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Postema, Floor A. M.; Oosterwijk, Jan C.; Hennekam, Raoul C.

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Genetic control of tumor development in malformation syndromes

Floor A.M. Postema[1] | Jan C. Oosterwijk[2] | Raoul C. Hennekam[1]

[1]Department of Pediatrics, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2]Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Correspondence
Raoul C. Hennekam, Department of Pediatrics, Amsterdam UMC - location AMC, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands.
Email: r.c.hennekam@amc.uva.nl

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Abstract

One of the questions that arises frequently when caring for an individual with a malformation syndrome, is whether some form of tumor surveillance is indicated. In some syndromes there is a highly variable increased risk to develop tumors, while in others this is not the case. The risks can be hard to predict and difficult to explain to affected individuals and their families, and often also to caregivers. The queries arise especially if syndrome causing mutations are also known to occur in tumors. It needs insight in the mechanisms to understand and explain differences of tumor occurrence, and to offer optimal care to individuals with syndromes. Here we provide a short overview of the major mechanisms of the control for tumor occurrences in malformation syndromes.

KEYWORDS

cancer, CNVs, epigenetics, genetic compensation, mosaicism, tumor predisposition syndrome

1 | INTRODUCTION

Typically an explanation of general genetic principles to lay persons starts like: genes code for proteins. These proteins may have different functions during different stages of life. Prenatally, a protein can influence cell differentiation and the basic embryonic patterning, while postnatally the same protein can affect cell growth and other functions (Ponder, 2001). A pathogenic variant in the gene coding for a protein may thus lead to birth defects, either isolated or in a combination, for example, a (malformation) syndrome, but may also cause disturbed control of cell growth, which may lead to (benign or malignant) tumor growth (Table 1). This basic concept of pleiotropy forms the background for lay persons to understand mechanisms explaining tumor development if a malformation or malformation syndrome is present.

A malformation syndrome and a tumor can co-occur in the same person. In some syndromes virtually all affected individuals will develop a tumor (e.g., basal cell carcinoma in Gorlin syndrome [#109400]). Such syndromes, with a high expressivity for tumors, are often indicated as tumor predisposition syndromes (TPS).[1] In other syndromes the associated tumors occur not in all affected individuals, but still more frequently than in the general population (e.g., Wilms tumor in Beckwith-Wiedemann syndrome [#130650]). Such syndromes are often indicated as TPSs with reduced expressivity of the tumors. In still other syndromes, tumor occurrence is not known to be increased, notwithstanding the fact that *somatic* variants in the causative gene are frequently found in tumor DNA (e.g., Cornelia de Lange syndrome [#122470] caused by germline *NPBL* variants, and acute myeloid leukemia in which somatic *NIPBL* variants are present) (Gorlin, 2004; Maas et al., 2016; Mazzola et al., 2019). The reasons why in malformation syndromes tumors occur in such a highly variable frequency is often unclear. Even though TPSs individually are infrequent disorders, as a group they form a significant cause of cancer in children (Merks, Caron, & Hennekam, 2005; Zhang et al., 2015). They offer insight into underlying mechanisms, they allow for better prediction of tumor risks, and may have major consequences for surveillance and care for individuals with these syndromes.

Here we provide a short review of the various genetic mechanisms in germline and somatic tissue that may affect risks to develop a tumor: differences in type and site of the variant within the gene, difference in bi-allelic (homozygous or compound heterozygous) and mono-allelic (heterozygous) occurrence of variants, difference in timing of the occurrence of variants, differences in roles of variants (cause or consequence), genetic compensation, epigenetic influences,

TABLE 1 Selected examples of genes in which germline variants can cause a syndrome and somatic variants have been demonstrated in tumors

