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Description of selected characteristics of familial glioma patients – Results from the Gliogene Consortium

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Contributors

SS, MLB, EBC, JBS, RL, DI, RBJ, JB, SO, NAV, MW, BJM, FD, SS, CJ, BM and RH Conceived and designed the study. SS, RB, BO and GA Analysed and interpreted the data. SS, RB, BO, GA, CCL, EBC, JSBS, DI, JS, CJ, RSH, SS, CIA, JLB, SHO, RBJ, DL, NAV, RM, MW, FGD, BJM, RL, BM and MLB reviewed the data. BO, SS and RB did the statistical analysis. The article was written by SS, RB and BO with support from BM, RL, RBJ, CJ and MLB. All authors revised drafts and approved the final version.

Conflict of interest statement

None declared.

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Abstract

Background—While certain inherited syndromes (e.g. Neurofibromatosis or Li-Fraumeni) are associated with an increased risk of glioma, most familial gliomas are non-syndromic. This study describes the demographic and clinical characteristics of the largest series of non-syndromic glioma families ascertained from 14 centres in the United States (US), Europe and Israel as part of the Gliogene Consortium.

Methods—Families with 2 or more verified gliomas were recruited between January 2007 and February 2011. Distributions of demographic characteristics and clinical variables of gliomas in the families were described based on information derived from personal questionnaires.

Findings—The study population comprised 841 glioma patients identified in 376 families (9797 individuals). There were more cases of glioma among males, with a male to female ratio of 1.25. In most families (83%), 2 gliomas were reported, with 3 and 4 gliomas in 13% and 3% of the families, respectively. For families with 2 gliomas, 57% were among 1st-degree relatives, and 31.5% among 2nd-degree relatives. Overall, the mean (±standard deviation [SD]) diagnosis age was 49.4 (±18.7) years. In 48% of families with 2 gliomas, at least one was diagnosed at <40 y, and in 12% both were diagnosed under 40 y of age. Most of these families (76%) had at least one grade IV glioblastoma multiforme (GBM), and in 32% both cases were grade IV gliomas. The most common glioma subtype was GBM (55%), followed by anaplastic astrocytoma (10%) and oligodendroglioma (8%). Individuals with grades I–II were on average 17 y younger than those with grades III–IV.

Interpretation—Familial glioma cases are similar to sporadic cases in terms of gender distribution, age, morphology and grade. Most familial gliomas appear to comprise clusters of two cases suggesting low penetrance, and that the risk of developing additional gliomas is probably low. These results should be useful in the counselling and clinical management of individuals with a family history of glioma.

Keywords

Glioma; Familial glioma; Clinical characteristics; Genetic counselling

1. Introduction

Intracranial gliomas account for approximately 70% of primary malignant brain tumours in adults.[1,2] The annual incident rates of tumours of neuroepithelial tissue in the United States

(US) in 2005–2009 were 6.6 per 100,000.[1] Nevertheless, these tumours are associated with high morbidity and mortality.

A family history of glioma is reported in 5–10% of patients[3–5] and several rare inherited syndromes including Neurofibromatosis type-1 (NF1) and 2 (NF2) and the Li-Fraumeni (LFS) have been associated with an elevated risk of the disease.[6] A specific surveillance programme is given to gene carriers of NF2 including regular screening with MRI to facilitate early surgery with less morbidity.[7] Recently, a targeted treatment, bevacizumab has proven to be beneficial for treatment of acoustic neuroma in NF2 patients.[8] Genetic testing in families with LFS has been debated over the years and a novel surveillance strategy using whole body MRI has recently been introduced enabling early stage disease of relevant cancers to be detected.[9]

Few studies have searched for either germ line or somatic mutations in familial clusters of glioma and germ line mutations in the p53 and cyclic AMP-dependent kinase number 2 (CDKN2) A genes were identified. Within the glioma tissue from non-syndromic cases, aberrations of genes coding for cell cycle regulatory proteins involved in the control of G1/S phase transition have been found. These include mutation or deletion of genes such as p53, retinoblastoma (RB1), CDKN2 A/B, as well as amplification and over expression of the CDK4 and CDK6 genes.[10]

Since the majority of cases reporting a family history of glioma have no identified genetic cause, it is important to characterise the phenotypic features of non-syndromic families. For example, in the initial breast cancer linkage studies, stratification of age of onset and associated cancers such as ovarian cancer was key to the success of identifying BRCA1/BRCA2.[11,12]

In 2004, the Gliogene Consortium was established[13] to ascertain families with glioma and identify susceptibility genes in high risk familial glioma pedigrees using high throughput linkage. The consortium assembled information on 376 glioma families in 14 centres in the US, Sweden, Denmark and Israel, during January 2007–February 2011. After genotyping 75 families evidence for disease locus for glioma susceptibility at 17q12-21.32q has been found.[14]

This report characterises demographic, familial and clinical features of non-syndromic glioma families.

2. Methods

The study was performed within the framework of a collaboration that collected familial glioma cases from the US and Europe (including Israel) (Appendix A). Approximately 15,000 newly diagnosed glioma cases were screened for family history of glioma during the study period (January 2007–February 2011). The eligibility criteria for inclusion were that the family had to have at least two pathologically confirmed intracranial primary gliomas, in 1st/2nd/3rd-degree relatives. Additional gliomas were included based on personal report even if not pathologically verified. Glioma was defined according to the International Classification of Diseases for Oncology,[15] morphology codes 86801, 9380/3-9451/3 (excluding 9381, 9390 and 9423), 9492/2-9493/0, 9505/1-9506/1, 9509, Y0793, Y4283, Y4323 and Y5243. Families with a known inherited genetic syndrome associated with glioma were excluded (Appendix B). The proband in each family was defined as the most recently diagnosed glioma case (usually the patient identified through the study).

