An integrated genomic analysis of anaplastic meningioma identifies prognostic molecular signatures

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Introduction

Anaplastic meningioma is a rare and aggressive brain tumor characterised by intractable recurrences and dismal outcomes.

Methods

Here, we present an integrated analysis of the whole genome, transcriptome and methylation profiles of primary and recurrent cohort of 50 anaplastic meningiomas.

Figure 1

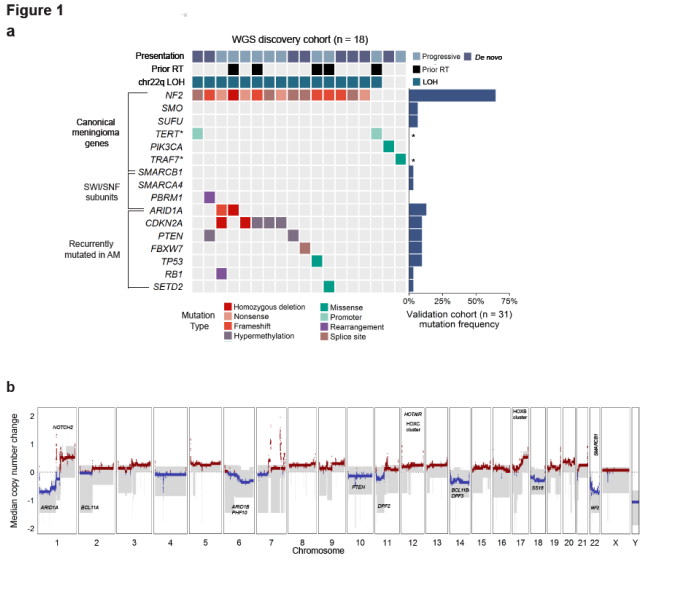

Figure 1 | The landscape of driver mutations and copy number alterations in anaplastic meningioma. (a) The landscape of somatic driver variants in primary anaplastic meningioma. Somatic mutation and promoter methylation data is shown for a discovery cohort of 18 primary tumours characterised by whole genome sequencing. Mutations in recurrently mutated genes, established meningioma genes and SWI/SNF complex subunits are included. Samples are annotated for chromosome 22q LOH, prior radiotherapy exposure, and clinical presentation (*de novo* verus progression from a lower grade meningioma). The barchart to the right indicates mutation frequency in a validation cohort of 31 primary tumors sequenced with a 366 cancer gene panel. Asterisks indicate genes not included in the targeted sequencing assay. **(c)** Aggregate copy number profile of primary anaplastic meningioma. For the 18 tumors characterised by whole genome sequencing, the median relative copy number change was calculated across the genome in 10 kilobase segments, adjusting for ploidy. The grey shaded area indicates the first and third quantile of copy number for each genomic segment. The solid red and blue lines represent the median relative copy number gain and loss, respectively, with zero indicating no copy number change. X-axis: Chromosomal position. Y-axis: median relative copy number change. Potential target genes are noted. AM, anaplastic meningioma; LOH, loss of heterozygosity; RT, radiotherapy.

Results

A key finding was the delineation of two distinct molecular subgroups that were associated with diametrically opposed survival outcomes.

Relative to lower grade meningiomas, anaplastic tumors harbored frequent driver mutations in SWI/SNF complex genes, which were confined to the poor prognosis subgroup.

