding Hedgehog Protein Palmitoylation and Signaling. *PLoS Genet., 10,* e1004340. ↗

Muenke, M., Roessler, E. (2010). The molecular genetics of holoprosencephaly. *Am J Med Genet C Semin Med Genet, 154,* 52-61. ↗

Pineda-Alvarez, DE., Hehr, U., Bale, S., Zhou, N., Odent, S., Roessler, E. et al. (2009). The mutational spectrum of holoprosencephaly-associated changes within the SHH gene in humans predicts loss-of-function through either key structural alterations of the ligand or its altered synthesis. *Hum. Mutat., 30,* E921-35. ↗

James, AW., Chang, L., Pan, A., Nguyen, A. (2013). A review of hedgehog signaling in cranial bone development. *Front Physiol, 4,* 61. ↗

Editions

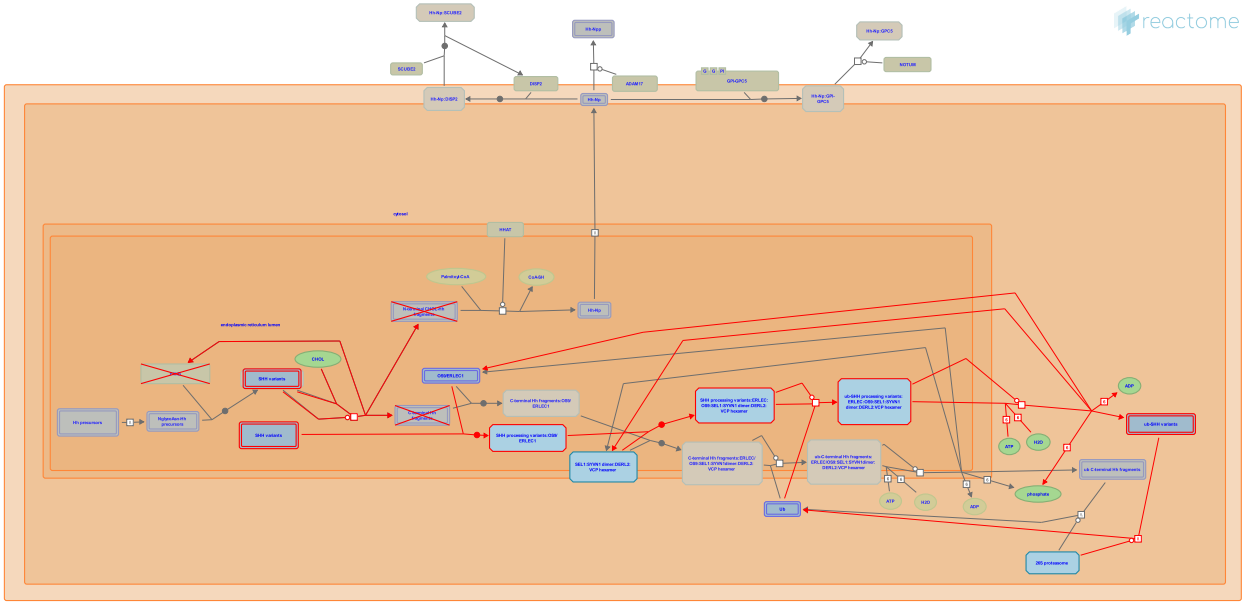
2014-04-30	Authored	Rothfels, K.
2014-05-16	Reviewed	Liu, Y C.
2014-05-19	Edited	D'Eustachio, P.

Hh mutants are degraded by ERAD ↗

Location: Hh mutants abrogate ligand secretion

Stable identifier: R-HSA-5362768

Diseases: holoprosencephaly, 46 XY gonadal dysgenesis



Hh signaling is required for a number of developmental processes, and mutations that disrupt the normal processing and biogenesis of Hh ligand can result in neonatal abnormalities. SHH is one of a number of genes that have been associated with the congenital disorder holoprosencephaly, which causes abnormalities in brain and craniofacial development (Roessler et al, 2009; reviewed in Roessler and Muenke, 2011). SHH variants associated with the condition affect the autocatalytic processing of the precursor and dramatically impair the production of the secreted active Hh-Np, abrogating signaling (reviewed in Pan et al, 2013).

