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A role for the p53 pathway in the pathology of meningiomas with *NF2* loss

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Abstract

The neurofibromatosis 2 locus (*NF2*) is inactivated through mutation and loss of heterozygosity (LOH) in 40–65% of all sporadic meningiomas, while the role of the p53 tumor suppression pathway in meningioma initiation and progression is still unclear. This study aims to determine if a p53 codon 72 arginine-to-proline polymorphism, found to be correlated with cancer development and cancer patient survival in other tumors, is associated with sporadic meningioma initiation or progression. We investigated *Pro72* incidence in a cohort of 92 sporadic meningiomas and analyzed its association with histological grade (WHO classification) and with *NF2* LOH (determined using polymorphic microsatellite markers on 22q). The *Pro72* allele was not found to be selected for in the cohort. However, in the subgroup of meningiomas with *NF2* LOH and carrying *Pro72*, 50.0% had high grade tumors (WHO grades II and III) compared to only 14.3% of those without *NF2* LOH (OR = 6.0, CI = 1.56–23.11, $P = 0.012$). The significant association occurred only when considering subgroups of meningiomas with or without *NF2* LOH, suggesting that not including *NF2* status when analyzing study cohorts may explain the variability seen in the literature where all meningiomas were grouped together. Our data suggests a role for the p53 pathway in the progression of meningiomas in which NF2 is inactivated, and highlights the importance of accounting for *NF2* LOH in future studies of meningiomas and the p53 pathway.

Keywords

NF2; Mdm2; p53; *Pro72*; Meningiomas

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Introduction

Arising from the arachnoid coverings of the brain and spinal cord, meningiomas account for 15–20% of primary neoplasms of the central nervous system, and have an estimated annual incidence of about 6 per 100,000 individuals [1]. Loss of heterozygosity (LOH) of chromosome 22, containing the *NF2* gene, has been found in 40–65% of all meningiomas [2-4]. *NF2* mutations are found in up to 60% of meningiomas and are usually associated with *NF2* LOH [3,5], suggesting that LOH of *NF2* is an early genetic event in meningioma pathogenesis. In addition to meningioma formation, *NF2* inactivation has also been associated with later tumor progression to higher grades [6,7], but this pattern of tumor development is not present in all tumors since the majority of meningiomas still occur as benign tumors [8]. These results suggest that although about half of meningiomas are associated with *NF2* LOH, only a small group of tumors are at risk for tumor progression. Our hypothesis is that other underlying genetic factors exist that are responsible for meningioma progression.

TP53, the gene encoding p53, mediates a major tumor suppression pathway of the cell. Since the first report in 1989 [9], p53 mutations have been found in approximately half of all cancers [10,11]. Despite this clear prominence of the p53 pathway in cancers, conflicting results are present in the literature over the role of the p53 pathway in meningiomas. Several lines of evidence suggest that the p53 pathway is not important in meningioma etiology such as the absence of *TP53* mutations in meningiomas [12-14], the lack of abnormal expression of p53 or Mdm2 in meningiomas or meningioma cell lines [15], and the similarity of p53 expression in orbital meningiomas of different histological grades [16]. Meanwhile, other studies suggest the involvement of the p53 pathway in meningioma development: the correlation of p53 protein expression with histological tumor grade and meningioma recurrence [17], the loss of detectable Mdm2 protein in high grade meningiomas [18], and a defective p53 response to gamma ray stress in meningioma cells [19]. In addition, the *NF2* protein product was reported to increase p53 stability through downregulating Mdm2 levels in mouse fibroblast [20]. It follows that loss of *NF2* may increase the likelihood of p53 suppression, thus decreasing tumor suppression activity and providing a possible mechanism for the involvement of the p53 pathway in meningiomas. We hypothesize that a genetic factor that modulates the activity of the p53 pathway may help regulate meningioma pathogenesis.

