Role of monoamine-oxidase-A-gene variation in the development of glioblastoma in males: a case control study

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Abstract
Background The Mono-amine oxidase-A (MAO-A) enzyme is involved in the degradation and regulation of catecholamines such as serotonin, dopamine, epinephrine and nor-epinephrine. Preclinical studies suggest that this enzyme may contribute to an environment favorable for growth of malignant glioma. The MAO-A gene is located on the X-chromosome and has at least one functional genetic polymorphism. The aim of the present study was to explore possible effects of MAO-A genotype on development of glioblastoma in males.

Methods Genotypes for 437 glioma cases and 876 population-based controls from the Swedish Glioma International Case-Control study (GICC) were compared. We analyzed the germline DNA using the Illumina Oncoarray. We selected seven single nucleotide polymorphisms (SNPs) located in the MAO-A gene, and imputed genotypes based on data from the 1000 genomes project. We used 1579 male glioblastoma cases and 1875 controls comprising the whole GICC cohort for subsequent validation of findings.

Results The rs144551722 SNP was a significant predictor of development of glioblastoma in males (p-value = 0.0056) but not in females even after correction for multiple testing. We conducted haplotype analysis to confirm an association between MAO-A gene and risk of glioblastoma (p-value = 0.016). We found similar results in the validation sample.

Conclusions These results suggest the possibility of a role for the MAO-A enzyme and the MAO-A gene in the development of glioblastoma in males.

Keywords MAOA genetics glioblastoma males

Introduction
The risk for developing glioma is roughly 1.4 times greater for males than females [1, 2]. We have recently described 25 genetic variants associated with development of glioma in both genders using a genome wide approach [3]. In addition, a recent study using a similar approach but focusing on the X-chromosome identified four regions of potential interest that remained statistically significant after correction for 250,000 significance tests [4]. In these studies, an agnostic, exploratory methodology was applied, according to which all available polymorphisms were analyzed, regardless of known function.

However, a potential useful alternative strategy in the study of genetically determined sex differences is the candidate gene study. In this context such a strategy might mean focusing on known x-linked genetic polymorphisms that, for theoretical reasons, might be expected to be related to glioma development.

One such candidate is the MAO-A-gene that is located on the X-chromosome (Xp 11.23) [5]. The gene codes for a protein that is involved in the degradation of several neurotransmitters most important serotonin, dopamine, epinephrine
and nor-epinephrine in a tissue specific manner. Functional variations in the MAO-A-gene have in several studies been associated with behavioral outcomes particularly in males. One early example is a study of a Dutch family, in which a stop codon in the gene, associated with severe antisocial behavior in males, was identified [6]. More recently much interest has been focused on a functional variable number of tandem repeat (VNTR)-polymorphism in the promoter region of the MAO-A gene commonly referred to as the MAOA-Linked Polymorphic Region (MAOA-LPR) [7, 8]. The low function variant of this VNTR has in several studies been linked to behavioral and neurophysiological phenotypes in males, [9–14] and to some lesser extent females [15, 16]. This has led to a common assumption within the field of behavioral genetics that the polymorphism may be important in the overall regulation of monoaminergic systems [17].

From a theoretical point-of-view there are at least three possible mechanisms by which variation in the MAOA-gene may be relevant to the development of glioma. The two first of these would be through the regulation of monoaminergic neurotransmission, particularly Serotonin and Dopamine [18].

Regulation of stem cell proliferation

It has been reported that both Dopamine and Serotonin influence proliferation of neural progenitor cells in the sub ventricular zone, [19–21] and the dentate gyrus [22], respectively. Converging evidence suggests that the cells that give rise to glioma development may share many important features with these progenitor cells [23, 24] suggesting the possibility that Dopamine and Serotonin may influence cell proliferation in glioma precursor cells as well. This would provide potential for functional genetic variation in a gene relevant to the regulation of these neurotransmitters to influence early glioma development.

Regulation of angiogenesis

Particularly Dopamine has in several studies been implicated as an inhibitor of angiogenesis through interaction with the Vascular endothelial growth factor (VEGF) pathway [25, 26]. Since angiogenesis is a key feature of glioma development, particularly in glioblastoma, a genetic polymorphism with the potential to regulate levels of an endogenous inhibitor of angiogenesis may also be a possible candidate gene.

Effects of oxidative stress

Findings of increased serum levels of reactive oxygen species (ROS) in patients who later develop Glioblastoma suggests a role for oxidative stress in the genesis of this disease [27]. Levels of oxidative stress including increased ROS has been associated with MAO-A over-expression in prostate cancer models [28, 29]. Therefore, it would seem to make sense that a functional polymorphism that regulates MAO-A transcription could influence levels of oxidative stress in a way that might influence glioma development.

