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REVIEW ARTICLE

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# Hepatoblastoma in molecularly defined, congenital diseases

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## Abstract

Beckwith–Wiedemann spectrum, Simpson–Golabi–Behmel syndrome, familial adenomatous polyposis and trisomy 18 are the most common congenital conditions associated with an increased incidence of hepatoblastoma (HB). In patients with these genetic disorders, screening protocols for HB are proposed that include periodic abdominal ultrasound and measurement of alpha-fetoprotein levels. Surveillance in these children may contribute to the early detection of HB and possibly improve their chances of overall survival. Therefore, physicians must be aware of the high HB incidence in children with certain predisposing genetic diseases.

**KEYWORDS**
cancer predisposition, congenital diseases, hepatoblastoma, screening, surveillance

## 1 | INTRODUCTION

With an estimated incidence of about 1–2 per million children younger than 15 years, hepatoblastoma (HB) is the most common childhood liver malignancy (Feng et al., 2019). The etiology of HB is unknown, and only a few predisposing factors have been defined so far. While the influence of certain factors (e.g., maternal tobacco use during pregnancy or infertility treatment) has been controversially debated (Johnson et al., 2013; McLaughlin et al., 2006; Puumala et al., 2012), low birth weight (especially less 1500 g) is widely acknowledged as an independent risk factor for HB development (Heck et al., 2013; Tanimura et al., 1998). In addition, certain congenital conditions are known to be associated with an increased incidence of HB. This review was carried out to raise awareness regarding HB in children with specific genetic disorders, placing a specific focus on their genetic background and screening recommendations.

**Abbreviations:** APC, adenomatous polyposis coli; AFP, alpha-fetoprotein; BWSp/BWS, Beckwith–Wiedemann spectrum/Beckwith–Wiedemann syndrome; FAP, familial adenomatous polyposis; GPC3, glypican-3; HB, hepatoblastoma; ICR, imprinting control region; ILO, isolated lateralized overgrowth; pUPD, paternal uniparental isodisomy; SGBS, Simpson–Golabi–Behmel syndrome; T18, trisomy 18.

## 2 | METHODS

A systematic, two-step literature review was performed in PubMed/MEDLINE. In the first step, the following search term combinations were used to search the database: "(hepatoblastoma) AND (syndrome)" or "(hepatoblastoma) AND (congenital)." Case reports, clinical studies and reviews on hepatoblastoma in children with congenital diseases that were written in the English language and were published before October 31, 2021, were included. Only cases with molecularly confirmed alterations in disease-causing genes were considered. Cases that reported undetermined molecular findings, hepatic tumors other than HB, or failed to reference a histopathological work-up of the tumor were excluded. In the second step, the database was searched for additional reports and screening recommendations in English regarding HB in included genetic conditions.

## 3 | RESULTS

### 3.1 | Overgrowth syndromes: Beckwith–Wiedemann spectrum and Simpson–Golabi–Behmel syndrome

The Beckwith–Wiedemann spectrum (BWSp) encompasses the conventional Beckwith–Wiedemann syndrome (BWS; OMIM #130650) with or without (epi-)genetic changes as well as more subtle phenotypes, including isolated lateralized overgrowth (ILO; OMIM #235000), with a confirmed molecular abnormality at chromosome region 11p15.5 (Brioude et al., 2018; Kalish, Biesecker, et al., 2017). Genes at this locus comprising *CDKN1C*, *IGF2*, and *H19* are involved in growth control and cell-cycle progression. These genes are physiologically expressed in a parent-of-origin specific, so-called imprinted manner due to the epigenetic status at their corresponding imprinting control region (ICR). In BWS, alterations at 11p15.5 are detectable in up to 80% of affected individuals (Weksberg et al., 2010). The most frequent pathogenetic anomalies include (epi-)genetic changes at ICR-1 (controls *H19* and *IGF2*; 5% prevalence) or ICR-2 (controls *CDKN1C*; 50% prevalence), paternal uniparental isodisomy (pUPD; 20% prevalence) and pathogenic variants in *CDKN1C* (5% prevalence) (Choufani et al., 2013). During their infancy and early childhood, affected individuals are predisposed to develop embryonal tumors, especially Wilms' tumor and HB, and, consequently, screening is recommended (Cohen, 2005). The risk of tumor development correlates significantly with the molecular subgroup, as children with the pUPD subtype, which is also frequently present in ILO, have the highest risk to develop HB (Cöktü et al., 2020; Mussa, Russo, et al., 2016; Shuman et al., 2006). Therefore, recent screening recommendations for BWSp include HB surveillance strategies that have been adapted according to the underlying molecular subgroup, whereas the exact risk stratification as well as diagnostic modalities are still under discussion. Specific recommendations based on each molecular subtype are summarized in Table 1. In contrast, the American Association for Cancer Research has continued to recommend uniform screening in BWSp until more clarity is available regarding HB incidence in the particular genetic subtype (Kalish, Doros, et al., 2017). However, individuals at risk of HB undergo hepatic ultrasound at least every 3 months in the first years of life. The significance of periodically measuring the serum AFP levels is controversial considering the elevated AFP values in children with BWSp and their variable decrease in the first 2 years of life (Duffy et al., 2019), although several case reports have indicated that serial AFP level measurements and tumor screening in children with BWSp are beneficial (Clericuzio et al., 2003; Kim et al., 2017; Mussa et al., 2011; Zarate et al., 2009). When hepatic surveillance can be discontinued is also still unclear. A recent study confirmed that HB rarely occurs in children with BWSp older than 30 months of age; therefore, these children are significantly younger when diagnosed as compared with unselected cases (Mussa, Duffy, Carli, Ferrero, & Kalish, 2019).

