The impact of translocations and gene fusions on cancer causation

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Abstract | Chromosome aberrations, in particular translocations and their corresponding gene fusions, have an important role in the initial steps of tumorigenesis; at present, 358 gene fusions involving 337 different genes have been identified. An increasing number of gene fusions are being recognized as important diagnostic and prognostic parameters in malignant haematological disorders and childhood sarcomas. The biological and clinical impact of gene fusions in the more common solid tumour types has been less appreciated. However, an analysis of available data shows that gene fusions occur in all malignancies, and that they account for 20% of human cancer morbidity. With the advent of new and powerful investigative tools that enable the detection of cytogenetically cryptic rearrangements, this proportion is likely to increase substantially.

Pathognomonic
A sign or symptom that is so characteristic of a disease that it is sufficient for diagnosis.

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Acquired chromosome abnormalities were first suggested to be causal factors in the origin of cancer by Boveri in 1914 (REF. 1). It remained an attractive hypothesis, but could not be examined critically until technical improvements half a century later enabled the reliable visualization of human chromosomes[2]. The discovery by Nowell and Hungerford[3] of the Philadelphia chromosome in chronic myeloid leukaemia (CML) — the first consistent chromosome change to be seen in a human cancer — clearly supported the view that chromosome abnormalities have an important role in the initiation of carcinogenesis. With the introduction of chromosome banding techniques[4], which revolutionized cytogenetic analyses through improved resolution, many specific, even pathognomonic, chromosome aberrations were soon detected in various tumour types. These findings, in parallel with the elucidation of the molecular genetic consequences of the cytogenetic abnormalities during the last two decades, have no doubt provided the conclusive verification of Boveri's remarkably prescient idea.

There is now a general agreement that cancer is, in essence, a genetic disease at the cellular level[5], with two dominating types of initiating genetic events having been identified: the inactivation of genes by deletion, mutation or epigenetic mechanisms, and the activation or deregulation of genes as a consequence of point mutation, amplification or balanced cytogenetic abnormalities. Although the impact of these two main pathogenetic pathways with regard to cancer development is well established, the relative part played by the various mechanisms remains unclear. This Review will focus on the contribution of gene fusions, mainly generated through chromosome translocations, to the carcinogenic process and cancer morbidity.

A brief history of chromosomal translocations

The first specific translocation identified in human neoplasia was t(9;22)(q34;q11)(BOX 1), resulting in the Philadelphia chromosome[6]. The molecular characterization of this translocation in CML in the early 1980s, revealing a fusion of the *BCR* and *ABL1* genes, and the t(8;14)(q24;q32) in Burkitt lymphoma, which juxtaposes *MYC* with the immunoglobulin heavy chain gene, dramatically increased our understanding of the pathogenetic significance of translocations and gene fusions in the origin of human cancers[7–9]. These discoveries stimulated interest in cancer cytogenetics as a powerful means to pinpoint the locations of cancer-initiating genes. As a consequence, the information on chromosome aberrations in neoplasia has steadily increased over the past two decades (FIG. 1). The total number of tumour cases in which clonal cytogenetic abnormalities have been reported has now reached 50,000, published in more than 11,500 articles[10]. The advent of molecular cytogenetic techniques, such as fluorescence *in situ* hybridization (FISH), multicolour FISH and array-based comparative genomic hybridization, has added a further level of sophistication to the analyses in that chromosomal breakpoints involved in structural rearrangements now can be mapped very precisely, even within genes[11–13]. Such cytogenetic characterization has been of the greatest importance

At a glance

- Chromosome aberrations are a characteristic feature of neoplasia, and acquired chromosome changes have now been reported in more than 50,000 cases across all main cancer types.
- Recurrent balanced chromosome rearrangements, in particular translocations, are strongly associated with distinct tumour entities, and there is compelling evidence that they represent an initial event in oncogenesis.
- Balanced chromosome abnormalities result in the formation of gene fusions and exert their tumorigenic action by two alternative mechanisms: overexpression of a gene in one of the breakpoints or the creation of a hybrid gene through the fusion of two genes, one in each breakpoint.
- A total of 358 gene fusions, involving 337 different genes, are known at present and have been described in all the main subtypes of human neoplasia.
- The prevalence of gene fusions varies considerably, from 0–100%, among different tumour types. Among malignant disorders, the proportions of gene fusion-positive cases are similar in haematological disorders, sarcomas and carcinomas.
- The gene fusions identified to date account for approximately 20% of human cancer morbidity.
- A number of conceptually important questions remain to be answered: why, how and when do chromosome aberrations originate? Are the resulting gene fusions sufficient for tumorigenesis, and if not, what is the pathogenetic relationship between these gene rearrangements and the other genetic and epigenetic alterations that characterize neoplastic cells?

in detecting genes associated with tumorigenesis and has, to date, led to the identification of 337 genes involved in fusions in benign and malignant neoplastic disorders[10]. These genes represent a substantial proportion of all mutated genes that have been implicated in oncogenesis[14,15].

Recurrent balanced rearrangements

Recurrent balanced rearrangements, most often translocations, have been detected in almost every tumour type[10]. Many such changes are known, for example, 267 in acute myeloid leukaemia (AML), the most comprehensively studied neoplastic disease, 155 in acute lymphoblastic leukaemia (ALL) and 75 in malignant solid tumours (TABLE 1). Many of these balanced abnormalities are — with remarkable specificity — associated with distinct tumour types and clinical features[16–21] as well as with characteristic global gene expression profiles[22–24]. This information has become an increasingly important tool in the management of cancer patients, helping to establish a correct diagnosis, select the appropriate treatment and predict outcome. Examples of characteristic, occasionally pathognomonic, balanced rearrangements and their clinical ramifications are given in TABLE 2.

It is important to emphasize that the balanced rearrangements might not be the sole anomaly. Tumour development is the result of a multistage process driven by the accumulation of new genetic changes: the well-known process of clonal evolution[25–28]. In short, the tumour genotype at any given time reflects the interplay between mutations and selective forces; that is, a Darwinian survival of the fittest at the cellular level, as postulated in the early 1950s[29–31]. Therefore, two different kinds of chromosome aberrations might, in principle, be detected in neoplasia. Primary abnormalities, which are occasionally found to be the only cytogenetic change, are most probably pathogenetically significant as initiating events (see below). Recurrent balanced aberrations often belong to this category[32]. On the other hand, secondary aberrations are acquired during tumour progression, and therefore probably have an important role at later disease stages. Typically, chromosome abnormalities that accumulate during tumour evolution are genomically unbalanced, such as monosomies, deletions, trisomies and duplications; however, they can occasionally be balanced[27]. In this context, it should be emphasized that seemingly balanced primary aberrations are often associated with cytogenetically cryptic deletions or duplications in the breakpoint region(s)[33,34].

Balanced rearrangements
Chromosome abnormalities that give rise to structurally altered chromosomes without the gain or loss of genetic material. Such changes comprise reciprocal translocations, inversions and insertions.

