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Chromosome evolution

Ingo Schubert

The idea of evolution as a principle for the origin of biodiversity fits all phenomena of life, including the carriers of nuclear inheritance, the chromosomes. Insights into the evolutionary mechanisms that contribute to the shape, size, composition, number and redundancy of chromosomes elucidate the high plasticity of nuclear genomes at the chromosomal level, and the potential for genome modification in the course of breeding processes. Aspects of chromosome fusion, as exemplified by karyotype evolution of relatives of *Arabidopsis*, have recently received special attention.

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Introduction

Chromosomes are the units of inheritance within the nuclei of all eukaryote cells. The specific DNA content of each chromosome is a single linear DNA double helix, which corresponds genetically to a linkage group. The evolution of linear eukaryotic chromosomes from the usually circular genomes of prokaryotes is not well understood. Linear chromosomes (with ends protected by telomeres) are a prerequisite for the accumulation of (redundant) DNA, and thus for the enormous quantitative and qualitative diversification of eukaryotic chromosomes. This is because dispersed repetitive sequences tend to recombine ectopically during DNA repair, often with deleterious consequences for circular but less so for linear DNA molecules.

Eukaryotic chromosomes may differ in size, shape and composition of DNA, proteins and RNA, as well as in their number and redundancy. All of these features are subject to evolutionary changes, and therefore might vary between and even within individual organisms. The entire chromosome complement of a nucleus, the karyotype, differs in a distinct manner between organisms of defined phylogenetic relationship (e.g. between species).

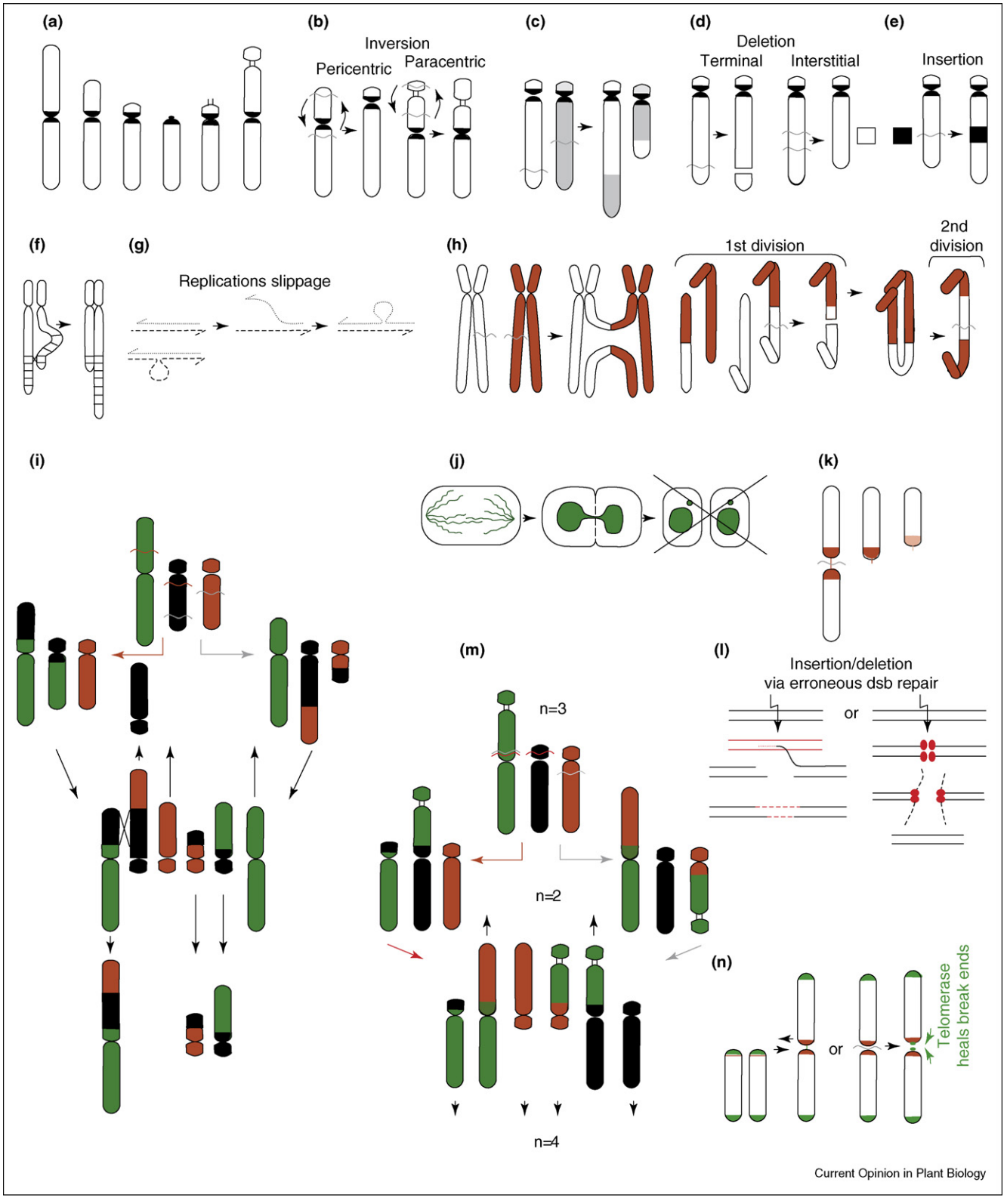
Here, I present a short overview of facts and hypotheses regarding the mechanisms that underlie evolutionary alterations of individual chromosomes and their organism-specific complements. I focus especially on recent insights regarding the alteration of diploid chromosome numbers among *Brassicaceae* by chromosome 'fusion'.

