Correspondence

Beckwith-Wiedemann Syndrome, Pancreatoblastoma, and the Wnt Signaling Pathway

To the Editor-in-Chief:

In a recent issue of *The American Journal of Pathology*, Abraham et al¹ reported frequent alterations in the wnt signaling pathway and chromosome 11p LOH (loss of heterozygosity) in sporadic and familial adenomatous polyposis-associated pancreatoblastomas. The molecular association between pancreatoblastoma and other embryonal tumors such as hepatoblastoma and Wilm's tumor has been previously suggested by the presentation of Beckwith-Wiedemann in children with these tumors.²⁻⁴ However, the study of Abraham et al¹ did not describe any case of pancreatoblastoma presenting with Beckwith-Wiedemann syndrome.

Here we report a case of pancreatoblastoma presenting in a four-year-old male with incomplete Beckwith-Wiedemann syndrome, consisting of hemihypertrophy of the right foot and leg (case 1). On examination the tumor was shown to have LOH of 11p, which included the 11p15 BWS gene region and *IGF2*.⁵ The genetic mechanism underlying this patient's 11p LOH must be constitutional, although only present in the cells of the limb showing hemihypertrophy. In contrast, all cases of sporadic pancreatoblastoma presented by Abraham et al¹ would have a tumor-specific 11p 15 LOH which has occurred as a somatic event. A second case of pancreatoblastoma presenting in a three-year-old female showed partial LOH of 11p.

Immunohistochemistry showed accumulation of β -catenin in the cytoplasm and nucleus of both pancreatoblastomas. Case 1 was found to have a missense mutation in exon 3 of the β -catenin gene (CTNNB1) which caused an amino acid substitution of serine 37 (TCT) to a phenylalanine (TTT). Serine 37 is one of the four threonine/serine phosphorylation sites essential for GSK-3 β -dependent phosphorylation and has been characterized as a ubiquitination-targeting motif. This S37F mutation was found in case P4 of Abraham et al.¹ Case P4 also showed 11p LOH, however the parental origin of the lost allele could not be determined. In case 1 described here, LOH of 11p 15.5 was maternal in origin.⁵ As stated by Abraham et al¹ maternal allelic loss of 11p 15.5 would be expected based on data from Wilm's tumor and hepatoblastoma. Sequence analysis of exon 3 in the second case of pancreatoblastoma did not reveal a mutation. Large deletions of the β -catenin NH₂-terminal regulatory

domain have been previously described in melanoma cell lines and colorectal cancers.⁶ Therefore, case 2 was screened for larger deletions using primers that scanned exon 3 and the adjacent introns of CTNNB1. However, a large deletion was not found. In this case nuclear accumulation of β -catenin without mutation of CTNNB1 could be caused by genetic alteration of down-regulators or negative repressors of the CTNNB1 gene such as APC, PP2A, Tef1, or AXIN1. Genes in the Wnt signaling pathway have been found to be mutated in many types of cancer. As case 2 was of Asian descent, mutation of the APC gene may be likely since the Asian population has been shown to have a high incidence of APC mutations leading to cellular β -catenin accumulation in hepatoblastoma.⁷ These cases provide further evidence that alterations in the wnt signaling pathway play a significant role in the progression of pancreatoblastoma tumorigenesis.

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