Consequences of balanced rearrangements

Most balanced structural rearrangements characterized at the molecular level have been found to exert their action through one of two alternative mechanisms. Either deregulation occurs, usually resulting in the overexpression of a seemingly normal gene in one of the breakpoints, or the creation of a hybrid, chimeric gene occurs through the fusion of parts of two genes, one in each breakpoint[7–9,35–37]. There is overwhelming evidence that these gene rearrangements represent important and early steps in the initiation of carcinogenesis. First, they are usually closely correlated with specific tumour phenotypes[18–21,38]. Second, it has been shown, mainly in haematological malignancies, that successful treatment is paralleled by a decrease or eradication of the disease-associated chimera[39–42]. Third, in experimental animal models, gene fusion constructs generally give rise to neoplastic disorders of the same kind as those seen in sporadic human neoplasms that carry the same gene fusion[43–50]. And finally, silencing fusion transcripts *in vitro* leads to the reversal of tumorigenicity, decreased proliferation and/or differentiation[51,52]. The identification of balanced structural chromosome changes is therefore of great importance, because the breakpoints involved point to the location of cancer-relevant genes. To date, 328 gene fusions have been identified in malignant disorders, and a total of 306 different genes in the breakpoints have been found to be rearranged and/or deregulated as a consequence of a chromosomal change in cancer[10].

The deregulation of a gene in one breakpoint is a well-documented mechanism in lymphoid leukaemias and lymphomas of both the B- and T-cell lineages. A good example is Burkitt lymphoma (FIG. 2), which harbours one of three translocations: t(8;14)(q24;q32), t(2;8)(p11;q24) or t(8;22)(q24;q11). In all three, the breakpoint in chromosome 8 is within or adjacent to the *MYC* gene. The other breakpoint is always within an immunoglobulin gene, encoding either the heavy chain (*IGH*) or the kappa (*IGK*) or lambda (*IGL*) light chains. As a consequence of the translocations, the *MYC* gene becomes constitutively expressed owing to the influence of regulatory elements of the immunoglobulin genes[7,8,35,53]. This mechanism — gene expression driven by immunoglobulin enhancers — accounts for two thirds and one fourth of all reported gene fusions in mature

Box 1 | Nomenclature of chromosomal aberrations

t(9;22)(q34;q11). Chromosome aberrations are described according to an internationally accepted nomenclature. Regions and bands along each chromosome arm are numbered consecutively from the centromere outward. The symbols p and q are used to designate the short and long arms of each chromosome, respectively. In designating a particular band, four items are required: the chromosome number, the arm symbol, the region number and the band number within that region. For example, 9q34 indicates chromosome 9, long arm, region 3, band 4. Letter designations are used to specify rearrangements, for example, t for translocation, inv for inversion, and ins for insertion. In the description of an abnormality, this designation is followed by the structurally altered chromosomes, separated by a semicolon, within parentheses; the breakpoints are then specified within another parenthesis and are listed in the same order as the chromosomes involved, again separated by a semicolon. Thus, t(9;22)(q34;q11) signifies a translocation between chromosomes 9 and 22 with breakpoints in bands 9q34 and 22q11, respectively.

Dermatofibrosarcoma protuberans
A low-grade malignant skin tumour composed of fibroblast-like cells.

Pericytoma
A mesenchymal tumour composed of cells that resemble pericytic cells.

B-cell malignancies and B-cell-lineage ALL, respectively[10]. An analogous scenario is seen in T-cell lymphomas and T-cell ALL in which regulatory elements of T-cell receptor (*TCR*) genes deregulate the expression of various 3′ partner genes[7,8,35], a mechanism represented in one fourth and one half, respectively, of the known gene fusions in these disorders[10]. Balanced chromosome rearrangements that lead to the exchange of regulatory control elements without affecting the coding sequence of the target gene seem to be very rare in other, non-lymphoid neoplastic disorders. However, deregulation as a consequence of, for example, promoter swapping or substitution, has been identified in some benign and malignant solid tumours, including dermatofibrosarcoma protuberans (a translocation involving the collagen type 1, α1 gene and the platelet-derived growth factor β gene; *COL1A1*–*PDGFB*)[54], pleomorphic adenoma of the salivary glands (a translocation involving the β-catenin gene with pleomorphic adenoma gene 1; *CTNNB1*–*PLAG1*)[55], pericytoma (a translocation involving the β-actin gene with glioma-associated oncogene homologue 1; *ACTB*–*GLI1*)[56], aneurysmal bone cyst (a translocation involving *COL1A1* with the ubiquitin-specific peptidase 6 gene; *COL1A1*–*USP6*)[57] and tenosynovial giant cell tumour (a translocation involving the collagen type 6, α3 gene with the colony stimulating factor 1 gene; *COL6A3*–*CSF1*)[58]. It should also be noted that there are a few examples of balanced translocations leading to a loss of gene function. In these instances, it seems as if the translocation merely represents one of many possible mechanisms of achieving gene inactivation[59–63].

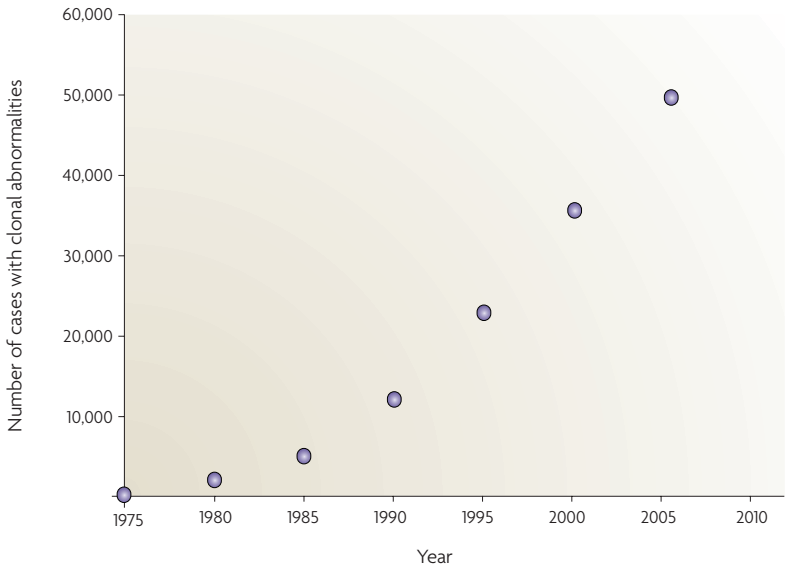

Figure 1 | **The number of cytogenetically abnormal neoplasms reported in the literature.** A steadily increasing number of neoplastic disorders, benign and malignant, have been investigated by different chromosome banding techniques since the early 1970s. The graph shows the accumulated number of cases in which a clonal cytogenetic abnormality has been reported. This information is continuously updated as part of the Mitelman Database of Chromosome Aberrations in Cancer, which catalogues detailed karyotypic descriptions, clinical and morphological features, and the geographic origin of all cases. The database also contains information on the molecular genetic consequences and the prognostic impact of acquired cytogenetic rearrangements in neoplasia.