The proto-oncogene product Mdm2, an E3 ubiquitin ligase, acts to both repress p53's transcriptional activity in the nucleus [21,22] and induce p53 degradation via the ubiquitin-proteasome system [23-25]. Excessive p53 downregulation by Mdm2 has been associated with accelerated tumor growth and metastatic cancer phenotypes [26-29]. Contrastingly, Mdm2 has also been implicated to be necessary for a tumor suppressive function of p53. Mdm2-mediated monoubiquitylation of p53 has been found to be necessary for p53 translocation from the nucleus to the mitochondria, where the p53 induces apoptosis in a stressed cell [30-32].

The p53 codon 72 arginine-to-proline polymorphism alters a cell's apoptotic potential via differential interaction with Mdm2 [33]. The *Arg72* allele has been found to have increased interaction with Mdm2, causing enhanced shuttling to the mitochondria and induction of transcriptionally independent apoptosis [33]. Meanwhile, the *Pro72* allele, which is found to be correlated with cancer development [34] and decreased cancer patient survival [35], is associated with decreased translocation of p53 from the nucleus [33]. In this case, p53 interaction with Mdm2 would suppress p53 and cause tumor development. Since NF2 has been found to inhibit Mdm2 [20], we hypothesize that *NF2* LOH in meningiomas increases Mdm2 function and allows for subsequent tumor progression to occur with additional presence of the *Pro72* allele.

Materials and methods

Subjects and sample collection

This study was approved by the Institutional Review Board of Massachusetts General Hospital/Partners HealthCare and informed written consent was obtained from all individuals donating tissue. Between August 2000 and December 2004, 142 meningioma patients had tumors resected at Massachusetts General Hospital and consented to banking of excess tumor tissues for research. From the 142 patients, 50 were excluded from this study due to lack of adequate blood or tumor DNA for analysis or presence of multiple intracranial tumors suggestive of Neurofibromatosis 2 or the syndrome of multiple meningiomas. Medical records review was performed using the Research Patient Database Registry, an internal research tool providing access to demographic information, radiology reports and pathology reports. Blood and tumor DNA were extracted using a standard extraction kit as previously described [36].

NF2 loss of heterozygosity

Loss of heterozygosity (LOH) of the *NF2* locus was determined as previously described [36]. Individuals heterozygous at *NF2*, as determined by analysis of blood DNA, were checked for loss of heterozygosity in tumor DNA at markers D22S193 (centromeric to *NF2*), *NF2*TET and D22S929 (intragenic), and D22S268 and D22S430 (telomeric to *NF2*).

p53 codon 72 polymorphism analysis

Determination of the polymorphism at codon 72 used a modification of the protocol described by Fan et al. [37] as follows. A 150 bp fragment containing the polymorphism was amplified in 100 ng of genomic DNA using the oligo-nucleotide primers 5′-AGATGAAGCTCCCAGAATGC-3′ (forward) and 5′-GTAGGTTTTCTGGGAAGGGA-3′ (reverse). A 10 μl total volume PCR contained 4 pM of each primer, 0.2 mM of each dNTP, 2 μl of Q solution, 1 μl of 10X buffer, and 0.25 U of Taq polymerase (Qiagen, Valencia, CA). Initial denaturation was carried out at 95°C for 5 min, followed by 35 cycles of 95°C for 30 s, 57°C for 30 s, 72°C for 1 min, and a final extension of 7 min at 72°C. PCR products were then digested using the endonuclease *BstUI* in 30 μl volumes according to the manufacturer's specifications (New England Biolabs, Beverly, MA). The restriction fragment length polymorphism was detected on an 8% polyacrylamide gel and visualized using ethidium bromide. No restriction site is present in the *Arg72* allele, while the 150 bp PCR product is digested into two fragments of 114 and 36 bp in the *Pro72* allele.