Gene	Germline variant			Somatic variant[a]
OMIM number	*Syndrome*[b] *OMIM number*	*Main characteristics*	*Main associated tumors*[c]	*Tumors*
APC 611731	Gardner syndrome #175100	Multiple lipoma, fibroma, osteoma, sebaceous cysts	Adenomatous colon polyps, medulloblastoma	Colorectal ca, gastric ca, NEN
ARID1B 614556	Coffin-Siris syndrome #135900	ID, hypertrichosis, unusual face, small fifth nails	Uncertain; ?Rhabdoid tumors	Neuroblastoma, bladder ca, lung ca, mesothelioma, breast ca, pancreas ca, biliary tract ca, lung ca
ATRX 300032	XL-AlphaThalassemia-ID syndrome #301040	ID, unusual face, hemoglobin H	–	Glioma, neuroblastoma, low grade NEN, pheochromocytoma, uterine sarcoma, pancreas ca, GI ca, breast ca
BRAF 164757	Cardiofaciocutaneous syndrome #115150	ID, unusual face, heart anomalies, ectodermal anomalies	Uncertain; ?Leukemia, ?Lymphoma	Melanoma, colorectal ca, lung ca, GI ca, leukemia
BRCA2 (homozyg) 600185	Fanconi anemia D1 #605724	Bone marrow failure, short stature, heart/renal/skeletal anomalies, skin pigmentation anomalies	Acute myeloid leukemia, Wilms tumor, neuroblastoma, brain tumors	Breast ca, prostate ca, ovarian ca, uterine sarcoma
CHD7 608892	CHARGE syndrome #2148000	ID, choanal atresia, coloboma eye, heart anomalies, disturbed growth; ear anomalies, deafness	–	Lung ca, colon ca, gastric ca, pancreas ca, leukemia
CREBBP 600140	Rubinstein-Taybi syndrome 1 #180849	ID, unusual face, broad thumbs/halluces, disturbed growth	<40 year – >40 year?	Leukemia, lymphoma, esophageal ca, ovarian ca, lung ca, thyroid ca, colorectal ca
EHMT1 607001	Kleefstra syndrome #610253	ID hypotonia, unusual face, seizures, heart anomalies	-	Leukemia
EP300 602700	Rubinstein-Taybi syndrome 2 #613684	ID, unusual face, microcephaly, maternal pre-eclampsia	<40 year – >40 year?	Breast ca, ovarian ca, esophageal ca, lung ca, colorectal ca, leukemia, lymphoma
ESCO2 609353	Roberts syndrome #268300	ID, unusual face, tetraphocomelia, cardiac/renal anomalies, disturbed growth	-	Breast ca, leukemia
EZH2 601573	Weaver syndrome #277590	ID, overgrowth, unusual face	Uncertain; ?Neuroblastoma	Leukemia, lymphoma
FGFR2 176943	Apert syndrome #101200	Craniosynostosis, syndactyly fingers/toes disturbed development, unusual face	–	Breast ca, gastric ca, esophageal ca, biliary tract ca, thyroid ca
FGFR3 134934	Achondroplasia #100800	Short stature, short limbs, macrocephaly	–	Bladder ca, multiple myeloma, lung ca, colorectal ca
FLNA 300017	Otopalatodigital syndrome 1 #311300	Skeletal anomalies, cleft palate, abnormal pigmentation skin,	–	Breast fibroepithelial tumors
GLI3 165240	Greig cephalopolysyndactyly syndrome #175700/	Skull anomalies, syndactyly, polydactyly	Uncertain; ?Brain tumors	Gastric ca

TABLE 1 (Continued)

Gene	Germline variant			Somatic variant[a]
OMIM number	*Syndrome*[b] *OMIM number*	*Main characteristics*	*Main associated tumors*[c]	*Tumors*
GPC3 300037	Simpson-Golabi-Behmel syndrome 1 #312870	Overgrowth, unusual face, distal limb anomalies	Uncertain; ?Embryonal tumors	Wilms tumor
JAG1 601920	Alagille syndrome #118450	Cholestasis, eye/heart anomalies, skeletal anomalies	–	Prostate ca, breast ca, brain adenoca
KMT2D 602113	Kabuki syndrome #147920	ID, unusual face, disturbed growth, skeletal anomalies	–	Breast ca, lymphoma
LMNA 150330	Hutchinson-Gilford progeria #176670	Short stature, hair loss, lipodystrophy, osteolysis, cardiovascular anomalies	–	Soft tissue sarcoma, colorectal ca, non-Langerhans histiocytosis, breast ca
LZTR1 600574	Noonan syndrome 2 #605275	Unusual face, short stature, heart anomalies	Schwannoma	Breast ca, liver ca
MID1 300552	Opitz GBBB syndrome 1 #300000	ID, unusual face, cleft lip/palate, hypospadias, imperforate anus, laryngotracheoesophageal anomalies	–	Lymphoma
NF1 613113	Neurofibromatosis #162200	Café-au-lait spots, fibromata, Lisch nodules	Neurofibroma, peripheral nerve sheath tumors, optic glioma, brain glioma, leukemia	Ovarium ca, melanoma, lung ca, breast ca, glioblastoma, pheochromocytoma, salivary gland ca, astrocytoma, leukemia
NFIX 164005	Marshall-Smith syndrome #602535	ID, skeletal dysplasia, unusual face, respiratory problems	–	Lung ca, breast ca
NSD1 606681	Sotos syndrome 1 #117550	ID, overgrowth, unusual face	Uncertain; ?Sacrococcygeal teratoma	Leukemia, cervical ca, vulva squamous cell ca
PAX3 606597	Waardenburg syndrome 1 #193500	Hair/skin/eye pigmentation anomalies, deafness, unusual face	–	Medulloblastoma, eye adnexa soft tissue tumor, rhabdomyosarcoma
PHF6 300414	Borjeson-Forssman-Lehmann syndrome #301900	ID, unusual face, obesity, behavioral problems	–	Leukemia, liver ca
PIK3CA 171834	PIK3CA related overgrowth Spectrum	Segmental overgrowth, megalencephaly, vascular malformations, lipoma	–	Colorectal ca, breast ca, lung ca, glioblastoma, gastric ca, NEN, vulva ca
PTCH1 601309	Gorlin syndrome #109400	Macrocephaly, jaw cysts, epidermal pits, bifid ribs	Basal cell ca, medulloblastoma, cardiac fibroma; ovarian fibroma	Basal cell ca, medulloblastoma, esophageal ca, lung ca
PTEN 601728	PTEN hamartoma tumor syndrome #158350	Macrocephaly, tricholemmomas, papilloma, pigmentation anomalies, ID	Breast ca, thyroid ca, endometrium ca, colon ca, renal ca, melanoma	Leukemia, breast ca, prostate ca, ovarian ca, uterus sarcoma, thyroid ca
PTPN11 600574	Noonan syndrome 1 #163950	Unusual face, short stature, heart anomalies	JMML, rarely other cancers	Leukemia, myelodysplastic syndrome, neuroblastoma
RET				Thyroid ca, lung ca, melanoma

