

Gene Section

Review

RAC3 (ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3))

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Identity

Hugo: RAC3

Other names: -

Location: 17q25.3 with 5' end towards the centromere. Nucleotide 203731-2061912 of contig NT_010663

Local order: Located telomeric to the BROV region. Centromeric to LRRC45 - Rac3 - DCXR telomeric

DNA/RNA

Note: 6 exons, spread out over approximately 2.4 kb

Description

The Rac3 gene encompasses 6 exons on chromosome 17. Exon 1 encodes residues 1-12, exon 2 residues 13-

36, exon 3 residues 37-75, exon 4 residues 76-96, exon 5 residues 97-149 and exon 6 residues 150-192.

Transcription

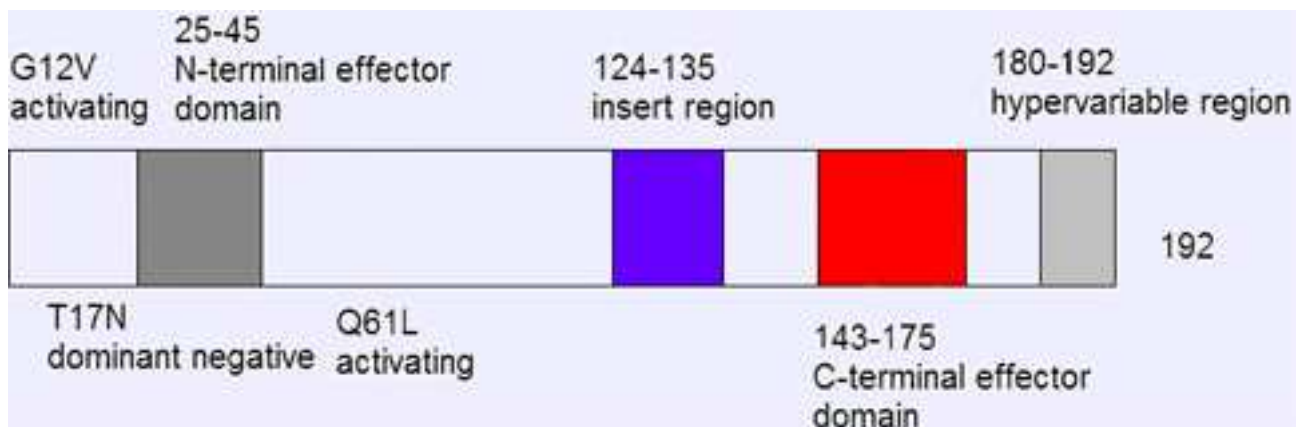
Human Rac3 mRNA is a single species of around 1 kb. No splice variants have been reported. Factors that would regulate gene expression on a transcriptional level have not yet been reported.

Pseudogene

No pseudogenes of Rac3 are reported in human.

Protein

Note: The Rac3 gene encodes a single protein of 192 amino acid residues.



Description

Rac3 is a small 21 kDa GTPase that acts as a molecular switch. In its active form, it is bound to GTP, whereas it is inactive in its GDP-bound form. Rac3s are controlled by guanine activating proteins (GEFs) that exchange bound GDP for GTP and by GTPase activating proteins (GAPs) that promote GTP hydrolysis. Because of the hydrophobic isoprenyl moiety at the C-terminal end, it is associated with membranes. In the cytoplasm it associates with the chaperone RhoGDI.

Expression

Rac3 mRNA was reported in human cell lines including GM04155 (lymphoblastic leukemia), K562 (CML), 5838 (Ewing sarcoma), HL60 (promyelocytic leukemia) and DU4475 (breast cancer). Rac3 expression was reported using semi-quantitative RT/PCR in gastric tumor and adjacent normal tissue as well as gastric cancer cell lines. Expression of Rac3 using RT/PCR (38 cycles) was reported in human brain, liver, kidney and pancreas poly A RNA and also 19% of brain tumors expressed Rac3 mRNA. Rac3-specific polyclonal antibodies were used to show Rac3 protein in the brain (deep cerebellar nuclei and the pons) in 7 day old mice. Low level expression of mouse rac3 has been reported in bone-marrow-derived monocytes and in B-lineage lymphoblasts using standard and RealTime RT/PCR.

Localisation

The Rac3 protein is located on endomembranes and cell membranes.

Function

Rac proteins regulate a variety of functions including cytoskeletal organization, cell cycle, reactive oxygen species production, and vesicle trafficking. In cultured cells they also are involved in cellular transformation. Studies of null mutant Rac3 mice showed that Rac3 regulates cerebellar functions and in a mouse model plays a role in leukemia development caused by the Bcr/Abl oncogene. Point mutations (N26D, F37L, Y40C, N43D) were introduced into different critical residues of the effector domain of Rac3 and the effects of these were investigated on the ability of Rac3 to regulate membrane ruffles, c-jun activation and transformation. Transformation was assayed as the ability to cooperate with activated Raf in focus formation of NIH3T3 cells and the ability to promote growth of these cells in soft agar.

