REVIEW ARTICLE

Current status of human chromosome 14

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Over the past three decades, extensive genetic, physical, transcript, and sequence maps have assisted in the mapping of over 30 genetic diseases and in the identification of over 550 genes on human chromosome 14. Additional genetic disorders were assigned to chromosome 14 by studying either constitutional or acquired chromosome aberrations of affected subjects. Studies of benign and malignant tumours by karyotype analyses and by allelotyping with a panel of polymorphic genetic markers have further suggested the presence of several tumour suppressor loci on chromosome 14. The search for disease genes on human chromosome 14 has also been achieved by exploiting the human-mouse comparative maps. Research on uniparental disomy and on the search for imprinted genes has supported evidence of epigenetic inheritance as a result of imprinting on human chromosome 14. This review focuses on the current developments on human chromosome 14 with respect to genetic maps, physical maps, transcript maps, sequence maps, genes, diseases, mouse-human comparative maps, and imprinting.

Interest in human chromosome 14 was stimulated in the early 1970s when a duplicated distal cytogenetic band of chromosome 14 was associated with Burkitt lymphoma.[1] A few years later, a partial trisomy syndrome for chromosome 14q was suggested to be associated with growth and mental retardation.[2] Purine nucleoside phosphorylase was the first gene mapped to chromosome 14, using a human-mouse somatic cell hybrid panel retaining a t(14;22) chromosome,[3] and shortly afterwards was shown to be deficient through haplotype studies in a family.[4] A folic acid sensitive site at 14q23,[5] variegate porphyria (*VP*),[6] alpha-1-antitrypsin (*AAT*),[7] familial hypertrophic cardiomyopathy (*CMH1*),[8] and Krabbe disease (*GALC*)[9] were the first loci to be mapped to specific intervals on chromosome 14. Extensive mapping efforts have been followed by sequencing of the chromosome. Although annotation of the sequence is currently incomplete, the results of the extensive sequencing efforts have allowed identification of over 550 genes on chromosome 14. This review describes the developments for human chromosome 14 with respect to genetic maps, physical maps, transcript maps, sequence maps, genes, diseases, mouse-human comparative maps, and imprinting, and provides a guide to resources available.

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GENETIC, PHYSICAL, TRANSCRIPT AND SEQUENCE MAPPING RESOURCES FOR CHROMOSOME 14

Genetic maps

Genetic maps of the human genome have been constructed to increase the informativeness and density of genetic markers. Refined chromosome 14 specific linkage maps were made by integrating markers from different genetic maps and by reassessing the genotype data. The progress in mapping was summarised annually at the Gene Mapping Meetings and two Chromosome 14 Workshops were held.[10 11] Early chromosome 14 genetic maps had very few blood serotype, RFLP, and VNTR genetic markers, and were biased with the highest density of markers in the distal 10% of the chromosome,[12 13] which showed above average recombination.[14] An STRP (short tandem repeat polymorphism) map comprising nine genetic markers, with heterozygosity values between 0.48 and 0.81, provided the first continuous linkage map along chromosome 14.[15] The markers were placed with over 1000:1 odds on an estimated 101 cM sex averaged chromosome 14 genetic map by linkage analysis on 40 CEPH reference families. The EUROGEM map of chromosome 14, about 146.2 cM (sex averaged) in length, showed 23 markers spaced about 10-20 cM apart, using corrected genotype data from the CEPH consortium.[16] A more gene rich map of 42 RFLP and STRP markers, 13 of them within known genes, was reported on a 163 cM sex averaged map, using data from 59 CEPH reference families[17] and physical positioning using patients with chromosome 14 aberrations.[18] A refined chromosome 14 CEPH consortium genetic map with 68 genetic markers included 13 genes, 37 STRP, one OLA (oligonucleotide ligation assay), and 17 RFLP markers, positioned every 3.5 cM.[19] Another extensive linkage map of chromosome 14 using genotype data from CEPH database 7 included 147 markers (32 RFLP and 115 STRP) that were placed on a 128 cM sex averaged genetic map, with an average intermarker distance of 1.85 cM.[20] Sixty-nine loci were positioned with over 1000:1 odds and seven loci were anchored to cytogenetic bands at the proximal, medial, and distal intervals of chromosome 14 by FISH mapping. All markers showed consistent positions with the markers of other genetic maps except the D14S42 and *TCRA* loci that had ambiguous placements. The underlying problems

Abbreviations: STRP, short tandem repeat polymorphism; OLA, oligonucleotide ligation assay; SNP, single nucleotide polymorphism; STS, sequence tagged site; EST, expressed sequence tag; LOH, loss of heterozygosity; TS, tumour suppressor

with the early genetic maps are that many markers were not common between the maps and the number of families genotyped could not always provide an unambiguous gene or marker order.

While microsatellite markers provide high heterozygosity, new technologies have made feasible the typing of more frequent biallelic markers or single nucleotide polymorphisms (SNPs). A dense genetic map of 459 novel non-redundant SNPs and 21 small insertions/deletions were identified from 825 chromosome 14 expressed sequence tagged and sequence tagged site sequences, by the screening of 12 unrelated Nigerians.[21] An additional 501 SNPs, identified by the screening of several world wide ethnic groups, were obtained from the public SNP database (www.ncbi.nlm.nih.gov/SNP). Of the 981 non-redundant biallelic genetic markers, 273 SNPs were located within 159 known genes with a range of two to 20 polymorphisms per gene. There are currently over 2100 SNPs reported on chromosome 14 by the large scale SNP mapping effort of the human genome project (www.ncbi.nlm.nih.gov/SNP/index.html). These resources will be of benefit in the identification of additional diseases on chromosome 14 through conventional genetic mapping approaches.