Statistical analysis

Histological grades of tumors were available from the pathology reports as assessed by the pathologist according to the criteria of WHO 2000 [38]. For the purpose of statistical analysis, atypical (WHO grade II) and malignant (WHO grade III) meningiomas were grouped together as high grade meningiomas and compared to low grade tumors (WHO grade I). Analysis of the p53 codon 72 polymorphism was performed by combining those patients heterozygous and homozygous for Pro72 into one single group whenever the group with homozygous Pro72 was too small to be analyzed independently. Associations between two dichotomous variables, for example, p53 codon 72 and *NF2* LOH, were tested using Fisher's exact test (two tailed). The corresponding odds ratios are conditional maximum likelihood ratio estimates. Tests were conducted at the $P = 0.05$ level of significance and confidence intervals are reported at the 95% level.

Results

Cohort characteristics are delineated in Table 1. Similar to previous findings, a 2.4:1 female to male ratio was found [39]. Meanwhile, a higher typical incidence of high grade tumors is present (29.3%; 27/92) [8], possibly because Massachusetts General Hospital is a tertiary care center. In our cohort, high grade tumors were seen in 24.6% (16/65) of women and 40.7% (11/27) of men (odds ratio (OR) = 2.1, confidence interval (CI) = 0.81–5.46, *P* value = 0.138). LOH of the *NF2* locus was seen with an incidence of 52.1% in the cohort, similar to previously reported values. *NF2* LOH was also significantly associated with high tumor grade, with 41.7% (20/48) of tumors having *NF2* loss being high grade tumors, compared to 15.9% (7/44) of those retained at the *NF2* locus (OR = 3.8, CI = 1.40–10.17, *P* = 0.011). However, when segregating by gender, the significance of this association was restricted to tumors from men. More than half (55.6%; 10/18) of the meningiomas from men with *NF2* LOH were high grade, while only 11.1% (1/9) of the tumors from men without *NF2* LOH were high grade (OR = 10.0, CI = 1.03–97.50, *P* = 0.042). Such a difference was not found to be significant among women (*P* = 0.157). LOH of the *NF2* locus was also associated with an early average age of tumor resection in men (52.3 years for tumors lost at *NF2* compared to 65.8 years for tumors without *NF2* LOH, unpaired Student's *t*-test, *P* = 0.02); this result was not found among tumors from women (59.2 years for tumors with *NF2* LOH compared to 55.7 years for tumors without *NF2* LOH). The reason for the increased prevalence of meningiomas among women has not yet been identified, but our results suggest that *NF2* LOH in meningiomas is more common among men, and is also associated with high tumor grade and earlier age of onset in a gender specific manner.

Data involving p53 codon 72 are presented in Table 2. Distribution of the p53 codon 72 polymorphism among meningioma cases was found to be consistent with Hardy–Weinberg equilibrium, with allelic frequencies of 45.6% (*Arg72/Arg72*), 44.6% (*Arg72/Pro72*), and 9.8% (*Pro72/Pro72*), and did not significantly differ from previous reports using primarily Caucasian control groups [40,41]. This supports previous studies that found no association between p53 polymorphisms and meningiomas in Nordic, British, and Slavic cohorts [40,42, 43]. In our patient cohort, LOH of the *NF2* locus in tumors was seen in 61.9% (26/42) of patients carrying the *Arg72/Arg72* genotype compared to only 44.0% (22/50) of patients carrying at least one *Pro72* allele, but without reaching statistical significance (OR = 2.1, CI = 0.90–4.77, *P* = 0.098). Age of tumor resection was not found to differ between codon 72 genotypes even after considering patients' gender and *NF2* status in the tumor (data not shown).

