SYNDROMES IN PEDIATRIC HIGH-GRADE GLIOMA
HGG-26. MLH1, MSH2, MSH6, AND PMS2 can be explored as potential therapeutic targets in H3 mutated pHGG.

BACKGROUND: High-grade gliomas (HGG) arise in any CNS location with a poor prognosis. HGGs in teenagers/young adults (TYA) are under-studied; this project aimed to characterise these tumours and identify therapeutic targets. METHODS: HGG samples (histone/H3-wildtype, n=207, FFPE/F/FF, 13-30 years) were collected from national/international collaborators. DNA methylation profiling (Illumina EPIC BeadArrays, brain tumour classifier (MNPv12.5 R package) classified cases against reference cohorts.

RESULTS: Of cases scoring >0.5, n=25 classified as PAX and n=8 as HAGAP, differing from primary diagnoses: 53.4% (n=86) classified as pediatric-type subgroups (pedHGG-RTK1A/B/C, 31.7%, n=51, associated with frequent PDGFRA, CDKN2A/B, SETD2, NF1 alterations), pedHGG-MYCN (8.1%, n=13, MYCN/ID2 amplifications), and pedHGG-RTK2A/B (7.5%, n=12). 18.0% (n=29) classified as subgroups frequently seen in adults including GBM-MES (15.5%, n=25, enriched for RB1, PTEN, NF1 alterations) and GBM-RTK1/2 (2.5%, n=4, CDK4 amplifications). 16 cases were assigned to novel, poorly-characterised subgroups with distinct methylation profiles and molecular features.
including paediatric-specific pedHGG-A/B (n=10 6.2%) and HGG-E (n=6 3.7%) subgroups, and HGG-B (n=2 1.0%), and GBM-CBM (n=5 3.1%, frequent cerebellar location) subgroups, associated with variable histological morphology. 8 cases showed hypermutator phenotypes, enriched in HGG-E. Age-distribution/molecular profile comparisons using publicly available methylation and sequencing data for HGG-B (n=9), GBM-CBM (n=26) and GBM-MES-ATYP (n=53), irrespective of age, shows they are TYA-specific subgroups with the latter containing fewer chr7 gains and chr10 losses, and more CDKN2A/B deletions and MET amplifications, compared with adult-specific GBM-MES-TYP. Across the cohort, other frequent copy number changes included gains in chr1q (54%, frequent in pedHGG-RTK1B/C/MYC, pedHGG-A/B), chr2 (22%, pedHGG-MYC), and chr13 losses (64%, pedHGG-RTK1B/C), Focal amplifications included CDK6 (1.4%, n=3) and EGRF (1.0%, n=2). CONCLUSION: TYA HGG comprise well-characterised, novel methylation subgroups with distinct methylation profiles and molecular characteristics, representing opportunities to refine treatment.