Gene mapping and medical genetics

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Genetic markers on chromosome 7

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SUMMARY Chromosome 7 is frequently associated with chromosome aberrations, rearrangements, and deletions. It also contains many important genes, gene families, and disease loci. This brief review attempts to summarise these and other interesting aspects of chromosome 7. With the rapid accumulation of cloned genes and polymorphic DNA fragments, this chromosome has become an excellent substrate for molecular genetic studies.

Chromosome 7 has been a subject of interest in medical genetics because of its frequent association with chromosome aberrations, rearrangements, and deletions, and because of the localisation of several important genes, gene families, and disease loci on this chromosome. It accounts for approximately 5% of the human genome and it is estimated to be 136 centimorgans (cM) in length and to contain 150 million basepairs of DNA. The short (p) and long (q) arm size ratio is approximately 1 to 1.5 (figure), but it varies significantly between prometaphase and midmetaphase.

Approximately 40 genetic loci were reported to be on chromosome 7 at the Eighth Human Gene Mapping Workshop (Helsinki, September 1985). There has been a dramatic increase of markers on this chromosome since then. The total number of gene loci and DNA markers characterised now well exceeds 400 (figure, table, K-H Grzeschik, 1987, personal communication, L-C Tsui et al, unpublished data). In addition, a chromosome 7 specific genomic library has been constructed by the Los Alamos and Lawrence Livermore National Laboratories using flow sorted chromosome 7 from a hamster-human hybrid cell line.

Genes and gene families

More than 35 genes of assigned functions have been localised to chromosome 7. They are listed in the table. Some of the genes, such as β-actin and procollagen, have been cloned and the gene structure analysed in detail; some have only been assigned by enzyme activities, such as biliverdin reductase and paraoxonase.

There are several gene families identified on chromosome 7. The T cell receptor β and γ chain genes have received most of the attention in the past few years. Both genes have complex gene structures and belong to the large immunoglobulin multigene family. Expression of these genes requires proper chromosome rearrangement joining different DNA segments together during T cell differentiation. The γ chain gene has been localised to the short arm, region p15.2. The β chain gene has been mapped to 7q3 but different subregion localisation data have been obtained by different investigators; it is still unclear whether the gene maps to q32 or q35.

The multidrug resistant phenotype of tumour cells is correlated with increased expression and amplification of the PGY-1 (mdr-1) locus which encodes a membrane glycoprotein called P glycoprotein. This protein is thought to function as an energy dependent export pump to reduce intracellular levels of anticancer drugs. Molecular cloning and mapping studies showed that the PGY-1 locus probably contains a number of related genes clustered within 7q21–q22.

The β-actin and procollagen genes also belong to multigene families but their related members are dispersed elsewhere in the genome.

Disease loci

A number of disease loci have been mapped to chromosome 7. The metabolic defects arginosuccinase...
nicaduria, mucopolysaccharidosis VII, and trypsinogen deficiency are probably the result of mutations within the genes encoding the enzymes that are involved in the biochemical pathway, namely argininosuccinic lyase, β-glucuronidase, and trypsinogen, respectively.\textsuperscript{100} Tritan colour blindness probably results from mutation of the blue-opsin gene.\textsuperscript{57}

Osteogenesis imperfecta describes a group of fragile bone disorders which are clinically heterogeneous.\textsuperscript{101} The syndrome can be divided into four phenotypic groups depending on the presence or absence of short stature, joint laxity, easy bruising, blue sclerae, presenile hearing loss, and dentinogenesis imperfecta. All of these symptoms are presumed to be the result of mutations in one of the six collagen genes. The genetics of OI have recently been reviewed in this Journal.\textsuperscript{102} The proc\textsubscript{2}(I) collagen gene which is involved in all four groups is located on the long arm of chromosome 7 (7q21.3→q22.1).