More direct experimental evidence for a role of the MAO-A enzyme in glioma development was recently provided in experiments reported by Kushal et al. [30]. These authors found increased levels of the MAO-A protein in glioma tissue. Furthermore, they found that inhibition of MAO-A activity was cytotoxic to glioma cells in-vitro and that it reduced proliferation, microvessel density, and invasion of glioma tissue in a rat model.

In line with the reasoning presented above, the purpose of the present study was to investigate the specific hypothesis that variation in the MAOA gene is associated with development of glioblastoma in males. We investigated this hypothesis using a case–control approach.

Methods

Swedish sample

The study subjects included in the risk analysis were those who participated in the Swedish Glioma International Case–Control (GICC) study. Details of patient recruitment, data collection, and quality control are available in previous publications [3, 31]. In brief, cases were between the ages of 18–80 years, and recruited between the years 2010 and 2013 from five hospitals in Sweden. In total, 472 histologically confirmed newly diagnosed glioma cases and 908 population-based controls were genotyped. We excluded subjects with < 99% sample genotyping call-rate, subjects with inconsistencies between reported sex and sex estimated by genotype, subjects with < 80% estimated European ancestry, subjects identified as outliers in principle component analyses and one of each pair of individuals with spurious relations (PI-HAT > 0.2). We also excluded cases with rare glioma diagnoses (SNOMED codes 93913, 93923, 94121, 94211, 94423, and 95051). After this quality control, 437 cases and 876 controls were included. There were 175 male and 94 female GBM cases.

SNP selection

We selected seven SNPs in the MAO-A gene. Because MAO-LPR was not directly sequenced in our study, we used Haploview (version 4.2) to select 3 SNPs with minor allele frequency > 0.1 that tag variation in the region of the MAO-LPR. For this purpose, we used reference data (± 10 kb from MAO-LPR) from the 1000 genomes...
projects (phase 3, European population) [32]. Details of the analyzed SNPs are shown in Table 1.

**Genotyping and imputation**

We used the Illumina Oncoarray to genotype the SNPs. We imputed untyped variants in the MAOA gene using the IMPUTE2 and SHAPEIT2 software, and data from the 1000 genomes project as reference [33–36]. Before imputation, we excluded SNPs with poor call-rate (< 95%), p-value from Hardy–Weinberg test < 1 \( \times \) 10\(^{-6}\), minor allele frequency < 0.01, and all A/T and C/G SNPs. Imputation info scores for SNPs in MAO-A are presented in Table 1. For imputed variants, genotypes were called based on the highest imputed genotype probability. A genotype call was set to “missing” in subjects where all three genotype probabilities for a variant were < 0.9.

**Statistical analysis**

We performed gender-stratification analyses to test the associations between genotype/allele frequencies and glioma risk using chi-square test/Fisher exact test. We conducted haplotype analysis of 5 SNPs in the MAO-A gene, and logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI). We applied Bonferroni correction for the SNP-analysis by setting the critical \( p \) level to 0.00714 (0.05/7).

**Validation set**

The cases and controls from the entire GICC study earlier presented was used for validation [31]. In total there were 2614 male glioma cases, of whom 1579 was glioblastoma. They were compared to 1875 male controls.

### Results

**Analysis of the Swedish sample**

**SNP-analysis**

Table 2 describes analyses of association between the seven selected SNPs in male cases and controls, and the p-values were < 0.05 for all seven SNPs. After correction for multiple testing the rs144551722 SNP remained significant (p-value = 0.0056). There were no significant effects for lower grade gliomas or glioblastomas (as can be seen in Table 3), for females.

**Haplotype analysis**

Second, a haplotype analysis including rs144551722, rs1465108, rs909525, rs979605, rs2239448 was performed in order to further investigate the relation between genotype and glioblastoma in males. The overall haplotype pattern was, as seen in Table 4, significant (p-value = 0.016).

**Validation in the whole GICC cohort**

**SNP-analysis**

After analyses of the Swedish sample, we conducted a validation analysis on the whole GICC cohort. As can be seen in Table 5, rs144551722, which was the only SNP to remain statistically significant after correction for multiple testing in the Swedish dataset, was significant in the whole GICC cohort as well (p < 0.05).

**Haplotype analysis**

As seen in Table 6 a replication of the haplotype analysis in the full GICC case control did not reach significance (p-value = 0.1).

