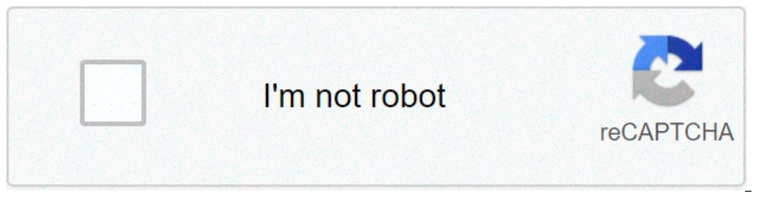

Continue

Different types of chromosomal abnormalities

CEN divides the chromosome into two arms: the short arm (p arm) and the long arm (q arm). Convention places the p-arm at the top in diagrammatic representations. Each arm terminates (pter, qter) in a telomere, a highly conserved repetitive gene sequence which inhibits end-end fusion, and which is important for attachments of chromosome ends to the nuclear envelope, particularly during meiosis. It is thought by many that diminution of telomere size is associated with cell ageing. When the short arm is nearly as long as the long arm, the chromosome is said metacentric; if it is shorter, the chromosome is said sub-metacentric; when it is very short, but still visible, the chromosome is said to be sub-telocentric; when extremely short, virtually invisible, the chromosome is said acrocentric. In the human karyotype, chromosome pairs 13, 14, 15, 21, 22 are acrocentric, and Y is sub-telocentric. In mammalian cells, the p-arm of many acrocentric chromosomes carry nucleolar organising regions (NORs) which contain genes coding for ribosomal RNA. This is true for all five pairs of acrocentrics in human cells. Certain staining techniques cause the chromosomes to take on a banded appearance, each arm presenting a sequence of dark and light bands of varying intensities. Patterns are specific and repeatable for each chromosome, allowing unambiguous identification and longitudinal mapping for locating gene positions and characterising structural changes. The number of bands observed is not fixed but is related dynamically to the state of chromosome contraction. Thus, prophase chromosomes have many more bands than metaphase ones. Patterns, and the nomenclature for defining positional mapping have been standardised to allow cytogeneticists to communicate and archive information for medical purposes. Numbering begins from the centromere and continues outward to the end of each arm. Conventionally, the arms are divided into a number of regions by means of easily recognisable "land-mark" bands, and bands numbered sequentially within each. Sub-bands are catered for by using a decimal system. e.g. the place of the star in the Figure 2 is: 21q22.3 CHROMOSOME ANOMALIES: CONSTITUTIONAL versus ACQUIRED, HOMOGENEOUS versus MOSAIC, NUMERICAL versus STRUCTURAL *: All the tissues ("the whole patient") hold the same anomaly (Figure). The chromosome error was already present in the embryo. It could have occurred before fertilisation, being present in one of the 2 gametes, or possibly in the fertilised zygote. If the anomaly is unbalanced (i.e. if some genes are not present in 2 copies, but in 1 or in 3), the patient is likely to present with 1- dysmorphy and/or 2- visceral malformations, and/or a 3- developmental/psychomotor delay (triad). "Constitutional anomalies" herein refers to the chromosome inborn syndromes, such as trisomy 21, Turner syndromes, and others. ACQUIRED: only one organ is involved, the other tissues being normal. The patient has a cancer of the affected organ. "Acquired anomalies" herein refers to malignancies. (Note: many of the descriptions in this paper, particularly the references to behaviour at Meiosis, cover the general field of structural changes. It is important to realise that relatively few aberrations that occur lead directly to cancer, although some of them will introduce conditions within the cell that may trigger other events that can cause malignant transformation. The terms "constitutional" and "acquired" are really quite general terms, and can be applied to any persistent change encountered in clinical practice. Within the context of this paper, the term Acquired anomalies will apply exclusively to malignant situations). * A chromosome anomaly can be:: when all the cells (studied) carry the anomaly. e.g. 1: a constitutional anomaly having occurred in a parental gamete (e.g. + 21) will be found in each of the cells of the resulting child (homogeneous trisomy 21). e.g. 2: an acquired anomaly in a leukaemia found in all the bone marrow cells studied (when growth of the normal cells is inhibited by the malignant process and cannot divide in culture (e.g. t(9;22) in chronic myelocytic leukaemia (CML)). Note: In practice, when an acquired anomaly is said homogeneous, it only means that no normal cell was karyotyped within the scored sample. : When only some cells carry the anomaly whilst others are normal (or carry another anomaly). Thus one may find clones of cells carrying a particular change, obviously all derived from the original cell where the anomaly first arose. e.g. 1: A non-disjunction (e.g. + 21) having occurred in the zygote after a few cell divisions: Only some of the embryo cells (and later, of the child's cells) will carry the anomaly (46, XY/47, XY, +21). e.g. 