The Interchromosomal Effect: Different Meanings for Different Organisms

Danny E. Miller[1]
Department of Pediatrics, Division of Genetic Medicine, University of Washington and Seattle Children's Hospital, Seattle, WA 98105
ORCID ID: 0000-0001-6096-8601 (D.E.M.)

ABSTRACT The term interchromosomal effect was originally used to describe a change in the distribution of exchange in the presence of an inversion. First characterized in the 1920s by early *Drosophila* researchers, it has been observed in multiple organisms. Nearly half a century later, the term began to appear in the human genetics literature to describe the hypothesis that parental chromosome differences, such as translocations or inversions, may increase the frequency of meiotic chromosome nondisjunction. Although it remains unclear if chromosome aberrations truly affect the segregation of structurally normal chromosomes in humans, the use of the term interchromosomal effect in this context persists. This article explores the history of the use of the term interchromosomal effect and discusses how chromosomes with structural aberrations are segregated during meiosis.

KEYWORDS achiasmate segregation; interchromosomal effect; inversions; nondisjunction; translocations

> "*Why, this means that a piece of one chromosome has been broken off and attached to a nonhomologous one—it was transposed! A fly with the deficiency dies but of course its life is saved when it carries the piece on another chromosome*."
>
> – Edgar Altenburg, as recounted by Herman Muller (1967)

INVERSIONS and translocations are two types of structural variants that can directly disrupt genes or alter gene expression. While they may lead to copy number abnormalities in an offspring, their effect on an individual are often purely structural, making them attractive to study in model systems. Early *Drosophila* researchers first recognized the impact these variants can have when they noticed that the frequency of crossing over was reduced between two homologous chromosomes if one homolog carried either an inversion or a translocation. Surprisingly, the reduction in exchange caused by heterozygosity for these aberrations was accompanied by a corresponding increase in crossing over on other pairs of normal-sequence chromosomes (Sturtevant 1919, 1921). This phenomenon, termed the interchromosomal effect, has subsequently been observed in other model organisms.

More than half a century after it was first described in *Drosophila*, the term interchromosomal effect appeared in a very different context in the human genetics literature, where it was used to describe the hypothesis that heterozygosity for a translocation involving one set of chromosomes could induce the nondisjunction of normal-sequence chromosomes not involved in the translocation (*cf*. Stoll *et al.* 1978; Lindenbaum *et al.* 1985; Couzin *et al.* 1987; Serra *et al.* 1990). Predictably, the usage of the term interchromosomal effect to describe two very different genetic phenomena has led to confusion. While it may not be appropriate, or even possible, to change the use of this term in either the human genetics or model organism literature, it is helpful to provide the historical context behind how this discrepancy arose, both as a bit of clarification and as a cautionary tale.

To begin this story, we need to briefly review the roles of exchange in mediating segregation and the methods by which meiotic cells cope with nonexchange chromosomes. During meiosis, homologous chromosomes pair and undergo crossing over, forming chiasmata between them. Chiasmata ensure the proper segregation of chromosomes away from each other at the first meiotic division—in other words, they properly disjoin—thus, crossovers are vital for proper chromosome segregation during meiosis. However, for a variety of reasons, not

doi: https://doi.org/10.1534/genetics.120.303656
Manuscript received May 13, 2020; accepted for publication September 15, 2020
[1]Address for correspondence: Department of Pediatrics, Division of Genetic Medicine, University of Washington and Seattle Children's Hospital, 4800 Sand Point Way NE, Seattle, WA 98105. E-mail: danny.miller@seattlechildrens.org

all pairs of homologous chromosomes undergo exchange. These reasons can include homologous chromosomes in which one carries an inversion that reduces the frequency of exchange, heterologous chromosomes involved in a translocation that interferes with exchange, and small chromosomes which never undergo exchange. Collectively, chromosomes that do not undergo exchange are referred to as achiasmate chromosomes. For meiosis to be successful, both achiasmate and exchange chromosomes must be segregated properly. This raises a few questions: how does the cell manage to segregate achiasmate chromosomes, and do the processes that mediate achiasmate segregation underlie the so-called interchromosomal effect as it is described in humans?

This perspective is a survey of the historical definition of the interchromosomal effect, and how both homologous and heterologous chromosomes are segregated during meiosis. We will begin with a discussion of the two types of structural variants that can give rise to these phenomena.

The Effect of Inversions and Translocations on Exchange

Drosophila melanogaster, with four pairs of chromosomes, is an excellent system for the study of achiasmate chromosome segregation, because the small fourth chromosomes do not undergo exchange. In 1919, Alfred Sturtevant published data regarding the frequency of exchange for two *D. melanogaster* second chromosome variants that together reduced crossing over across both arms of the second chromosome (Sturtevant 1919). When one of these variants was studied separately, it reduced crossing over only on the right arm of chromosome 2. However, as a homozygote it had no noticeable effect on the frequency of exchange. This was one of two variants in The Fly Room with a similar phenotype. The second had been mapped to the distal end of the third chromosome and had a similar localized effect on crossing over (Muller 1916a–d; Sturtevant 1919).

