Asymmetry in chromosome pairing: a major factor in de novo mutation and the production of genetic disease in man

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SUMMARY At the outset of the meiotic pairing process in man, trial and error mismatching and misalignment, both within homologous pairs and between heterologues, can be observed cytologically. Pairing starts at early zygotene principally within subtelomeric regions where the synaptonemal complex initiates. In the present paper, evidence for the primary role in synaptic initiation of a GC rich minisatellite in the human XY pseudoautosomal segment is presented, and circumstantial evidence is provided to support the view that GC rich sequences (minisatellites and Alu repeats) function to promote pairing within autosomes. The known sequence hypervariability of proterminal human minisatellites, it is suggested, arises as a secondary consequence of unequal exchange after misalignment between tandem repeats at the outset of the pairing process. Unequal exchange within misaligned repeat sequences at early prophase of meiosis could make a major contribution to de novo germinal mutation (conversion, duplication, deficiency, inversion, translocation), with serious consequences in man for the production of hereditary disease. For somatic tissues, rare mispairing between G rich repeats followed by unequal exchange could be a key step in cancer progression. It might also explain somatic mosaicism in some non-neoplastic clinical conditions.

A close approximation of homologous chromosome regions is an essential prerequisite for the exchange of genetic material. Yet, despite decades of cytogenetic investigation,¹ the basic underlying mechanism by which eukaryote chromosomes achieve full homologous synapsis at meiotic prophase has so far eluded discovery. A principal impediment in the past has been lack of knowledge at the molecular level, a situation which has now changed quite remarkably. Among the many discoveries made by molecular biologists in recent years has been the finding that numerous families of repetitive DNA sequences are dispersed around eukaryote genomes.² Loci with variable numbers of tandem repeats, VNTRs or 'minisatellites',³⁻⁶ have proved the most useful in genetic analysis, the repeat lengths being so variable from one person to another that they provide a source of DNA fingerprinting.³⁻⁴ Most minisatellites are GC rich³⁻⁶ and show a strong tendency to cluster within proterminal regions (terminal R bands) of human chromosomes,⁶⁻⁸ including within the XY pseudoautosomal

region,⁹⁻¹⁰ and these are also regions of high recombinational proficiency.¹¹⁻¹² The occurrence of minisatellites across a range of eukaryotes, including plants,¹³⁻¹⁴ suggests a conserved function, but this has not been precisely identified. Nevertheless, owing to features such as the G richness of their common core sequence, which closely resembles the *chi* sequence in *E coli*, Jeffreys *et al*³⁻⁴ have suggested that proterminal minisatellites might be recombinational signals in man.

A second important discovery has been that R and G (dark) bands in the human genome are each characterised by distinct families of short interspersed repeat sequences, the SINES, Alu family dominating in R bands, and the LINES, L1 family dominating in G bands.¹⁵ Alu repeats are GC rich and L1 repeats are AT rich, but, again, no function has been ascribed to these repeats.

In the present paper, I wish to present data and supporting evidence for my belief that a prime function of GC rich repeated sequences in eukaryotes is the initiation of pairing at meiosis. In man, the extreme variability of proterminal GC rich tandem repeats (VNTRs)³⁻⁶ arises, I believe, out of their

synaptic role, unequal crossing over occurring within misaligned repeat arrays at early zygotene when a search for homology is first being made. Interstitial GC rich minisatellites and Alu-like sequences may also function in pairing initiation, the latter perhaps providing homology for pairing within gene loci. Asymmetrical alignment during synaptic trial events could, by unequal exchange,¹⁶ generate an infinite variety of mutations from minor allelic changes (conversions) to structural rearrangements, for example, deletions, duplications, inversions, and translocations, contributing to genetic disease in man.^{17 18} The model has implications in cancer progression, since chance mispairings and unequal exchanges within GC rich sequences of somatic cells could also generate mutational change.^{19 20} They might also form the basis of somatic mosaicism in some non-neoplastic conditions.²¹

Evidence for the function of a human GC rich minisatellite in meiotic pairing initiation

