

Review Article

Getting a Clue from 1q: Gain of Chromosome 1q in Cancer

Puri L and Saba J*

Department of pediatric cancer researcher, children's Hospital Oakland Research Institute, USA

*Corresponding author

Julie D. Saba, Department of pediatric cancer researcher, children's Hospital Oakland Research Institute, 5700 Martin Luther King Jr. Way, Oakland, CA 94609, USA; Tel: 510-450-7690; Fax: 510-450-7910; Email: jsaba@chori.org

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Abstract

Cytogenetic abnormalities including the gain and loss of chromosomes play an important role in oncogenesis. Aberrations involving chromosome 1 are one of the most common anomalies reported among human neoplasms and have been observed in both solid tumors and hematological malignancies. This review highlights the prognostic import of cytogenetic abnormalities involving 1q in childhood cancers and weighs the evidence supporting some candidate genes that may underlie this phenomenon. Gain of chromosome 1q has been frequently noted in pediatric malignancies including Wilms tumor, neuroblastoma, Ewing sarcoma and brain tumors such as ependymoma and high grade gliomas and the presence of this anomaly is usually associated with disease recurrence and poor prognosis. Risk stratifications incorporating the presence or absence of additional 1q material are being integrated into many clinical management protocols. However the candidate genes on the long arm of chromosome 1 that serve as drivers of tumorigenesis still remain unidentified. Identification of these candidate genes and characterization of their specific functions may potentially help scientists develop therapeutic strategies that could improve prognosis in patients whose malignant cells harbor additional 1q material.

Keywords

- Pediatric malignancy
- Childhood cancer
- Cytogenetic
- Chromosome 1
- 1q

ABBREVIATIONS

BBSFOP: Baby Brain Soci t  Fran aise d'Oncologie P diatrique; **CCSG:** Children's Cancer Study Group; **CNS:** central nervous system; **HGG:** high grade glioma; **NTRK1:** neurotrophic tyrosine kinase receptor, type 1; **RAR:** retinoic acid receptor; **RAS:** rat sarcoma; **SIOP:** International Society of Paediatric Oncology; **SPRR:** small proline rich proteins

INTRODUCTION

Significant improvements have been made in the field of pediatric cancer over the last decade with increasing cure rates for various malignancies. This is partly due to improvements in risk stratification by recognizing various tumor specific molecular abnormalities and developing therapies targeting these aberrations. Such abnormalities include structural alterations, insertional mutagenesis, chromosomal translocations and gene amplification, resulting in oncogene activation. Aberrations involving chromosome 1 are one of the most common anomalies reported among human neoplasms and have been well-described in both solid tumors and hematological malignancies [1]. Among solid tumors, 1q alterations have been reported in breast, lung and germ cell tumors [2, 3]. Gain of chromosome 1q is usually associated with poor prognosis and disease recurrence. The aberrations can be seen as trisomy of the entire long arm, as an isochromosome 1q, as a trisomy or as a duplication of a smaller region, especially 1q23-1q32 [4-6]. It has been suggested that

three or more copies of a gene (or genes) in this region provide a selective advantage to cancer cells. Furthermore, the finding of partial or complete 1q trisomy being more frequent in recurrent than in primary tumors could suggest that this change may be associated with tumor progression [7].

Chromosome 1q in Brain Tumors

Brain tumors represent the most common solid tumor type in childhood. Ependymomas are the third most common central nervous system (CNS) tumors and are associated with a mortality rate as high as 40% [8]. Currently the risk stratification for ependymoma patients is based solely on clinical parameters, and extent of primary tumor resection remains the most consistently reported predictor of outcome [9]. Until recently, no reliable biological marker that can accurately predict outcome in a sizeable population has been identified. Gain of chromosome 1q has been reported as a frequent genetic aberration in both primary and recurrent childhood intracranial ependymomas [10]. Kilday *et al.* surveyed 48 ependymomas, and gain of 1q was the most frequent imbalance in primary (17%) and recurrent ependymomas (33%). It was also noted to be an independent predictor of tumor progression across the pooled trial cohort and both United Kingdom Children's Cancer Study Group/International Society of Paediatric Oncology (UKCCSG/SIOP) CNS 9204 clinical trial and Baby Brain Soci t  Fran aise d'Oncologie P diatrique (BBSFOP) group protocol [11]. The only clinical variable associated with adverse outcome was incomplete tumor

resection. Integrating tumor resectability with 1q25 status enabled stratification of cases into disease progression risk groups for all three trial cohorts. Higher resolution cytoband analysis revealed 1q21–25, 1q32, and 1q42–44 to be amongst the most frequently gained sub-regions on this arm (11/48, 23%) [11]. This suggests that gain of chromosome 1q has prognostic significance and should be incorporated into future trials along with other clinical parameters.