The explanation for these puzzling results came from studies of *Drosophila simulans*, which revealed that some genes were in a different order when compared to the *D. melanogaster* genetic map (Sturtevant 1921). Because these species had a common ancestor, Sturtevant realized that the change in gene order likely did not occur as a consequence of normal crossing over, but instead could have occurred only if these genes had been moved or inverted in relation to one another in one or the other species since their lineages diverged.[1]

With this, Sturtevant demonstrated that heterozygous inversions can have consequences during meiosis. For example, single crossover events within inversions that do not span the centromere can create two chromatids that do not segregate properly during meiosis. He also showed that the frequency of exchange between an inversion and a normal-sequence chromosome is reduced both within the inversion and near the inversion breakpoints. Sturtevant concluded that this observation explained the previously described "crossover genes" that suppressed exchange in the region they were mapped to when heterozygous but allowed free exchange as homozygotes (Muller 1916a–d; Sturtevant 1917, 1919; Miller *et al.* 2019).

How is it, then, that inversions suppress exchange? Inversions can be divided into two types: paracentric inversions, which do not involve the centromere, and pericentric inversions, which span the centromere (Figure 1A). Any single exchange event within a paracentric inversion will create one acentric and one dicentric chromosome fragment that will not segregate properly during meiosis (Figure 1C). Single exchange events within pericentric inversions produce deletions and duplications that can segregate properly during meiosis but are likely to be lethal during development (Figure 1C). Double crossover events within inversions produce viable chromatids as long as both events occur on the same chromatids, but they occur far less frequently than expected compared to wild type because crossovers occur at a low frequency near inversion breakpoints (Sturtevant and Beadle 1936). Thus, the cell appears to have a mechanism by which to reduce the frequency of crossovers within an inversion; this is discussed below.

Translocations differ from inversions because they involve the movement of genetic material from one chromosome to another. The movement of an entire chromosome arm onto another chromosome was first observed in grasshoppers by William Robertson and became known as a Robertsonian translocation (Figure 1B) (Robertson 1916). A second class of translocations, known as reciprocal translocations, involves the exchange of genetic material between two nonhomologous chromosomes. If no genetic material is lost as a consequence of the reciprocal translocation then it is known as a balanced translocation. Translocations have well-known clinical consequences in humans. For example, the translocation of chromosome 21 onto the end of another chromosome, a Robertsonian translocation, accounts for ~5% of trisomy 21 cases (Zhao *et al.* 2015). Translocations can be recurrent as well, such as the frequent reciprocal translocation between human chromosomes 11 and 22 that occurs within repetitive DNA (Hill *et al.* 2000).

Heterozygous translocations also act as region-specific dominant suppressors of exchange. Studying translocations between the *D. melanogaster* third and fourth chromosomes, Dobzhansky (1930) reported a decrease in crossing over on the third chromosome near the translocation breakpoints. For any translocation recovered, the reduction was more pronounced closer to a translocation breakpoint. Dobzhansky eventually recovered translocations involving all chromosomes, including the Y, and found similar patterns of reduced exchange for all of them (Dobzhansky 1931). Larger studies of translocation breakpoints have since confirmed this

[1]Sturtevant's name is the only one on the 1921 manuscript, but he later acknowledges that the idea was suggested by Morgan (Sturtevant 1965). This was not uncommon in the Fly Room as credit for an idea was not as important as the testing of the idea itself—a tradition that continues within the fly community today.