The first clue that a human GC rich minisatellite might initiate chromosome pairing came from a study into the meiotic pairing behaviour of the X and Y axes in prophase spermatocytes of an STS deficient man showing a cytologically visible deletion at Xpter in his somatic karyotype (Mohandas *et al*, in preparation). Molecular analysis showed that all of the Xp pseudoautosomal region, as well as the MIC2 and STS genes, were deleted. At early zygotene, when XY pairing between the terminal regions of the two short arms normally starts in man,²² no pairing initiation was seen in this rare patient, despite the fact that the Xp and Yp telomeres lay in close proximity in about one half of

all cells examined at this stage. This observation indicated that telomeric recognition was, in itself, insufficient for proterminal pairing initiation and synaptonemal complex (SC) formation. The deleted region included the entire Xp pseudoautosomal segment, and the most distal DNA sequences to have been mapped within it so far show a GC rich polymorphic minisatellite *DXYS14* (probe 29A24) of six to 15 copies lying within only 25 kbp of the telomere, with homologous copies at distal Yp.^{9 23} This unique observation prompted the question as to whether the GC rich repetitive sequences within the minisatellite *DXYS14*, and other GC rich minisatellites in the pseudoautosomal region, were in fact responsible for synaptic initiation in the XY pair. If so, was there circumstantial evidence that GC rich tandem repeats might function also in this way within the autosomal component of the human genome?

Synapsis and crossing over in man

Unlike the XY pair in which synapsis initiates at a single distal location, human autosomes can initiate their pairing at two ends and they also show interstitial points of synaptic initiation which are common in oocytes, but rarer in spermatocytes.¹ The striking observation in both human oocytes and spermatocytes is, however, that pairing and SC formation most conspicuously begin at early zygotene in subtelomeric regions of all autosomes, and some time before interstitial stretches of the SC are seen (fig 1). The rich clustering of highly variable GC rich minisatellites also within human autosomal protermini^{6 7} is therefore of some significance, for it

FIG 1 Electron microscope (EM) microspread preparation of an early zygotene human spermatocyte at the time of pairing initiation. Only within subtelomeric regions has formation of the SC started, interstitial segments still being only barely visible as single unpaired lateral elements. Bar=10 μ m. Silver nitrate stain.

is very reminiscent of the situation found within the XY pair.^{9 10 23}

The process of chromosome pairing in any eukaryote, from initiation at zygotene to desynapsis at diplotene, can readily be followed at electron microscope level by studying the behaviour of the SC, the tripartite proteinaceous structure which holds homologues together for recombination.¹ The SC is obviously required for crossing over as little recombination takes place in its absence,²⁴ but its presence alone does not guarantee crossing over, as the numerous published examples of illegitimate SC formation can testify.^{1 25 26} Pairing at the SC level, in fact, seems to be an extremely flexible process and not necessarily indicative of homology.

Carpenter²⁷ has argued that synapsis can begin in any place where two unpaired lateral elements (LE) come close enough to one another. She sees the early zygotene stage as a time when a large number of transient synaptic trials takes place, non-homo-

logous pairings within the SC occurring frequently until 'homology' checking is finished and stable homologous pairing is established. Gross examples of LE misalignments and non-homologous 'ectopic' pairings have in fact been observed in our own studies into normal human oocytes and spermatocytes examined at the early pachytene stage of meiotic prophase²⁸ (fig 2), these originating in early zygotene at the time of pairing initiation and being about ten times more common in oocytes.²⁸ The longer overall SC complement length in oocytes²⁹ may perhaps be an important factor here, making them more error prone. Moreover, considerable variation between fetuses is found in the frequency of such errors,²⁸ indicating perhaps a certain 'genetic pairing instability' between different people. The clear presence of interchanges between non-homologues (translocations) at this time in meiotic prophase (fig 2c, d) indicates the previous occurrence of ectopic pairing and crossing over.

FIG 2 Human EM microspreads at the pachytene stage showing gross evidence of synaptic mismatch and misalignment in terminal segments (arrows). (a) Non-homologous partner switch and misalignment in an oocyte. (b) Triple association between one homologous SC and a single non-homologous lateral element in an oocyte. (c, d) Non-homologous interchange (translocation) after ectopic pairing in (c) spermatocyte, (d) oocyte. (Fig 2a, b, and d reproduced from Speed,²⁸ with permission.)