The collagen genes have also been prime candidates for the gene mutation in Marfan syndrome, which is a group of autosomal dominant connective tissue disorders with skeletal, cardiac, and ocular defects.\textsuperscript{103} A 20 amino acid insertion was found in 50\% of the proc\textsubscript{2}(I) chains in one patient and was thought to be the cause of the disease.\textsuperscript{104} DNA sequence analysis of the proc\textsubscript{2}(I) collagen gene revealed a 38 bp insertion in this patient.\textsuperscript{105} However, subsequent studies showed that this 38 bp insertion is a common DNA fragment length polymorphism among random normal subjects\textsuperscript{106} and there is no linkage relationship between the disease locus and the proc\textsubscript{2}(I) collagen gene in family studies.\textsuperscript{107,108}

Ehlers-Danlos syndrome is another heterogeneous group of disorders with collagen defects.\textsuperscript{109} Their clinical manifestations include laxity of joints, soft and extensible skin which may also be fragile, and excessive bruising. At least one form of this syndrome has been proposed to result from abnormal cleavage of the N-peptide of the proc\textsubscript{2}(I) chain.\textsuperscript{110}

Cystic fibrosis (CF) is the most common severe
<table>
<thead>
<tr>
<th>Genes</th>
<th>Symbol</th>
<th>Name or probe</th>
<th>Mode</th>
<th>References</th>
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<tbody>
<tr>
<td>pter→p15</td>
<td>COL5</td>
<td>Collagen-like 5</td>
<td>A</td>
<td>8</td>
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<tr>
<td>pter→p14</td>
<td>GCTG</td>
<td>( \gamma )-glutamylcyclotransferase</td>
<td>S</td>
<td>9</td>
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<td>pter→p22</td>
<td>PSP</td>
<td>Phosphoserine phosphatase</td>
<td>S</td>
<td>10</td>
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<tr>
<td>pter→q11</td>
<td>H1L</td>
<td>Histone H1-like genes</td>
<td>A</td>
<td>11</td>
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<td>pter→q22</td>
<td>NPY</td>
<td>Neuropeptide Y</td>
<td>S.RE</td>
<td>12</td>
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<tr>
<td>pter→q22</td>
<td>ACTB</td>
<td>( \beta ) -actin</td>
<td>S.RE</td>
<td>13</td>
</tr>
<tr>
<td>pter→q22</td>
<td>PDGFA</td>
<td>Platelet derived growth factor</td>
<td>RES</td>
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</table>