(Continues)

TABLE 1 (Continued)

Gene	Germline variant			Somatic variant[a]
OMIM number	*Syndrome*[b] *OMIM number*	*Main characteristics*	*Main associated tumors*[c]	*Tumors*
164761	Congenital central hypoventilation #209880	Dysregulated autonomic nervous system M. Hirschsprung	Neuroblastoma, ganglioneuroma, ganglioneuroblastoma	
RMRP 157660	Cartilage-hair syndrome #250250	Short stature, short limbs, sparse hair, immunological anomalies	Uncertain;? Cutaneous lymphoma	Breast ca, leukemia
RPS6KA3 300075	Coffin-Lowry syndrome #303600	ID, unusual face, movement anomalies, short stature	–	Liver ca
RUNX2 600211	Cleidocranial dysplasia #119600	Underdeveloped clavicles, ossification anomalies, dental anomalies	Uncertain; ?Acute lymphoblastic leukemia	Osteoblastoma
SMARCA2 600014	Nicolaides-Baraitser syndrome #601358	ID, short stature, unusual face, sparse hair, limb anomalies	–	Ovarian ca, adenoid cystic ca
SMARCB1 601607	Coffin-Siris syndrome #614608	ID, hypertrichosis, unusual face, small fifth nails	Schwannoma; ?Rhabdoid tumors	Rhabdoid ca, meningioma, renal ca
SUFU 607035	Gorlin syndrome 109,400	Macrocephaly, epidermal pits, bifid ribs	Basal cell ca, medulloblastoma, cardiac fibroma; ovarian fibroma	Meningioma, medulloblastoma, melanoma
TCF4 602272	Pitt-Hopkins syndrome 610,954	ID, unusual face, breathing anomalies	–	Colorectal ca, medulloblastoma
TGFBR1 606237	Loeys-Dietz syndrome 1 #609192	Arterial aneurysms/tortuosity, unusual face, bifid uvula	–	Colorectal ca, gastric ca, breast ca
TP63 603273	EEC syndrome #604292	Distal limb anomalies, cleft lip/palate, ectodermal dysplasia	–	Lung ca, esophageal ca, head/neck ca, prostate ca, cervix ca
TRPS1 604386	Trichorhinophalangeal syndrome 1 #190350	Unusual face, sparse hair, short stature, distal limb anomalies	Uncertain; ?Subependymoma	Endometrium ca, breast ca
TSC1 605284	Tuberous sclerosis 1 #191100	Hamartoma of brain, skin, heart, kidney, and lung, seizure	Angiomyolipoma; neuroendocrine tumor, lymphangioleiomyomatosis astrocytoma, renal cell ca	Bladder ca, astrocytoma, renal ca, ovarian ca, endometrium ca, liver ca
TWIST1 601622	Saethre-Chotzen syndrome #101400	Craniosynostosis, unusual face, distal limb anomalies	–	Cervix ca
ZEB2 605802	Mowat-Wilson syndrome #235730	ID, unusual face, disturbed colon motility	–	Leukemia, colorectal ca, cervix ca

Abbreviations: ca, cancer; GI, gastro-intestinal; ID, intellectual deficit; JMML, juvenile myelomonocytic leukemia; NEN, neuroendocrine neoplasm; syndr, syndrome; –, none reported.

[a]The row of order is not representative for the frequency of tumors as for many genes the frequency of somatic variants in the various tumors is not yet known; subdivisions of tumor types are not tabulated in this overview table. Tumors are tabulated if variant(s), CNVs, gene fusions or translocations involving the gene have bene published; upregulations or downregulations, methylation abnormalities, and so forth are not scored positively. Therefore, genes may still have marked influences on development, growth, and management of other tumors if not tabulated here.

[b]A single syndrome caused by a germline variant is tabulated but frequently several (pleiotropic) entities are caused by variants in the gene involved.

[c]Only tumors reported in a (proven or likely) increased frequency compared to population frequency are mentioned, to exclude co-occurrence by coincidence.

as well as combinations of several of these mechanisms. Various genetic mechanisms are summarized schematically in Figure 1. A complete description of all mechanisms is not well possible in a single article; therefore, we refer interested readers to publications dedicated to the various mechanisms.

2 | METHODOLOGY

The pathogenesis of general tumor development has been reported in such a vast number of publications that a systematic overview of the total literature is impossible. Even a systematic overview of most single mechanisms will have to deal with many thousands publications. Therefore, the present manuscript is not the result of a systematic review. Instead, it has been built on an idiosyncratic review that we started ~10 years ago. This review has gradually been expanded, in part due to emerging additional mechanisms reported in literature or based on remarks from colleagues when discussing the topic. The present manuscript is based on this review, to which some recent perspectives have been added.