Unequal crossing over within repeated sequences

A vast number of published reports exists on unequal crossing over within repeated sequences of eukaryote genomes.¹⁶⁻¹⁸ In regions of tandem repeat, unequal crossing over can readily arise when there are two or more identical sites and hence substantial opportunity for misalignment between reiterated copies. Thus, the *Bar* mutation in *Drosophila*³⁰ is a direct tandem duplication of seven bands of the polytene map. Unequal crossing over results when the distal repeat of one chromosome recombines with the proximal repeat in the opposite homologue to yield *Bar*⁺ revertants and double *Bar* progeny. Data from *Drosophila* also show how unequal crossing over can occur in portions of the genome where tandem duplication is not evident. After investigation into the molecular structure of reciprocal duplication/deficiency products of unequal crossing over in females heterozygous for various *white* (*w*) alleles, Goldberg *et al.*³¹ showed that asymmetrical pairing between staggered transposons (nomadic repetitive 'BEL' sequences) was responsible. Even very small (8 kb) displaced regions of homology within the BEL repeats were able to pair with one another with a considerable frequency, despite separation by 60 kb and despite being surrounded by extensive regions of standard homology. Other repetitive transposable elements such as 'copia' in *Drosophila* and *Ty* elements in yeast can also provide homology for unequal exchange.³¹ Tartof¹⁸ estimates that the frequency of transposon mediated unequal exchange in *Drosophila* might be as high as 3×10^{-3} per meiosis, a very high rate for a mutagenic process, and one which, he points out, has considerable implications for a species like man (see below).

Pairing initiation within GC repeats and its consequences

The preferential (though not exclusive) clustering of GC rich minisatellites in the protermini of human chromosomes, where meiotic pairing is seen principally to begin after telomeric association, is, I believe, strong circumstantial support for the belief that the two might be causally related. A recent *in vitro* study³² has shown that G rich motifs in human DNA can, by special G-G bonding, form self-associating structures (G4-DNA), a property not shared by AT rich sequences. Sen and Gilbert³² have suggested that G4-DNA might be responsible for meiotic pairing. Were G rich motifs to be important in pairing, proterminal minisatellites with their high G content core sequence would be powerful primary sites for synaptic initiation within

terminal R bands. Moreover, their extreme variability might arise out of this early lead in pairing, since misalignment and unequal exchange owing to synaptic trial and error could be a common occurrence at the outset of the pairing process. G rich interstitial minisatellites and short repetitive Alu sequences might also initiate pairing along arms (in interstitial R bands), R band regions opening up at the prophase of meiosis to facilitate the process.³³ AT rich repeats may play a more passive role in pairing, being brought into alignment later when homology is becoming established. The finding of shorter length allelic changes in AT rich minisatellites in man¹⁰ could be a reflection of this progression to homology. Other regional constraints on crossing over in AT rich regions (dark G bands) might occur, however, attributable to a denser DNA conformation.³⁴

By pachytene, it is envisaged that homology will be established and only reciprocal recombination will occur, a gradient of declining unequal exchange being expected between the zygotene and pachytene stages. The full machinery of chiasma formation³⁵⁻³⁶ will then be brought into play as a requirement for orderly segregation within bivalents. Many non-reciprocal exchanges (conversion type events) will not generate chiasmata,³⁵ solving the apparent paradox of why recombination appears to occur almost anywhere in the genome of eukaryotes and yet chiasmata resulting from reciprocal crossing over are seen to be so clearly non-random in location.¹¹ Conversions appear to be at least as common as reciprocal crossovers in eukaryotes but are not subject to interference.²⁷ Their occurrence is quite independent of reciprocal crossing over and does not interfere with it in any way.²⁷⁻³⁵ Both initial alignment of chromosomes at zygotene and precise pairing at pachytene, together with their attendant crossover events, appear to be mediated by recombination nodules,²⁷ and zygotene DNA synthesis,¹⁻³⁶ delayed from S phase, appears also to serve a role, although it is not yet clear what this might be. However, it is of some interest that zyg-DNA has a GC content of 50 to 53%,¹ similar to that found for Alu repeats.¹⁵