Differential diagnoses of BWS include the Simpson–Golabi–Behmel syndrome (SGBS; OMIM #312870), a rare overgrowth syndrome caused by alterations in the gene for glypican-3 (*GPC3*) at

**TABLE 1** Risk-stratified surveillance recommendations for HB in BWSp based on molecular subgroups.

| | HB screening | Hepatic ultrasound[a] and duration | AFP screening |
|---|---|---|---|
| (Brioude et al., 2018) | | | |
| • BWS w/o molecular evidence | No | No | No |
| • ICR-1 | No | No | No |
| • ICR-2 | No | No | No |
| • 11p15 pUPD | Yes | Every 3 months till 7 yrs | No |
| • CDKN1C-mutation | No | No | No |
| (Maas et al., 2016) | | | |
| • BWS w/o molecular evidence | Yes | Every 3 months till 4 yrs | No |
| • ICR-1 | No | No | No |
| • ICR-2 | No | No | No |
| • 11p15 pUPD | Yes | Every 3 months till 4 yrs | No |
| • CDKN1C-mutation | facultative | Every 3 months till 4 yrs | No |
| (Mussa, Molinatto, et al., 2016) | | | |
| • BWS w/o molecular evidence | Not mentioned | Not mentioned | Not mentioned |
| • ICR-1 | No | No | No |
| • ICR-2 | No | No | No |
| • 11p15 pUPD | Yes | Every 3 months till 5 yrs | Yes |
| • CDKN1C-mutation | No | No | No |

Abbreviations: w/o, without; yrs, years of age.

[a]Explicit ultrasound imaging of the liver for detection of HB.

chromosome band Xq26 (Pilia et al., 1996). Due to its phenotypical similarities with BWS, molecular investigations of the *GPC3* gene may be considered, if 11p15.5 alterations in male individuals with overgrowth syndrome are not detectable (Knopp et al., 2015). SGBS is associated with an increased risk of embryonal tumors: In addition to reports of Wilms' tumors, several case reports of HB in molecular-verified SGBS have been published (Buonuomo et al., 2005; Kosaki et al., 2014; Li et al., 2001; Mateos et al., 2013; Shimojima et al., 2016). Notably, all cases occurred in children younger than 19 months of age, but no genotype–phenotype correlation has been established yet due to the rarity of HB in SGBS. Respective surveillance recommendations in SGBS resemble screening protocols for children with BWSp, including abdominal ultrasound and serum AFP screening every 3 months till at least the 4th year of age (Brioude et al., 2019; Kalish, Doros, et al., 2017; Lapunzina, 2005).