3 | RESULTS

3.1 | Syndromes and tumors can have DNA-variants differing in type and/or site within a gene

For some genes the type and location of variants have been demonstrated to differ between the syndromic germline cases and the somatic tumor cases. An example of this phenomenon is the developmental gene *FAT4*. If the germline variants are found in the cadherin repeat domain, this may lead to reduced activity of FAT4, causing a syndrome characterized by intellectual disability, unusual face and, in a subgroup, lymphatic dysplasia [#616006] (Alders et al., 2014; Zhang et al., 2016). In cancer cells somatic variants can be found in the cadherin domain but also in all other domains of *FAT4*, causing a disturbed tumor suppressor function and contributing to several types of tumors such as melanoma, pancreatic cancer and gastric cancer (Zhang et al., 2016). The *FAT4* germline variants found in the syndrome and those found in the tumors differ in type and site (Table S1). We searched for other genes without overlap between variants causing the syndrome and (somatic) variants detected in tumors, but have been unable to find any. This may indicate that a complete lack of overlap is an uncommon mechanism.

Variants differing in type and site within a gene can alter functions of a protein in different ways: sometimes functions involved in tumor development, sometimes completely different functions, and thus leading to phenotypic heterogeneity. PTEN may serve as an example: pathogenic variants in *PTEN* have been shown to work through changes in conformation of PTEN and subsequent changes in communication with other protein's inter- and intracellular pathways. Typically, some variants disturb predominantly networks involved in cancer development while other variants disturb predominantly networks involved in autism spectrum disorders (Smith, Thacker, Seyfi, Cheng, & Eng, 2019). In addition, a single gene frequently produces slightly different variations of proteins (isoforms) due to alternative splicing. The functional effect of pathogenic variants in different isoforms may differ, and therefore even per tissue (Sonawane et al., 2017; Vitting-Seerup & Sandelin, 2017). Another example of differences depending on the type of variants, are missense mutations in *RET*. These result in general in a mutant RET-protein with a loss of function, and are associated with Hirschsprung disease [#142623]. But localized *RET* missense mutations of specifically cysteine, cause a gain of function and are associated with the development of various forms of cancer such as medullary thyroid cancer and the TPS Multiple Endocrine Neoplasia type 2 [#171400; #171300] (Edery et al., 1994; Mulligan et al., 1993).

Differences in site and nature of variants cannot be the only mechanisms, as for other genes, germline variants causing syndromes and somatic variants found in tumors are identical. For example, one of the somatic variants in *BCOR* causing AML is c.2488_2489delAG (Ng et al., 2018). This same variant can also cause oculo-facio-cardio-dental (OFCD) syndrome [#300166], if present in the germline (Horn et al., 2005). Still, AML or other types of cancer have not been reported in OFCD cases harboring this germline variant, although thus far the numbers are still small and follow-up is limited.

3.2 | Bi-allelic and mono-allelic variants

Typically, the phenotype resulting from homozygosity/compound heterozygosity or heterozygosity for a variant will differ. Bi-allelic variants of the tumor suppressor gene *BRCA2* cause Fanconi anemia [#605724], which gives an increased risk developmental anomalies and childhood malignancies such as AML, Wilms tumor, neuroblastoma and brain tumors (Myers et al., 2012). Heterozygous germline variants in the same *BRCA2* confer an increased risk of breast, ovarian and prostate cancer [#612555] but do not lead to an increased chance of congenital anomalies (Kwiatkowski et al., 2020; Levy-Lahad & Friedman, 2007). If in a tissue a heterozygous *BRCA2* variant carrier a second hit occurs (usually through LOH), this results in loss of function and the development of cancer (two-hit hypothesis) (Warren, Lord, Masabanda, Griffin, & Ashworth, 2003). Parks and co-workers have demonstrated that based on the two-hit hypothesis, rare germline variants with somatic variants are likely causative for a larger share of cancer occurrence than initially anticipated (Park, Supek, & Lehner, 2018).

3.3 | Syndromes and tumors can differ due to timing of variants

A variant can be present in a gene at the time of fertilization (germline mutation) or can occur later on in a tissue (either prenatally or postnatally), that is, a somatic mutation leading to mosaicism. In some genes this timing of the occurrence of a variant can determine the presence

