### Table 3
Genetic risk estimates for serious effects in humans from 0.01 Gy of low-LET radiation from application of the direct method to mouse data

<table>
<thead>
<tr>
<th>Basis of estimate</th>
<th>Expected frequency in the first generation (Number per million live births)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>From exposure of males</td>
</tr>
<tr>
<td>Phenotypic changes in mice living 3 weeks or longer</td>
<td>10-20 (^c)</td>
</tr>
<tr>
<td>dying between birth and 3 weeks of age</td>
<td>5-10 (^b)</td>
</tr>
<tr>
<td>Total, each sex</td>
<td>15-30</td>
</tr>
<tr>
<td>Total, both sexes</td>
<td>15-44 (^d)</td>
</tr>
</tbody>
</table>

\(^a\) Lower estimate based on induced leucopenia; multiplication factor 36.6. The data, collected at high dose rates, have been corrected based on specific locus results.

\(^b\) Based on many experiments on the amount of induced death and on two experiments that indicate that part of total occurring after birth.

\(^c\) Data unavailable. Estimate assumed to be 4% of total of irradiated males, an upper bound suggested by specific-locus experiments. Because of qualitative differences in mutations between males and females, there is additional uncertainty in this risk estimate.

\(^d\) Includes risks for all types of inheritance, including translocations, unbalanced products of reciprocal translocations and reciprocal translocations that act like dominant mutations.

### Table 4
Estimates of minimal genic doubling doses from analysis of end-points of genetic effects in survivors of the atomic bombings [NS]

<table>
<thead>
<tr>
<th>Genetic effect</th>
<th>Observed total background incidence</th>
<th>Estimated mutational contribution to background incidence (^a)</th>
<th>Mutational component (^b) (%)</th>
<th>Regression parameters</th>
<th>Doubling dose ((S_d)) (^c) at lower confidence limits of 90%, 95%, 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavorable</td>
<td>0.0502</td>
<td>0.0017-0.0027</td>
<td>3.4-5.4</td>
<td>(b = 0.0026 \pm 0.0028) (\alpha = 0.039 \pm 0.0058)</td>
<td>0.14-0.23 0.18-0.29 0.21-0.33</td>
</tr>
<tr>
<td>pregnancy outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1 mortality</td>
<td>0.0458</td>
<td>0.0016-0.0026</td>
<td>3.5-5.7</td>
<td>(b = 0.00076 \pm 0.0015) (\alpha = 0.063 \pm 0.0018)</td>
<td>0.51-0.83 0.68-1.10 0.81-1.32</td>
</tr>
<tr>
<td>F1 cancer</td>
<td>0.0012</td>
<td>0.00002-0.00003</td>
<td>2.0-4.0</td>
<td>(b = 0.00008 \pm 0.00032) (\alpha = 0.0010 \pm 0.00033)</td>
<td>0.04-0.07 0.05-0.11 0.07-0.15</td>
</tr>
<tr>
<td>Sex-chromosome aneuploids</td>
<td>0.0030 (^d)</td>
<td>0.0030</td>
<td>100</td>
<td>(b = 0.0004 \pm 0.00006) (\alpha = 0.0025 \pm 0.00043)</td>
<td>1.23 1.60 1.91</td>
</tr>
<tr>
<td>Loci encoding for proteins</td>
<td>0.000013 (^d)</td>
<td>0.000013</td>
<td>100</td>
<td>(b = 0.0001 \pm 0.00001) (\alpha = 0.00001 \pm 0.00001)</td>
<td>0.99 2.27 7.41</td>
</tr>
</tbody>
</table>

\(^a\) Per diploid locus.

\(^b\) Equal to mutational contribution divided by observed total background incidence \((\times 100 / 0.01)\).

\(^c\) The doubling dose is equal to \((1/S_d)\) (equivalent to the reciprocal of the excess relative risk per sv/100). The minimal doubling dose is the reciprocal of \((1/\alpha + b)\) + the normal derivative at the desired probability level times the square root of the variance of \(\beta\).

\(^d\) Observed zygotic mutation rates.
Table 5
Incidence of genetic disease and risk estimates in humans from 0.01 Gy of low-LET radiation from application of the indirect method

<table>
<thead>
<tr>
<th>Genetic disease</th>
<th>Incidence per million live births</th>
<th>Effect of 0.01 Gy per generation per million live births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UNSCEAR [UI]</td>
<td>BEIR V [CI]</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Autoosomal dominant</td>
<td>10,000</td>
<td>2,500</td>
</tr>
<tr>
<td>Clinically severe</td>
<td>10,000</td>
<td>2,500</td>
</tr>
<tr>
<td>Clinically mild</td>
<td>7,500</td>
<td>400</td>
</tr>
<tr>
<td>X-linked</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>2,500</td>
<td>2,500</td>
</tr>
<tr>
<td>Chromosomal</td>
<td>400</td>
<td>600</td>
</tr>
<tr>
<td>Structural anomalies</td>
<td>3,400</td>
<td>3,800</td>
</tr>
<tr>
<td>Numerical anomalies</td>
<td>60,000</td>
<td>20,000-30,000</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>600,000</td>
<td>Not estimated</td>
</tr>
<tr>
<td>Multifactoral disease</td>
<td>600,000</td>
<td>600,000</td>
</tr>
<tr>
<td>Heart disease</td>
<td>300,000</td>
<td>300,000</td>
</tr>
<tr>
<td>Cancer</td>
<td>300,000</td>
<td>300,000</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>14</td>
</tr>
</tbody>
</table>

* Probably very small.

