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Human chromosome 22

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SUMMARY The acrocentric chromosome 22, one of the shortest human chromosomes, carries about 52 000 kb of DNA. The short arm is made up essentially of heterochromatin and, as in other acrocentric chromosomes, it contains ribosomal RNA genes. Ten identified genes have been assigned to the long arm, of which four have already been cloned and documented (the cluster of lambda immunoglobulin genes, myoglobin, the proto-oncogene *c-sis*, *bcr*). In addition, about 10 anonymous DNA segments have been cloned from chromosome 22 specific DNA libraries. About a dozen diseases, including at least four different malignancies, are related to an inherited or acquired pathology of chromosome 22. They have been characterised at the phenotypic or chromosome level or both. In chronic myelogenous leukaemia, with the Ph¹ chromosome, and Burkitt's lymphoma, with the t(8;22) variant translocation, the molecular pathology is being studied at the DNA level, bridging for the first time the gap between cytogenetics and molecular genetics.

Chromosome 22 is interesting for two main reasons: it is short, which facilitates the construction of a molecular map with cloned pieces of DNA, and it is involved in a relatively high number of inherited and acquired diseases, in particular malignancies.

Cytogenetics of normal human chromosome 22

Chromosome 22 is one of the shortest human chromosomes. It contains about 1.8% of the total haploid genome, that is, about 52 Mb of DNA, slightly more than chromosome 21. This is five times less than chromosome 1, the largest of all chromosomes, and three times less than the X chromosome, the most extensively mapped. Because of its condensed small size, chromosome 22 lends itself well to isolation by flow sorting,¹ especially when the long arm is shortened by a rearrangement. It has an acrocentric shape with a polymorphic short arm, because of variable amounts of heterochromatin in the region p11.1→p11.2 and because of the presence of one or more satellites of various sizes at pter.

Ribosomal RNA genes are located at p12, as shown by NOR staining. The non-polymorphic long arm is made of early replicating euchromatin, suggesting the presence of GC rich DNA and possibly numerous 'active' genes. The different banding patterns are defined at three resolution levels in the diagram of ISCN² (fig 1). In standard conditions the long arm appears quite homogeneous and very dark with R banding but very pale with Q or G banding techniques. Because of this, its integrity is difficult to ascertain with the last two techniques and high resolution banding techniques are necessary to elucidate some rearrangements.

Content of chromosome 22

To date about 25 loci defined by a known gene or a genetic marker have been assigned to this chromosome (table 1).

NON-CLONED GENES AND LOCI

Before the advent of molecular genetics, few loci had been positively assigned to chromosome 22. These were ribosomal DNA on the short arm³ and four enzymes on the long arm: mitochondrial aconitase;

FIG 1 Diagrammatic representation of chromosome 22 according to the ISCN.² G banding is obtained at three different levels of definition of the karyotype: (a) 400 bands, (b) 550 bands, (c) 850 bands.

so-called diaphorase 1 (*DIA1*), corresponding to cytochrome b5 reductase; arylsulphatase A (*ARSA*) and N-acetylgalactosaminidase (*NAGA*).⁴⁻¹¹ They have been localised by physical regional mapping, using translocations and somatic hybrids.¹²⁻¹³

Three other loci have been provisionally assigned to chromosome 22: the antigen of the P blood group (*PI*),¹⁴ a surface antigen referred to as S13 but not subsequently confirmed,¹⁵ and the protective protein for β galactosidase (*PPGB*).¹⁶ With the exception of blood group P, assigned to chromosome 22 by linkage analysis,¹⁴ these assignments were obtained by conventional phenotypic studies of human-rodent somatic hybrids, and in some cases regionally assigned by deletion mapping. More recently, α -L-iduronidase (*IDUA*) has been assigned to chromosome 22, and more precisely to the region between pter and q11 by deletion mapping and gene dosage.¹⁷

CLONED DNA SEGMENTS OF CHROMOSOME 22 (TABLE 2)

To date only four identified genes have been cloned

TABLE 1 List of loci (genes, markers, diseases) on chromosome 22.

