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Cranial meningiomas in 411 NF2 patients with proven gene mutations: Clear positional effect of mutations, but absence of female severity effect on age at onset

MJ Smith¹, JE Higgs¹, NL Bowers¹, D Halliday², J Patterson³, J Gillespie⁴, SM Huson¹, SR Freeman⁵, S Lloyd⁵, SA Rutherford⁶, AT King⁶, AJ Wallace¹, RT Ramsden⁵, DGR Evans¹

1. Department of Genetic Medicine, St Mary's Hospital, Manchester Academic Health Sciences Centre (MAHSC), University of Manchester, Manchester, UK.
2. Department of Clinical Genetics, The Oxford Radcliffe Hospitals NHS Trust, Oxford, UK
3. Dept of Medical Genetics, Addenbrookes NHS Trust, Hills Road, Cambridge, UK.
4. Department of Neuroradiology, Salford Royal Foundation Trust, Manchester, UK
5. Department of Otolaryngology, Manchester Royal Infirmary, Manchester, UK
6. Department of Neurosurgery, Salford Royal Foundation Trust, Manchester, UK

Professor D Gareth R Evans
Department of Genetic Medicine, St Mary's Hospital
Oxford Road
Manchester M13 9WL
United Kingdom
Tel: +44 (0)161 276 6228
Fax: +44 (0)161 276 6145
Email: gareth.evans@cmft.nhs.uk

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Abstract

Background: Meningiomas have been reported to occur in approximately 50% of neurofibromatosis type 2 (NF2) patients.

The *NF2* gene is commonly biallelically inactivated in both schwannomas and meningiomas. The spectrum of *NF2* mutations consists mainly of truncating (nonsense and frameshift) mutations. A smaller number of patients have missense mutations, which are associated with a milder disease phenotype.

Methods: We analysed cumulative incidence and gender effects as well as the genotype-phenotype correlation between the position of the *NF2* mutation and the occurrence of cranial meningiomas in a cohort of 411 NF2 patients with proven *NF2* mutations.

Results and Conclusion: Patients with mutations in exon 14 or 15 were least likely to develop meningiomas. Cumulative risk of cranial meningioma to age 50 years was 70% for exons 1-3, 81% for exons 4-6, 49% for exons 7-9, 56% for exons 10-13 and 28% for exons 14-15. In our cohort of 411 patients, we found no overall gender bias for occurrence of meningioma in NF2 disease. Cumulative incidence of meningioma was close to 80% by 70 years of age for both males and females, but incidence by age 20 years was slightly increased in males (male, 25%; female, 18%; $p=0.023$). Conversely we also found an increased risk of meningiomas in women with mosaic NF2 disease.

Key words:

Meningioma, NF2, Merlin, mutation position effect

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant disease characterised by the development of schwannomas, meningiomas and ependymomas, with the great majority of patients having bilateral schwannomas of the eighth cranial nerve [1, 2]. Intracranial meningiomas are the second most common type of tumour found in NF2 patients, although the factors determining which individuals will develop meningiomas are unclear.

Spinal meningiomas may occur in up to one third of NF2 patients [3, 4]. However, they are frequently asymptomatic and many are only detected incidentally when imaging is carried out for an unrelated purpose. Spinal meningiomas are not screened for routinely and they are difficult to distinguish from schwannomas by imaging alone. Therefore, the exact prevalence is unclear.

The *NF2* gene is biallelically inactivated in most schwannomas and meningiomas. The spectrum of *NF2* mutations consists mainly of truncating (nonsense and frameshift) mutations [5, 6]. A smaller number of patients have missense mutations, which are associated with a milder disease phenotype [7, 8]. Although the *NF2* tumour spectrum and molecular findings are reasonably well described, description of disease severity has largely been related to mutation type rather than position within the *NF2* gene [7, 8, 9, 10, 11, 12]. A positional effect has only been described for splice site mutations, with mutations in the 3' end of the gene leading to milder disease [13, 14].

The *NF2* gene product, Merlin, is a cytoskeletal protein that provides a functional link between the cell membrane and the actin cytoskeleton [15]. The N-terminus contains a FERM (4.1, ezrin, radixin, moesin) domain, which is responsible for binding various interacting proteins [16]. This can be further divided into three sub-domains. The first sub-domain (amino acids 20-100) has a ubiquitin-like structure, the second sub-

domain (amino acids 101-215) has an acyl CoA binding protein-like structure and the third sub-domain (amino acids 216-313) has a structure similar to phosphotyrosine binding protein (PTB), pleckstrin homology domain (PH), or Enabled/VASP Homology 1 (EVH1). These three domains fold into a “cloverleaf” conformation [17]. The FERM domain is followed by an α -helical domain (amino acids 314-478) which can fold to bring the C-terminal domain (amino acids 479-595) close to the N-terminus. In its folded conformation Merlin is inhibited from binding actin.