Table 6
Estimates of gametic doubling doses for acute, high-dose irradiation of spermatogonia derived from specific-locus, specific-phenotype systems in the mouse [N7]

<table>
<thead>
<tr>
<th>System</th>
<th>Origin of treated males</th>
<th>Doubling dose (Gy)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data summarized in</td>
</tr>
<tr>
<td>Russell seven-locus</td>
<td>101 x C3H</td>
<td>0.44</td>
<td>[E5, S12]</td>
</tr>
<tr>
<td>Dominant visible</td>
<td>Various</td>
<td>0.16</td>
<td>[L4]</td>
</tr>
<tr>
<td>Dominant castaet</td>
<td>101/E1 x C3H/E1</td>
<td>1.57</td>
<td>[F3]</td>
</tr>
<tr>
<td>Skeletal malformations</td>
<td>101</td>
<td>0.26</td>
<td>[E1]</td>
</tr>
<tr>
<td>Histocompatibility lost</td>
<td>C57B1/6DN</td>
<td>&gt;2.60</td>
<td>[B1]</td>
</tr>
<tr>
<td>Reccessive lethals</td>
<td>DBA</td>
<td>0.51</td>
<td>[S40]</td>
</tr>
<tr>
<td></td>
<td>C3H/E1 x 101/E1</td>
<td>0.80, 1.77</td>
<td>[L8]</td>
</tr>
<tr>
<td></td>
<td>DBA, C3H</td>
<td>4.00</td>
<td>[L9]</td>
</tr>
<tr>
<td>Loci encoding for proteins</td>
<td>Various</td>
<td>0.11</td>
<td>[N7]</td>
</tr>
<tr>
<td>Reccessive viables</td>
<td>C3H/E1 x 101/E1</td>
<td>3.89</td>
<td>[L8]</td>
</tr>
</tbody>
</table>
### Table 7
Correction factors used with the direct method to obtain estimates of risk of dominant genetic disease in humans [S6]

<table>
<thead>
<tr>
<th>Step</th>
<th>Quantity or correction factor</th>
<th>Correction procedure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skeletal mutations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>Mutation frequency (1 + 5 Gy; 24-h fractionation; ( \gamma ) rays)</td>
<td>37 + 2646</td>
<td>1.4 ( 10^3 )</td>
</tr>
<tr>
<td>1B</td>
<td>Mutation rate (per 0.01 Gy)</td>
<td>Divide (1A) by 600</td>
<td>2.3 ( 10^3 )</td>
</tr>
<tr>
<td>1C</td>
<td>Correction for dose fractionation and dose-rate effects</td>
<td>Multiply (1B) by 1/1.9 and 1/3</td>
<td>4.0 ( 10^4 )</td>
</tr>
<tr>
<td>1D</td>
<td>Extrapolation from skeletal effects to all dominants (proportionality correction factor)</td>
<td>Multiply (1C) by 10</td>
<td>40 ( 10^4 )</td>
</tr>
<tr>
<td>1E</td>
<td>Correction for severity</td>
<td>Divide (1D) by 2</td>
<td>20 ( 10^4 )</td>
</tr>
</tbody>
</table>

| **Risk of dominant genetic disease to the first-generation progeny per 0.01 Gy of paternal exposure** | | | 20 \( 10^4 \) |

| **Cataract mutations** | | | |
| 2A   | Mutation frequency (4.55 + 4.55 Gy; 24-h fractionation; \( \gamma \) rays) | 6 + 5,231 | 1.15 \( 10^3 \) |
| 2B   | Mutation rate (per 0.01 Gy) | Divide (2A) by 910 | 1.26 \( 10^3 \) |
| 2C   | Correction for dose fractionation and dose-rate effects | Multiply (2B) by 1/1.2 and 1/3 | 3.5 \( 10^2 \) |
| 3A   | Mutation frequency (5.34 Gy acute \( \gamma \) rays) | 3 + 10,212 | 0.29 \( 10^2 \) |
| 3B   | Mutation rate (per 0.01 Gy) | Divide (3A) by 534 | 5.5 \( 10^1 \) |
| 3C   | Correction for dose-rate effect | Multiply (3B) by 1/3 | 1.8 \( 10^1 \) |
| 4A   | Mutation frequency (6 Gy, acute \( \gamma \) rays) | 3 + 11,095 | 0.27 \( 10^1 \) |
| 4B   | Mutation rate (per 0.01 Gy) | Divide (4A) by 600 | 4.5 \( 10^1 \) |
| 4C   | Correction for dose-rate effect | Multiply (4B) by 1/3 | 1.5 \( 10^1 \) |
| 5    | Average of (2C), (3C) and (4C) weighted by the number of mutants | | |
| 6    | Extrapolation from dominant cataracts to all dominants | Multiply (5) by 36.8 | -10 \( 10^1 \) |

| **Risk of dominant genetic disease to the first-generation progeny per 0.01 Gy of paternal exposure** | | | -10 \( 10^2 \) |

---

*The correction factors are based on specific-locus experiments carried out at Oak Ridge.*

