ations to molecularly-classify adult diffuse glioma: IDH mutation and 1p/19q codeletion. TERT promoter mutation has also been shown to be associated with age at diagnosis and patient outcome. We hypothesized that germline variants may increase susceptibility to, or interact with, these somatic alterations to accelerate the development of specific molecular subtypes of glioma. To test our hypothesis, we performed a GWAS by glioma molecular subtype – as defined by presence or absence of IDH and TERT somatic mutation and 1p/19q codeletion – utilizing a two-stage design and subsequent meta analysis that included 3001 total glioma cases and 2697 total controls. Data were imputed using the Michigan Server and logistic regression was used, adjusting for age and sex. The Cancer Genome Atlas (TCGA) data were used to perform an expression quantitative trait loci (eQTL) analysis on candidate germline variants. Variants in 2q37 and 7p22 were associated with IDH-mutated glioma (meta analysis p< 5x10-8). The eQTL analyses demonstrated significant associations between 2q37 variants and expression of nearby genes as well as associations between 7p22 variants and nearby genes (p< 0.0001). In conclusion, we identified and validated novel germline variants in two genes that are associated with etiology of IDH-mutated adult diffuse glioma.

GENE-26. HOST GENETIC VARIATIONS IN MACROPHAGE MIGRATION INHIBITOR FACTOR CONFER WORSE PROGNOSIS IN GLIOBLASTOMA

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Genetic and systemic prognostic factors have been identified in glioblastoma (GBM) that correlate with survival, but patient-specific genomic risk factors that impact prognosis or response to immunotherapies have not been elucidated. GBM promotes an immune suppressive microenvironment via many mechanisms including the production of macrophage migration inhibitory factor (MIF) by GBM cancer stem cells, which activates myeloid derived suppressor cells (MDSCs). Increased circulating and intracranial MDSCs as well as intratumoral MIF expression in GBM patients portend a worse overall prognosis. Endogenous MIF expression is dependent on two genetic microsatellite loci: single nucleotide polymorphisms (SNPs) and CATT repeats within the promoter. To determine whether these genetic variations were linked to GBM development and/or prognosis, we assessed peripheral nucleated blood from 520 GBM patients for the MIF SNPs and CATT repeats. MIF microsatellite frequencies were similar between the normal population and GBM patients indicating loci variability was not a risk factor for GBM development. However, newly diagnosed IDH wild-type GBM patients with a minor allele SNP who received standard of care therapy had a 3.1 month shorter progression free survival (PFS), and a 4.3 month shorter overall survival (OS) when compared to patients with two major allele SNPs. This association was seen also with the CATT-repeat analyses. Furthermore, in a multivariate analysis for PFS that included age, sex, Karnofsky performance status, MGMT methylation status, 1p/19q co-deletion, and SNP status as covariates, only age and SNP status were independently associated with shorter PFS. Taken together, patients with variant MIF microsatellite loci experienced shorter PFS and decreased OS compared to those with the most common loci. These results are currently being validated in a separate 1700 patient cohort with the intent of understanding how MIF expression influences myeloid populations within the GBM microenvironment and then developing novel peripheral GBM screening markers for aggressiveness.

GENE-27. MENINGIOMA RECURRENCE: ROLE OF M1/M2 TUMOUR-ASSOCIATED MACROPHAGE INFILTRATION

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BACKGROUND: Meningioma, a most common brain tumour, has a high rate of recurrence. Tumour-associated macrophages (TAMs) are the most abundant immune cell type in meningioma. TAMs display functional phenotypic diversity and may establish either an inflammatory and anti-tumoural or an immunosuppressive and pro-tumoural microenvironment. TAM subtypes present in meningioma and potential contribution to growth and recurrence is unknown. METHODS: Fluorescence immunohistochemistry was used to evaluate the distribution and quantify M1 and M2 TAM populations in 30 meningioma tissues. Association between quantified M1 and M2 cells and M1/M2 ratio to tumour characteristics including WHO grade, tumour recurrence, size, location, peri-tumoural edema and patient demographics such as age and sex was examined. RESULTS: TAM cells accounted for ~17% of all cells in tumour tissues. Importantly, greater than 80% of infiltrating TAMs were discovered to be of a polarized pro-tumoural M2 phenotype which positively associated with tumour size. TAM subtype profiles differed significantly between non-recurrent (n=18) and recurrent meningioma (n=12) (P=0.044). Specifically, the M1/M2 cell ratio was decreased by ~250% in recurrent tumours. CONCLUSION: This study is the first to confirm existence of pro-tumoural M2 TAMs in the meningioma microenvironment and a potential role in tumour growth and recurrence.

