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# Is there an association with constitutional structural chromosomal abnormalities and hematologic neoplastic process? A short review

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**Abstract** The occasional observation of constitutional chromosomal abnormalities in patients with a malignant disease has led to a number of studies on their potential role in cancer development. Investigations of families with hereditary cancers and constitutional chromosomal abnormalities have been key observations leading to the molecular identification of specific genes implicated in tumorigenesis. Large studies have been reported on the incidence of constitutional chromosomal aberrations in patients with hematologic malignancies, but they could not confirm an increased risk for hematologic malignancy among carriers of structural chromosomal changes. However, it is of particular interest that constitutional structural aberrations with breakpoints similar to leukemia-associated specific breakpoints have been reported in patients with hematologic malignancies. Because of insufficient data, it remains still unclear if these aberrations represent random events or are associated with malignancy. There has been a substantial discussion about mechanisms involved in constitutional structural chromosomal changes in the literature. The documentation of more patients with constitutional structural chromosomal changes could be of major importance. Most importantly, the molecular investigation of chromosomal regions involved in rearrangements could give useful information on the genetic events underlying constitutional anomalies, contributing to isolation of genes important in the development of the neoplastic process. Regarding constitutional anomalies in patients with hematologic disorders, a survey of the

cytogenetic data of our cytogenetics unit is herein also presented.

**Keywords** Cytogenetics · Constitutional structural chromosomal changes · Translocations · Hematologic malignancies

## Introduction

Over the past four decades, it has become clear that acquired nonrandom chromosomal changes are associated with specific malignant diseases. Acquired chromosome abnormalities occur during life and are limited to a specific tissue. On the other hand, constitutional chromosomal rearrangements are either inherited from a carrier parent or occur *de novo* during gametogenesis and are present in all tissues. Acquired chromosomal changes in malignant diseases involve loss or gain of chromosomal material and rearrangements that may result in various structural aberrations. Among acquired structural chromosomal changes, reciprocal translocations have been found in a variety of malignant diseases mainly including leukemias, lymphomas, and sarcomas and they have been implicated in the etiology of the neoplastic diseases with the involvement of specific genes [1]. However, there are many unanswered questions related to the cause of translocations and involvement of specific genes. For example, what causes chromosomal translocations? It was suggested that the breaks could be random and selection of those whose genetic alterations provide a cell with a proliferative advantage could be the critical factor [2].

Approximately one in 150 newborns will have a constitutional chromosomal abnormality, while balanced structural changes represent about one third of these

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aberrations [3–5]. It is now well recognized that certain constitutional chromosomal aberrations confer a tumor predisposition [6, 7]. Investigations of families with hereditary cancers and constitutional chromosome abnormalities have led to the molecular identification of specific genes implicated in tumorigenesis. Therefore, constitutional structural chromosomal changes detected in patients with malignant diseases have been key observations leading to localization of genes involved in carcinogenesis, such as the loci involved in retinoblastoma patients with 13q deletion and the loci in Wilms' tumor patients with 11p deletion [8, 9]. Furthermore, the NF1 gene in neurofibromatosis was found by cloning the chromosome 17 breakpoint in a reciprocal translocation detected in a patient with neurofibromatosis [10]. The observation that constitutional structural chromosomal aberrations are associated with a predisposition to cancer has led to a two-hit hypothesis for cancer development. The first hit is a constitutional abnormality involving a specific gene and the second hit is an acquired inactivation of the other allele by mutation or other genetic change [11].

In this short review, we summarize the most important large series related to incidence of constitutional structural chromosomal abnormalities in patients with hematologic malignancies. Moreover, we describe data from the literature regarding constitutional structural chromosomal aberrations observed in hematologic cancers and discuss their potential role, if any, in the development of malignancy. A survey of the cytogenetic data of our cytogenetics unit regarding constitutional anomalies in patients with hematologic disorders is herein also presented.

### **Incidence of constitutional structural chromosomal changes in hematologic malignancies**

Constitutional chromosomal aberrations including numerical and structural rearrangements are found in approximately 0.6–0.92% of the newborns [3–5]. Certain constitutional chromosomal abnormalities have been associated with an increased risk for malignancy. A number of studies have so far described the simultaneous occurrence of constitutional chromosomal changes and cancer, while, in some families with an increased incidence of cancer, hereditary translocations have been found [12–19]. The occasional observation of constitutional chromosomal abnormalities in patients with a malignant disease has led to a number of studies on their potential role in cancer development. Some numerical chromosomal aberrations have been found to be associated with an increased risk for malignancy. For example, patients with Klinefelter syndrome are at increased risk for development of germ cell tumors, while Down syndrome patients have an increased

risk for myeloid malignancies [6, 7]. However, it remains still unclear whether the constitutional structural aberrations, especially reciprocal translocations, are a coincidental feature or a predisposing factor in the development of the malignant disease. The most frequently occurring constitutional reciprocal translocation in man is t(11;22)(q23;q11). Studies showed a significant association of breast cancer with that translocation [16].