The absence of somatic mutations in exons 14 and 15 of the *NF2* gene in sporadic meningiomas [5, 6] prompted us to investigate whether a positional effect of germline mutations existed for meningiomas. We also felt the evidence base for counselling regarding gender effect on severity of meningioma disease was also relatively under investigated for *NF2*. Here describe the rates of cranial meningioma onset in a cohort of 411 patients with *NF2* in whom a germline or mosaic mutation has been identified and compare severity of disease with relation to the position of the *NF2* mutation. We also investigate the effect of gender on meningioma risk.

Materials and Methods

We undertook a retrospective review of 411 patients from our database with a diagnosis of NF2. Patients were referred to the Regional Molecular Genetics Service at St Mary's Hospital in Manchester for mutational analysis. Only individuals with a proven germline or mosaic mutation were included.

Mutation analysis of the patients' peripheral blood was undertaken as previously described [18, 19]. Briefly, genomic DNA samples were amplified with primers for all 17 exons of the *NF2* gene and direct sequencing was used in addition to Multiple Ligation Dependant Probe amplification (MLPA) to identify mutations. Where no mutation was identified, further analysis using DNA of the patient's tumour tissues, where available, was undertaken using a previously described technique [18].

All patients have had cranial MRI scans to identify meningioma disease presence and number of tumours. Previously operated meningiomas were included in numbers. Age at initial diagnosis of meningioma was recorded.

Kaplan-Meier analysis was used to assess age at onset of cranial meningioma. Mutation groups were defined as 1) exons 1-3, which encode the first FERM sub-domain of the Merlin protein product; 2) exons 4-6, which encode the second FERM sub-domain; 3) exons 7-9 encoding the third FERM sub-domain; 4) exons 10-13, coding for the α -helical domain and 5) exons 14-15, which encode the C-terminal domain. Large deletions removing the promoter and exon 1 and whole gene deletions were excluded from the analysis. Multi-exon deletions within the gene were grouped according to the first exon affected by the deletion. Numbers of patients with and without cranial meningiomas were compared using the chi-squared test.

Results

In our cohort of 411 NF2 patients, 215 were male and 196 were female. Sixty six individuals were mosaic. In total 199/411 (48%) NF2 patients had at least one cranial meningioma that was identified on MRI scan or at surgery.

Effect of mutation position

The position and prevalence of each mutation type identified in the *NF2* gene and the proportion of individuals in each category with at least one cranial meningioma are presented in Table 1. As expected, the prevalence of cranial meningiomas was lower in individuals with a missense mutation (26%) or splicing mutation (35%), compared with truncating mutations (nonsense or frameshift, 58%). No significant difference was seen between patients with nonsense or frame shift mutations and those with a large deletion.

Mutations within the first two FERM sub-domains had the greatest impact in risk of cranial meningioma (61% and 58% with meningioma, respectively). Mutations occurring in the third FERM sub-domain or within the α -helical domain conferred a lesser risk of cranial meningioma (39% and 45%, respectively). The α -helical domain appears to confer a higher risk than the third FERM domain, although the difference is not significant and is due to a few high risk mutations in the second half of exon 10, at the junction between these two domains. Mutations occurring at junctions between other domains were also seen to have an increased risk (Figure 1b). Patients with mutations in the C-terminal domain were the least likely to develop a cranial meningioma (24%).

The Kaplan-Meier plot in Figure 1 shows a significant difference between the 5' and 3' mutations: exons 1-3, exons 4-6, exons 7-9 and exons 10-13 compared to exons 14-15 ($p < 0.0001$). Cumulative risk of cranial meningioma to age 50 years was 70% for

exons 1-3, 81% for exons 4-6, 49% for exons 7-9, 56% for exons 10-13 and 28% for exons 14-15. The hazard ratio (HR) for mutations in exons 7-15 was 0.499 (95% CI 0.376 to 0.663) compared to mutations in exons 1-6 ($p < 0.0001$). A similar hazard ratio of 0.48 (0.27-0.81) was obtained by comparing truncating mutations in exons 14 and 15 with truncating mutations in exons 1-6 (Figure 2). The risk of cranial meningioma up to age 50 years was only 44% for truncating mutations in exons 14 and 15 (similar to the risk for all mutation types in these exons) compared to 83% for truncating mutations in exons 1-6 (HR 0.48; $p = 0.0065$). The average age of diagnosis for a cranial meningioma in patients with a mutation in exons 1-13 was 24.8 years, compared to exons 14 and 15 of 34.2 years.