GENE-28. LONGITUDINAL MOLECULAR TRAJECTORIES OF DIFFUSE GLIOMA IN ADULTS

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Treatment options for adult patients with glioma has remained largely unchanged over the past three decades. Targeted inhibitors and immunotherapies have improved outcomes for many cancer types but their relevance in glioma is unclear. The inevitability of glioma disease recurrence demands an understanding of mechanisms driving therapy resistance. The Glioma Longitudinal Analysis (GLASS) *Consortium* was initiated to establish a definitive portrait of the recurrence process and to discover vulnerabilities that render the tumor sensitive to therapeutic intervention. GLASS is a community-driven effort that seeks to overcome the logistical challenges in constructing adequately powered longitudinal genomic glioma datasets by pooling data from patients treated at institutions worldwide. Currently, the GLASS Data Resource comprises DNA sequencing data (exome and/or whole-genome) from 288 patients of whom high-quality data in at least two time points are present from 222 patients (n = 134 IDHwt, n = 63 IDHmutant-noncodel, n = 25 IDHmutant-codel). We inferred longitudinal mutation, copy number, clonal frequency, and neoantigen profiles and demonstrated that driver genes found at initial disease persisted into recurrence. Treatment with alkylating-agents resulted in a hypermutator phenotype at different rates across glioma subtypes, most frequently among IDHmutant-noncodels, and hypermutation was not associated with differences in overall survival. Acquired aneuploidy was frequently detected in recurrent IDHmutant-noncodel gliomas and further converged with acquired cell cycle pathway alterations and poor outcomes. We showed that the clonal architecture of each tumor remains largely intact over time and that genetic drift was associated with increased survival. Finally, we found that neoantigens were exposed to stable selective pressures throughout a tumor's progression. Our results collectively suggest that the strongest selective pressures occur early during glioma development and that current therapies shape this evolution in a largely stochastic manner. The GLASS Data Resource provides a genomic reference to study the patterns of glioma evolution.

GENE-29. INCREASED COPY NUMBER BURDEN (CNB) IS ASSOCIATED WITH GRADE IN IDH-MUTANT, 1p/19q-CODELETED OLIGODENDROGLIOMAS.

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BACKGROUND: Oligodendrogliomas are classified as either WHO grade II or III depending on histologic features. Grade often influences treatment decisions. However, there is variability in patient outcome within tumors of similar grade. We hypothesized that copy number burden (CNB) and specific copy number variants (CNV) might be associated with oligodendroglioma grade and prognosis. METHODS: Copy number array analyses were performed on 285 molecular oligodendrogliomas (IDH-mutant, 1p/19q-whole arm-codeleted) from the Mayo Clinic internal and consult neuropathology practice and 167 TCGA molecular oligodendrogliomas. CNB was defined as the total number of copy number alterations. The association of CNB and CNV with grade and overall survival (when available) was assessed. All Mayo and TCGA data were evaluated using the ChAS software suite (Thermo- Fisher) and blindly reviewed by a clinical cytogeneticist (RBJ). RESULTS: The mean CNB was 5.0 and 10.4 in the Mayo WHO grade II and III oligodendrogliomas, respectively ($p = 5.4 \times 10^{-17}$). Among the TCGA WHO grade II and III oligodendrogliomas the mean CNB was 4.4 and 5.3, respectively ($p = 0.034$). Common CNVs (occurring in at least 5% of cases) were -4/4q-, +8/8q+, -9/9p-/cnLOH 9p, +11/11q+, -14/14q-, -15 and -18/18q-. Of these, -9/9p-/cnLOH 9p was significantly associated with higher grade in both the Mayo and TCGA cohorts ($p = 8.3 \times 10^{-10}$ and 0.018, respectively). In the TCGA cohort the presence of >10 CNVs or +11/11q+ was associated with a poorer survival ($p = 0.016$ and 0.006, respectively). CONCLUSIONS: CNB is significantly associated with WHO grade in IDH-mutant,