A number of studies have reported on the incidence of constitutional chromosomal aberrations in patients with hematologic malignancies (Table 1). Alimena et al. [20], in a series of patients with hematologic malignancies cytogenetically studied, found 21 cases with a constitutional anomaly. These patients represented approximately 1.5% of the cases successfully karyotyped. Among 21 cases with a constitutional anomaly, four cases presented a Robertsonian translocation and one case a reciprocal translocation. Benitez et al. [21] reviewing 5,500 patients with hematologic malignant diseases (718 patients from their laboratory and 4,782 from unselected series in the literature) found 59 cases with a constitutional chromosomal abnormality. Among them, 19 cases had structural abnormalities (ten cases with a Robertsonian translocation, seven cases with a reciprocal translocation, and two cases with an inversion or a ring chromosome, respectively). A detailed analysis of these data showed that the incidence of balanced alterations was similar in hematologic patients and newborns, although, in hematologic patients, the Robertsonian translocations presented an incidence double of that seen at birth. However, this difference was not significant. Thus, in that study, an association of constitutional translocations with malignancy had not been well defined. The Groupe Francais de Cytogénétique Hématologique [22], in a retrospective review on cytogenetic data of patients with hematologic malignancies, found 56 patients with constitutional anomalies. Among them, 22 patients presented structural rearrangements. The question of whether the patients with these aberrations were at greater risk of hematologic malignancy remained unanswered. Cerretini et al. [23] reviewed 4,164 patients with various hematologic disorders cytogenetically studied in their laboratory to analyze the frequency of constitutional chromosome abnormalities and to evaluate their association with hematologic malignancies. Twenty-four cases presented constitutional anomalies including five cases with structural abnormalities and 19 cases with numerical aberrations. One patient with Down syndrome had also a pericentric inversion of chromosome 9. Nonsignificant differences among the frequency of patients with constitutional anomalies from their hematologic series and those reported in the newborns were found. Welborn [24] evaluated the frequency of constitutional chromosomal abnormalities in 5,633 patients with hematologic malignancies. Constitutional chromo-

**Table 1** Constitutional structural chromosomal abnormalities in patients with hematologic malignancies in the literature and this series

Ref no	Number of patients with hematologic malignancy	Constitutional structural chromosomal abnormalities	Reciprocal translocations	Robertsonian translocations	Inversions	Other structural abnormalities
12	312	1		1		
20	1,400	5	1	4		
21	5,500	19	7	10	1	1
22	?	22	7	10	4	1
23	4,164	6	1	4	1	
24	5,633	26	14	5	6 <sup>a</sup>	2
<i>P</i> <sup>b</sup>	2,429	11	2		9	

<sup>a</sup> One of them presented also a reciprocal translocation

<sup>b</sup> Findings of the present series

some aberrations were found in 50 patients. Among them, 26 cases presented structural chromosomal abnormalities including Robertsonian translocations (five cases), reciprocal translocations (14 cases, one of which additionally had an inversion), and inversions (five cases), while two cases presented del(18q) or r(18), respectively. Moreover, the author, to further investigate the type of constitutional balanced structural chromosomal abnormalities observed in hematologic malignancies and to evaluate their possible association with neoplastic process, collected data from the literature and compared it with the incidence of specific constitutional chromosome aberrations in the newborn population. There were a total of 157 patients with a hematologic malignancy, who carried a constitutional balanced structural chromosomal abnormality, found from the literature and their laboratory. Among them, 65 cases presented Robertsonian translocations; 58 had reciprocal translocations, while 34 cases had inversions. The most common Robertsonian translocation was der(13;14) and it was observed in 41 patients. Reciprocal translocations and inversions involved several chromosomes. Chromosomes 5, 7, and 9 were the most commonly involved in inversions. The results from that review suggested that the link between most constitutional karyotypes and the incidence of hematologic malignancy is random.

Betts et al. [12] investigated 578 children with neoplasms for the presence of balanced constitutional chromosome aberrations. Among them, 312 patients had a hematologic malignancy. They found five patients with a balanced constitutional anomaly and only one of them, who carried a Robertsonian translocation, had a diagnosis of a

hematologic malignancy. The incidence of constitutional anomalies within that study group was statistically significant when calculated against the expected incidence of constitutional balanced aberrations in the newborns, though, in that study, the number of patients was small.