Physical maps

The Whitehead Institute for Genome Research (www-genome.wi.mit.edu) physical map of chromosome 14 comprises 590 YAC clones.[22] These YAC clones, useful for positioning of markers but unsuitable for sequencing, were arranged into five contigs by sequence tagged site (STS) content mapping of over 350 chromosome 14 STS markers.[22] A scaffold of 27 BAC clones was also physically mapped to chromosome 14, with an average spacing of 1 to 3 Mb, using FISH.[23] The aim was to provide a framework of BAC clones that would serve as nucleation points for sequencing of the human genome, and as probes for molecular cytogenetic analyses. In addition to these public efforts to construct physical contigs on chromosome 14, several small contigs consisting of YAC, BAC, cosmid and a combination of these clones were reported by several groups in the search for disease genes[24–28] such as oculopharyngeal muscular dystrophy at 14q11.2-q12[24] and tetramelic mirror image polydactyly at 14q13.[26] These physical contigs provided valuable resources for the initial identification of chromosome 14 specific transcripts.

The construction of these physical contigs was assisted by a framework of genetic markers, in addition to a framework of STS markers that were mapped onto the G3 and/or GeneBridge4 (GB4) radiation hybrid panels by the Sanger Centre (www.sanger.ac.uk), Whitehead Institute for Genome Research (www-genome.wi.mit.edu), and Stanford Human Genome Centre (www-shgc.stanford.edu). One disadvantage of mapping onto these panels is that a marker can be mapped to an incorrect chromosome as a result of artefacts from PCR or paralogous sequences. An alternate approach was used to map 1001 novel STS markers with an average spacing of 90 kb on chromosome 14, using an in vitro radiation hybrid mapping approach, called Happy Mapping. Briefly, chromosome 14 DNA isolated by flow cytometry was fragmented by irradiation and used for mapping. The mapping resolution of this technique was dependent on the size of the fragmented DNA chosen. This method was different from mapping on radiation hybrid panels in that there was more fragmented DNA representative of the entire chromosome that allowed more accurate positioning of markers.

Transcript maps

Several transcript maps have been reported for limited regions of chromosome 14.[30–33] The public sequencing of cDNAs from several cDNA libraries led to the generation of expressed sequence tags (ESTs), comprising predominantly 3′ untranslated sequences. These were used to form "UniGene clusters" (proposed genes) of cDNAs with at least 97% identity to each other.[34]. The assembly of physical maps has progressed by the mapping of ESTs, and the grouping of ESTs to form clusters of possible genes. In 1996, 16 354 unique ESTs, from a total of 20 104 ESTs were mapped within a genome wide framework of about 1100 Généthon genetic markers.[35] Subsequent significant progress included 434 ESTs mapped to chromosome 14 using a CEPH YAC library of 32 000 clones, and by mapping on the G3 and GB4 Radiation Hybrid panels.[35] Of over 30 000 ESTs, 1047 were later mapped on chromosome 14 using the G3 (framework of 2091 genetic markers) and/or the GB4 (framework of 1641 genetic markers) radiation hybrid panels.[36] The recent in silico analyses of EST and mRNA sequences mapping to human chromosome 14 has defined over 800 Unigene clusters on this chromosome (www.ncbi.nlm.nih.gov/UniGene). The equivalency of predicted genes or Unigene clusters and actual genes will require confirmation.

Sequencing

A working draft of over 85% of the human genome is currently made available by the world wide consortium of public Genome Sequencing Centers and Celera Genomics.[37 38] Généscope (www.genoscope.cns.fr) is the designated centre for the sequencing of human chromosome 14. Other genome centres and independent research groups had sequenced parts of chromosome 14 such as the T cell receptor cluster at 14q11.2, 1 Mb of the immunoglobulin heavy chain gene cluster at 14q32.3, and several regions of the Alzheimer disease locus at 14q24 (reviewed by Weissenbach[39]). These auxiliary sequencing centres provided over 15% of the genomic sequence for chromosome 14.[40]

The sequencing strategy performed by Généscope is based on a sequence tag connector method.[40] This strategy involves the concurrent building of a physical and sequence map. Initially, 50 selected markers were ordered at high odds along the chromosome using the GB4 Radiation Hybrid Panel, and used as probes for the screening of high density human BAC genomic filters from the Caltech and Roswell Park libraries. All positive BAC clones were assessed for redundancy and rearrangements by fingerprinting before being sequenced. Fully sequenced BAC clones were queried against a database of clone end sequences available from The Institute of Genome Research (TIGR) or in house BAC end sequences, to identify minimal overlapping clones and to select the next BAC clone for sequencing. Chromosome walking was performed in a bidirectional manner and the progress of walking was assessed on the TNG radiation hybrid panel that had a framework of 2350 chromosome 14 mapped markers. Based on the analysis of genomic sequence from each clone belonging to chromosome 14, there is an estimated 22% overall redundancy in the tiling path. Annotation of the genomic sequence with respect to known genes, predicted genes, and markers is available from the National Centre for Biotechnology Information (www.ncbi.nlm.nih.gov), Ensemble (www.ensembl.org), Genome Channel (compbio.ornl.gov/channel/index.html), and Genome Catalog (genome.ornl.gov/GCat/ species.shtml).