Evolution of chromosome shape and size

The shape of monocentric chromosomes is determined by the position of the primary constriction, the centromere, which subdivides a chromosome into 'arms' of equal or unequal size (Figure 1a). Additionally, a nucleolus organizing region (NOR), the site of 45S repetitive DNA (rDNA), may mark a chromosome either at a terminal or an interstitial position, giving rise to a secondary constriction and a distal 'satellite' in the latter case (Figure 1a).

The shape of chromosomes can be altered by pericentric inversion, which involves breakpoints at different distances on either side of the centromere, or by paracentric inversion, in which breakpoints occur on one arm at different distances on either side of a NOR (Figure 1b). Shape and size of chromosomes can be altered by reciprocal translocation, which exchanges unequal parts between the chromosomes involved (Figure 1c); by loss of dispensable parts (i.e. deletion; Figure 1d); by insertion (e.g. via transposition; Figure 1e); or by sequence amplification (or loss) (i) via unequal sister chromatid exchange (i.e. mitotically; Figure 1f), (ii) via unequal crossover (i.e. meiotically) or, (iii) when microscopically detectable amounts of chromatin are involved, via replication slipping (Figure 1g). Except for replication slipping, these alterations represent primary chromosome rearrangements, reflecting mis-repair of DNA damage, in particular by non-homologous end-joining of double-strand breaks. Unstable products of primary rearrangements, such as ring chromosomes (resulting from intrachromosomal translocation) or dicentric chromosomes (resulting from asymmetric translocations) might initiate 'breakage-fusion-bridge' cycles [1]. Such cycles involve repeated disruption and fusion of dicentric chromosomes during nuclear divisions (until the cycle is stopped by addition of telomeric sequences at the breakpoints) and cause duplications, deletions and/or inversions as secondary rearrangements in the chromosomes (Figure 1h). Secondary rearrangements can also be caused by meiotic crossover between homologous regions of translocation (or inversion) of

Figure 1



Mechanisms and consequences of events that might alter number, size and shape of eukaryotic linear and monocentric chromosomes. **(a)** The various shapes of chromosomes from left to right: metacentric, submetacentric, acrocentric, telocentric, acrocentric with terminal NOR, and satellited metacentric with interstitial NOR. **(b)** Pericentric (left) and paracentric inversion involving the NOR (right). **(c)** Reciprocal symmetric exchange

chromosomes, when combined in the heterozygous condition (Figure 1i).