### Table 1  Analyzed SNPs in the MAO-A gene

| SNP numbers | Location | Most severe consequence | Alleles | Info | Certainty |
|-------------|----------|-------------------------|---------|------|-----------|
| rs5905513   | 43491842 | Intergenic variant      | G/A     | 0.837| 0.925     |
| rs144551722 | 43491877 | Intergenic variant      | G/A     | 0.784| 0.948     |
| rs5906260   | 43498619 | Intergenic variant      | C/T     | 0.998| 0.999     |
| rs1465108   | 43538209 | Intron variant          | A/G     | 0.995| 0.998     |
| rs909525    | 4355202  | Intron variant          | C/T     | 0.978| 0.991     |
| rs979605    | 43601363 | Intron variant          | A/G     | 0.999| 1         |
| rs2239448   | 43602679 | Intron variant          | T/C     | 0.999| 1         |
Table 2  Association of MAO-A polymorphisms in Swedish 770 males

| SNP          | Control (N = 516) | GBM case (N = 175) | Non GBM case (N = 79) | p Value for GBM | p Value for non GBM |
|--------------|-------------------|--------------------|------------------------|-----------------|---------------------|
|              | N (%)             | N (%)              | N (%)                  |                 |                     |
| rs5905513 A | 211 (48.96)       | 84 (61.31)         | 28 (43.75)             | 0.0154          | 0.5198              |
|              | G                 | 220 (51.04)        | 53 (38.69)             | 0.0076          | 0.6865              |
| rs144551722 G | 392 (87.89)       | 148 (96.10)        | 65 (94.20)             | **0.0056**      | 0.1807              |
|              | A                 | 54 (12.11)         | 6 (3.90)               | 0.0089          | 0.8017              |
| rs5906260 T | 337 (65.31)       | 134 (76.57)        | 54 (86.35)             | 0.0108          | 0.5621              |
|              | C                 | 179 (34.69)        | 41 (23.43)             | 0.0148          | 0.7363              |
| rs1465108 G | 333 (64.91)       | 133 (76.00)        | 53 (67.09)             | 0.0167          | 0.7617              |
|              | A                 | 180 (35.09)        | 42 (23.43)             | 0.0148          | 0.7363              |
| rs909525 T  | 317 (62.52)       | 128 (73.56)        | 52 (66.67)             | 0.0108          | 0.5621              |
|              | C                 | 190 (37.48)        | 46 (26.44)             | 0.0108          | 0.5621              |
| rs979605 G  | 340 (65.89)       | 133 (76.00)        | 54 (68.35)             | 0.0108          | 0.5621              |
|              | A                 | 34 (6.30)          | 2 (1.20)               | 0.000           | 0.000               |
| rs2239448 C | 339 (62.52)       | 133 (76.00)        | 54 (68.35)             | 0.0148          | 0.7363              |
|              | T                 | 177 (37.48)        | 42 (24.00)             | 0.0148          | 0.7363              |

Bold is used to highlight significant p-values after Bonferroni correction for 7 tests (p = 0.05/20 = 0.0072)