To determine the effect of the polymorphism on meningioma progression we compared the frequency of high-grade tumors among the different genotypes. There was no association between the overall polymorphism distribution and tumor grade, with high grade tumors accounting for 28.6%, 31.7%, and 22.3% of the patients carrying the *Arg72/Arg72*, *Arg72/Pro72*, and *Pro72/Pro72* genotypes, respectively. When considering the effect of *NF2* LOH on tumor grade in patients carrying at least one *Pro72* allele (*Pro72/Pro72* or *Arg72/Pro72*), we found that patients with *NF2* LOH in the meningioma developed high grade tumors in 50.0% (11/22) of the cases, compared to only 14.3% (4/28) of patients without *NF2* LOH (OR = 6.0, CI = 1.56–23.11, *P* = 0.012). In contrast to this association found among patients with the *Pro72* allele, no significant association was found among patients with the *Arg72/Arg72* genotype (OR = 2.3, CI = 0.52–10.20, *P* = 0.316), demonstrating a change correlated with the p53 codon 72 genotype.

Discussion

This study of a human cohort presents bipartite findings involving *NF2* LOH in meningiomas. First, *NF2* LOH has been found to be associated with both high tumor grade and an early average age of tumor resection among men, but not women. Second, aggressive meningiomas

were found to be associated with *NF2* LOH only among individuals with the *Pro72* allele of the p53 codon 72, but not among those with the *Arg72/Arg72* genotype.

Meningiomas have long been known to exhibit receptors to sexual steroids [44], suggesting that hormonal influences may explain the sexually dimorphic characteristics of this disease. However, discrepancies on the proliferative effects of sexual hormones on meningiomas and failure of variations in sexual receptor expression to explain the increased prevalence of meningiomas in women suggests that more complex factors are at play [45]. Though gender differences are clearly observed in meningiomas, their cause(s) still remain elusive. The fact that NF2 has not been independently linked to any sort of sexual dimorphism suggests that some additional mechanism of meningioma development may occur in women. If such a mechanism were distinct from *NF2* LOH, it serves as one rationalization for why our first set of findings might occur with significance only among men.

The distribution of the p53 codon 72 polymorphism among our meningioma patients was not significantly different from that found in previously reported control groups [40,41], suggesting that alteration of the p53 pathway by a change at codon 72 does not affect meningioma initiation. The findings in our study of a human cohort are consistent with a previous study of an $NF2^{flox2/flox2}$ meningioma mouse model, which received *adCre* injections into the cerebral spinal fluid to target *NF2* at the level of the leptomeninges. When introducing the additional genetic background of *p53* hemizygosity into the mice, no increase in the rate of meningioma formation was found [46].

When considering the additional aspect of meningioma progression, we found that the presence of the *Pro72* allele predisposed to an increased relevance of *NF2* LOH in affecting tumor progression. In accord with several previous studies [18,19,47], our findings support a role for the p53 pathway in the progression of meningiomas, particularly among those having *NF2* LOH. The study of the $NF2^{flox2/flox2}$ meningioma mouse model had also considered the possible effect of *p53* hemizygosity upon meningioma progression, but was unable to observe any differences [46]. The *p53* hemizygous mice developed aggressive sarcomas that necessitated premature sacrifice, possibly masking a contribution of *p53* inactivation on meningioma progression.

NF2 is one of several proteins known to downregulate the inhibitory action of Mdm2 on p53 [20,48-50]. Thus, a potential model for the role of *NF2* LOH in meningiomas is that depletion of NF2 increases Mdm2 levels, thereby decreasing the activity of the p53 tumor suppression pathway and predisposing to tumor progression. Hence, we find increased tumor progression susceptibility among meningiomas that exhibit *NF2* LOH as an early genetic event. In accord with a previous study [18], our findings suggest that increased susceptibility of meningioma progression can arise through abnormally strong inhibition of the p53 pathway caused by loss of a factor that inhibits Mdm2-mediated negative regulation of p53. Since our findings depend on segregating the cohort according to *NF2* status, perhaps the inadvertent merging (into one group) of meningiomas with *NF2* LOH and those arising via other mechanisms has masked this relevance of the p53 pathway in previous studies that have suggested that alterations in the p53 pathway do not appear to contribute to the risk of sporadic meningioma formation or progression [15,16,40,42,43].