A classic example of a translocation resulting in the creation of a chimeric gene is the t(9;22)(q34;q11) in CML, ALL and AML (FIG. 3). This translocation brings together the 5′ part of the *BCR* gene at 22q11 and the 3′ part of the *ABL1* tyrosine kinase-encoding gene at 9q34, leading to a hybrid BCR–ABL1 protein with increased tyrosine kinase activity[7–9,64]. Many hybrid genes, accounting for approximately 75% of the known gene fusions in malignant disorders, have been identified in various haematological malignancies and solid tumours, including epithelial, germ cell, neuroglial, embryonal nervous system, adipocytic, fibroblastic and fibrohistiocytic, myogenic, vascular, chrondroid and osteogenic tumours[10]. There are no apparent principal quantitative or qualitative differences among the genes that participate in such chimeras in different tumour types. The two main groups — transcription factors and tyrosine kinases — which account for 50% of the genes involved, are distributed quite equally among haematological disorders and solid tumours[65]. Although there is usually a very good association between specific tumour types and specific chimeric genes, there are some notable exceptions. The most striking is t(12;15)(p13;q25), leading to the fusion of *ETV6* with the neurotrophic tyrosine kinase receptor type 3 gene (*ETV6*–*NTRK3*), which occurs in tumours of totally different histogenetic derivations, namely AML, mesoblastic nephroma of the kidney, soft tissue fibrosarcoma and adenocarcinoma of the breast[66].

An increasing number of genes involved in fusions have been found to be promiscuous in that they can recombine with many different partner genes; well known examples are mixed lineage leukaemia (*MLL*)[67], *ETV6* (REF. 68) and Ewing sarcoma breakpoint region 1 (*EWSR1*)[69] with more than 40, 20 and 10 partners, respectively. Occasionally, a mutual fusion partner can link such genes, forming clusters of interrelated gene fusions. Any system consisting of entities that interact pair-wise, such as the genes involved in fusions, can be described in terms of a network, and by calculating how many times each gene was involved in fusions with other genes, it was recently shown[70] that the organization of the gene fusion network follows a power law degree distribution — a typical feature of scale-free networks. The defining

Table 1 | **Frequencies of balanced chromosome aberrations and gene fusions in cancer**

Diagnosis	Number of balanced aberrations	Number of recurrent balanced aberrations	Number of gene fusions	Estimated proportion with gene fusions
Haematological disorders				
Acute myeloid leukaemia	1,785	267	109	20%
Myelodysplastic syndromes	498	54	28	<1%
Chronic myeloid leukaemia	750	152	15	100%
Chronic myeloproliferative disorders	194	17	19	<1%
Acute lymphoblastic leukaemia	1,139	155	82	30%
Mature B-cell neoplasms	1,713	227	69	30%
Mature T-cell neoplasms	425	21	20	15%
Hodgkin lymphoma	63	2	5	<1%
Malignant solid tumours				
Respiratory system	282	3	2	<1%
Digestive system	435	11	2	<1%
Breast	343	13	3	<1%
Female genital organs	176	9	3	<1%
Male genital organs	41	0	4	80%
Urinary tract	225	7	7	<1%
Endocrine system	39	3	15	35%
Nervous system	412	9	1	<1%
Skin	238	5	0	<1%
Bone	216	3	7	15%
Soft tissues	342	16	33	20%

The numbers of balanced aberrations, recurrent balanced aberrations and gene fusions are based on data contained in REF. 10. The estimates in the last column take into consideration the relative frequencies of all morphological tumour entities within each organ system.

characteristic of such networks, in contrast to random networks, is that the distribution of links, if plotted on a double-logarithmic scale, results in a straight line[71]. Scale-free structures have been increasingly recognized during recent years in several naturally occurring complex biological, ecological, social and physical networks[71], and the results indicate that the origin of gene fusions might be governed by the same principle[70].

The gene fusion network is characterized by a few highly connected genes (such as *MLL*, *ETV6* and *EWSR1*) and a large number of genes with few links. An important biological question in this context is whether the network will eventually grow towards one single united network when more gene fusions have been annotated. With the aim of providing data to support or refute this idea, we have updated the previously published network[70] by connecting all genes involved in the 358 presently known gene fusions in neoplasia. It is striking that as many as 317 of the 358 (89%) fusions form three large networks (FIG. 4), compared with 72% in the previously published network based on 291 gene fusions. Therefore, with the inclusion of 67 new gene fusions, the network topology becomes clearly less fragmented, supporting the possibility that the presently known hybrid genes might in fact be components of one single network. Further indirect support for this view might come from the fact that there are no obvious constraints for mutual fusion partners to connect sub-clusters of genes characteristically involved in different morphological tumour entities. As can be seen in FIG. 4a, one network harbours haematological *ETV6*, *IGH* and *NUP98* fusions, the predominantly lymphoma-associated *BCL6* fusions as well as epithelial *RET* fusions. The second network (FIG. 4b) contains the predominantly haematological *MLL* fusions connected to the *HMGA2* fusions typically found in soft tissue tumours. The third network (FIG. 4c) includes the lymphoma-associated *ALK* fusions, the carcinoma-associated transcription factor for IGHM enhancer 3 (*TFE3*) fusions, and the sarcoma-associated *EWSR1* fusions. The implications in functional terms of the assumption that there might be one unified gene fusion network remain to be elucidated.

The fact that most cytogenetically balanced changes that have been characterized at the molecular level lead to gene fusions does not mean that all such gene rearrangements are exclusively formed by balanced chromosome aberrations. For example, there are several gene fusions that are typically detected in the context of an unbalanced cytogenetic rearrangement, such as

Table 2 | **Characteristic balanced chromosome rearrangements and their clinical ramifications**

Chromosome rearrangement	Gene fusion	Clinical characteristics
Haematological disorders		
t(1;22)(p13;q13)	*RBM15–MKL1*	Acute megakaryoblastic leukaemia in infants (non-Down syndrome)
t(2;5)(p23;q35)	*NPM1–ALK*	Anaplastic large T-cell lymphoma with CD30 and ALK expression in children and adolescents
t(8;14)(q24;q32)	*IGH–MYC*	Burkitt lymphoma/leukaemia, highly aggressive but good prognosis with intensive chemotherapy treatment
t(8;21)(q22;q22)	*RUNX1–RUNX1T1*	Acute myeloid leukaemia, M2 type, with dysplastic features and Auer rods, good prognosis
t(9;22)(q34;q11)	*BCR–ABL1*	Chronic myeloid leukaemia, sensitive to treatment with imatinib and other tyrosine kinase inhibitors
t(12;21)(p13;q22)	*ETV6–RUNX1*	B-cell precursor acute lymphoblastic leukaemia in children, good prognosis
t(14;16)(q32;q23)	*IGH–MAF*	Multiple myeloma, poor prognosis
t(15;17)(q22;q21)	*PML–RARA*	Acute promyelocytic leukaemia, sensitive to treatment with all trans-retinoic acid, good prognosis
Malignant solid tumours		
t(X;1)(p11;q23)	*PRCC–TFE3*	Papillary renal cell carcinoma in children and adolescents
t(2;3)(q13;p25)	*PAX8–PPARG*	Follicular thyroid carcinoma (but also present in follicular adenoma)
t(7;16)(q33;p11)	*FUS–CREB3L2*	Low-grade malignant fibromyxoid soft tissue sarcoma
t(7;17)(p15;q11)	*JAZF1–SUZ12*	Endometrial (uterine) stromal sarcoma
t(9;22)(q31;q12)	*EWSR1–NR4A3*	Soft tissue chondrosarcoma with abundant myxoid matrix in adults
t(11;22)(p13;q12)	*EWSR1–WT1*	Desmoplastic small round cell tumour, usually intra-abdominal, mainly in children and young adults with a striking male predominance, poor prognosis
t(11;22)(q24;q12)	*EWSR1–FLI1*	Ewing sarcoma, mainly in children and adolescents and mainly skeletal
t(15;19)(q14;p13)	*BRD4–NUT*	Poorly differentiated carcinoma affecting midline structures in children and adolescents, very poor prognosis