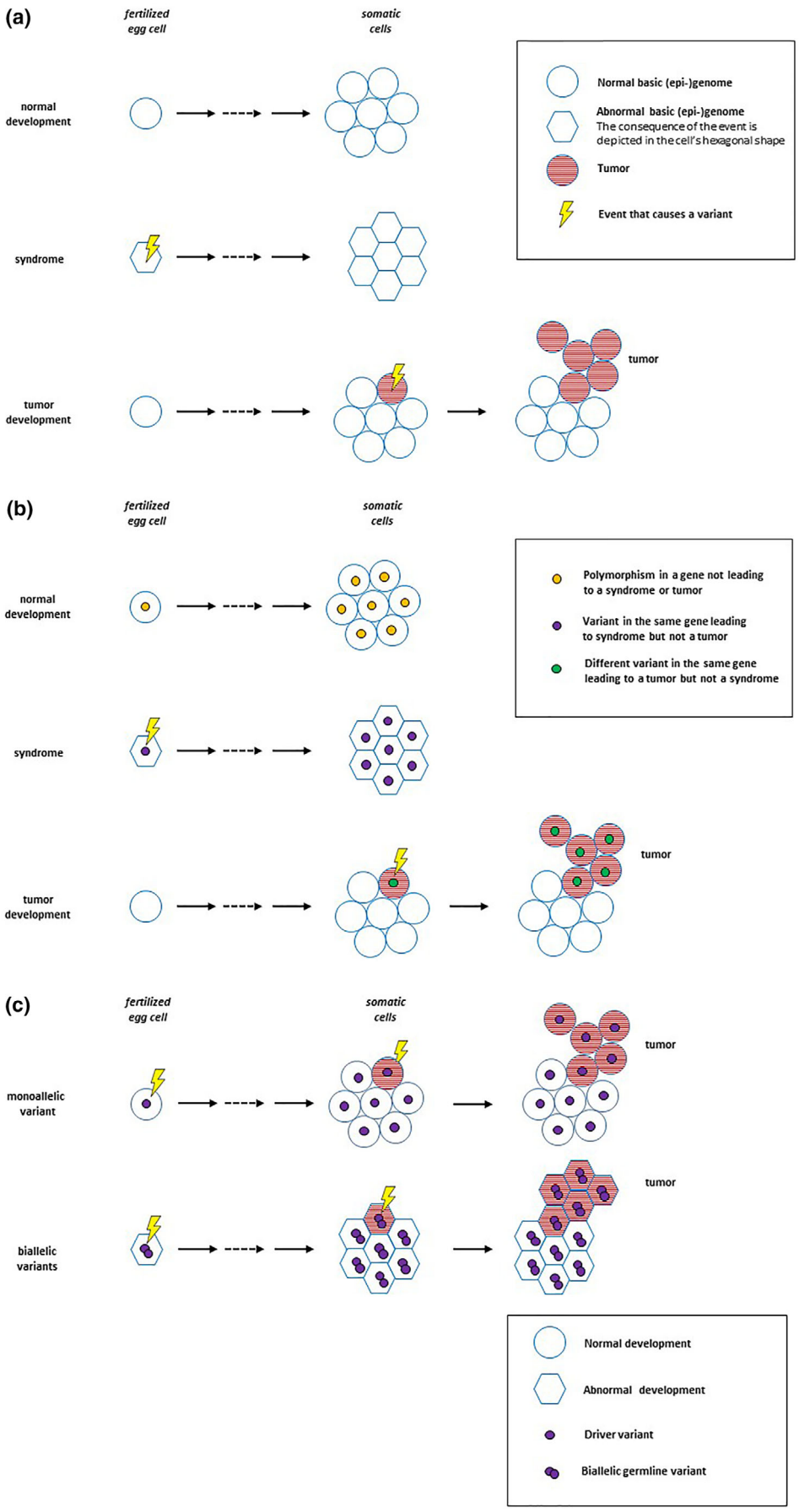

FIGURE 1 General principles (b) Site/nature of variants. (c) Biallelic (Homozygous or compound heterozygous) vs mono-allelic (heterozygous) variants. (d) Timing. (e) Driver or passenger. (f)Genetic compensation [Color figure can be viewed at wileyonlinelibrary.com]