*Based on the McKusick catalogue of autosomal phenotypes, 1975 edition [M7]; at that time, it was estimated that about 74 out of 328 clinically important autosomal dominant conditions in man involved one or more parts of the skeleton (about 20%); however, since skeletal defects are more easily diagnosed than those of other organ systems, the true figure was assumed to be about 10%.*

*The correction for dose-fractionation effects (1/1.2) is based on concurrent specific-locus studies in Neuberger.*

*Based on the McKusick catalogue of autosomal phenotypes, 1978 edition [M7]; at that time, it was estimated that 20 out of 736 of all known and proven dominant mutations (2.7%) were associated with one or another form of cataract in man; recent analysis by Favor [F3], based on the McKusick catalogue of autosomal phenotypes, 1986 edition [M7], shows that these numbers are, respectively, 28 and 1,172, i.e. 2.4% of known dominant mutations are associated with cataracts. The multiplicative factor is therefore 41.*
Glossary

allele
an alternative form of a gene at a given locus. Being diploid organisms, humans may have two alleles at a given locus, i.e. a normal and a mutant allele. Abbreviation of allelomorph

allelic association
the association of two alleles at distinct loci beyond chance expectation. Normally a consequence of close linkage: loci within a megabase usually show some allelic association

allelic disorders
disorders, which may be phenotypically different, that are due to mutations in the same gene

alu repetitive sequence
repetitive sequence found about 500,000 times in human genome. The sequence contains a recognition site for the restriction enzyme AluI and is around 300 base pairs in length.

amplification
an increase in the number of copies of a particular DNA fragment. Can occur under natural circumstances, e.g. amplification of a repeat sequence, as in fragile-X syndrome, or during laboratory procedures such as cloning or polymerase chain reaction

aneuploid
a chromosome number that is not an exact multiple of the haploid number; an individual with an aneuploid chromosome number. Usually refers to an absence (monosomy) or an extra copy (trisomy) of a single chromosome

annealing
see hybridization

anticipation
phenomenon in which the severity of a genetic condition appears to become more severe and/or arise at an earlier age with subsequent generations

antisense strand (of DNA)
the non-coding strand of the DNA double helix that serves as the template for mRNA synthesis

association
the occurrence of an allele with a disease more often than chance should allow

autosome
any chromosome other than a sex chromosome. Men have 22 pairs of autosomes and an X- and a Y-chromosome; women have the same autosome pairs and two X-chromosomes. In the Paris convention, written 46XY and 46XX

bacteriophage
see phage. Bacterial virus used as a vector for cloning segments of DNA

band
a chromosomal segment defined by distinct staining. Both lighter and darker segments are called bands and are numbered from the centromere outwards, with smaller bands classified by a second number. Bands 11, 12, 13, 21, 22, 31 could be a continuous series.

base pair (bp)
in the DNA double helix, a purine and pyrimidine base on each strand that interact with each other through hydrogen bonding. The number of base pairs is often used as a measure of the length of a DNA segment, e.g. 500 bp.

base sequence
the order of nucleotide bases in a DNA molecule. Length is usually defined in base pairs.

blastomere
one of the cells produced by cleavage of a fertilized ovum, forming the blastoderm

breakpoint
refers to sites of breakage when chromosomes break (and recombine)

carrier
an unaffected individual who is heterozygous at a particular locus for a normal gene and an abnormal gene which, although it may be detectable by laboratory tests, is not expressed phenotypically. Various used to cover both permanent non-expression in recessives and X-linked recessives and temporary non-expression in dominants (e.g. Huntington’s chorea). More recently used to describe unaffected individuals who carry unstable or dynamic mutations that can expand and cause a genetic condition in offspring

cDNA
complementary DNA. The synthetic DNA equivalent of messenger RNA (mRNA) with a sequence complementary to the DNA strand from which it is derived

cDNA library
a collection of clones containing inserts of overlapping cDNA fragments representing expressed sequences (mRNA). cDNA libraries differ from one tissue or cell type to another.
centimorgan (cM) the unit of genetic distance defined as the length of a segment of chromosome which has a 1% chance of recombining at meiosis. See also recombination percentage. Equivalent segments of chromosomes usually recombine more frequently at oogenesis than at spermatogenesis. Because even numbers of recombinant events between two strands cancel out, the recombination percentage is always less than the genetic distance and can never exceed 50%. The percentage recombination and the genetic distance in centimorgans are very similar when linkage is close (i.e. less than 10%).

centromere the part of the chromosome by which it is moved at cell division and which separates it into two arms, appearing as a distinct "waist" on microscopy. Point of spindle attachment to the chromosome during meiosis and mitosis

chimaera an organism compounded from two or more zygotes. A mosaic is formed from variant cells derived from the same zygote.

chiasma the crossing of chromatid strands of homologous chromosomes during meiosis

chorionic villus sampling procedure used to obtain fetal cells for prenatal diagnosis; involves biopsy of the placental membranes. Now usually done transabdominally from 8 weeks of pregnancy during mitosis each chromosome replicates into two DNA strands called chromatids. At meiosis recombination is due to chiasmata between non-identical pairs of chromatids.

chromatin the composite of DNA and proteins that comprises chromosomes

chromosome thread-like, deep-staining bodies situated in the nucleus. They are composed of DNA and protein and carry the genetic information.