Literature references

Muenke, M., Roessler, E. (2010). The molecular genetics of holoprosencephaly. *Am J Med Genet C Semin Med Genet, 154*, 52-61. ↗

Pineda-Alvarez, DE., Hehr, U., Bale, S., Zhou, N., Odent, S., Roessler, E. et al. (2009). The mutational spectrum of holoprosencephaly-associated changes within the SHH gene in humans predicts loss-of-function through either key structural alterations of the ligand or its altered synthesis. *Hum. Mutat., 30*, E921-35. ↗

James, AW., Chang, L., Pan, A., Nguyen, A. (2013). A review of hedgehog signaling in cranial bone development. *Front Physiol, 4*, 61. ↗

Editions

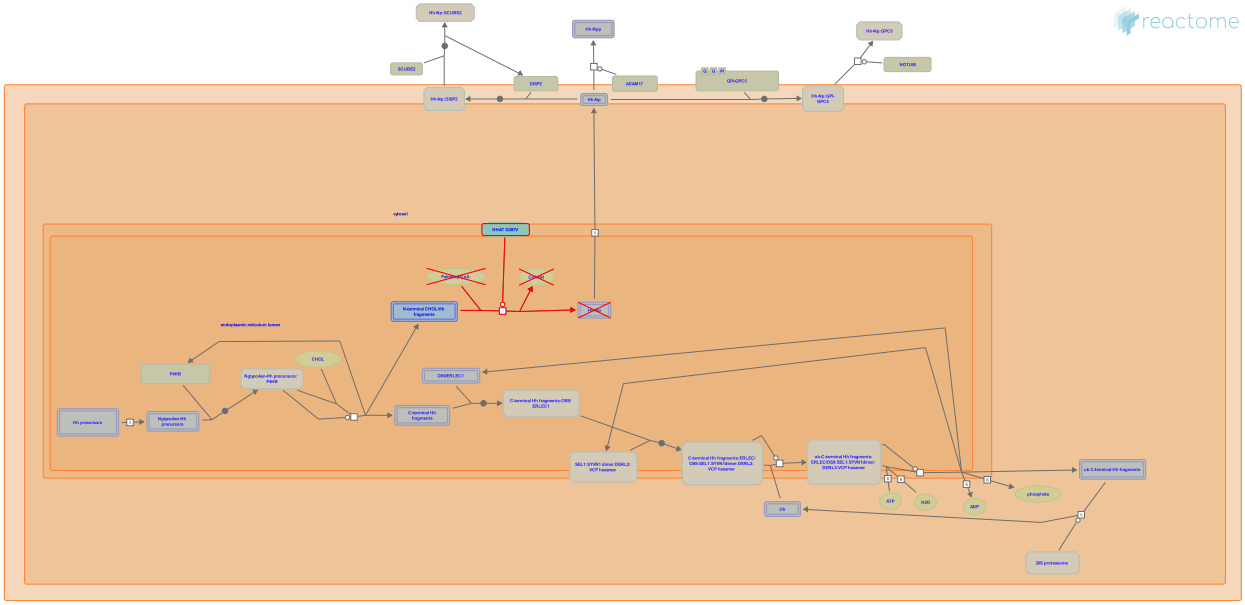
2014-04-16	Authored	Rothfels, K.
2014-05-16	Reviewed	Liu, Y C.
2014-05-19	Edited	D'Eustachio, P.

HHAT G278V doesn't palmitoylate Hh-Np ↗

Location: Hh mutants abrogate ligand secretion

Stable identifier: R-HSA-5658034

Diseases: 46 XY gonadal dysgenesis



A loss-of-function mutation in HHAT that abrogates palmitoylation of Hh ligand is associated with Syndromic 46, XY Disorder of Sex Development, which results in testis dysgenesis (Callier et al, 2014).

Literature references

Rolland, A., Bernard, P., Callier, P., Antonarakis, SE., Nef, S., Faivre, L. et al. (2014). Loss of Function Mutation in the Palmitoyl-Transferase HHAT Leads to Syndromic 46,XY Disorder of Sex Development by Impeding Hedgehog Protein Palmitoylation and Signaling. *PLoS Genet., 10*, e1004340. ↗

Editions

2014-05-13	Authored	Rothfels, K.
2014-05-16	Reviewed	Liu, Y C.
2014-05-19	Edited	D'Eustachio, P.

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