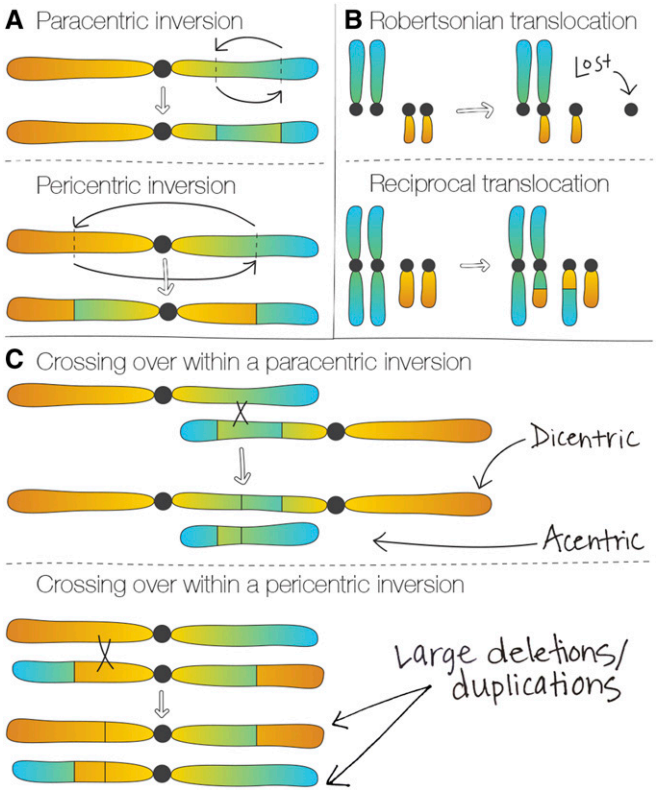

Figure 1 Inversions and translocations are two types of structural variants that can lead to disease in humans. (A) Inversions that do not involve the centromere are known as paracentric inversions, while those that involve the centromere are known as pericentric inversions. (B) Translocations involve the movement of genetic material between two chromosomes. This can either be the movement of an entire chromosome arm onto another, known as a Robertsonian translocation, or the exchange of large parts of two arms between chromosomes, known as a reciprocal translocation (a balanced translocation is a reciprocal translocation in which no genetic material is lost; in an unbalanced translocation, some genetic material is lost). (C) A single exchange event within a paracentric inversion results in an acentric and a dicentric chromatid, neither of which segregates properly during meiosis. Here, two of four chromatids are shown. Single crossovers within a pericentric inversion will lead to two chromatids that segregate properly during meiosis but have large deletions and duplications that may be lethal to the developing organism.

suppression of exchange (Roberts 1972; Hawley 1980; Sherizen *et al.* 2005).

It is worth noting that, although much of the exchange suppression observed in inversion heterozygotes reflects the consequences of exchange within the inverted region, the occurrence of exchange is strongly suppressed in the vicinity of both breakpoints. This effect, like the exchange suppression observed in translocation heterozygotes, clearly demonstrates that heterozygosity for discontinuities caused by breakpoints produces dominant polar suppression of crossing over, suggesting that homologous synapsis may be hindered. Unfortunately, the mechanisms that generate that suppression still remain unclear, although clues are emerging (Thomas *et al.* 2005; Crown *et al.* 2018; Altendorfer *et al.* 2020).

The Interchromosomal Effect in *Drosophila*: the Effect of Structural Variants on Exchange

While it was the crossover-reducing property of heterozygous inversions that led to their identification, it was soon apparent that they increased the frequency of exchange on other chromosomes (Sturtevant 1919, 1921). For example, during her analysis of a variant with one inversion on each arm of chromosome 2, Ward (1923) observed both a decrease in exchange on that chromosome and an increase of exchange on other normal-sequence pairs of chromosomes. Later studies of chromosomes carrying multiple inversions revealed dramatic increases in exchange on freely recombining chromosomes when crossing over was reduced on two or more chromosome arms (Figure 2) (Morgan *et al.* 1932, 1933; Hinton 1965; Crown *et al.* 2018). This change in the distribution of exchange in the presence of a heterozygous inversion is known as the interchromosomal effect (Schultz and Redfield 1951). An *intra*chromosomal effect has also been observed in *Drosophila*, in which a single inversion on one end of the X chromosome resulted in an increase in exchange in a different interval on the same chromosome (Sturtevant and Beadle 1936; Grell 1964).

Inversions in other organisms can alter the distribution of exchange similar to what has been observed in *Drosophila* (Dresser *et al.* 1994; Massip *et al.* 2010; del Priore and Pigozzi 2015), and the inter- and intrachromosomal effects have also been observed in other organisms such as grasshopper (White and Morley 1955), maize (Bellini and Bianchi 1963), and *Arabidopsis* (Termolino *et al.* 2019). Of course, exceptions do exist. For example, local recombination suppression by an inversion in *Caenorhabditis elegans* is associated with an increased frequency of exchange in regions outside of the inversion only on the same chromosome arm, but not on other chromosomes (Zetka and Rose 1992). Thus, in *C. elegans*, there appears to be only an intrachromosomal effect, possibly due to strict crossover control mechanisms in *C. elegans* (Saito and Colaiácovo 2017).

