Integrative genomic and transcriptome analysis of oligodendroglioma using next generation sequencing technology

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Oligodendroglioma (ODG) constitutes a clinically, pathologically and molecularly unique subset of primary glial brain tumour. There is a definitively linked deletion of chromosome 1p and 19q in patients with ODG with prolonged survival and improved response to chemotherapy. However, the molecular mechanisms leading to better prognosis in these patients are not yet understood, and to date, no genome-wide sequencing studies have been performed on oligodendroglial neoplasms.

To characterize the whole genomes of two 1p/19q co-deleted ODG brain tumour initiating cell lines (ODG BTICs) we performed whole genome shotgun sequencing to 30X haploid coverage using the SOLiD technology. We also generated whole genome sequencing data from matched normal peripheral blood DNA. We used this data to identify 2582 candidate somatic mutations. To assess the relevance of the identified mutations to primary tumors, we performed whole exome Illumina sequencing of a panel of 15 1p/19q-codeleted primary tumors and whole transcriptome sequencing of 5 of those including the tumours matched to the two ODG BTICs. .

We clearly identified the 1p/19q co-deletion in the ODG BTICs based on CNV and LOH analysis, along with a number of other chromosomal aberrations. We have identified the canonical R132H mutation in *IDH1* along with somatic mutations in other genes of interest such as *ARID1A* and *MSH6*. We have characterized changes in gene expression and we're using de novo assembly to identify novel splicing and gene fusion events from the transcriptome data. In addition, the exome sequencing data is being used to identify large scale deletions and copy number variations.

We hypothesize that unlike other forms of brain cancer such as glioblastoma multiforme (GBM) that presents with a number of driver mutations, ODG manifests through changes in metabolic pathways. When compared to a larger cohort, we hope to identify recurrent events that would lead to a better understanding of the biology of these tumors, and potentially, the discovery of druggable targets.