The size of metaphase chromosomes varies from less than 1 μm to more than 10 μm, but upper and lower tolerance limits for chromosome size are apparently determined by the genome size, chromosome number and karyotype structure of a given species. In both dicots [2] and monocots [3], chromosome arms longer than half of the spindle axis (increasingly) cause mitotic instability during telophase. This is caused by incomplete separation of the corresponding sister chromatid arms and subsequent breakage of non-separated chromatid arms during the formation of the new cell wall (Figure 1j). On the other hand, chromosomes that are smaller than a certain size limit (typically <1% of the genome) frequently do not segregate correctly during meiosis, even if an original centromere is present [4,5]. We do not yet know whether lack of crossover or of 'lateral support' for the centromere [4], or another reason, is responsible for this failure.

Evolution of DNA composition with emphasis on tandem repeats

The DNA composition of chromosomes can be altered evolutionarily by primary and secondary rearrangements as described above. Unusual rearrangements have included the loss of canonical telomeres that has occurred, for example, in some arthropods [6] and in *Allium* [7,8]. *Drosophila* compensated the loss of telomeric repeats by positioning by retrotransposons (Het-A and TART) of the pericentromeric heterochromatin; these retrotransposons have been transposed to all chromosome termini at a frequency sufficient to compensate for the replication-mediated shortening of chromosome ends (for review see [9]). Alternatively, Chironomids possess terminal blocks of tandem repeats [10] that are apparently preserved by unequal recombination via a conversion-like process. A similar process has been suggested to explain both a telomerase mutant of *Kluyveromyces lactis* [11] and the *Allium* karyotype [12]. Telomeric sequences may occupy interstitial positions because of translocation or inversions. Interstitial telomeric sequences are apparently less frequent in plants than in mammals [13] and are considered to be hot spots of chromosome breakage [14].

Nucleolus organizer (as well as 5S rDNA) positions are highly polymorphic and well known for their potential intragenomic mobility [15]. It is not yet clear whether unequal recombination or transposition processes are responsible for this mobility. A case for the presumed evolutionary loss of abundant terminal NORs in *Arabidopsis* is described below.

Centromere positions can shift not only by inversion or translocation but also by stable inactivation of centromeres on dicentric chromosomes [16•] and by rare *de novo* formation on acentric chromosome fragments (Figure 1k, [17•]). In wheat–barley addition lines in which barley telosomes were truncated at their centric ends, it was shown that barley centromeric repeats (i.e. satellite sequences and retroelements) were neither necessary nor sufficient to form a functional centromere [17•].

In the course of evolution, heterochromatic blocks of tandem repeats, such as the sub-terminal knobs of maize and related species, might also appear (e.g. via unequal recombination [Figure 1f] or by nested transposition of retroelements) or become deleted (reviewed in [18]). Repetitive sequences might be seeded by transposition or by integration between break-ends from other genomic positions during non-homologous end-joining, an erroneous variant of double-strand break repair. Removal of such sequences by exonucleolytic extension of breaks during the same process is also possible (Figure 1l). Even a weak bias that turns the repair system towards either of

