Timing of 11p15.5 alterations during development defines different modes of evolution toward hepatoblastoma with various clinical presentations

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Aims: Beckwith-Wiedemann syndrome (BWS), characterized by partial overgrowth due to mosaic genomic/epigenomic alterations of the 11p15.5 locus, predisposes to hepatoblastoma (HB). Furthermore, most HB without predisposition syndrome harbor 11p15.5 alterations acquired during tumorigenesis. We have recently described intermediate cases with localized 11p15.5 mosaicism in the non-tumor liver in the absence of clinical BWS. We aimed to better understand the timing and functional consequences of 11p15.5 alterations.

Methods: In this retrospective study, we screened for 11p15.5 alterations in 77 HB and their non-tumor liver using DNA sequencing, methylation-specific-multiplex-ligation-dependent-probe-amplification (MS-MLPA) assay, and RNAscope in situ hybridization. We used spatial transcriptomics and single-nucleus RNAseq to decipher the mechanisms and consequences of mosaic alterations.

Results: We identified pre-neoplastic mosaic 11p15.5 alterations in 12/76 HB without clinical BWS, with strong enrichment in younger patients, where mosaicism accounted for 22,2% of cases. Patients with mosaicism had no overgrowth and no 11p15.5 alteration in their blood, suggesting that the mosaicism was confined to the liver. Furthermore, single-nucleus RNAseq analysis identified 11p15.5 alteration in hepatocytes and cholangiocytes but not in other liver cell types. Overall, this suggests that localized mosaicism is due to a late alteration during liver development, contrasting with earlier alterations leading to clinical BWS and body-wide effects. However, localized mosaicism had functional consequences, notably the perturbation of liver zonation.

Conclusions: The identification of frequent 11p15.5 mosaicism broadens the number of HB cases with predisposition. We recommend systematic screening of non-tumor liver to enhance our understanding of different modes of tumor evolution.

Keywords: hepatoblastoma; 11p15.5; mosaicism; predisposition; Beckwith-Wiedemann syndrome