<table>
<thead>
<tr>
<th>Genes</th>
<th>Symbol</th>
<th>Name or probe</th>
<th>Mode</th>
<th>References</th>
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<tr>
<td>p22.1→q21</td>
<td>DIA2</td>
<td>Diaphorase</td>
<td>S</td>
<td>15, 16</td>
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<tr>
<td>p21→p14</td>
<td>HOX-1</td>
<td>Mouse HOX-1 homologue</td>
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<tr>
<td>p21→q22</td>
<td>ASL</td>
<td>Argininosuccinate lyase</td>
<td>S.RE</td>
<td>18, 19</td>
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<tr>
<td>p15</td>
<td>TCRG</td>
<td>T cell receptor, ( \gamma ) chain</td>
<td>S.RE</td>
<td>20, 21</td>
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<tr>
<td>p14→cen</td>
<td>BLVR</td>
<td>Biliverdin reductase</td>
<td>S.RE</td>
<td>22, 23</td>
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<tr>
<td>p13→p11</td>
<td>EGFR</td>
<td>Epidermal growth factor receptor (=ERBB)</td>
<td>S.RE</td>
<td>24-28</td>
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<tr>
<td>p12→p14</td>
<td>ERBB</td>
<td>( \nu )-erbB oncogene homologue</td>
<td>(avian erythroblast leukaemia virus)</td>
<td>29–32</td>
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<tr>
<td>p13→q22</td>
<td>MDH2</td>
<td>NAD malate dehydrogenase</td>
<td>S</td>
<td>33</td>
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<tr>
<td>p11→q11</td>
<td>ASNS</td>
<td>Asparagine synthetase</td>
<td>S.RE</td>
<td>+ 34, 35</td>
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<tr>
<td>cen→q11.2</td>
<td>MYH5</td>
<td>Myosin heavy polypeptide, adult skeletal muscle</td>
<td>A</td>
<td>36</td>
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<tr>
<td>q21→q22</td>
<td>ERV3</td>
<td>( \nu )-erv3 homologue</td>
<td>S.RE</td>
<td>37, Tsui et al., unpublished data</td>
</tr>
<tr>
<td>q21.3→q22.1</td>
<td>COL1A2</td>
<td>Collagen, type I ( \alpha )2</td>
<td>S.RE</td>
<td>+ 38–43</td>
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<td>q22</td>
<td>PGI1</td>
<td>P glycoprotein</td>
<td>S.RE.A</td>
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<tr>
<td>q22</td>
<td>GUSB</td>
<td>( \beta ) -glucuronidase</td>
<td>S.RE</td>
<td>47, Tsui et al., unpublished data</td>
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<tr>
<td>q22</td>
<td>EPO</td>
<td>Erythropoietin</td>
<td>S.RE</td>
<td>+ 48–50</td>
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<tr>
<td>q22</td>
<td>PCN</td>
<td>Paraoxonase</td>
<td>F</td>
<td>51–54</td>
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<tr>
<td>q22→q31</td>
<td>MET</td>
<td>met proto-oncogene</td>
<td>RES.A</td>
<td>+ 45, 55, 56</td>
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<td>q22→qter</td>
<td>BCP</td>
<td>Blue cone pigment</td>
<td>RE</td>
<td>57</td>
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<tr>
<td>q22→qter</td>
<td>CPA</td>
<td>Carboxypeptidase A</td>
<td>RE</td>
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<tr>
<td>q22→qter</td>
<td>ACTBP5</td>
<td>( \beta ) -actin pseudogene 5</td>
<td>S.RE</td>
<td>13</td>
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<tr>
<td>q22→qter</td>
<td>TRY1</td>
<td>Trypsin 1</td>
<td>S.RE</td>
<td>+ 58, 59</td>
</tr>
<tr>
<td>q31</td>
<td>CF</td>
<td>Cystic fibrosis</td>
<td>F</td>
<td>59–63</td>
</tr>
<tr>
<td>q32 or q35</td>
<td>TCRB</td>
<td>T cell receptor, B chain</td>
<td>RES.A</td>
<td>+ 64–69</td>
</tr>
<tr>
<td>q35→q36</td>
<td>BND3L</td>
<td>Band 3-like, fibroblast</td>
<td>RES</td>
<td>+ 70</td>
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<tr>
<td>q22</td>
<td>ASSP11</td>
<td>Argininosuccinate synthetase  pseudogene 1</td>
<td>RES</td>
<td>+ 71, 72</td>
</tr>
<tr>
<td>PAI-1</td>
<td></td>
<td>Plasminogen activator inhibitor</td>
<td>S.RE</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytochrome P450 protein</td>
<td>S.RE</td>
<td>+ 74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>glucocorticoid inducible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>q22</td>
<td>INFB2</td>
<td>( \beta ) 2 interferon</td>
<td>S.RE</td>
<td>+ 75</td>
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<tr>
<td>q22</td>
<td>UP</td>
<td>Urduc phosphorylase</td>
<td>S</td>
<td>76</td>
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<tr>
<td>q22</td>
<td>HADH</td>
<td>Hydroxacyl-CoA dehydrogenase</td>
<td>S</td>
<td>77</td>
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<tr>
<td>q22</td>
<td>PO4DB</td>
<td>Procollagen-proline, 2-oxoglutarate - 4-oxogenase, ( \beta ) chain</td>
<td>S</td>
<td>78</td>
</tr>
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</table>

**DNA segments**

| pter→p14    | D7S10  | p15-11 | RES  | 79     |
| pter→q22    | D7S11  | Phage 6 | RES  | + 20   |
| pter→q22    | D7S12  | pB78   | RES  | 79.80  |
| p12→qter    | DFN9   | pA4-8  | RES  | 81     |
| p11→q11     | D7Z1   | Chromosome 7 specific alpha satellite sequences | RES  | + 82, 83 |
| q22→q31     | D7S8   | p13-11 | RES  | + 45, 79 |
| cen→q22     | D7S6   | pA48   | RES  | + 79   |
| cen→q22     | D7S14  | pA28   | RES  | + 79, 80 |
| q22         | D7S15  | Lam4-917 | RES  | + 45, 60 |
| q22         | D7S13  | B79a   | RESA  | + 79, 84, V Buckle, 1987, personal communication |
| q22→q31     | D7S16  | 7C22   | RES.A | + 85, 86 |
| q22         | D7S1   | pA21H3 | RES  | + 87, 88 |
| q22         | p7-15  | RES   |     | 89     |
| q22         | p7-11  | RES   |     | 90     |
| q22         | p7-12  | RES   |     | 91     |
| q22         | p7-13  | RES   |     | 92     |

