cohort migration in the form of tubular invasion by far takes the dominating place.

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E-cadherin in solid pseudopapillary tumors of the pancreas-Reply

We appreciate the comments of Dr Chetty regarding our manuscript and agree with the notion that the immunohistochemical staining pattern of E-cadherin in solid pseudopapillary neoplasm (SPN) is dependent on the type of antibody used [1]. The immunohistochemical staining pattern of E-cadherin seems to be determined by which domain is recognized by the antibody. Like the results by Chetty et al, we found that nuclear expression of E-cadherin in 53 (94.7%) of 56 SPN cases was shown using clone 36 directed against the cytoplasmic domain of E-cadherin (BD Transduction Laboratories, Franklin Lakes, NJ, USA) [2], whereas none of 50 cases of SPN showed membranous or nuclear expression for E-cadherin when using clone 4A2C7 directed against the cytoplasmic domain of E-cadherin from Zymed (San Francisco, CA, USA). As for pancreatic endocrine neoplasm (PEN), we did not perform immunohistochemical staining using clone 36. However, we consider that the antibody for E-cadherin we used (clone 4A2C7, Zymed) is more useful in the differential diagnosis between SPNs and PENs because none of PEN cases was positive for E-cadherin in our study, in contrast to the results by Chetty et al in which 59.6% of PEN cases showed loss of membrane expression of E-cadherin [3]. The important thing is that we need to specify the type of antibody used (eg, clone name) because the expression pattern of E-cadherin depends on which antibody for E-cadherin is used. Nuclear expression of E-cadherin has been reported in other neoplasms such as clear cell renal cell carcinoma and Merkel cell carcinoma as well as SPN of pancreas [4,5]; however, the exact mechanism leading to E-cadherin accumulation and nuclear translocation remains to be fully elucidated [6].

We think Dr Chetty raised an important issue that needs to be pointed out. Further investigation is required to understand the biologic significance of aberrant expression of E-cadherin.

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Hep G2 is a hepatoblastoma-derived cell line

To the Editor,

Hepatoblastoma (HB) is an embryonal malignancy of hepatocellular origin and the most common primary liver tumor of childhood, often presenting in the first years of life [1]. Pediatric hepatocellular carcinoma is a rare tumor associated with much worse prognosis and aggressive behavior than HB and significantly less responsive to chemotherapy. It may occur as early as 1 year of age and in children may not be preceded by cirrhosis. Distinguishing between these tumors is sometimes difficult, especially in older children, so our laboratory is developing molecular

genetic tests and has used the well-established cell line Hep G2 for this purpose.

The histologic type of the liver tumor from which the HepG2 cell line was originated has been the subject of significant confusion for almost 30 years. During that time, HepG2 has been widely used in a variety of fields such as liver metabolism, development, oncogenesis (chemocarcinogenesis and mutagenesis), and hepatotoxicity. More than 9000 HepG2 references can be found in the scientific literature (PubMed) from 1979 to March 2009; it is referred to as hepatocarcinoma or hepatoma more than 7000 times and as hepatoblastoma less than 500 times.

The HepG2 cell line was originally established in 1979 by Barbara Knowles and colleagues, and mistakenly reported as a hepatocellular carcinoma [2]. A "Human hepatoma-derived cell line" patent was filed in 1980 by investigators at The Wistar Institute in Philadelphia. Since then, Hep G2 has been listed on the ATCC repository (American Type Culture Collection, Rockville, MD, USA) as a human cell line (HB 8065) "derived from the liver tissue of a 15-year-old white male with a well-differentiated hepatocellular carcinoma." The mistaken classification of the Hep G2 tumor of origin has created confusion between investigators and a divided body of scientific literature.

With the help of Dr Knowles' former colleague, Ivan Damjanov, we had the opportunity to review the histopathologic background of the tumor from which Hep G2 was originated, excised by extended lobectomy from the liver of a 15-year-old white male. The tumor is a classic example of an epithelial hepatoblastoma (Fig. 1). Our group has investigated the Hep G2 genetic profile by array comparative genomic hybridization (CGH) analysis (Fig. 2) and compared it with a series of HB (manuscript in preparation) as well as with previously reported HB karyotypes and CGH profiles. Interestingly, the ATCC (American Type Culture Collection) catalog indicates that HepG2 carries a chromosome 1 rearrangement, as reported in 1980 [3], which was not detected by a CGH, probably due to its balanced nature. However, we did detect losses of the chromosome 4q3 region, which have been associated with the t(1;4) translocation, the most commonly reported translocation in HB [4], as well as other characteristic HB chromosomal abnormalities, including trisomies 2 and 20.

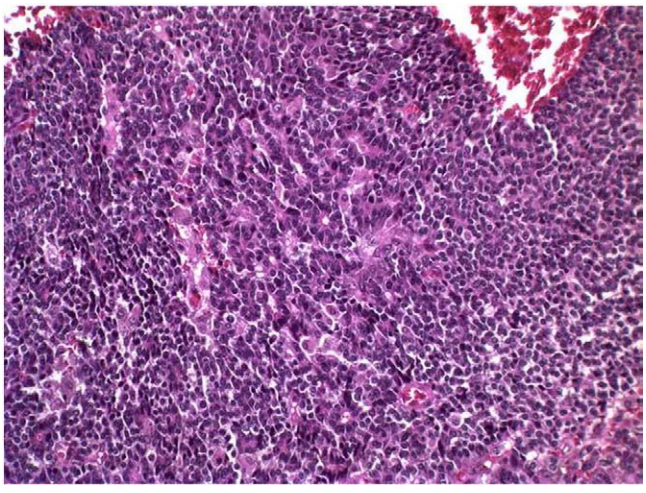

Fig. 1 Original resection specimen. The tumor is composed of small poorly differentiated hepatoblasts that often form small tubules mimicking the embryonal liver (hematoxylin-eosin, original magnification ×250).