An alternative approach to investigate the potential relationship between constitutional chromosomal abnormalities and the development of a malignant disease is the retrospective follow-up of persons with known constitutional anomalies to determine if the risk for tumor development is increased (Table 2). Hasle et al. [25] investigated the occurrence of cancer in a cohort of 183 persons with constitutional chromosome 7 abnormalities. They found five cases with cancer. There were no cases of leukemia. Although acquired chromosome 7 abnormalities are frequently found in patients with hematologic disorders, in that study, the overall risk of developing hematologic cancer was not increased. Recently, Bache et al. [26], collecting the results of chromosome examination from all cytogenetic laboratories in Denmark between 1961 and 2002, found 4,816 carriers of a constitutional structural abnormality. Information on inheritance of the constitutional structural chromosomal abnormalities was available for 1,349 carriers (28%). The members of this cohort were followed up and the occurrence of cancer was measured. During the follow-up period, 222 cancers were diagnosed in 209 carriers. Among them, 39 cases presented hematologic malignancies including patients with leukemias, lymphomas, and multiple myeloma. The results showed that there was no overall increased risk for cancer among carriers. Furthermore, no significant changes in the risk for

**Table 2** Development of hematologic malignancies in carriers of constitutional structural chromosomal abnormalities in the literature

Ref no	Number of persons with constitutional structural chromosomal abnormalities	Number of patients with hematologic malignancy	Reciprocal translocations	Robertsonian translocations	Inversions	Other structural abnormalities
25	183	0				
26	4,816	39	12	6	9	12

any of the type-specific cancers were found in the largest subgroups of constitutional structural chromosomal abnormalities including balanced reciprocal or Robertsonian translocations and inversions. The authors could not confirm an increased risk for breast cancer among carriers of the recurrent translocation  $t(11;22)(q23;q11)$ , as it was previously indicated by Lindblom et al. [16]. Interestingly, they found a significantly decreased risk for cancer among persons who had inherited their anomaly from their father, while the risk of those who had inherited the anomaly from their mother was as expected. In addition, the authors found 12 constitutional structural anomalies with a breakpoint potentially associated with a known cancer-related gene, whereas potential new loci associated with type-specific cancers were suggested.

Reviewing on patients cytogenetically studied by G-banding technique in our cytogenetics unit, we found 2,429 patients with hematologic malignancies. Regarding constitutional balanced rearrangements detected in this group of patients, we found two patients with acute leukemia, who carried the balanced reciprocal translocations,  $t(3;5)(p25;q22)$  and  $t(1;14)(p31;q21)$ , respectively [27]. Also, nine patients carried a constitutional pericentric inversion of chromosome 9,  $inv(9)(p11q13)$ . This anomaly was not limited to one specific subtype of hematologic malignancy, but it was found sporadically among all types of hematologic malignancies. Pericentric inversion  $inv(9)(p11q13)$  is the most frequent constitutional pericentric inversion in man with an incidence of 1% in the general population, while constitutional balanced reciprocal translocations are found in approximately 0.09% of the newborns. Therefore, the incidence of balanced structural constitutional chromosomal changes in our series of patients was not increased.

### **Is there an association with structural constitutional chromosome aberrations and hematologic neoplastic process?**

Recurrent acquired balanced chromosomal aberrations are associated with many types of hematologic malignancies leading to critical gene fusions or other gene alterations [28, 29]. In addition, it is possible to infer a link by looking for changes in the same chromosomal regions of patients with acquired aberrations as those affected by constitutional anomalies. For example, the constitutional inversion  $inv(7)(q22q34)$  described in a myelodysplastic patient led to the identification of other hematological patients with acquired chromosomal changes in the same region [30]. Moreover, the *RUNX1* gene located on 21q22 is involved in the translocation  $t(8;21)$  observed in acute myelogenous leukemia (AML). Families with germ line mutations in *RUNX1* gene have an increased risk for AML development [31].

Although large studies could not confirm an increased risk for hematologic malignancy among carriers of structural chromosomal changes, it is of particular interest that constitutional translocations with breakpoints similar to leukemia-associated specific breakpoints have been reported in a number of patients with hematologic malignancies [13, 18, 24, 32–34]. This might indicate that the constitutional translocation by itself probably plays a role in the neoplastic process. However, the fact that other family members as carriers of hereditary translocations have no evidence of a hematologic disorder might indicate that the constitutional abnormality is not causative in the hematologic disorder. Conversely, it is also possible that an additional acquired mutation is required for the malignant transformation. This is in keeping with the multistep hypothesis of malignant transformation.

