**Supplementary Figure 1**. **Principal components analysis (PCA) plots of the population ancestry of cases and controls**. HapMap CEU individuals are plotted in blue circles, CHB+JPT are plotted in green circles, YRI individuals are plotted in red circles. Familial glioma cases, TCGA glioma cases and Controls are plotted as blue, orange and grey crosses respectively.



# Supplementary Table 1. Details of glioma cases sequenced. Shown for each family sequenced are the proband’s personal history of cancer and any known details of relatives affected with brain tumours.\*, sample sequenced; M, Male; F, Female; Mo, Mother; Fa, Father; m, maternal; p, paternal; B, brother; S, sister; A, aunt; U, uncle; C, cousin; GMo, Grandmother; GFa, Grandfather; GU, Great uncle; GA, Great aunt; GNe, Grandnephew; Ne, Nephew; Ni, Niece; GGMo, Great grandmother; D, Daughter; So, Son; H, Half; Cr, First cousin once removed; Cd, Double cousin; C2, Second cousin.

| **Family** | **Centre** | **Proband - sex, histology (age of diagnosis)** | **Brain tumours in family - relation (sex), histology (age of diagnosis)**  | **N** |
| --- | --- | --- | --- | --- |
| FAM\_1 | French | M, Grade II astrocytoma (31)\* | B (M), Grade III anaplastic astrocytoma (48)\* | 2 |
| FAM\_2 | French | F, Grade III anaplastic oligoastrocytoma (27**)\*** | Fa (M), GBM (51)\* | 2 |
| FAM\_3 | French | M, GBM (61)\* | B (M), GBM (65)\*; S (F), Astrocytoma; B (M), PBT, Mo (M), GBM, mC (F), GBM | 2 |
| FAM\_4 | French | M, Glioma medulla\* | Mo (F), Anaplastic astrocytoma (61)\*, mGMo (F), PBT | 2 |
| FAM\_5 | French | M, GBM (44)\* | mC (M), GBM\* | 2 |
| FAM\_6 | French | M, Grade II oligoastrocytoma (40)\* | mC (M), glioma\* | 2 |
| FAM\_7 | French | M, Grade II oligodendroglioma (30)\* | pU (M), GBM\*; Mo, Grade II Meningioma (50) | 2 |
| FAM\_8 | French | M, Grade III oligodendroglioma (46)\* | B (M), Anaplastic oligoastrocytoma (56)/COAD\*; B (M), head + neck | 2 |
| FAM\_9 | French | M, Grade II oligodendroglioma (45)\* | S (F), GBM\* | 2 |
| FAM\_10 | French | M, Brainstem glioma\* | S (F), Grade II oligodendroglioma (41)\*; B (M), Grade III oligodendroglioma | 2 |
| FAM\_11 | French | M, Ganglioma (36)\* | B (M), GBM (51)\*; pGMo (F), PBT | 2 |
| FAM\_12 | Danish | M, GBM (46)/Anaplastic astrocytoma (46) | fC (M), Anaplastic astrocytoma (58)\* | 2 |
| FAM\_13 | Danish | F, Dysembroplastic neuroepithelial tumour (27)/Glioma, unclassified (27)\* | Mo (F), Diffuse astrocytoma (46)\*; mGMo (F), PBT (21); mU (M), Medulloblastoma (13) | 2 |
| FAM\_14 | Danish | F, Anaplastic oligodendroglioma (67)\* | B (M), Anaplastic oligodendroglioma (63)\*; mC (F), Breast (60)/Meningioma (62) | 2 |
| FAM\_15 | Danish | F, BCC (75)/GBM (77)\* | S (F), GBM (78)\* | 2 |
| FAM\_16 | Danish | M, GBM (73)\* | S (F), Astrocytoma, juvenile pilocytic (41)\*; mC (M), GBM (76)/Glioma unclassified\*; mA (F), GBM (66); mU (M), PBT; mGNi (F), thyroid (40) | 3 |
| FAM\_17 | Danish | F, Diffuse astrocytoma (24)\* | S (F), Diffuse astrocytoma (26)\* | 2 |