Another group of CNS tumors in children encompasses high grade gliomas (HGG) that comprise 15 to 20% of all childhood brain tumors; 70 to 90% of these patients die within two years of diagnosis [12]. Brain stem gliomas occur rarely in adults, and the prognosis in adults is better than in children. Paugh and colleagues analyzed HGG samples from 78 pediatric patients and noted that gain of chromosome 1q was the most frequent finding (29%), followed by high amplitude gains encompassing *PDGFRA* (platelet derived growth factor receptor alpha) (12%) [13]. Gain of chromosome 1q was also noted to be significantly more frequent in irradiation-induced glioblastoma. There was a significant association between 1q gain and decreased survival among patients with glioblastoma ($p=0.04$), although it could not be confirmed if this effect was independent of the treatment modality used. The investigators also compared structural aspects of these chromosomal imbalances in pediatric and adult glioblastomas. Pediatric glioblastomas were distinguished from adult glioblastomas by frequent gain of chromosome 1q and paucity of chromosome 7 gain and 10q losses [13]. Based on these findings, identification of one or more candidate genes on chromosome 1q, particularly in the region of 1q21–25, might be important in identifying pathways involved in the biology of these tumors and establishing reliable prognostic markers.

Chromosome 1q in Neuroblastoma

Neuroblastoma, the most common extracranial solid tumor, is another pediatric malignancy in which gain of 1q is shown to be associated with progressive disease. It is the main cause of cancer-related death in pre-school age children [14]. Risk stratification is based on age of the patient, stage of the disease, histology and *MYCN* amplification. Genetic changes in neuroblastoma that are recognized to correlate with prognosis include *MYCN* amplification, alterations in DNA ploidy index, and deletion of 1p in tumors. Trisomies of chromosome 1q along with 17q in neuroblastoma were initially identified by Gilbert *et al.*, in 1984 and found to be associated with disease progression [15]. Since then, various studies have noted gain of 1q to be a recurrent finding. Hirai *et al* analyzed 27 neuroblastoma samples and found that 50% of stage 4 patients and all cases with progressive disease had chromosome gain at 1q21–25 [16]. Using dual core fluorescent in situ hybridization, the location of the 1q21–25 gain was refined to encompass an increase in copy number on 1q23 suggesting that amplification at 1q23 may play a role in progressive neuroblastoma [16].

Chromosome 1q in Wilms Tumor

Wilms tumor is the most common pediatric renal tumor. A majority of the children have favorable histology and good outcome. However, about 15% of patients with favorable histology and 50% of patients with anaplastic type Wilms tumor

experience recurrence [17]. The National Wilms Tumor Study Group has identified that loss of heterozygosity of chromosome 1p and 16q are associated with inferior outcomes [18,19]. However these anomalies have been found in only 4.6% of the patients enrolled in the third and fourth National Wilms Tumor Studies. Other genetic abnormalities have also been identified, and gain of chromosome 1q has been noted to be a recurrent finding associated with a poorer prognosis [19]. A total of 212 samples from patients in various stages of Wilms tumor were analyzed using multiplex ligand dependent probe amplification. Tumors from 58 (27%) patients showed evidence of gain of 1q [18]. The 8-year event free survival was 76% (95% CI, 63–85%) for those with 1q gain and 93% (95% CI, 87%–96%) for those who lacked 1q gain ($p=0.0024$). The overall survival was also found to be lower in the group with gain of 1q (89%) as compared to the group that lacked gain of chromosome 1q (98%, $p=0.0075$) [18]. It is also associated with a significant increase in the risk of disease recurrence (risk ratio estimate, 2.72; $p=0.0089$). Other groups have also found gain of chromosome 1q to be a frequent chromosomal aberration in favorable histology Wilms tumor. Natrajan *et al* analyzed 76 Wilms tumor samples by microarray-based comparative genomic hybridization and found that gain chromosome 1q was present in 40% of the patients and was strongly associated with a poor prognosis [20]. A strong correlation was observed between gain of 1q and losses of 1p and 16q, suggesting that these abnormalities arise from a single chromosomal mechanism. On further analysis they also identified recurrent low-level gains at 1q25.3, 1q31 and 1q42, thus suggesting that there may be more than one region of gain/over expression associated with Wilms tumor on chromosome 1q [20]. Given the significantly high percentage of 1q and its strong association with disease recurrence, it becomes more critical to identify the candidate genes involved for possible targeted therapy.

Chromosome 1q in Sarcomas

Ewing sarcoma is the second most common bone tumor and is characterized by a balanced translocation $t(11;22)(q24;q12)$ which is present in 85 to 90% of the patients. In addition to 22q12 rearrangements, non-random chromosomal aberrations have been detected in more than 50% of the patients [21]. Hattinger *et al* analyzed tumors from 134 patients and found that structural aberrations in the long arm of chromosome 1 were present in 21% of the patients [22]. Gain of chromosome 1q was associated with adverse overall survival and event-free survival and this finding may suggest the need for assessing chromosome 1q anomalies routinely in all patients with Ewing sarcoma, irrespective of the clinical stage, in order to make additional risk stratification [22]. Gain of 1q has been reported in other sarcomas as well [1]. Forus *et al* surveyed 54 soft tissue sarcomas by comparative genomic hybridization (CGH) analysis and detected frequent amplification of the 1q21–q22 region, indicating that 1q21–q22-located genes may also play an important role in the development and/or progression of such tumors [3].