Robertsonian translocations are the most common constitutional structural abnormalities occurring in man. Robertsonian rearrangements have the highest mutation rates of structural chromosome aberrations based on surveys of newborns and spontaneous abortions. Constitutional Robertsonian translocations have also been described in patients with hematologic disorders [24, 26, 35]. Moreover, acquired Robertsonian translocations have been reported in hematologic malignancies. Welborn [36] reported 237 patients with hematologic malignancies (from the literature and their series) who had an acquired Robertsonian translocation.

Regarding constitutional reciprocal translocations, the chromosomes and breakpoints involved in these aberrations are unique to each family. However, the familial translocation  $t(11;22)(q23;q11)$  has been reported in more than 100 unrelated families and it has been associated with breast cancer [16]. Among patients with hematologic malignancies, Welborn [24] found 58 carriers of a reciprocal translocation in the literature and their series. Based on the expected population incidence, the author concluded that the reciprocal translocations do not predispose to hematologic malignancies. However, many investigators, based on hereditary translocations, reported on the probability that constitutional translocations represent a predisposing factor in the development of hematologic malignancies. Thus, in some families with an increased incidence of hematologic malignancy, hereditary translocations have been described [13, 17, 18, 33]. Markkanen et al. [17] described a family with an inherited translocation  $t(3;6)(p14;p11)$ . Carriers of this translocation developed hematologic neoplasias, while healthy translocation carriers were also detected. Acquired reciprocal translocations are the hallmark of hematologic malignancies, resulting very frequently in fusion gene products, which are implicated in the pathogenesis of these disorders [29].

Recurrent familial inversions involving several chromosomes have been described in the literature. The most

frequent pericentric inversion is  $\text{inv}(9)(\text{p}11\text{q}13)$ , with an incidence of 1% in the general population. Since the chromosomal breakpoints are in repetitive sequences, this inversion is considered clinically insignificant. Therefore, evidence suggests that there is no association of this anomaly with the hematologic malignancy. However, in a few studies, an acquired pericentric inversion  $\text{inv}(9)(\text{p}11\text{q}13)$  in hematologic malignancies was described, the significance of which remains unknown [37–39]. Moreover, constitutional balanced pericentric inversions involving several other chromosomes in patients with hematologic malignancy have been described in the literature. Interestingly, constitutional pericentric inversions of chromosome 16 appear similar to that associated with acute leukemia [24, 40]. Regarding constitutional paracentric inversions, the inversion  $\text{inv}(7)(\text{q}11\text{q}22)$  is one of the most commonly identified paracentric inversions in humans [41]. Stanley et al. [19] described two unrelated patients with acute leukemia who carried the same constitutional inversion of chromosome 7,  $\text{inv}(7)(\text{q}11\text{q}22)$ . In one of these families, there was a three-generation history of hematologic malignancies. Moreover, the constitutional paracentric inversion  $\text{inv}(7)(\text{q}22\text{q}34)$  has been described in patients with hematologic disorders [24]. Interestingly, as mentioned above, the identification of a constitutional inversion  $\text{inv}(7)(\text{q}22\text{q}34)$  in a myelodysplastic patient led to the identification of other myelodysplastic/AML patients with acquired chromosomal changes in the same region [30]. The chromosomal band 7q22 is a recurring region involved in myelocytic malignancies, and several genes have been mapped to this region [32]. Johnson et al. [30] mapped the breakpoint of a constitutional inversion  $\text{inv}(7)(\text{q}22\text{q}34)$  to a 650-kb region containing the ASNS gene.

Hematologic malignancy is a wide range of heterogeneous diseases and acquired balanced chromosomal abnormalities are associated with many types of hematologic malignancies leading to critical gene fusions or other gene alterations. Although constitutional structural aberrations with breakpoints similar to leukemia-associated specific breakpoints have been reported in patients with hematologic malignancies, an association of specific constitutional structural anomaly with specific subtype of disease has not been detected. In this regard, the molecular characterization of constitutional anomalies is considered of major importance. Therefore, an attempt to molecularly analyze constitutional anomalies was made by several investigators [30, 42–45].