The data for translocation heterozygotes are more complicated, because conflicting data exist as to whether translocation-associated reductions in crossing over lead to an increase of exchange on other chromosomes (Williamson 1966). Among nearly 9000 offspring from *Drosophila* females heterozygous for a translocation between chromosomes 2 and 3, Zimmering and Barbour (1952) found no difference in single crossovers on the X chromosome but a slight increase in double crossover events. Later work by Hinton provided a more complicated view regarding the effect of a translocation on exchange. Studying 26 translocations between chromosomes 2 and 3, Hinton found that some translocations increased the frequency on the X, others decreased it, and others had no effect (Hinton 1965). The impact on exchange seemed to be related to the size of genetic material translocated: if most of one arm of chromosomes 2 and 3 were swapped, he saw a decrease in exchange on the X, but, if only

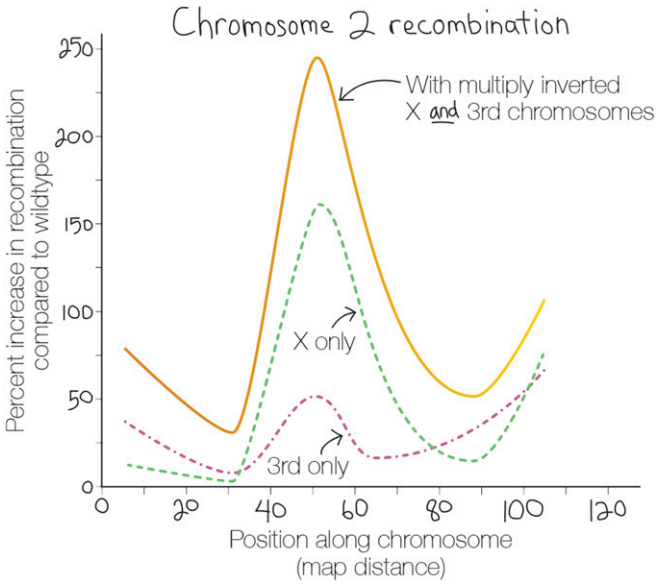

Figure 2 The interchromosomal effect is seen by measuring the frequency of exchange on a freely recombining chromosome in the presence of one or more multiply inverted chromosomes [adapted from Schultz and Redfield (1951)]. In the presence of a single chromosome with multiple inversions (green or pink lines), the frequency of exchange on the second chromosome increases in the centromere-proximal and telomere regions. When two multiply inverted chromosomes are present (yellow line), the frequency of exchange in the centromere-proximal and telomere regions is higher than either multiply inverted chromosome alone. In all cases, the increase in exchange comes from shifting DSBs fated to become gene conversions into a crossover-fate pathway instead (Crown *et al.* 2018).

a small part of the arms were swapped, he observed an increase in exchange.

Studies of the effect of translocations in other organisms have also produced mixed results. In *C. elegans*, translocations appear to affect recombination in different ways, with some reducing recombination on only one side of the translocation breakpoint while the other side remains relatively normal (McKim *et al.* 1988). Increases in exchange in the presence of a translocation have also been observed in both grasshopper and maize (White 1963; Auger and Sheridan 2001). Thus, there is no clear answer as to whether translocations in general cause an interchromosomal effect on exchange, or if the impact is specific to the position of the translocation.

The Mechanism of the Interchromosomal Effect

Despite abundant data demonstrating the presence of the interchromosomal effect, the mechanism behind it remained unclear for nearly 100 years (Lucchesi and Suzuki 1968). We know that during meiosis, cells make programmed DNA double-strand breaks (DSBs), which are then repaired as either crossovers or gene conversions (GCs). Crossovers, which are required for the accurate segregation of homologous chromosomes, involve the exchange of flanking markers, while GCs involve the copying of genetic material from one homolog to another. In general, most DSBs are repaired as GCs—that is, the cell makes more DSBs than it needs to resolve into crossovers (Lenzi *et al.* 2005; Mehrotra and McKim 2005; Gruhn *et al.* 2013).

How does the cell increase the number of exchanges on some chromosome arms while decreasing them on others? Are additional DSBs made, or are DSBs that would otherwise have become noncrossover gene conversions (NCOGCs) redirected down a crossover-fate pathway? It is conceivable that, if one pair of homologs could not undergo exchange, the cell could make more DSBs, with some of those additional DSBs being repaired as crossovers on those chromosomes able to undergo exchange. Indeed, such a DSB-feedback loop exists in budding yeast and *C. elegans* (Keeney *et al.* 2014). However, cytologic data in *D. melanogaster* indicate that, in the presence of a multiply inverted chromosome, the number of DSBs does not increase (Mehrotra and McKim 2005). Indeed, whole-genome sequencing of *D. melanogaster* individuals from females with one or more multiply inverted chromosomes also revealed that the overall number of DSBs is not increased in the presence of multiple inversions, but that existing DSBs that are destined to become GCs are instead repaired as crossovers (Crown *et al.* 2018). It has been shown that, in *Drosophila*, the increase in exchange associated with the interchromosomal effect is dependent on the widely conserved checkpoint protein *pch2* (Joyce and McKim 2010). This also suggests that the cell monitors the number of crossovers, and progression can be delayed when crossover frequency is reduced (Joyce and McKim 2010).