Using inducible cell lines, the *Arg72* allele of p53 codon 72 was previously reported to have superior binding to Mdm2 as compared to the *Pro72* allele. This was associated with enhanced tumor suppressive activity via Mdm2-dependent localization of p53 to the mitochondria for induction of transcriptionally independent apoptosis [33]. Meanwhile, the *Pro72* allele remains more in the nucleus and must therefore mediate tumor suppression via transcriptional means. Interaction of this *Pro72* allele with Mdm2 would therefore act to inhibit the p53 activities and

increase the possibility of tumor development. Our study finds a selection for *NF2* LOH in high grade tumors among meningiomas with the *Pro72* allele, suggesting that the primary mechanism of p53-mediated tumor suppression in meningiomas with *NF2* LOH might be the one associated with the *Arg72* allele: mitochondria mediated apoptosis. A decreased activity of this mechanism due to the presence of the *Pro72* allele makes the meningioma more likely to progress to higher grade. Further experiments are necessary to test these hypotheses.

In summary, this study supports the importance of *NF2* LOH in affecting the nature of meningioma pathology and prognosis. With a mechanistic perspective of the p53 codon 72 polymorphism, this study finds evidence for a two-tiered mechanism in the formation of high grade meningiomas: after *NF2* LOH occurs in tumorigenesis, the p53 pathway, when provoked, induces protective apoptosis through action at the mitochondria; polymorphism variants that disrupt the balance of components in this branch of the p53 pathway increase the risk of progression to high grade tumors. Further study and biochemical work is needed to fully understand the factors at work here, but our initial results suggest that future rational therapies for those meningiomas with *NF2* inactivation might include options that impact the p53 pathway.

We are aware of the limited number of samples in our cohort, so conclusions in this study are made with caution. Nevertheless, the findings contribute to a better understanding of meningiomas pathogenesis, particularly on the role of *NF2* LOH with regard to gender and the p53 pathway. Altogether, the data offers the suggestion that meningiomas arising with and without *NF2* LOH may perhaps present two different molecular microenvironments having the same deleterious macroscopic manifestation.

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References

1. Lantos, PL.; VandenBerg, SR.; Kleihues, P. Tumours of the nervous system. In: Graham, DL.; Lantos, PL., editors. Greenfield's neuropathology. Arnold; London: 2002.
2. aRuttledge MH, Xie YG, Han FY, et al. Deletions on chromosome 22 in sporadic meningioma. Genes Chromosomes Cancer 1994;10:122–130. [PubMed: 7520265]doi:10.1002/gcc.2870100207
3. Ruttledge MH, Sarrazin J, Rangaratnam S, et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. Nat Genet 1994;6:180–184. [PubMed: 8162072]doi: 10.1038/ng0294-180
4. Lekanne Deprez RH, Riegman PH, van Drunen E, et al. Cytogenetic, molecular genetic and pathological analyses in 126 meningiomas. J Neuropathol Exp Neurol 1995;54:224–235. [PubMed: 7876890]doi:10.1097/00005072-199503000-00009
5. Ueki K, Wen-Bin C, Narita Y, et al. Tight association of loss of merlin expression with loss of heterozygosity at chromosome 22q in sporadic meningiomas. Cancer Res 1999;59:5995–5998. [PubMed: 10606247]
6. Nunes F, Shen Y, Niida Y, et al. Inactivation patterns of NF2 and DAL-1/4.1B (EPB41L3) in sporadic meningioma. Cancer Genet Cytogenet 2005;162:135–139. [PubMed: 16213361]doi:10.1016/j.cancergencyto.2005.04.003
7. Al-Mefty O, Kadri PA, Pravdenkova S, et al. Malignant progression in meningioma: documentation of a series and analysis of cytogenetic findings. J Neurosurg 2004;101:210–218. [PubMed: 15309910]
8. Lamszus K. Meningioma pathology, genetics, and biology. J Neuropathol Exp Neurol 2004;63:275–286. [PubMed: 15099018]

