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Rapid diagnosis of medulloblastoma molecular subgroups.

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Abstract

PURPOSE: Microarray studies indicate medulloblastoma comprises distinct molecular disease subgroups, which offer potential for improved clinical management.

EXPERIMENTAL DESIGN: Minimal mRNA expression signatures diagnostic for the Wnt/Wingless (WNT) and Sonic Hedgehog (SHH) subgroups were developed, validated and used to assign subgroup affiliation in 173 tumours from four independent cohorts, alongside a systematic investigation of subgroup clinical and molecular characteristics.

RESULTS: WNT tumours (12% (21/173)) were diagnosed >5 years of age (peak, 10 years), displayed classic histology, CTNNB1 mutation (19/20), associated chromosome 6 loss and have previously been associated with favourable prognosis. SHH cases (24% (42/173)) predominated in infants (<3 years) and showed an age-dependent relationship to desmoplastic/nodular pathology; all infant desmoplastic/nodular cases (previously associated with a good outcome) were SHH-positive, but these relationships broke down in non-infants. PTCH1 mutations were common (34%; 11/32), but PTCH1 exon1c hypermethylation, chromosome 9q and REN (KCTD11) genetic loss were not SHH-associated, and SMO or SUFU mutation, PTCH1 exon1a or SUFU hypermethylation did not play a role, indicating novel activating mechanisms in the majority of SHH cases. SHH tumours were associated with an absence of COL1A2 methylation. WNT/SHH-independent medulloblastomas (64% (110/173)) showed all histologies, peaked at 3-6 years, and were exclusively associated with chromosome 17p loss.

CONCLUSIONS: Medulloblastoma subgroups are characterised by distinct genomic, epigenomic and clinico-pathological features, and clinical outcomes. Validated array-independent gene expression assays for the rapid assessment of subgroup affiliation in small biopsies, provide a basis for their routine clinical application, in strategies including molecular disease-risk stratification and delivery of targeted therapeutics.

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