Many questions remain about the crossover-suppressing properties of both inversion and translocation breakpoints. While the mechanism of DSB repair in translocation heterozygotes remains to be studied at the molecular level, it is likely to be similar to changes seen in inversion heterozygotes. It is also unclear over what distance an inversion breakpoint suppresses exchange. While data from several studies suggest that this suppression extends ~1–2 Mb from inversion breakpoints, confirmation requires further study (Novitski and Braver 1954; Miller *et al.* 2016a,b, 2018; Crown *et al.* 2018).

The Interchromosomal Effect as Used in Human Genetics

While the original use of the term interchromosomal effect described the change in genome-wide exchange frequency in the presence of an inversion, more recent work in humans and other mammals has used the term to mean something entirely different: the nondisjunction of a normal pair of homologous chromosomes in the presence of a translocation involving other chromosomes (*cf.* Estop *et al.* 2000; Eichenlaub-Ritter 2005; Barasc *et al.* 2019). A PubMed search for "interchromosomal effect" in mid-2020 yielded ~150 results. About half of these studies were published after the year 2000, and the majority are studies of the impact translocations have

on chromosome segregation in humans. For example, Anton *et al.* (2010) studied spermatozoa from carriers of a Robertsonian translocation to determine the impact of any translocation on the segregation of chromosomes 18, X, and Y, which they describe as the interchromosomal effect.

How did interchromosomal effect come to describe nondisjunction in the presence of a translocation in humans? When describing the term, many of these studies cite a 1963 publication by Jerome Lejeune (1963). Those papers that do not directly cite Lejeune generally cite another reference that describes the interchromosomal effect by citing Lejeune. Lejeune's paper is based on a lecture given in 1962 on numerical chromosome abnormalities in humans (Lejeune 1963).

In his paper, Lejeune asks if translocations can cause other chromosomes to segregate abnormally, and concludes that, based on three cases from the literature, autosomal rearrangements do increase the probability of abnormal segregation of sex chromosomes. For example, he cites one case describing a female carrying a translocation between chromosomes 2 and 22 who had a daughter with Turner syndrome (thus she had only one X chromosome) who also inherited the translocation from her mother (Biesele *et al.* 1962). These observations are used to put forth a hypothesis: "... autosomal rearrangements can increase the probability of abnormal segregation for the sex chromosomes, which are not themselves involved in the structural change." To support this hypothesis, Lejeune cites two studies from *Drosophila*:

"This hypothesis can be related to the observation made in *Drosophila*, that structural changes in autosomes do increase the frequency of abnormal segregation of the X (Morgan and Sturtevant 1944) especially if the X chromosomes themselves show structural changes (Cooper *et al.* 1955)."

While Lejeune does not use the term interchromosomal effect in his paper, he cites work on the interchromosomal effect in *Drosophila*, which may be the initial source of confusion. Addressing the nature of this difference in meaning requires us to consider two topics: (1) is there an effect of translocation heterozygosity on the segregation of chromosomes not involved in the translocation; and (2) if such an effect does exist, what role might the processes referred to as "distributive segregation" play in mediating that effect?

The Impact of Inversions and Translocations on Meiotic Chromosome Segregation in Model Organisms

Inversion and translocation heterozygotes clearly affect the distribution of crossing over, but what is their impact on chromosome segregation during meiosis? Because chiasmata are the primary mechanism for ensuring the proper segregation of meiotic chromosomes, it is not surprising that the frequency of nondisjunction is higher for those pairs of chromosomes that fail to undergo exchange. For example, in *Drosophila*, wild-type X chromosomes normally fail to undergo exchange in 5%–10% of oocytes, and yet the frequency of spontaneous X chromosome nondisjunction is much lower at ~0.2% (Zitron and Hawley 1989). If the female is heterozygous for one or more X chromosome inversions, the frequency of nondisjunction increases only slightly to ~0.2–0.4%, (Forbes 1962; Zitron and Hawley 1989; Xiang *et al.* 2007).

This small increase in nondisjunction on the aberration-bearing homolog pair is accompanied by a decrease of nondisjunction among homologous chromosomes that can undergo exchange, presumably because of the increased frequency of exchange on those chromosomes. In studying females heterozygous for inversions of chromosome 3, Szauter saw a decrease in X chromosome nondisjunction (Szauter 1984), similar to previous observations made by Cooper *et al.* (1955). However, females heterozygous for inversions on two different chromosomes will show elevated levels of nondisjunction for both chromosomes (Forbes 1962; Zimmering 1976; Zitron and Hawley 1989). Several lines of evidence suggest that these increased levels of nondisjunction are due to heterologous segregation (Baker and Hall 1976). As an example, consider the case where two nonexchange X chromosomes segregate from an achiasmate chromosome 2 while the remaining chromosome 2 segregates at random.

$$\mathrm{X,X} \longleftrightarrow 2$$

$$\longleftarrow 2 \longrightarrow$$

When inversions occur on two different chromosomes, the increased nondisjunction is associated with two-by-two segregation. This results in random segregation without a need for homology. Thus, while these two types of segregation occur with equal probability:

$$\mathrm{X,X} \longleftrightarrow 2,2$$

$$\mathrm{X},2 \longleftrightarrow \mathrm{X},2$$

this type of segregation is relatively rare:

$$\mathrm{X,X},2 \longleftrightarrow 2$$

The central lesson here is that inversion heterozygosity can increase the frequency with which other pairs of homologs nondisjoin, but only if those other pairs also fail to cross over. The mechanism for that effect is well understood and will be discussed next.