Location	Symbol	Full name	Associated disease
p12	<i>RNR5</i>	Ribosomal RNA	
p11	<i>DNF19S5</i>	Anonymous repetitive family	
pter→q11	<i>D22S3*</i>	Anonymous unique DNA segment	
pter→q11 (tetrasomy)	<i>CES</i>		Cat eye syndrome
pter→q11 (monosomy)	<i>DGS</i>		DiGeorge syndrome
pter→q11	<i>IDUA</i>	α -L-iduronidase	HS, SS
q11	<i>IGLV</i> and <i>IGLC</i>	Immunoglobulin λ light chain: V and C regions	BL t(8;22) variant
q11	<i>BCR1</i>	Breakpoint cluster region	CML t(9;22)
q11	<i>D22S9*</i>	Anonymous unique DNA segment	
q11→qter	<i>ACO2</i>	Aconitase 2 (mitochondrial)	
q11→qter	<i>D22S4</i>	Anonymous unique DNA segment	
	<i>D22S5*</i>	Anonymous unique DNA segment	
	<i>D22S6</i>	Anonymous unique DNA segment	
	<i>D22S7</i>	Anonymous unique DNA segment	
	<i>D22S8</i>	Anonymous unique DNA segment	
q12	<i>ES</i>		Ewing's sarcoma t(11;22)
q12→qter	<i>D22S1*</i>	Anonymous unique DNA segment	
q12→qter	<i>MB*</i>	Myoglobin	
q12→qter	<i>PI†</i>	PI blood group antigen	
q12.3→q13.1	<i>SIS</i>	c-sis proto-oncogene (=PDGF, B chain)	
q13→qter	<i>NAGA</i>	α -N-acetylgalactosaminidase	
q13.31→qter	<i>ARSA</i>	Arylsulphatase A	ML
q13.31→qter	<i>DIA1†</i>	Diaphorase 1 (=NADH cytochrome b5 reductase)	RCM (types I and II)
Not assigned regionally	<i>PPGB</i>	Protective protein for β galactosidase	GS
	<i>D22S2</i>	Anonymous unique DNA segment	
	<i>D22S10*</i>	Anonymous unique DNA segment	
	<i>D22Z1*</i>	Anonymous repetitive DNA segment	

*Polymorphic at the genotype level. †Polymorphic at the phenotype level. HS=Hurler's syndrome; SS=Scheie's syndrome; BL=Burkitt's lymphoma; CML=chronic myelogenous leukaemia; ML=metachromatic leucodystrophy; RCM=recessive congenital methaemoglobinaemia; GS=galactosialidosis.

TABLE 2 Cloned DNA segments from chromosome 22.

DNA segments	Name of locus	Assignment	Known RFLPs
Identified genes			
Immunoglobulin lambda light chain	<i>IGLV</i>	q11	Many
V and C genes	<i>IGLC</i>	q11	<i>EcoRI</i>
'Breakpoint cluster gene'	<i>BCR1</i>	q11	
Myoglobin	<i>MB</i>	q12→qter	<i>TaqI</i>
c-sis (PDGF B)	<i>SIS</i>	q12-3→q13-1	<i>HindIII</i>
α-N-acetylgalactosaminidase	<i>NAGA</i>	q13→qter	
Anonymous DNA segments			
Single copy segments			
	<i>D22S1</i>	q12→qter	<i>TaqI</i> , <i>BglII</i>
	<i>D22S2</i>	?	
	<i>D22S3</i>	pter→q11	<i>EcoRI</i>
	<i>D22S4</i>	q11→qter	
	<i>D22S5</i>	q11→qter	<i>BamHI</i> , <i>EcoRI</i>
	<i>D22S6</i>	q11→qter	
	<i>D22S7</i>	q11→qter	
	<i>D22S9</i>	q11	<i>TaqI</i> , <i>MspI</i>
	<i>D22S10</i>	?	Many
Multiple copy segments			
chromosome 22 specific	<i>D22Z1</i>	?	<i>HincII</i> , <i>PvuII</i>
Multiple copy segments			
repetitive family on several chromosomes	<i>DNF19S5</i>	p11	

coding for (1) the immunoglobulin 'lambda light chain components, (2) myoglobin, (3) the proto-oncogene c-sis, and (4) α-N-acetylgalactosaminidase (*NAGA*). Another gene of unknown function has been discovered in relation to the chromosome lesion of chronic myelogenous leukaemia (CML), the so-called 'breakpoint cluster region' (*BCR1*).

The immunoglobulin lambda chain cluster (locus IGLV-IGLC)

Hieter *et al.*¹⁸ accomplished the first cloning of the genes coding for the constant region (*IGLC*). They found that, unlike the single C kappa and C heavy chain genes, the *IGLC* comprised a cluster of at least six related C lambda genes (numbered λC1 to λC6), each with its associated J segment, and spanning a stretch of about 40 kb. The genes exhibit a high degree of homology, about 95% at the nucleotide level with even fewer differences at the amino acid level.¹⁹ The protein corresponding to three of these genes had been distinguished before in myeloma products as the non-allelic isotypes Mcg (λC₁), Ke⁻Oz⁻ (λC₂), Ke⁻Oz⁺ (λC₃).¹⁸ The peculiar arrangement of the Ig C lambda cluster, in which each Cλ gene is preceded by its own J sequence, suggests that the Cλ cluster has evolved by successive duplication of J-C DNA units.¹⁹ In addition three lambda-like C genes have recently