(Figure 1 Legend Continued) of segments unequal in size. **(d)** Terminal or interstitial deletion. **(e)** Insertion (e.g. via transposition). **(f)** Unequal somatic recombination (sister chromatid exchange) between tandem repeats out of register. **(g)** Replication slippage and repair of the double-stranded DNA according to the newly synthesized strand (dotted) causes duplication (above) or deletion (below). **(h)** Breakage-fusion-bridge cycles [1] can alter chromosome size and shape via random disruption of dicentric chromatids (which result from asymmetric reciprocal translocation) during anaphase. Such disruptions yield deletion, duplication or inversion through fusion of broken ends after replication and another breakage during the next nuclear division (shown only for the upper product of the first bridge). The cycle might stop by healing of breaks when telomeric sequences become attached. **(i)** Secondary chromosome rearrangement caused by meiotic crossover (X) between partially homologous chromosomes in heterozygotes: two translocations between three chromosomes are shown. From this meiocyte, the new chromosome segregates together with the other two translocation chromosomes to one pole (arrows directed downward), whereas on the other pole, the wildtype situation is reconstituted (arrows directed upward). **(j)** Sister chromatids of chromosome arms longer than half of the spindle axis extension do not completely separate during mitotic nuclear division. The resulting telophase bridge becomes disrupted by the newly growing cell wall and yields deletions (micronuclei) and apoptotic meristem cells. **(k)** A metacentric chromosome after centric fission yields a telocentric chromosome that becomes truncated at its centric end and eventually forms a novel centromeres, as observed for barley chromosomes in a gametocidal wheat background [17•]. **(l)** Recombinative double-strand break (dsb) repair with insertion (left) of sequences from other genomic regions before final ligation or with deletions (right) that result from exonucleolytic digestion at break ends before ligation. **(m)** Alteration of diploid chromosome number by mis-segregation from meiotic multivalents of an individual that is heterozygous for two translocations between a metacentric and two acrocentric chromosomes with breakpoints close to the centromeres. The resulting gametes with reduced (2) or increased (4) chromosome number are viable, provided that the small deletions or duplications concerning the short arms of the acrocentrics can be tolerated. **(n)** Fusion of acrocentric chromosomes into metacentric ones is reversible if the telomeric sequences that flank the centromeres remain conserved (left); alternatively, a metacentric chromosome may split into stable telocentrics when the centric breaks are healed by attaching telomeric sequences.

these options might, in evolutionary time scales, lead to 'obese' or 'lean' genomes [19].

Evolution of number and redundancy of chromosomes

According to the 'minimum interaction hypothesis' of Imai *et al.* [20], karyotype evolution generally tends towards an increasing number of acrocentric chromosomes, thereby minimising the risk of deleterious rearrangements. The opposite tendency, the reduction of chromosome number and formation of metacentric chromosomes, is considered to be the result of 'rare back-eddies' that are generated at random and tolerated or even favoured when they provide short-term advantages.

The number (2n = 2 to >100) and redundancy of chromosomes can vary due to interspecific hybridisation yielding allopolyploids or due to autopolyploidisation (e.g. by spindle inhibition). In the progenies of polyploids (or as a result of segregation disturbances in diploids), one or more chromosomes be complete or partial aneuploids. Mono- and nullisomics are viable only in polyploid backgrounds. Owing to 'diploidisation' processes, the loss of hyperploid chromosomes and chromosome regions occurs frequently. Thus, in so-called paleopolyploids (such as *Arabidopsis thaliana* or *Brassica* species), several rounds of polyploidisation are often still evident in the form of multiple segment copies (e.g. [21–23]), whereas the actual number of chromosomes no longer indicates ancient polyploidisation events.

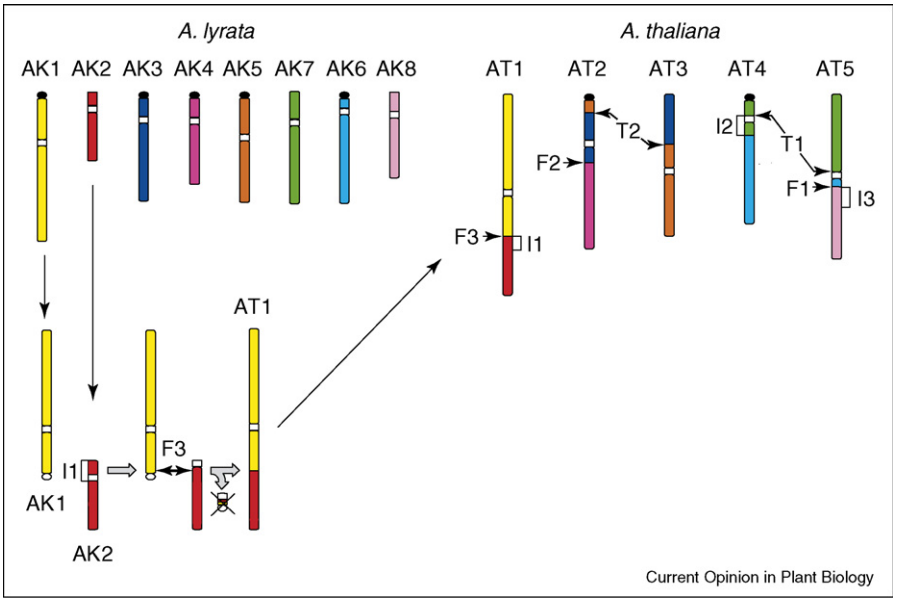
At the euploid level, mis-segregation from meiotic multivalents within individuals that are heterozygous for two whole-arm translocations, involving one metacentric and two acrocentric chromosomes, can alter the diploid chromosome number simultaneously in both directions. Such translocations yield either duplications or deletions that affect the centric ends of the involved acrocentrics (Figure 1m; [24]). An increase of chromosome number from 2n = 12 to 2n = 14 has been experimentally proven for the field bean [25]. The complementary karyotypes with reduced chromosome number are viable only if the corresponding deletions are tolerated.