Table 3  Association of MAO-A polymorphisms in Swedish 530 females

| SNP          | Control (N = 360) | GBM Case (N = 94) | Non GBM case (N = 76) | p Value for GBM | p Value for non GBM |
|--------------|-------------------|-------------------|------------------------|-----------------|---------------------|
|              | N (%)             | N (%)             | N (%)                  |                 |                     |
| rs5905513 AA | 68 (28.94)        | 9 (16.36)         | 15 (30.00)             | 0.0889          | 0.2147              |
|              | AG                | 112 (47.66)       | 27 (49.09)             | 18 (36.00)      | 0.000               |
|              | GG                | 55 (23.40)        | 19 (34.55)             | 17 (34.00)      | 0.000               |
| rs144551722 GG| 230 (79.04)       | 58 (86.57)        | 48 (87.27)             | **0.2769**      | 0.4147*             |
|              | GA                | 58 (19.93)        | 8 (11.94)              | 7 (12.73)       | 0.000               |
|              | AA                | 3 (1.03)          | 1 (1.49)               | 0 (0.00)        | 0.000               |
| rs5906260 TT | 164 (45.81)       | 39 (41.94)        | 38 (50.00)             | 0.2563          | 0.3379              |
|              | CT                | 161 (44.97)       | 40 (43.01)             | 28 (36.84)      | 0.3379              |
|              | CC                | 33 (9.22)         | 14 (15.05)             | 10 (13.16)      | 0.3379              |
| rs1465108 GG | 164 (45.81)       | 38 (41.30)        | 38 (50.00)             | 0.2725          | 0.3759              |
|              | GA                | 160 (44.69)       | 40 (43.48)             | 28 (36.84)      | 0.3759              |
|              | AA                | 34 (9.50)         | 14 (15.22)             | 10 (13.16)      | 0.3759              |
| rs909525 TT  | 149 (43.06)       | 29 (32.58)        | 33 (45.21)             | 0.1544          | 0.4298              |
|              | TC                | 156 (45.09)       | 45 (50.56)             | 28 (38.36)      | 0.4298              |
|              | CC                | 41 (11.85)        | 15 (16.85)             | 12 (16.44)      | 0.4298              |
| rs979605 GG  | 180 (50.00)       | 42 (44.68)        | 37 (48.68)             | 0.1812          | 0.8674              |
|              | GA                | 149 (41.39)       | 38 (40.43)             | 31 (40.79)      | 0.8674              |
|              | AA                | 31 (8.61)         | 14 (14.89)             | 8 (10.53)       | 0.8674              |
| rs2239448 CC | 180 (50.00)       | 42 (44.68)        | 37 (48.68)             | 0.1812          | 0.8674              |
|              | CT                | 149 (41.39)       | 38 (40.43)             | 31 (40.79)      | 0.8674              |
|              | TT                | 31 (8.61)         | 14 (14.89)             | 8 (10.53)       | 0.8674              |

*Fisher exact test
### Table 4  Haplotype analysis of 5 SNPs in the MAO-A gene in 154 Swedish males with glioblastoma and 441 controls

| Haplotypea | Control N (%) | GBM N (%) | OR 95% CI | p Value |
|------------|---------------|------------|-----------|---------|
| GGTGC      | 303 (70.6)    | 126 (29.4) | 1.00      |         |
| GGTAT      | 12 (85.7)     | 2 (14.3)   | 0.40 (0.06, 1.50) | 0.236  |
| GGCGC      | 17 (77.3)     | 5 (22.7)   | 0.71 (0.23, 1.83) | 0.505  |
| GACAT      | 56 (78.9)     | 15 (21.1)  | 0.64 (0.34, 1.15) | 0.155  |
| AACGC      | 10 (90.9)     | 1 (9.1)    | 0.24 (0.01, 1.28) | 0.176  |
| AACAT      | 43 (89.6)     | 5 (10.4)   | 0.28 (0.10, 0.66) | 0.008  |

a SNP numbers: rs144551722, rs1465108, rs909525, rs979605, rs2239448
Global p-value = 0.016

### Table 5  Association of MAO-A polymorphisms in males in the whole GICC cohort

| SNP          | Control (N = 1875) | GBM case (N = 1579) | Non GBM Case (N = 1035) | p Value for GBM | p Value for non GBM |
|--------------|---------------------|---------------------|-------------------------|----------------|---------------------|
| rs5905513    | A  1036 (44.7)      | 913 (57.8)          | 436 (42.1)              | 0.13           | 0.185               |
|              | G  839 (55.3)       | 666 (42.2)          | 599 (57.9)              |                |                     |
| rs144551722  | G  1520 (81.1)      | 1322 (83.7)         | 851 (82.2)              | 0.0441         | 0.455               |
|              | A  355 (18.9)       | 257 (16.3)          | 184 (17.8)              |                |                     |
| rs5906260    | T  1311 (69.9)      | 1122 (71.1)         | 740 (71.5)              | 0.477          | 0.396               |
|              | C  564 (30.1)       | 457 (28.9)          | 295 (28.5)              |                |                     |
| rs1465108    | G  1301 (69.4)      | 1115 (70.6)         | 739 (71.4)              | 0.434          | 0.272               |
|              | A  574 (30.6)       | 464 (29.4)          | 296 (28.6)              |                |                     |
| rs909525     | T  1235 (65.9)      | 1058 (67)           | 703 (67.9)              | 0.492          | 0.268               |
|              | C  640 (34.1)       | 521 (33)            | 332 (32.1)              |                |                     |
| rs979605     | G  1298 (69.2)      | 1105 (70)           | 741 (71.6)              | 0.656          | 0.19                |
|              | A  577 (30.8)       | 474 (30)            | 294 (28.4)              |                |                     |
| rs2239448    | C  1299 (69.3)      | 1104 (69.9)         | 295 (28.5)              | 0.711          | 0.22                |
|              | T  576 (30.7)       | 475 (30.1)          | 740 (71.5)              |                |                     |