been discovered,¹⁹ comprising two new Cλ genes, provisionally designated '14.1' and '16.1', and a pseudogene 'Ψ18.1'. Preliminary results indicate that these genes are also on chromosome 22 (G F Hollis, personal communication) at a still unknown distance from the λC₁-C₆ cluster. An interesting model of evolution of the λC gene family, stemming from sequence knowledge, has been proposed by Chang *et al.*¹⁹ The λC₁-λC₆ cluster is polymorphic because of a variable degree of repetition of a 5 kb sequence in the 8 kb *EcoRI* fragment comprising λC₂ and λC₃, with allelic RFLPs of 8, 13, 18, and 23 kb.²⁰ Hybridisation studies on somatic hybrids and direct in situ chromosome hybridisation have assigned *IGLC* to chromosome 22²¹ and more precisely to the 22q11 region.^{22 23}

Less is known, in contrast, on the number and organisation of the lambda V genes. The first clone obtained was genomic and corresponded to a so far undescribed lambda V region subgroup, called subgroup O.²⁴ It hybridises with a family of about 10 cross hybridising genes on chromosome 22 at low stringency, and only two at high stringency, all mapping proximally to 22q11.²⁴ Subsequently, cDNA clones for lambda V region sequences corresponding to subgroups I,²⁵ III,²⁶ and VI²⁷ have been obtained. The actual total copy number of V lambda genes is unknown, but should exceed 20.^{27 28} In situ hybridisation with a λVI cDNA showed that *IGLV*, like *IGLC*, maps at 22q11.²⁹ We still do not know what the distance is between *IGLV* and *IGLC*, but in the light of Burkitt's lymphoma with the t(8;22) variant translocation, in which chromosome 22 breaks at 22q11, it can be inferred that *IGLV* is proximal to *IGLC*.^{29 30} The involvement of chromosome 22 in Burkitt's lymphoma will be considered in a later section. Using the genomic probe V4A corresponding to an 8 kb sequence comprising a λVO gene,²⁴ the *IGLV* locus was found to be highly polymorphic with at least seven enzymes.³¹ These RFLPs are compatible with both multiple single base variations and rearrangements within an *EcoRI* 8 kb frame*.

Myoglobin (locus MB)

The human myoglobin gene was cloned by Jeffreys *et al.*³³ Its organisation and structure have been established by Weller *et al.*³⁴ and Akaboshi.³⁵ It is a single gene with three exons and two introns, as in all the members of the globin family, which evolved from ancestral myoglobin by successive duplications and transposition to chromosome 16 (α globin family) and chromosome 11 (β globin family). *MB* is

*Very recently a cluster of three V kappa genes has been unexpectedly localised on chromosome 22.³²

distal to a breakpoint at 22q11·2 and is therefore in the 22q12→qter segment.³¹ It exhibits a *TaqI* RFLP in the first intron.³¹

The c-sis proto-oncogene (locus SIS)

The proto-oncogene *c-sis*, homologue of the simian sarcoma virus transforming gene *v-sis*, has been assigned by molecular hybridisation to chromosome 22,^{36, 37} and more precisely by in situ hybridisation to 22q13·1.³⁸ It encodes the B chain precursor of PDGF (platelet derived growth factor).^{39, 40} PDGF consists of dimers of homologous polypeptide chains, denoted A and B. The gene encoding the A chain was believed to reside in the vicinity of its B homologue. This problem was recently clarified by Betsholtz *et al.*⁴¹ who, after cloning and characterising the PDGF A chain gene, found it on chromosome 7 (7pter→7q22). Therefore, after duplication of the ancestral PDGF gene, the A and B chain genes have acquired different chromosomal locations. The two gene products retain an overall amino acid sequence homology of 40%.⁴¹ A *HindIII* RFLP has been found in the intron between exons 3 and 4 of *c-sis*.³¹

N-acetylgalactosaminidase (locus NAGA)

The *NAGA* locus codes for a lysosomal enzyme, also called α galactosidase B. It maps at 22q12→qter,¹¹ and it is not yet related to any disease. Since a brief abstract on its cloning,⁴² there has been no further report on this gene.

The BCR1 locus

This is defined by a 5·8 kb DNA segment of chromosome 22 which has been cloned at the 22q11 breakpoint of the Ph¹ chromosome of CML.⁴³ This segment is the central part of a 45 kb gene⁴⁴ that is fused to a truncated *c-abl* gene from chromosome 9 and expressed as a chimeric RNA and protein. This locus will be discussed in the CML section.

