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Molecular and Prognostic Heterogeneity within *MYC* and *MYCN* Amplified Medulloblastomas.

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Molecular and prognostic heterogeneity within *MYC* and *MYCN* amplified medulloblastomas

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MYC and *MYCN* are the most commonly amplified oncogenes in medulloblastoma; their association with poor prognosis in disease-wide studies has supported their adoption as high-risk disease biomarkers in current clinical trials. However, recent observations suggest some patients with *MYC*/*MYCN* amplified tumours achieve long term survival and may suffer unnecessary side effects associated with intensified therapies. To further understand this heterogeneity, we characterised the molecular, clinical and pathological features of focussed cohorts of *MYC* (n=37) and *MYCN* (n=57) amplified tumours (identified by FISH and/or copy number profiling), and assessed their associations with disease outcome. Within the *MYCN* cohort (24 $MYCN_{SHH}$; 24 $MYCN_{Group4}$; 3 $MYCN_{Group3}$; 6 NA), patient survival was subgroup-dependent; patients with $MYCN_{Group4}$ and no other clinico-pathological risk factors (subtotal resection, metastatic disease or LCA pathology) had a favourable event free survival (EFS). In contrast, $MYCN_{SHH}$ was associated with LCA ($MYCN_{SHH}$ vs $MYCN_{Group4}$, p< 0.0001) and a dismal EFS regardless of additional risk factors. *TP53* mutation was a frequent feature of $MYCN_{SHH}$ (12/23), usually in conjunction with Chromosome 17p loss and *GLI2* amplification, and conferred a quicker time to progression within $MYCN_{SHH}$ (p=0.05). LCA pathology was the poorest prognostic factor in *MYC*-amplified tumours. The majority (20/30) of sub-grouped *MYC*-amplified tumours were MYC_{Group3}. Rare MYC_{Group4} tumours (5/30), had fewer (<50%) amplified tumour cells and a better EFS than MYC_{Group3} (p=0.04). These data highlight the importance of subgroup identification as a basis for refined stratification of medulloblastoma risk using *MYC/MYCN* amplification, and suggest that $MYC/MYCN_{Group4}$ as isolated risk-factors do not confer high-risk disease.

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