cis on the same chromosome, usually quite close. The opposite of trans, which relates to the other homologue. cis effects are due to physical action between segments of the same DNA strand; trans effects are due to diffusion. Historically implies on the same chromosome. In molecular biology refers to an effect on a gene directed by the sequence of that gene or very close to it on the same chromosome (in contrast to trans effects, which are produced by other factors, such as the transcription factors encoded by other genes). The terms are commonly used to describe factors that influence gene expression.

cleavage mitotic segmentation of the fertilized ovum, the size of the zygote remaining unchanged and the cleavage cells, or blastomeres, becoming smaller and smaller with each division

cloning production of genetically identical cells (clones) from a single ancestral cell; cloning is utilized in molecular biology to propagate single or discrete DNA fragments of interest.

coding sequence those parts of the gene from which the genetic code is "translated" into amino acid sequences of a protein

codon when both alleles are expressed in the heterozygote a group of three adjacent nucleotides that codes for particular amino acids or for the initiation or termination of the amino acid chain

codon usage given the degeneracy of the genetic code, refers to the preference of codons used to specify particular amino acids. Often differs among species and among different genes and proteins

complementary two nucleotide sequences are complementary when they can form a perfect double helix because they have a mirror-image relationship

compound heterozygote an individual who has different mutant alleles at a given locus

congenital existing at, and usually before, birth; referring to conditions present at birth, regardless of their causation

consanguinity relationship by descent from a common ancestor, a consanguineous mating is between individuals who have one or more common ancestors. As all individuals have common ancestors it is usually restricted to couples with a common pair of grandparents, e.g. first cousins.
consensus sequence  a minimum nucleotide sequence found to be common (although not necessarily identical) in different genes and in genes from different organisms that is associated with a specific function. Examples include binding sites for transcription factors and splicing machinery.

conserved sequence  base sequence in a DNA molecule (or an amino acid sequence in a protein) that has remained essentially unchanged throughout evolution

contiguous gene syndrome  syndrome due to abnormalities of two or more genes that map next to each other on a chromosome; most often caused by a deletion that involves several contiguous genes

contig map  genetic map showing the order of (contiguous) DNA fragments in the genome

cosmid  a cloning vector derived from a natural bacterial parasite capable of accommodating up to 40 Kb of DNA (see plasmid)

coupling  when alleles from two loci are known to be on the same chromosome; the opposite of repulsion. Also, all alleles derived from one parent

crossing-over  the exchange of segment of a chromosome in meiosis. Small chromosomes usually have a single chiasma, so that of the four chromosomes entering gametes two are hybrid and two unchanged, e.g. if the parental chromosomes are ABCDE and abcd, the gametes could be ABCDE, ABode, abcDE and abcd. The middle two are recombinant chromosomes with a crossover between loci B and C.

DNA  deoxyribonucleic acid. The long double-stranded molecule whose sequence of the four possible nucleotide bases provides the genetic information. The strands are held together by hydrogen bonds between nitrogenous bases that constitute the code: adenine (A) and thymine (T) which pair with each other, and guanine (G) and cytosine (C), which pair with each other.

DNA marker  a DNA sequence variation that is easily detectable; examples include restriction fragment length polymorphisms and dinucleotide and trinucleotide repeat polymorphisms.

DNA methylation  attachment of methyl groups to DNA, most commonly at cytosine residues. May be involved in regulation of gene expression

DNA polymerase  enzyme responsible for replication of DNA

DNA sequence  the relative order of base pairs

degeneracy  (of the genetic code) different codons code for the same amino acid

deletion  loss of a portion of a gene or chromosome; a type of mutation; a synonym of deficiency

diploid  containing two chromosome sets. The normal condition of most human cells except gametes; megakaryocytes, Purkinje cells and a few others have multiple sets.

dizygotic  twins derived from two distinct zygotes

domain  a discrete portion of a protein (and corresponding segment of gene) with its own function. A protein may have several different domains and the same domain may be found in different proteins.

dominant  a trait that is expressed in the heterozygote, sometimes only late in life

dominant mutations  mutations that produce an abnormal clinical phenotype (disorder or trait) when present in the heterozygous state

dominant negative mutations  homozygous mutations in which the product of the mutant allele interferes with the function of the normal allele

doubling dose  the dose of radiation that, under a given set of conditions, will lead to an overall mutation frequency that is double the spontaneous frequency

downstream  a DNA sequence is written from the left, or 5' direction or to the right, or 3' direction. Downstream refers to the 3' direction, i.e. the stop codon for a gene is downstream (3') of the coding sequences of that gene.

dysmorphology  study of abnormalities of morphologic development

electrophoresis  an analytical method used to separate nucleic acid, peptide or protein fragments based on size and charge of the molecule; typically smaller fragments travel further through the media (gel) in which separation is carried out.
enchromatin
darkly stained chromatin

enhancers
DNA sequences that increase transcription of a nearby gene; they can act in either orientation, may be either 5' or 3' to the gene or within an intron.

euchromatin
the chromatin that is thought to contain active or potentially active genes. Light (vs. dark) bands on G-banding

exon
a region of a gene containing a coding sequence. Most genes have several exons separated by introns, which are usually longer.