Families were identified through either a screening questionnaire administered to glioma patients in the clinic setting (verified for completeness through population registries in

Europe), medical record review of glioma patients' reported family history of brain tumours, or the Internet (www.gliogene.org).

Eligible probands were consented and completed a questionnaire (administered in-person or by telephone). The questionnaire included a detailed family history on all 1st/2nd/3rd-degree relatives and information on all known glioma cases in the family. All living affected relatives were interviewed, and following consents, blood or saliva samples were collected. If the glioma case had died, information was obtained from the next-of-kin (description of recruitment sites and methods, Supplementary Table 1).

For each family the following data were available: family size, number of generations, relationship to the proband, and for each family member, sex, race, ethnic background and current age or age at death. The information on glioma cases included number of affected individuals in the family, degree of relationship to the proband, age of glioma diagnosis and histological type. Tumour grade was based on the 2007 World Health Organisation (WHO) Classification of Tumors of the Central Nervous System.[16]

The study was approved by the relevant local institutional review board in each country. All participants signed an informed consent form.

Families were divided into prevalent or incident depending on the date of glioma diagnosis in the proband. A prevalent proband was defined as a glioma diagnosis before 2007 and an incident proband as a diagnosis from 2007. This grouping was performed to enable a separate data analysis of an unselected group (incident cases) that represents the entire population of glioma patients as opposed to prevalent cases which might be selected by better prognosis or other factors.

The final dataset was complete for demographic variables such as degree of relationship and race. For the total study population ($n = 9797$), gender was unknown for 17 individuals (0.17%), whereas vital status was unknown for 511 (5.2%). Age was missing in 2901 individuals (30%), of which, 3% had a 1st-degree relationship to the proband and 56% had a 2nd-degree relationship. Age at diagnosis was missing for 3 of the 841 glioma cases. Only 10 glioma cases were not pathologically confirmed. Most analyses included all glioma cases (verified and unverified); analyses of tumour grade were based on histologically confirmed tumours only ($n = 831$).

Statistical tests of differences in characteristics by groups of cases were performed as chi-square tests for categorical variables and t-tests for continuous variables.

3. Results

In total, 376 families including 9797 individuals were available for analysis (Table 1).

The mean number of individuals per family was 26.1 ± 11.8, and the mean number of siblings in the proband's generation was 4.0 ± 2.1 (including the proband). Most families (66%) included data on four generations (range 3–6). Fig. 1 shows the pedigree of one of the families in which 3 generations were affected with glioma. In all centres, a male predominance within families was shown.

The mean age of the entire study population was 57 ± 22 y (range 1–111); the highest mean age was reported in Denmark (63 ± 21 y) and the lowest in Israel (47y ± 24 y).

Whites comprised 97% ($n = 9464$), Hispanic 2% ($n = 179$), Arab 0.7%, Black 0.7% and Asian 0.2% (data not shown).

In total 841 gliomas were reported (Table 2). Most families had 2 glioma cases (83%) in two generations (67%). For families with 2 glioma cases, 57% had a 1st-degree relationship (35.5% between siblings, 33% and 26.5% between the proband and father/mother, respectively and 7% in the proband's offspring); and 31.5% had a 2nd-degree relationship. For 49% of these families, one case was male and one was female while 30% were composed of 2 males and 21% of two females.

For families with 2 gliomas, early onset (i.e. diagnosis <40 y) was seen for one case in 48% of the families and in 12% for both cases. Average age at onset (i.e. 40–59 y) was seen for one case in 61% of the families and in 16% for both cases. Late onset glioma (i.e. P60 y) was seen for one case in 50% of the families and for both in 13%. Of these families, where the histological grades were determined ($n = 251$), concordant grades were seen in 44%; in 76% of families at least one glioma was grade IV, and in 32% both were grade IV.

Of the 831 pathologically verified gliomas, a specific histopathologic diagnosis was classified for 739 tumours (89%) (Table 3). Most gliomas (56%) were classified as grade IV and 73% were classified as high grade (III/IV). The most common subtype was glioblastoma multiforme (GBM) which accounted for 55% of all gliomas and 98.5% of grade IV tumours. Anaplastic astrocytoma was diagnosed in 10% of all tumours (60% of grade III) and oligodendroglioma in 8% (36% of grade II). The most common subtype classified as grade I was juvenile pilocytic astrocytoma in 2% of all tumours. In 37 families with 2 gliomas, both were diagnosed under 40y (Table 2). Of these, 13.5%, 40.5%, 20% and 26% were of grades I, II III and IV, respectively. In 57% of these families glioma grades were mixed (high + low), in 30% both gliomas were low grade and in 13.5% both were high grade.

The 376 families were divided into prevalent ($n = 157$) or incident ($n = 219$) families (Table 4). Of the 841 gliomas reported, 481 were from incident families and 360 from prevalent families. There were more cases of gliomas among males, with a male to female (M/F) ratio of 1.15 ($p = 0.05$). In the incident cases the M/F ratio was 1.25 (1.41 and 1.18 in the incident groups from Europe and the US, respectively, $p = 0.4$).