Gender effect

Overall, no gender bias was observed between the number of males (105/215, 49%) and females (94/196, 48%) who developed at least one cranial meningioma (Figure 3a). By 50 years of age approximately 60% of both men and women had developed a cranial meningioma and by 60 years this increased to over 70%. There was no overall significant difference in age of cranial meningioma onset between males and females with the curves closely aligned after 30 years of age. However, these totals disguise an age related effect. There was a significantly greater risk of males developing a cranial meningioma below 20 years of age compared to females ($p = 0.023$). The gender differences for age at onset were sustained across all mutation position groups with cranial meningiomas being detected earlier in males in the first 20 years of life.

Overall, a higher number of cranial meningiomas was found in females than males ($p < 0.0001$). The 105 males with cranial meningiomas had a total of 223 cranial meningiomas (median 2; range 1-10; mean per patient 1.05), whereas the 94 females

with cranial meningiomas had a total of 282 cranial meningiomas (median 2; range 1-10; mean per patient 1.42). However, this was mainly due to a small number of females with ≥ 4 cranial meningiomas, four of whom had 10 cranial meningiomas each, compared to only one male with 10 cranial meningiomas.

Effect of somatic mosaicism

We also analysed the effects of somatic mosaic mutations on risk of cranial meningioma formation. The rates of somatic mosaicism have been reported to be approximately 30% of *de novo* NF2 mutations in patients presenting with bilateral vestibular schwannomas and up to 60% in patients presenting with a *de novo* mutation and a unilateral vestibular schwannoma [20]. In our current cohort, 27% of patients with a new mutation were mosaic, comprising 23% of males with a new mutation and 32% of females with a new mutation.

In total, 36/64 (56%) of individuals with mosaic NF2 had at least one cranial meningioma and the mutation position effect can still be seen in somatic mosaic individuals. Of six individuals, mosaic for a mutation in exons 14-15, only one (aged 34) had a cranial meningioma. The ages of the six individuals without meningiomas ranged from 35-63 years.

The risk of cranial meningioma in mosaic patients was found to be greater in women 24/36 (67%) than men 12/28 (43%). Women with somatic mosaic disease were also at a greater risk of developing cranial meningiomas compared to women with non-mosaic NF2 ($p=0.0475$). This effect was not seen in men, but in women the effect correlated with a significantly higher proportion of mosaic females with truncating mutations and a lower number of mutations in exons 14 and 15 than non-mosaic women.

Discussion

Within the general population, meningiomas account for over 30% of all primary brain and central nervous system tumours (CBTRUS, 2010). NF2 disease is known to confer an increased risk of meningioma and intracranial meningiomas have been reported to occur in approximately 50% of NF2 patients. The molecular genetic factors that determine which patients will develop a meningioma are unclear.

In this study we analysed the germline mutations in a series of 411 patients with NF2, to determine whether the type and position of these mutations within the *NF2* gene influence the likelihood of developing cranial meningiomas. As expected, we found that patients with a truncating mutation were more likely to have a cranial meningioma than those with a non-truncating mutation.

In addition to the effect of mutation type, we have demonstrated a clear positional effect of *NF2* gene mutations on the risk of developing a cranial meningioma in NF2 disease, with mutations towards the 5' end of the gene being associated with a higher prevalence of cranial meningioma. The highest risk regions for each domain occur at the junctions between domains. We did find that NF2 patients with a constitutional mutation in exon 14 or 15 may develop a cranial meningioma, although the tumours occur much less frequently in these patients and develop at a later age ($p < 0.001$). A similar positional effect on disease severity in NF2 has previously been described for splice site mutations [13, 14]. Although no formal statistical analysis was carried out, interestingly, no meningioma was found in any of the 13 exon 14/15 mutation-bearing individuals [14].

The positional effect was seen across all mutation types, with truncating mutations in exons 1-13 conferring a higher risk than those in exons 14 and 15. If all truncating mutations resulted in complete loss of Merlin protein as predicted, we would

expect to see no positional effect for this type of mutation. Therefore, our findings provide evidence that at least some nonsense or frameshift mutations must generate mutant proteins, rather than abolishing the protein product through nonsense mediated decay.

