Age associated increase in the prevalence of chromosome 22q loss of heterozygosity in histological subsets of benign meningioma

M E Baser, T Y Poussaint

J Med Genet 2006;**43**:285–287. doi: 10.1136/jmg.2005.035162

Chromosome 22q loss of heterozygosity (LOH) is the most common allelic loss in benign meningioma and is thought to be the earliest initiating event in meningioma formation. We used published data and logistic regression to evaluate the association of 22q LOH with age at diagnosis in 318 transitional, fibroblastic, and meningothelial meningiomas. After adjustment for anatomical location, the odds ratio of 22q LOH per year of age was >1 in each histological type of meningioma, and was significantly >1 in transitional and fibroblastic meningioma. This finding is compatible with involvement of the neurofibromatosis 2 tumour suppressor gene, *NF2*, on chromosome 22q in the high incidence of benign meningioma in the elderly.

Meningioma is the second most common central nervous system tumour in adults. In one population based study, the age adjusted annual incidence of meningioma (intracranial and spinal tumours combined) was 4.7 per 100 000 in women and 2.0 per 100 000 in men.¹ The incidence is much higher in studies of the elderly that include asymptomatic meningioma.² The overall 5 year survival rate of patients with benign meningioma is 70%; the survival rate is higher in patients with skull base meningiomas and in younger patients.³

In addition to meningiomas that occur sporadically, meningiomas occur in about half of patients with neurofibromatosis 2 (NF2), a rare autosomal dominant disease that is caused by constitutional heterozygous inactivating mutations of the *NF2* tumour suppressor gene on chromosome 22q.^{4–5} Somatic *NF2* mutations are found in about half of sporadic meningioma.^{6–8} There are several differences between NF2 associated meningioma and sporadic meningioma. Multiple meningiomas are common in NF2. NF2 associated meningiomas usually occur at younger ages than sporadic meningiomas, and NF2 associated meningiomas usually have transitional or fibroblastic histology rather than meningothelial histology.

The complex processes of meningioma tumorigenesis and progression have been reviewed recently.⁹ The most common allelic loss in benign meningioma is 22q loss of heterozygosity (LOH), which occurs in about half of such tumours.^{7–10–13} LOH of 22q is thought to be the earliest initiating event in meningioma formation, while allelic losses at other loci such as 1p and 14q are associated with progression from benign meningioma to atypia and anaplasia.^{9–14}

In this study, we used published data and logistic regression to evaluate the association of 22q LOH with age at diagnosis in histological subsets of benign meningioma. After adjustment for anatomical location, the odds ratio of 22q LOH per year of age was >1 in each histological type of

meningioma (transitional, fibroblastic, and meningothelial), and was significantly >1 in transitional and fibroblastic meningioma. This result is compatible with involvement of the *NF2* gene in the high incidence of benign meningioma in the elderly.

METHODS

Published studies of 22q LOH in benign/WHO grade I meningiomas with transitional, fibroblastic, or meningothelial histology were identified through PubMed and the International *NF2* Mutation Database.¹⁵ Studies were included in the analysis if microsatellite marker based methods were used to determine 22q LOH. Individual tumours were included in the analysis if there were data on histology and the patient's age at diagnosis; a subset of tumours had information on anatomical location. The literature was cross indexed to exclude multiple reports of the same tumour. The sporadic nature of the tumours was specified in most of the published studies. Additionally, as the penetrance of NF2 associated disease features increases with increasing age, meningiomas that were diagnosed at ages <20 years were excluded because of possible association with undiagnosed NF2.

In total, 318 meningiomas from 10 studies met these criteria (Wellenreuther *et al.*,⁷ $n = 49$; Ruttledge *et al.*,⁸ $n = 21$; Dumanski *et al.*,¹⁰ $n = 65$; Leone *et al.*,¹¹ $n = 42$; Kros *et al.*,¹² $n = 34$; Lekanne Deprez *et al.*,¹³ $n = 39$; Weber *et al.*,¹⁴ $n = 19$; Papi *et al.*,¹⁶ $n = 9$; Ng *et al.*,¹⁷ $n = 20$; and Kim *et al.*,¹⁸ $n = 20$). The studies used different sets of microsatellite markers, but in four of the largest studies, the prevalence of 22q LOH was highest in fibroblastic meningiomas and lowest in meningothelial meningiomas.^{7–10–12}

Statistical analysis

The χ^2 test and Fisher's exact test were used for univariate analyses. Logistic regression was used to evaluate the association between presence or absence of 22q LOH and the covariates of age at diagnosis and anatomical location using data from the 177 tumours that had information on anatomical location. Separate models were computed for each histological type of meningioma. Anatomical location was coded as a binary variable (non-skull base or skull base). Associations were evaluated using odds ratios (OR) of 22q LOH and their 95% confidence intervals (CI) from the logistic regression models.