So-called fusion–fission cycles (Figure 1n) have been discussed for nearly a century as a reason for alternation of chromosome number (for review see [26]). Such events are reversible when centromeric and telomeric sequences of the telocentrics that are involved in centric fusion persist in the resulting metacentric chromosome, as appears to have been the case on the field bean chromosome 1 [27]. Otherwise, centric fission with or without centromere pre-duplication [28] can yield isochromosomes or stable telocentrics, the latter being formed when telomeric sequences are patched to the centromeric breakpoints (Figure 1n), as known from the healing of broken wheat chromosomes [29]. A cyclic fission of metacentrics and conversion of the resulting telocentrics by pericentric inversion into new metacentric chromosomes is postulated to generate karyotypes that have increasing numbers of acrocentrics [30].

Chromosome fusions were claimed to be responsible for the evolutionary reduction of the chromosome number of an ancestor with eight chromosome pairs towards *A. thaliana* (n = 5). Comparative genetic maps of *A. thaliana* and *Arabidopsis lyrata* (n = 8) [31,32] and of *A. thaliana* and *Capsella rubella* (n = 8) [33], as well as a DNA sequence-derived phylogenetic tree [34], revealed that the nearly identical linkage groups of *A. lyrata* and *C. rubella*, the two species with eight chromosome pairs, resemble an ancestral state. The colinear regions within the *A. thaliana* genome suggested that the reduction in chromosome number from eight to five is linked with three chromosome fusions, two reciprocal translocations, and at least three inversion events (Figure 2; [35]).

Recently, comparative (cross-species) chromosome painting using contiguous bacterial artificial chromosome (BAC) pools from *A. thaliana*, which were arranged according to (parts of) the linkage groups of *A. lyrata*, made it possible to assign all of the *A. lyrata* chromosomes to distinct *A. lyrata* linkage groups and to integrate centromeres and NORs of *A. lyrata* into the genetic map of *A. lyrata* [36•]. This work confirmed genetic mapping data and made it possible to specify the events in chromosome evolution that led to the karyotype of *A. thaliana*. For example, the inversions between the *A. lyrata* linkage groups 2 and 8 and the corresponding regions within the *A. thaliana* genome comprise the entire short arms of the corresponding *A. lyrata* chromosome. Thus, chromosome 1 of *A. thaliana* (AT1) apparently originated by reciprocal translocation between the ancestral chromosomes AK1 and AK2 (for Ancestral Karyotype 1 and 2), after a pericentric inversion converted AK2 into an acrocentric chromosome (Figure 2). Because the translocation breakpoints occurred at the chromosome termini, the second translocation product consisted mainly of the centromere of AK2 and two telomeres. This minichromosome was apparently lost because it lacked essential genes and failed to pair properly during meiosis. The same scenario fits the 'fusion' event involving AK8 and one of the translocation products of AK6 and AK7, which formed AT5. The 'fusion' of AK4 to one of the products of a reciprocal translocation between AK3 and AK5, which formed AT2, can be interpreted in the same way. In case of linkage group 4, no inversion compared to *A. lyrata* is detectable, but a paracentric inversion, comprising the whole short arm of AK4, could have preceded a pericentric inversion that re-established the colinearity [36•]. These assumptions explain why no remnants of AK2, AK4 and AK8 centromeres are found within the sequence of the corresponding linkage groups of *A. thaliana* [21],