(Continued)
Genetic markers on chromosome 7

**TABLE Genes and DNA probes (continued).**

<table>
<thead>
<tr>
<th>Regional assignment</th>
<th>Gene symbol</th>
<th>Name or probe</th>
<th>Mode* RFLP</th>
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<tbody>
<tr>
<td>Other determinants</td>
<td>NM</td>
<td>Neutrophil migration</td>
<td>D</td>
<td>89</td>
</tr>
<tr>
<td>q22→qter</td>
<td>GCF1</td>
<td>Growth control factor 1</td>
<td>S</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>NHCIP2</td>
<td>Non-histone chromosome protein 2</td>
<td>S</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>PYHG3</td>
<td>Protein spot in 2D gel</td>
<td>S</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>YHG3</td>
<td>Protein spot in 2D gel</td>
<td>S</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>S7</td>
<td>Surface antigen</td>
<td>S</td>
<td>93</td>
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</table>

*A=in situ hybridisation; S=somatic cell genetics; F=family studies; RE=recombinant DNA techniques; D=deletion mapping.

Autosomal recessive disorder in the Caucasian population.110 The frequency of the mutant gene is estimated to be as high as 5% in some studies.111 Patients with CF have major symptoms including obstructive pulmonary disease, pancreatic enzyme insufficiency, and raised sweat electrolyte levels. Although a general malfunction in the secretory epithelia seems to be a consistent finding in CF,112-115 the basic defect has yet to be discovered. Mapping of the CF locus has been the subject of intensive investigations in the past two years.51-54 59-63 85 106-129 Through the mapping of a large number of DNA markers surrounding the disease locus, the most probable chromosome location for CF is within band 7q31.55 56 62 63 85 86 126 Genetic diagnosis has also been possible with the tightly linked DNA markers.127-129

Chromosome aberrations

There is a large number of documented cases of patients with short arm (7p-) deletions and translocations130-147 and most of them have been summarised recently.147 The majority (60%) of deletions involve the terminal band p22 and about half of these also have band p21 or p15 deleted. Two cases of recurrent spontaneous abortions seem to indicate the involvement of 7p.148 149 The remaining cases are interstitial deletions of various lengths, spanning between p21 to p13. The most frequent clinical abnormalities associated with 7p deletions are cranial dysmorphism, cleft palate, saddle nose, small, dysplastic, and low set ears, foot malformations, congenital heart disease, and genital malformations. However, the size and location of the chromosome segments involved do not show any obvious correlation with these or other symptoms.

Chromosome abnormalities have also been reported for the long (q) arm of chromosome 7. In contrast to the 7p- condition, the 7q- syndrome exhibits relatively consistent dysmorphic findings. Patients with terminal 7q deletions150-162 have growth deficiency, developmental delay, microcephaly, low birth weight, bulbous nasal tip, anomalous auricles, cleft lip/palate, genital malformations in males, and ocular anomalies. One-third of terminal del(7q) patients also have a history of perinatal feeding problems, abnormal EEG with or without seizures, ocular hypertelorism, micrognathia, and chest abnormalities.

Interstitial 7q deletions can be divided into three classes based on the chromosomal regions involved, namely, q11→q21 (or q22), q21→q31 (or q32), and q32→q34, all of which show delayed development as their common feature. The clinical presentations seem to agree well with this classification.160 In the q11→q21 (or q22) class, patients139 163-167 generally show feeding problems and some malformation in addition to their developmental delay. The main features in the del(7)(q21→q31 or q32) patients160 165 168-175 are delayed development, feeding difficulties, ear malformations, simian creases, low birth weight, and an unusual ‘cat like’ cry. A relatively small number of patients have been studied for the q32→q34 deletion,160 176 177 but developmental delay, broad nasal bridge, bulbous nasal tip, ocular hypertelorism, and large mouth seem to be consistent within this last class.