RESULTS

The characteristics of the tumours are presented in table 1. The median age at diagnosis was 58 years (range 20 to 87). The sex ratio (3.4:1 female:male) was similar to the sex ratio for meningioma in the general population.¹ The prevalence of 22q LOH was higher in men (51 of 72 tumours, 71%) than in women (143 of 246 tumours, 58%) (Fisher's exact test,

$p = 0.055$). As expected, the distribution of histological types varied by anatomical location. Among the 177 tumours with information on anatomical location, 29 (30%) of 96 transitional meningiomas were in the skull base, compared with four (13%) of 31 fibroblastic meningiomas and 21 (42%) of 50 meningothelial meningiomas (χ^2 test, $p = 0.022$, table 2).

Overall, 22q LOH was present in 194 (61%) of the 318 meningiomas, but there were notable differences between and within histological types (table 2). LOH of 22q was present in 84 (60%) of 140 transitional meningiomas, 61 (86%) of 71 fibroblastic meningiomas, and 49 (46%) of 107 meningothelial meningiomas (χ^2 test, $p < 0.001$). Among meningothelial meningiomas, 22q LOH was present in 17 (59%) of 29 tumours in non-skull base locations, but in only three (14%) of 21 tumours in the skull base (Fisher's exact test, $p = 0.003$).

The prevalence of 22q LOH increased with increasing age at diagnosis in each histological type of meningioma, significantly so in transitional and fibroblastic meningioma (table 2). In transitional meningioma, the prevalence of 22q LOH was 69% in older people and 53% in younger people (Fisher's exact test, $p = 0.059$). In fibroblastic meningioma, the prevalence of 22q LOH was 97% in older people and 77% in younger people (Fisher's exact test, $p = 0.019$).

The results of the logistic regression models are presented in table 3. After adjustment for anatomical location, the OR of 22q LOH per year of age was >1 in each histological type of meningioma, and was significantly >1 in transitional and fibroblastic meningioma. The point estimates for the OR of 22q LOH per year of age were 1.04 in transitional meningioma, 1.09 in fibroblastic meningioma, and 1.03 in meningothelial meningioma.

DISCUSSION

This is the largest study to date of 22q LOH in benign meningioma and the first to evaluate the association of 22q LOH with age at diagnosis in histological subsets of benign meningioma. The age associated increase in the prevalence of 22q LOH in each histological type of meningioma is compatible with involvement of the *NF2* gene in the high incidence of meningioma in the elderly. The increased prevalence of 22q LOH could be due to increasing genomic instability or deficient DNA repair. Genomic instability in meningioma (as indicated by number of chromosomes) does not increase significantly with increasing age.¹⁹ This suggests that deficient DNA repair may be the most likely explanation;

Table 1 Characteristics of 318 benign meningiomas

Characteristic	n	%
Gender		
Female	246	77
Male	72	23
Age at diagnosis (years)		
<60	169	53
≥60	149	47
Histology		
Transitional	140	44
Fibroblastic	71	22
Meningothelial	107	34
Anatomical location		
Non-skull base	123	69
Skull base	54	31

60 years of age was used as the cutoff point because the median age at diagnosis of meningioma was 58 years. $n = 177$ for anatomical location. The specific locations of non-skull base meningiomas were 99 tumours in the convexity, nine tumours in the spine, seven tumours in the posterior fossa, seven tumours in the falx, and one tumour in the orbit.

Table 2 Univariate analyses of histology, age at diagnosis, and anatomical location of 318 benign meningiomas in relation to presence or absence of 22q LOH

Histology, age at diagnosis, and anatomical location	22q LOH		p
	–	+	
Transitional			
Age at diagnosis (years)			0.059
<60	36	40	
≥60	20	44	
Anatomical location			0.045
Non-skull base	28	39	
Skull base	19	10	
Fibroblastic			
Age at diagnosis (years)			0.019
<60	9	30	
≥60	1	31	
Anatomical location			1.000
Non-skull base	1	26	
Skull base	0	4	
Meningothelial			
Age at diagnosis (years)			0.335
<60	32	22	
≥60	26	27	
Anatomical location			0.003
Non-skull base	12	17	
Skull base	18	3	

60 years of age was used as the cutoff point because the median age at diagnosis of meningioma was 58 years. $n = 177$ for anatomical location.