In sporadically occurring meningiomas, women are approximately three times as likely to develop a meningioma as men (CBTRUS, 2010). A female preponderance has also been reported previously within NF2 patients [21].

In contrast, several reports have shown that males are more likely to develop a meningioma within the first two decades of life [22]. Meningiomas are much less common in childhood than in adults and around 40% of childhood meningiomas occur within the context of NF2.

In our current cohort of 411 NF2 patients, we found no evidence for an overall increased risk of cranial meningioma in females. Overall, there was no difference in risk of cranial meningioma between males and females, although our data support the finding that males are more likely than females to develop cranial meningiomas before 20 years of age. It is possible that a female preponderance after 20 years of age is masked by the increased risk to males from the predominant tumour causing diagnosis of NF2. Diagnosis with a symptomatic vestibular schwannoma in many NF2 patients gives rise to the simultaneous identification of often asymptomatic meningioma disease.

We did find that women were more likely to develop more than one cranial meningioma than men. In addition, there was an overall increased risk to women with somatic mosaic disease of developing a cranial meningioma than women with non-mosaic NF2.

In conclusion, mutations in exons 14 and 15 confer a reduced risk of cranial meningioma than mutations in exons 1-13. There is a similar risk of cranial meningioma

for males and females with NF2 over their lifetime; however men under 20 years of age have a higher incidence of cranial meningioma. This information is of value when counselling patients about their risk of cranial meningioma.

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Competing interests

The authors have no competing interests to declare.

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Figure legends

Figure 1. The position of mutations in the *NF2* gene affects the likelihood of developing a meningioma. The Kaplan-meier plot (a) shows the risk of meningioma within each functional domain. Gene regions are divided into exons 1-3, exons 4-6, exons 7-9, exons 10-13 and exons 14-15 or exons 1-6, exons 7-13 and exons 14-15. The bar graph (b) shows the overall risk of meningioma for mutations in individual exons. 5' regions confer a higher risk than 3' regions and exons encoding the junctions between functional domains confer a higher relative risk than the rest of the domain.

Figure 2. Truncating mutations (nonsense and frameshift) alone also show a positional effect on meningioma risk. The Kaplan-Meier plot (a) shows that exons 14 and 15 confer a lower relative risk of meningioma than exons 1-13 and (b) the bar graph shows a similar risk pattern for truncating mutations as for all mutation types combined.

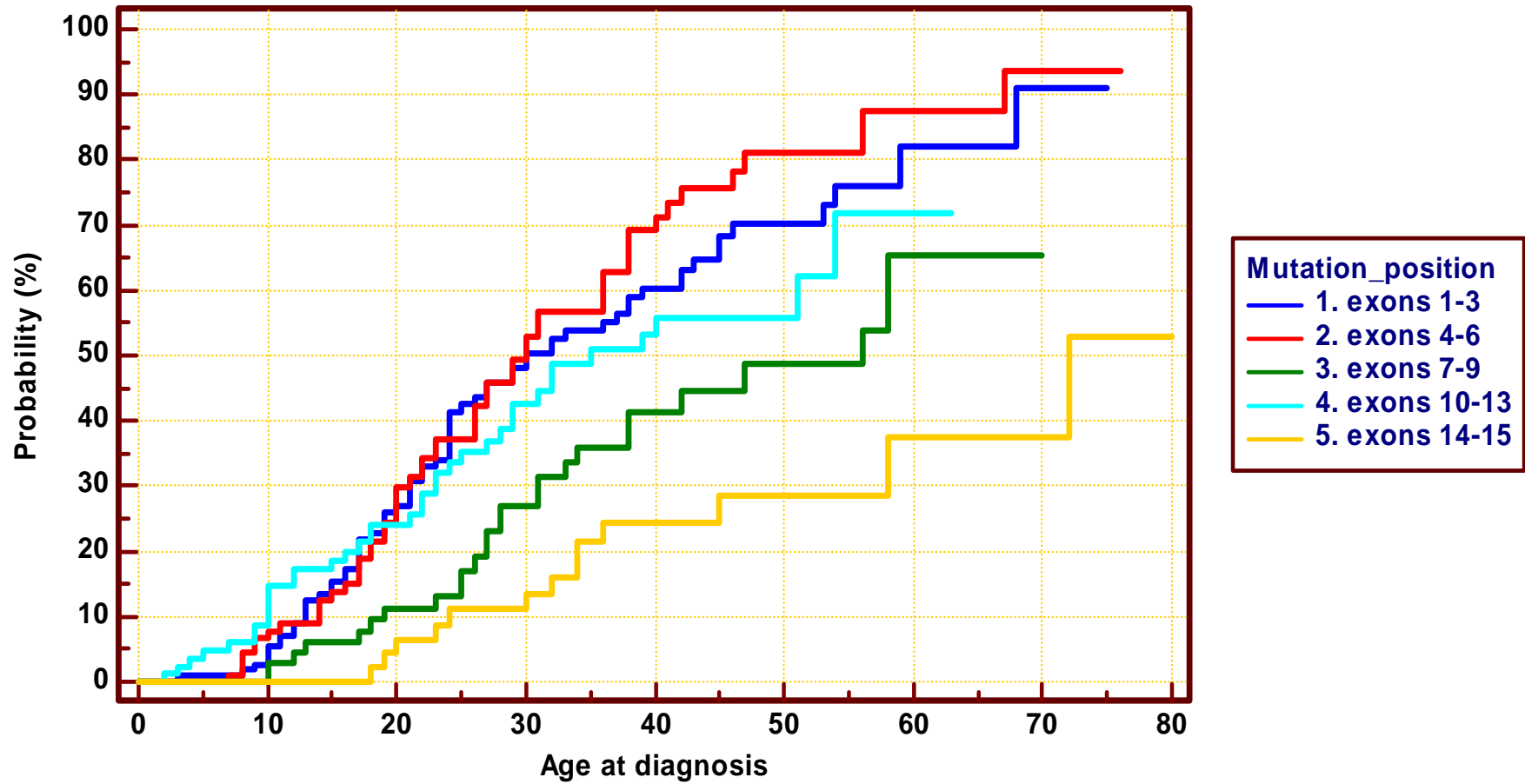
Figure 3. There is no overall difference in the likelihood of developing a meningioma between males and females (a) However, males are at a higher risk of meningioma below the age of 20 years (b).