### 3.2 | Familial adenomatous polyposis

Familial adenomatous polyposis (FAP; OMIM #175100) is an autosomal-dominant cancer predisposition syndrome caused by an inactivating germline mutation in the *adenomatous polyposis coli* (*APC*) tumor suppressor gene. This mutation leads to the development of innumerable colorectal adenomatous polyps and, subsequently, intestinal carcinomas. Various extraintestinal manifestations, such as neoplasms of soft and hard tissue or the central nervous system, have been associated with FAP (Groen et al., 2008). In addition, several case reports have confirmed that children with pathogenic germline *APC* variants have a significant risk of developing HB (Alkhouri et al., 2010; Augustyn & Wallerstein, 2009; Cetta et al., 1997; Evers et al., 2012; Rosina et al., 2021; Sanders & Furman, 2006; Thomas et al., 2003). The main clinical characteristics as well as the prognosis of individuals with HB and FAP does not seem to differ from those of patients with sporadic HB (Trobaugh-Lotrario et al., 2018). Still, no generally accepted consensus exists regarding screening for FAP in patients with HB or vice versa (Achatz et al., 2017). In up to 14% of children with presumptively sporadic HB, however, an *APC* germline mutation is present (Aretz et al., 2006; Yang et al., 2018). Since an HB diagnosis may precede an FAP diagnosis by many years, genetic testing may provide an opportunity to initiate colorectal carcinoma surveillance in a timely manner. Therefore, several authors have recommended screening for *APC* gene mutations in all patients with HB, even if they do not have a strong family history or other stigmata of FAP (e.g., hypertrophy of the retinal pigment epithelium) (Lazzareschi et al., 2009; Trobaugh-Lotrario et al., 2018; Yang et al., 2018). In contrast, approximately 2.5% of individuals with a pathogenic germline *APC* variants develop HB. Genotype–phenotype correlations have so far failed to identify specific *APC* mutations that predispose individuals with FAP toward developing HB (Giardiello et al., 1996; Hirschman et al., 2005). The surveillance of affected children includes periodically conducting abdominal sonography and measuring the serum AFP until they are 5 years of age (Aretz et al., 2006; Kennedy et al., 2014).

### 3.3 | Trisomy 18

Trisomy 18 (T18) is the second most common autosomal trisomy syndrome after trisomy 21. Although the phenotype varies in individuals, the constitutional presence of an additional chromosome 18 results in various malformations, including congenital heart defects. These malformations contribute markedly to morbidity and mortality in these children (Cereda & Carey, 2012). Consequently, infant mortality is high, and only 8–13% of affected children survive the first year of life according to published cohorts (Nelson et al., 2016; Wu et al., 2013). Intensive care, including sophisticated surgery, has improved the prognosis and life expectancy of selected individuals significantly (Kosiv et al., 2017). However, a growing body of evidence indicates that these children are at risk of developing HB. To date, about 50 cases of HB in T18 have been reported, representing the most frequent malignancy in these infants (Farmakis et al., 2019; Satgé et al., 2016). The female gender seems to confer a survival advantage in T18, and females are markedly predominant among children with T18 and HB. (Meyer et al., 2016; Nelson et al., 2016; Satgé et al., 2016). As liveborn children may be at risk of developing HB, authors of a recent review proposed that abdominal ultrasounds and serial AFP level measurements should be performed every 3 months up until at least the 4th year of age, taking into consideration the lack of validated, age-correlated AFP levels in children with T18 (Farmakis et al., 2019).

### 3.4 | Single case reports

In addition to previously mentioned genetic conditions, which are characterized by an increased incidence of HB, several case reports have been published on HB in individuals with various congenital diseases (Table 2). The significance of the association between HB and these conditions is still undetermined.

## 4 | DISCUSSION

Only a few molecularly defined diseases have been associated with a high risk of developing HB, but the contribution of these underlying genetic alterations to tumorigenesis is still incompletely understood. In unselected HB, aberrant Wnt/beta-catenin signaling is commonly present and a hallmark of this entity (Eichenmüller et al., 2014). The nuclear level of beta-catenin, which is encoded by the *CTNNB1* gene, is regulated precisely by several feedback mechanisms controlling proliferation and differentiation in embryogenesis and hepatic development. Genetic alterations that affect this pathway can cause either the enhancement of beta-catenin activation or its restrained inhibition. This, in turn, results in an imbalance in signaling, which may direct the cell state toward malignant proliferation (Armengol et al., 2011). Somatic mutations in the *CTNNB1* gene are common in unselected HB (Jeng et al., 2000; Koch et al., 1999). Interestingly, the *APC* protein is part of the beta-catenin degradation complex and, consequently, acts as a negative regulator. Mutations in the tumor