### Table 6  Haplotype analysis of 5 SNPs in the MAO-A gene in 2307 males with glioblastoma and 1850 controls from the whole Glioma International Case–Control (GICC) study

| Haplotypea | Control N (%) | GBM N (%) | OR 95% CI | p Value |
|------------|---------------|------------|-----------|---------|
| GGTGC      | 1169 (39.7)   | 1778 (60.3) | 1.00      |         |
| GGTAT      | 56 (48.3)     | 60 (51.7)   | 0.70 (0.48, 1.04) | 0.067  |
| GGCGC      | 66 (41.2)     | 94 (58.8)   | 0.94 (0.67, 1.31) | 0.74   |
| GACAT      | 210 (39.2)    | 326 (60.8)  | 1.02 (0.84, 1.24) | 0.848  |
| AACGC      | 47 (49)       | 49 (51)     | 0.69 (0.45, 1.05) | 0.072  |
| AACAT      | 302 (42.6)    | 407 (57.4)  | 0.89 (0.75, 1.05) | 0.159  |

a SNP numbers: rs144551722, rs1465108, rs909525, rs979605, rs2239448
Global p-value = 0.1
Discussion

The purpose of the present study was to investigate the hypothesis that polymorphisms in the MAO-A-gene are associated with development of glioma in males. As described in the introduction there are several theoretical reasons to assume a potential involvement of the MAO-A-enzyme in glioma development. However, the direct impetus for performing the study was a recently published series of experiments demonstrating direct effects of the MAOA protein on central features of glioma development [30]. The MAO-A-gene is x-linked and variation in the functional MAO-A-LPR is known to interact with androgens in vitro and in vivo [12, 37]. Both facts make it reasonable to assume that the effects would be considerably stronger in males.

The results of the present study are generally in line with these predictions. That is one of the SNPs that was selected to tag the genetic region spanning the MAO-LPR (rs144551722) in the present study was significantly associated with glioblastoma in the Swedish sample. A replication study in the full GICC cohort showed weaker findings, but still confirmed an association between glioblastoma and the G/C variant of the rs144551722.

Taken as a whole our results support the hypothesis that MAOA-genotype may play a role in development of glioblastoma in males. One possible explanation for differences in the strength of results between samples may of course be that the findings are spurious. Among other possible explanations may be that some genetic or environmental risk exposures that interact with the MAOA-genotype may be more common amongst Swedes, or differences in the frequency of the genotype in different populations. So for instance, the MAOA-gene particularly the MAOA-LPR is from behavioral genetics studies known for interacting with environmental factors to predict behavioral outcomes. A similar gene by environment interaction effect in predicting glioma development may have had differential effects in the two case–control sets depending on sociocultural conditions. Furthermore, since the MAOA-LPR is known to influence behavioral outcomes, behavioral differences may also have shaped environmental exposures differently in the two groups. However, no common environmental agents have consistently been associated with glioma risk, apart from the exposure of high dose ionizing radiation, which is a rare event. In our previous studies, we have observed an association with vitamin E, potentially also mediated by the ROS system, but these finding still need independent validation [31].

One important way of further determining whether the tentative general conclusion of a link between development of glioblastoma in males and the rs144551722 is valid will of course be further replication studies. Doing so would be important since an association between rs14551722 and male GBM (as well as a possible association between this disease and MAOA-LPR) would have at least three potentially significant implications for glioma research.

Understanding of the role of monoaminergic pathways in glioma development

As discussed in the introduction there is evidence from previous research to suggest that monoaminergic function might be an important factor in shaping the environment in which gliomas thrive [23–30]. There is also additional evidence to suggest that the MAO-A enzyme may be a key player in regulating these systems [21]. One of the most important aspects of a link between glioma development and MAO-A-genotype is as a validation of this line of inquiry in glioma research.

Strengthening the logic for clinical trials involving MAO-inhibitors

One possibility suggested by the recent pre-clinical study on glioma development is that MAO-inhibiting drugs might possibly become a useful pharmacological adjunct in the treatment of glioma. A finding of a link between MAO-A-genotype and development of glioblastoma in the present case–control data sets seems to strengthen the logic in pursuing this possibility further.

The possibility of MAO-A-genotype as a clinical marker

From a clinical perspective, gliomas share several common features but there are also important individual differences in essential aspects of the disease. That is, there are considerable variations in for instance growth rate, response to therapeutic interventions etc. between individual glioma cases. Although there are some useful molecular markers that may help clinicians make meaningful differentiations between subgroups of gliomas such as IDH-1 mutation status most such factors remain unknown. Could MAO-A genotype status eventually prove to be a useful clinical marker in glioma cases? Our study does not provide an answer to this question but does suggest that further investigation of this possibility in future studies might be meaningful.

