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Gene Section
Review

NRF1 (nuclear respiratory factor 1)

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Identity

Other names: ALPHA-PAL (Alpha palindromic-binding protein); EWG; HBZ17; OTTHUMP00000184912; TCF11

HGNC (Hugo): NRF1

Location: 7q32.2

Note: NRF1 is located at contig NT 079596 of Genebank, 28668299-28812556 bp.

There is a confusion in bibliographic databases as well as among scientific communities due to following reasons: i) The shared symbol of NRF1 for nuclear respiratory factor 1 gene and for 'nuclear factor (erythroid-derived 2)-like 1' which has an official symbol of NFE2L1; ii) The nuclear respiratory factor 1 gene symbol for human is NRF1, where as the symbol of this same gene for rat and mice is Nrf1. Confusion between NRF1 and Nrf1 (NFE2Ll) started in early 1990s. Chan et al. (1993) identified a distinct human bZIP transcription factor, NFE2L1, which they designated NRF1 (NFE2-related factor-1).

Later on Tiranti et al. (1995) mapped the NRF1 gene to 7q32 and referred to the gene as NFE2L1. The majority of the scientists working on NFE2L1or NFE2L1-regulatable proteins continue to use Nrf1 in their manuscripts instead of NFE2L1. The same is true for pharmaceutical firms who sell NFE2L products. This not only creates a major problem for new researchers in the field, but produces erroneous interpretation of the research findings.

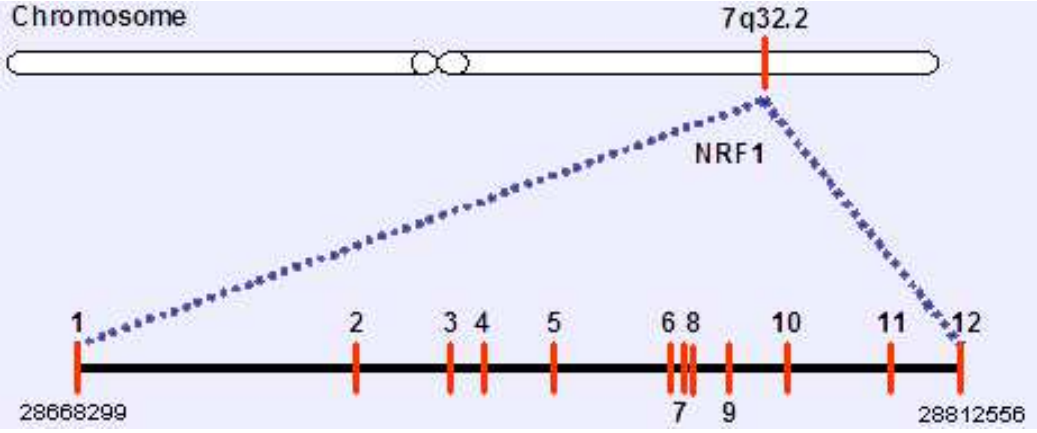
DNA/RNA

Note

NRF-1/a-PAL (nuclear respiratory factor-1/a-palindrome-binding protein) is a transcription factor. It belongs to the NRF1/Ewg family. The optimal NRF-1 binding site is (T/C)GCGCA(C/T)GCGC(A/G).

Description

DNA size 144.26 kb; mRNA size 2578 bp 12 exons.



Protein

Description

503 amino acids; 53.5 kDa protein.
Post translational modifications: phosphorylation enhances DNA binding. DNA binding 109-305 (197), region 1-78 (78) is required for dimerization, region 301-476 (176) required for transcriptional activation, motif 88-116 (29) is nuclear localization signal, compositional bias 41-66 (26) Asp/Glu-rich (acidic), compositional bias 80-86 (7).
Isoforms:
Two isoforms have been identified.
- Isoform long (identifier: Q16656-1): this isoform has been chosen as the 'canonical' sequence.
- Isoform short (identifier: Q16656-2): the sequence of this isoform differs from the canonical sequence, amino acid residues from 256-321 are missing.

Expression

It is widely expressed, and strongest expression is in skeletal muscle.

Localisation

Nucleus.