DISEASES OF HUMAN CHROMOSOME 14

Genes and diseases

The long arm of chromosome 14, about 93 Mb in size, is estimated to contain over 1800 genes if one gene is localised at every 30 to 50 kb. However, with the availability of draft genomic sequence for human chromosome 14, the estimated number of genes has been reduced to around 550. The reduction of estimated genes in the human genome is postulated as a result of more complex spatiotemporal expression and alternative splicing patterns of genes.[37 38] With an improved quality of genomic sequence and the verification of predicted genes, the number of genes on chromosome 14 may increase. To date,

Table 1 Genes identified for diseases on chromosome 14

Disease	OMIM accession number	Map location	Gene
Retinitis pigmentosa	162080	14q11.1-q11.2	Neural retina leucine zipper (*NRL*)
Lysinuric protein intolerance	603593	14q11.2	Solute carrier family 7, member 7 (*SLC7A7*)
Congenital ichthyosiform erythroderma	190195	14q11.2	Transglutamase-1 type I (*TGM1*)
Oculopharyngeal muscular dystrophy	602279	14q11.2-q13	Poly(A) binding protein, nuclear 1 (*PAB2*)
Familial hypertrophic cardiomyopathy	160760	14q12	Myosin, heavy polypeptide 7 (*MYH7*)
Deafness, autosomal dominant 9	603196	14q12-q13	Cochlin (*COCH*)
Autosomal dominant oligodontia	167416	14q13	Paired box homeobox gene 9 (*PAX9*)
Nucleoside phosphorylase deficiency	164050	14q13.1	Nucleoside phosphorylase (*NP*)
Carbohydrate deficient glycoprotein syndrome type II	602616	14q21	Mannosyl(alpha 1,6) glycoprotein beta 1,2-N acetylglucosaminyl-transferase (*MGAT2*)
Glycogen storage disease VI	232700	14q21-q22	Glycogen phosphorylase, liver (*PYGL*)
Elliptocytosis	182870	14q22-q23.2	Spectrin, beta, erythrocytic (*SPTB*)
Dystonia DOPA responsive	600225	14q22.1-q22.2	GTP cyclohydrolase 1 (*GCH1*)
Molybdenum cofactor deficiency type C	603930	14q23	Gephyrin (*GPH*)
Micropthalmia, cataracts, and iris abnormalities	142993	14q24.3	*C elegans* ceh-10 homeo domain containing homologue (*CHX10*)
Alzheimer disease 3	104311	14q24.3	Presenilin 1 (*PSEN1*)
Micropthalmia, cataracts, and iris abnormalities	142993	14q24.3	*C elegans* ceh-10 homeo domain containing homologue (*CHX10*)
Methylmalonate semialdehyde dehydrogenase deficiency	603178	14q24.3	Aldehyde dehydrogenase 6 family, member A1 (*ALDH6A1*)
Machado-Joseph disease	109150	14q24.3-q31	Spinocerebellar ataxia 3 (*SCA3*)
Krabbe disease	245200	14q31	Galactosylceraminidase (*GALC*)
Graves disease	603372	14q31	Thyroid stimulating hormone receptor (*TSHR*)
Alpha-1-antichymotrypsin deficiency	107280	14q32.1	Alpha-1-antichymotrypsin (*AACT*)

mutational analyses have shown 21 genes on human chromosome 14 to be associated with 21 genetic diseases (table 1). The disease loci for which the relevant genes have not yet been identified are listed in table 2. Catalogues of genes and/or diseases of human chromosome 14 are available at Online Mendelian Inheritance in Man (www3.ncbi.nlm.nih.gov/omim), LocusLink (www.ncbi.nlm.nih.gov/ LocusLink), GeneCards (bioinformatics.weizmann.ac.il/cards), and Genome Database (gdbwww.gdb.org). Other possible diseases associated with chromosome 14 are described below and are listed in table 3.

Possible diseases associated with specific gain or loss of gene function

The majority of genetic diseases were localised to chromosome 14 by linkage studies. However, by studying the gain or loss of function of specific genes, additional disease loci have been proposed on chromosome 14. A locus for fibrodysplasia ossificans progressiva was proposed, based on the overexpression of the *BMP4* (bone morphogenetic protein 4) gene in the lymphoblast cell lines of 26 out of 32 patients affected with fibrodysplasia ossificans progressiva.[41] The *BMP4* gene maps to 14q22-q23. A locus for congenital thyroglobulin defect, at 14q13, was proposed based on quantitative RT-PCR analysis on total RNA extracted from the lymphoblast cell line of an affected patient.[42] The proband showed almost complete loss of expression of the *TTF1* (thyroid transcription factor 1) gene that maps to 14q13. A locus for tyrosinaemia type Ib was proposed at 14q24.3, based on the study of a male proband who showed loss of maleylacetoacetate isomerase activity in hepatocyte and skin fibroblast biopsies.[43] The *MAAI* gene maps to 14q24.3. For the three genetic loci mentioned, the gain or loss of function of the genes on chromosome 14 as the main cause of each disease is yet to be confirmed.

Diseases associated with chromosome 14 aberrations

Subjects who are carriers of specific chromosome 14 aberrations are often affected with common features suggesting that the phenotype is the result of a common genetic aetiology. A locus for tetramelic mirror image polydactyly (*TIMP*) at 14q13 between the markers D14S306 and AFM200ZH4 was proposed through characterisation of a patient affected with tetramelic mirror image polydactyly and left inguinal hernia, and a t(2;14)(p32.3;q13) chromosome.[26] An EST (GI:748802) with unknown identity was identified within 300 kb of the translocation breakpoint on chromosome 14. No additional familial or chromosomal cases of tetramelic mirror image

Table 2 Diseases on chromosome 14 with unidentified genes

Disease	OMIM acession number	Map position
Distal myopathy 1	160500	14q11.2-q12
Deafness, autosomal recessive 5	600792	14q12
Idiopathic basal ganglia calcification	213600	14q13
Arrhythmogenic right ventricular dysplasia 3	602086	14q12-q22
Hereditary benign chorea	118700	14q13-q21
Spastic paraplegia type 3A	182600	14q11.2-q24.3
Deafness, autosomal dominant, non-syndromic, sensorineural 23	605192	14q21-q22
Arrhythmogenic right ventricular dysplasia 1	107970	14q23-q24
Leber congenital amaurosis type III	604232	14q24
Insulin dependent diabetes mellitus	601208	14q24.3-q31
Autosomal recessive microphthalmia	251600	14q32
Usher syndrome type 1A	276900	14q32
Multinodular goitre 1	138800	14q3