|  |  |  |  |   |
| FAM\_18 | French | M, GBM\* | B (M), GBM | 1 |
| FAM\_19 | French | M, Grade III anaplastic oligoastrocytoma (55)\* | U (M), PBT | 1 |
| FAM\_20 | French | M, Grade III oligoastrocytoma (52)\* | Mo (F), Brain-stem glioma | 1 |
| FAM\_21 | French | M, Grade III oligodendroglioma (54)\* | mA (F), PBT | 1 |
| FAM\_22 | French | M, Oligodendroglioma\* | Mo (F), GBM | 1 |
| FAM\_23 | French | M, Grade III oligodendroglioma (44)\* | S (F), PBT | 1 |
| FAM\_24 | French | M, GBM (68)\* | B (M), GBM | 1 |
| FAM\_25 | French | M, GBM\* | Mo (F), PBT | 1 |
| FAM\_26 | French | M, Anaplastic oligoastrocytoma (31)\* | GFa (M), Oligoastrocytoma/astrocytoma | 1 |
| FAM\_27 | French | F, Melanoma-glioma\* |  | 1 |
| FAM\_28 | French | F, Grade II oligoastrocytoma\* | S (F), Astrocytoma | 1 |
| FAM\_29 | French | F, Malignant neural glioma (26)\* | pGMo (F), Astrocytoma; GGMo, Probable brain tumour | 1 |
| FAM\_30 | French | F, Anaplastic astrocytoma\* | GA (F), PBT | 1 |
| FAM\_31 | French | F, Grade III oligodendroglioma\* | S (F), Thalamic tumour | 1 |
| FAM\_32 | French | M, GBM\* | S (F), PBT | 1 |
| FAM\_33 | French | F, Grade III oligodendroglioma\* | B (M), PBT; S (F), PBT | 1 |
| FAM\_34 | French | F, GBM (65)\* | Fa (M), PBT | 1 |
| FAM\_35 | French | M, GBMO-melanoma\* |  | 1 |
| FAM\_36 | French | M, Grade III anaplastic astrocytoma (61)\* | B (M), Grade III/IV gemistocytic astrocytoma | 1 |
| FAM\_37 | French | F, GBM\* | S (F), GBM; | 1 |
| FAM\_38 | French | M, Grade II oligodendroglioma (54)\* | pU (M), PBT | 1 |
| FAM\_39 | French | M, Ganglioma (32)\* | mGFa (M), PBT; mC (M), PBT | 1 |
| FAM\_40 | French | F, Grade III oligodendroglioma (49)\* | A (F), PBT | 1 |
| FAM\_41 | French | F, GBM (51)\* | B (M), Cerebral lymphoma | 1 |
| FAM\_42 | French | M, Gemistocytic astrocytoma (28)\* | Fa (M), Anaplastic astrocytoma (52); pA (F), PBT | 1 |
| FAM\_43 | French | F, GBM (53)\* | Mo (F), GBM | 1 |
| FAM\_44 | French | M, Grade II oligodendroglioma (50)\* | D (F), Medulloblastoma | 1 |
| FAM\_45 | French | F, Grade III oligodendroglioma\* | Mo (F), PBT | 1 |
| FAM\_46 | French | F, GBMO-melanoma\* |  | 1 |
| FAM\_47 | French | M, GBM\* | C (F), Glioma unspecified | 1 |
| FAM\_48 | French | F, GBM (51)\* | C (M), PBT; C (M), PBT | 1 |
| FAM\_49 | French | F, Glioma unspecified (29)\* | U (M), PBT | 1 |
| FAM\_50 | French | M, Grade II astrocytoma (48)/colon cancer\* | Suspected history of turcot syndrome | 1 |
| FAM\_51 | French | F, Grade II astrocytoma (43)\* | GFa (M), PBT | 1 |
| FAM\_52 | French | F, GBM (50)/ breast (36)\* | Fa (M), Malignant cerebellar astrocytoma (54) | 1 |
| FAM\_53 | French | F, Grade III oligodendroglioma (27) | mU (M), Glioma unspecified | 1 |
| FAM\_54 | French | F, GBMO-melanoma\* |  | 1 |
| FAM\_55 | French | F, Grade II oligoastrocytoma (72)/Thyroid adenocarcinoma\* |  | 1 |
| FAM\_56 | French | F, Gliomatosis cerebri-choroidal melanoma\* |  | 1 |
| FAM\_57 | French | M, Gliomatose astrocytoma grade II/III (21)\* | Multiple PBTs in family | 1 |