Anonymous DNA segments of chromosome 22

Ten single segments from chromosome 22 have been isolated (table 2),^{45–50} most of them from the chromosome 22 specific DNA library (*EcoRI* complete digest) constructed after chromosome sorting by Krumlauf *et al.*¹ Five of them (D22 S1, S3, S5, S9, S10) have displayed RFLPs (table 2). There are two other chromosome 22 specific DNA libraries prepared under the auspices of the US National Laboratory Gene Library Project, one after *HindIII* digestion (M A Van Dilla, Lawrence Livermore National Laboratory, California), the other after *EcoRI* digestion (L L Deaven, Los Alamos National Laboratory, New Mexico). Since all these chromosome 22 libraries were

obtained after complete digestion, they do not contain overlapping clones and cannot be used for chromosome walking.

Preliminary linkage map of chromosome 22

We have studied five loci exhibiting RFLPs: *IGLV*, *IGLV*, *SIS*, *MB*, and *D22SI*, and two phenotypic markers: P1 blood group controversially assigned to chromosome 22^{14, 51, 52} and *DIAI*, already confirmed to be on chromosome 22^{7, 8} and for which quantitative polymorphism has been found in Algeria.⁵³ Multilocus linkage analysis⁵⁴ was performed after investigating each marker in pedigree from CEPH (Centre d'Etude des Polymorphismes Humains, J Dausset) and from Algeria. A preliminary linkage map spanning the long arm of chromosome 22 was obtained, and the maximum likelihood order is:

$$\theta=0\cdot10 \quad \theta=0\cdot22 \quad \theta=0\cdot17$$

(*IGLV*, *IGLV*)—*D22SI*—*MB*—*SIS*.⁵⁵ This reference map was used to confirm the evidence of the localisation of the *PI* polymorphic locus of the P blood group on chromosome 22, which had been previously suggested but contested. The *PI* locus lies close to *SIS*, and the odds of *PI* being linked to the marker map is 96·5:1 (equivalent of lod score=1·67). The phenotypically polymorphic *DIAI* locus was found to have a location score⁵⁴ of 11·5, corresponding to odds in favour of *DIAI* being linked to the marker map of $3\cdot2\times10^{11}$, although its location on the long arm could not be determined with accuracy. The physical and linkage maps agree, and a comparison stresses that these two mapping methods are complementary to each other.

Chromosome 22 and disease

The pathology of chromosome 22 is rich, both at the somatic and at the constitutional level (table 3).

SOMATIC ABNORMALITIES OF CHROMOSOME 22
Several monoclonal malignancies exhibit specific abnormalities of chromosome 22, restricted to the tumour cell clone.

The Philadelphia chromosome (Ph¹) and CML

This was the first chromosome marker to be specifically related to a given human malignancy: chronic myelogenous leukaemia (CML).⁵⁷ CML is a clonal disorder of a pluripotent stem cell in which 90% of the patients have the Ph¹ marker. It is found in neutrophils, monocytes, erythroblasts, megakaryoblasts,⁵⁸ and sometimes in lymphocytes.⁵⁹ Classically it corresponds to a t(9;22)(q34;q11·2), and Ph¹ is the 22q— derivative. In about 5% of cases

FIG 2 Morbidity map of chromosome 22. Diseases are in bold letters. Dotted arrows indicate breakpoints not yet characterised at the DNA level. Relevant genes or markers are also indicated. Brackets are used when a locus or a disease has not yet been ordered relative to neighbouring markers.

however, there is a different chromosomal rearrangement,⁶⁴⁻⁶⁹ either because the partner of chromosome 22 is not chromosome 9 but any other one except the Y chromosome, or because there is a complex translocation involving more than two chromosomes, always chromosome 22 but not always 9. High resolution studies on prometaphase chromosomes indicated that in the standard Ph^1 the translocation is apparently reciprocal, with breakpoints occurring precisely at 9q34.1 and 22q11.2.⁷⁰⁻⁷¹ They also helped to show that some variant translocations also involve chromosome 9. This was further confirmed by in situ hybridisation with the *c-abl* and *bcr* probes.⁷²⁻⁷³ The breakpoint on chromosome 22 is proximal to the proto-oncogene *c-sis*.⁷⁴⁻⁷⁵

The molecular dissection of the junction between DNA from chromosome 22 and from chromosome 9 on Ph^1 is a great accomplishment. First it was shown that the proto-oncogene *c-abl*, normally located near the telomere of chromosome 9, was transposed

onto the 22q- (Ph^1) derivative,⁷⁶ and that the breakpoint mapped in a patient within 14 kb 5' of *c-abl*.⁷⁷ Then the chimeric DNA fragment was cloned and used as a probe to investigate several Ph^1 positive CML patients. The breakpoint was variable on the *c-abl* side (chromosome 9), whereas it always clustered in a sequence of 5.8 kb on the chromosome 22 side, called *bcr* for 'breakpoint cluster region'.⁴³ *bcr* was found to be constantly rearranged in CML patients, suggesting its possible role in the pathogenesis of CML.