Table 3 Summary of potential tumour suppressor loci on chromosome 14

Tumour suppressor locus	Proposed cytogenetic positions	Molecular definitions	References
Colorectal carcinoma	14q32	D14S65-D14S250 D14S20-qter	See text
Malignant mesothelioma	14q11.1-q13 14q22-q24 14q32	D14S283-D14S64 D14S258-D14S284 ?	See text
Neuroblastoma	14q12 14q23 14q32	D14S80 (?) D14S63 (?) D14S62-D14S987 D14S17-D14S23	See text
Lung carcinoma	14q13 14q11-q24	D14S306 (?) D14S80-D14S261	See text
Gastrointestinal stromal tumours	14q11-q12 14q23-q24.3	D14S283 (?) D14S258 (?)	See text
Non-papillary renal cell carcinoma	14q24.2-qter	?	80–82
Uterine leiomyoma	14q24.1	D14S298-D14S540	83–85
Primary head and neck squamous cell carcinoma	14q13-q21 14q31-q32.1	D14S288-D14S269 D14S45-D14S78	90
Nasopharyngeal carcinoma	14q11.2 14q12-q13 14q32-qter	TCRD-D14S80/D14S283 D14S278-D14S288 D14S51-qter	91
Renal oncocytoma	14q13-q21 14q23-q24.4 14q32	D14S288 (?) D14S63-D14S74 D14S78-D14S826	92, 93
Ovarian carcinoma	14q12-q13 14q32.1-q32.2	D14S80-D14S70 D14S65-D14S267	94
Breast carcinoma	14q31-q32	D14S62-D14S5195	95
Soft tissue tumours	14q11-qter	?	96
Endometrial carcinoma	14q11.2-qter	TCRD-qter	97
Meningioma	14q24.3-q31 14q32.1-q32.2	D14S55-D14S68 D14S45-D14S78	98
Stomach adenocarcinoma	14q11-qter	?	99

polydactyly have been reported to be associated with chromosome 14 to date. A locus for anterior polar cataract (*CAPD*) at 14q24-qter was proposed, based on two studies.[44 45] The first study reported four subjects with a balanced t(2;14)(p25;q24) chromosome and affected with anterior polar cataract in a three generation pedigree.[44] A second study reported a female proband with unilateral nuclear cataract (a form of anterior polar cataract) and other congenital disorders.[45] The index case had a mosaic 46,XX/46,XX,del(14)(q32.3) karyotype. This latter case was non-informative in the localisation of the locus for anterior polar cataract in the medial region of chromosome 14; however, it suggested an additional locus for anterior polar cataract at the distal band of chromosome 14. A locus for recessive achromatopsia 1 (*ACHM1*), also known as rod monochromacy 1 (*RMCH1*), was proposed on chromosome 14 based on a female proband who carried maternal uniparental isodisomy of chromosome 14.[46] The proband showed rod monochromacy, short stature, mild developmental delay, premature puberty, small hands, and small feet, features prevalent within the maternal uniparental disomy 14 syndrome.

Other examples of chromosome aberrations associated with human chromosome 14 have been reported. Patients who are carriers of ring chromosome 14 have been proposed to have a specific syndrome.[47–49] Severe, early onset seizures are a feature of all these patients. Other common features include growth and mental retardation, microcephaly, elongated face, downward slanting/narrow palpebral fissures, epicanthus, flat/broad nasal bridge with anteverted nostrils, and generalised hypotonia/hypertonia. A few reported patients have one or more of the following: hypoplasia of the corpus callosum, dilatation of the lateral ventricles, cortical atrophy of the cerebrum, and porencephaly.[49] Other defects sometimes associated with ring chromosome 14 include retinal pigment defects, epidermal pigment defects, frontal bossing, low set ears, hypertelorism, pulmonary infection, and lymphoedema of the hands and feet.[47–49] The phenotypic variability of ring chromosome 14 syndrome may be the result of differences in the position of the chromosome breakpoint, extent of the deletion, and the degree of mosaicism. A 14q32.3 deletion syndrome was proposed by Ortigas *et al*.[50] Patients who are carriers of a terminal deletion usually have a small head, high forehead with lateral hypertrichosis, epicanthic folds, ptosis, broad nasal bridge, high arched palate, single palmar crease, and mild to moderate developmental delay.[50] The variability in phenotype is because of differences in the extent of the deletions and possible parental origin effects which will be described later. The reason that subjects with terminal deletions of chromosome 14 do not have seizures, as observed in patients with ring chromosome 14, is unknown. A mosaic trisomy 14 syndrome was proposed from the study of at least fifteen subjects who were carriers of mosaic trisomy 14,[51–55] and frequently showed growth and psychomotor retardation, broad nose with anteverted nostrils, dysplastic and/or low set ears, micrognathia, short neck, congenital heart disease, and micropenis/cryptorchidism.[51–54] Other features include a prominent forehead, hypertelorism, narrow palpebral fissures, large mouth, long philtrum, cleft/high arched palate, delayed bone ossification, translucent film over the eyes, abnormal skin pigmentation, and asymmetry of the body.[51–54] The phenotypic variability observed in mosaic trisomy 14 syndrome can probably be explained by the degree of trisomy 14 mosaicism.