| FAM\_58 | French | F, GBM\* | So (M), PBT | 1 |
| FAM\_59 | French | F, Malignant glioma\* | B (M), GBM/renal cancer | 1 |
| FAM\_60 | French | F, GBM\* | Mo (F), GBM | 1 |
| FAM\_61 | French | F, Oligoastrocytoma (26)\* | Mo (F), GBM | 1 |
| FAM\_62 | French | M, Grade II ependymoma (27)\* | Mo (F), Glioma unspecified; pU (M), PBT | 1 |
| FAM\_63 | French | M, Grade II astrocytoma (54)\* | C (M), PBT | 1 |
| FAM\_64 | French | M, Oligoastrocytoma (35)\* | Fa (M), Oligodendroglioma; B (M), Oligoastrocytoma (21) | 1 |
| FAM\_65 | French | F, Grade II oligodendroglioma (50)\* | B (M), Pilocytic astrocytoma | 1 |
| FAM\_66 | French | F, Anaplastic oligodendroglioma\* | C (M), PBT; A (F), PBT | 1 |
| FAM\_67 | French | M, GBM (68)\* | B (M), PBT | 1 |
| FAM\_68 | French | M, Grade III anaplastic astrocytoma (57)\* | Mo (F), PBT | 1 |
| FAM\_69 | French | M, Grade III oligodendroglioma (76)\* | Fa (M), PBT | 1 |
| FAM\_70 | French | M, Anaplastic astrocytoma\* | Fa (M), GBM; C (M), GBM | 1 |
| FAM\_71 | French | M, GBM (34)\* | mGFa (M), Glioma unspecified | 1 |
| FAM\_72 | French | F, Oligoastrocytoma (30)\* | Multiple PBTs | 1 |
| FAM\_73 | French | F, GBM-melanoma\* |  | 1 |
| FAM\_74 | French | M, Grade III anaplastic astrocytoma (57)\* | B (M), PBT (51) | 1 |
| FAM\_75 | French | M, GBM\* | B (M), GBM | 1 |
| FAM\_76 | French | F, Grade III anaplastic oligoastrocytoma (37)\* | Fa (M), GBM | 1 |
| FAM\_77 | French | M, GBM-melanoma\* |  | 1 |
| FAM\_78 | French | F, Grade II oligodendroglioma-melanoma\* |  | 1 |
| FAM\_79 | French | F, Grade II oligoastrocytoma (48)\* | S (F), PBT | 1 |
| FAM\_80 | French | M, Grade III anaplastic astrocytoma (20)\* | Fa (M), Glioma papilloma  | 1 |
| FAM\_81 | French | M, Gliosarcoma (71)\* | F (M), GBM | 1 |
| FAM\_82 | French | M, GBM (61)\* | F (M), PBT | 1 |
| FAM\_83 | French | M, Grade II astrocytoma/colorectal polyps\* | C (M), PBT (40) | 1 |
| FAM\_84 | French | M, GBM-melanoma\* |  | 1 |
| FAM\_85 | French | M, Grade II oligodendroglioma (47)\* | B (M), PBT | 1 |
| FAM\_86 | French | M, GBM with oligodendroglioma (32)\* | C (M), Glioma unspecified | 1 |
| FAM\_87 | French | F, Gemistocytic astrocytoma\* | mGMo (F), GBM | 1 |
| FAM\_88 | French | F, Grade II oligodendroglioma (38) / melanoma (34) | GFa (M), PBT | 1 |
| FAM\_89 | French | M, Xanthoastrocytoma\* | Mo (F), PBT | 1 |
| FAM\_90 | French | F, GBM (48)\* | mU (M), PBT | 1 |
| FAM\_91 | French | M, GBM (56)\* | Mo (F), PBT | 1 |
| FAM\_92 | French | M, Glioma\* | C (M), Oligodendroglioma (33); C (M), Medulloblastoma (11) | 1 |
| FAM\_93 | French | F, GBM (67)\* | B (M), GBM (49) | 1 |
| FAM\_94 | French | M, GBM\* | Fa (M), GBM | 1 |
| FAM\_95 | French | M, Grade II oligodendroglioma (46)\* | B (M), PBT, Mo (F), PBT | 1 |
| FAM\_96 | French | M, Grade II oligodendroglioma-melanoma\* |  | 1 |
| FAM\_97 | French | M, GBM (51)\* | B (M), PBT | 1 |
| FAM\_98 | French | M, Grade II astrocytoma (37)\* | Mo (F), PBT; A (F), PBT | 1 |