The mean age at diagnosis for the whole group was 49.4 ± 18.7 y, however; the mean age at diagnosis for the incident cases was 4y higher than that of the prevalent cases (51 ± 19 y versus 47 ± 18 y, respectively $p = 0.004$). The mean age at diagnosis in the probands was 50.1 ± 17.1 y for the incident cases compared to 43 ± 15.6 y for the prevalent cases, while in the non-probands, the mean age at diagnosis was 51.6 ± 20.4 y for the incident cases compared to 50.5 ± 19.2 y for the prevalent cases (data not shown). The difference between the mean age at diagnosis of the probands of the incident cases compared to the prevalent cases was around 7 y ($p = 0.00003$); these differences were even more marked in probands from the European centres where mean age at diagnosis was 52 ± 15.5 y and 36.9 ± 16.3 y for the incident and prevalent groups, respectively ($p = 0.0002$) (data not shown). The distribution of age at diagnosis by study centre (US versus Europe) for prevalent and incident cases is presented in Fig. 2. About a third of the gliomas from the incident families (39% from European centres and 31.3% from the US) were diagnosed between 40 and 59 y. In the prevalent families, 43% were diagnosed in this age category and 68% were diagnosed over 40 y (inclusive).

Differences in the distribution of tumour grade were also seen between the incident and prevalent families ($p = 0.009$). In the prevalent cases, there were more grade II and less grade IV compared to the incident cases (28% and 50% versus 18% and 60.5%, respectively). Among the US incident cases, 80% were high grade tumours compared with 72% of European cases ($p = 0.07$). The mean age at diagnosis was 17.6 y younger for grades

I–II (37.2 y) compared to grades III–IV (54.8 y) ($p < 0.001$). A similar difference in age by grade was seen for all incident and prevalent groups.

Low grade gliomas (I/II) were distributed equally between the sexes, whereas for high grades (III/IV), gliomas were more common among males (56%). High grade gliomas from European incident families had the highest proportion of males (63%).

Twenty-six individuals reported having 2 gliomas (Table 5). For all, progression in grade was seen except for 2 cases where the first and second gliomas were both grade II. The second gliomas appeared between 0 and 14y from the first one (average = 5 y). In 6 cases the grade of the first glioma was unknown and the second was between grades II–IV. In 50% of the cases, progression from low to high grade was seen.

4. Discussion

This study characterises the largest series of non-syndromic glioma families to date with at least two gliomas per family, describing 376 families (841 gliomas) derived from 14 centres in the US, Europe and Israel.

Despite the fact that only 5–10% of all cancer cases are familial,[3–5] it is well established that family history is a strong risk factor for almost all cancers.[17] Nevertheless, additional clinical features are required to differentiate between sporadic and hereditary cases, which include early age of onset and specific tumour characteristics.

In this study, although the mean pedigree size was 26 relatives and most pedigrees (66%) were of four generations, most families (83%) comprised only two glioma cases, of which 57% were between individuals with a 1st-degree relationship and 32% with a 2nd-degree relationship.

The existence of multiple cancer cases in several generations is often used as evidence that inherited factors are at play.[17] However, various definitions for the number of necessary cases within the family and degree of relationship exist. For example, among the definitions for familial breast and ovarian cancer are 3 or more cases of breast cancer occurring under 60y or 2 cases of breast cancer diagnosed before 50 y or at any age if bilateral.[18]

The relatively small sample sizes of most series of brain tumours have limited the study of familial aggregation of these tumours. A few studies have reported on selected characteristics of familial gliomas. de Andrade et al screened 639 glioma probands (5088 relatives) from MD Anderson (1992–1995) and found 16 families with a family history of brain tumours. Of these, 62.5% were between relatives with a 1st-degree relationship and 37.5% with a 2nd-degree relationship (compared to 57% and 31.5%, respectively, in our study).[19]

In a study of 369 consecutive glioma patients recruited between 1983 and 1994 in Finland,[20] 24 families with 53 glioma patients were identified. The relationship between the glioma patients was 1st-degree in 9 families (37.5%), 2nd-degree in 7 families (29%), 3rd-degree in 5 families (21%) and 5th-degree in 3 families (12.5%). A Swedish study yielded similar results.[3]

The data on age at diagnosis in other series of familial cases are limited. In the study by de Andrade the mean age at diagnosis of the glioma cases was 42.5y for 1st-degree relatives and 40.3 for 2nd-degree relatives.[19] In the study by Paunu, the mean age at diagnosis of the familial cases was 32 y compared to 43 y in glioma patients without a family history.[20]

The mean age of glioma diagnosis in our study, was 49.4 y which is in line with most reports of sporadic cases. The average age of diagnosis was 54 y in an international multi-source review[21] of primary brain tumours, and in a pooled case-control study 51.7 y,[22] and Sadetzki reported 58.8 y, in a nationwide study that included glioma cases aged 18 y and above.[23] The age distribution at diagnosis seen in our study was similar to Globocan data;[24] 29% and 28% of diagnoses in both data sets were seen at an early age (<40 y), and 38% and 34%, respectively were diagnosed between 40 and 59 y. In our series, in about 50% of the families with two cases, one had an early onset glioma (<40 y) and in 12% both cases were of early onset.

However, a comparison of age at diagnosis between different studies is difficult because of lack of uniformity between series (i.e. some include all primary brain tumours while others discuss specific types, some include all ages while others report only on adults). Our study included glioma patients diagnosed at any age, however, most centres recruited the probands from adult clinics and thus there may be higher representation of adult patients. In addition, the different collection methods employed by the different centres (some of which are tertiary centres) could allow for selection bias due to non-representation of entire geographical areas.