2: Very common in leukaemia and other cancers subject to continuous chromosome change. Only a percentage of mitoses carry the anomalies, while other cells are normal. An example from an acute lymphoblastic leukaemia with one normal clone, one clone with a specific change, and a third with additional changes (46, XY / 46, XY, t(4;11) / 46, XY, t(4;11), i(7q)). * A chromosome anomaly can be: NUMERICAL: If there is one (or more) chromosome(s) in excess (trisomy) (e.g. +21) or missing (monosomy) (e.g. XO if a gonosome is lost, or - 5). Note that the karyotype is always unbalanced in case of a numerical anomaly. STRUCTURAL: If structural changes occur within the chromosomes themselves, not necessarily accompanied by any numerical change. The change is balanced, if there is no loss or gain of genetic material. Unbalanced, if there is deletion and/or duplication of chromosome segment(s). CHROMOSOME ANOMALIES - MECHANISMS AND NOMENCLATURE I - NUMERICAL ANOMALIES A - HOMOGENEOUS 1 - Homogeneous due to meiotic non-disjunction (Figure) 1.1. Autosomes non disjunction in first meiotic division produces 4 unbalanced gametes. non disjunction in second division produces 2 unbalanced and 2 normal gametes. Gametes with an extra autosome produce trisomic zygotes. The majority of trisomies are non-viable (e.g. trisomy 16) and a miscarriage occurs, sometimes so early that nothing is noticed. A few trisomies are more or less compatible with life, e.g. trisomies 21, 13, 18, and 8. Nullosomic gametes (missing one chromosome) produce monosomies. Monosomies are more deleterious than trisomies and almost all lead to early miscarriage. The only autosomal monosomy in humans which might be compatible with life is monosomy 21, but this is still a debatable situation. Non-disjunction can affect each pair of chromosomes and rarely more than one pair may be involved in the same meiotic cell (multiple non-disjunction most often involves a gonosome). Non-disjunction is not a rare event, but its occurrence is generally underestimated due to the early spontaneous elimination of most unbalanced conceptuses. With reference to the drawings, remember that, in the male, all 4 types of gametes will be effectively present in the sperm. In the female, only 1 of the types (presumably randomly selected on each occasion?) will normally participate in fertilisation, the other three being eliminated in the polar bodies). 1.2. Gonosomes Gonosome unbalance is much less deleterious, and various trisomies can occur, as well as monosomy X (There must always be at least one X for viability). Table: Zygotes produced for each type gamete: Empty boxes indicate a non-viable conceptus. Boxes XX and XY with ° are normal zygotes from normal gametes. Boxes with * are normal zygotes from unbalanced gametes. gametesO Y XXYYY XXXYYXXYXXYY OXXY*XX*XYYXXYXXYY XXXY-XX-XXY XYYXXXXXYYXXXY XXXX*XXYXXXXXYXXYYXXXXXXXXY XXXXXXXXXYXXXXXXXXYXXXXX XXXXXXXXXXXXYXXXXX 2 - Homogenous due to a fertilisation anomaly Produce polyploidy. Triploidies are the most frequent, 3N = 69 chromosomes: e.g. 69, XXX, or 69, XXY, or 69, XYY. These are found in 20 % of spontaneous miscarriages. A live birth can occur, but the baby dies shortly afterwards. Mechanisms of formation of triploidies: digyny: non-expulsion of the 2nd polar body. diandry: fertilisation of 1 oocyte I by 2 spermatozoa. Diandry is 4 times more frequent than digyny. Tetraploidy, 4N = 92 chromosomes. Found in 6 % of spontaneous miscarriages. Literature records very few live births, but with death soon after. Hydatidiform moles are usually polyploid. Thus, these fertilisation errors are frequent, comprising about 2 to 3 % of fertilised eggs. B - MOSAICISM A mosaic individual is made of 2 (or more) cell populations characterised by difference(s) in the chromosomes. These cell populations, however, come from 1, and only 1, zygote (When recording, a mosaic is denoted by a slash between the various clones observed, e.g. trisomy 21 presenting as a mosaic: 46, XY / 47, XY, +21). Numerical anomaly is usually due to a mitotic non-disjunction: 1 daughter cell will get both chromatids of one of the homologues, the other none; so the former will be trisomic, the latter monosomic. Note: Viability of the two daughter cells may differ. In the above-mentioned trisomy 21 example, the clone monosomic for 21 is non-viable and has disappeared. The phenotype of surviving individuals is more or less affected, according to the proportion of the various clones. Variability of clone proportions is affected by various factors: The precocity of the event e.g. (45, X / 47, XXX) with no cells having 46 chromosomes: zygotic event; (45, X / 46, XX / 47, XXX) : post-zygotic event. If 46, XX cells are the most numerous, the anomaly must have occurred late in development; if it occurred at the 32-cell, or 64-cell