Table 3 Logistic regression models for histological subsets of meningioma with presence or absence of 22q LOH as the outcome

Histological type and covariates	OR	95% CI
Transitional		
Age at diagnosis (per year)	1.04	1.01 to 1.07
Anatomical location		
Non-skull base	1.00*	
Skull base	0.95	0.81 to 1.11
Fibroblastic†		
Age at diagnosis (per year)	1.09	1.01 to 1.17
Meningothelial		
Age at diagnosis (per year)	1.03	0.99 to 1.08
Anatomical location		
Non-skull base	1.00*	
Skull base	0.09	0.02 to 0.41

This table summarises the results of three logistic regression models, one for each histological type of meningioma. Gender did not contribute significantly to any of the models and there were not significant interactions between age at diagnosis and anatomical location.

*Reference group; †anatomical location was not included as a covariate for fibroblastic meningioma because there were only four fibroblastic meningiomas in the skull base. OR, odds ratio; CI, confidence interval.

additional studies of allelic loss in normal meningeal tissue from older people may be useful in addressing this question.²⁰

Somatic *NF2* mutations and 22q LOH are more common in transitional and fibroblastic meningioma than in meningothelial meningioma.^{7 12 21} Somatic *NF2* mutations cause loss of expression of the NF2 protein,²² which is strongly associated with 22q LOH.²³ *NF2* mRNA²⁴ and the NF2 protein^{25 26} are absent in transitional and fibroblastic meningioma, but are present in meningothelial meningioma.

The low prevalence of 22q LOH in skull base meningothelial meningiomas may reflect anatomical differences in initiating events among the histological subsets of meningioma. Kros *et al*¹² noted that the prevalence of 22q LOH was particularly low in anterior skull base meningiomas, but there was insufficient information for most of the tumours in

this study to distinguish between locations in the anterior and posterior skull base.

This study focused on 22q LOH, for which there is sufficient published data for statistical analyses, but other genetic and hormonal factors have been implicated in the genesis of benign meningioma.⁹ It is likely, for example, that such factors are more important than 22q LOH in the aetiology of skull base meningothelial meningiomas, which have a very low prevalence of 22q LOH. About half of benign meningiomas do not have losses of 22q, and there are losses of 1p and 3p in some of these tumours.²⁷ Loss of protein 4.1 family gene expression and gain of progesterone receptor expression occur in benign meningioma.^{28–30} In addition to *NF2*, other genes on 22q may be involved in meningiomagenesis, for example, *BAM22*,³¹ *MNI*,³² and *IN11*.³³ Further research is needed to identify the various genes that are involved in the genesis of the different histological types of benign meningioma.

ACKNOWLEDGEMENTS

We thank H Joe, J M Friedman, D Parry, D Zurakowski, and B Korf for helpful discussions.

Authors' affiliations

M E Baser, Los Angeles, CA, USA

T Y Poussaint, Department of Radiology, Children's Hospital and Harvard Medical School, Boston, MA, USA

Competing interests: there are no competing interests.

Correspondence to: Dr T Y Poussaint, Associate Professor of Radiology, Harvard Medical School, Director, PBTC Neuroimaging Center, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115, USA; tina.poussaint@childrens.harvard.edu

