Published in final edited form as:
Acta Neuropathol. 2012 March ; 123(3): 457–459. doi:10.1007/s00401-012-0948-x.

GNAQ and *GNA11* mutations in melanocytomas of the central nervous system

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Keywords

Central nervous system; Genetics; GNA11; GNAQ; Melanocytoma; Mutation

Melanocytic tumors in the central nervous system (CNS) include metastatic melanoma and less commonly primary melanocytic tumors, which usually arise from melanocytes of the leptomeninges. The latter include, in order of increasing biologic potential, melanocytomas, melanocytic neoplasms of intermediate grade/differentiation and primary melanomas.(2) Primary leptomeningeal melanocytic neoplasms belong to a larger taxonomic group of benign and malignant tumors arising from melanocytes that are not associated with epithelia. The group also includes blue nevi, melanomas arising in association with blue nevi (so-called “malignant blue nevi”), uveal nevi and uveal melanomas (4, 5, 7). Neoplasms in this group share morphologic features such as predominance of spindled and epithelioid cells, conspicuous pigmentation and absence of epithelial involvement, along with frequent mutations of *GNAQ* or *GNA11*, two closely related G-proteins of the Gq family that encode critical amino acids required for the GTPase function of the proteins. *GNAQ* or *GNA11* mutations occur in a mutually exclusive pattern and affect codon 183 in exon 4 or codon 209 in exon 5 of either gene.(7) Mutations at these sites cripple enzymatic function and lead to a constitutively activated GTP-bound state. When in this state, *GNAQ* and *GNA11* act as dominant-acting oncogenes that activate several critical signalling pathways including the MAP-kinase pathway (5, 7).

A recent study reported mutations in exon 5 of *GNAQ* in 6/12 (50%) melanocytomas, 5 of which were in paraspinal locations.(3) We extended this analysis to include exons 4 and 5 of both *GNAQ* and *GNA11*. Five cases of CNS melanocytoma were identified from the consultation files of one of the authors (M.K.R.). Sections were cut from formalin-fixed, paraffin-embedded tumor tissue, and stained with hematoxylin-eosin; immunohistochemistry was performed. Tumor DNA was extracted from tissue carefully microdissected from deparaffinized, unstained sections. Direct (Sanger) sequencing for

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CONFLICT OF INTEREST The authors declare that they have no conflict of interest.

exons 4 and 5 of each of *GNAQ* and *GNA11* was performed using methods described previously.(7)

The clinical and pathologic features of the tumors are summarized in Table 1. The tumors occurred in 3 males and 2 females, with a median age of 42 years (range 29-61 years). They were composed of spindle-shaped, oval or epithelioid cells arranged in nests and vague whorls. Tumor cells ranged from amelanotic (Fig. 1a) to conspicuously pigmented (Fig. 1c). Immunohistochemically, all tumors were diffusely positive for S-100 and HMB-45, and negative for epithelial membrane antigen. Mutations were identified in exon 4 of *GNAQ* (1 case, Fig. 1b) and exon 5 of *GNA11* (1 case, Fig. 1d). The mutations [*GNAQ*:(c.548G>A, p.(Arg183Gln) and *GNA11*:c.626A>C, p.(Gln209Pro)] are identical to those seen in uveal melanoma and intradermal melanocytic proliferations (6, 7). Our results expand the spectrum of *GNAQ* and *GNA11* mutations that may occur in melanocytomas. To our knowledge, this is the first description of mutations in *GNA11* and in exon 4 of *GNAQ* in melanocytomas.

The occurrence of *GNAQ* and *GNA11* mutations in melanocytomas,(3) dermal melanocytic tumors(6, 7) and uveal melanomas(6, 7) suggests the possibility of a developmental link between the cells of origin of these tumors. Indeed, this thesis is supported by the recent description of a developmental pathway in which a subgroup of melanocytes derives from Schwann cell precursors.(1) Although we identified a *GNAQ* exon 4 mutation in 1 of 5 cases of melanocytoma, exon 4 mutations in either *GNAQ* or *GNA11* are rare in uveal melanomas (7/145, 4.8%) and blue nevi (2/96, 2.1%) (7). Mutational analysis of larger numbers of tumors is required to determine the true incidence of the different mutations in *GNAQ* and *GNA11*, and to investigate associations of specific mutations with clinical features, pathologic characteristics, and biologic behavior of melanocytomas.