stage, all, none or part of the embryo could be affected, since by this stage, the cells destined for the primitive streak, and hence the embryo proper have been segregated, and the aberration might be confined to the membranes or placenta. The distribution of the cell populations during embryogenesis. In this case, the proportions of the various clones will vary from one organ to another. in vivo selection pressure on the different clones (this may occur in vitro as well, when the cell populations have different kinetics). A mosaic must not be confused with a chimaera. In a chimaera, the cells originate from two (or more) zygotes. They are produced by: mixture, or exchange of cells, from different zygotes (e.g. early fusion of 2 embryos). cross blood circulation between dizygotic twins with grafting of blood progenitors. syngamy: abnormal fertilisation (e.g. 2 spermatozoa, the oocyte, plus the 2nd polar body, making one individual XX/XY with so-called "2 fathers and 2 mothers") In chimaeras, the 2 cell populations may or may not have different karyotypes, the genes, however, are different. Note: Mosaicism is frequent in malignancies, either because normal cells can still be karyotyped, or because the malignant clone produces sub-clones with additional anomalies (clonal evolution). II - STRUCTURAL ANOMALIES (see also: An Introduction to Chromosomal Aberrations) A - Introduction Visually, chromosomes can appear to break, and broken ends can rejoin in various ways: either as they were: restitution or, in case of 2 (or more) breaks, with interactive re-joining to make a structural aberration (exchanges). Initial breaks are thought to be at the level of the DNA, and are probably frequent events. DNA repair then occurs. For various reasons, DNA repair is insufficient in chromosome instability syndromes. Most often, the break occurs in a non-coding sequence, and does not result in a mutation. Initial breaks can occur anywhere, short arms of acrocentics included. Ultimately, what is important for the individual, is to retain 2 (normal) copies of each gene, no more, no less. This is particularly true for the embryo, where a full balanced genetic complement is vital for normal development. Embryos with unbalanced constitutional anomalies have 1 or 3 copies of a whole set of genes, and abnormal development results. Note: a full balanced complement is not absolutely necessary for the functioning of many differentiated tissue cells, particularly if they are not called upon to divide. Nevertheless, relatively small imbalances can have dire consequences, even in somatic cells. A good example is the case of the Rb gene, implicated in the formation of retinoblastoma . Normal individuals carry 2 functional copies, but one of these can be inactivated by mutation or removal (loss of heterozygosity) and the cell continues normal function through the normal allele (which is now acting as a tumour suppressor gene). Loss of the second allele by removal (or mutation) leads to the formation of the tumour." It is important that these 2 gene copies are normal: Should the break occur within the domain of a gene, wrong re-joining can in activate it, switch on, or off its activity at the wrong time, or produce a hybrid gene with bits of an oncogene, encoding for a fusion protein with oncogenic properties (see Malignant blood diseases). Note: Many of the structural aberrations formed are cell lethal, and are soon eliminated from the cell population. Of those that survive and are transmitted, the most frequent are translocations, small inversions and deletions. Note: Rearranged chromosomes that are transmitted are called derivative chromosomes (der) and they are numbered according to the centromere they carry. Thus a reciprocal translocation between chromosome 7 and chromosome 14 will result in a der(7) and a der(14). B - Main structural anomalies (Figure) 1 - Reciprocal translocation A mutual exchange between terminal segments from the arms of 2 chromosomes. Provided that there is no loss or alteration at the points of exchange, the new arrangement is genetically balanced, and called a: Balanced rearrangement. Recorded as t, followed by a bracket with the numerals of the 2 chromosomes, and a second bracket indicating the presumptive breakpoints (e.g. t(9;22)(q34;q11)). Transmission to descendants (constitutional anomalies) At meiosis, where there is pairing of homologous chromosome segments (normal chromosomes form a bivalent), followed by crossing-over, translocations may form a quadrivalent (tetravalent, in Greek) and this leads to segregation problems. At meiosis anaphase I, chromosomes separate without centromere separation; this separation occurs at anaphase 2. Segregation of chromatids in the case of a quadrivalent (Figure) can be according the following: alternate type, which produces normal gametes, or gametes with the parental balanced translocation. The baby will have a normal phenotype (unless cryptic imbalance is present). adjacent 1 type, (this is frequent): Associates a normal chromosome (e.g. chromosome a) with the rearranged (or derivative) from the other pair (der(b)). It gives rise to "duplication-deficiency": there is an excess of some bits and a lack of other bits. adjacent 2 type, (this is very rare): Associates a normal chromosome with the derivative from the same pair (e.g. a + der(a)). 