As described above both a strength and a weakness of the present study was that it utilized an evidence-based candidate-gene approach. That is, the study was a direct test of a hypothesis derived from previous research. The advantage is that positive findings made in this way will tend to make biological sense, and that it allows for the discovery...
of statistically meaningful effects that are not as extreme as those required in theory blind approaches.

However, it should in this context be noted that the rs144551722 has no demonstrated functionality in itself. Instead, it was selected for study because of its close proximity to the MAOA-LPR region which is known to be functional [7, 8]. The question whether future replications can validate our findings will of course be important since, experience shows that false positive findings in candidate gene studies have been a common feature in the literature. Such studies would of course also benefit from direct genotyping of the MAOA-LPR.

In summary, the results of the present study need additional replication, and a larger sample size, but tentatively suggest the possibility that MAOA-genotype might be associated with glioma development in males. If true, these findings open opportunities for further research concerning glioma tumorigenesis, possible therapeutic effects of MAO-inhibitors, and the possible predictive value of MAOA-genotype as a diagnostic marker in males.

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Compliance with ethical standards

Conflicts of interest None of the authors have any conflicts of interest to declare.

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References

1. Crocetti E, Trama A, Stiller C, Caldarella A, Soffietti R, Jaal J, Weber DC, Ricardi U, Slowinski J, Brandes A, RARECARE Working Group (2012) Epidemiology of glial and non-gliarial brain tumours in Europe. Eur J Cancer. 48(10):1532–1542. https://doi.org/10.1016/j.ejca.2011.12.013

2. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Cronin K, Chen HS, Feuer EJ, Stinchcomb DG, Edwards BK (eds) SEER Cancer Statistics Review, 1975–2007, National Cancer Institute. Bethesda, https://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER web site, 2010

3. Melin BS, Barnholtz-Sloan JS, Wrensch MR, Johansen C, Il’yasova D, Kinnersley B, Ostrom QT, Labreche K, Chen Y, Armstrong G, Liu Y, Eickel-Passow JE, Decker PA, Labusisère M, Idhaib A, Hoang-Xuan K, Di Stefano AL, Mekhtiari K, Delattre JY, Broderick P, Galan P, Gouskias K, Schramm J, Schoemaker MJ, Fleming SJ, Herms S, Heilmann S, Nöthen MM, Wichmann HE, Schreiber S, Swerdlov A, Lathrop M, Simon M, Sanson M, Andersson U, Rajaraman P, Chanock S, Linet M, Wang Z, Yeager M, GliomaScan Consortium, Wienecke JK, Hansen H, McCoy L, Rice T, Kosel ML, Sicotte H, Amos CI, Bernstein JL, Davis F, Lachance D, Lau C, Merrell RT, Schildkraut J, Ali-Osman F, Sadetzki S, Scheurer M, Shete S, Lai RK, Claus EB, Olson SH, Jenkins RB, Houlston RS, Bondy ML (2017) Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. Nat Genet. 49(5):789–794. https://doi.org/10.1038/ng.3823

4. Ostrom QT, Kinnersley B, Wrensch MR, Eickel-Passow JE, Armstrong G, Rice T, Chen Y, Wienceke JK, McCoy LS, Hansen HM, Amos CI, Bernstein JL, Claus EB, Lachance DH, Lai RK, Merrell RT, Olson SH, Sadetzki S, Schildkraut J, Shete S, Rubin JB, Lathia JD, Berens ME, Andersson U, Rajaraman P, Chanock SJ, Linet MS, Wang Z, Yeager M, Houlston RS, Jenkins RB, Melin B, Bondy ML, Barnholtz-Sloan JS (2018) Sex-specific glioma genome-wide association study identifies new risk locus at 3p21.31 in females, and finds sex-differences in risk at 8q24.21. Sci Rep 8:7352. https://doi.org/10.1038/s41598-018-24580-z

5. Lan NC, Heimann C, Gal A, Klisak I, Orth U, Lai E et al (1989) Human monoamine oxidase A and B genes map to Xp 11.23 and are deleted in a patient with Norrie disease. Genomics 4:552–559

6. Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA (1993) Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science 262(5133):578–580

7. Sabol SZ, Hu S, Hamer D (1998) A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet 103:273–279

8. Deckert J, Catalanò M, Syagailo YY, Bosi M, Okladnova O, Di Bella D et al (1999) Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum Mol Genet 8:2037–2042. https://doi.org/10.1093/hmg/8.20.2037