Molecular characterization of Hep G2, including signaling pathway analysis, has also demonstrated features of HB. A large deletion of the exon 3 of the β-catenin (*CTNNB1*) gene (a key Wnt pathway molecule mutated in more than 85% hepatoblastomas) identical to those described in epithelial HBs, has been documented in Hep G2 [5]. The Hep G2 gene expression profiling demonstrated, in addition to Wnt pathway activation, cell growth and survival pathways deregulation, similar to that of fetal and embryonal hepatoblastomas [6].

The histopathologic background of this tumor, its genetic profile demonstrating some of the most characteristic HB chromosomal abnormalities, and the presence of β-catenin mutation-associated Wnt pathway activation, provides compelling histologic and biologic evidence that HepG2 originated as a hepatoblastoma and not a hepatocellular carcinoma. We believe the correct attribution of the tumor of origin of this cell line is of crucial interest for investigators studying the biology of hepatocellular neoplasms, particularly those engaged in novel biology-based classifications, clinical stratification, and therapeutic interventions for pediatric and adult patients.

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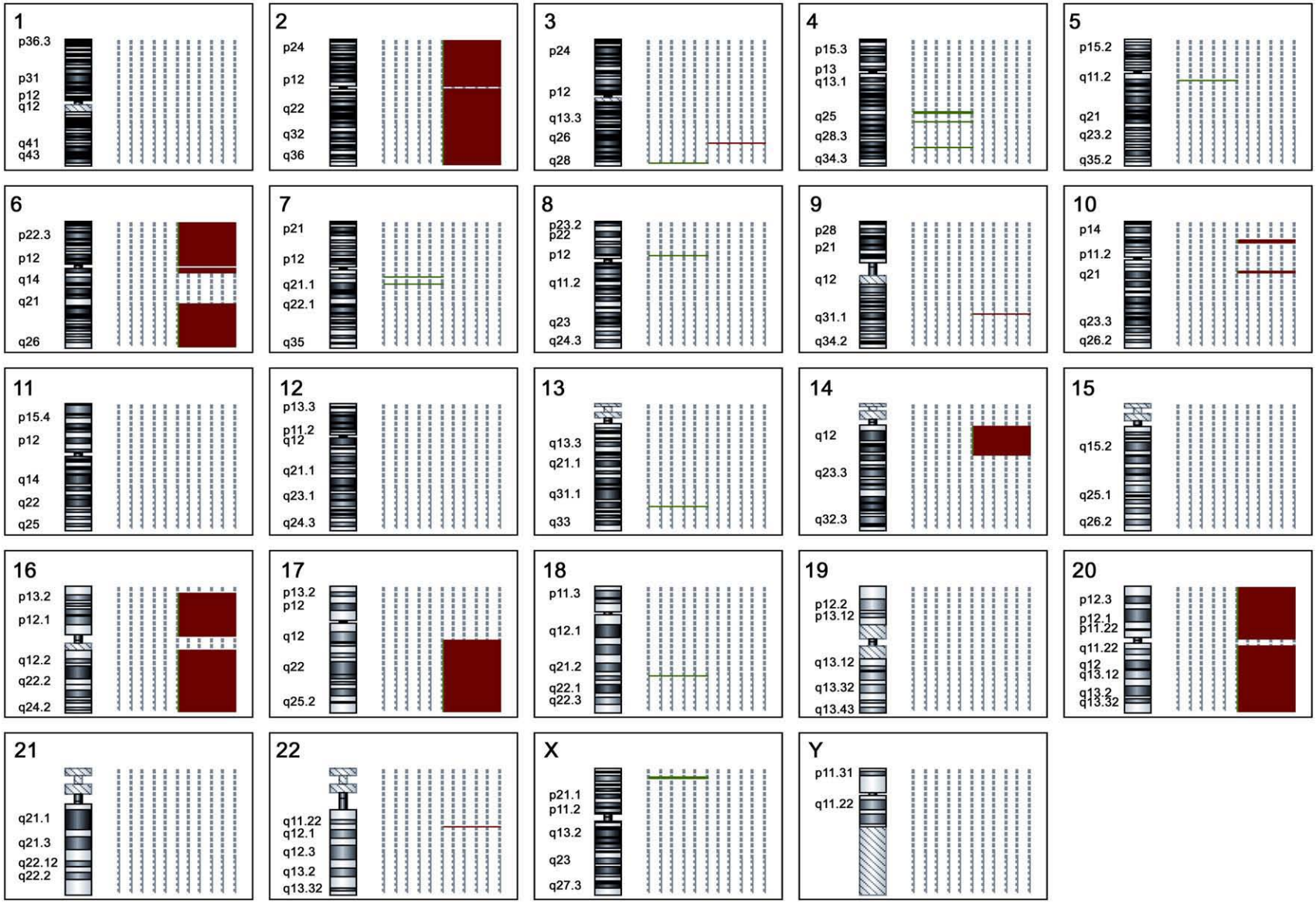

Fig. 2 An overview of copy number changes HepG2 genome using the 244K OLIGO (60 mer) array (Agilent, Santa Clara, CA, USA). The center line for each chromosome represents log ratio equal to zero. Loss in copy number is shown in green, whereas gain in copy number is shown in red. There are whole chromosome copy number gains of chromosomes 2, 16, and 20 and segmental gains involving chromosomes 6, 14, and 17.

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