On the other hand the role of *c-abl* was suggested by its amplification in the human Ph^1 positive K562 cell line.⁷⁷⁻⁷⁹ It was then found that the original *bcr* segment comprises four exons from the middle of a 45 kb gene with 13 exons.⁴⁴ This gene itself was called '*bcr*', and the corresponding locus *BCR1*. In Ph^1 the 5' half of *bcr* is fused tail-to-head (same orientation) to a variable portion of *c-abl*.⁴⁴ Remarkably, although the breakpoint is variable on the *c-abl* side,⁴⁴ the resulting chimeric gene is still

TABLE 3 Diseases related to chromosome 22.

Disease	Cytogenetics	Affected gene	Locus involved	DNA
<i>Acquired</i>				
CML	Ph ¹ =t(9;22)	bcr and <i>c-abl</i>	<i>BCR1</i> (chrom 22) and <i>ABL</i> (chrom 9)	Chimeric bcr/ <i>c-abl</i> gene
ALL (variants)	t(9;22)	?	?	breakpoint between <i>IGLC</i> and <i>BCR</i>
Burkitt's lymphoma	t(8;22)	Igλ	<i>IGL(V,C)</i> (chrom 22)	Igλ juxtaposed
Ewing's sarcoma	t(11;22)	<i>c-myc</i>	<i>MYC</i> (chrom 8)	downstream <i>c-myc</i>
Neuroepithelioma	t(11;22)			
Neuroendocrine tumour	t(11;22)			
Meningioma*	22 monosomy			
Acoustic neuroma†	?		<i>IGLC</i> or <i>SIS</i> or <i>D22S1</i>	Loss of allele
<i>Constitutional</i>				
t(11;22) recurrent syndrome	t(11;22)			
Ring 22	r(22)			
Cat eye syndrome	21pter→q11			
DiGeorge syndrome	tri- or tetrasomy			
	21pter→q11 deletion			
Recessive congenital methaemoglobinaemia		NADH-cytochrome b5 reductase	<i>DIA1</i>	
Metachromatic leucodystrophy		Arylsulphatase A	<i>ARSA</i>	
Hurler and Scheie syndromes (MPS type I)		α-L-iduronidase	<i>IDUA</i>	
Galactosialidosis		β galactosidase-neuraminidase protective protein	<i>PPGB</i>	

*Two reports of constitutional aberration.^{143 144}
†Only one preliminary report.¹⁵⁰

'in frame' and is transcribed into a chimeric mRNA of 8 kb, longer than the normal *c-abl* mRNA.^{44 80-83} It is ultimately translated into a 210 K abnormal protein.^{84 85} This chimeric protein, starting on the N terminal side with a *bcr* sequence and ending on the C terminal side with a *c-abl* sequence, is endowed with a strong tyrosine kinase activity, contrasting with the weak kinase activity of the normal *c-abl* product.^{84 85}

There are still many unanswered questions regarding the pathogenesis and the role of Ph¹. For example, what is the function of the normal *bcr* region, which seems to be a real gene, expressed in normal fibroblasts and encoding a putative protein of 68 K?⁴⁴ Why do *bcr* and *c-abl* fuse preferentially? What is the metabolic and cellular effect of the fused 210 K chimeric protein? Is the gene fusion the primary cause or a secondary effect of the disease? Interestingly, the variable breakpoint on the *c-abl* side occurs precisely in the 5' domain of alternative exon splicing that was recently shown to occur in normal cells.⁸⁶

The joining of *bcr* and *c-abl* is highly specific in

CML because (1) it is present in all Ph¹ positive CML patients, (2) it is found in CML with complex translocations,⁸⁷⁻⁸⁹ and (3) it is sometimes found in Ph¹ negative CML with normal karyotype.^{90 91} In which the DNA rearrangement is submicroscopic.

The Ph¹ chromosome has also been found in other malignancies, particularly in ANLL, ALL, or CLL,^{57 92-96} and also in multiple myeloma.^{97 98} The available data from molecular analysis indicate that the breakpoint in the so-called Ph¹ of ALL is more proximal than in CML, and that the *bcr* gene is not involved.⁹⁹⁻¹⁰¹ This suggests that the *bcr-abl* rearrangement is more specific to CML than the Ph¹ chromosome itself, and also shows that in ALL the activation of *c-abl*, if any, must be promoted by different mechanism.