9. Baker SJ, Fearon ER, Nigro JM, et al. Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. Science 1989;244:217–221. [PubMed: 2649981]doi:10.1126/science.2649981
10. Levine AJ. p53, the cellular gatekeeper for growth and division. Cell 1997;88:323–331. [PubMed: 9039259]doi:10.1016/S0092-8674(00)81871-1
11. Hollstein M, Rice K, Greenblatt MS, et al. Database of p53 gene somatic mutations in human tumors and cell lines. Nucleic Acids Res 1994;22:3551–3555. [PubMed: 7937055]
12. Das A, Tan WL, Smith DR. p53 point mutation is rare in meningiomas from Singaporean patients. Asian J Surg 2005;28:7–10. [PubMed: 15691789]
13. Ellison DW, Lunec J, Gallagher PJ, et al. Accumulation of wild-type p53 in meningiomas. Neuropathol Appl Neurobiol 1995;21:136–142. [PubMed: 7609844]doi:10.1111/j.1365-2990.1995.tb01040.x
14. Ohgaki H, Eibl RH, Schwab M, et al. Mutations of the p53 tumor suppressor gene in neoplasms of the human nervous system. Mol Carcinog 1993;8:74–80. [PubMed: 8397797]doi:10.1002/mc.2940080203
15. Pykett MJ, Landers J, George DL. Expression patterns of the p53 tumor suppressor gene and the mdm2 proto-oncogene in human meningiomas. J Neurooncol 1997;32:39–44. [PubMed: 9049861]doi:10.1023/A:1005779406636
16. Hei Y, Zhang XW, Wang Y, et al. The features of pathology and immunohistochemistry in orbital meningiomas. Zhonghua Yan Ke Za Zhi 2006;42:998–1001. [PubMed: 17386138]
17. Ohkoudo M, Sawa H, Hara M, et al. Expression of p53, MDM2 protein and Ki-67 antigen in recurrent meningiomas. J Neurooncol 1998;38:41–49. [PubMed: 9540056]doi:10.1023/A:1005946001915
18. Amatya VJ, Takeshima Y, Inai K. Methylation of p14(ARF) gene in meningiomas and its correlation to the p53 expression and mutation. Mod Pathol 2004;17:705–710. [PubMed: 15073599]doi:10.1038/modpathol.3800111
19. Al-Khalaf HH, Lach B, Allam A, et al. The p53/p21 DNA damage-signaling pathway is defective in most meningioma cells. J Neurooncol 2007;83:9–15. [PubMed: 17245624]doi:10.1007/s11060-006-9301-3
20. Kim H, Kwak NJ, Lee JY, et al. Merlin neutralizes the inhibitory effect of Mdm2 on p53. J Biol Chem 2004;279:7812–7818. [PubMed: 14679203]doi:10.1074/jbc.M305526200
21. Momand J, Zambetti GP, Olson DC, et al. The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation. Cell 1992;69:1237–1245. [PubMed: 1535557]doi:10.1016/0092-8674(92)90644-R
22. Thut CJ, Goodrich JA, Tjian R. Repression of p53-mediated transcription by MDM2: a dual mechanism. Genes Dev 1997;11:1974–1986. [PubMed: 9271120]doi:10.1101/gad.11.15.1974
23. Haupt Y, Maya R, Kazaz A, et al. Mdm2 promotes the rapid degradation of p53. Nature 1997;387:296–299. [PubMed: 9153395]doi:10.1038/387296a0
24. Honda R, Tanaka H, Yasuda H. Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53. FEBS Lett 1997;420:25–27. [PubMed: 9450543]doi:10.1016/S0014-5793(97)01480-4
25. Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. Nature 1997;387:299–303. [PubMed: 9153396]doi:10.1038/387299a0
26. Jones JM, Attardi L, Godley LA, et al. Absence of p53 in a mouse mammary tumor model promotes tumor cell proliferation without affecting apoptosis. Cell Growth Differ 1997;8:829–838. [PubMed: 9269892]
27. Laurie NA, Donovan SL, Shih CS, et al. Inactivation of the p53 pathway in retinoblastoma. Nature 2006;444:61–66. [PubMed: 17080083]doi:10.1038/nature05194
28. Bond GL, Hu W, Bond EE, et al. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell 2004;119:591–602. [PubMed: 15550242]doi:10.1016/j.cell.2004.11.022
29. Ku TK, Nguyen DC, Karaman M, et al. Loss of p53 expression correlates with metastatic phenotype and transcriptional profile in a new mouse model of head and neck cancer. Mol Cancer Res 2007;5:351–362. [PubMed: 17426250]doi:10.1158/1541-7786.MCR-06-0238
30. Erster S, Mihara M, Kim RH, et al. In vivo mitochondrial p53 translocation triggers a rapid first wave of cell death in response to DNA damage that can precede p53 target gene activation. Mol Cell Biol 2004;24:6728–6741. [PubMed: 15254240]doi:10.1128/MCB.24.15.6728-6741.2004