COL1A1–PDGFB in dermatofibrosarcoma protuberans with supernumerary ring chromosomes[54], alveolar soft part sarcoma chromosome region candidate 1 (*ASPSCR1*)–*TFE3* in an unbalanced der(17)t(X;17)(p11;q25)[72], or *NUP214–ABL1* (REF. 73) occurring on amplified episomes in T-cell ALL. Moreover, there are now also several examples in which gene fusions have been produced by the juxtaposition of the two genes in the breakpoints delineating, most often cryptic, deletions. Such fusions include *STIL–TAL1* in ALL[74], *MLL–ARHGEF12* (Rho guanine nucleotide exchange factor 12), *MLL–CBL* and *MLL–TIRAP* (TIR domain containing adaptor protein) in AML[75–77], *FIP1L1–PDGFRA* in hypereosinophilic syndrome[78], hyaluronan synthase 2 (*HAS2*)–*PLAG1* in lipoblastoma[79], *GOPC–ROS1* in astrocytoma[80] and transmembrane protease serine 2 (*TMPRSS2*)–*ERG* in prostate cancer[81,82]. It will be exciting to see how often gene fusions are the outcome of the many deletions that have been described, not only by cytogenetics[83] but also, and to a much larger extent, by array-based analyses of genomic imbalances[84–86].

Episomes
Submicroscopic extra-chromosomal circular DNA structures.

Hypereosinophilic syndrome
A haematological disease defined as persistent eosinophilia associated with signs of organ involvement and dysfunction.

Gene fusions in haematological disorders

To date, 264 gene fusions, involving 238 different genes, have been identified in haematological disorders, including malignant lymphomas. These represent 75% of all gene fusions presently known in human neoplasia. The fact that so many have been found in haematological disorders has led to the widely held opinion that they, in contrast to solid tumours, are caused by such gene fusions. However, we believe that this is a misconception based on a selective view of the available data. Actually, the prevalence of most individual gene fusions is very low. Many of them have not been found in unselected patient cohorts and, in fact, cases characterized by gene fusions represent only a minority of haematological disorders[21]. The few well-known specific changes seen in practically 100% of a particular leukaemia or lymphoma type — *BCR–ABL1* in CML, *IGH–CCND1* in mantle cell lymphoma, *MYC* deregulation in Burkitt lymphoma and *PML–RARA* in acute promyelocytic leukaemia — are the exceptions to the rule. Evidence substantiating this statement will be presented below, using AML as an illustrative example.

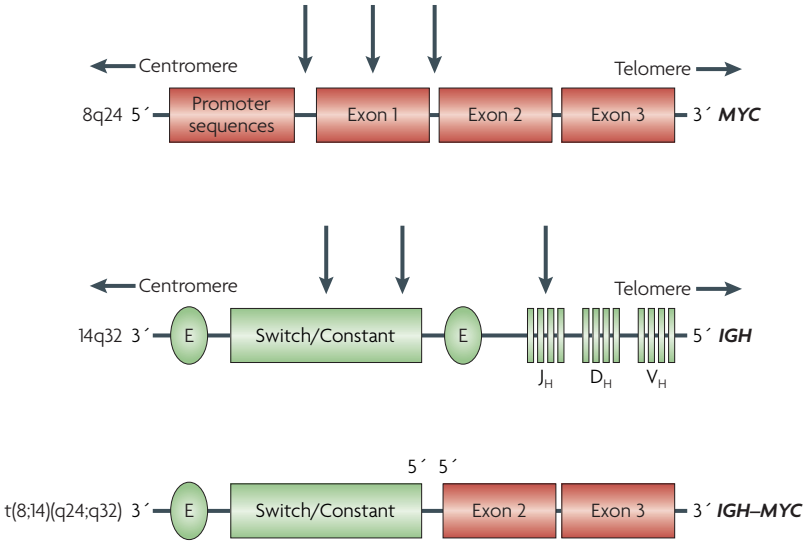

Figure 2 | **Gene fusion leading to gene upregulation.** The t(8;14)(q24;q32) translocation, the most common translocation in Burkitt lymphoma, leads to the deregulation of the *MYC* gene at 8q24 through its juxtaposition with regulatory elements of the immunoglobulin heavy chain (*IGH*) gene at 14q32; that is, the *MYC* gene is constitutively activated because its expression is driven by immunoglobulin enhancers (E). The *MYC* gene has three exons, and is oriented with its 5′ end towards the centromere. The breaks show considerable variability and might be scattered over an area larger than 200 kb at the 5′ part of the gene upstream of exon 2, the first coding exon. As a consequence, the two protein-encoding exons are always spared and are translocated to the *IGH* locus in 14q32. The breaks in the *IGH* gene usually take place within switch regions, but can also involve joining regions; occasionally the breaks take place in a variable or a constant region. The *IGH* gene is oriented with its 5′ part towards the telomere, so the translocation leads to a 5′–5′ (head-to-head) fusion of *MYC* with sequences from the *IGH* locus.

AML is the most extensively cytogenetically characterized human neoplastic disorder, representing 33% of all haematological malignancies and 27% of all malignant disorders with chromosomal abnormalities reported in the literature[10] (FIG. 5a). A total of 267 recurrent balanced aberrations have been identified and 109 gene fusions have been characterized (TABLE 1). In TABLE 3, the 10 most prevalent recurrent balanced aberrations and their corresponding fusion genes in unselected cases of AML are listed. The frequencies of the 4 most common are 2–4%; then, the prevalence drops quite dramatically to <0.1% for t(7;11)(p15;p15). Furthermore, most of the 11q23 aberrations are even less frequent. They are listed as one entity in TABLE 3 because they lead to an *MLL* rearrangement, but the promiscuous *MLL* gene has >40 known partners in AML[67], and therefore most of these are individually very rare. In total, the 10 most common gene fusions, including the various *MLL* chimeras, constitute 15% of all AML cases. The remaining balanced aberrations are extremely uncommon, with frequencies between <1/1,000 and <1/10,000; together they constitute 5% at most of all AML cases. Therefore, only approximately 20% of AMLs are characterized by translocations or other balanced exchanges, an incidence in agreement with population-based series from Germany[87] and the UK[88].

The situation is quite similar in ALL and mature B- and T-cell neoplasms, 15–30% of which harbour gene fusions, whereas only a small minority (<1%) of Hodgkin lymphomas, myelodysplastic syndromes and chronic myeloproliferative disorders are characterized by chimeric genes (TABLE 1). Therefore, the quite common view that most haematological disorders are caused by gene fusions is definitely an oversimplification. Instead, the pathogenetic mechanisms involved in most cases, comprising those with a normal karyotype or with unbalanced changes, remain to be clarified.