Selection bias may have also been increased by the inclusion of prevalent cases in the study (which was carried out in order to enlarge the sample size of families with glioma). Considering the fatality rate of gliomas this could lead to survival bias since the prevalent group is characterised by lower grades which are usually diagnosed at an earlier age. Thus, the analysis was performed together and separately for both groups of patients although we believe that the incident cases better represent the complete group of glioma patients. Indeed, our results demonstrate that while there was a 7-year difference in the mean age at diagnosis between the incident and prevalent probands, the difference between mean age at diagnosis for the incident and prevalent cases of the non-proband group was minor (51.6 versus 50.5, respectively). In this context, another limitation that could reduce the completeness of the data should be mentioned. Underreporting of cancers, and/or missing data on family members could exist due to data collection based on self-report. Distribution of tumour grade and histological subtype of the familial cases reported in this study is similar to that of sporadic cases described in the literature. In our study, the majority of the families (78%) had at least one grade IV glioma (mostly GBM), and in 32% of families with two gliomas, the histology was consistent with both cases having grade IV. The most common glioma subtype was GBM (55%), followed by anaplastic astrocytoma (10%), and oligodendroglioma (8%). CBTRUS data show that GBM accounts for 53.9%, anaplastic astrocytomas 6.7% and oligodendroglioma 6.4% of all brain tumours.[1]

Published data also indicate that age distribution differs by tumour histology. A comparison of age at diagnosis by histology between data of the CBTRUS and our study shows an average age of onset of 64y versus 57.5y for GBM, 51 versus 44.9 for anaplastic astrocytoma, 45 versus. 44.5 for astrocytoma NOS, 48 versus 49.7 for anaplastic oligodendroglioma, 41 versus 41.8 for oligodendroglioma and 43 versus 46.5 for malignant glioma NOS, respectively.[1] Similarities were also seen when stratifying the age distribution by grade; Ohgahi (2009) reported mean ages at diagnosis of 18.5, 42, 47 and 62 y for grades I, II, III and IV, compared to 21.8, 40.4, 46.2 and 57.5 y in our study, respectively.[25] These data show that generally the age distribution of gliomas seen in our families is similar to those reported in sporadic cases.

Our study results point at male predominance; consistent with the described 30–60% higher proportion of males with gliomas[1,19,22,23,26,27] although the exact M/F ratio differed by centre. The M/F ratio seen for the incident cases of the European centres is in line with that

reported for sporadic cases (1.4), indicating that the gender distribution of familial gliomas is similar to that of sporadic gliomas.

Most families included in our study from the US were white. This demographic distribution is different from the distribution in the general population of the USA where 15.4% are African-American.[1] This distribution is also different from the ethnic distribution of gliomas in the US where 89.6% of all brain and CNS tumours are in whites and 10.4% are in African-Americans. This raises the question whether these differences are due to different genetic backgrounds, environmental risk factors or the selective recruitment method in the US which did not truly represent the African-American population. The selectivity of our study population is supported by another study by Dubrow who showed that 79.5% of gliomas are among whites, 10% among Hispanics, 5% in African-Americans and an additional 5% are Asians.[26]

5. Conclusions

This largest series of families with two or more glioma cases enabled us to explore phenotypic features of non-syndromic familial glioma.

In contrast to other familial cancers, familial gliomas do not seem to appear more frequently at an early age, with a distinct morphology or a different sex ratio compared to sporadic forms of the disease. While the mode of inheritance of glioma could not be established, dominant inheritance with low penetrance might be considered since in most families (83%) only two glioma cases were seen in consecutive generations.

These data provide information for those engaged in the counselling of relatives of glioma cases indicating that the risk of developing additional gliomas is probably low.

The existence of other cancer types that might exist in family members should be explored to complete the description of the clinical phenotype of familial gliomas.

6. Research in context

We performed a search on PubMed using the terms: ‘familial glioma’, ‘familial brain tumors’, ‘glioma etiology’ and ‘risk factors for glioma formation’ in order to compare familial gliomas with sporadic gliomas with respect to demographic characteristics and clinical manifestations. As expected, most publications dealt with rare inherited genetic syndromes predisposing to glioma, (e.g. NF1 and NF2, tuberous sclerosis, etc.).We found a few publications dealing with very small series of non-syndromic families with glioma. An additional search was performed with the terms ‘sporadic brain tumors’, ‘Sporadic gliomas’ and ‘glioma clinical features’, as well as ‘familial cancer’.

Considering the rarity of data regarding demographic and clinical characterisation of non-syndromic familial gliomas, the aim of the present report was to describe these features in a large series of glioma families, which were identified in the framework of the multicentre, worldwide collaboration called the Gliogene study.

7. Interpretation

In contrast to other familial cancers, familial gliomas do not seem to appear more frequently at an early age, with a distinct morphology or a different sex ratio compared to sporadic forms of the disease.

Most familial gliomas appear to comprise only two cases suggesting low penetrance. These data provide information for those engaged in the counselling of relatives of glioma cases indicating that the risk of developing additional gliomas is probably low.

The existence of other cancer types that might exist in family members should be explored to complete the description of the clinical phenotype of familial gliomas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. List of centres collecting data

Brigham and Women’s Hospital, Boston, Mayo Clinic, Rochester, M.D. Anderson Cancer Center, Houston, Memorial-Sloan Kettering New York, Case Western Reserve University, Cleveland, Texas Children’s Cancer Center, Baylor, Houston, Columbia University, New York, NorthShore University Health System, Evanston, Duke Comprehensive Cancer Center, Durham, USCF, San Francisco, University of Illinois, Chicago) (Umeå University, Stockholm, Sweden, Danish Cancer Society, Copenhagen, Denmark, and The Gertner Institute, Chaim Sheba Medical Center, Israel.

Appendix B. List of excluded glioma syndromes

Neurofibromatosis 1 (NF1), Neurofibromatosis 2 (NF2), Tuberous sclerosis, Von Hippel-Lindau, Retinoblastoma, Li-Fraumeni, Turcots syndrome, Nevoid basal cell carcinoma syndrome, Cowden disease.