9. Caspi A, McClay J, Moffitt TE, Craig IW et al (1996) Role of genotype in the cycle of violence in maltreated children. Science 274:456–460

10. Leppert J, Ohrvik J, Alm PO, Lindström L, Oreland L (2006) Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal behaviour. Acta Psychiatr Scand 113(1):51–58

11. Schoemaker MJ, Fleming SJ, Heilmann S, Nöthen MM, Wichmann HE, Schreiber S, Swerdlov A, Lathrop M, Simon M, Sanson M, Andersson U, Rajaraman P, Chanock S, Linet M, Wang Z, Yeager M, GliomaScan Consortium, Wienecke JK, Hansen H, McCoy L, Rice T, Kosel ML, Sicotte H, Amos CI, Bernstein JL, Davis F, Lachance D, Lau C, Merrell RT, Schildkraut J, Ali-Osman F, Sadetzki S, Scheurer M, Shete S, Lai RK, Claus EB, Olson SH, Jenkins RB, Houlston RS, Bondy ML (2017) Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. Nat Genet. 49(5):789–794. https://doi.org/10.1038/ng.3823

12. Ostrom QT, Kinnersley B, Wrensch MR, Eickel-Passow JE, Armstrong G, Rice T, Chen Y, Wienceke JK, McCoy LS, Hansen HM, Amos CI, Bernstein JL, Claus EB, Lachance DH, Lai RK, Merrell RT, Olson SH, Sadetzki S, Schildkraut J, Shete S, Rubin JB, Lathia JD, Berens ME, Andersson U, Rajaraman P, Chanock SJ, Linet MS, Wang Z, Yeager M, Houlston RS, Jenkins RB, Melin B, Bondy ML, Barnholtz-Sloan JS (2018) Sex-specific glioma genome-wide association study identifies new risk locus at 3p21.31 in females, and finds sex-differences in risk at 8q24.21. Sci Rep 8:7352. https://doi.org/10.1038/s41598-018-24580-z
functional MAO-A VNTR and testosterone predicts antisocial behavior. Neuropsychopharmacology 33(2):425–430

Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Hariri AR, Pezawas L, Blasi G et al (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. Proc Natl Acad Sci USA 103:6269–6274

Passamonti L, Fera F, Magariello A, Cerasa A, Gioia MC, Muglia M, Nicoletti G, Gallo O, Provicinciali L, Quattrone A (2006) Monoamine oxidase-a genetic variations influence brain activity associated with inhibitory control: new insight into the neural correlates of impulsivity. Biol Psychiatry 59(4):334–340

Sjöberg RL, Nilsson KW, Wargelius HL, Leppert J, Lindström L, Oreland L (2006) Adolescent girls and criminal activity: role of MAOA-LPR genotype and psychosocial factors. Am J Med Genet B 144:159–164. https://doi.org/10.1002/ajmg.b.30360

Nikulina V, Widom CS, Brzustowicz LM (2012) Child abuse and neglect, MAOA, and mental health outcomes: a prospective examination. Biol Psychiatry 71(4):350–357. https://doi.org/10.1016/j.biopsych.2011.09.008

Harro J, Oreland L (2016) The role of MAO in personality and drug use. Prog Neuropsychopharmacol Biol Psychiatry 69:101–111. https://doi.org/10.1016/j.pnpbp.2016.02.013

Caragher SP, Hall RR, Ahsan R, Ahmed AU (2018) Monoamines in glioblastoma: complex biology with therapeutic potential. Neuro Oncol 20(8):1014–1025. https://doi.org/10.1093/neuonc/nox210

Baker SA, Baker KA, Hagg T (2004) Dopaminergic nigrostriatal projections regulate neural precursor proliferation in the adult subventricular zone. Eur J Neurosci 20(2):575–579

Höglinger GU, Rizk P, Muriel MP et al (2004) Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 7(7):726–735

Winner B, Desplats P, Hagl C et al (2009) Dopamine receptor activation promotes adult neurogenesis in an acute Parkinson model. Exp Neurol 219(2):543–552

Brezun JM, Daszuta A (1999) Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. Neuroscience 89(4):999–1002

Singh SK, Hawkins C, Clarke ID et al (2004) Identification of human brain tumour initiating cells. Nature 432(7015):396–401