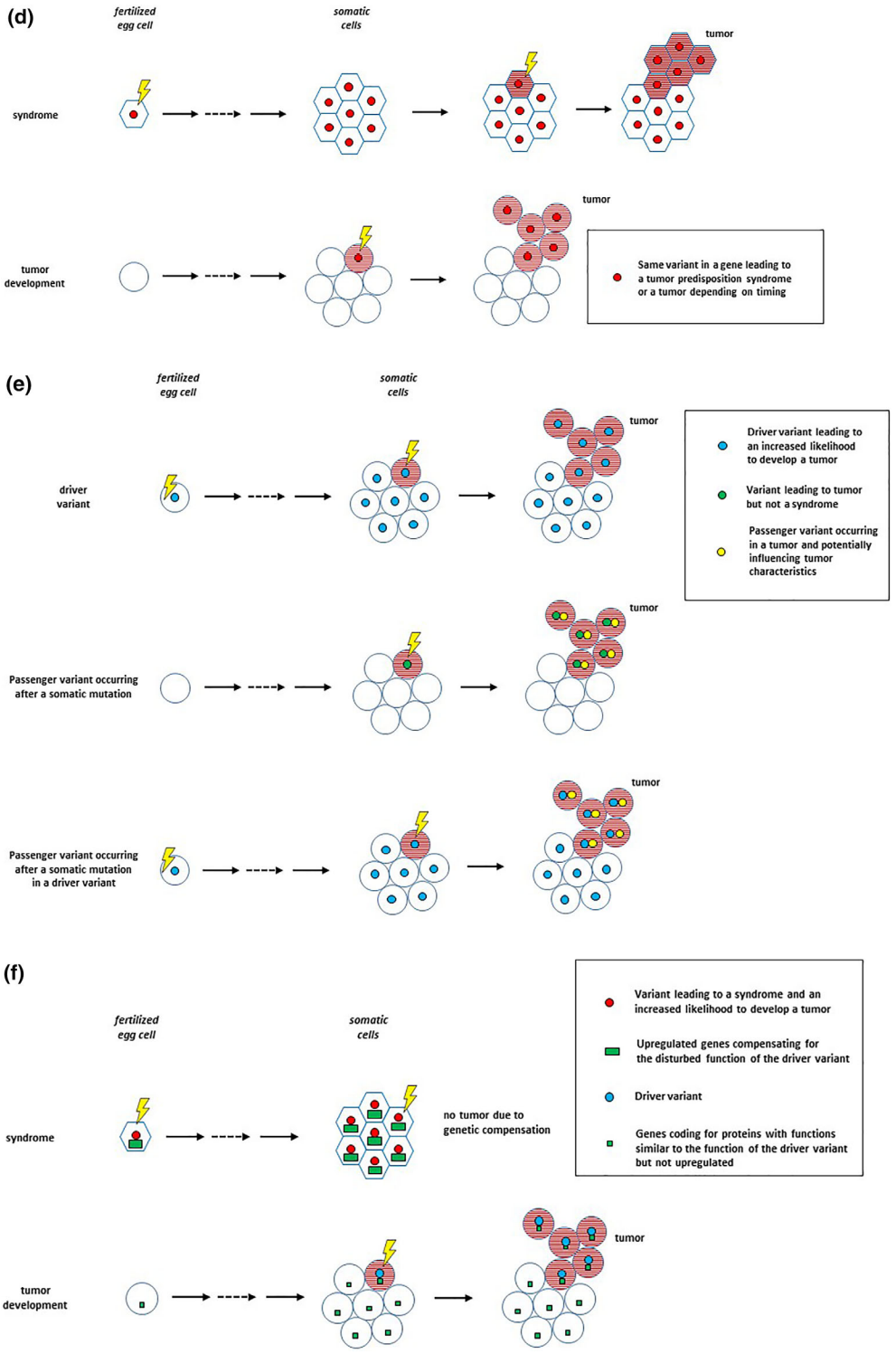

FIGURE 1 (Continued)

or absence of a syndrome, but the increased tumor risk is always present. For instance, *PTCH1* plays an important role during embryogenesis in the craniofacial development (Metzis et al., 2013). Germline variants in *PTCH1* cause Gorlin syndrome with craniofacial and skeletal abnormalities, and in which the risk to develop basal cell carcinoma (BCC) is over 90% (Evans & Farndon, 1993). *PTCH1* is a human tumor suppressor gene that encodes for sonic hedgehog ligands and works as a negative regulator of the sonic hedgehog signaling pathway (Agren, Kogerman, Kleman, Wessling, & Toftgard, 2004). It represses downstream signaling of the co-receptor smoothened (SMOH) and this way prevents cells from uncontrolled proliferation. *PTCH1* is also frequently mutated somatically in isolated, nonsyndromic BCCs and

several other tumor types (Gielen et al., 2018). Pathogenic *PTCH1* variants causing Gorlin syndrome and those causing isolated BCCs can be identical (Table S2) (Boutet et al., 2003; Lindstrom, Shimokawa, Toftgard, & Zaphiropoulos, 2006). As numbers are still relatively small, it cannot be excluded that over time some variants will be found to be more frequent in the syndrome than in the tumor, or vice versa.

3.4 | Variants can be a cause but also be a consequence in tumors

In malformation syndromes, pathogenic germline (or early somatic) variants in genes are (almost) invariably the cause of the syndrome, but (somatic) variants detected in tumors may either be the cause (driver) or the consequence (passenger) of tumorigenesis. Driver genes are genes that contain variants that eventually confer a selective growth advantage to the cell in which it occurs (Stratton, Campbell, & Futreal, 2009; Vogelstein et al., 2013). Passenger variants are circumstantial variants. They have no effect on the initial neoplastic process, but they may still be important and determine further characteristics of tumors such as the chance to metastasize or reactions to therapeutic agents (Vogelstein et al., 2013).

In common solid tumors such as breast cancer and colon cancer, somatic variants are detected in an average of 33 to 66 genes (Vogelstein et al., 2013). Classic epidemiologic studies have suggested that solid tumors typically require five to eight alterations in driver genes to develop into cancer (Vogelstein et al., 2013). Variants in driver genes may lead to failure of chromosome repair mechanisms, for instance due to changes in chromatin domains (Lupianez, Spielmann, & Mundlos, 2016), chromosome territories (Folle, 2008), and other changes of the spatial configuration of the genome (Umlauf & Mourad, 2019). As a result variants start to occur at random during tumor evolution, resulting in passenger variants in most tumors (Merid, Goranskaya, & Alexeyenko, 2014). Indeed, tumors with mismatch repair defects can harbor up to thousands of variants (Vogelstein et al., 2013).

Nicolaides-Baraitser syndrome [#601358] is caused by germline variants in *SMARCA2*, and is characterized by marked intellectual disability, seizures, specific facial characteristics and limb abnormalities, but without known increased risk to develop tumors (Sousa & Hennekam, 2014). Still, *SMARCA2* variants are frequently detected in tumors such as cancers in colon, liver and lung (Table S3) (Helming, Wang, & Roberts, 2014). *SMARCA2* regulates transcription activation and repression of a series of genes by altering the chromatin structure around these genes, and is thought to act as a tumor suppressor (Guerrero-Martinez & Reyes, 2018). However, SMARCA2 has not been indicated as a driver to develop cancer (Forbes et al., 2017).

Characterizing the functioning of an altered gene can even be more complicated. In DNA repair disorders the variants and CNVs can arise both as consequence of the impaired DNA repair, and subsequently can act as driver, or as consequence (passenger) in tumors (Torgovnick & Schumacher, 2015; Walsh et al., 2017). Furthermore, for some genes driver variants may cause that gene to function as a driver of tumorigenesis, but other variants in the same gene may cause this gene to act as a tumor suppressor gene (Dogruluk et al., 2015; Yu et al., 2017). So the distinction of variants in genes acting as driver or passenger is not absolute: the same gene can contain variants acting as driver or as passenger. *PIK3CA* can contain well-known driver variants such as the c.3140A > G variant [p.His1047Arg] leading to gain-of-function and thus increased PI3K activity, but passenger variants can occur as well, depending on site and nature of the variant (Dogruluk et al., 2015; Hart et al., 2015).