Received 22 May 2005

Revised version received 17 June 2005

Accepted for publication 18 June 2005

Published Online First 24 June 2005

REFERENCES

- Antinheimo J, Sankila R, Carpen O, Pukkala E, Sainio M, Jääskeläinen J. Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. *Neurology* 2000;**54**:71–6.
- Krampla W, Newrkl S, Pfisterer W, Jungwirth S, Fischer P, Leitha T, Hruby W, Tragl KH. Frequency and risk factors of meningioma in clinically healthy 75-year-old patients: results of the Transdanube Ageing Study (VITA). *Cancer* 2004;**100**:1208–12.
- McCarthy BJ, Davis FG, Freels S, Surawicz TS, Damek DM, Grutsch J, Mench HR, Laws ER Jr. Factors associated with survival in patients with meningioma. *J Neurosurg* 1998;**88**:831–9.
- Trofatter JA, MacCollin MM, Rutter JL, Murrell JR, Duyao MP, Parry DM, Eldridge R, Kley N, Menon AG, Pulaski K, Haase VH, Ambrose CM, Munroe D, Bove C, Haines JL, Martuza RL, MacDonald ME, Seizinger BR, Short MP, Buckler AJ, Gusella JF. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell* 1993;**72**:791–800.
- Rouleau GA, Mérel P, Lutchman M, Sanson M, Zucman J, Marineau C, Hoang-Xuan K, Demczuk S, Desmaze C, Plougastel B, Pulst SM, Lenoir G, Bijsma E, Fashold R, Dumanski J, de Jong P, Parry D, Eldridge R, Aurias A, Delattre O, Thomas G. Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. *Nature* 1993;**363**:515–21.
- Mérel P, Hoang-Xuan K, Sanson M, Moreau-Aubry A, Bijsma EK, Lazaro C, Moisan JP, Resche F, Nishisho I, Estivill X, Delattre JY, Poisson M, Theillet C, Hulsebos T, Delattre O, Thomas G. Predominant occurrence of somatic mutations of the *NF2* gene in meningiomas and schwannomas. *Genes Chrom Cancer* 1995;**13**:211–16.
- Wellenreuther R, Kraus JA, Lenartz D, Menon AG, Schramm J, Louis DN, Ramesh V, Gusella JF, Wiestler OD, von Deimling A. Analysis of the neurofibromatosis 2 gene reveals molecular variants of meningioma. *Am J Pathol* 1995;**146**:827–32.
- Rutledge MH, Sarrazin J, Rangaratnam S, Phelan CM, Twist E, Merel P, Delattre O, Thomas G, Nordenskjöld M, Collins VP. Evidence for the complete inactivation of the *NF2* gene in the majority of sporadic meningiomas. *Nat Genet* 1997;**6**:180–4.
- Perry A, Gutmann DH, Reifenberger G. Molecular pathogenesis of meningiomas. *J Neurooncol* 2004;**70**:183–202.
- Dumanski JP, Rouleau GA, Nordenskjöld M, Collins VP. Molecular genetic analysis of chromosome 22 in 81 cases of meningioma. *Cancer Res* 1990;**50**:5863–7.
- Leone PE, Bello MJ, de Campos JM, Vaquero J, Sarasa JL, Pestana A, Rey JA. *NF2* gene mutations and allelic status of 1p, 14q and 22q in sporadic meningiomas. *Oncogene* 1999;**18**:2231–9.
- Kros J, de Greve K, van Tilborg A, Hop W, Pieterman H, Avezaat C, Lekanne dit Deprez R, Zwarthoff E. *NF2* status of meningiomas is associated with tumour localization and histology. *J Pathol* 2001;**194**:367–72.
- Lekanne Deprez RH, Riegman PH, van Drunen E, Warringa UL, Goren NA, Stefanko SZ, Koper JW, Avezaat CJ, Mulder PGH, Zwarthoff EC, Hagemeijer A. Cytogenetic, molecular genetic and pathological analyses in 126 meningiomas. *J Neuropathol Exp Neurol* 1995;**54**:224–35.
- Weber RG, Boström J, Wolters M, Baudis M, Collins VP, Reifenberger G, Lichter P. Analysis of genomic alterations in benign, atypical, and anaplastic meningiomas: toward a genetic model of meningioma progression. *Proc Natl Acad Sci USA* 1997;**94**:14719–24.
- Baser ME, International *NF2* Mutation Database Contributors. The distribution of constitutional and somatic mutations in the neurofibromatosis 2 gene. *Hum Mutat* (in press).
- Papi L, De Vitis LR, Vitelli F, Ammannai F, Mennonna P, Montali E, Bigozzi U. Somatic mutations in the neurofibromatosis type 2 gene in sporadic meningiomas. *Hum Genet* 1995;**95**:347–51.