Implications of the model for human genetic disease inheritance

The idea of G rich repetitive sequences functioning as pairing initiators at meiosis, with the inherent potential for unequal exchange after misalignment, has far reaching implications for man. Human genetics publications are replete with examples of de novo mutational change arising within the germ line, much of which could be the consequence of

FIG 3 A hypothesised complex gene in which an unequal crossover between two misaligned repeat sequences (**) has produced a duplication and deficiency for locus a.

asymmetrical pairing and unequal exchange. In my view, such errors are likely to arise within repeat sequences at the time when an initial search for synaptic homology is being made at very early meiotic prophase. If short interspersed repeats (like Alu sequences) act to provide homology for pairing, an infinite variety of mutations, from minor gene conversions to duplications, deficiencies (fig 3), and inversions could arise, while ectopic pairing between heterologues could produce de novo translocations. Evidence for the occurrence of gene conversions in the human fetal globin³⁷ and immunoglobulin³⁸ genes exists, while molecular data show that unequal crossover events have occurred within Alu repeats giving duplication/deletion products at the hypercholesterolaemia³⁹ locus and within the α globin cluster.⁴⁰ Unequal exchanges within Alu sequences on Xp and Yp are documented in the origin of some XX males.⁴¹

In cancers, imprecise exchanges appear to have occurred within Alu repeats to produce the specific translocations associated with human chronic myeloid leukaemia t(9;22)⁴² and in murine plasmacytomas T(15;12),⁴³ the latter being a translocation similar to that found in Burkitt's lymphoma t(8;14) in man. The evidence for unequal exchange in these sporadic tumours indicates that asymmetrical pairing between repetitive sequences on non-homologues not only occurs in the germ line but can also occur in somatic cells (although this is expected to be a much rarer event), and a first step by which potentially malignant cells establish homozygosity or hemizygosity for somatically recessive cancer genes^{19 20 44} may be found in this process of mismatch.

The fragile X locus at Xq27 may be seen as a site resembling in its behaviour the *Bar* locus in *Drosophila*. Amplification within repetitive sequences at the common fragile site could produce the 'premutation',⁴⁵ with further amplification or deletion

brought about by unequal crossing over giving rise to the full Martin-Bell syndrome.⁴⁶ For human reciprocal translocations, imprecise exchange around breakpoints occurring in germ cells will be expected to give rise to associated congenital defect in offspring, and many known examples of mental and physical handicap associated with de novo translocation are in fact documented.⁴⁷ A recent molecular investigation⁴⁸ into the breakpoint sequences of an X;21 translocation in a girl with Duchenne muscular dystrophy shows G rich motifs on both sides of a breakpoint with clear evidence that imprecise exchange has occurred during its formation. For balanced reciprocal translocations in a variety of species, including man, pairing is frequently disturbed around breakpoints⁴⁹⁻⁵² with resulting crossover suppression.⁴⁹ This could arise out of disruption caused in what normally would be a pairing site at meiosis.

For proterminal GC rich minisatellites in man, the emphasis in past publications has always been on their 'recombinational' proficiency.³⁻⁶ In my view, the cart has been put before the horse; for it is their 'pairing' proficiency which I believe should be emphasised first and foremost. Without pairing there can be no recombination, and if G rich repetitive sequences initiate synapsis, there is likely to be maximum opportunity in GC rich minisatellites for mismatch and unequal exchange. Moreover, those same minisatellites which show instability in the germ line might be expected to show similar characteristics in somatic tissues, and in normal as well as cancer cells, a prediction which appears to hold true.⁵³

Far from believing that simple repeats interspersed around eukaryotic genomes may constitute 'junk' DNA and be lacking in function,⁵⁴ I believe their role in synapsis to be one of major importance and one which has been largely overlooked by molecular

investigators. Perhaps human gene mapping should concentrate its efforts on hot spots of recombination throughout the entire genome and study in detail the DNA sequences existing at those sites, as Siniscalco¹⁷ has previously suggested. This could lead to a fuller understanding of how a specific mutant phenotype might have arisen out of an unequal exchange event within any particular gene locus.

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