The effect of translocations on the segregation of uninvolved chromosomes is more complicated. Muller was likely the first to directly measure the rate of nondisjunction in female flies carrying translocations between chromosomes 2 and 3, and he found that it did not occur at a high enough frequency to be detected (Muller 1930). A larger study by Hinton (1965), which also involved a translocation between chromosomes 2 and 3, revealed no X chromosome nondisjunction events, confirming Muller's result that nondisjunction

of structurally normal X chromosomes in the presence of an autosomal translocation is quite low.

The failure of a reciprocal translocation between the large second and third chromosomes to increase the frequency of nondisjunction is easily explained by the pairing of the chromosomes during meiosis. The two normal-sequence second and third chromosomes will pair with the two translocated chromosomes to form the quadrivalent seen in most textbooks (Figure 3). All four arms of the quadrivalent will undergo crossing over and this will not affect the segregation of either the X or the fourth chromosomes.

Other types of translocations can interfere with exchange and thus increase the frequency of nondisjunction of other chromosomes—but only if there are frequently nonexchange chromosomes. An example is a translocation between the *Drosophila* X and fourth chromosomes that transfers the distal 3/4 of the euchromatin of the X onto the fourth with the end of the fourth chromosome now capping the X chromosome. The distal 3/4 of the X attached to the end of a fourth chromosome will pair and recombine at high frequency with a structurally normal X chromosome (Hawley 1980). The proximal 1/4 of the euchromatin that remains attached to the original X centromere will be unpaired and almost always fails to recombine with the normal X. This element will now be achiasmate, and can also interfere with the segregation of other achiasmate chromosomes, such as the two structurally normal nonexchange fourth chromosomes.

Thus, while translocations do not generally affect the segregation of nonhomologous chromosomes, achiasmate elements of translocation heterozygotes can interfere with the segregation of other achiasmate chromosomes. How is it then that achiasmate chromosomes are segregated, and why does adding an additional achiasmate chromosome increase the frequency of nondisjunction?

Achiasmate Chromosome Segregation

One can think of the pool of achiasmate chromosomes that might exist in a fly oocyte as consisting of two populations: pairs of achiasmate homologs, and chromosomes without partners (often referred to as heterologous chromosomes). Achiasmate homologous chromosomes can include the X chromosome, which fails to undergo exchange 5%–10% of the time, as discussed above, as well as the small fourth chromosome in *D. melanogaster*, which never undergoes exchange yet is able to disjoin properly the majority of the time (Zitron and Hawley 1989). This is not unlike humans, in which up to 5% of chromosomes 21 and 22 have been observed to fail to undergo exchange (Gruhn *et al.* 2013). Notably, this frequency is higher than the observed incidence of trisomy 21 at birth of ~1 in 700–800 (Allen *et al.* 2008).

To explain proper segregation of achiasmate homologs, Sturtevant and Beadle proposed that "exchange is not a necessary requirement for regular disjunction of the X chromosomes in *Drosophila*," implying the existence of an exchange-independent back-up mechanism (Sturtevant and Beadle 1936). Based on studies by Karpen and his collaborators (McKee and Karpen 1990) as well as on their own data, Whyte *et al.* (1993) proposed that the segregation of both nonexchange X chromosomes and of the 4's was mediated by the persistence of heterochromatic homology until prometaphase. This hypothesis was later validated by Dernburg *et al.* (1996) with cytological studies.

Rhoda Grell focused on the segregation of heterologous chromosomes, such as compound chromosomes and free duplications (or the example of the heterologous segregation of the achiasmate X and second chromosomes described above). Very little is understood about the mechanisms of heterologous segregation, other than the clear demonstration by Dernburg *et al.* (1996) that segregation is not preceded by heterologous pairings. Unfortunately, Grell considered both heterologous and homologous achiasmate segregation as part of a singular process she named distributive segregation (Grell 1959, 1964). Sadly, this confusion persists even after the discovery of mutants that disrupt achiasmate homologous segregation, but do not impair heterologous segregation (Hawley *et al.* 1993).

