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Gene Section
Review

GNAQ (guanine nucleotide binding protein (G protein), q polypeptide)

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Identity

Other names: G-ALPHA-q; GAQ

HGNC (Hugo): GNAQ

Location: 9q21.2

Local order: Between GNA14, CEP78.

DNA/RNA

Description

The GNAQ gene is composed of 7 exons spanning a region of 310993 nucleotides.

Transcription

Transcript length is 6539 bp. Length of ORF is 1080 bp.

Pseudogene

GNAQP in 2q14.3-q21.

Protein

Description

Amino acid residues: 359. Molecular weight: 42141 daltons.
GNAQ is a proto oncogene which encodes for alpha subunit of 'q' class of heterotrimeric GTP binding protein.

Expression

GNAQ is ubiquitously expressed in all tissues.

Localisation

Cytoplasm. Signaling occurs at the membrane.

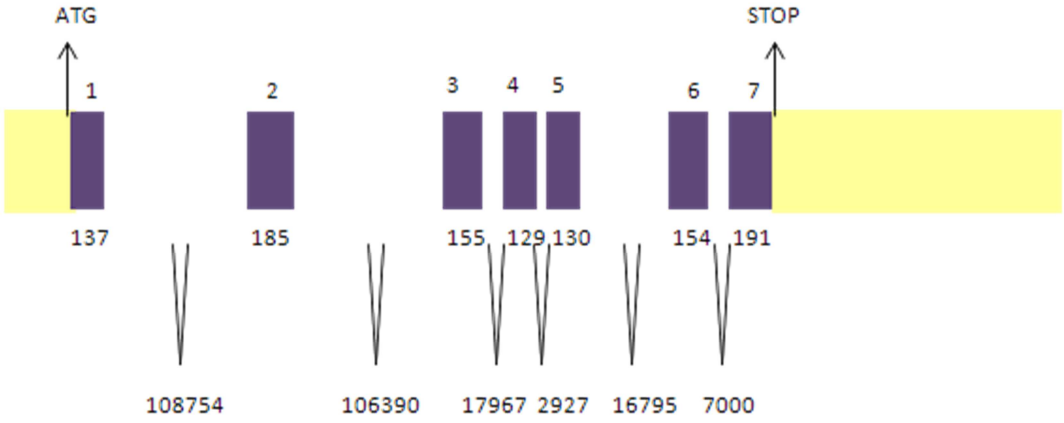
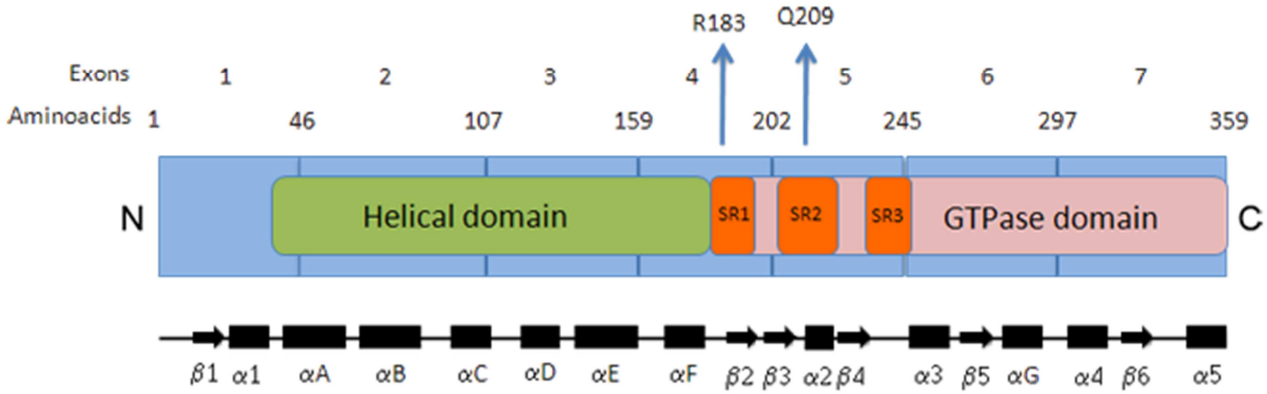


Diagram of GNAQ gene. The transcribed exons are represented in purple, the 5' and 3' untranslated region is represented in yellow. The exon numbers are indicated on the top and the number of base pairs per exon is indicated at the bottom. Introns are represented by black bars along with the number of base pairs. The arrows represent the start and stop codons.