3:1 type, (this is rare): - Either a derivative chromosome and the 2 normal homologues (e.g. a, b, der(b)) segregate to one daughter cell, and the other derivative (der(a)) to the other, - Or a normal homologue with the 2 derivative chromosomes (b, der(a), der(b)) to one cell, and the normal chromosome (a) to the other. In either case, this will result in zygotes with 47 or 45 chromosomes. Characteristics: Reciprocal translocations are, in most cases, balanced rearrangements and the carrier has a normal phenotype. At meiosis, they enhance malsegregations (especially when an acrocentric is involved in the translocation): Adjacent 1, adjacent 2, or 3:1 types lead to miscarriages, or to the birth of a malformed child. The more unbalanced a zygote is, the less the probability that the child will reach birth. Crossing over during meiosis has no consequence on the structure/morphology of the chromosomes (which is not the case in inversions or in some other rearrangements). Breakpoints can occur at the centromeres, leading to whole arm exchanges. Complex translocations: Three, or more breaks and more than two chromosomes can participate in exchange, leading to some very complicated rearrangements. The surviving, balanced forms are seen usually as cyclical translocations. The recent introduction of FISH-painting indicates that such complex translocations are much more frequent than we have realised. Note There will be no mechanical transmission problems at mitosis. Note: Reciprocal and Complex translocations can also occur in somatic cells at any time after birth; they are particularly frequent in cancer processes. 2 - Robertsonian translocation Fusion of 2 acrocentrics very close to the centromeres, most often in the p arms, giving rise to a dicentric chromosome (having 2 centromeres). The rearranged chromosome includes the long arms of the 2 acrocentrics, while most of the short arm material is lost. Almost always, one of the centromeres is inactivated, so that the translocation behaves as a monocentric giving no segregation problems. The karyotype of a Robertsonian carrier has therefore 45 chromosomes. However, it is said to be balanced, as the loss of the short arm has no phenotypic effect. Recorded as t, with the numerals of each of the 2 chromosomes followed by q in brackets (e.g. t(14q21q)). Characteristics: Centric fusions represent the most common chromosome anomaly; they have played an important role in speciation. The role of the acrocentrics in nucleolar organisation favours Robertsonian translocations. Those NORs that are active in a cell form functional nucleoli. Frequently, two, or more, of these nucleoli fuse, thus bringing the parent p-arms into very close proximity within the nucleus, and this will favour interchange formation between them. A dicentric-forming event close to the centromeres will delete the terminal regions of the acrocentric short arms, leaving a dicentric Robertsonian translocation. However, in certain cases, the presence of a nucleolus can act as a physical barrier, precluding close proximity and reducing the probability of interchange. They can occur de novo, or be transmitted through several generations. They are prone to malsegregations (Figure); Robertsonian translocations involving chromosomes 13 and/or 21 produce viable embryos with trisomies 13 or 21. The proportion of associations between the various acrocentrics in human cells is variable, the association 14-21 being the most frequent. Robertsonian translocations between homologues always lead to unbalanced gametes. 3 - Deletion Loss of a segment, either interstitial or terminal, from a chromosome (Figure). Invariably, but not always, results in the loss of important genetic material. This loss is sometimes called "partial monosomy". Deletion is therefore an unbalanced rearrangement. Recorded as del, followed by a bracket with the number of the chromosome, and a second bracket indicating the breakpoint(s) and the deleted region (e.g. del(5)(q14q34)); 2 breakpoints are recorded when the deletion is clearly interstitial; only 1 breakpoint is recorded when the deletion seems terminal. A true terminal deletion would leave the surviving chromosome without a telomere. For a long time, cytogeneticists have believed that these telomeres have a special structure, and are functional necessities for the integrity of the chromosome. If this were so, apparently terminal deletions must actually be interstitial, being capped by a telomere. FISH-painting using telomere-specific probes has shown this supposition to be correct. 