**TABLE 2** Additional case reports of hepatoblastoma in molecularly confirmed genetic disorders.

| Genetic condition | Affected chromosome locus/gene | Sex | Weight at birth | Age at diagnosis of HB | AFP at presentation[a] | HB histology |
|---|---|---|---|---|---|---|
| ARPKD (Kummerfeld et al., 2010) | *PKHD1* | M | 830 G | 18 months | 1702 kU/l | Mixed epithelial type |
| ARPKD (Luoto et al., 2014) | *PKHD1* | M | N/A | 5 years | 6553 | N/A |
| ARPKD (Kadakia et al., 2017) | *PKHD1* | F | N/A | 18 months | 800 | Pure fetal epithelial type |
| Cardio-facio-cutaneous syndrome (Al-Rahawan et al., 2007) | *MEK1* | M | "10th percentile" | 35 months | 2966 | Mixed epithelial type |
| DiGeorge syndrome (Scattone et al., 2003) | 22q11.2 | M | 3700 G | "perinatal" | 460.347 | Mixed epithelial type |
| DiGeorge syndrome (McDonald-McGinn et al., 2006) | 22q11.2 | M | N/A | 3 months | N/A | Mixed type[b] |
| DiGeorge syndrome (McDonald-McGinn et al., 2006) | 22q11.2 | M | N/A | 15 months | N/A | Mixed epithelial + mesenchymal type |
| DiGeorge syndrome[c] (Rosina et al., 2021) | 22q11.21 | M | 2600 G | N/A | 266.4 | Fetal epithelial type |
| Fanconi anemia (Kopic et al., 2011) | *FANCD1/BRCA2* + gain chr. 3q | F | 1900 G | 4¼ years | 103,512 | Mixed epithelial + mesenchymal type |
| Fragile–X syndrome (Wirojanan et al., 2008) | *FMR1* | M | 4167 G | 2 years | N/A | N/A |
| Kagami–Ogata syndrome (Kagami et al., 2015) | pUPD(14) | N/A | N/A | 13 months | N/A | Mixed epithelial type |
| Kagami–Ogata syndrome (Horii et al., 2012) | pUPD(14) | F | 2558 G | 7 months | 43,963 | "well-differentiated" |
| Li–Fraumeni syndrome (Toguchida et al., 1992) | *p53* | F | N/A | 3 months | N/A | N/A |
| McCune–-Albright syndrome (Johansen et al., 2019) | *GNAS* | M | N/A | 5 years | 5700 kU/l | Embryonal type |
| MECP2 duplication syndrome (Trobaugh-Lotrario et al., 2016) | *MECP2* | M | 1194 G | 2 years | 12,199 | Mixed epithelial type |
| Noonan syndrome (Yoshida et al., 2008) | *PTPN11* | M | N/A | 1 month | 142,000 | Mixed epithelial type |
| Osteopathia striata with cranial sclerosis (Fujita et al., 2014) | *WTX* | F | 3138 G | 32 months | 557 | N/A |
| Prader–Willi syndrome (Hashizume et al., 1991) | Chr. 15 | M | 1856 G | 17 months | 23,564 | "poorly differentiated HB" |
| Rubinstein–Taybi syndrome (Milani et al., 2016) | *CREBBP* | F | 2885 G | 11 months | N/A | Mixed epithelial type |
| Sotos syndrome (Kato et al., 2009) | *NSD1* | M | 2876 G | 21 months | 84,000 | N/A |
| Trisomy 9p (partial) (Schnater et al., 2005) | Chr. 9p | M | 3550 G | 3 months | 338,520 | Epithelial type |
| Trisomy 13 (Shah et al., 2014) | Chr. 13 | F | 2990 G | 15 months | 55,300 | Mixed epithelial + mesenchymal type |
| Wolf–Hirschhorn syndrome (Bayhan et al., 2017) | Chr. 4 | F | 1220 G | 2½ years | 53,997 | Epithelial type |

Abbreviations: ARPKD, Autosomal recessive polycystic kidney disease; Chr, chromosome; F, female; G, gram; M, male; N/A, not available.
[a]ng/ml if not other specified.
[b]No specification.
[c]This patient had a mutation of the *APC* gene additionally.