Chromosome 1q in Other Pediatric Malignancies

Other pediatric malignancies in which gain of 1q has been implicated include retinoblastoma [23], Burkitt's lymphoma [24], acute myeloid leukemia [25] and rhabdomyosarcoma [26].

Candidate Cancer-Related Genes on Chromosome 1q

It is now evident that gain of long arm of chromosome 1q is a recurrent aberration in various malignancies and is invariably associated with poor outcomes and disease recurrence. However the candidate genes on chromosome 1q that could be involved in tumorigenesis remain unidentified. Some investigation of this question has been undertaken in sarcomas where several candidate genes located in the 1q21-23 region have been identified. These include *OTF-1*, *NTRK1*, and *SPRR3* and *S100* family of calcium-binding proteins (CACY and CAPL genes) [1,7,27-31]. The neurotrophic tyrosine kinase receptor, type 1 (*NTRK1*) is membrane-bound receptor that upon binding phosphorylates itself and other members of the mitogen activated protein kinase pathway [32]. Members of the small proline rich protein (*SPRR*) class of proteins are differentially regulated in various types of epithelia, and their expression is modulated in response to environmental insult, aging and following carcinogenic transformation [33-35]. The elevated expression of calcyclin, a cell-cycle-regulated protein, has been observed in highly metastatic melanoma cell lines. Utilizing microarray-based comparative genomic hybridization on a series of 76 Wilms tumor samples, Natrajan *et al.* Identified gains in 1q as correlating with an increased risk of relapse [20]. Further, the authors identified several candidate genes including *RAB25*, *NES*, *CRABP2*, *HDGF* and *NTRK1* within the region of 1q22-q23 [20]. *RAB25* is a small GTPase encoded by a gene that is also present in a similar region of copy number gain in breast and ovarian cancers and whose overexpression is associated with poor outcome in these tumors [36]. *RAB25* is a member of the rat sarcoma (*RAS*) oncoprotein small GTPase superfamily. Members of the *RAB* superfamily play important roles in regulating signal transduction and various cellular processes, including cell differentiation and proliferation [37]. *NES* encodes for nestin, a protein expressed by dermatomal cells and myoblasts. It has been shown to be a transient component of the dynamic intermediate filament network during muscle development [38]. Nestin is overexpressed in some rhabdomyosarcomas [39], neuroectodermal tumors, glioblastomas, astrocytomas, and oligodendrogliomas [40,41]. The *CRABP2* gene encodes Cellular Retinoic Acid Binding Protein 2, which shuttles retinoic acid from the cytosol into the nucleus through its ligand-activated nuclear localization signal [42]. Downregulation of *CRABP2* has been associated with poor survival in head and neck squamous cell carcinoma and breast cancer [43]. Further, *CRABP2* expression can inhibit cell growth in various types of carcinomas, an effect exerted in part by its ability to deliver retinoic acid to retinoic acid receptors (*RAR*), thus leading to induction of anti-proliferative *RAR* target genes [44-48]. This effect is consistent with the fact that retinoic acid signaling promotes the differentiation of stem cells, and reduced *RAR* signaling may be required for tumorigenesis. However, *CRABP2* overexpression has been found in Wilms tumor as described above, as well as in various other types of malignancy including ovarian cancer [49] and leukemia [50,51]. These opposing observations could be explained if *CRABP2* exerted effects that were either *RAR*-independent, cell-type specific, or if effects were mediated by a neighboring gene. *HDGF* encodes Hepatoma Derived Growth Factor, a heparin-binding protein that stimulates the proliferation of endothelial

cells, vascular smooth muscle cells and fibroblasts [52,53]. *HDGF* has been found to be over expressed in several types of carcinomas including hepatocellular carcinoma, pancreatic cancer, and gastric and esophageal carcinomas, where it plays a key role in the development and progression of these cancers [54-59]. Further studies to identify the genes on chromosome 1q that contribute to carcinogenesis are needed to help characterize the pathways involved in disease progression. Doing so will aid in development of targeted therapies and thus improve prognosis for patients in which this cytogenetic abnormality is noted.

CONCLUSIONS

In summary, gain of 1q is a frequently occurring genetic aberration in various malignancies, including both solid tumors and leukemia's and is more commonly associated with disease relapse and a poor prognosis. Thus, it is critical to evaluate its utility as a prognostic marker in these cancers. Evaluation of chromosome 1q in prospective studies with sizeable patient populations will help assess its value in risk stratification. At the same time, it is crucial to identify the candidate genes that may contribute to tumor genesis and account for the poor prognosis conferred by 1q amplification. Such knowledge will facilitate the identification of critical pathways that could be targeted to prevent disease progression and metastasis. Since 1q amplification is present in malignancies arising from a variety of different tissues of ectodermal, endodermal and mesodermal origin, it is likely that the genes affected are involved in universal pathways leading to oncogenesis, such as those affecting cell proliferation, cell cycle regulation, cell death, and differentiation. Evaluation of gain of chromosome 1q in future clinical trials could provide an important clue about the mechanisms involved in tumor genesis and disease metastasis.

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