3.1. Constitutional deletion Deletion in an autosome: Has major phenotypic repercussions (e.g. del(18p) ; del(18q) ; del(4p): Wolf-Hirschhorn syndrome; del(5p): cri du chat syndrome; (see chromosome inborn syndromes); therefore these heavily handicapped persons cannot transmit the anomaly to any descendant. The rearrangement most often occurs de novo (only 10 to 15 % of deletion cases come from the malsegregation of a parental rearrangement. The deletion may be accompanied by partial trisomy of another chromosome (duplication/deficiency): See section on reciprocal translocations). Special case: Microdeletions; may be transmitted (e.g. del(13)(q1400q1409): retinoblastoma). Deletion in a gonosome: Causes sexual differentiation and gametogenesis impairments (except distal Yq deletions) (e.g.: del(Xp): Turner syndrome). 3.2. Acquired deletion: An example would be the loss of a tumour suppressor gene (e.g.: del(13)(q14.00q14.09): retinoblastoma). 4 - Ring Can be a centric or acentric event. Persistent (transmitted) rings are always centric. A centric ring involves the deletion (often small) of the ends of both arms (including the telomeres) and rejoining of the median segment to itself in a circular structure. Is an unbalanced rearrangement, for although the terminal segments lost may not involve vital genetic material, duplication anomalies which occur in ring structures often lead to mechanical problems at mitosis, accompanied by continuous changes in ring size and composition. If sister-chromatid exchanges follow chromosome replication (Figure, right), the ring can form a dicentric ring, or a pair of interlocked rings which will lead to bridge breakage and loss at anaphase of mitosis. The ensuing fusion-fission cycle leads to variable ring sizes and additional duplications and losses of genetic material. Multiple and inter-locked rings can also be produced. Recorded as r, followed by a bracket with the number of the chromosome, and a second bracket indicating the breakpoints, if they are identifiable (e.g. r(13)(p12q33)). Bearing in mind the instability of ring composition mentioned above, break-point designations may not be accurate, or represent the initial change. Arise most often de novo, and are rarely transmitted to descendants (because a ring is unstable, cell divisions lead to impaired gametogenesis; see Figure, left part). --> frequency of mosaicisms. The repercussions on the phenotype are therefore variable, with signs of trisomy or of deletion. In humans, the most frequent ring in constitutional anomalies concerns chromosome 13. 5 - Inversion Inversion occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively inverts it. Recorded as inv, followed by a bracket with the number of the chromosome, and a second bracket indicating the breakpoints, where these can be determined (e.g. inv(9) (p11q13)). Only large inversions are normally detected. Inversions are, in the main, balanced rearrangements, and the carrier has a normal phenotype. (Note: If one break-point is in the middle of a gene imbalance for this particular gene will result). 5a - Paracentric inversion An inversion is termed paracentric when the segment involved lies wholly within one chromosome arm. Are rare (or more likely rarely detected since the majority probably involve very small segments). The most frequent paracentric inversions in constitutional anomalies involve chromosomes 3, 7, and 14. Carriers are often fertile (males as much as females), and about half of descendants have a normal karyotype, and the other half have the balanced rearrangement (like the parent). There are only a few offsprings with unbalanced forms, since unbalanced forms are often too deleterious to give rise to a viable conceptus. There are a few recorded cases of malformed descendants having an apparent balanced constitution. At meiosis, there is pairing of homologous segments, which results in the formation of an inversion loop. Crossing over within the loop (see top of the Figure) produces an acentric fragment (lost) and a chromosome bridge linking the 2 centromeres at anaphase. The bridge either: Disrupts, and, according to where it breaks, there will be duplication/deficiency of certain segments in the daughter cells, or prevents cell separation producing only 1 daughter cell with double the amount of genetic material, or the dicentric will be excluded from both daughter cells, and will form a micronucleus, or the dicentric is included entire into one daughter cell. In the last case, there will be, at telophase of second division: one normal cell, one cell