suppressor gene *APC*, as in FAP, may disinhibit the canonical Wnt signaling pathway and contribute to tumorigenesis of HB (Stamos and Weis, 2013). Furthermore, altered gene expression in the chromosomal region 11p15.5 has been observed in the development of sporadic HB as genetic and epigenetic changes in *H19* and *IGF2* are present in unselected HB resembling constitutional genetic findings in BWSp (Albrecht et al., 1994; Fukuzawa et al., 1999; Gray et al., 2000; Honda et al., 2008; Rumbajan et al., 2013). Likewise, Carrillo-Reixach et al. (2020) identified epigenetic modifications of the 14q32.2-32 locus as a new hallmark in a subgroup of HB. Accordingly, an increased HB incidence is assumed in Kagami–Ogata syndrome, a very rare imprinting disorder of the 14q32.2 region (Horii et al., 2012; Kagami et al., 2015). In addition, the GPC3 protein, which has been assumed to interact with the Wnt/beta-catenin pathway (Capurro et al., 2014; Song et al., 2005) and with IGF2 (Pilia et al., 1996; Xu et al., 1998), is also overexpressed in unselected HB (Toretsky et al., 2001; Zynger et al., 2008). However, the molecular mechanism by which *GPC3* alterations contribute to the tumorigenesis of HB has not been fully elucidated.

Since the sex ratio is inverted in children with T18 and HB, an alternative molecular pathway in these cases might promote tumorigenesis. In cytogenetic analysis of unselected HB, trisomy, or at least gain of chromosome 18, are rarely seen (Tomlinson et al., 2005). Thus, it is still a matter of debate whether trisomy 18 contributes independently to the development of HB through the numeric aberration per se. In this regard, Pereira et al. (2012) reported HB in a girl with

mosaic T18, but her tumor cells did not harbor a third chromosome 18.

In general, the reported molecular similarities suggest the existence of a common genetic background between HB in unselected patients and in children with congenital diseases. It is interesting to note that children with overgrowth syndromes seem to be significantly younger when diagnosed with HB as compared with patients that lack this genetic predisposition, indicating that tumorigenesis has an inherent molecular "head start" in these patients. However, as HB only occurs in exceptional cases of patients with genetic conditions, additional somatic driver mutations may be required for its manifestation. Some of the case reports may have overestimated the contribution of the underlying genetic aberration to the development of HB, and additional promoting factors must be reconsidered. As, for example, low birth weight is recognized as an independent risk factor for HB, it is difficult to evaluate the isolated impact of the genotype separately, especially in single case studies.

Moreover, co-morbidities affect the treatment of HB in children with underlying congenital diseases, and this has to be taken into account. In particular, children with congenital diseases and HB might experience unexpected and more severe side effects to cytotoxic therapy, requiring reductions in the doses of cytotoxic drugs and individual treatment planning. In patients with certain conditions (e.g., T18), the prognosis depends heavily on the morbidity caused by the constitutive chromosomal aberration. Treatment strategies range from providing comfort care to curative, multimodal treatment, including liver transplantation (Fernandez et al., 2011; Inoue et al., 2018; Kitanovski et al., 2009).

Surveillance might contribute to the early detection of HB in children with the previously described congenital conditions, but the recommendations differ somewhat (e.g., in terms of the duration or relevance of periodic AFP measurement). Despite these differences, they all include regular abdominal screening in the first years of life. In general, early-stage disease recognition in HB may result in less invasive surgical approaches being taken and less toxic treatment modalities being used, as well as resulting in improved survival rates (Allan et al., 2013; Czauderna et al., 2016). Data on Wilms' tumors in BWSp disorders clearly indicate that tumors detected by surveillance are more likely to be localized (Mussa, Duffy, Carli, Griff, et al., 2019). Likewise, Trobaugh-Lotrario et al. (2014) observed superior overall survival in BWS patients and higher frequency of low-stage HB identified by surveillance as compared with children who were not enrolled in any screening. Although this study was retrospective and only included a small number of patients, these findings underscore the benefit of HB screening in congenital diseases.

## 5 | CONCLUSION

In conclusion, HB in the context of congenital conditions is a rare and life-threatening condition. Therefore, screening protocols are recommended in patients with the most common genetic conditions, as these are assumed to increase the chance of early diagnosis, when the tumor is still focal and has not yet been systemically disseminated. Since embryonal tumors tend to develop rapidly, short screening intervals are crucial, but these require a high level of compliance from affected families. Physicians need to be familiar with the increased incidence of HB and the surveillance strategies that can be applied in predisposing genetic diseases, including overgrowth syndromes, FAP and T18.

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## CONFLICT OF INTERREST

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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