Burkitt's lymphoma with the t(8;22) variant
Burkitt's lymphoma (BL) is a monoclonal malignant proliferation of B cells, almost always related to Epstein-Barr virus in the so-called endemic region of black Africa, but not in other regions.¹⁰² It is perhaps the only human malignancy with an obligate

tory chromosome rearrangement: t(8;14) in 75% of cases, t(2;8) in 5%, and t(8;22) in 20% of cases.¹⁰³⁻¹⁰⁶

In BL translocations, the chromosome breakpoints invariably occur at the site of the proto-oncogene *c-myc* on chromosome 8 (8q24) and at the site of immunoglobulin genes on the partner chromosome: heavy chains on chromosome 14 (14q32), kappa light chain on chromosome 2 (2p12), and lambda light chain on chromosome 22 (22q11). This fact has raised considerable interest, and it is impossible to review here all the publications on the molecular biology of BL, even in the less frequent t(8;22) variant.¹⁰⁷⁻¹¹⁰ In brief, BL is the first example in which chromosome translocation and gene transposition have been shown to induce oncogenesis by proto-oncogene (*c-myc*) activation, as proposed by Klein in a prophetic paper.¹¹¹ In BL with t(8;22), the breakpoint occurs at 22q11.2,¹¹² inside the Ig lambda cluster, either inside *IGLC*,²³ or between *IGLV* and *IGLC*,²³ or in *IGLV*.²⁹

At the DNA level many features distinguish the t(8;22) variant of BL from the common t(8;14). (1) *c-myc* stays on chromosome 8, where an incoming $\text{C}\lambda$ or $\text{V}\lambda$ gene from chromosome 22 is fused in a head-to-tail fashion (same orientation). (2) The breakpoint is mostly far (>45 kb) downstream from an intact *c-myc*.²⁶ (3) There are very few cases (lines BL37 and KK124) in which the breakpoint could be cloned and localised at a reachable distance in the 3' flanking region of *c-myc*.^{30 113}

In BL it is generally accepted that *c-myc*, an 'immortalising' oncogene, is deregulated, becomes constitutively expressed, and participates in the still mysterious process of cell transformation. This deregulation is relatively easy to explain in some BL with t(8;14) in which the *c-myc* gene has lost its 5' regulatory exon, or has been placed under the control of an immunoglobulin enhancer,¹⁰⁹ but in most cases this does not occur, especially in the t(8;22) BL variants. A possible deregulating effect of somatic point mutations occurring in critical non-coding regions of *c-myc* has also been advocated in the t(8;14) common variants.^{114 117} Some of us recently found discrete alterations of the *c-myc* restriction map in BL cell lines with t(8;22), representing somatic point mutations clustering in and around the first non-coding exon.¹¹⁸ We do not know how a remote juxtaposition to a lambda Ig gene can produce such events in the *c-myc* gene, nor if they are directly responsible for its deregulation. The exact role of *c-myc* in B cell oncogenesis is still not known, nor is the nature of a possible other cooperating 'oncogene'.

It was the study of the BL with t(8;22) which

enabled the localisation of the *IGLV* genes proximal to *IGLC* at 22q11.^{29 30} By molecular hybridisation with $\text{C}\lambda$ probes it was shown that the breakpoint at 22q11 of the t(8;22) BL type is more proximal than that of the Ph¹.^{119 120}

Ewing's sarcoma and neuroepithelioma

In 1983, a specific t(11;22)(q24;q12) translocation was reported independently by two groups investigating fresh tumour cells¹²¹ and established lines¹²² from Ewing's sarcoma (ES). This finding was further confirmed in a number of cases (more than 40).¹²³⁻¹²⁸ Variant translocations such as t(2;11;22), t(9;20;22),¹²¹ and t(2;12;22)¹²⁹ were also reported, indicating that chromosome 22 was the critical chromosome. The ES breakpoint appears to be the most distal on chromosome 22 of all the rearrangements described on this chromosome. This was suspected already upon standard cytogenetic examination of the first cases reported,^{121 122} and further confirmed to be distal to $\text{C}\lambda$ ¹³⁰ and to *bcr*¹³¹ (fig 2). It is proximal to *c-sis* which is translocated onto chromosome 11 without being modified or activated.^{131 132}

An apparently identical translocation was also found in peripheral neuroepithelioma¹³³ without implication of *c-sis*.¹³⁴ Very recently, a similar translocation has been reported in a neuroendocrine tumour of the small intestine.¹³⁵ Although there is an identical chromosomal lesion in all these tumours, we still do not know what DNA sequence from chromosome 22, if any, is involved. It should be emphasised that all these malignancies have a common neuronal origin*.