Function

NRF-1 was first discovered as an activator of the cytochrome c gene (Evans and Scarpulla, 1989). Now we know that this transcription factor activates the expression of several key genes regulating cell growth and development, nuclear genes required for respiration, heme biosynthesis, and mitochondrial DNA transcription and replication.
A genome-wide analysis has revealed that NRF-1 binding elements are present in genes involved in DNA replication, mitosis, and cytokinesis, suggesting that NRF-1 plays an important role in cell cycle regulation. Similarly, computation analysis of NRF-1 gene regulation by querying the TRANSFAC database revealed that the TGCGCATGCGCA motif of the consensus NRF1 binding site is present in genes encoding proteins regulating cell growth (CKS2, CDC6, CDC7, CDC25C, NPAT), replication (ORC6L, FEN1), and DNA repair (DNA polymerase alpha, MLH1, MSH2, PCNA, Prim2A, TOP1, ATM, XRCC2, GTSE, SMC4L1, KIF22, PP5C, cyclin B1, cyclin G2, RAD54B, PRC1, CBX5). NRF-1 and CREB elements significantly co-occur on promoters of cell cycle-regulated genes. NRF-1 also binds to the gene promoters of cysteine proteases (CAPNS1 and CASP2), chemokines (CXR5, CKLF), the putative breast adenocarcinoma marker BC2, BRCA2, BCCIP, tumor suppressors (putative tumor suppressor, 101F6 and tumor suppressor deleted in oral cancer-related 1). These NRF-1 target genes control cell adhesion, cell spreading, migration, proliferation, apoptosis, and tumor invasion. NRF-1 responds to redox signaling pathways through post-translational modifications and through its specific interaction with transcriptional co-activators.

Homology

The percent Identity below represents identity of NRF-1 over an aligned region in UniGene.
M. musculus: 99.8 (percentage identity)
M. domestica: 99.8
E. caballus: 99.8
B. taurus: 99.8
C. lupus familiaris: 99.6
G. gallus: 99.6
D. rerio: 93.7
X. laevis: 92.9
D. melanogaster: 51.5

Mutations

Note
Two novel single nucleotide polymorphisms (SNPs) in the NRF1 gene SNPs are found to be associated with type 2 diabetes in a Han Chinese population.

Implicated in

Estrogen-dependent breast cancer

Note
NRF-1 is a redox sensitive transcription factor. Some of the same mitogenic pathways that are sensitive to oxidant levels and estrogen are also directly regulated by NRF-1. For example, the expression of CDC25C, which is required for progression of the cell cycle, is regulated by both E2 and reactive oxygen species (ROS) and its promoter contains NRF-1 binding motif. The expression of cyclin D1 is also regulated by both E2 and ROS. There are several estrogen-regulatable genes, which are also regulated by ROS. Cell cycle regulation by the cdks and cyclins is dependent upon cell adhesion mediated by integrins, which control expression of cell cycle genes via ROS. Many of the genes associated with high-risk breast tumors appear to participate in cell cycle regulation, including those encoding CDC2 and PRC1. As noted above, both genes are NRF-1 regulatable. Importantly, in human breast cancer cells, the expression of almost 15% of the genes significantly affected by E2 contains the NRF-1 binding element, and the NRF-1 binding signature is significantly enriched in the promoters of genes induced by estrogen treatment. We have recently shown that inhibitors of mitochondrial oxidant production prevent E2-induced expression of cell cycle genes containing NRF-1 binding sites (cyclin B1, PCNA, and PRC1), decrease E2-induced NRF-1 expression, and delay growth. These findings show that E2 stimulates NRF-1 expression and cell cycle progression of breast cancer cells through ROS, possibly by altering NRF-1 activity.

Breast cancer

Disease

Motifs bound by ELK1, E2F, NRF1 and NFY positively correlate with malignant progression of breast cancer.

Colorectal tumors

Note

NRF-1 is also the main transcription factor regulating the expression of human TOMM34 gene that encodes a cytosolic protein with chaperone-like activity. TOMM34 helps import some preproteins to the mitochondria by keeping them in an unfolded, import-compatible state. TOMM34 was found to be upregulated frequently in colorectal tumors, suggesting that it also has a role in the growth of cancer cells.

Hepatoma and thyroid oncocytoma

Note

NRF-1 overexpression has been observed in hepatoma and thyroid oncocytoma.

Diabetes Mellitus, Type 2

Note

Two novel single nucleotide polymorphisms (SNPs) in the NRF1 gene SNPs (-46127T>C and +98560A>G) are associated with type 2 diabetes in a Han Chinese population. NRF1 genetic polymorphisms may be a suspectibility factor for type 2 diabetes by conferring abnormalities in triglyceride metabolism.

Two common haplotypes of NRF1 gene are found to be associated with type 2 diabetes in the Korean population. A haplotype (H2) is associated with a decreased risk of type 2 diabetes and another haplotype (H4) is associated with an increased risk of type 2 diabetes.

Endurance exercise capacity

Note

In young Chinese men of Han origin, two NRF1 genotypes have been found to be associated with the baseline and/or training response of human aerobic capacity. NRF1 is a critical component of the energy-sensing mechanism in mammalian cells, and translates physiological signals, including those induced by exercise, into increased capacity for mitochondrial biogenesis and oxidative phosphorylation.

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