Appendix C. The members of the Gliogene Consortium

Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, Texas (Sanjay Shete, Robert K. Yu); Department of Community and Family Medicine, Geisel School of Medicine, Dartmouth College, Lebanon, NH, United States (Christopher Amos); Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas (Kenneth D. Aldape); Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas (Mark R. Gilbert); Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, Texas (Jeffrey Weinberg); Department of Pediatrics, Section of Hematology and Oncology, Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, Texas (Ching C. Lau, Eastwood Honchiu Leung, Caleb Davis, Rita Cheng, Chris Man, Rudy Guerra, Sivashankarappa Gurusiddappa, Michael E. Scheurer, Melissa L. Bondy, Georgina N. Armstrong, Yanhong Liu); Division of Genetics and Epidemiology, Institute of Cancer Research, Sutton, Surrey, United Kingdom (Richard S. Houlston, Fay J. Hosking); Yale University School of Medicine, New Haven, Connecticut (Elizabeth B. Claus); Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts (Elizabeth B. Claus); Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, Ohio (Jill S. Barnholtz-Sloan, Andrew E. Sloan, Gene Barnett, Karen Devine, Yingli Wolinsky); The Neurological Institute of Columbia University, New York, New York (Rose Lai, Erika Florendo, Delcia Rivas, Christina Corpuz); Cancer Control and Prevention Program, Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina (Dora Il'yasova, Joellen Schildkraut); Cancer and Radiation Epidemiology Unit, Gertner Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel (Siegal Sadetzki, Galit Hirsh Yechezkel, Revital Bar-Sade Bruchim, Lili Aslanov); Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel (Siegal Sadetzki); Department of Neurology; Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (Christoffer Johansen, Matilde Henriksen); Neurosurgery Department, Rigshospitalet University, Copenhagen, Denmark (Jannick Brennum, Michael Kosteljanetz), Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York (Jonine L. Bernstein, Sara H. Olson, Erica Schubert), Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, New York (Lisa DeAngelis); Mayo Clinic, Rochester, Minnesota (Robert B. Jenkins, Daniel Lachance, Amanda Rynearson, Renee Weatherly); Department of Radiation Sciences Oncology, Umeå University, Umeå, Sweden (Beatrice S. Melin, Roger Henriksson, Ulrika Andersson), Department of Medical Biosciences, Umeå University, Umeå, Sweden (Thomas Brännström); Evanston Kellogg Cancer Care Center, North Shore University Health System, Evanston, Illinois (Nicholas A. Vick); Departments of Neurological Surgery and Epidemiology and Biostatistics (Margaret Wrensch, John Wiencke, Joe Wiemels, Lucie McCoy) Division of Epidemiology and Biostatistics, University of Illinois at Chicago, Chicago, Illinois (Bridget J. McCarthy, Faith G. Davis).

Appendix D. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2012.11.009.

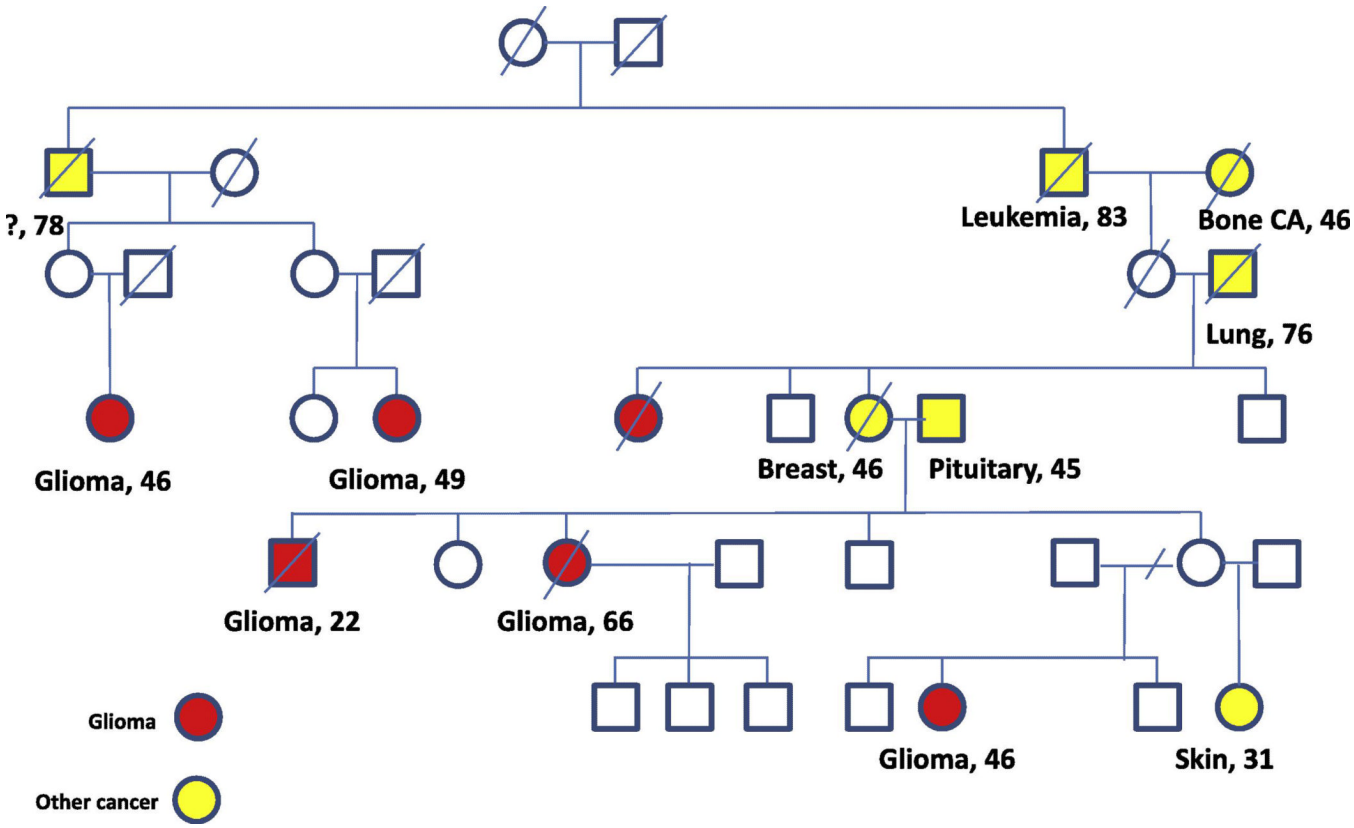

Fig. 1.
A pedigree showing three generations of brain cancer (6 glioma cases).