Haematological malignancies associated with chromosome 14

Many acquired chromosome 14 inversions and translocations have been observed in B cell and T cell associated haematological malignancies. Acute and chronic T cell lymphomas are associated with dysregulation of the *TCL1A* (T cell lymphoma 1A) gene, and possibly the *TCL1B* (T cell lymphoma 1B) and *TCL6* (T cell lymphoma 6) genes at 14q32.1, and/or the *TCRA* (T cell receptor alpha) and *TCRD* (T cell receptor delta) genes

at 14q11.2.[55] Like the *TCR* genes at 14q11.2, the *TCL1A*, *TCL1B*, and *TCL6* genes are positioned in a cluster at 14q32.1.[55 56] The *TCL1B* and *TCL6* genes undergo complex alternative splicing with each other.[56] Unlike the extensive studies that have shown the role of the *TCR* gene cluster at 14q11.2 in haematological malignancies, only expression studies and a transgenic mouse model of the *TCL1A* gene have shown the association of the *TCL1A* gene with malignancies.[55 57] The functions of the other genes at the *TCL1A* cluster are yet to be determined. The 14q11.2 and 14q32.1 regions are also frequent hot spots for chromosomal rearrangements such as t(14;14)(q11;q32.1), t(7;14)(q35;q32.1), and inv(14)(q11q32.1), found in chronic T cell lymphomas/leukaemias.[55] Interestingly, these acquired chromosomal aberrations have also been found in patients with ataxia telangiectasia, a recessive disorder characterised by cerebral ataxia, oculocutaneous telangiactasia, varying degrees of immune deficiency, and malignancies of T cell origin.[58] T lymphoid malignancies and Hodgkin's disease resulting from translocation breakpoints at 14q32 may also involve the *AKT1* (v-akt murine thymoma viral oncogene homologue 1) proto-oncogene,[59] located at 14q32. The TCL1A protein coactivates AKT1 by interacting with the pleckstrin domain and promotes oligomerisation of the AKT protein.[59] The *CEBPE* (CCAAT enhancer binding protein epsilon) gene at 14q11.2, which is expressed in myeloid and T lymphoid cells, is another proposed gene for lymphoid and myeloid malignancies on chromosome 14.[60]

B cell lymphomas are frequently associated with rearrangements in the immunoglobulin heavy chain gene cluster (*IGH*) at 14q32.3.[61] Errors during VDJ recombination are thought to be the primary cause of many translocations involving 14q32.3 and other chromosomes. The 5′ IGH intronic μ enhancer (Eμ) and 3′ enhancers located downstream of each constant alpha region (Cα) become juxtaposed to non-IGH chromosomal DNA in many translocation chromosomes. This leads to the dysregulation of genes contained on the non-chromosome 14 derivative owing to illegitimate somatic recombination between μ and γ or α, or altered expression mediated by the μ or α enhancers. Such mechanisms are proposed for many types of B cell lymphomas such as multiple myelomas, mantle cell lymphoma, follicular lymphoma, diffuse large cell lymphoma, mucosa associated lymphoid tissue, diffuse large cell B cell lymphoma, marginal zone B cell, and primary effusion lymphoma.[61] Other haematological malignancies are observed when lymphocyte stem cells acquire trisomy 14.[62–64] Here, trisomy 14 is the result of a normal chromosome 14 and an isochromosome 14, or three normal chromosomes 14, two of which are uniparental. Patients with acquired trisomy 14 lymphocyte stem cells usually manifest the myelodysplastic syndrome spectrum, which includes refractory anaemia with ringed sideroblasts, excess of blasts, or excess of blasts in transformation.[62–64] This is followed by acute myeloid leukaemia and then a typical chronic myeloid leukaemia in the absence of a Philadelphia chromosome.[62–64] A few cases of myeloproliferative disorders have also been reported to be associated with chromosome 14.[65] For these haematological malignancies which are the result of amplified copies of an oncogene, well studied oncogenes like *FOS* (v-fos FBJ murine osteosarcoma viral oncogene homologue), *TCL1A*, *AKT1*, and *TGFβ3* (transforming growth factor beta 3) are excellent candidate genes on chromosome 14 that warrant further investigation in myelodysplastic and myeloproliferative disorders.

Malignant tumours associated with chromosome 14

The loss of function of tumour suppressor genes or the gain of function of oncogenes are primary causes of tumorigenesis. These could result from chromosome aberrations, intragenic mutations, gene conversions, and inactivation of genes by an epigenetic mechanism in somatic cells. An association of chromosome 14 with several types of tumour has been identified through studies of loss of heterozygosity (LOH) and by karyotyping. As a result, minimal regions harbouring tumour suppressor genes at the proximal, medial, and distal regions on chromosome 14 have been defined. Additional tumour loci on chromosome 14 may be identified by searching for recurrent chromosome 14 aberrations tabled in the extensive collection of chromosome 14 related neoplasias, reported by the Cancer Genome Anatomy Project (cgap.nci.nih.gov/Chromosomes/RecurrentAberrations). Some identified tumour suppressor (TS) loci on chromosome 14 are described below, and summarised in table 3.

A TS locus for colorectal carcinoma was initially suggested on chromosome 14 by karyotype analyses.[66 67] More precise localisation was achieved by allelotype analysis on 66 primary colorectal carcinomas of unknown karyotype, with six microsatellite markers.[68] Fifty percent of the tumours showed LOH for one or more markers. A consistent minimal region of deletion was identified between the markers D14S65 and D14S250 at 14q32, an estimated 8 cM interval. Ten tumours showed microsatellite instability, six of which also had LOH at 14q32. No correlation was evident between the extent of deletion and severity of tumour, except that the frequency of LOH at 14q32 in distal large intestine tumour (55.6%) was more prevalent than in proximal intestinal tumours (26.7%). These findings were supported by previous studies using RFLP markers,[66 67] and extended the TS locus more telomeric to the D14S20 marker.

Two or three TS loci for malignant mesothelioma were proposed. Previous studies suggested partial monosomy of chromosome 14 in primary malignant mesothelioma by comparative genomic hybridisation.[69] A minimal region on chromosome 14 for malignant mesothelioma was defined by LOH studies on 18 primary mesothelioma tumours using 23 microsatellite markers.[70] Ten of 18 tumours showed LOH of at least one locus, with the markers D14S283, D14S972, and D14S64 at 14q11.1-q12 and D14S258, D14S77, and D14S284 at 14q23-q24 being the most frequent. Allelotyping of 30 malignant mesotheliomas with 21 microsatellite markers showed allelic loss at 14q11.2-q13.2 and 14q22.3-q24.3 in 13 of 30 tumours. Allelic loss was also shown with markers at the 14q32 band.