expressivity
the extent to which a genetic defect is expressed

F₁, F₂ etc.
the first (F₁) or second (F₂) generation of progeny of a mating

founder effect
a genetic effect due to the establishment of a new population by a few original founders who carry only a small fraction of the total genetic variation of the original population, with the consequence that some mutant alleles may reach unusually high frequencies in the new population. [Examples: the 2,000 Dutch settlers in South Africa in the 17th and 18th centuries, who did not marry outside the small ethnic group, eventually giving rise to a population of about 3 million. Frequency of familial hypercholesterolemia (FH) heterozygotes: 1/85 to 1/100 and 95% of mutations accounted for by only three alleles. Likewise, the current population of French Canadians of 5.8 million descended from 7,000 French settlers between 1608 and 1763. One familial hypercholesterolemia mutation accounts for about 60% of the heterozygotes in this group.]

frameshift mutation
a mutation that alters the normal triplet reading frame so that codons downstream from the mutation are out of register and not read properly

fragile site
gap or defect noted in the continuity of a chromosome when stained, e.g. fragile-X site. Many are apparent only when cells are cultured under special conditions.

gamete
mature reproductive cell (sperm or ovum); contains a haploid set of chromosomes (23 for humans)

gene
the unit responsible for transmitting an inherited character; the region of DNA that specifies the synthesis of a protein

gene targeting
artificial modification of a gene in a specific and directed fashion. Typically refers to substituting one DNA sequence for another to inactivate a gene or introduce or correct a mutation in a gene

genetic locus
a specific position or location in the genome

genetic fingerprint
a pattern of restriction fragments detected by probes that recognizes alleles at highly polymorphic loci; this is effectively unique to all individuals except identical twins.

genetic marker
an allele used in following the inheritance pattern of loci in cell lines, pedigrees or populations

genetic distance
the functional distance between two loci defined through recombination; it is measured in centimorgans; for small values (<10%) it is approximately equal to the recombination percentage.

genetic drift
the tendency for variations to occur in the genetic composition of small isolated inbreeding populations by chance. Such populations become genetically different from the original population from which they were derived.

genome
the complete genetic composition of an individual's chromosome; the complete set of genes characteristic of a species

genome DNA
DNA from a genome containing all coding (exon) and non-coding (intron and other) sequences, in contrast to cDNA, which contains only coding sequences

genomic library
a collection of clones containing DNA inserts of overlapping DNA fragments representing the entire genome of an organism

genotype
the alleles present in an individual at a locus or loci under consideration

germ cell
see gamete

germ-line mosaicism
presence of two or more cell lines in the gonadal cells. Implies risk of transmission of mutations present in the gonads to offspring
gonadal mosaicism
haploid
hemizygous
heterochromatin
heterozygote
histones
homeobox domain
homologies
homologous
homologous chromosomes
homologous recombination
housekeeping genes
human gene therapy
hybridization (annealing)
imprinting
in situ hybridization
insert
insertion
intron (intervening sequences)
karyotype
kilobase (kb)
library
linkage

see germ-line mosaicism
containing one chromosome set as found in gametes after meiosis. The normal condition for gametes. The human haploid number is 23, half the diploid number of 46.
the condition of cells with respect to genes when only one set is present, as for genes on the X-chromosome in the male
chromatin composed of repetitive DNA; stains as dark (versus light) bands in G-banding
an individual with two different alleles at a particular locus (adj. heterozygous)
proteins associated with DNA in chromosomes
a short DNA sequence common to a group of DNA binding proteins involved in pattern formation in early embryogenesis
similarities found in DNA or protein sequences when individuals of the same or different species are compared
matched. The other of a pair of chromosomes
chromosomes containing the same linear gene sequences. In a normal mating, 1 of a pair of homologous chromosomes is derived from each parent. Humans normally have 22 pairs of homologous chromosomes and 2 X-chromosomes or 1 X- and 1 Y-chromosome.
substitution of a segment of DNA by another that is identical (homologous) or nearly so. Occurs naturally during meiotic recombination; also used in the laboratory for gene targeting to modify the sequence of a gene
genes that encode proteins necessary for basic cellular functions. They are expressed in virtually all cells.
insertion of normal DNA directly into cells to correct a genetic defect
the artificial conjunction of two complementary DNA strands, one of which usually carries a radioactive marker. Also used for the production of cells containing chromosomes from more than one species
phenomenon in which an allele at a given locus is altered or inactivated depending on whether it is inherited from the mother or the father. Implies a functional difference in genetic information depending on whether it is inherited from the father or the mother
use of a nucleic acid probe to detect the presence of a DNA sequence in chromosome spreads or in interphase nuclei or of an RNA sequence in cells. It is used to map gene sequences to chromosomal sites and to detect gene expression.
in molecular genetics, refers to DNA sequence of interest that has been inserted into a cloning vector such as a plasmid or bacteriophage
type of mutation in which a DNA sequence of variable length is inserted into a gene disrupting the normal structure of that gene
the DNA sequences that interrupt the protein-coding sequences of a gene. The region of a gene that separates exons or coding sequences. They are removed during processing of mRNA. Introns may contain sequences involved in regulating expression of a gene.
the chromosome set; the number, size and shape of the chromosomes of a somatic cell may be displayed diagrammatically as an idiogram.
a thousand bases. A common unit for specifying the size of genes and physical distances along a DNA region
a collection of clones in which overlapping genomic or cDNA fragments have been inserted into a particular cloning vector
the non-independent meiotic segregation of alleles at different loci, which is usually because the loci concerned are all on the same chromosome, and only separable by recombination. Linked loci are within measurable genetic distance of one another on the same chromosome, or are members of the same linkage group, e.g. on the same chromosome. Distant loci on the same chromosome may show independent segregation and now show linkage. They are then described as syntenic.
linkage disequilibrium
see allelic association

locus
the position on a chromosome. Usually that of a gene, but may refer to a DNA marker

lod score
a statistical method used to determine if a set of linkage data indicates two loci are linked or unlinked. A lod (log of odds ratio) score of +3 (1,000:1 odds) is commonly accepted to indicate that linkage exists, and a score of -2 (100:1 odds against) excludes linkage.