Meningioma and nervous system malignancies

Sporadic meningioma is a relatively benign tumour in which a uniform chromosomal aberration is found: total or partial loss of one chromosome 22. It was first discovered by Zang and Singer¹³⁶ and Zankl and Zang¹³⁷ and to date more than 200 cases have been documented.¹³⁸⁻¹⁴⁰ The constant monosomy of chromosome 22 is striking, as well as the fact that in about 10% of the cases only the region distal to 22q11.2 is missing.^{58 141 142} Interestingly, two recent papers reported the occurrence of meningioma in subjects with constitutional abnormalities of chromosome 22: a ring chromosome 22 in one case¹⁴³ and a Robertsonian t(14;22) in a pedigree with familial meningioma.¹⁴⁴ Loss or rearrangements of chromosome 22 have also been reported in central nervous system tumours, such as astrocytomas and gliomas.^{140 143 145 146}

* Ewing's sarcoma, originally described as a diffuse endothelioma of bone, develops in bone tissue, but is not osteogenic.

The molecular explanation of the tumours associated with total or partial loss of chromosome 22 is still unknown, but this situation suggests the possible existence on chromosome 22 (distal to 22q11.2 ?) of an 'anti-oncogene', like the *Rb1* locus on chromosome 13,¹⁴⁷ and the *WAGR* locus on chromosome 11.^{148 149} This hypothesis can be tested by investigating RFLPs at chromosome 22 loci, in both constitutional and tumour DNA of each subject, looking for loss of heterozygosity in the latter. Very recently this approach was used to demonstrate the loss of genes on chromosome 22 in seven subjects with acoustic neuroma.¹⁵⁰

CONSTITUTIONAL ABNORMALITIES

Balanced t(11;22) translocation

This is one of the most frequent balanced chromosomal translocations in the population and more than 150 independent families with t(11;22) have been reported.¹⁵¹⁻¹⁵³ It is usually discovered in families where some subjects are infertile, or in children carrying a small supernumerary chromosome 22 corresponding to der(22).^{152 154} These children are trisomic for the distal part of chromosome 11 and the proximal part of chromosome 22. They exhibit a characteristic phenotype,^{151 155} and the diagnosis can be made at first sight. The dysmorphic syndrome is similar to that of trisomy 11qter¹⁵⁵ and is very different from that caused by the rare trisomy 22.¹⁵⁶⁻¹⁵⁸ Analysis of prometaphase chromosomes showed that in all the families the breakpoint is the same, at 11q23.2 and 22q11.2.¹⁵³ This suggests that there is a preferential recombination site on both chromosomes, if one admits a pluricentric origin of the chromosomal accident.

At the molecular level, in situ hybridisation experiments with a $C\lambda$ probe suggested that the breakpoint is in the $C\lambda$ cluster¹³⁰ or proximal to it.^{130a} However, after selection of the der(11) chromosome of a similar case by flow sorting and hybridisation with both $C\lambda$ and $V\lambda$ probes, some of us found that it carried both genes.¹⁵⁹ This would indicate that, at least in the latter case, the breakpoint is proximal to IGLV and the most proximal of all breakpoints at 22q11 (fig 2).

Unbalanced aberrations of chromosome 22

As one would expect with a chromosome rich in early replicating R bands, there are very few examples of true constitutional chromosome 22 aneusomy. Complete trisomy 22 is probably lethal because it is frequently found in early aborted embryos. It has been detected in stillborn babies, either homogeneously or in mosaic form.¹⁶⁰ The published cases of complete or partial trisomy 22 in living subjects are in fact generally related to the above mentioned recurrent t(11;22).

There are few cases of true partial imbalance of small segments of the chromosome 22 long arm, due more often to unbalanced translocations than to accidents affecting only chromosome 22.^{158 161}

Ring chromosome 22 is rare and gives a well defined phenotype with mental retardation, cerebellar ataxia, and peculiar facial dysmorphism.^{162 163}

The cat eye syndrome comprises ocular coloboma, imperforate anus, cardiac defects, mental retardation, and a small supernumerary bisatellited chromosome.^{164 165} The nature of this extra chromosome is difficult to identify on a strict cytogenetic basis and it has been considered to represent trisomy or tetrasomy of 22pter→q11^{166 167} or partial trisomy of chromosome 13.¹⁶⁸ Molecular hybridisation with chromosome 22 specific DNA probes recently solved this question, showing that the isodicentric chromosome carries three or four copies of *D22S9* mapping at 22q11.¹⁶⁹ It hybridised with *IGLV* but not with *D22S1*¹⁷⁰ which places the breakpoint between these two loci (fig 2).