Distributive Segregation and Human Nondisjunction

Lejeune used what would become Grell's distributive segregation model to support the idea that autosomal translocations can influence the segregation of sex chromosomes, increasing their nondisjunction: "[a]lso nonrandom segregation of the Y chromosome can be produced by autosomal rearrangements (Grell 1959)." Approximately 1 year after Lejeune's 1963 paper, Grell and Valencia extended his argument by describing how the distributive pairing hypothesis could apply to human chromosome abnormalities (Grell and Valencia 1964). In doing so, they formally applied the term distributive pairing, not the interchromosomal effect, to describe Lejeune's observations of chromosome segregation defects.

Using anecdotal evidence (including many of the same cases Lejeune used) from the human literature at the time, Grell and Valencia (1964) provide an "admittedly speculative" argument that distributive pairing helps to explain how karyotype abnormalities in humans can lead to nondisjunction. For example, they claim that nondisjunction of an X or Y chromosome could be explained by a chromosome carrying a translocation paring with the X during oogenesis, resulting in nondisjunction of the X chromosome. This claim is supported by no primary data, but instead by two cases in which a parent with a translocation had an offspring with a sex chromosome abnormality (at the time it was not possible to definitively determine in which parent the nondisjunction event occurred) (Grell and Valencia 1964).

Expanding the concept of distributive segregation to humans was speculative. The cases that were used to support each hypothesis were difficult to interpret in the absence of additional data such as the parent of origin for a nondisjunction event. A salient example of why this information is helpful

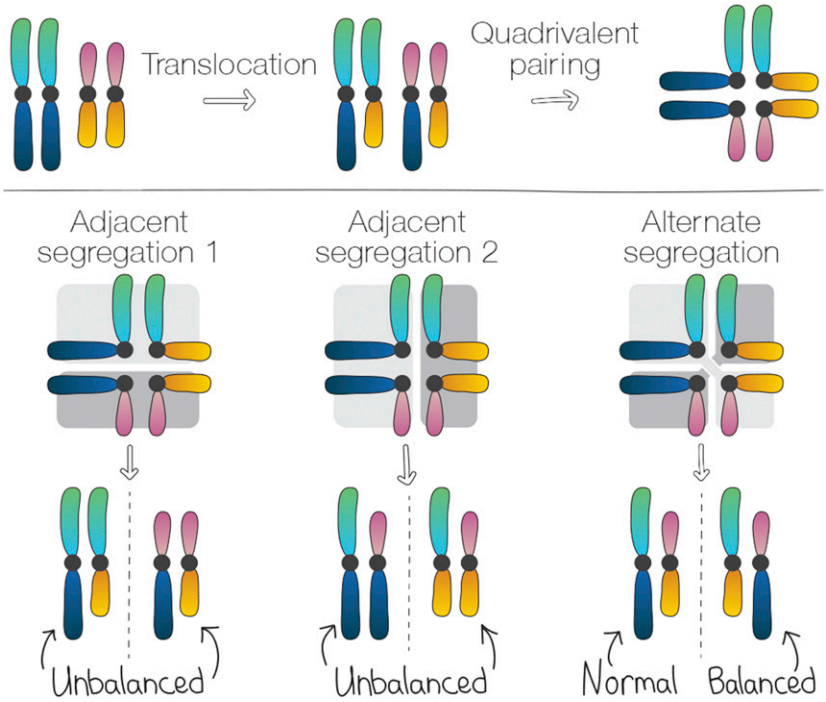

Figure 3 Translocations can pair as quadrivalents, which allows exchange between homologous chromosome arms. Chromosomes in the quadrivalent configuration can segregate one of three ways. Adjacent segregations result in unbalanced gametes, the viability of which is variable and usually depends on the amount of genetic material duplicated or deleted. Alternate segregation results in viable gametes, one with a normal karyotype and one carrying the translocation.

comes from a study by Schinzel *et al.* (1992), who examined seven individuals with trisomy 21 in which one parent carried a translocation. They found that while the father carried the translocation in five of the cases, in all cases the additional chromosome 21 was maternally inherited (Schinzel *et al.* 1992). This is an example of the use of a modern molecular technique that allows for precise studies on the frequency of nondisjunction in the presence of translocations which can be used to address the impact of a translocation in human meiosis.

Do Translocations Increase the Frequency of Nondisjunction in Humans?

Warburton directly addressed the impact of a translocation on nondisjunction and found no evidence suggesting there was an increased rate of nondisjunction in the presence of a translocation (Warburton 1985). Using data from amniocentesis of nearly 1400 pregnancies in which one of the parents were known reciprocal translocation carriers, Warburton found no increased frequency of trisomy. She also asked a second question in her study: are inherited translocations found more often than expected by chance in individuals with a trisomy? If there was a relationship between the two events, one would expect there to be an increased frequency of inherited translocations in individuals with a trisomy. Data from a registry of individuals with trisomy 21 and of nonviable pregnancies with a trisomy did not show an increased frequency of inherited reciprocal translocations. Warburton also observes that support for the original hypothesis that translocations increase the frequency of nondisjunction was mostly from anecdotal reports of families in which a trisomy or monosomy X was found in an offspring of a parent with a balanced translocation. Thus, Warburton's data suggest there is not an increased frequency of nondisjunction in the presence of a translocation.