Heritable partial trisomy 7q can also be divided on the basis of the chromosomal regions involved,178 which are q22→q31 or qter,179-182 q31→qter,183-186 and q32 (or q33)→qter.136 178-194 Retardation of development and low set ears are the common clinical features of all three groups but significant differences are noted among them.178 Strabismus, epicanthus, and frontal bossing seem to be unique to trisomy 7(q22→q31), wide open fontanelle, cleft palate, microretrognathia, and early prenatal death to q31→qter, and kyphoscoliosis and hypotonia to q32 (or q33)→qter. Hypertelorism and small palpebral fissures appear to be common in the first and second groups, and low birth weight, small nose,
and skeletal anomalies in the second and the third groups. Thus, trisomy 7q31→qter is more serious than the other two. 178

Paracentric inversion is infrequent in man but chromosome 7 appears to be affected the most often. This topic has been reviewed recently. 195-196 Most paracentric inversions are apparently harmless and the heterozygous carriers of inv(7) were primarily detected in cases involving infertility, repeated abortions, malformation, and advanced maternal age. 195-207 As in the other chromosome 7 aberrations, the paracentric inversions appear to be non-randomly distributed within this chromosome. The majority of the breakpoints are located in bands q11 and q22, and the inverted segment was q11→q22 in half of the cases.

More recently, uniparental disomy has been proposed as a mechanism for human genetic disease. 208 In the reported case, the presence of two identical copies of the maternal chromosome 7 and the absence of paternal chromosome 7 were thought to be the cause of cystic fibrosis in a patient who also had short stature.

Somatic cell chromosome aberrations

Monosomy 7 is frequently associated with secondary blood disorders, namely, acute non-lymphocytic leukaemia (ANLL) or myelodysplastic syndrome (MDS), which often occurs in patients undergoing aggressive therapy (irradiation or chemotherapy or both) for a previous malignant disease (for example, Hodgkin’s disease). 209-210 A recent review 220 has indicated that more than 90% of these patients show hypodiploidy and monosomy 7 was found in more than 60% of the abnormal cases. There is a highly specific correlation between chromosome 7 abnormality and chemotherapy (p<0-01). 220 A correlation has also been shown between monosomy 7 and haematological disorders in persons exposed to chemical carcinogens in the work place. 221-225 Deletion and translocation of 7q accounts for all of the cases with partial monosomy 7 in the latter category, the common deleted segment being 7q32 or q34. 226 Monosomy 7 and deletion of 7q also seem to be involved in de novo ANLL (or MDS) according to some 227-229 but not all studies. 219 227

Chromosome 7 abnormalities have been implicated in several other cancer conditions, including ataxia telangiectasia, 230-232 erythroleukaemia, 233-234 gamma heavy chain disease, 235 lung carcinoid tumour, 236 prostate carcinoma, 237 transitional cell carcinoma of the ureter, 238 bilateral renal oncocytoma, 239 and malignant melanoma. 240-243 In vitro cell culture studies suggest that chromosome 7 is particularly unstable and vulnerable. 244-246 Interestingly, the translocation and deletion breakpoints discussed above seem to coincide well with the fragile sites observed on this chromosome, namely, FRA7A (rare, 7p11.2 247 248), FRA7B (7p22 249), FRA7C (7p14.2 249), FRA7D (7p13 250 251), FRA7E (7p21.2 249), FRA7F (7q22 250), FRA7G (7q31.2 249 251), and FRA7H (7q32-3 249 250). In a recent classification of fragile sites, 7q32 is listed as one of the most common fragile sites. 252

Oncogenes

Direct involvement of genes on chromosome 7 in tumour formation or malignancy has been suggested. Enhanced expression of the epidermal growth factor (EGF) receptor (cellular homologue of the viral erbB gene) in malignant melanoma, 253 epidermal carcinoma, 254-257 pancreatic carcinoma, 258 and glioblastoma 259 cell lines has been correlated with 7p abnormalities and polysomy 7. A strong correlation has been observed between the presence of a 7q abnormality and the expression of the T cell growth factor receptor (Tac) in a group of patients with T cell leukaemia. 260 The possibility of activation of the Tac gene via the T cell receptor β chain gene has been proposed. Chromosome 7 abnormalities have also been detected in some patients with chronic T lymphocyte tumours, but the breaks are located in different bands. 261