mapping
the process of determining the location of a gene by either direct observation or family study

marker
a detectable physical location on a chromosome. It can be a restriction enzyme cutting site, a gene, or a di- or trinucleotide repeat polymorphism whose presence and inheritance can be monitored.

maternal inheritance
inheritance pattern displayed by mitochondrial genes that are propagated from one generation to the next through the mothers; the mitochondria of the zygote comes almost entirely from the ovum.

megabase (Mb)
one million base pairs of DNA sequence roughly equal to 1 cM of genetic distance

Mendelian
a trait obeying Mendel’s first law of independent segregation of the alleles at the same locus conveyed by each parent

meiosis
the type of cell division that occurs during gamete formation and results in the halving of the diploid somatic number of chromosomes so that each gamete is haploid and contains one of each chromosome pair. These post-mitotic chromosomes are usually partly paternal and partly maternal in origin.

messenger RNA (mRNA)
processed RNA that serves as a template for protein synthesis or for synthesis of cDNA

microsatellite
highly polymorphic DNA marker comprised of mononucleotides, dinucleotides, trinucleotides or tetranucleotides that are repeated in tandem arrays and distributed throughout the genomes. The best studies are the CA (alternatively GT) dinucleotide repeats. They are used for genetic mapping.

minisatellites
highly polymorphic DNA markers comprised of a variable number of tandem repeats that tend to cluster near the telomeric ends of chromosomes. The repeats often contain a repeat of 10 nucleotides. They are used for genetic mapping.

missense mutation
mutation that causes one amino acid to be substituted for another

mitochondrial (mt) DNA
DNA distinct from nuclear DNA in that it is mostly unique sequence DNA and codes for proteins that reside in mitochondria

mitosis
the type of cell division that occurs in somatic cells

monogenic
a synonym of Mendelian, i.e. governed by only one gene

monozygotic
twins derived from a single zygote

morphogenesis
evolution and development of form, as the development of the shape of a particular organ or part of the body

mosaicism
an individual with substantial proportions of two or more cell lines derived from a single zygote

motif
three-dimensional structure of gene product (protein) with known or implied function, i.e. DNA binding, traverse membrane etc. Often inferred from cDNA sequence

multifactorial
refers to the type of inheritance determined by many factors including both genes and the environment. If these are assumed additive, estimates of heritability may be made. In Mendelian and infective disorders a single factor will have a deciding role in manifestation, although not necessarily in severity or the potential for prevention or treatment. See also polygenic

mutation
a permanent and heritable change in genetic material (includes point mutations, deletions and changes in number or structure of chromosomes)

mutation frequency
number of mutations observed divided by number of progeny or cells examined

non-disjunction
failure of two members of a chromosome pair to disjoin (separate) during cell division

nonsense mutation
mutation that changes a codon for an amino acid to a termination or stop codon and leads to premature termination of translation
nucleosome
the basic structural unit of chromatin, in which DNA is wrapped around a core of histone molecules

nucleotide
a purine or pyrimidine base to which a sugar (ribose or deoxyribose) and 1, 2 or 3 phosphate groups are attached

nucleus
the organelle in eukaryotic cells that contains the genetic material

oligonucleotide
a short piece of DNA, typically 5-50 nucleotides

oncogene
a gene, one or more forms of which is associated with cancer. Many oncogenes are involved, directly or indirectly, in controlling the rate of cell growth.

open reading frame
a stretch of DNA following an initiation codon that does not contain a stop codon. Open reading frames in a nucleotide sequence suggest an exon and therefore a gene.

Paris convention
the notation system in which the karyotype is defined by the number of chromosomes followed by the sex chromosomes and information, if any, on an abnormality, e.g. 46XY, 47XYY (+21); 45XO; 47XXX. The position on a chromosome is defined by p and q (petit and queue) for the short and long arm and then by numbers defining bands and sub-bands, which are numbered outwards from the centromere. Usually there are 2-4 major bands and 2-5 minor bands, the term band covering both deeply and lightly staining segments.

pedigree
a diagrammatic representation of a family history

penetrance
the frequency of expression of a trait or genotype. The proportion of individuals observed to show a particular phenotypic effect of a mutant gene compared with the number expected on the basis of Mendelian inheritance

phage
a virus that infects bacteria and is a useful cloning vector for medium size pieces of DNA between 5 and 25 kb

phenocopy
an environmentally induced mimic of a genetic disorder

phenotype
the appearance (physical, biochemical and physiological) of an individual that results from the interaction of environment and genotype. Often used to define the consequences of a particular mutation

physical map
a map of physical landmarks on a DNA fragment or chromosome measured in base pairs. Landmarks include restriction endonuclease recognition sites, DNA sequence and chromosomal bands.

plasmid
extrachromosomal small circular DNA molecule capable of autonomous replication within a bacterium. Commonly used as a cloning vector for small pieces of DNA, typically 50-5,000 bases

poly A RNA
RNA transcript that contains a tail of poly A residues at its 3' end; implies that an RNA sequence is mRNA. The poly A residues serve as stop signals to terminate transcription.