The DiGeorge syndrome (DGS) is a dysembryogenic disorder characterised by developmental abnormalities of the III to IV pharyngeal pouch, featuring aplasia or hypoplasia of the thymus and the parathyroid glands, cardiac malformations, and cervicofacial dysmorphism.¹⁷¹ The clinical picture is dominated by early cardiac failure. In survivors, hypocalcaemia or susceptibility to infections due to cellular immunodeficiency are the major manifestations.¹⁷² Familial cases have been reported in 14 out of 123 families.¹⁷²⁻¹⁸²

De la Chapelle *et al*¹⁷⁶ described an unbalanced translocation, -22,+der(20),t(20;22)(q11;q11), in four affected children from the same family. These patients were trisomic for the short arm of chromosome 20 and monosomic for the pter→q11 region of chromosome 22. After this observation, other cases in which the same proximal part of one chromosome 22 was missing have been reported in subjects exhibiting unbalanced chromosomal translocations between 22 and various autosomes: 3, 10, or 20,^{183 184} 4,¹⁸⁰ and 1 (O Raoul, personal communication). Another familial case with an apparently balanced t(2;22)(q13;q11.1) translocation has been reported.¹⁸⁴ If we count the older observations of DGS with chromosome 22 monosomy,^{185 186} there are now 14 cases in which this syndrome is associated with an aberration involving chromosome 22. There are only two cases in which cytogenetic aberrations were present but did not apparently involve chromosome 22.^{172 187} It is therefore tempting to consider, as proposed by de la Chapelle *et*

al,¹⁷⁶ that the disease is caused by a DNA defect on chromosome 22, in the juxtacentromeric part of the long arm, at least in some cases. In this regard the DGS would appear to be an inborn error of morphogenesis¹⁸⁸ rather than a teratogenic disease. The defect might involve still unknown developmental genes, and obviously this deserves further molecular studies with cloned probes mapping in the proximal region of 22q. On this line, Cannizzaro and Emanuel¹⁸⁹ investigated two cases of DGS in which the 22pter→q11 region was lost and the 22q11→qter region was translocated to the long arm of chromosome 10¹⁸³ or 4.¹⁸⁰ By in situ hybridisation with a Cλ probe they showed that, in both cases, the breakpoint was proximal to an intact IGLC cluster. This places the DGS breakpoint in the same region as BL with t(8;22), or more proximally (fig 2).

ENZYMOPATHIES

There are three monogenic recessive diseases due to well documented structural defects of enzymes encoded on chromosome 22.

Hurler and Scheie syndromes (mucopolysaccharidosis I; McKusick number 25280), a lysosomal disease due to α-L-iduronidase deficiency (locus *IDUA*).¹⁹⁰⁻¹⁹²

Metachromatic leucodystrophy (sulphatide lipidosis or cerebroside sulphatase deficiency; McKusick number 25010), a lysosomal disease due to arylsulphatase A deficiency (locus *ARSA*).¹⁹³⁻¹⁹⁵

Recessive congenital methaemoglobinaemia (NADH methaemoglobin reductase or NADH diaphorase deficiency; McKusick number 25080) due to cytochrome b5 reductase deficiency (locus *DIA1*)¹⁹⁶⁻¹⁹⁷ with its two forms: type I without mental retardation (enzyme defect restricted to RBC) and type II with mental retardation and neurological symptoms (systemic enzyme deficiency).¹⁹⁸⁻¹⁹⁹

A fourth enzymopathy, *galactosialidosis* (combined neuraminidase deficiency and β galactosidase deficiency or Goldberg syndrome; McKusick number 25654), is a lysosomal disease featuring a combination of mucopolysaccharidosis and sphingolipidosis, due to lack of the 32 K protective protein which stabilises both β galactosidase and neuraminidase against intralysosomal digestion (locus *PPGB*).¹⁶⁻²⁰⁰

Each of these diseases poses interesting problems, mainly regarding their clinical and biological heterogeneity. They will be solved, hopefully, when cloned probes are available to unravel the features of the normal and abnormal genes involved.

A MORBID MAP OF CHROMOSOME 22 (FIG 2)

We have seen that, despite its short size, chromosome 22 has a rich pathology. We show in fig 2 the location on chromosome 22 of the different sites where pathological events give rise to a known disease. As pointed out by Yu *et al*²⁰¹ and Cannizzaro *et al*,²⁰² 22q11 is a hot spot of chromosome breakage. It is also the site of active DNA rearrangements, either normal, yielding an active lambda Ig gene, or abnormal, causing Burkitt's lymphoma, CML, or ALL. The proximal region of the long arm is also involved in two developmental diseases, cat eye syndrome and DiGeorge syndrome.

Burkitt's lymphoma and CML were the first models in which it was shown that a translocation can produce a harmful gene fusion. How it is harmful is not yet known. Other malignancies, like Ewing's sarcoma, meningioma, neuroepithelioma, neuroendocrine tumour, and now acoustic neuroma, are still unchallenged enigmas at the DNA level. Interestingly, they are all derived from nerve tissue, even possibly Ewing's sarcoma.²⁰³ There is little doubt that the new generation of mapping methods²⁰⁴ will soon provide a complete map of this chromosome and help to solve these problems.

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