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Gene Section
Review

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

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Identity

HGNC (Hugo): RAC3

Location: 17q25.3

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

Note

With 5' end towards the centromere.

Nucleotide 203731-2061912 of contig NT_010663.

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

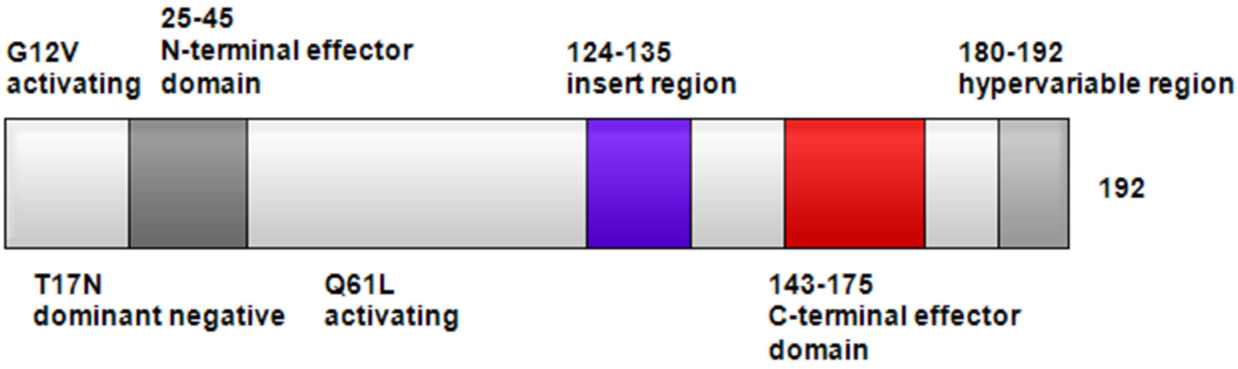
The Rac3 gene encodes a single protein of 192 amino acid residues.

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. Racs are controlled by guanidine 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.



Schematic representation of the Rac3 protein (not to scale). Mutations that generate mutants that are locked in a certain conformation - constitutively active or dominant negative - are shown. The C-terminal end contains the CTVM motif that is post-translationally modified the three last amino acid residues are removed and the C residue is geranyl-geranylated.

Low level expression of mouse rac3 has been reported in bone-marrow-derived monocytes and in B-lineage lymphoblasts using standard and Real-Time RT/PCR. Expression of Rac3 is inferred because of the effect of siRNA knockdown in cell lines including HCT116 colon cancer, MDA-MB231 breast cancer, HeLa, and PC3 prostate cancer (Zhu et al., 2011). Real-time RT/PCR showed Rac3 mRNA in prostate cancer biopsy samples (Engers et al., 2007). Analysis of gene expression profiling datasets (Chang et al., 2005) in breast cancer samples showed Rac3 expression (Walker et al., 2011).

Localisation

The Rac3 protein is located on endomembranes and cell membranes. Nuclear localization was also reported (Walker et al., 2011).

Function

Rac proteins regulate a variety of functions including cytoskeletal organization, cell cycle, reactive oxygen species production, and vesicle trafficking. In its activity on reactive oxygen species production, Rac3 is able to activate Nox1, Nox2 and Nox3 (Miyano et al., 2009; Miyano and Sumimoto, 2012). 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. Rac3 was found to negatively regulate autophagy in colon, breast and prostate cancer cell lines, since its knockdown stimulated LC3-II expression (Zhu et al., 2011). Different effects on migration are reported. Rac3 negatively regulates diapedesis of PC3 cells, since knockdown using siRNA increases migration of PC3 prostate cancer cells through a BMEC layer (Chatterjee et al., 2011). In contrast, overexpression of Rac3 in MCF7 breast cancer cells stimulates E2-induced migration (Walker et al., 2011).

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). Rac belongs to the extended Rho family of small G-proteins. Biochemically, Rac1 and Rac3 are closely related and have overlapping (Corbetta et al., 2009; Pennucci et al., 2011; Basso et al., 2011) as well as distinct functions. Rac3 differs from Rac1 in the presence of a residue in its C-terminal end, S151, which is A151 in Rac1 and mediates binding of Rac3 to ERα (Walker et al., 2011). Rac3 and Rac1 also differ in their effect on NIE-115 neuroblastoma cells, in which Rac3 induces cell rounding and Rac1 induces spreading (Hajdo-Milasinovic et al., 2007; Hajdo-Milasinovic et al., 2009).

Implicated in

Breast cancer

Note

Using in situ hybridization, Rac3 was reported to lies 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 showed 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.
In the MCF7 breast cancer cell line, E2-stimulated migration was decreased by siRNA-mediated knockdown of Rac3, and Rac3 interacted with the ERα in a ligand-dependent manner (Chatterjee et al., 2011).
Meta-analysis of gene expression profiling datasets of breast cancer samples (Chang et al., 2005) for Rac3 showed that expression levels correlated with increased probability of metastatic events (Walker et al., 2011).

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.

Prostate cancer

Note
Using real-time RT/PCR, increased Rac3 mRNA was detected in involved prostate cancer biopsy samples compared to adjacent normal tissue (Engers et al., 2007).

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: ProbeID:6597734 TaqMan 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: ProbeID:3104502 Small 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: ProbeID:3104501 Small 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: ProbeID:1163472 Resequencing 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: ProbeID:1163461 Resequencing 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: ProbeID:1157480 Resequencing 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. ProbeID:1152860 Resequencing 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: ProbeID:1152824 Resequencing 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: ProbeID:1151274 Resequencing 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: ProbeID:1151272 Resequencing 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: ProbeID:1151270 Resequencing 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: ProbeID:1151269 Resequencing 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'-CTAGAAGACGGTGCACTT-3'.

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