Gene fusions in solid tumours

Compared with haematological disorders, our knowledge of the karyotypic features of solid tumours is fragmentary at best. All solid tumours, benign and malignant, make up only 27% of the total number of cases with an abnormal karyotype reported in the literature[10]; in fact, we know less about the cytogenetics of the most common malignant tumours — that is, the various carcinomas — today than we did for AML 20 years ago. In addition, there are technical and analytical problems that limit the information value of the existing data. First, the chromosome morphology is often poor, or at least inferior to that in leukaemias and lymphomas, which means that many of the published cases have only been partially karyotyped. Secondly, the karyotypes are usually so complex that even when the quality is very good, it is practically impossible to identify each abnormality. A further analytical problem is the presence of cytogenetically unrelated clones, which are found in less than 3% of leukaemias, lymphomas and mesenchymal tumours, but have been reported in up to 80% of various carcinomas[26,89–91]. It is nevertheless very promising that in spite of the problems encountered, several recurrent balanced aberrations and gene fusions have been identified. At present, 70 gene fusions, involving 83 different genes, have been identified in malignant solid tumours (TABLE 4).

Sarcomas. The most extensively studied malignant solid tumours, in relation to their incidence in the general population, are bone and soft tissue sarcomas, a clinically and morphologically heterogeneous group of neoplasms of mesenchymal or neuroectodermal origin. There are now 41 known gene fusions in 17 different sarcoma types (TABLE 4). As in the haematological malignancies, the available data on sarcomas strongly indicate that gene fusions occur much more often in some subtypes than in others. For example, whereas close to 100% of Ewing sarcomas, myxoid liposarcomas and synovial sarcomas harbour chimeric genes involving *EWSR1*, DNA-damage-inducible transcript 3 (*DDIT3*) and synovial sarcoma X breakpoint 1, 2 or 4 (*SSX1*, *SSX2* or *SSX4*) genes, respectively, no gene fusion has so far been reported in osteosarcoma, conventional chondrosarcoma or leiomyosarcoma[10]. As several of the fusion-gene-carrying sarcomas are rare, the overall fraction of bone and soft tissue sarcomas with chimeric genes is only 15–20% (TABLE 1).

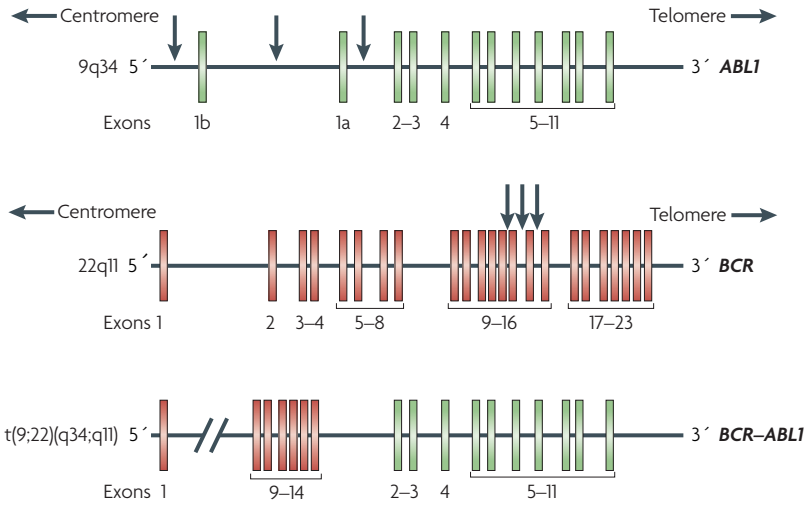

Figure 3 | **Gene fusion leading to a chimeric gene.** The Philadelphia chromosome, which originates through the translocation t(9;22)(q34;q11), juxtaposes the 5′ part of the *BCR* gene at 22q11 with the 3′ part of the *ABL1* gene at 9q34, resulting in the creation of a hybrid *BCR–ABL1* fusion gene. The *ABL1* gene is oriented with its 5′ end towards the centromere of chromosome 9. The gene spans more than 230 kb and contains two alternative first exons, 1b and 1a, followed by exons 2–11. Exon 1b is located approximately 200 kb upstream of exon 1a. The breakpoints are scattered over a large area (greater than 300 kb) at the 5′ end of the gene, either upstream of the first alternative exon 1b, between the two alternative exons, or between exons 1a and 2. Irrespective of the breakpoint location, splicing of the hybrid transcript yields an mRNA in which *BCR* sequences are fused to *ABL1* exon 2. The *BCR* gene has its 5′ end towards the centromere of chromosome 22, spans approximately 135 kb and has 23 exons. In most patients with chronic myeloid leukaemia, and at least one third of patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia, the break occurs in a 5.8 kb major breakpoint cluster region that spans exons 12–16.

Carcinomas. Thyroid carcinoma was the first epithelial tumour type in which a gene fusion, *RET–CCDC6*, was detected[92]. So far, another 14 gene fusions, 9 of which involve the *RET* gene, have been identified in various morphological subsets of thyroid carcinoma (TABLE 4); taken together, some 40% of thyroid carcinomas carry one of these chimeric genes[93]. There are other examples of morphologically and/or clinically distinct carcinoma subtypes with very high frequencies of gene fusions, such as CREB regulated transcription co-activator 1 (*CRTC1*)–mastermind-like 2 (*MAML2*) in mucoepidermoid carcinoma of the salivary glands[94] and *BRD4–NUT* in aggressive midline carcinoma[95]. However, these tumour types are exceedingly rare, representing only a very small fraction of cancer in general. In most of the common malignant solid tumour types, such as carcinomas of the breast, respiratory system and digestive tract, gene fusions are much less common, occurring in <1% of cases (TABLE 1).

The generally rare occurrence of gene fusions or balanced chromosome abnormalities in malignant epithelial tumours has led to the commonly held view that they only have a minor role in the pathogenesis of carcinomas, in contrast to haematological disorders and sarcomas. However, we have previously proposed that epithelial tumours might be characterized by fusion genes that have not yet been identified[65]. This prediction has recently been substantiated in prostate cancer by a conceptually new approach. Tomlins *et al.*[96] used bioinformatics to look for genes with a very high expression in microarray analyses. Among the top 10 outlier genes were *ERG* and *ETV1* — two genes known to be involved in fusions in other tumour types. The genes were subsequently found to be fused to the 5′ part of the prostate-specific gene *TMPRSS2*. They then performed FISH on a series of primary prostate cancers and found that 23 of 29 (79%) cases harboured either *TMPRSS2–ERG* or *TMPRSS2–ETV1* fusions. These results have been confirmed by several groups[97–101]. In addition, it has been shown that the *TMPRSS2–ERG* fusions might be caused by interstitial deletions or other unbalanced rearrangements in chromosome arm 21q[81,82,98,99]. A third molecular subtype of prostate cancer, characterized by the fusion of *TMPRSS2* to another ETS family member, *ETV4*, has now also been identified in 2% of the cases[102]. Prostate cancer is therefore the first common cancer associated with a very high frequency of a gene fusion. These findings are truly remarkable and point to a paradigmatic shift in our view of carcinoma pathogenesis.