Table 1. Effect of mutation type and position on risk of meningioma

Exon group	Proportion with meningioma	Missense	Nonsense or frame shift	Splice site	In frame deletion or large deletion
	Number of patients with meningioma/ total NF2 patients with mutation in this exon group	Number of patients with meningioma/ total NF2 patients with missense mutation	Number of patients with meningioma/ total NF2 patients with nonsense or frameshift mutation	Number of patients with meningioma/ total NF2 patients with splice site mutation	Number of patients with meningioma/ total NF2 patients with in frame del or large deletion mutation
1-3	69/114 (61%)	2/9 (22%)	54/76 (71%)	8/22 (36%)	5/7 (71%)
4-6	53/91 (58%)	3/4 (75%)	29/48 (60%)	19/36 (53%)	2/3 (67%)
7-9	26/67 (39%)	0/5 (0%)	16/30 (53%)	8/29 (28%)	2/3 (67%)
10-13	38/84 (45%)	1/3 (33%)	30/56 (54%)	6/20 (30%)	1/5 (20%)
14-15	13/55 (24%)	2/10 (20%)	7/25 (28%)	4/20 (20%)	0
Total	199/411 (48%)	8/31 (26%)	136/235 (58%)	45/127 (35%)	10/18 (56%)

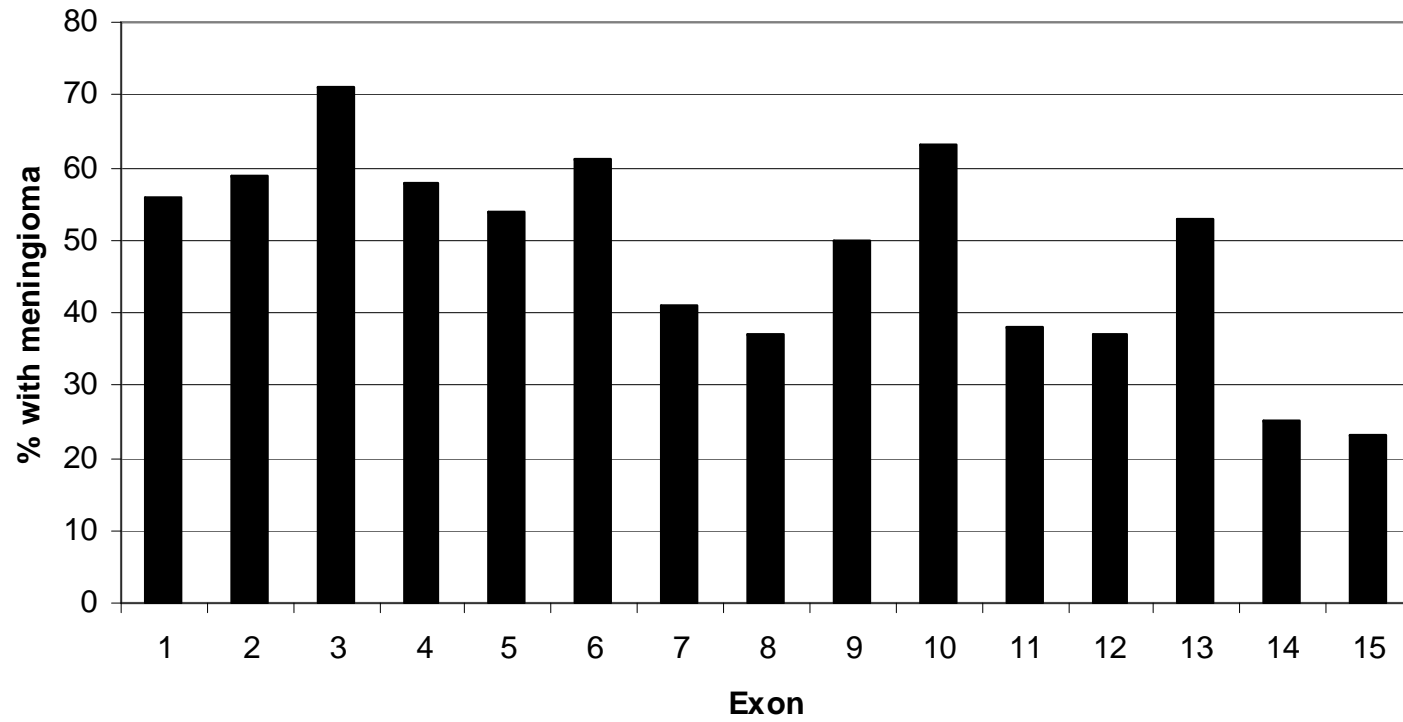
1a

