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Presentation Abstract

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Presentation Title:	Comprehensive and integrative genomic characterization of diffuse lower grade gliomas
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Abstract Body:

Background
Diffuse lower grade gliomas (LGGs) are infiltrative neoplasms of the central nervous system that include astrocytoma, oligodendroglioma and oligo-astrocytoma histologies of grades II and III. We present a comprehensive analysis of 293 LGGs using multiple advanced genomic, transcriptomic and proteomic platforms from The Cancer Genome Atlas to provide a deeper understanding of the molecular features of this group of neoplasms, to classify them in a clinically-relevant manner, and to provide a public resource that identifies potential targets for emerging therapies.

Results
Clustering of gene expression, miRNA expression, protein expression, DNA methylation and DNA copy number profiles identified respectively four, four, four, five and three clusters. When combined, the clustering results overwhelmingly pointed towards a natural grouping of LGG into three superclusters, which can be explained as follows: 1. *IDH1/IDH2* wildtype 2. *IDH1/IDH2* mutant and chromosome arms 1p/19q intact 3. *IDH1/IDH2* mutant and co-deletion of chromosome arms 1p/19q. The three groups all included samples from grade II and III astro-, oligo- and oligo-astrocytoma histologies. Based on this result we evaluated genomic alterations according to these three LGG categories.
The *IDH* wildtype subtype was characterized by a GBM like phenotype, included focal gains of *EGFR*, *CDK4* and *MDM4*, mutations in *NF1*, *EGFR* and *PTEN*, and a GBM like poor median outcome of 18 months. Approximately 55% of these cases were grade III (anaplastic) astrocytomas, while the remainder were from a mixed grade and histology. The *IDH* mutant/1p-19q intact group showed focal amplification of *PDGFRA*, *MYC* and *CCND2*, 100 % mutated *TP53* and 80% with mutations in *ATRX*. This group was not dominated by a single grade or histology, but represented all types. Finally, the *IDH* mutant and 1p/19q co-deleted subtype harbored frequent mutations in *CIC*, *FUBP1*, *NOTCH1*, *TERT*, relatively few copy number alterations and was populated for 84% by oligodendrogliomas. The two *IDH* mutant groups associated with a favorable median survival of 90 months.

Discussion
Based on integrated analysis of genome, transcriptome, methylome and proteome we showed that LGG naturally separates into three distinct groups that traversed grades and histologies. Importantly, we identified a subtype with an LGG-like histology but a molecular GBM profile, suggesting that the GBM standard of care, concomitant radiotherapy and temozolomide, may be warranted for these patients. We propose that classification of LGG should be revised based on *IDH1/IDH2* mutation and 1p/19q deletion status.

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