Mosaic variants in *PIK3CA* cause the PIK3CA overgrowth syndrome [no OMIM] (Keppler-Noreuil et al., 2015). Overgrowth syndromes have by definition a disturbed regulation of growth in height, weight and/or skull circumference, and typically have also an increased tumor risk, the prototype being Beckwith-Wiedemann syndrome [#602631] (Maas et al., 2016). But activating *PIK3CA* mutations typically require additional genetic variants to induce tumors, explaining at least in part the absence of an increased tumor risk in individuals with PIK3CA related overgrowth syndromes (Postema, Hopman, Deardorff, Merks, & Hennekam, 2017). Non-syndromic PIK3CA-associated tumors occur in ectodermal and endodermal epithelia like endometrium and breast, while the overgrowth occurs in tissues derived from the mesoderm and neuroectoderm, which may indicate that in addition a positive or negative (or both) tissue specific selection may be acting (Madsen, Vanhaesebroeck, & Semple, 2018). The mechanism(s) through which this acts remains unsure, both for PIK3CA-associated tumors as for limitation in tissue of tumor development in general. The molecular relatedness of somatic overgrowth and tumor development containing *PIK3CA* mutations is further illustrated by the fact that they both react on PIK3CA inhibitor treatment (Venot et al., 2018).

3.5 | Genetic compensation occurs in germline variants

Pathogenic variants in genes can be compensated for in function and this can lead to an alteration in the consequences of the variant. It has been suggested to work through series of transcription factors that form a network that maintains the expression of the group of transcription factors, aiming at a stable function of genes in the network. This transcriptional adaptation indicates that a pathogenic variant in one gene may alter the regulation and expression of other, related genes, leading to functional compensation: genetic compensation (El-Brolosy & Stainier, 2017). The exact mechanisms underlying genetic compensation remain poorly understood (El-Brolosy & Stainier, 2017). Long noncoding RNAs (lncRNAs) are known as one of the regulators of gene expression (Salehi, Taheri, Azarpira, Zare, & Behzad-Behbahani, 2017). LncRNAs can function in different ways, typically by chromatin modification, genomic imprinting, chromosomal dosage compensation and alternative splicing (Salehi et al., 2017). The mechanism of genetic compensation clarifies why certain germline variants can have no phenotypic consequences, whereas, at the same time, postfertilization inhibition of transcription of the same gene by a

morpholino can cause phenotype alterations (Rossi et al., 2015). Genetic compensation of variants by transcriptional adaptation has only been described in the germline (Niwa, 2018), and it remains unknown whether it can also occur later in development, that is, in somatic cells. Reports on therapeutic interventions have shown genetic compensation in somatic cells: *RUNX1* inhibition can effectively suppress leukemia cells, but cells may retain proliferation activity due to upregulation of *RUNX2* and *RUNX3*, compensating the combined level of RUNX family expression (Kamikubo, 2018).

The opposite is also possible: a mutated gene acts in a pathway and causes a syndrome. Due to an additional variant in another gene acting in the same pathway the individual with a tumor develops a more aggressive form of the tumor. An individual with a malformation syndrome due to the mutated gene who has the additional variant in the other gene as well, has an increased chance to develop a tumor. An example is formed by *RABL3* variants which act in the RAS/MAPK pathway (Nissim et al., 2019). A mutated RABL3 protein may accelerate prenylation of KRAS and may thus influence cell proliferation in individuals with hereditary pancreatic cancer. In an animal model, mutated RABL3 caused growth disturbances and skeletal abnormalities similar to those observed in humans with a RASopathy (such as Noonan syndrome [#163950] and Costello syndrome [#218040]). Possibly this mechanism explains the variability of tumor occurrences in RASopathies (Rauen et al., 2018).

3.6 | Epigenetic influences

Epigenetics refers to "hereditary differences in activity and expression of genes that occur without altering the DNA sequence" (Berger, Kouzarides, Shiekhattar, & Shilatifard, 2009; Waddington, 1942). The major mechanisms involved are DNA methylation, noncoding RNAs and histone modifications and nucleosome positioning (Esteller, 2008), and a vast number of genes is involved in these mechanisms. Variations in these genes have been found to cause malformation syndromes such as the cohesinopathies (Zakari, Yuen, & Gerton, 2015), imprinting disorders (Eggermann et al., 2015; Wilkins & Ubeda, 2011), and those caused by histone modifications (Martire & Banaszynski, 2020). Some of these disorders are known to be associated with an increased chance to develop a tumor, such as Roberts syndrome [#268300] (Mannini, Menga, & Musio, 2010), and Beckwith-Wiedemann syndrome (Maas et al., 2016), but in most there is no known increased risk for tumors, or there is a good other explanation for a tumor, like the marked and relentless reflux and increased chance to develop esophagus carcinoma in Cornelia de Lange syndrome (Kline et al., 2018). Still, variants in the same genes as those that cause the malformation syndromes, can be found frequently in various tumors, such as osteosarcoma, myeloid dysplasias, and breast cancer (Bao-Caamano, Rodriguez-Casanova, & Diaz-Lagares, 2020; De Azevedo et al., 2020; Rinke, Chase, Cross, Hochhaus, & Ernst, 2020). Due to one or more of the above mentioned mechanisms, and likely additional, yet unknown mechanisms, epigenetic influences may demonstrate tissue specific differences (Cusanovich et al., 2018), which in part may explain the lack of tumor development in syndromes. The use of epigenetics in biomarker studies and therapies falls outside the scope of the present manuscript (Bates, 2020).