Risk of meningioma



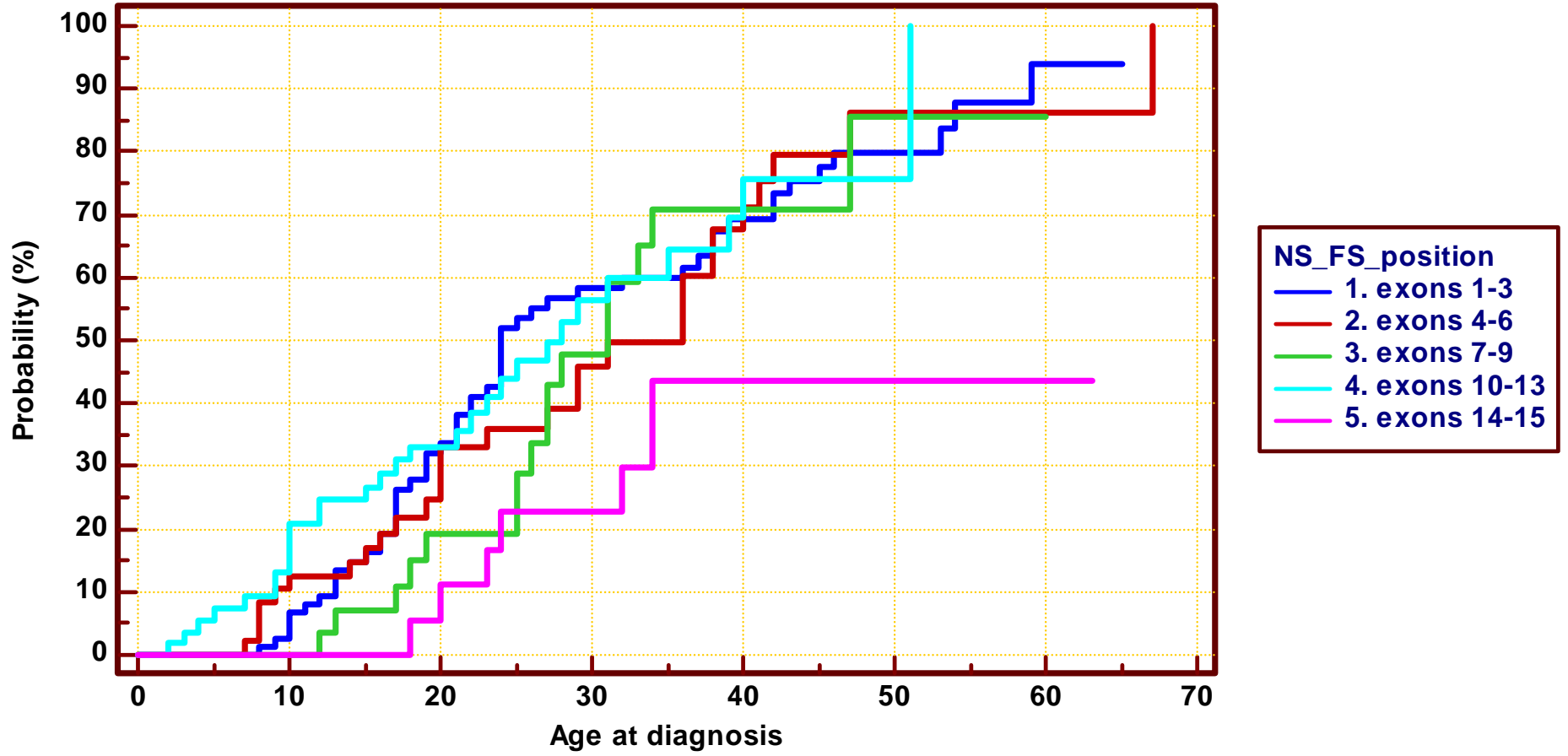
1b

Meningioma risk



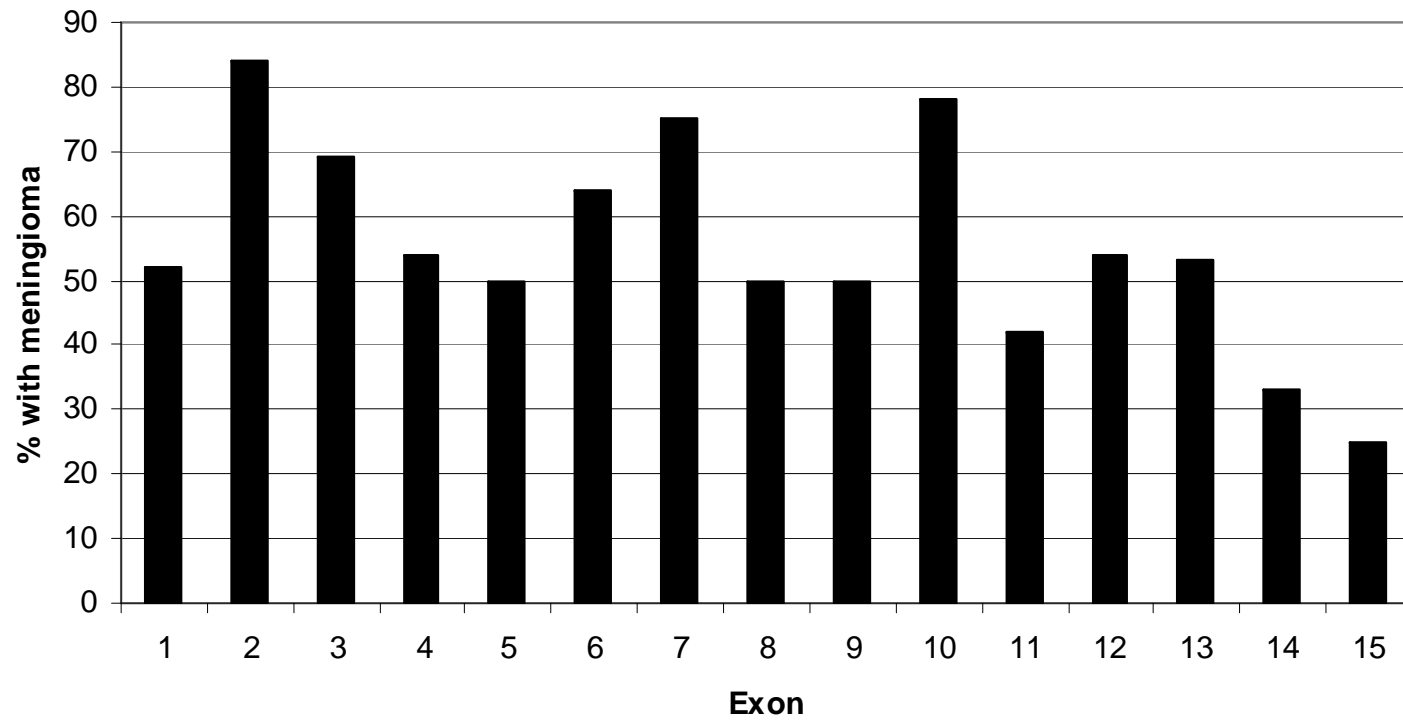
2a

Risk of meningioma in nonsense/frameshift mutation type



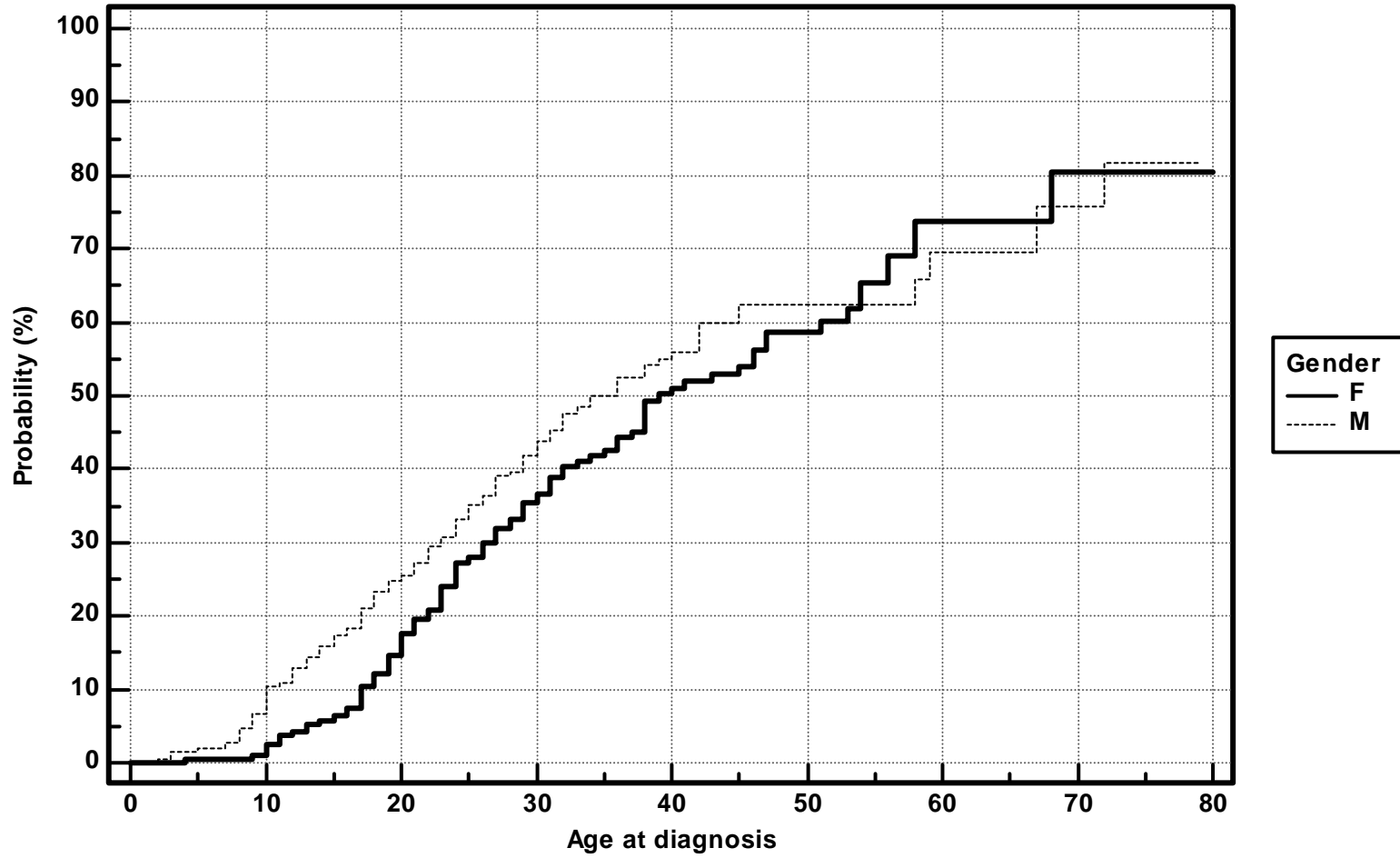
2b

Meningioma risk (truncating mutations)



3a

Risk of meningioma



3b

Risk of meningioma censored at age 20