Schematic diagram of functional domains of GNAQ protein. The blue boxes represent the exons with exon numbers and the amino acid numbers on the top. The inner boxes represent the different domains: Helical domain (Green), Switch regions (Orange) (SR1: 182-192, SR2: 204-224, SR3: 236-247) are involved in conformational change based on the binding of GDP or GTP, GTPase domain (Pink) is essential for hydrolysis of GTP to GDP. N and C represent the amino and carboxy terminals of the protein respectively. The two arrows (R183, Q209) represent the hotspot mutations. Adapted from Mizuno and Itoh, 2009.

Function

GNAQ mediates signal between the G protein coupled receptor (GPCR) and downstream effectors. Receptor activation by ligand binding causes the activation of GNAQ by catalyzing the release of GDP and binding of GTP. In its active form GTP-bound GNAQ causes the release of the beta and gamma subunits of the heterotrimeric G-protein. GTP-GNAQ and beta and gamma subunits transfer the receptor-mediated signal to downstream effectors through secondary messengers which participate in diverse signaling pathways to evoke different effectors. The known effectors for GNAQ include PLC beta, p63-RhoGEF, Trio, and Duet (Maize et al., 2005; Eom et al., 2009). GNAQ has been shown to activate the MAP kinase pathway, possibly via DAG-mediated activation of protein kinase C isoforms. GNAQ has an intrinsic GTPase domain at the C terminus which causes the hydrolysis of GTP to GDP and the G-alpha-GDP re-associates with G-beta and G-gamma subunits.

Homology

GNAQ is one of the four members belonging to the Gq-alpha family. Compared to GNAQ the other three members G11alpha, G14alpha, G16 alpha have 90%, 80%, and 57% amino acid sequence homology, respectively (Eom et al., 2009).

Mutations

Note

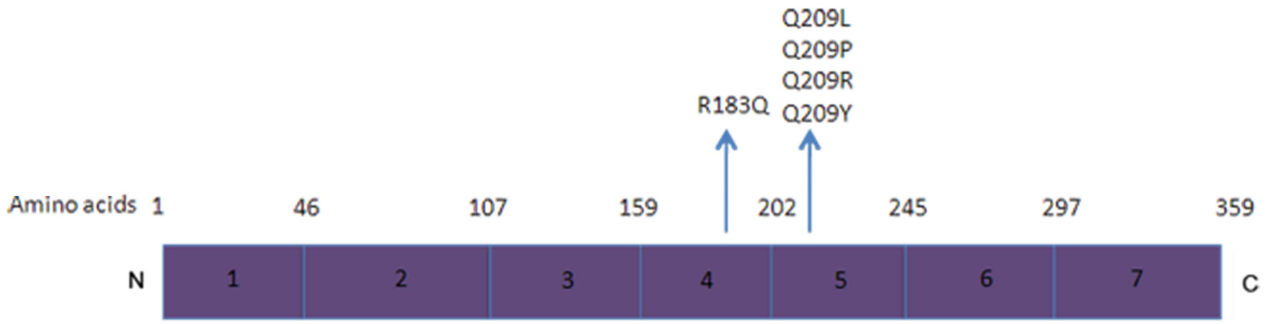
Somatic mutations of GNAQ affect codons 183 and 209 resulting in R183Q, Q209L, Q209P, Q209R, and Q209Y.

Germinal

No germinal mutations have been described.

Somatic

Somatic mutations in GNAQ have been described in melanocytic neoplasia (Hubbard et al., 2006; Onken et al., 2008; Küsters-Vandevelde et al., 2009). In Uveal Melanoma, 97% of the hotspot mutations cause the amino acid substitution Q209L, the other 3% of mutations cause amino acid change to R183Q. The Glutamine 209 of GNAQ is similar to residue 61 of RAS protein. The Q209 and R183 mutations cause complete or partial loss of intrinsic GTPase activity respectively thereby locking the protein in a constitutively active form. Q209 and R183 mutations occur in a mutually exclusive pattern in human neoplasia. Mutations in GNAQ are also mutually exclusive from the hotspot mutations in GNA11, which belongs to the same family and shares 90% sequence homology. GNAQ mutations are not concomitant with other common oncogenic mutations in BRAF, NRAS or KIT found in melanocytic neoplasia.



Schematic representation of GNAQ mutations in melanocytic neoplasms. The purple boxes represent the exons with the exon numbers indicated within the boxes, amino acid numbers indicated on top. The arrows represent the two hotspot mutations along with the amino acid change. N and C represent the amino and carboxy terminal of GNAQ protein.