The impact of gene fusions on cancer morbidity

Only a rough approximation can be made about the general impact of the known balanced chromosome rearrangements and gene fusions on the causation of human cancer. The main problem is that cancer incidences differ substantially among geographical regions and ethnic groups[103,104]. However, an attempt will be made using recent statistics from Sweden[105], which reflect data in Western Europe and North America reasonably well, and the estimated proportions of gene fusions per tumour type (TABLE 1). The results are summarized in FIG. 5b.

CML accounts for 0.2% of all cancers, and considering that 100% of CMLs harbour the *BCR–ABL1* fusion gene, the general impact of this particular fusion on cancer morbidity is 0.2%. On the other hand, in all other chronic myeloproliferative disorders (CMDs), which are four times as common as CML (0.8%), a gene fusion is found in less than 1%. Therefore, the contribution of gene-fusion-positive CMDs to the total cancer burden would, at most, be 0.008%. The corresponding figures for other haematological malignancies are 0.2% for ALL and AML combined, 0.007% for myelodysplastic syndromes, 1% for mature B- and T-cell neoplasms and 0.003% for Hodgkin lymphoma. Therefore, the total impact of haematological disorders with gene fusions on cancer morbidity in general is only 1.4%.

Among the malignant solid tumours, which represent 90% of all malignancies, most common tumour types (TABLE 1) do not carry gene fusions in more than 1% of the cases. Therefore, the general impact of gene fusions on cancer morbidity for malignancies of the respiratory system, digestive system, breast, female genital organs, urinary tract, nervous system and skin, taking into account their respective incidences, is less than 0.7%. Bone and soft tissue tumours, 15–20% of which harbour gene fusions, are rare diseases, accounting for less than 1% of all cancers, and therefore the impact of gene fusions is <0.2%. Malignant endocrine tumours, mainly thyroid carcinomas, are equally rare (roughly

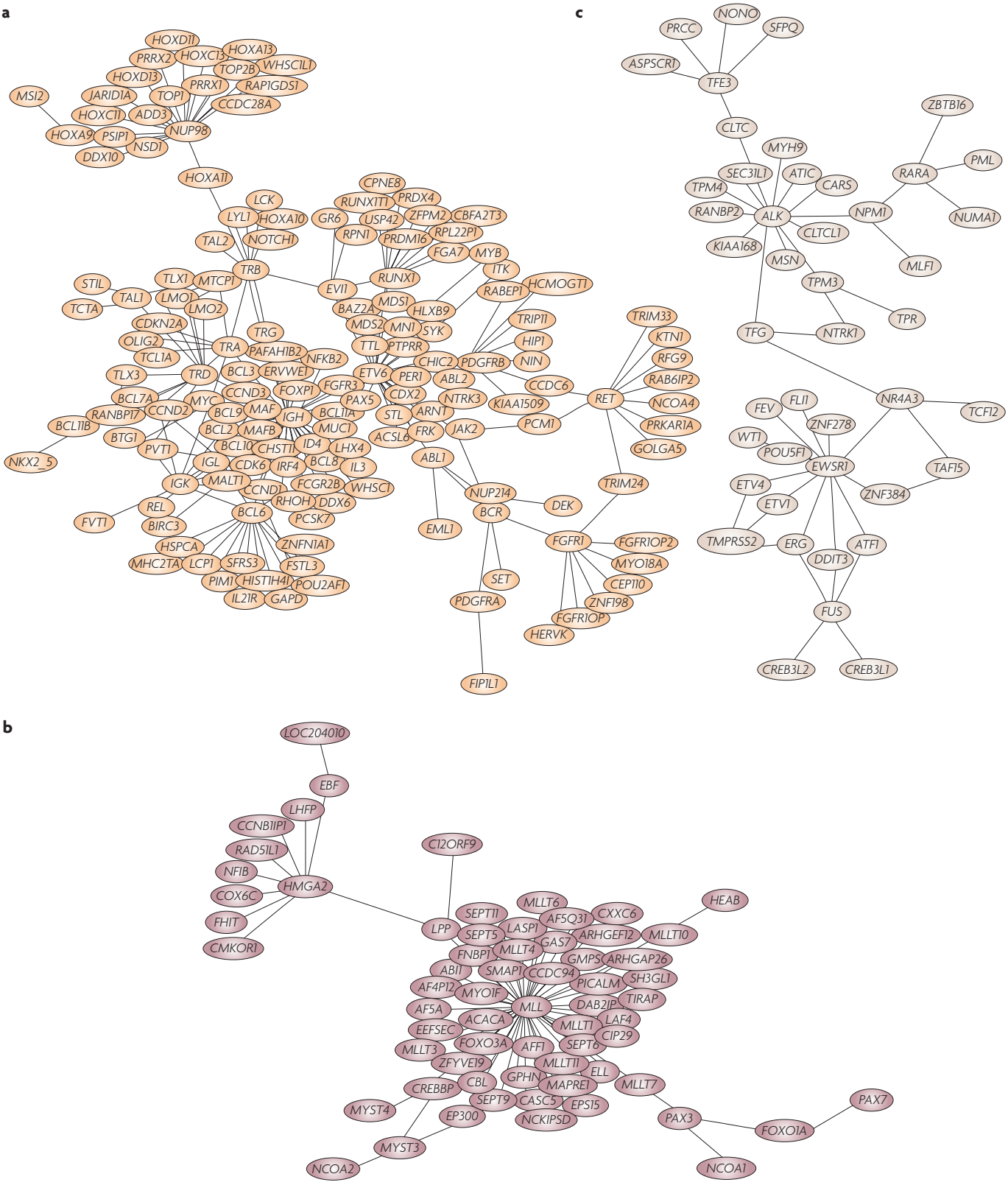

Figure 4 | **Interconnected networks of gene fusions.** An increasing number of genes involved in gene fusions have been found to be quite promiscuous, having several partners that in turn might recombine with other genes in various tumour types. This leads to the formation of interconnected networks. Of the 358 gene fusions currently known in benign and malignant neoplastic disorders, almost 90% form three clusters, each of which contains connected sub-clusters of genes typically involved in morphologically distinct tumour types.