| FAM\_99 | French | M, Anaplastic oligoastrocytoma\* | Mo (F), PBT; mU (M), PBT | 1 |
| FAM\_100 | French | F, Grade III oligodendroglioma (35)\* | C (M), Grade II glioma | 1 |
| FAM\_101 | French | M, GBM-melnoma\* |  | 1 |
| FAM\_102 | French | M, GBM (52)\* | mGMo (F), GBM | 1 |
| FAM\_103 | French | M, GBM (62)\* | B (M), GBM | 1 |
| FAM\_104 | French | M, Grade III anaplastic oligoastrytoma (40)\* | Fa (M), PBT | 1 |
| FAM\_105 | French | F, Anaplastic astrocytoma (30)\* | Mo (F), GBM; pC (F), PBT | 1 |
| FAM\_106 | French | M, GBM\* | Ne (M), PBT | 1 |
| FAM\_107 | French | M, GBM\* | So (M), Anaplastic astrocytoma | 1 |
| FAM\_108 | French | F, GBM (18)\* | C (F), Cerebellar astrocytoma | 1 |
| FAM\_109 | French | M, GBM\* | Mo (F), GBM | 1 |
| FAM\_110 | French | M, Anaplastic oligodendroglioma\* | B (M), PBT | 1 |
| FAM\_111 | French | M, Glioma\* | U (M), Cerebellar tumour | 1 |
| FAM\_112 | French | M, GBM (72)\* | S (M), GBM | 1 |
| FAM\_113 | French | M, GBM (58)\* | Fa (M), PBT | 1 |
| FAM\_114 | Danish | F, Diffuse astrocytoma (45, 50, 52)\* | B (M), GBM (37) | 1 |
| FAM\_115 | Danish | M, Diffuse astrocytoma (25)\* | Fa (M), Oligodendroglioma (39, 42, 46); pHA (F), GBM (60) | 1 |
| FAM\_116 | Danish | M, Anaplastic astrocytoma (58)\* | Fa (M), Giant cell GBM (40) | 1 |
| FAM\_117 | Danish | F, Diffuse astrocytoma (51)\* | B (M), Diffuse astrocytoma (41) | 1 |
| FAM\_118 | Danish | F, GBM (35)\* | pGA (F), GBM (50) | 1 |
| FAM\_119 | Danish | M, GBM (64)\* | Fa (M), Oligodendroglioma (61) | 1 |
| FAM\_120 | Danish | F, Thyroid (28)/GBM (47) | Fa (M), GBM (68) | 1 |
| FAM\_121 | Danish | F, GBM (69)\* | B (M), GBM (65); B (M), Eye (45); pA (F), BCC (77)/Melanoma (81)/PBT (88) | 1 |
| FAM\_122 | Danish | F, Anaplastic oligoastrocytoma (55)\* | So (M), Fibrillary astrocytoma (27)/Anaplastic astrocytoma (28); pGFa (M), PBT (48); mHC (M), Oligodendroglioma (42)/GBM (46); mHC (F), Meningioma (56) | 1 |
| FAM\_123 | Danish | F, Diffuse astrocytoma (29)/Diffuse astrocytoma (32)/Anaplastic astrocytoma (35)\* | pC (F), Diffuse astrocytoma (29); pGA (F), Oligoastrocytoma (68); pCr (M), GBM (37)/GBM (38) | 1 |
| FAM\_124 | Danish | F, Anaplastic astrocytoma (57)\* | S (F), GBM (45); Mo (F), Anaplastic astrocytoma (83) | 1 |
| FAM\_125 | Danish | M, GBM (80)\* | Fa (M), Oligodendroglioma (59); pC (F), Meningioma (59); pCr (M), Diffuse astrocytoma (46) | 1 |
| FAM\_126 | Danish | M, Glioma unclassified (69)\* | Mo (F), GBM (58) | 1 |
| FAM\_127 | Danish | M, GBM (77)\* | B (F), GBM (69); mA (F), Diffuse astrocytoma (73) | 1 |
| FAM\_128 | Danish | F, GBM (53)\* | Cd (M), Oligoastrocytoma (31), Anaplastic oligodendroglioma (34) | 1 |
| FAM\_129 | Danish | M, Anaplastic oligoastrocytoma (43)\* | mC (M), GBM (39) | 1 |
| FAM\_130 | Danish | M, Oligodendroglioma (44)/oligodendroglioma (60)\* | mGFa (F), Anaplastic oligodendroglioma (74) | 1 |
| FAM\_131 | Danish | F, GBM (43)\* | pGFa (M), GBM (58) | 1 |
| FAM\_132 | Danish | F, Oligodendroglioma (38)/Oligodendroglioma (43)\* | Fa (M), GBM (46) | 1 |