Acknowledgments

Harry J. Lloyd Translational Research Award and Lucille Castori Fellowship [R.M.]; Max-Kade Fellowship and Jubilaeumsfonds of the Oesterreichische Nationalbank (13837) [T.W.]; US National Institutes of Health (R01 CA131524 and CA142873) and a Melanoma Research Alliance Team Science Award [B.C.B.]

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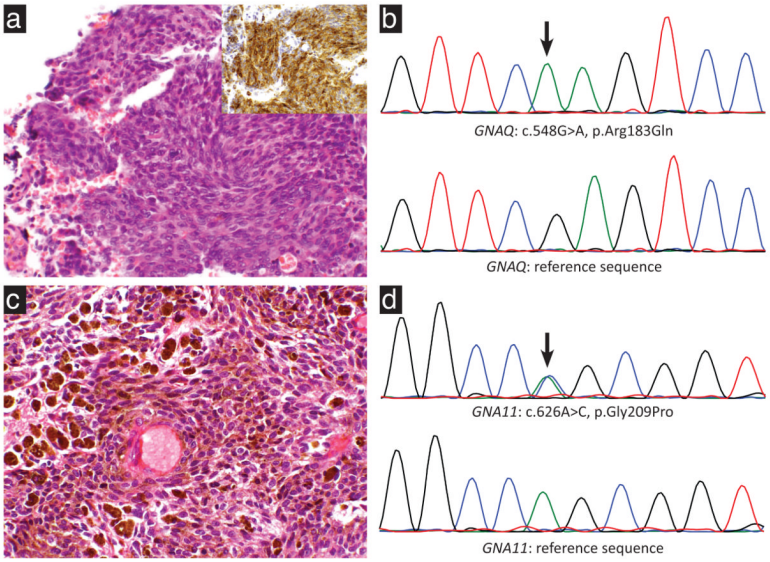

Figure 1.

a) Case 1 – A monomorphous population of slightly spindled, amelanotic cells in vaguely whorling array is present (hematoxylin-eosin, x100). Inset - Diffuse cytoplasmic immunolabeling for HMB-45 confirms the melanocytic nature of the tumor cells (immunoperoxidase with hematoxylin counterstain, x100). b) Case 1 - sequencing electropherogram of the tumor (upper panel) shows a homozygous point mutation (arrow) in exon 4 of *GNAQ*; the corresponding region of the reference sequence is illustrated in the lower panel [nucleotide assignment: A=green; C=blue; G=black; T=red]. c) Case 2 – Spindled and pigmented tumor cells are present, some of which whorl about a blood vessel (hematoxylin-eosin, x100). d) Case 2 - sequencing electropherogram of the tumor (upper panel) shows a heterozygous point mutation (arrow) in exon 5 of *GNA11*; the corresponding region of the reference sequence is illustrated in the lower panel [nucleotide assignment: A=green; C=blue; G=black; T=red].

TABLE

Clinical and pathologic features of melanocytomas

Case no.	Age Sex	Site	Diagnosis	Predominant cell type(s)	*GNAQ/GNA11* mutations
1	59 M	T9 intradural, extramedullary	Melanocytoma	Spindle	***GNAQ*, exon 4**: c.548G>A, p.(Arg183Gln)
2	29 M	Foramen magnum	Melanocytoma	Spindle	***GNA11*, exon 5**: c.626A>C, p.(Gln209Pro)
3	42 M	T4-5 intradural, extramedullary	Melanocytoma,	Spindle	Wt
4	39 F	Posterior fossa	Melanocytic neoplasms of intermediate grade/differentiation	Spindle and epithelioid	Wt
5	61 F	C5-7 intradural, extramedullary	Melanocytoma	Spindle	Wt

M = male; F = female; Wt = wild type for *GNAQ* and *GNA11*