

## Gene Section

### Mini Review

# GNA11 (guanine nucleotide binding protein (G protein), alpha 11 (Gq class))

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## Identity

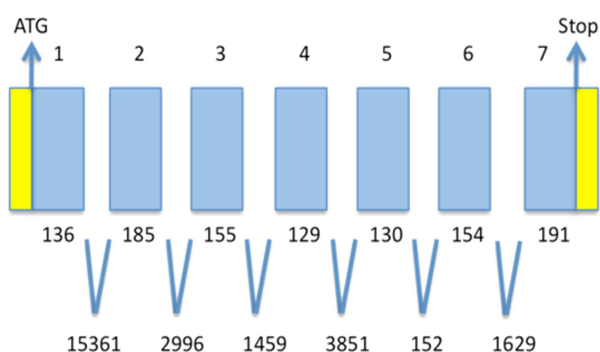
**Other names:** GNA-11; GA11

**HGNC (Hugo):** GNA11

**Location:** 19p13.3

**Local order:** Between AES and AC0052641.

## DNA/RNA



Numbers pertain to amount of nucleotides in exons and introns of human GNA11. Untranscribed sequences are yellow, transcribed ones are blue. The arrows refer to the start and stop codon.

## Description

The GNA11 gene is composed of 7 exons spanning a region of 27044 bp.

## Transcription

The transcribed mRNA has ORF is 1080 nucleotides.

## Pseudogene

Processed pseudogene GNA11 is on chromosome 7, 65970152 to 65971210.

## Protein

### Description

Aminoacids: 359. Molecular weight: 42123 daltons. GNA11 is a proto-oncogene that belongs to the Gq family of the G alpha family of G protein coupled receptors. It is highly homologous to GNAQ.

### Expression

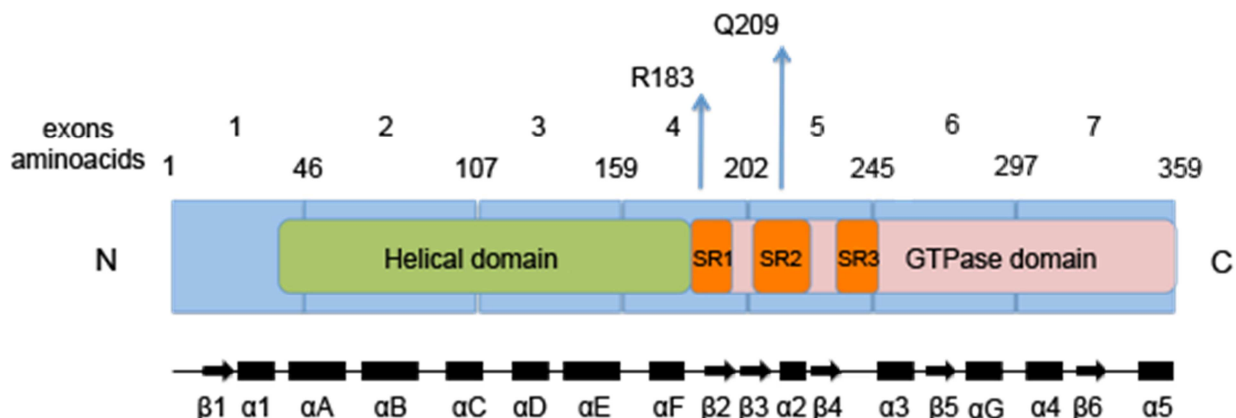
GNA11 is generally expressed ubiquitously, an exception being platelets, where only GNAQ is expressed.

### Localisation

Cytoplasmic. Signaling occurs at the membrane, which requires N-terminal lipid modification (palmitoylation) of the protein.

### Function

GNA11 is a G protein alpha unit associating with a beta and a gamma subunit. Upon ligand binding to G protein coupled receptors, GNA11 binds GTP, which leads to activation and disassociation from the beta and gamma subunits. Known downstream signaling partners are phospholipase C (PLC) beta and RhoA.



The diagram shows the general functional domains of G alpha 11 in respect to the amino acid residues and the corresponding exons. The alpha helical domain is found in all G alpha family members. Switch regions (SR), the areas that change their conformation based on if GTP or GDP is bound, are shown in orange (SR1: 182-192, SR2: 204-224, SR3: 236-247). The location of the 183 and 209 mutations are shown and affect switch regions 1 and 2 respectively. The GTPase domain is both essential for hydrolyzing bound GTP as well as binding downstream effectors. Adapted from Mizuno and Itoh, 2009.