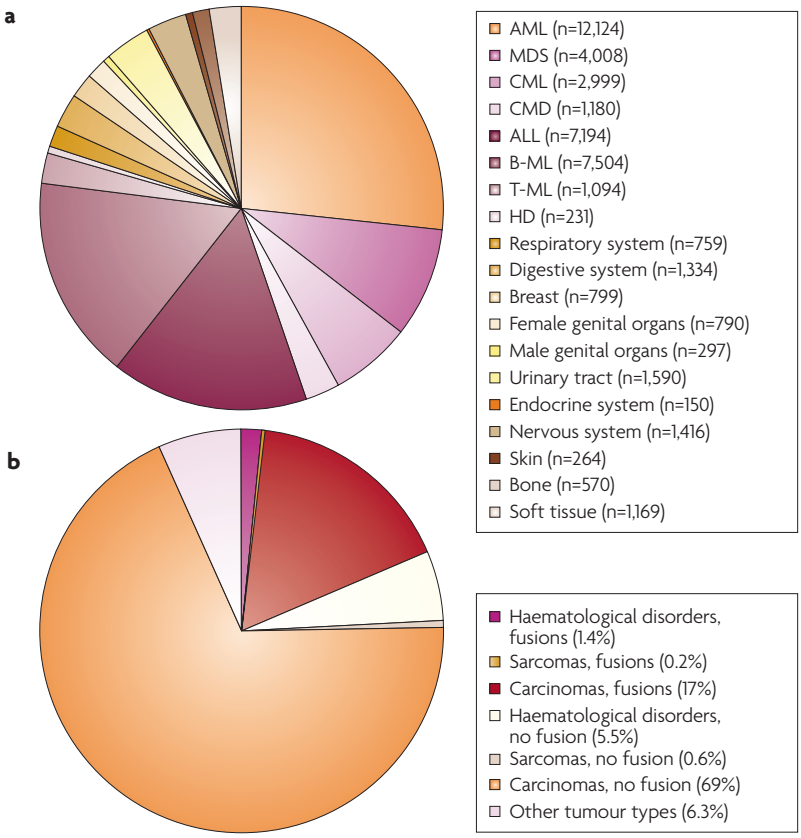

Figure 5 | **The distribution of 45,472 cytogenetically abnormal malignant disorders reported in the literature and the impact of gene fusions on cancer morbidity. a** | The number of cases with clonal chromosome abnormalities in various diseases. The distribution is heavily biased in favour of haematological malignancies, which constitute 80% of the total. The bone and soft tissue tumours are also overrepresented. By contrast, the available cytogenetic data on the common malignant epithelial tumours clearly do not parallel their incidence and impact on cancer morbidity and mortality. **b** | The impact of gene fusions on cancer morbidity. Taking into account recent cancer incidence statistics of haematological disorders, sarcomas and carcinomas and the proportions of known gene fusions in these entities (TABLE 1), the impact of such fusions on general cancer morbidity has been estimated. The designation 'other tumour types' encompasses solid tumours of unknown origin as well as nervous system tumours, among which only one gene fusion has been reported. Germ cell tumours are included among the carcinomas. The figure shows that approximately 20% of all cancer cases can be attributed to gene fusions, with similar proportions among the three main cancer groups. However, it should be stressed that the frequencies of fusion-positive cases vary considerably within the different subtypes (from <1% to 100%; TABLE 1) and that the high prevalence of gene fusions in carcinomas is mainly due to the *TMPRSS2–ERG* and *TMPRSS2–ETV1* chimeras in prostate cancer. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; B-ML, mature B-cell neoplasms; CMD, chronic myeloproliferative disorders; CML chronic myeloid leukaemia; HD, Hodgkin lymphoma; MDS, myelodysplastic syndromes; T-ML, mature T-cell neoplasms.

1%), but have gene fusions more often: the impact of these would be <0.4%. The remaining tumour group, namely malignancies of the male genital organs, is heavily dominated by prostate cancer. As this particular tumour type accounts for almost 20% of all cancers and contains a gene fusion in 80% of cases[96], the total impact of the fusions on cancer morbidity is as high as 16%. Taken together, the total impact of malignant solid tumours with gene fusions on cancer morbidity in general is approximately 17%.

Therefore, among all malignant neoplasms, haematological malignancies and solid tumours combined, slightly less than 20% can be explained by presently known gene fusions.

Questions to address and future directions

In spite of the dramatic increase in our knowledge of chromosome aberrations and their corresponding gene fusions in human neoplasia during the past two decades, several fundamental and interrelated questions remain to be addressed.

How many more gene fusions will be discovered? Is it possible that 100% of all human neoplasms actually harbour gene fusions? The observation that the number of gene fusions corresponds to the number of cases cytogenetically investigated[65] strongly indicates that many more gene fusions remain to be identified through the analysis of metaphase chromosomes. However, these fusions will probably be individually very rare, and therefore contribute little to overall cancer morbidity. On the other hand, as shown in prostate cancer[96], common gene fusions might be discovered by other means, such as genome-wide expression and/or copy number analyses. The sequencing efforts now underway as part of the Cancer Genome Atlas will hopefully be valuable in this regard.

Why do gene fusions arise? It seems reasonable to assume that DNA double-strand breaks are required for most, if not all, chromosome aberrations that result in gene fusions[35,106,107], and it has been convincingly shown that many external agents induce chromosome breaks[108]. Furthermore, in the early 1970s it was suggested, based on experimental animal studies, that nonrandom chromosomal patterns in neoplasia are dependent on the inducing agent[109]. This proposition has been substantiated in some human malignancies associated with occupational, environmental and/or genotoxic exposures[110–112]. However, only a few agents have been clearly shown to increase the risk of particular translocations or gene fusions, namely DNA topoisomerase II poisons[111–114] and radiation[107,115,116]. Therefore, for most gene fusions no specific initiating factor has been identified, but further epidemiological and experimental studies that address this important issue might prove to be fruitful. In addition to external 'inducing agents', host factors might also have a role in the origin of gene fusions.

There are many inherited cancer-predisposing disorders, including the well-known chromosome breakage syndromes, associated with instability at the chromosomal and/or DNA level[117]. However, to the best of our knowledge, malignancies with gene fusions are exceedingly rare in patients with such disorders. Taken together, there is, as yet, little evidence favouring any substantial impact of specific external or internal factors on the genesis of translocations and gene fusions. Therefore, for the time being, gene fusions in general have to be considered to be chance events.

Table 3 | **The 10 most common balanced aberrations in AML**

Aberration	Gene fusion	Frequency (%)
t(8;21)(q22;q22)	*RUNX1–RUNX1T1*	4.3
t(15;17)(q22;q21)	*PML–RARA*	4.1
der(11q23)	*MLL* fusions	2.4
inv(16)(p13q22)	*CBFB–MYH11*	2.3
t(9;22)(q34;q11)	*BCR–ABL1*	0.7
inv(3)(q21q26)	*RPN1–EVI1*	0.6
t(6;9)(p22;q34)	*DEK–NUP214*	0.3
t(1;22)(p13;q13)	*RBM15–MKL1*	0.2
t(8;16)(p11;p13)	*MYST3–CREBBP*	0.1
t(7;11)(p15;p15)	*NUP98–HOXA9*	<0.1

AML, acute myeloid leukaemia.

How do gene fusions arise? The three-dimensional chromosome architecture within the interphase nucleus is probably pivotal to the occurrence of gene fusions, particularly the spatial proximity of the genes involved[118,119]. In fact, the loci involved in the formation of *BCR–ABL1* in CML[120], *PML–RARA* in acute promyelocytic leukaemia[121], *RET–CCDC6* in thyroid cancer[122], and *IGH–MYC*, *IGH–CCND1* and *IGH–BCL2* in B-cell malignancies[123] have been found to be close to each other in the corresponding normal cell types. Whether this holds true for other gene fusions remains to be ascertained. This notwithstanding, we think it is unlikely that the position of the genes involved is sufficient to explain the origin of the many gene fusions known at present. Clearly, there are other factors that facilitate illegitimate recombinations, including shared sequence motifs at the chromosome breakpoints[35,107,114,124]. Although such recombinogenic motifs seem to account for only a minority of the rearrangements, it should be emphasized that most gene fusions remain poorly characterized at the DNA level. Future sequence efforts will hopefully shed some light on this important issue.