Later studies looking at individual meiotic products also found no increased frequency of nondisjunction in translocation heterozygotes. Studying sperm from two males carrying balanced translocations of either chromosomes 11 and 17, or 1 and 11, Spriggs *et al.* (1992) found no evidence of an increased rate of nondisjunction. Specifically, they found that these two individuals had a frequency of aneuploidy of 0.7% and 2.0%, lower than the wild-type rate of 2.4% based on sperm from males analyzed by their laboratory. While they do not show the data, they also note that examining the karyotypes of at least 160 sperm from each of seven additional men carrying a translocation revealed no significant increase in aneuploidy.

Microarray-based studies by Alfarawati *et al.* (2012) of both oocytes and cleavage-stage embryos provided insights into whether nondisjunction in the presence of a translocation is a meiotic or mitotic phenomenon. In a sample of 10,837 chromosomes from individuals with translocations (both reciprocal and Robertsonian), they identified 553 aneuploid chromosomes. This was compared to 9598 aneuploid chromosomes in a sample of 204,406 chromosomes from individuals not carrying a translocation. They find the overall difference in frequency significant (0.047 in wild type *vs.* 0.051 in translocation carriers). A careful examination of their data revealed no significant difference in aneuploidy among reciprocal-translocation carriers, but a significant

difference for Robertsonian translocation carriers. Among those Robertsonian translocation carriers, the frequency was significantly increased only in cleavage-stage embryos, not in oocytes. This suggests that the increased frequency of nondisjunction may be a mitotic, not meiotic, phenomenon.

Despite this powerful negative evidence, the concept of translocations disrupting homologous chromosome segregation remains very alive in human genetics today. Studies addressing this question have given strikingly inconsistent results. While some reports have suggested that nondisjunction is increased in the presence of a translocation (Douet-Guilbert *et al.* 2005; Ogur *et al.* 2006; Mateu-Brull *et al.* 2019), others have found no such association (Spriggs *et al.* 1992; Blanco *et al.* 1998; Estop *et al.* 2000; Godo *et al.* 2015) and some have found chromosome-specific nondisjunction (Anton *et al.* 2010). Other studies have reported more granular results, such as a study that found no increase in nondisjunction in the presence of translocations but did find an increase in nondisjunction in the presence of a chromosome 10 aberration (Tulay *et al.* 2014), or another reporting a similar increase in the presence of a pericentric inversion on chromosome 9 (Amiel *et al.* 2001).

Many of the studies cited above relied on fluorescent in situ hybridization (FISH) of sperm, a technique whose accuracy has been shown to be variable between users and laboratories, thus these conflicting results could simply be evidence of a technical artifact during sample preparation and analysis (Munné 2012). These inconsistent results suggest that additional work is needed to determine what influence, if any, chromosome aberrations have on chromosome segregation during meiosis in humans. Numerous studies have shown that aneuploidy during early embryonic development is common (McCoy 2017), which should be kept in mind when analyzing results from cleavage-stage embryos. The type of careful analysis performed by Alfarawati and colleagues (2012) should provide guidance for future studies addressing this question.

Concluding Thoughts

Although the use of the term interchromosomal effect to describe chromosome nondisjunction in the presence of a chromosome aberration has been established in the human genetics literature, it is clear that this was not the original meaning of the term. The aim of this perspective was to provide historical context for the interchromosomal effect and to delineate how it came to be used to describe two different phenomena. Is there a better term to describe nondisjunction of a chromosome in the presence of a translocation if that chromosome itself is not involved in the translocation—and does that phenomenon even exist? One cannot help but wonder if this is a case in which the use of an inappropriate paradigm might be precluding a more open search for the molecular etiology of nondisjunction.

Early work used the term distributive pairing (Grell and Valencia 1964) to describe the phenomenon as it was described by Lejeune (1963). This usage was not adopted by other studies, and it is not strictly accurate. This is partly because early work in model organisms did not have a specific term to describe nondisjunction in the presence of a translocation since the phenomenon was never observed. Furthermore, the data are conflicting on whether there is truly an interchromosomal effect in humans, thus additional carefully designed studies are needed to truly understand the impact of a translocation on the frequency of nondisjunction in humans. Advances in molecular tools and techniques are allowing new and exciting questions to be asked about the interchromosomal effect, which will advance our understanding about the distribution of exchange and chromosome dynamics in both meiosis and mitosis.

Acknowledgments

I thank Angela Miller for figure illustration and editing assistance; Nicole Crown, Terry Hassold, and R. Scott Hawley for helpful discussions; and two anonymous reviewers for their thoughtful comments.

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Communicating editor: A. Wilkins