Figure 2

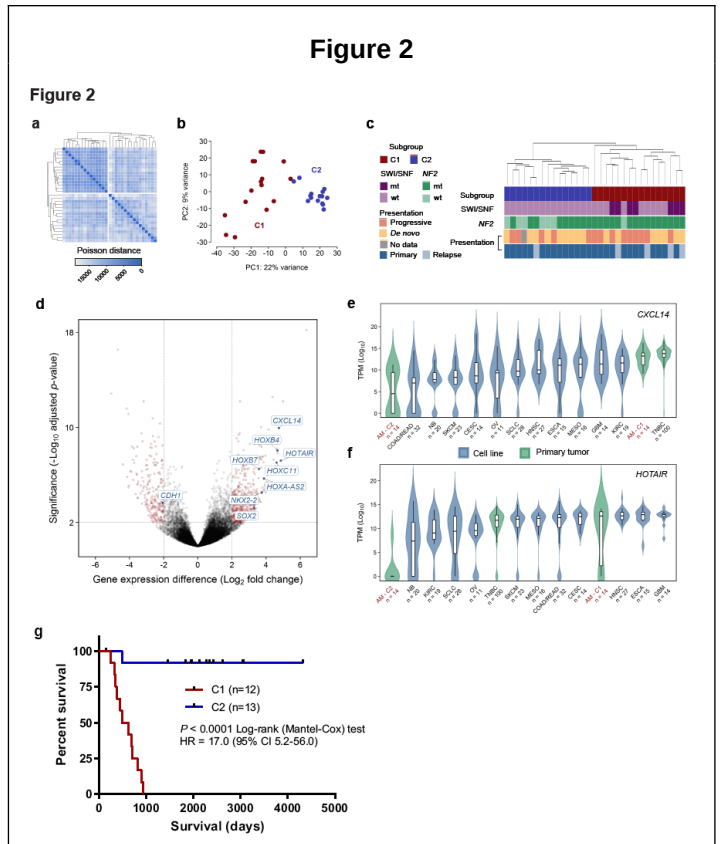

Figure 2 | Transcriptomic classification of anaplastic meningioma. (a) Unsupervised hierarchical clustering and **(b)** Principal component analysis of anaplastic meningioma gene expression revealed two subgroups (denoted C1 and C2). **(c)** Dendrogram obtained by unsupervised clustering annotated with clinical and genomic features. **(d)** Volcano plot depicting genes differentially expressed between C1 versus C2 anaplastic meningioma samples. The horizontal axis shows the $\log_2$ fold change and the vertical axis indicates the $-\log_{10}$ adjusted *p*-value. Genes with an adjusted *p*-value < 0.01 and absolute $\log_2$ fold change > 2 are highlighted in red with particular genes of interest indicated. **(e, f)** Box plots of (e) CXLC14 and (f) HOTAIR expression across 31 anaplastic meningomas classified into C1 and C2 subgroups, 100 primary breast tumors, and 219 cancer cell lines from 11 tumor types. Upper and lower box hinges correspond to first and third quartiles, horizontal line and whiskers indicate the median and 1.5-fold the interquarntile range, respectively. Underlying violin plots show data distribution and are color-coded according to specimen source (blue, cell line; red, pimary tumor). **X-axis indicates tumor type and number of samples in cohort.** Y-axis shows NF2 Log_{10} TPM values. **(g)** Kaplan-Meier curves showing overall survival for 25 (of 28) anaplastic meningioma patients in C1 and C2 subgroups for whom follow-up data was available. Dashes indicate timepoints at which subjects were censored at time of last follow-up. TPM, transcripts per kilobase million; AM, anaplastic meningioma; TNBC, triple negative breast carcinoma; wt, wild-type; mt, mutated; HR, hazard ratio; CI, confidence interval; PC, principal component.

Figure 3

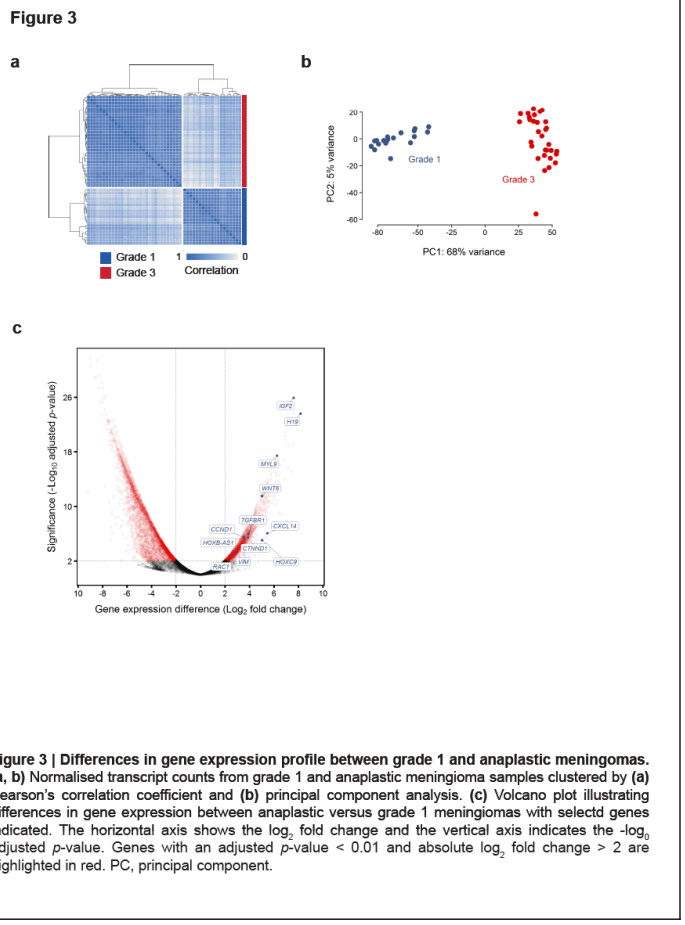

Figure 3 | Differences in gene expression profile between grade 1 and anaplastic meningomas. (a, b) Normalised transcript counts from grade 1 and anaplastic meningioma samples clustered by **(a)** Pearson's correlation coefficient and **(b)** principal component analysis. **(c)** Volcano plot illustrating differences in gene expression between anaplastic versus grade 1 meningiomas with selectd genes indicated. The horizontal axis shows the $\log_2$ fold change and the vertical axis indicates the $-\log_{10}$ adjusted *p*-value. Genes with an adjusted *p*-value < 0.01 and absolute $\log_2$ fold change > 2 are highlighted in red. PC, principal component.

Conclusions

Our analyses of the largest cohort of anaplastic meningiomas to date discern two biologically distinct variants of anaplastic meningioma with potential prognostic and therapeutic significance.

Learning Objectives

Histologically diagnosed anapaestic meningiomas comprise of two biologically distinct gripes with very different prognosis.

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