Concerning solid tumors, to identify candidate genes for renal tumorigenesis, constitutional translocations were molecularly investigated. Foster et al. [46] characterized a constitutional translocation  $\text{t}(3;6)(\text{q}22;\text{q}16)$  associated with multicentric renal cell carcinoma without evidence of von Hippel-Lindau target gene dysregulation. No known genes were disrupted by the translocation breakpoints, but several

candidate tumor suppressor genes map within close proximity to the breakpoints. Poland et al. [47] investigated a constitutional balanced translocation  $\text{t}(3;8)(\text{p}14;\text{q}24)$  found in patients with bilateral clear cell renal cell carcinoma. The findings confirm that balanced translocations disrupting the TRC8 and FHIT genes result in an increased genetic susceptibility for bilateral clear cell renal cell carcinoma. Furthermore, the molecular cloning of the translocation breakpoints from constitutional chromosome changes in patients with hematologic disorders could lead to the isolation of genes important in the development of the neoplastic process. Hill et al. [44] reported the molecular cloning of a constitutional translocation  $\text{t}(7;22)(\text{p}13;\text{q}11)$  carried by three family members who have each developed a hematologic malignancy. The authors concluded that the genes identified around the breakpoint have been associated with various cancers and may be important risk factors in hematologic malignancy. Also, molecular investigation of the constitutional translocation  $\text{t}(3;6)$  detected in patients with hematologic malignancies showed a possible disruption of a gene by this translocation breakpoints [42].

Although large studies could not confirm an increased risk for hematologic malignancy among carriers of structural chromosomal changes, the possibility that these anomalies contribute to the neoplastic process could not be excluded. Therefore, regarding balanced structural constitutional anomalies and hematologic malignancies, a number of questions have arisen that need answers. For example, what is the cause of constitutional balanced structural abnormalities? Is there only a genetic susceptibility for chromosome breakage at certain regions or environment factors only contribute to this breakage vulnerability? Are both genetic and environmental factors implicated in chromosome breakage? Most importantly, why do certain acquired structural abnormalities seen in hematologic malignancies involve the same breakpoints as those observed in constitutional anomalies? How do the constitutional anomalies contribute, if so, to the malignant process? What is the cause of specific acquired balanced structural chromosomal changes in hematologic malignancies? Are both genetic and environmental factors implicated in specific acquired anomalies?

There is substantial discussion in the literature about mechanisms involved in constitutional structural chromosomal changes. Various reports suggested that constitutional structural chromosomal changes could affect genes that would be mutated during meiosis or somatic malignant transformation [19, 24, 48]. Welborn [24] described possible mechanisms in which the constitutional abnormalities may predispose to malignancy: (a) the balanced aberration may not be truly balanced but may have missing or extra genetic material; (b) the balanced aberration may

result in abnormal gene function, creating new fusion genes or interfering with the regulatory control of gene function.

Yet, our understanding of the mechanisms of acquired balanced structural chromosomal changes in cancer remains incomplete. Chromosomal translocations are thought to arise by a DNA double-strand break followed by aberrant DNA repair. Failure in the DNA damage response and double-strand break repair can lead to chromosomal instability resulting in neoplastic transformation [49].

Furthermore, it is known that patients with chromosome breakage syndromes have chromosomal translocations and they are characterized by defects in the DNA damage response in cancer cells, due to errors in mismatch base repair during DNA replication. Causes of DNA damage include attack by ionizing radiation, ultraviolet light, topoisomerase II inhibitors, or other environment factors. Patients with chromosome breakage syndromes have a high risk of malignancy. For example, Bloom syndrome patients develop both myeloid and lymphoid malignancies, whereas Fanconi anemia patients usually develop myelodysplastic syndromes or acute myeloid leukemia. Patients with ataxia telangiectasia with mutations of ATM gene develop primarily B or T cell lymphoid malignancies [49, 50].

In conclusion, it is known that acquired balanced chromosomal aberrations are associated with many types of hematologic malignancies leading to critical gene fusions or other gene alterations. However, the role of constitutional chromosomal abnormalities in hematologic malignancies has not been as yet clarified. Although large studies could not confirm an increased risk for hematologic malignancy among carriers of structural chromosomal changes, it is of particular interest that constitutional structural aberrations with breakpoints similar to leukemia-associated specific breakpoints have been reported in patients with hematologic malignancies, indicating that constitutional anomalies may involve chromosome regions harboring oncogenes and tumor suppressor genes. Thus, to my opinion, it seems probable that there is a relationship between constitutional structural chromosomal anomalies and the development of hematologic malignancies. I consider that there might be a genetic susceptibility for chromosome breakage and rejoining at certain regions. Subsequently, exposure to certain environmental factors could accumulate more DNA damage leading to genetic instability and development of hematologic neoplastic diseases. The documentation of more patients with constitutional structural aberrations and hematologic malignant diseases could be of major importance. Most importantly, the molecular cloning of the chromosomal breakpoints involved in constitutional rearrangements in patients with hematologic disorders could give useful information on the genetic events underlying constitutional anomalies contributing to isolation of genes important in the development of the neoplastic process.

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