with the balanced inversion, one cell devoid of this chromatid, and one cell with the dicentric. This dicentric will either: i) enter the fission-fusion cycle (leading to complex and numerous rearrangements), or ii) prevent diakinesis (leading to a tetraploidy), or iii) inactivate 1 of its 2 centromeres, which would stabilise the rearrangement. Other crossing over are possible, some would lead to 100 % of unbalanced products (see bottom of the Figure). In practice, a high selection pressure favours normal daughter cells, or those carrying the balanced inversion (as often in genetics, we have the paradox that a very heavy anomaly will have less consequence on the offspring, as the sex cells/eggs/embryos carrying it will be efficiently eliminated: the observable sample is highly biased, a general rule in biology). 5b - Pericentric inversion An inversion is said pericentric when the two break-points involved are sited on opposite sides of the centromere, and rejoining effectively inverts the central centromere-bearing segment. Some pericentric inversions are very frequent, and are called chromosome variants: inv(9)(p11q13): found in 1/400 individuals (with large geographic variations). Offsprings with unbalanced forms have not been regularly found (crossing over in heterochromatin is very exceptional). inv(Y): found in 1 to 2/1000 male individuals. A pericentric inversion can provoke miscarriages, sterility (more often in the male), and lead to unbalanced products at meiosis. During meiosis, crossing over in the inversion loop will produce recombinant chromosomes (rec) with duplication of one segment and deficiency of another (a duplication p - deficiency q will be recorded as rec dup(p)). Note: Duplicated-deficient segments are those outside of the inversion loop (see Figure, bottom right). If the inversion is large, the probability of crossing over in the inversion loop will be higher, and duplicated-deficient segments (outside the loop) smaller. However, the risk will then be greater, since the probability that the conceptus is viable is higher. Conversely, a small inversion has a lower probability of crossing over in the small inversion loop. However, if it occurs, the very large duplicated-deficient segments will have a strong negative selection pressure effect, and the risk of a malformed offspring will be lower. Notes on paracentric and pericentric inversions: Crossing over outside the inverted segments (out of the loop) are without consequence. Wherever the crossing over occurs in the loop, the consequence will be the same. 2 (or an even number of) chiasmata within the loop cancel each other. 6 - Isochromosome Loss of a complete arm, "replaced" by the duplication of the other arm (equivalent to a monosomy for one arm and trisomy for the other). This is an unbalanced rearrangement. Recorded as i, followed by a bracket with the number of the chromosome and the arm (e.g. i(17q) or i(17)(q10): duplication of the q arm and loss of the p arm). This rearrangement is frequent on X chromosome (Turner syndrome with i(Xq)). It is also frequent as an acquired anomaly in cancers (e.g. i(17q), secondary anomaly in chronic myelocytic leukaemia). Mechanisms of formation of an isochromosome are varied (Figure). If it arises in the first meiotic division, the duplicated material will be heterozygous. In somatic cells, the most likely origin is from an isochromatid deletion, with sister union, occurring within the centromeric region. 7 - Insertion An interstitial segment of a chromosome is deleted and transferred to a new position in some other chromosome, or occasionally, into its homologue, or even somewhere else within the same chromosome. The inserted segment may be positioned with its original orientation (with respect to the centromere) or inverted. This is usually a balanced rearrangement. Recorded as ins, followed by a bracket with the number of the chromosome which receives the segment preceding the number of the chromosome which donates the segment (if different). A second bracket indicates the one breakpoint where it inserts, followed by the 2 breakpoints which define the ends of the deleted segment. e.g. ins(2)(p13q31q34) and ins(5;2)(p12;q31q34): the segment q31q34 from a chromosome 2 is inserted respectively in p13 of this chromosome 2, and in p12 of a chromosome 5. An insertion can be direct (dir ins) if the segment keeps its orientation in relation to the centromere (the most proximal band remaining the closest to the centromere; In the example above, band q31 precedes band q34). An insertion can be inverted (inv ins) if the most proximal band becomes the farthest from the centromere e.g. ins(2)(p13q34q31) and ins(5;2)(p12;q34q31), the distal band number preceding the proximal one. This aberration can be balanced and stable in somatic cells, and be transmitted