The met proto-oncogene, located within the 7q31 region, 56 was shown to have transforming potential in vitro when activated. 55 The transforming activity was first discovered in a mouse NIH/3T3 cell transformation assay with DNA isolated from a MNNG treated human osteosarcoma (HOS) cell line, 262 and it is therefore unlike most other proto-oncogenes, which were initially identified through viral oncogenes. DNA sequence analysis showed that the met gene belongs to the tyrosine kinase gene family and is closely related to the human insulin receptor and the viral abl gene. 56 Subsequent studies revealed that the activation of met in the MNNG-HOS cell line involved a gene fusion event which resulted in the replacement of the 5' portion of the proto-oncogene by sequences originating from chromosome 1. 263 264 The normal cellular function of met is as yet unknown.

The integration of the simian virus 40 genome in human chromosome 7 has been associated with cellular transformation. 265 The site of viral integration appears to be non-random 250 and maps to region 7q31. 266 Whether the transformation is the result of viral gene (T antigen) expression or disruption of cellular genes remains to be investigated.
Genetic markers on chromosome 7

Gene loci previously mapped to chromosome 7

There are a number of gene loci previously assigned to chromosome 7 but subsequently reassigned to a different chromosome. The two classical markers, the Colton (Co) and the Kidd (Jk) blood groups, were thought to be on chromosome 7 based on several lines of direct and indirect evidence. Recent data suggest that they are located elsewhere and probably unlinked (J Mohr, 1987, personal communication).

The mapping of the histone genes is interesting. Unlike the sea urchin and Drosophila histone genes which are clustered and tandemly repeated, the human genes, as well as those in yeast and mouse, are clustered but have no apparent repeats. Previous investigations, based on in situ hybridisation with probes derived from a histone mRNA enriched RNA fraction from human cells or sea urchin histone cDNA, showed that the human histone genes are either located within band 7q22 or 7q22–36. However, when specific gene probes were used, these genes were found to be in several different chromosome regions; one cluster containing H3 and H4 has been localised to 1cen–q25 and other clusters containing core (H3, H4, H2A, and H2B) alone or core together with H1 have been assigned to 1cen–q31, 6p12–q16, and 12p11–2–q21. A small number of grains was observed between the 7pter–q11 when a H1 specific probe was used in the latter in situ hybridisation experiment, but no signal was detectable by gel blot hybridisation analysis with two somatic hybrid cell lines, each containing chromosome 7 as the only human chromosome. The sequences detected on chromosome 7 by in situ hybridisation may represent cross hybridisation of other histone genes, a possibility that remains to be tested.

Genetic linkage map

Since the localisation of CF to 7q31, joint studies have been carried out to examine the linkage relationship among markers in this region. Six loci have been analysed further and the gene order with greatest statistical support is COLIA2–D7S13–D7S16–met–D7S8–TCRB. The most likely location of the CF gene on this map is between met and D7S8. A linkage map has also been generated for almost the entire length of chromosome 7 with randomly isolated DNA markers; the map spans 250 cM in females and 170 cM in males, values much greater than previously estimated. The most significant differences between the male and female genetic map appears to be within the portion of 7q bound by COLIA2 and TCRB.

Comparative mapping

The use of conserved linkage groups among mammals and primates has been an alternative approach to understanding the human gene map and evolution of chromosomes. Comparative mapping studies showed that human chromosome 7 markers are distributed over six different mouse chromosomes and that the mouse chromosome 5 and 6 sequences are found in both the long and short arms of human chromosome 7. Since the mapping of the histone genes to chromosome 7 it has been possible to compare the human gene map to the mouse genetic map. The results of these studies have been used to propose a new human genetic map, which is compiled in Table 1. The map spans 900 cM and includes 95 markers, 80 of which are located on chromosome 7.

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Genetic markers on chromosome 7

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Genetic markers on chromosome 7

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