Tumour suppressor loci for neuroblastoma on chromosome 14 have been proposed predominantly in Japanese patients. LOH of the RFLP marker D14S1 at 14q32 was shown in six of 12 tumours[72] and confirmed with additional RFLP markers at 14q32.[73 74] Initial definition of a minimal region for neuroblastoma distal to the D14S13 marker, by allelotyping of markers at 14q32, was supplemented by LOH studies on 108 neuroblastomas with 23 polymorphic markers to refine the size of the telomeric minimal region.[75 76] LOH was found in 18% of the tumours and subsequently a minimal critical region for neuroblastoma was defined between markers D14S1 and D14S16 in 17 of 19 tumours. The remaining two tumours showed LOH distal to D14S16, between markers D14S17 and D14S23, more distal markers, suggesting a second locus for neuroblastoma at 14q32. The highest resolution deletion mapping of 14q32, with 12 microsatellite markers on 54 neuroblastomas, found LOH in 17 of 54 tumours between the markers D14S62 and D14S987, an estimated 1.1 Mb interval within the first proposed telomeric neuroblastoma locus.[77] Other studies using comparative genomic hybridisations and cytogenetic analyses suggested that rearrangements in the proximal and medial regions of chromosome 14q also contribute to the genesis of neuroblastomas.[78 79] These findings were supported by genotyping of 17 polymorphic loci in 19 tumours, of which nine showed LOH with the markers D14S80 (14q12) and D14S63 (14q23).[76]

A potential TS locus for human lung cancer has been suggested by comparative mapping.[86] An autosomal dominant resistance locus to urethane induced pulmonary adenoma was localised to mouse chromosome 12, homologous to human

chromosome 14, suggesting a potential locus on human chromosome 14q11-q24. Genotyping of 30 primary lung adenocarcinomas with 15 microsatellite markers mapping to 14q11-q24, defined a minimal region between the markers D14S261 and D14S80 in seven tumours. LOH in other types of lung cancers including squamous cell carcinoma and small cell carcinoma showed LOH at 14q11-q12 in 30% of 25 cases of squamous cell carcinoma and 42% of 24 cases of small cell carcinoma. By another approach, malignant transformations of human bronchial epithelial cells were produced by treating immortalised cells with varying doses of "high linear energy transfer radon simulated alpha particles".[87] Subsequent LOH analyses with 17 markers showed that eight of 16 tumour transformed cell lines had a 0.5-1.7 cM loss around the D14S306 marker at 14q13. Another cell line showed LOH between the markers D14S283 and D14S274 at 14q11-q21.

Two TS loci on chromosome 14 were proposed for gastrointestinal stromal tumours based on comparative genomic hybridisation and loss of heterozygosity analyses of 30 gastrointestinal stromal tumours.[88] Frequent LOH of the D14S283 marker at 14q11.2-q12 and the D14S258 marker at 14q23-q24.3 regions were found, suggesting the involvement of possible TS genes such as *APEX* (apurinic/apyrimidinic endonuclease) at 14q11.2.[88] These findings were supported by cytogenetic analyses and molecular studies on 12 gastrointestinal stromal tumours, in which eight of 12 tumours had LOH of the whole or part of chromosome 14.[89]

Other potential TS loci proposed on chromosome 14 are listed in table 3. The tumour suppressor loci listed in table 3 and those described above share overlapping minimal regions in many instances. The specific genes of each tumour remain to be identified. Furthermore, whether a single gene is implicated in the genesis of two or more different tumours is yet to be resolved. Such information will be useful in determining the prognosis and treatment of specific tumours.

MOUSE-HUMAN COMPARATIVE MAPS

The study of conserved synteny between mouse and human chromosomes is necessary for understanding the evolutionary basis of chromosome divergence between these two species, and as a guide to the discovery of human disease genes. Such relationships are identified by determining the framework and order of homologous segments of syntenic genes between mouse and human chromosomes. Homology relationships between mouse and human are also necessary in the planning of knock-out or knock-in transgenic mice in order to study the phenotypic consequences of multiple genes in contiguous gene syndromes. More than 1500 mouse genes with human orthologues have been mapped, with 113 blocks of conserved synteny identified between these two species.[100] At least 85% of the conserved blocks occur on mouse autosomes, while the genes of mouse X chromosome are almost entirely syntenic with the genes of human X chromosome.[100]

The gene content and order of human chromosome 14 shows conservation of synteny with genes mapping mainly to mouse chromosomes 12 and 14 (fig 1).[101] More than two thirds of human chromosome 14, that is from the 14q12-qtel interval, exhibits almost continuous homology with mouse chromosome 12. The exceptions are the *BMP4* (bone morphogenetic protein 4), *ERO1L* (ERO1-like), *GCH* (GTP cyclohydroxylase 1), *GNG2* (guanine nucleotide binding protein gamma 2), *KTN1* (kinectin 1), *PTGER2* (prostaglandin E receptor 2), and *OTX2* (*Drosophila* orthodenticle homologue 2) genes, mapping to human chromosome 14q21-q23, which have orthologues that map to mouse chromosome 14.[101] Other genes like *SEC23A* (secretory 23 homologue A), *PSMA3* (proteosome alpha subunit 3), and *CNIL* (cornichon-like), mapping at human chromosome 14q21-q23, have orthologues possibly mapping to mouse chromosomes 2, 3, and 10 respectively (www.ncbi.nlm.nih.gov/Homology/). The human genes mapping proximal to the human chromosome 14q11.2-q12 cytogenetic border have orthologues mapping to mouse chromosome 14.[101] An exception is the *BNIP3* (BCL2 interacting protein 3) gene at 14q11.2-q12 that has an orthologue mapping to mouse chromosome 3.[102] A comparison of the gene order at human chromosome 14q10-q11 and mouse chromosome 14 further shows linkage discontinuity[101]; the map positions of human chromosome 14 orthologues on mouse chromosome 14 are disrupted by mouse chromosome 14 genes that have orthologues which map to many other human chromosomes.[101] Information on human-mouse chromosome homology relationships and/or sequencing progress of the mouse genome are available from the Mouse Genome Database (www.informatics.jax.org), National Centre for Biotechnology Information (www.ncbi.nlm.nih.gov/Homology/), and UK Human Genome Mapping Project resource centre (www.hgmp.mrc.ac.uk/GenomeWeb/comp-gen-db.html).