Lee JH, Lee JE, Kahng JY, Kim SH, Park JS, Yoon SJ, Um JY, Kim WK, Lee JK, Park J, Kim EH, Lee JH, Lee JH, Chung WS, Ju YS, Park SH, Chung JH, Kang SG, Lee JH (2018) Human glioblastoma arises from subventricular zone cells with low-level driver mutations. Nature 560(7717):243–247. https://doi.org/10.1038/s41586-018-0389-3

Basu S, Sarkar C, Chakraborty D et al (2004) Ablation of peripheral dopaminergic nerves stimulates malignant tumor growth by inducing vascular permeability factor/vascular endothelial growth factor-mediated angiogenesis. Cancer Res 64(16):5551–5555

Sarkar C, Chakraborty D, Chowdhury UR, Dasgupta PS, Basu S (2008) Dopamine increases the efficacy of anticancer drugs in breast and colon cancer preclinical models. Clin Cancer Res 14(8):2502–2510

Björklom B, Wibom C, Jonsson P, Mörlen L, Andersson U, Johannesen TB, Langseth H, Anti H, Melin B (2016) Metabolomic screening of pre-diagnostic serum samples identifies association between α- and γ-tocopherols and glioblastoma risk. Oncotarget 7(24):37043–37053. https://doi.org/10.18632/oncotarget.9422

Wu JB, Shao C, Li X, Li Q, Hu P, Shi C, Li Y, Chen YT, Yin F, Liao CP, Stiles BL, Zhou HE, Shih JC (2014) Chung LW monoamine oxidase A mediates prostate tumorigenesis and cancer metastasis. J Clin Invest 124:2891–2908

Shih JC (2018) Monoamine oxidase isoforms: genes, functions and targets for behavior and cancer therapy. J Neural Transm 125:1553–1566

Kushal S, Wang W, Vaikari VP, Kota R, Chen K, Yeh TS, Jhaiveri N, Groszen SL, Olenyuk BZ, Chen TC, Hofman FM (2016) Shih JC Monoamine* oxidase A (MAO A) inhibitors decrease glioma progression. Oncotarget 7:13842–13853

Amirian ES, Armstrong GN, Zhou R, Lau CC, Claus EB, Sloan JSB, Il’yasova D, Shiddkraut J, Osman FA, Sadetzi K, Johansen C, Houliston RS, Jenkins RB, Lachane D, Olson SH, Bernstein JL, Merrell RT, Wrensch MR, Davis FG, Lai R, Shete S, Amos CI, Scheurer ME, Aldape K, Alafuozoff I, Bräntström T, Broholm H, Collins P, Giannini C, Rosenblum M, Tihan T, Melin BS, Bondy ML (2016) The glioma international case-control study: a report from the genetic epidemiology of glioma international consortium. Am J Epidemiol 183(2):85–91. https://doi.org/10.1093/aje/kwv235

Kersey PJ, Allen JE, Allot A, Barba M, Boddu S, Bolt BJ, Carvalho-Silva D, Christensen M, Davis P, Grabmueller C, Kumar N, Liu Z, Maurel T, Moore B, McDowall MD, Maheswari U, Naamati G, Newman V, Ong CK, Paulini M, Pedro H, Perry E, Russell M, Sparrow H, Tapanari E, Taylor K, Vullo A, Williams G, Zadissia A, Olson A, Stein I, Wei S, Tello-Ruzi M, Ware D, Luciani A, Potter S, Finn RD, Urban M, Hammond-Kosack KE, Bolser DM, De Silva N, Howe KL, Langridge N, Maslen G, Staines DM, Yates A (2018) Ensembl genomes 2018: an integratedomics infrastructure for non-vertebrate species. Nucleic Acids Res 46(D1):D802–D808. https://doi.org/10.1093/nar/gkw1011

Howie B, Fuchsberger C, Stephens M, Marchini J (2012) Abecasis GR Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat Genet 44(8):955–959. https://doi.org/10.1038/ng.2354

Howie B, Marchini J, Stephens M (2011) Genotype imputation with thousands of genomes. G3 (Bethesda) 1: (6):457–470. https://doi.org/10.6018/g3.111.001198

Howie BN, Delaneau O, Marchini J, Zagury JF (2011) A linear and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet 5(6):e1000529. https://doi.org/10.1371/journal.pgen.1000529

Delaneau O, Marchini J, Zagury JF (2011) A linear complexity phasing method for thousands of genomes. Nat Methods 9(2):179–181

Ou XM, Chen K, Shih JC (2006) Glucocorticoid and androgen activation of monoamine oxidase A is regulated differently by R1 and Sp1. J Biol Chem 281(30):21512–21525