polyamines
compounds with many amino groups that are associated in the cell with nucleic acids

polygenic
inheritance determined by many genes at different loci, each with small additive effects. A simple example is height within either sex. See also multifactorial

polymerase
see DNA polymerase, RNA polymerase

polymerase chain reaction (PCR)
a method to amplify a DNA sequence using a heat-stable polymerase and two sets of primers that define the sequence to be amplified. Several variations have been developed for specific needs. May be combined with reverse transcription of mRNA to cDNA to amplify an mRNA, so-called RT-PCR

polymorphism
the occurrence in a population of two or more genetically determined forms in such frequencies that the rarest of them could not be maintained by mutation alone. Used in various distinct senses, especially in RFLPs where it is used to imply alternative forms. Usually implies commonest allele is less than 99% so that over 2% of individuals are heterozygous.

polyploid
an abnormal chromosomal complement that exceeds the diploid number and is an exact multiple of the haploid number
position cloning strategy for identifying and cloning a gene based on its location in the genome rather than on the biologic function of its product. Usually involves linking the gene locus of interest to one that has already been mapped

pre-mutation a permanent and heritable change in a gene that does not have phenotypic consequences (does not cause disease) but predisposes to a “full” mutation that may

primary transcript the initial RNA transcript of a gene, before processing to mRNA; it contains introns as well as exons.

primer short polynucleotide chain that anneals to a nucleic acid template and promotes copying of the template from the primer site

proband a synonym of propositus or proposita. The affected individual who brings the family to medical attention

probe single-stranded DNA or RNA molecule of specific base sequence, labelled either radioactively or by other means, that is used to detect a complementary base sequence by hybridization. A labelled fragment of DNA (usually labelled with a radioactive isotope) used to identify a complementary sequence

promoter a sequence on a gene that is upstream (5’) to coding sequences to which RNA polymerase binds and initiates transcription of a gene

protein a large molecule composed of one or more chains of amino acids in a specific sequence; the sequence is determined by the sequences of nucleotides in the gene coding for the protein. Proteins are required for the structure, function and regulation of the body’s cells, tissues and organs, and each protein has unique functions. Examples are hormones, enzymes and antibodies.

pseudogene sequence of DNA that is very similar to a normal gene but has been altered slightly so that it is not expressed

RNA ribonucleic acid, the nucleic acid found mainly in cytoplasm. Messenger RNA (mRNA) transfers genetic information from the nucleus to the ribosomes in the cytoplasm and acts as a template for the synthesis of polypeptides; transfer RNA (tRNA) transfers activated amino acids from the cytoplasm to messenger RNA; ribosomal RNA (rRNA) is a component of the ribosomes that function as the site of polypeptide synthesis.

reading frame register in which translation machinery reads the genetic tripeptide code

recessive a trait that is expressed in individuals who are homozygous for a particular allele

recessive mutations mutations that produce an abnormal clinical phenotype when present in the homozygous or hemizygous state. Heterozygosity for the mutation, i.e. carrier state, may often be detected in persons whose clinical phenotype is normal.

recombinant DNA DNA that is artificially transferred from the genome of one organism to that of another

recombinant DNA molecules DNA molecules of different origins that are combined and manipulated in the laboratory

recombinant DNA technologies laboratory procedures used to manipulate DNA fragments, e.g. cut, modify and ligate, and introduce them into an organism so that their number can be amplified as the organism replicates, i.e. cloning

recombination the formation of a new combinations of linked genes by crossing-over between their loci during meiosis

recombination percentage equivalent segments usually recombine more frequently at oogenesis than at spermatogeneration. Because even numbers of cut-and-join events between two strands cancel out, the recombination percentage, often termed theta, is always less than the genetic distance and can never exceed 50%. They are almost the same at less than 10%, which is just over 10 cM.

repulsion when specific alleles at two different loci are derived from different parents. The opposite of coupling

restriction enzyme bacterial-derived enzyme that recognizes a specific, short nucleotide sequence and cuts DNA at that site