Homology

Rac3 is most closely related to Rac1 and Rac2. On a nucleotide level human Rac3 has 77% identity with Rac1, 83% identity with Rac2 and 69% identity with RhoG. On an amino acid level, Rac3 and Rac1 differ in 14/192 residues (92% identical), whereas Rac3 and

Rac2 differ in 22/192 residues (89% identical). Rac3 belongs to the extended Rho family of small G-proteins. Biochemically, Rac1 and Rac3 are closely related.

Implicated in

Breast cancer

Note: Using in situ hybridization, Rac3 was reported to lie outside of the BROV region commonly deleted in Breast and Ovarian Cancer.

Activated Rac3 protein was reported in MDA-435, T47D and MCF7 breast cancer cell lines and 1 of 3 patient samples using a GST-Pak pull-down assay to detect activated Rac.

siRNA against Rac3 inhibits SNB19 glioblastoma and BT549 breast cancer cell line invasion in an in vitro assay.

It was shown that introduction of a constitutively active Rac3 into the MDA-MB-435 breast cancer cell line caused increased invasion and motility in vitro.

Transgenic mice with tissue specific expression of constitutively active (V12)Rac3 in the mammary gland were generated. Post-lactational female mice had delayed involution.

Gastric cancer

Note: Semi-quantitative RT/PCR was used to examine Rac3 mRNA expression in gastric cancer tissues and 7 gastric cell lines. Rac3 expression was detected in the tumor samples but there was no statistically significant difference between the expression levels in gastric cancer and adjacent non-tumorous tissues. The cell lines had a varying but detectable Rac3 expression.

Brain tumors

Note: RT-PCR was used to evaluate Rac3 mRNA expression in human brain tumor tissues. Expression of rac3 was reported in 3/9 meningiomas, 1/11 astrocytomas, 1/6 pituitary adenomas. The PCR fragments were subcloned and sequenced, and mutations were reported in Rac3 in 12/19 brain tumors including E10V, V14E, D35N, P35S, N43D, V46A, D57V, R57P, L67V, S83F, V85A, E100G, H104L, P109H, R120H, T125P, S158P, P180T, V182E, V182A, H184L and G186E.

To be noted

Note: There is a second gene that is named RAC3 in some publications. This protein is functionally and structurally unrelated to the small GTPase Rac3. This is the steroid receptor coactivator-3, or nuclear receptor coactivator SRC-3/AIB1/ACTR/pCIP/RAC3/TRAM-1. Probes 1-12 from NM_005052-links-probes

1: ProbeTaqMan gene expression (TaqMan) probe Hs00414037_g1 for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP

binding protein Rac3) (RAC3). Developed for real time qRT-PCR gene expression profiling. Reagent is available from Applied Biosystems.

2: ProbeSmall interfering RNA (siRNA) probe for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3). Has been used for RNA interference (RNAi). Reference Chan et al., 2005

3: ProbeSmall interfering RNA (siRNA) probe for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3). Has been used for RNA interference (RNAi). Reference Chan et al., 2005

4: ProbeResequencing amplicon (RSA) probe RSA001057586 for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3). Developed for SNP discovery.

5: ProbeResequencing amplicon (RSA) probe RSA001057592 for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3). Developed for SNP discovery.

6: ProbeResequencing amplicon (RSA) probe RSA001229136 for Homo sapiens genes ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3) and leucine rich repeat containing 45 (LRRC45). Developed for SNP discovery.

7: ProbeResequencing amplicon (RSA) probe RSA001400685 for Homo sapiens genes ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3) and leucine rich repeat containing 45 (LRRC45). Developed for SNP discovery.

8: ProbeResequencing amplicon (RSA) probe RSA001401207 for Homo sapiens genes ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3) and leucine rich repeat containing 45 (LRRC45). Developed for SNP discovery.

9: ProbeResequencing amplicon (RSA) probe RSA001457703 for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3). Developed for SNP discovery.

10: ProbeResequencing amplicon (RSA) probe RSA001457859 for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3). Developed for SNP discovery.

11: ProbeResequencing amplicon (RSA) probe RSA001458006 for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3). Developed for SNP discovery.

12: ProbeResequencing amplicon (RSA) probe RSA001458005 for Homo sapiens gene ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3) (RAC3). Developed for SNP discovery.

13: Chan et al. (2005) reported TaqMan primers useful in quantifying human Rac3 expression.

14: Pan et al. (2004) reported primers for semi-quantitative RT/PCR for human Rac3 that yielded a 249 bp

15: Hwang et al. (2005) reported primers for RT-PCR of human RNA. Fw primer was 5'-AATTCATGCAGGCCATCAAGT-3' and the reverse primer 5'-CTAGAAGACGGTGCACCT-3'.

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