When do gene fusions arise? It is clear that tumours with balanced chromosome rearrangements and gene fusions can be diagnosed at any age; for example, the t(8;16)(p11;p13), which gives rise to the *MYST3–CREBBP* chimera, has been reported in a newborn child as well as in a 92-year-old patient[10]. However, when the translocations arise is a moot point. For childhood haematological malignancies, there is ample evidence, based on twin studies and PCR analyses for specific gene fusions in Guthrie spots, that they might be formed *in utero* several years before overt leukaemia[125]. To what extent leukaemias in adults have a clonal origin that can be traced many years back, perhaps even to early childhood, is not known. For solid tumours, a lack of appropriate pre-neoplastic tissue samples collected before diagnosis has precluded similar investigations. It would undoubtedly be of great interest, for example, in cancer epidemiological studies, to identify more exactly when in life translocations and gene fusions arise in different cell types. However, it is difficult to envisage how such information could be achieved; perhaps, as stated by Boveri already in 1914 (REF. 1), it will never be possible to study a tumour in '*statu nascendi*'.

In which cells do gene fusions arise? During the past decade, cancer stem cells have attracted much attention[126,127]. It is now generally accepted that haematological malignancies are sustained by leukaemic stem cells, capable of both initiating and maintaining the disease. More recently, a cancer stem cell concept has been shown to be applicable to some malignant solid tumours, such as tumours of the breast, colon, lung, and central nervous system[128–132]. A fundamental question is whether gene fusions arise in corresponding normal stem cells or whether they occur at a later differentiation stage. A paradigmatic example of a translocation originating in a stem cell is the Philadelphia chromosome in CML, as shown in the early 1960s[133]. Similarly, a few gene fusions have been shown to be present in the stem cell compartment or in early progenitors in acute leukaemias[134–136], but most leukaemia-associated gene fusions have not been investigated in this respect. In solid tumours, such studies are presently difficult to perform because so little is known about the differentiation hierarchy in the tissues from which they derive. However, recent data indicate that bone-marrow-derived mesenchymal progenitor cells might be involved in sarcoma development[137,138]. Still, it will be an arduous task to design and carry out experiments that will identify and characterize the target cells, but only then will it be possible to understand why some gene fusions, such as *ETV6–NTRK3*, occur in various morphologically and clinically distinct neoplasms[66], whereas most others seem to be restricted to very specific tumour types.

Are gene fusions sufficient for neoplastic transformation? Several lines of evidence strongly indicate that they are not. The most compelling argument is that many have been found in healthy individuals, using sensitive PCR assays[139]. Furthermore, cells that carry leukaemia-associated gene fusions might occasionally be detectable several years after successful treatment, that is, when the patients are still in long-term complete remission[140,141]. Also, long and disparate latency periods before overt leukaemia in twins born with the same gene fusion, transmitted *in utero*, have been well documented[125]. Finally, there is circumstantial and direct evidence from murine leukaemia models that additional events are a prerequisite for malignant transformation[45,48,142–144]. Therefore, available data strongly indicate that secondary changes, probably mutations, are necessary, at least in the context of haematological malignancies. By contrast, there is some evidence that the expression of certain sarcoma-associated gene fusions is sufficient for the transformation of bone marrow-derived mesenchymal progenitor cells in mice[137,138]. Whether the same holds true for other solid tumours, or for gene-fusion-driven carcinogenesis in humans, remains to be clarified, as does the spectrum of mutated genes associated with different gene

Table 4 | **Gene fusions in malignant solid tumours**

Tumour type	Gene fusion(s)
Sarcomas	
Alveolar soft part sarcoma	*ASPSCR1–TFE3**
Angiomatoid fibrous histiocytoma	*EWSR1–ATF1*, FUS–ATF1**
Bone sarcoma, undifferentiated	*EWSR1–POU5F1*
Chondrosarcoma, myxoid	*EWSR1–NR4A3*, TAF15–NR4A3*, TCF12–NR4A3, TFG–NR4A3*
Clear cell sarcoma	*EWSR1–ATF1**
Dermatofibrosarcoma protuberans	*COL1A1–PDGFB**
Desmoplastic small round-cell tumour	*EWSR1–WT1*, EWSR1–ERG*
Endometrial stromal sarcoma	*JAZF1–PHF1*, JAZF1–SUZ12*, EPC1–PHF1*
Ewing sarcoma or primitive neuroectodermal tumour	*EWSR1–ERG*, EWSR1–ETV1*, EWSR1–ETV4*, EWSR1–FLI1*, EWSR1–FEV*, FUS–ERG*, EWSR1–ZNF278*
Ewing-like soft tissue sarcoma	*CIC–DUX4**
Fibromyxoid sarcoma, low grade	*FUS–CREB3L2*, FUS–CREB3L1*
Fibrosarcoma, infantile	*ETV6–NTRK3**
Inflammatory myofibroblastic tumour	*CARS–ALK*, CLTC–ALK*, RANBP2–ALK*, TPM3–ALK*, ATIC–ALK, SEC31L1–ALK, TPM4–ALK*
Liposarcoma, myxoid	*EWSR1–DDIT3*, FUS–DDIT3**
Rhabdomyosarcoma, alveolar	*PAX3–FOXO1A*, PAX7–FOXO1A*, PAX3–MLLT7, PAX3–NCOA1*
Rhabdomyosarcoma, pleomorphic	*PAX3–FOXO1A*
Synovial sarcoma	*SS18–SSX1*, SS18–SSX2*, SS18–SSX4*, SS18L1–SSX1*
Carcinomas	
Aggressive midline carcinoma	*BRD4–NUT**
Breast carcinoma	*ETV6–NTRK3*, ODZ4–NRG1*, TBL1XR1–RGS17*
Kidney carcinoma	*ALPHA–TFEB*, ASPSCR1–TFE3*, PRCC–TFE3*, CLTC–TFE3, NONO–TFE3, SFPQ–TFE3*
Mucoepidermoid carcinoma	*MECT1–MAML2**
Prostate carcinoma	*TMPRSS2–ERG, TMPRSS2–ETV1, TMPRSS2–ETV4, RPS10–HPR*
Thyroid carcinoma	*AKAP9–BRAF*, PAX8–PPARG*, RET–CCDC6*, RET–GOLGA5*, RET–KTN1*, RET–NCOA4*, RET–PCM1*, RET–PRKAR1A*, RET–RAB6IP2*, RET–RFG9*, RET–TRIM24*, RET–TRIM33*, TFG–NTRK1*, TPM3–NTRK1*, TPM3–TPR*
Other	
Astrocytoma	*GOPC–ROS1*
Mesoblastic nephroma	*ETV6–NTRK3**

*Recurrent gene fusions.

fusions in both haematological and solid neoplasms. Furthermore, our understanding of the pathogenetic impact of gene fusions will have to take into account the surprisingly large number of other somatic mutations recently identified in human malignancies[15].

As in all areas of research, the solution to one problem begets several new ones. Consequently, there are more unanswered questions today than ever before concerning the role of translocations and gene fusions in the causation of malignant disorders. Bearing in mind the many gene fusions known at present, and those yet to be discovered, it will be a great challenge for many years for scientists in different fields of study to fully understand their causes and consequences.

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Competing interests statement

The authors declare that they have no competing financial interests.

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DATABASES

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