for many cell generations. However, it is pretty devastating at meiosis. In many cases the inserted segment will not be large enough to cause the formation of a quadrivalent. Even so, random segregation at Meiosis 1 means that half of the gametes will be imbalanced. If the segment is large enough the permit occasional quadrivalent formation, then, as Figure shows, 25% of gametes will be normal if the insertion is direct, but none if the insertion is inverted (where we have the added complication of a dicentric bridge and acentric fragment to complicate further the situation). (Note: it is difficult to imagine pairing without a "loop", but this remains speculation. What it would actually look like in reality is an interesting thought. Someone, studying synaptonemal complexes must have seen a pachytene/diplotene spread of such a configuration - if not in man, certainly in mouse or hamster). Interesting exercise for students: work out all the gametic constitutions which result. 8 - Duplication Direct: A segment of chromosome is repeated, once or several times, the duplicated segment keeping the same orientation with respect to the centromere ("tandem duplication"). Inverted: The duplicated segment takes the opposite orientation. Is an unbalanced rearrangement. Recorded as dup, followed by a bracket with the number of the chromosome, and a second bracket indicating the breakpoint(s) and the duplicated region. 9 - Dicentric A chromosome with 2 centromeres: Simplistically, it is the alternative rejoining mode of the reciprocal translocation, but it can originate by several other mechanisms. It is an unbalanced rearrangement, leading to mechanical separation problems at anaphase ("bridges"). Recorded as dic, or psu dic (pseudo dicentric), when one of the centromeres inactivates, precluding anaphase bridge formation. Inactivation seems principally to be a function of the intercalary distance between the centromeres. Persistent dicentrics are frequent in the case of Robertsonian translocations, but very rare as a constitutional anomaly, unless the short arm of an acrocentric is involved. Rare as an acquired anomaly. Dicentrics (other than Robertsonian translocations) are highly unstable unless: one of the centromeres inactivates. the inter-centromeric distance is very short so that the 2 centromeres can act as one. The only proofs of the presence of 2 active centromeres are: the presence of bridges at anaphase. the presence of non-disjunctions. the presence of isochromosomes from each of the 2 chromosomes, resulting from breaks in the bridge with lateral fusion (Sister Union fusion, between chromatids). proof that inactivation of 1 centromere occurred is obvious when the 2 chromatids are separated instead of being tightly attached at the centromere location (Premature separation of a centromeric region may also result from several other causes - reduction in paracentric heterochromatin for one, so this "proof" is not absolute). 10 - Complex Rearrangements Involving more than 2 chromosomes and/or more than 3 breakpoints. As pointed out above, such aberrations now appear to be much more frequent than we have realised. Many changes seen in cancer cells are of this type. Frequency of malformations in apparently balanced carriers (genetic counselling). 11 - Marker A non-recognisable, persistent chromosome, recorded as mar. either small supernumerary element in the constitutional karyotype, with or without phenotypic repercussions. Issue in prenatal diagnosis. or a variable sized, often big, element in a cancer process. Since FISH-painting techniques have been developed, many markers have been shown to be highly rearranged chromosomes, involving many participants and many breakpoints. 12 - Double minute; Homogeneously staining region Double minute: recorded as DM. Appear as very small, usually paired dots. Quite often numerous, but because they are acentric, segregation is irregular and numbers very variable. In the simplest case they represent interstitial deletions, and would normally be rapidly lost from a cell population. Multiple copies indicates a much more complex situation. There is evidence from some mouse cell lines that supernumerary chromosomes and multiple double minutes are inter-changeable aberrations. Homogeneously staining region: recorded as HSR. Variable sized, often important, material multiply duplicated in (a) chromosome(s). Experimentally, HSR regions can be produced in response to chronic exposure to certain toxins. DM and HSR may indicate (onco)gene amplification when found in malignant processes, particularly in solid tumours. Written2000-05Jean-Loup Huret, Claude Leonard, John RK Savage MRC Radiation, Genome Stability Unit, Harwell, Didcot, OX11 0RD, UK   For comments and suggestions or contributions, please contact us jlhuret@AtlasGeneticsOncology.org.