31. Marchenko ND, Wolff S, Erster S, et al. Monoubiquitylation promotes mitochondrial p53 translocation. EMBO J 2007;26:923–934. [PubMed: 17268548]doi:10.1038/sj.emboj.7601560
32. Sansome C, Zaika A, Marchenko ND, et al. Hypoxia death stimulus induces translocation of p53 protein to mitochondria. Detection by immunofluorescence on whole cells. FEBS Lett 2001;488:110–115. [PubMed: 11163756]doi:10.1016/S0014-5793(00)02368-1
33. Dumont P, Leu JI, Della Pietra AC 3rd, et al. The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet 2003;33:357–365. [PubMed: 12567188]doi:10.1038/ng1093
34. Marin MC, Jost CA, Brooks LA, et al. A common polymorphism acts as an intragenic modifier of mutant p53 behaviour. Nat Genet 2000;25:47–54. [PubMed: 10802655]doi:10.1038/75586
35. Tommiska J, Eerola H, Heinonen M, et al. Breast cancer patients with p53 Pro72 homozygous genotype have a poorer survival. Clin Cancer Res 2005;11:5098–5103. [PubMed: 16033823]doi:10.1158/1078-0432.CCR-05-0173
36. Heinrich B, Hartmann C, Stemmer-Rachamimov AO, et al. Multiple meningiomas: investigating the molecular basis of sporadic and familial forms. Int J Cancer 2003;103:483–488. [PubMed: 12478663]doi:10.1002/ijc.10840
37. Fan R, Wu MT, Miller D, et al. The p53 codon 72 polymorphism and lung cancer risk. Cancer Epidemiol Biomarkers Prev 2000;9:1037–1042. [PubMed: 11045785]
38. Kleihues, P.; Cavenee, WK., editors. Pathology and genetics of tumours of the nervous system. International Agency for Research on Cancer; Lyon: 2000.
39. DeAngelis LM. Brain tumors. N Engl J Med 2001;344:114–123. [PubMed: 11150363]doi:10.1056/NEJM200101113440207
40. Malmer B, Feychting M, Lonn S, et al. p53 Genotypes and risk of glioma and meningioma. Cancer Epidemiol Biomarkers Prev 2005;14:2220–2223. [PubMed: 16172235]doi:10.1158/1055-9965.EPI-05-0234
41. Sturm I, Bosanquet AG, Hummel M, et al. B-CLL, the codon 72 polymorphic variants of p53 are not related to drug resistance and disease prognosis. BMC Cancer 2005;5:105. [PubMed: 16109171]doi:10.1186/1471-2407-5-105
42. Malmer BS, Feychting M, Lonn S, et al. Genetic variation in p53 and ATM haplotypes and risk of glioma and meningioma. J Neurooncol 2007;82:229–237. [PubMed: 17151932]doi:10.1007/s11060-006-9275-1
43. Biros E, Kalina I, Kohut A, et al. Allelic and haplotype frequencies of the p53 polymorphisms in brain tumor patients. Physiol Res 2002;51:59–64. [PubMed: 12071291]
44. Cahill DW, Bashirelahi N, Solomon LW, et al. Estrogen and progesterone receptors in meningiomas. J Neurosurg 1984;60:985–993. [PubMed: 6716168]
45. Korhonen K, Salminen T, Raitanen J, et al. Female predominance in meningiomas cannot be explained by differences in progesterone, estrogen, or androgen receptor expression. J Neurooncol 2006;80:1–7. [PubMed: 16703453]doi:10.1007/s11060-006-9146-9
46. Kalamarides M, Niwa-Kawakita M, Leblois H, et al. Nf2 gene inactivation in arachnoidal cells is rate-limiting for meningioma development in the mouse. Genes Dev 2002;16:1060–1065. [PubMed: 12000789]doi:10.1101/gad.226302
47. Ozen O, Demirhan B, Altinors N. Correlation between histological grade and MIB-1 and p53 immunoreactivity in meningiomas. Clin Neuropathol 2005;24:219–224. [PubMed: 16167545]
48. Mayo LD, Dixon JE, Durden DL, et al. PTEN protects p53 from Mdm2 and sensitizes cancer cells to chemotherapy. J Biol Chem 2002;277:5484–5489. [PubMed: 11729185]doi:10.1074/jbc.M108302200
49. Pomerantz J, Schreiber-Agus N, Liegeois NJ, et al. The Ink4a tumor suppressor gene product, p19Arf, interacts with MDM2 and neutralizes MDM2's inhibition of p53. Cell 1998;92:713–723. [PubMed: 9529248]doi:10.1016/S0092-8674(00)81400-2
50. Sionov RV, Moallem E, Berger M, et al. c-Abl neutralizes the inhibitory effect of Mdm2 on p53. J Biol Chem 1999;274:8371–8374. [PubMed: 10085066]doi:10.1074/jbc.274.13.8371