Categories	Subtypes	GNA11 Ex5		GNAQ Ex5		Neither		Total
		number of samples	%	number of samples	%	number of samples	%	
Blue nevi	Amelanotic blue nevus	0	0.0%	7	70.0%	3	30.0%	10
	Cellular blue nevus	3	8.3%	26	72.2%	7	19.4%	36
	Common blue nevus	4	6.7%	39	65.0%	17	28.3%	60
	Nevus of Ito	0	0.0%	0	0.0%	7	100.0%	7
	Nevus of Ota	1	5.0%	2	10.0%	17	85.0%	20
	Malignant blue nevus	1	16.7%	2	33.3%	3	50.0%	6
Total		9	6.5%	76	54.7%	54	38.8%	139
Ocular melanocytic tumors	Conjunctival melanoma	0	0.0%	0	0.0%	9	100.0%	9
	Uveal melanoma, primary	52	31.9%	73	44.8%	38	23.3%	163
	Uveal melanoma, metastasis	13	56.5%	5	21.7%	5	21.7%	23
	Uveal nevus	0	0.0%	1	100.0%	0	0.0%	1
Total		65	33.2%	79	40.3%	52	26.5%	196
Other nevi	Common nevus	0	0.0%	0	0.0%	22	100.0%	22
	Congenital nevus	0	0.0%	0	0.0%	17	100.0%	17
	Deep penetrating nevus	0	0.0%	0	0.0%	27	100.0%	27
	Spitz nevus	0	0.0%	0	0.0%	19	100.0%	19
	Atypical Spitz tumor	0	0.0%	0	0.0%	20	100.0%	20
Total		0	0.0%	0	0.0%	105	100.0%	105
Extra-ocular melanomas	Acral	0	0.0%	0	0.0%	47	100.0%	47
	CSD	0	0.0%	1	1.4%	73	98.6%	74
	Mucosal	0	0.0%	0	0.0%	62	100.0%	62
	NonCSD	0	0.0%	0	0.0%	90	100.0%	90
Total		0	0.0%	1	0.4%	272	99.6%	273
Grand Total								713

Table representing the exon 5 mutation frequencies of GNAQ and GNA11 in melanocytic neoplams.

Implicated in

Blue nevi

Note

The hotspot mutation of Q209 in Exon 5 is found in 55% of blue nevi. The R183 mutation in Exon 4 is less common and is found in 1% of blue nevi. The mutations of GNAQ or its paralog GNA11 are expected to be early events in oncogenesis. A mutation in either gene alone is often found in benign proliferations of dermal melanocytes such as blue nevi.

Prognosis

Blue nevi are typically benign melanocytic nevi that rarely progress to melanoma (malignant blue nevus).

Cytogenetics

Blue nevi typically lack the presence of chromosomal aberrations.

Categories	Subtypes	GNA11 Ex5		GNAQ Ex5		Neither		Total
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Table representing the exon 5 mutation frequencies of GNAQ and GNA11 in blue nevi.

Categories	Subtypes	GNA11 Ex5		GNAQ Ex5		Neither		Total
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Table representing the exon 5 mutation frequencies of GNAQ and GNA11 in uveal melanoma.

Uveal melanoma

Note

The hotspot mutation of Q209 in Exon 5 is found in 45% of primary uveal melanoma and 22% of metastatic uveal melanomas. R183 mutation in Exon 4 is less common and is found in 3% of uveal melanoma.

Prognosis

Uveal melanoma is the most common primary intraocular malignancy with a 10 year survival rate of approximately 50%. Uveal melanoma has a high propensity of metastasis to the liver. The prognosis of uveal melanoma is highly dependent on the presence of additional genetic alterations, primarily loss of chromosome 3 and trisomy 8q.

Cytogenetics

Uveal melanoma has been shown to have frequent chromosomal aberrations like monosomy 3, trisomy 8q and recently 80% of uveal metastasis have been shown to have mutations in BAP1.

Primary melanocytic neoplasms of the central nervous system

Note

Recently GNAQ Q209 mutations have also been shown

to be present in primary melanocytic neoplasms of the central nervous system, (in this study GNAQ exon 4 was not investigated). Primary melanocytic neoplasms of the central nervous system (CNS) are rather rare tumors, originating from melanocytes that are considered to be derived from the leptomeninges. The tumors represent a spectrum in terms of malignant potential. Some are classified as low-grade melanocytomas, others as intermediate malignancy and some as overtly malignant melanomas.

Prognosis

Highly varied, depending on the grade of the tumor.

Other diseases

Note

So far no activating mutations of GNAQ in other cancers have been reported. Collectively four studies to date have sequenced more than 1500 tumor samples of a collection of various major tumor types and failed to identify any mutations in other settings than the ones described above.

There have been two reports indicating that promoter associated expression of GNAQ may be of importance. One of the reports indicates the presence of a dinucleotide SNP in the promoter region as a genetic risk factor for cardiac hypertrophy. The second report links promoter associated expression differences to polycystic ovary syndrome, raising the possibility that expression levels could be relevant in some settings.

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