UNIPARENTAL DISOMY AND IMPRINTING STUDIES ON HUMAN CHROMOSOME 14

Genomic imprinting is the epigenetic marking of certain regions of chromosomes that results in monoallelic gene expression, depending upon the parent of origin. Evidence for imprinting effects associated with human chromosome 14 is supported by the observation of subjects affected with a spectrum of clinical features and having maternal or paternal uniparental disomy (UPD) of chromosome 14 (reviewed by Kamnasaran[103]). Since subjects with heterodisomy of chromosome 14 have the same phenotype as those with an isodisomy of chromosome 14, genomic imprinting is the possible cause of the phenotype rather than homozygosity of recessive genes. The loss of monoallelic expression or the gain of biallelic expression of an imprinted gene is a possible cause of an imprinting defect associated with uniparental disomy of chromosome 14.

Initial evidence of imprinting associated with human chromosome 14 arose from studies of imprinting effects associated with the distal region of mouse chromosome 12. Mouse pups with paternal or maternal duplications of the distal tip showed delayed growth and late embryonic or neonatal lethality.[104] Later studies of mouse pups with uniparental disomy for mouse chromosome 12 also showed abnormalities. Mouse embryos with maternal UPD(12) died perinatally and had growth retardation, defects in the second branchial arch patterning, and defects in myogenesis.[105] The paternal UPD(12) mice concepti exhibited placentomegaly and defects in myogenesis and chondrogenesis.[105]

Evidence for imprinting on human chromosome 14 was suggested by maternal and paternal uniparental disomy 14 syndromes. The clinical signs of subjects with maternal uniparental disomy 14 syndrome include short stature, precocious puberty, intrauterine growth retardation, hypotonia, scoliosis, obesity, mental/motor delay, recurrent otitis media, arrested hydrocephalus, small hands, short philtrum, fleshy nasal tip, high broad forehead, and hyperextensible joints.[106] The clinical signs in subjects with paternal UPD(14) include developmental delay, polyhydramnios, small thorax, short broad neck, depressed nasal bridge, hairy forehead, protruding philtrum, small palpebral fissures, camptodactyly, and blepharophimosis.[107] The fact that undergrowth and overgrowth anomalies were observed in the clinical spectrum of the maternal and paternal UPD(14) syndromes, provides further support for genomic imprinting as the suspected cause.

Uniparental disomy studies, while suggesting the presence of imprinted regions on human chromosome 14, are uninformative with respect to localising imprinted intervals. Partial trisomies of chromosome 14 were correlated with the parental origin of segments along chromosome 14 and the phenotype within the maternal and paternal UPD(14)

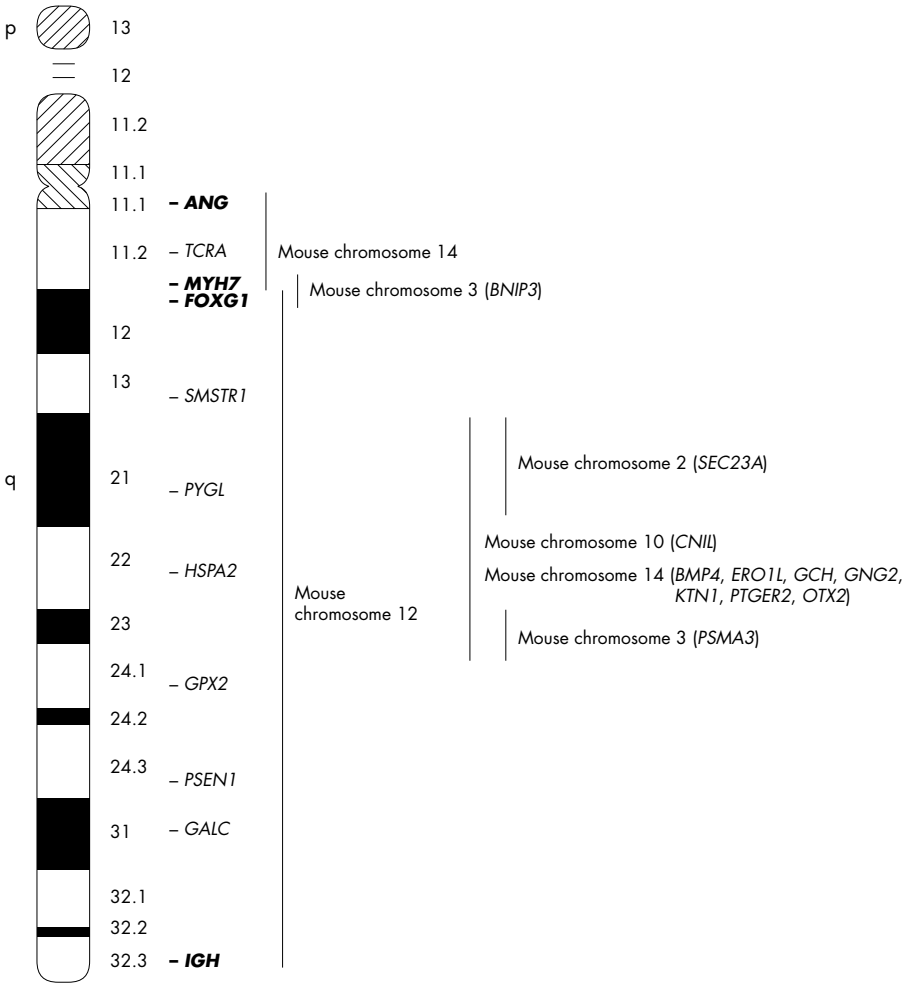

Figure 1 Summary of homology relationships between human chromosome 14 and mouse chromosomes. Known genes that define the evolutionary boundaries (in bold) and other selected genes are shown.