Table 1

Demographic and clinical characteristics of the sporadic meningioma patient cohort

Sex	Men: 27	Age of tumor resection (yrs)	57 ± 12.5
	Women: 65		
Ethnicity	Caucasian: 83	Tumor grade	Benign: 65
	African: 2		Atypical: 23
	Asian: 2		Malignant: 4
	Unrecorded: 5	*NF2* status	Loss: 48
			Retained: 44

Table 2

Distribution of the p53 codon 72 polymorphism among sporadic meningioma patients

p53 codon 72 alleles	*NF2* status	Women			Men			All		
		High grade	Low grade	Total	High grade	Low grade	Total	High grade	Low grade	Total
Arg72/Arg72	*NF2* LOH	5	11	16	4	6	10	9	17	26
	NF2 retained	2	9	11	1	4	5	3	13	16
	Total	7	20	27	5	10	15	12	30	42
With *Pro72* [percentage of row total for (2 × 2) values]	*NF2* LOH	5	9	14	6	2	8	*11 (50)*	*11 (50)*	22
	NF2 retained	4	20	24	0	4	4	*4 (14.3)*	*24 (85.7)*	28
	Total	9	29	38	6	6	12	15	35	50
All [percentage of row total for (2 × 2) values]	*NF2* LOH	10	20	30	*10 (55.6)*	*8 (44.4)*	18	*20 (41.7)*	*28 (58.3)*	48
	NF2 retained	6	29	35	*1 (11.1)*	*8 (88.9)*	9	*7 (15.9)*	*37 (84.1)*	44
	Total	16	49	65	11	16	27	27	65	92

Italicized values (2 × 2) were found to have $P < 0.05$ with the Fisher's exact test