PLC beta upon activation releases inositol triphosphate (IP3) and diacylglycerol (DAG) from membrane phosphatidylinositol-3-phosphate. RhoA activation is mediated through proteins such as p63 RhoGef, Duet and Trio by GNAQ, and may thus also be mediating Rho activation by GNA11. GNA11 activation has been shown to induce MAP Kinase activation, possibly via DAG-mediated activation of protein kinase C isoforms. Many other proteins shown to bind GNAQ and or GNA11 have been reported, many with regulatory functions, thus named GRK (G Protein regulatory kinases) or RGS (regulator of G protein signaling) proteins.

**Homology**

GNA11 is part of the G q family of alpha proteins. This family consists of GNAQ, GNA11, GNA14 and GNA15. On an aminoacid level GNA11 is 90% homologous to GNAQ, 82% homologous to GNA14 and 55% homologous to GNA15.

**Mutations**

**Note**

The mutations that have been described in melanocytic neoplasia have previously been demonstrated to inhibit the GTPase function and lead to decreased (R183) or completely (Q209) abolished ability to hydrolyze GTP to GDP, locking the protein in the GTP bound, constitutively active state. Experimental in vitro and in vivo data has shown that fitting with the degree of GTPase inhibition Q209 mutations are more potent activators than R183 mutations.

**Germinal**

No known germinal mutations.

**Somatic**

Q209 mutations have been described in uveal melanomas (32% primary, 57% metastasis) and blue nevi (6.5%).

R183 mutations have only been described in uveal melanoma (2% primary, 6% metastasis). Overall frequencies and distribution of GNA11 mutations as compared to GNAQ in uveal and cutaneous melanocytic tumors are listed in the table below.

Categories	n°	GNA11	GNAQ	Either
Blue Nevi	139	7%	56%	63%
Uveal melanoma, primary	163	34%	48%	82%
Uveal melanoma, metastasis	23	62%	28%	90%
Uveal nevus	1	0%	100%	100%
Conjunctival melanoma	9	0%	0%	0%
Other nevi	105	0%	0%	0%
Extra-ocular melanomas	273	0%	1%	1%
Total	713			

In the table, frequencies of mutations in GNAQ and GNA11 found in different melanocytic proliferations are listed.

**Implicated in**

**Blue nevi (6.5%)**

**Note**

The mutations of GNA11 or its paralog GNAQ 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. Segmental dermal melanocytic hyperplasia of the first trigeminal branch are called Nevi of Ota. In Caucasians Nevus of Ota is a risk factor for uveal melanoma. Similar segmental lesions in the shoulder area are termed Nevus of Ito. These proliferations of dermal melanocytes and blue nevi are benign, but can evolve into melanoma at a low frequency.

### Prognosis

Blue nevi as well as segmental melanocytoses are typically harmless, with only a low probability of progressing to melanoma.

### Uveal melanoma

#### Note

Primary uveal Melanoma (34%), Uveal melanoma metastases (62%).

Uveal melanoma is an aggressive form of eye cancer. It represents the most common eye cancer and has an incidence of about 2-8 people per million in Caucasians. It can originate in the ciliary body, the iris or most commonly the choroid.

### Prognosis

Uveal melanoma is an aggressive cancer with a 10 year survival rate of approximately 50%. The primary tumor is often only recognized at a stage where it has already metastasized. Metastasis in uveal melanoma occurs predominantly to the liver. The prognosis of uveal melanomas is highly dependent on the presence of additional genetic alterations, loss of chromosome 3 in particular.

### Cytogenetics

A frequent chromosomal aberration associated with poor prognosis is the loss of chromosome 3. A gene on this chromosome called BAP1, found to be mutated over 80% of metastasizing uveal melanomas, was recently identified.

### Other entities

#### Note

Activating mutations of GNA11 have not been found in other malignancies although a recent publication screened a panel of 922 different tumor samples. There is a reporting of reduced mRNA and protein levels of GNA11 in breast cancer. This indicates expression levels of GNA11 may be relevant in some settings.

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