- Ng H-k, Lau K-m, Tse JYM, Lo K-w, Wong JHC, Poon W-s, Huang DP. Combined molecular genetic studies of chromosome 22q and the neurofibromatosis type 2 gene in central nervous system tumors. *Neurosurgery* 1995;**37**:764–73.
- Kim J-H, Lee S-H, Rhee C-H, Park S-Y, Lee J-H. Loss of heterozygosity on chromosome 22q and 17p correlates with aggressiveness of meningiomas. *J Neuro-Oncol* 1998;**40**:101–6.
- van Tilborg AAG, Al Allak B, Velthuisen CJM, de Vries A, Kros JM, Avezaat CJ, de Klein A, Beverloo HB, Zwarthoff EC. Chromosomal instability in meningiomas. *J Neuropathol Exp Neurol* 2005;**64**, 312–22.
- Moragoda L, Jaszewski R, Kuldarni P, Majumdar APN. Age-associated loss of heterozygosity of tumor suppressor genes in the gastric mucosa of humans. *Am J Physiol Liver Physiol* 2002;**282**:G932–6.
- Evans JJ, Jeun S-S, Lee JH, Harwalkar JA, Shoshan Y, Cowell JK, Golubic M. Molecular alterations in the neurofibromatosis type 2 gene and its protein rarely occurring in meningothelial meningiomas. *J Neurosurg* 2001;**94**:111–17.
- Sainz J, Huynh DP, Figueroa K, Ragge NK, Baser ME, Pulst S-M. Mutations of the neurofibromatosis type 2 gene and lack of the gene product in vestibular schwannomas. *Hum Mol Genet* 1994;**3**:885–91.
- Ueki K, Wen-Bin C, Narita Y, Asai A, Kirino T. Tight association of loss of merlin expression with loss of heterozygosity at chromosome 22q in sporadic meningiomas. *Cancer Res* 1999;**59**:5995–8.
- Wellenreuther R, Waha A, Vogel Y, Lennartz D, Schramm J, Wiestler OD, von Deimling A. Quantitative analysis of neurofibromatosis type 2 gene transcripts in meningiomas supports the concept of distinct molecular variants. *Lab Invest* 1997;**77**:601–6.
- Lee JH, Sundaram V, Stein DJ, Kinney SE, Stacey DW, Golubic M. Reduced expression of schwannomin/merlin in human sporadic meningiomas. *Neurosurgery* 1997;**40**:578–87.
- Hitozumatsu T, Iwaki T, Kitamoto T, Mizoguchi M, Suzuki SO, Hamada Y, Fukui M, Tateishi J. Expression of neurofibromatosis 2 protein in human brain tumors: an immunohistochemical study. *Acta Neuropathol* 1997;**93**:225–32.
- Carlson KM, Bruder C, Nordenskjöld M, Dumanski JP. 1p and 3p deletions in meningiomas without detectable aberrations of chromosome 22 identified by comparative genomic hybridization. *Genes Chrom Cancer* 1997;**20**:419–24.
- Perry A, Cai DX, Scheithauer BW, Swanson PE, Lohse CM, Newsham IF, Weaver A, Gutmann DH. Merlin, DAL-1, and progesterone receptor expression in clinico-pathologic subsets of meningioma: a correlative immunohistochemical study of 175 cases. *J Neuropathol Exp Neurol* 2000;**59**:872–9.
- Gutmann DH, Donahoe J, Perry A, Lemke N, Gorse K, Kittiniyom K, Rempel SA, Gutierrez JA, Newsham IF. Loss of DAL-1, a protein 4.1-related tumor suppressor, is an important early event in the pathogenesis of meningiomas. *Hum Mol Genet* 2000;**9**:1495–2000.
- Nunes F, Shen Y, Niida Y, Beauchamp R, Stemmer-Rachamimov AO, Ramesh V, Gusella J, MacCollin M. Inactivation patterns of *NF2* and DAL-1/4.1B (EPB41L3) in sporadic meningioma. *Cancer Genet Cytogenet* 2005;**162**:135–9.
- Peyrard M, Franssen I, Xie YG, Han FY, Rutledge MH, Swahn S, Collins JE, Dunham I, Collins VP, Dumanski JP. Characterization of a new member of the human beta-adaptin gene family from chromosome 22q12, a candidate meningioma gene. *Hum Mol Genet* 1994;**3**:1393–9.
- Lekanne Deprez RH, Riegman PH, Groen NA, Warringa UL, van Biezen NA, Malijs AC, Bootsma D, de Jong PJ, Menon AG, Kley JA, Seizinger BR, Zwarthoff EC. Cloning and characterization of MN1, a gene from chromosome 22q11, which is disrupted by a balanced translocation in a meningioma. *Oncogene* 1995;**10**:1521–8.
- Schmitz U, Mueller W, Weber M, Sevenet N, Delattre O, von Deimling A. IN11 mutations in meningiomas at a potential hotspot in exon 9. *Br J Cancer* 2001;**84**:199–201.