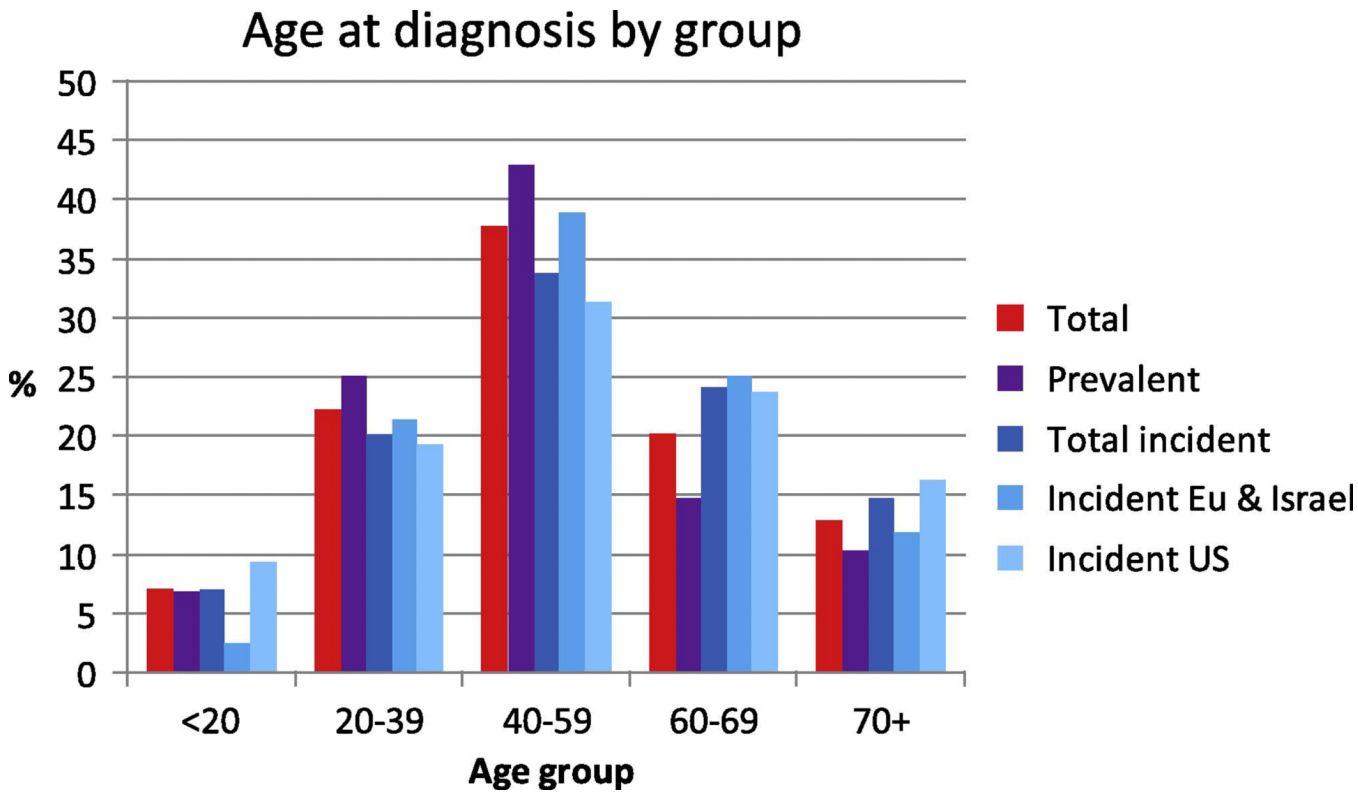

Fig. 2.
Distribution of age at diagnosis of glioma in incident and prevalent cases by study centre (United States [US] and Europe & Israel).

Table 1

Demographic characteristics of the study population by country, GLIOGENE 2007–2011.

	Total		**Centres**							
			US*		**Sweden**		**Denmark**		**Israel**	
	N	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
No. of families	376		279		30	47	47		20	
No. of individuals	9797		6811		750	1418	1418		818	
Family size										
Mean ± SD	26.1±11.8		24.3±9.5		25±8.9		30.2±9.7		40.9±26.3	
Median	24		22		23		33		33.5	
Range	7–128		7–74		13–49		11–51		16–128	
No. of siblings in the proband's generation										
Mean ± SD	4.0±2.1		4.0±2.0		3.3±1.0		4.0±2.5		4.6±2.9	
Median	3		4		3		3		3	
Range	1–14		1–11		2–5		1–14		1–11	
No. of generations in the pedigrees										
3	47	12.5	37	13.3	4	13.3	2	4·3	4	20.0
4	248	66.0	192	68.8	24	80.0	23	48.9	9	45.0
5	78	20.7	50	17.9	2	6.7	20	42.6	6	30.0
6	3	0.8	0	0	0	0.0	2	4.3	1	5.0
*Average male to female ratio in family***										
M/F ratio	1·09		1·09		1·11		1·03		1·14	
*Age (of all individuals)****										
Mean ± SD	57.3±21.8		56.4±21.4		60.1 ±21.7		62.6±20.6		47.0±23.6	
Range	1–111		1–103		1–111		1–103		2–103	
<20	418	6.1	276	6.2	29	4.5	50	3.8	63	13.1
20–39	1025	14.9	662	14.9	91	14.2	138	10.4	134	27.9
40–49	866	12.6	589	13.2	66	10.3	144	10.9	67	14.0
50–69	2351	34.1	1594	35.8	222	34.7	413	31.3	122	25.4
70+	2236	32.4	1332	29.9	234	36.3	576	43.6	94	19.6