Figure 2



Chromosome number reduction from n = 8 to n = 5 during the evolution of *A. thaliana.* Top left: Idiogram of *A. lyrata* including centromere and NOR positions, with each chromosome corresponding one of the linkage groups of the ancestral karyotype (AK–AK8). Top right: The syntenic regions within the idiogram of *A. thaliana* indicate that two translocations (T1 and T2), three fusions (F1–F3), and three inversions (I1–I3) were involved in the evolution of the *A. thaliana* karyotype [32,35]. Bottom: Because I1 represents a pericentric inversion, comprising the entire sort arm of AK2, a subsequent reciprocal translocation between the short-arm end of AK1 and the centric end of the inverted AK2 apparently resulted in the 'fusion' chromosome AT1 (without remnants of AK2 centromeric sequences) and the loss of the small and dispensable translocation product that contains the centromere of AK2 and two chromosome ends (modified according to [36•]). Similar events explain the origin of the 'fusion' chromosomes AT2 and AT5, see text. White squares represent centromeres, terminal ovals represent NORs.

whereas the remaining five centromeres are flanked by the same markers in *A. lyrata* and *A. thaliana* maps [37,38].

Chromosome painting, even without the availability of genetic maps, revealed that the same principle applies to chromosome number reduction during the evolution of related species, such as *Neslia paniculata* (n = 7), *Hornungia alpina* (n = 6) and *Turritis glabra* (n = 6) [36•].

Of the chromosome breakpoint positions belonging to the rearrangements that contributed to the karyotype evolution described above, about 85% were found close to centromeres or at the chromosome termini, which harbour most of the (tandem) repeats in these genomes. The repeat proportion is if we assume that the ancestral karyotype contained several terminal NORs, as does the karyotype of *A. lyrata*. This observation explains why only one of the five (terminal) NORs of *A. lyrata* coincides positionally with one of the two NOR positions of the *A. thaliana* karyotype (that on AT2) and how NOR positions might have been lost. Furthermore, it is in accordance with previous observations that most experimentally induced chromosome rearrangements occur within regions of extended repeat composition and are the result of preferential mis-repair by ectopic recombination between non-allelic repeats [39]. This assumption gained further support from telomerase-deficient *A. thaliana* mutants whose terminal NORs were involved in chromosome rearrangements approximately 10 times more often than expected at random [40].

Taken together, the combination of phylogenetic, genomic, genetic and cytogenetic data shows that what appears as chromosome 'fusion' is often the result of a reciprocal translocation that leads to products of very different size and to the subsequent loss of the small translocation product. Among the relatives of *Arabidopsis* at least, this type of rearrangement is a common evolutionary event, probably because of the preferential clustering of tandem repeats around centromeres and at the chromosome termini of these relatively small genomes.

Conclusions

The evolution of chromosome shape, size, composition, number and redundancy might result in a wide diversity of karyotypes, notwithstanding the fact that optimal ranges for certain parameters and upper and lower tolerance limits for chromosome size seem to exist for some groups of organisms. Chromosomes evolve by classical primary and secondary rearrangements, and by ploidy alterations subsequent to interspecific hybridisation and/or mitotic or

meiotic errors. Primary and most secondary rearrangements are due to erroneous ligation of DNA strands during repair processes. Transposition, errors during replication, unequal recombination and insertions and/or deletions during double-strand break repair via recombination, might also contribute to evolution by promoting the shrinkage or expansion of individual chromosomes. Addressing chromosome evolution by combination of different experimental approaches might reveal new insights, such as the re-interpretation of chromosome number alteration by so-called fusions among *Arabidopsis*-related *Brassicaceae*. Owing to the reduced fertility of heterozygous carriers and/or reduced gene flow caused by suppressed recombination, rearranged chromosomes contribute to reproductive isolation, and to speciation [41].

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