| FAM\_133 | Danish | F, Spinal cord paraganglioma (51)\* | Mo (F), GBM (63) | 1 |
| FAM\_134 | Danish | F, GBM (53)\* | pA (F), BCC (52)/GBM (71) | 1 |
| FAM\_135 | Danish | M, GBM (42)\* | mA (F), Pilocytic astrocytoma (30) | 1 |
| FAM\_136 | Danish | M, GBM (60) | pU (M), Oligodendroglioma (60) | 1 |
| FAM\_137 | Danish | M, GBM (43)/GBM (44)\* | Fa (M), Fibrillary astrocytoma (25); mC2 (M), GBM (29); mCr (M), Diffuse astrocytoma (28) | 1 |
| FAM\_138 | Danish | M, Anaplastic oligoastrocytoma (69)\* | Fa (M), Diffuse astrocytoma (66) | 1 |
| FAM\_139 | Danish | F, Anaplastic oligodendroglioma (41)\* | S (F), Meningioma (40); pC (F), Adrenal (30)/ | 1 |
| FAM\_140 | Danish | F, Ependymoma (51)\* | Fa (M), GBM (63) | 1 |
| FAM\_141 | Danish | M, Diffuse astrocytoma (32)/Gemistocytic astrocytoma (33)\* | Mo (F), Anaplastic astrocytoma (33) | 1 |
| FAM\_142 | Danish | M, Diffuse astrocytoma (37)\* | S (F), Oligoastrocytoma (37)/Oligoastrocytoma (45)/Anaplastic oligodendroglioma (46) | 1 |
| FAM\_143 | Danish | F, GBM (73)\* | B (M), GBM (63) | 1 |
| FAM\_144 | Danish | F, Diffuse astrocytoma (58)\* | mA (F), GBM (F); mGU (M), Anaplastic oligodendroglioma (60) | 1 |
| FAM\_145 | Danish | M, GBM (76)\* | Fa (M), Glioma (57); pA (F), Thyroid (67)/Skin unknown (78) | 1 |
| FAM\_146 | Danish | F, Glioma unclassified\* | pC (M), GBM | 1 |
| FAM\_147 | Danish | F, GBM (53)\* | Fa (M), GBM | 1 |
| FAM\_148 | Danish | F, GBM (63)\* | Fa (M), GBM (64) | 1 |
| FAM\_149 | Danish | M, GBM (56)/GBM (56) | HB (M), Oligodendroglioma (40) | 1 |
| FAM\_150 | Danish | M, Anaplastic oligodendroglioma\* | Fa (M), PBT; Mo (F), Meningioma | 1 |

Supplementary Table 2. Per-gene association analysis in glioma cases. The SKAT-O test was applied to protein altering variants (*Pnon-syn*) and synonymous variants (*P*synon).Shown are all genes with >1 protein altering variant and *Pnon-syn* <1x10-4.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gene** | **Ensembl gene** | **N** | ***Pnon-syn*** | ***Psynon*** |
| *AMT* | ENSG00000145020 | 8 | 2.21x10-5 | 0.070 |
| *HCP5* | ENSG00000206337 | 9 | 2.28 x10-5 | 1.00 |
| *MICA* | ENSG00000204520 | 9 | 2.28 x10-5 | 1.00 |
| *TBC1D21* | ENSG00000167139 | 3 | 3.55 x10-5 | 1.00 |
| *ZNF577* | ENSG00000161551 | 13 | 4.29 x10-5 | 1.00 |
| *UBD* | ENSG00000213886 | 5 | 4.80 x10-5 | 1.00 |
| *SEMA3A* | ENSG00000075213 | 19 | 4.98 x10-5 | 0.092 |
| *EQTN* | ENSG00000120160 | 8 | 5.60 x10-5 | - |
| *DPH1* | ENSG00000108963 | 6 | 5.63 x10-5 | 1.00 |
| *GABRA2* | ENSG00000151834 | 2 | 5.86 x10-5 | 0.404 |
| *TET2* | ENSG00000168769 | 21 | 6.00 x10-5 | 0.060 |
| *CCDC113* | ENSG00000103021 | 11 | 6.26 x10-5 | 1.00 |
| *RIMS2* | ENSG00000176406 | 20 | 6.62 x10-5 | 0.29 |
| *WDR19* | ENSG00000157796 | 23 | 7.00 x10-5 | 0.34 |
| *N4BP2L2* | ENSG00000244754 | 28 | 8.23 x10-5 | 0.55 |
| *PDK4* | ENSG00000004799 | 11 | 8.53 x10-5 | 0.064 |
| *ZNF804B* | ENSG00000182348 | 55 | 9.45 x10-5 | 0.053 |
| *ENPP2* | ENSG00000136960 | 17 | 9.67 x10-5 | 0.545 |