* *Centres collecting data in the US:* Baylor, Brigham and Women's, Case Western Reserve University, Columbia, Duke, Memorial Sloan Kettering, MD Anderson Cancer Center, Mayo Clinic, NorthShore University HealthSystem, UCSF, University of Illinois at Chicago.

** For 17 individuals gender is unknown.

*** For 2901 individuals age is unknown.

Table 2

Distribution of gliomas in the families by selected characteristics.

All Glioma families *n* = 376		
Gliomas per family	***n***	**%**
2	311	82.7
3	50	13.3
4	11	2.9
5	3	0.8
10	1	0.3
Total gliomas	841	100
Generations of gliomas in the families		
1	108	28.7
2	253	67.3
3	15	4.0
2 Gliomas in family *n* = 311 families		
Degree of relationship[*]		
Number of 1st degree	166	56.9
Number of 2nd degree	92	31.5
Number of 3rd degree	34	11.6
Gender		
Male/male	92	29.6
Male/female	153	49.2
Female/female	66	21.2
Age at diagnosis (y)		
Early onset (<40 y)	187	60.1
Both <20 y	4	1.3
Both 20–39 y	19	6.1
One <20; one 20–39 y	14	4.5
At least one <40 y	150	48.2
Average onset	239	76.8
Both 40–60 y	49	15.8
At least one 40–60y	190	61.1
Late onset	196	63.0
Both ≥60 y	41	13.2
At least one ≥60 y	155	49.8
Tumour grade[**]		
Same grade for both gliomas	110	43.8
I/I	5	2.0
II/II	14	5.6
III/III	10	4.0
IV/IV	81	32.3
Different grades of gliomas	141	56.2

All Glioma families *n* = 376		
Gliomas per family	***n***	**%**
I/II	4	1.6
I/III	2	0.8
I/IV	12	4.8
II/III	25	10.0
II/IV	56	22.3
III/IV	42	16.7

*For 19 families the degree of relationship was unknown.

**For 60 families (out of 311 families with 2 gliomas) data for one of the tumours behavior were unknown.

Table 3

Histological classification of gliomas (WHO grades 2007), $n = 739^{*}$.

Grade							
I		**II**		**III**		**IV**	
Classification	**n (%)**	**Classification**	**n (%)**	**Classification**	**n (%)**	**Classification**	**n (%)**
Total	**35 (4.7)**	**Total**	**165 (22.3)**	**Total**	**126 (17.1)**	**Total**	**413 (55.9)**
Paraganglioma of spinal cord/ paraganglioglioma	1 (0.1)	Astrocytoma, diffuse	49 (6.6)	Astrocytoma, anaplastic	75 (10.1)	Ependymoblastoma	0
Astrocytoma, juvenile pilocytic	14 (1.9)	Astrocytoma, fibrillary	10 (1.4)	Ependymoma, anaplastic	3 (0.4)	Giant Cell Glioblastoma	2 (0.3)
Desmoplasmic infantile astro/ganglioglioma	0	Astrocytoma, gemistocytic	7 (0.9)	Ganglioglioma, anaplastic	1 (0.1)	Glioblastoma multiforme	407 (55.1)
Gangliocytoma	0	Astrocytoma, pilomyxoid	0	Glioma, unclassified anaplastic	4 (0.5)	Gliosarcoma	4 (0.5)
Gangliocytoma, dysplastic of cerebellum	0	Astrocytoma, protoplasmic	0	Oligoastrocytoma (mixed), anaplastic	12 (1.6)		
Ganglioglioma, desmoplastic infantile	0	Ependymoma	8 (1.1)	Oligodendroglioma, anaplastic	31 (4.2)		
Optic nerve glioma	1 (0.1)	Oligoastrocytoma (mixed glioma)	29 (3.9)				
Papillary glioneuronal tumour	0	Oligodendroglioma	59 (8.0)				
Rosette forming glioneuronal tumour of 4th ventricle	0	Pleomorphic xanthoastrocytoma	3 (0.4)				
Angiocentric glioma	0	Central Neurocytoma	0				
Subependymoma	0	Extraventricular Neurocytoma	0				
Astrocytoma, pilocytic	4 (0.5)	Cerebellar liponeurocytoma	0				
Astrocytoma, subependy giant cell	0	Chordoid glioma of 3rd ventricle	0				
Dysembryoplastic neuroepithelial tumour	4 (0.5)						
Ependymoma, myxopapillary	6 (0.8)						
Ganglioglioma	5 (0.7)						

*For 92 cases of the 831 verified gliomas the histological classification was unknown.

Table 4

Distribution of glioma cases by date of diagnosis* and selected demographic and clinical characteristics.