4 | DISCUSSION

In this article we reviewed in short a number of genetic mechanisms which play a role in the etiology of tumors in malformation syndromes. We illustrate that the empiric variation in co-occurrence of tumors in malformation syndromes cannot be explained by a single mechanism: several mechanisms play a role, which may even co-occur in the same individual. Many of these mechanisms are still insufficiently understood, their frequencies of occurrence are usually unknown, whereas hitherto undescribed mechanisms may proof to play a role as well. Cellular interference may serve as an example of such additional mechanism: if in a person there are two cell lines with a different genetic make-up, typically by mosaicism, the cells may have different adhesion properties which may cause sorting abnormalities and disturbed intercellular connections. Well known examples are the X-linked disorders frontonasal dysplasia and PCDH19-related epilepsy, in which male mosaics and females mosaic due to random X-inactivation are affected, and nonmosaic males (with the mutated gene in all cells) are normal (Gecz & Thomas, 2020; Twigg et al., 2013). It is assumed that only mosaicism for genes with cell surface properties and for which there is a functional redundancy in the nonmosaic hemizygous male can lead to this mechanism. Cellular interference has not been reported in tumors, but it is well possible there are genes involved in tumor development with such properties. Another mechanism that needs further studies are mitochondrial mutations of which it was suggested that these do not act as driver mutations but normal mitochondrial activity is needed for maintenance of tumor cells (Ju et al., 2014). How mitochondrial activity influences tumor growth and whether it has also an influence in tumor development is unknown (Lawless, Greaves, Reeve, Turnbull, & Vincent, 2020).

Whether the influence of copy number variations (CNVs; gains and losses of DNA sequence >1 kb) offers an explanation for the difference in tumor development in individuals with a syndrome is not yet clear. On one hand CNVs occur in otherwise healthy individuals in a relatively high percentage (Redon et al., 2006). On the other hand CNVs can be the explanation of malformations and malformation syndromes (Martin, Kirkpatrick, & Ledbetter, 2015). Some CNVs are known to be associated with an altered frequency of a particular tumor type (both increase and decrease), such as Down syndrome [#190685] (Antonarakis et al., 2020), but in many other CNVs this is at the present not known, probably mainly due to lack of sufficient follow-up data. Still, we may expect that increased risks will exist in a number of CNVs due to the number of genes involved in the deletions and duplications. CNVs may also influence both the development and progression of tumors in Mendelian disorders: an excess of CNVs was reported in families with Li-Fraumeni syndrome [#151623], caused by *TP53* variants, and the families with the highest number of CNVs had the highest frequency of tumors (Shlien et al., 2008). The authors

suggested that the CNVs can also act as the "genetic foundation on which larger somatic chromosome duplications and deletions develop in tumors" (Shlien et al., 2008). CNVs may also develop as part of a syndrome in DNA repair disorders, and this can have an influence on tumor development and progression as well. A CNV may also cause an altered positioning of chromosome segments. This has attracted much attention recently by the description of topologically associating domains (TADs) (Campbell, 2019; Valton & Dekker, 2016). The influence of CNVs, either in the germline or in the tumor tissues, in tumor progression and reaction to treatments falls outside the scope of the present manuscript.

Further investigating these mechanisms should be instrumental to understand variation in phenotype in syndromes. This implies thorough long-term follow-up studies in patients with malformation syndromes. Initial description of individuals with newly recognized entities often deals with younger patients, who may not yet show an increase in tumors at that age and in whom this become evident only later on. An example is Primrose syndrome [#259050] in whom the increased frequency of testis tumors only became evident when a sufficient number of adult males were known (Melis et al., 2020). Follow-up data on a sufficiently large number of individuals with a syndrome may also lead to the opposite: the initial report of an increased frequency of tumors in patients with Rubinstein-Taybi syndrome [#180849] (Miller & Rubinstein, 1995) was found to be incorrect for patients with the syndrome below 40 years of age when a sufficiently large number of patients was re-evaluated (Boot et al., 2018), likely due to publication bias in the early days of description of this syndrome. Furthermore, careful assessment for the presence of malformations in (young) cancer patients is essential, as well as studying whether there is a difference in tumor risk in those with inherited and de novo variants in the same gene. We favor studies in individuals who do not develop tumors notwithstanding their known genetic predisposition. Studying these latter "superheroes of disease resistance" (Chen et al., 2016) may add fundamental insight not only into pathogeneses but also regarding prevention and (targeted) therapy (Liu et al., 2015).

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

There are no additional data, all data are available in the manuscript.

ORCID

Raoul C. Hennekam https://orcid.org/0000-0002-6745-1522

ENDNOTE

[1] The term TPS is ambiguous as a tumor not only indicates a benign or malignant neoplasia but also tissue masses and swellings that arise by other mechanisms such as inflammation or trauma. The term neoplasia predisposition syndrome would be the correct term. However, the term TPS is commonly use in international literature and for that reason we use it here as well.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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