restriction fragments DNA fragments that result from digestion of DNA with restriction enzymes
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>restriction endonuclease</td>
<td>a group of enzymes each of which cleaves DNA at specific base sequences (recognition site)</td>
</tr>
<tr>
<td>restriction map</td>
<td>a map of a DNA sequence with restriction enzyme recognition sites serving as landmarks</td>
</tr>
<tr>
<td>restriction site</td>
<td>shortened term for restriction endonuclease recognition sequence</td>
</tr>
<tr>
<td>retrovirus</td>
<td>RNA viruses that encode the enzyme reverse transcriptase so that their RNA can be transcribed into DNA in the host cell; modified retroviruses are used as vectors to introduce genes (or portions thereof) of interest into eukaryotic cells.</td>
</tr>
<tr>
<td>reverse transcriptase</td>
<td>an enzyme that catalyses the synthesis of DNA from an RNA template (and thus can also make cDNA from mRNA)</td>
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<tr>
<td>RFLP</td>
<td>restriction fragment length polymorphism. The occurrence of two or more alleles in a population differing in the lengths of fragments produced by a restriction endonuclease</td>
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<tr>
<td>RNA polymerase</td>
<td>enzyme that synthesizes (transcribes) RNA from a DNA template</td>
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<tr>
<td>RNA splicing</td>
<td>process by which introns are removed from primary RNA transcripts, leaving only exons that encode the amino acid sequence of a protein</td>
</tr>
<tr>
<td>segregation</td>
<td>separation of alleles at meiosis</td>
</tr>
<tr>
<td>sequencing</td>
<td>determination of the order of nucleotides in a DNA or RNA fragment, or the order of amino acids in a protein</td>
</tr>
<tr>
<td>sequencing gel analysis</td>
<td>electrophoretic technique by which nucleotide size differences as little as a single base pair can be discerned</td>
</tr>
<tr>
<td>sequence-tagged sites (STSS)</td>
<td>short sequences of genomic DNA for which the base sequence is known. Polymerase chain reaction can be used to amplify the known sequences, which can serve as physical landmarks for mapping.</td>
</tr>
<tr>
<td>sex chromosome</td>
<td>the chromosomes that primarily govern sex determination (XX in women and XY in men). The other chromosomes are autosomes.</td>
</tr>
<tr>
<td>somatic cells</td>
<td>all cells in the body except gametes and their precursors</td>
</tr>
<tr>
<td>somatic cell hybrid</td>
<td>a hybrid cell line derived from fusion of cells from different sources. Human/rodent hybrids containing a small amount of human genetic material, such as a single chromosome, are used in human gene mapping.</td>
</tr>
<tr>
<td>somatic mosaicism</td>
<td>the presence of two or more cell lines in somatic (non-germinal) cells</td>
</tr>
<tr>
<td>Southern blotting</td>
<td>a technique, developed by E.M. Southern in 1975, for transferring DNA to a backing sheet prior to hybridization. Northern and Western blots are non-eponymous variations relating to RNA and protein analyses. DNA is fractionated by electrophoresis, transferred to a membrane (blotted) and detected by a complementary labelled probe that hybridizes to the DNA, revealing information about its identity, size and abundance.</td>
</tr>
<tr>
<td>splicing</td>
<td>removal of introns during the processing of mRNA</td>
</tr>
<tr>
<td>stop codon</td>
<td>one of the three codons (UAG, UAA or UGA) that cause termination of protein synthesis</td>
</tr>
<tr>
<td>synteny</td>
<td>loci on the same chromosome which may or may not be within range of detection through cosegregation</td>
</tr>
<tr>
<td>tandem repeat sequences</td>
<td>multiple copies of the same base sequence on a chromosome. When the number of repeats varies in the population, they are useful as DNA markers.</td>
</tr>
<tr>
<td>telomeres</td>
<td>refers to the ends of chromosomes that contain characteristic repetitive DNA sequences</td>
</tr>
<tr>
<td>termination codon</td>
<td>see stop codon</td>
</tr>
<tr>
<td>transfection</td>
<td>transfer of a DNA fragment into prokaryotic or eukaryotic cells</td>
</tr>
<tr>
<td>trans</td>
<td>(a) historically implies on a different chromosome; (b) in molecular biology, refers to an effect on a gene caused by a factor distinct from the sequence of that gene, in contrast to cis effects, which are encoded in the sequence of the gene. Cis and trans are commonly used to describe factors that influence gene expression. On different chromosomes, usually quite close. The opposite of cis</td>
</tr>
<tr>
<td>transcript</td>
<td>refers to an mRNA molecule that encodes a protein</td>
</tr>
<tr>
<td>transcription</td>
<td>the synthesis of an RNA molecule (transcript) from a DNA template in the cell nucleus catalyzed by RNA polymerase</td>
</tr>
</tbody>
</table>
**transcription start site**

Site within a gene where transcription of RNA begins

**transgenic**

Containing foreign DNA. For example, transgenic mice contain foreign DNA sequences in addition to the complete mouse genome

**translation**

Assembly of amino acids into peptides based on information encoded in mRNA, i.e. mRNA sequence of bases is translated into sequence of amino acids in a peptide or protein. Occurs on ribosomes

**translocation**

The transfer of genetic material from one chromosome to another non-homologous chromosome, usually through a reciprocal event at meiosis

**trisomy**

The state of having three homologous chromosomes instead of the usual pair, as in trisomy 21 (Down’s syndrome)

**triploid**

A cell with three times the haploid number of chromosomes, i.e. three copies of all chromosome types

**uniparental disomy**

Situation in which an individual has two homologous chromosomes (or chromosomal segments) from one parent and none from the other. May be heterodisomy if both chromosomes from the single parent are present or disodisomy if two copies of the same parental chromosome are present

**unique sequence DNA**

Non-repetitive DNA that potentially codes for mRNA and protein

**upstream**

A DNA sequence is written from the left, or 5', direction to the right, or 3' direction. Upstream refers to the 5' direction, i.e. regulatory elements of a gene are typically located upstream (5') of the coding sequences of that gene

**vector**

The vehicle into which DNA is inserted prior to cloning in bacteria. Includes plasmids, phage and cosmids

**X-inactivation**

The random turning off of all the genes on one of the X-chromosomes in somatic cells during early embryonic development

**X-linked**

Genes carried on the X-chromosome. The term sex-linked should only be used on the very rare occasions both X- and Y-chromosomes are involved

**zygote**

The diploid cell resulting from the union of the haploid male (sperm) and female (ovum) gametes
ANNEX G: HEREDITARY EFFECTS OF RADIATION

References


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