	Total		Incident*				Prevalent*			
	Total	Europe & Israel#	US	Total						
	n = 376 families		*n* = 219 families		*n* = 73 families		*n* = 146 families		*n* = 157 families	
	n = 841 gliomas		*n* = 481 gliomas		*n* = 159 gliomas		*n* = 322 gliomas		*n* = 360 gliomas	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Gender										
Males	450	53.5	267	55.5	93	58.5	174	54	183	50.8
Females	391	46.5	214	44.5	66	14.5	148	46	177	49.2
M/F ratio (all)	1.15		1.25		1.41		1.18		1.10	
Age at diagnosis ** (*n* = 838)										
Mean ± SD	49.4 + 18.7		51.0 ± 19.0		51.1 ± 16.4		50.9 ± 20.1		47.2 ± 18.1	
Range	1–92		1–92		4–82		1–92		1–91	
<20	59	7.0	34	7.1	4	2.5	30	9.4	25	6.9
20–39	186	22.2	96	20.1	34	21.4	62	19.4	90	25.1
40–59	316	37.7	162	33.8	62	39.0	100	31.3	154	42.9
60–69	169	20.2	116	24.2	40	25.2	76	23.8	53	14.8
70+	108	12.9	71	14.8	19	11.9	52	16.3	37	10.3
Tumour grade *** (*n* = 739 ***)										
I	35	4.7	20	4.7	6	4	14	5.1	15	4.7
II	165	22.5	77	18.2	36	24	41	15.0	88	27.8
III	126	17.0	70	16.5	30	20	40	14.7	56	17.7
IV	413	55.9	256	60.5	78	52	178	65.2	157	49.7
Age at diagnosis by grade *****										
Grades I–II	37.2 ± 16.1		38.5 ± 17.4		42.7 ± 16.2		35.3 ± 17.8		35.9 ± 14.8	
Grades III–IV	54.8 ± 16.4		55.8 ± 16.4		55.1 ± 14.8		56.1 ± 17.2		53.4 ± 16.3	
Tumour grade by gender (*n* = 739 ****)										
Grades I–II total	200	100	97	100	42	100	55	100	103	100
Males	99	49.5	44	45.4	21	50	23	41.8	55	53.4
Females	101	50.5	53	54.6	21	50	32	58.2	48	46.6
Grades III–IV total	539	100	326	100	108	100	218	100	213	100
Males	300	55.7	191	58.6	68	63	123	56.4	109	51.2
Females	239	44.3	135	41.4	40	37	95	43.6	104	48.8

* When the glioma in the proband was diagnosed from 2007 all gliomas in the family were included in the incident cases column; when the glioma in the proband was diagnosed before 2007 all gliomas in the family were included in the prevalent cases column.

** Excluding three cases with unknown age at diagnosis; comparison between mean age at diagnosis of incident and prevalent $p = 0.003$.

*** *P*-value = 0.00009 (total incidents versus prevalent).

**** For 92 cases of the 831 verified tumours, tumour histological behavior was unknown, and for 58 cases of the 481 verified tumours from the total incident cases, tumour histological behavior was unknown.

*****For grades I–II P-value = 0.3 (total incident versus total prevalent).

#Europe & Israel – Families from the Israeli centre were included in the Europe classification.

Table 5

Distribution of glioma morphologies, grade and age at diagnosis in probands and other family members having 2 gliomas ($n = 26$).

Patient no.	1st brain tumour			2nd brain tumour			Time period between 1stBT to 2nd BT (y)
	Morphology	Grade	Age	Morphology	Grade	Age	
1	Astrocytoma, unclassified	0*	29	Glioblastoma multiforme	IV	40	11
2	Astrocytoma, anaplastic	III	61	Glioblastoma multiforme	IV	62	1
3	Astrocytoma, anaplastic	III	63	Glioblastoma multiforme	IV	63	0
4	Astrocytoma, anaplastic	III	40	Glioblastoma multiforme	IV	47	7
5	Oligoastrocytoma (mixed glioma)	II	43	Glioblastoma multiforme	IV	57	14
6	Astrocytoma, diffuse	II	38	Glioblastoma multiforme	IV	40	2
7	Astrocytoma, anaplastic	II	5	Glioblastoma multiforme	IV	7	2
8	Oligodendroglioma	II	23	Glioblastoma multiforme	IV	32	9
9	Oligoastrocytoma (mixed), anaplastic	II	27	Glioblastoma multiforme	IV	28	1
10	Astrocytoma, fibrillary	II	28	Glioblastoma multiforme	IV	30	2
11	Astrocytoma, fibrillary	II	10	Glioblastoma multiforme	IV	11	1
12	Oligoastrocytoma (mixed glioma)	II	56	Glioblastoma multiforme	IV	57	1
13	Astrocytoma, unclassified	0	56	Glioblastoma multiforme	IV	58	2
14	Oligodendroglioma	II	42	Glioblastoma multiforme	IV	46	4
15	Glioma, unclassified	0	30	Glioblastoma multiforme	IV	34	4
16	Oligoastrocytoma (mixed glioma)	II	28	Oligoastrocytoma (mixed glioma)	II	29	1
17	Oligodendroglioma	II	32	Oligoastrocytoma (mixed), anaplastic	III	36	4
18	Astrocytoma, diffuse	II	42	Oligodendroglioma	II	45	3
19	Glioma, unclassified	0	31	Oligodendroglioma	II	35	4
20	Oligodendroglioma	II	54	Oligodendroglioma, anaplastic	III	61	7
21	Oligodendroglioma	II	41	Oligodendroglioma, anaplastic	III	52	11
22	Glioma, unclassified	0	47	Oligodendroglioma, anaplastic	III	61	14
23	Oligoastrocytoma (mixed glioma)	II	31	Oligodendroglioma, anaplastic	III	34	3
24	Oligodendroglioma	II	37	Oligodendroglioma, anaplastic	III	46	9
25	Glioma, unclassified	II	42	Oligodendroglioma, anaplastic	III	44	2
26	Oligoastrocytoma (mixed glioma)	II	37	Oligodendroglioma, anaplastic	III	45	8

0 = unknown grade.