syndromes to suggest imprinted intervals.[109] Over 50 anomalies were examined in 31 cases of partial trisomy 14. An association was found between 14q24.3-qter and 14q31.1-qter and subjects with low birth weight, short philtrum, and small hands, features prevalent in maternal UPD(14) subjects. This suggested biallelic expression of maternally expressed imprinted genes as the cause of the phenotype. A weak association was found between distal paternal trisomy of chromosome 14 and broad neck. Potentially imprinted regions on chromosome 14 were identified by comparison of phenotypes of 17 maternal and four paternal UPD(14) cases with 33 chromosome 14 deletion cases of paternal or maternal origin.[110] Using this strategy, imprinted regions at 14q11-q13, 14q22-q24, and 14q31-q32 were suggested. Small thorax, blepharophimosis, hirsute forehead, and joint contractures were confined to 14q12-q13 and 14q31-qter, low birth weight and delayed growth were confined to 14q11.1-q13 and 14q31-qter, and fleshy nasal tip and scoliosis were confined to 14q22-q24.3 and 14q31-qter. Both maternal and paternal imprinted genes were proposed to reside at these intervals.

Additional definition of imprinted regions on chromosome 14 was suggested in a female proband with developmental delay, generalised hypotonia, macrocephaly, and joint laxity who had a partial maternal heterodisomy at 14q23-14q24.2.[111] Furthermore, a paternal imprinted region on chromosome 14 was suggested based on a father and daughter who were carriers of a direct duplication (14)(q23.4q31) chromosome.[112] The father was clinically normal, but the daughter was affected with mild developmental delay, microcephaly, and mild facial anomalies.[112] The proband's flat midface, bulbous nose, and upward slanting palpebral fissures were the only features in common with other subjects who had similar inherited direct or inverted duplications of chromosome 14.[112]

A cluster of imprinted genes first identified on mouse chromosome 12[113 114] have been identified on human chromosome 14. *MEG3* (maternal expressed gene 3), mapping at 14q32.2 and potentially non-coding, was identified as imprinted by studying the expression of a polymorphism within the *MEG3* gene.[115] *MEG3* showed maternal monoallelic expression in chorionic villi and human fetal tissue.[115] A second imprinted gene also mapping at 14q32.2 about 100 kb proximal to *MEG3* is *DLK1* (delta like 1). The *DLK1* gene showed paternal monoallelic expression in several human fetal tissues, including heart, kidney, and brain, based on studying the expression of a polymorphism identified.[116] *DLK1* encodes a protein of the EGF-like homeotic family, and may be involved in various cellular differentiation events. The possible role of *DLK1* in somite differentiation suggests this gene as a candidate for scoliosis, as observed in maternal UPD(12) syndrome.[116] The sheep callipyge (beautiful buttocks) locus (*CLPG*) has also served as a model to identify distal human chromosome 14 imprinted genes.[117–119] The sheep *CLPG* locus is homologous to human chromosome 14q32. Sheep exhibiting the callipyge phenotype show muscular hypertrophy of the hindquarters inherited in a manner designated as polar overdominance; only heterozygous sheep with the *CLPG* mutation express the phenotype when the mutation is inherited from their sire. Sequence and tissue specific expression analyses of a 250 000 bp genomic region of the *CLPG* locus recently led to the identification of possibly six imprinted genes, including *DLK1* and *MEG3*, in the skeletal muscle of sheep.[119] The remaining four genes, *DAT*

(DLK1 associated transcript), *PEG11* (paternal expressed 11), *MEG8* (maternal expressed 8), and *ANTIPEG11* (antisense PEG11), are additional imprinted genes that are potentially non-coding.[119] Two or more of these imprinted sheep transcripts could belong to a single gene. Moreover, the human orthologous genes of *DAT*, *PEG11*, *MEG8*, and *ANTIPEG11* need to be identified and their imprinted patterns studied in specific human tissues. Another possible imprinted locus at the medial region of human chromosome 14 is acrodysplasia, based on comparative mapping of a mouse paternally imprinted transgene locus on mouse chromosome 12 that results in cranial and limb defects.[120] Further information on imprinted genes and chromosomal regions is provided by the Mammalian Genetics Unit (www.mgu.har.mrc.ac.uk/imprinting).

SUMMARY

Extensive resources for the genetic localisation, physical mapping, and identification of disease genes are now available for human chromosome 14. Other means of identifying candidate disease genes will arise through comparative mapping and sequence analyses, particularly with identification of mouse homologous genomic sequences. An improvement in the amount and quality of chromosome 14 genomic sequence will further increase the number of identified genes and genetic markers, and also provide insight into the regulation and evolutionary properties of this chromosome. So far, over 30 diseases have been identified by standard linkage analyses, with 21 causative genes identified. Over 20 potential tumour suppressor loci have been identified by allelotyping. Other potential candidate disease loci have been mapped by the study of chromosome aberrations. The finding of epigenetic inheritance owing to imprinting on chromosome 14, by studies of numerical and structural chromosome aberrations, and expression analysis of candidate genes, has also influenced our understanding of the mechanisms underlying the disease phenotype associated with this chromosome. The wealth of information obtained on human chromosome 14 will be of clinical benefit for the counselling and prenatal diagnosis of subjects affected with a genetic disorder associated with this chromosome, in addition to genotype-phenotype correlation studies.

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