Aneuploidy (trisomy or monosomy) is the most commonly identified chromosome abnormality in humans, occurring in at least 5% of all clinically recognized pregnancies. Most aneuploid conceptuses perish in utero, which makes this the leading genetic cause of pregnancy loss. However, some aneuploid fetuses survive to term and, as a class, aneuploidy is the most common known cause of mental retardation. Despite the devastating clinical consequences of aneuploidy, relatively little is known of how trisomy and monosomy originate in humans. However, recent molecular and cytogenetic approaches are now beginning to shed light on the non-disjunctional processes that lead to aneuploidy.

Dosage imbalance of whole chromosomes typically results in inviability. So, it is not surprising that, in most organisms, meiotic non-disjunction is a rare occurrence. In the yeast Saccharomyces cerevisiae, for example, the likelihood of an individual chromosome segregating during meiosis is as low as 1 in 10,000 (for example, see REF. 1). Similarly, in Drosophila melanogaster, estimates of X-chromosome non-disjunction in the female germ line range from ~1 in 1,700 to ~1 in 6,000 (REF. 2) and autosomal non-disjunction is probably as rare. In mammals, the frequency of meiotic errors seems to be higher; nevertheless, in the organism that has been best studied (the mouse), the overall incidence of aneuploidy (trisomy or monosomy) among fertilized eggs does not exceed 1–2% (REF. 4).

Our species provides a notable exception to this general rule. An estimated 10–30% of fertilized human eggs have the ‘wrong’ number of chromosomes, with most of these being either trisomic or monosomic. This has profound clinical consequences: approximately one-third of all miscarriages are aneuploid, which makes it the leading known cause of pregnancy loss and, among conceptions that survive to term, aneuploidy is the leading genetic cause of developmental disabilities and mental retardation.

The basis for the difference in incidence between our own and other species remains obscure. However, we now know a lot about the non-disjunctional origin of human aneuploidies, especially those that derive from meiotic errors. In this review, we summarize our current understanding of human aneuploidy by: first, discussing available data on the incidence of aneuploidy in different types of human conception; second, reviewing studies of the mechanism of origin of human monosomies and trisomies; and finally, discussing available information on putative aneuploidy-inducing factors. However, before summarizing these data, it is useful to first review the basics of meiosis and meiotic chromosome segregation in our species.

**Meiosis and meiotic abnormalities**

The meiotic pathway is extraordinarily conserved and, therefore, it is not surprising that humans follow the same basic programme as do most other organisms. Meiosis generates haploid gametes through a specialized cell division process that consists of one round of DNA replication followed by two cell divisions. The first division, or meiosis I (M1), involves the segregation of homologous chromosomes from each other, whereas meiosis II (MII) involves the seg-
The successful segregation of homologues rather than sister chromatids at the first division requires unique chromosome behaviours that include: first, the maintenance of physical connections between homologues until anaphase I, a role that is fulfilled by the sites of recombination, or chiasmata; and second, some form of physical constraint on the centromeres of sister segregation of the sister chromatids, and is therefore analogous to a mitotic division. These unique divisions are preceded by an equally unique meiotic prophase, during which homologous chromosomes synapse and undergo recombination.

Although these basic features hold for both human males and females, there are important sex-specific differences in the time of onset, duration and outcome of the meiotic processes (Fig. 1). In the human male, meiosis begins with puberty and the important events are sequential: in the adult testis, cells progress from prophase to metaphase I and on to metaphase II without an intervening delay, and each cell that enters meiosis produces four sperm. By contrast, the meiotic process in the human female is extraordinarily protracted: all oocytes initiate meiosis during fetal development, but after homologous chromosomes undergo synapsis and initiate recombination, the oocyte enters a period of meiotic arrest. Resumption of meiosis and the completion of the first division occur years later in the ovary of the sexually mature woman, just before the oocyte is ovulated.

Figure 1 | Meiotic ‘timelines’ for humans. The fate of germ cells is dictated by the somatic environment. In both the developing ovary and the testis, germ cells undergo mitotic proliferation prenatally, but the time of entry into meiosis and the duration of meiosis is strikingly different between the sexes. Females: in the fetal ovary, a brief period of mitotic proliferation is followed by the entry of all cells into meiotic prophase. Several germ cells undergo apoptosis during this time, substantially reducing the pool of developing oocytes. Before birth, all surviving oocytes enter a period of extended meiotic arrest and, by the time of birth, all quiescent oocytes have become surrounded by somatic cells, forming primordial follicles. In a sexually mature woman, individual primordial follicles are stimulated to initiate growth throughout the reproductive lifespan. Typically, one fully grown oocyte is ovulated each month and several growing oocytes become atretic. This process continues until the cohort of oocytes is depleted and the woman enters menopause. Males: in the fetal testis, a brief period of mitotic proliferation is followed by an extended period of mitotic arrest. After birth, the male germ cells, or spermatogonia, resume mitotic proliferation and, with sexual maturity, cells are stimulated to undergo meiotic cell divisions. Because spermatogonia continue to proliferate mitotically and to send daughter cells into meiosis, sperm production is maintained throughout the lifetime of the male. Throughout the meiotic divisions, individual spermatocytes remain connected by cytoplasmic bridges. These connections are lost during the post-meiotic process of spermiogenesis, which involves tight packing of the chromatin, growth of the sperm tail and the sloughing of virtually all the cytoplasm into the residual bodies (depicted as empty cells).
As detailed in the following sections, errors in meiotic chromosome segregation occur frequently in the human female, especially during the first meiotic division. Typically, all such errors are referred to as non-disjunction; however, various mal-segregation mechanisms are possible. As illustrated in FIG. 2, failure to resolve chiasmata between homologous chromosomes at anaphase I results in ‘true’ non-disjunction, whereby both homologues segregate together. In addition, the premature resolution of chiasmata — or the failure to establish a chiasma between a pair of homologues — can result in the independent segregation of homologues at MI, which leads to an error if both segregate to the same pole of the MI spindle. Finally, an MI error can also involve the segregation of sister chromatids, rather than homologous chromosomes. For example, premature separation of sister chromatids (PSSC) at the first meiotic division can result in the segregation of a whole chromosome, and a single chromatid to each pole (FIG. 2). As detailed below, available evidence indicates that each type of MI error can occur in our species.

Typically, MII errors are thought to result from the failure of sister chromatid separation (FIG. 2). Other, more complicated, models have been proposed to explain the association between aberrant genetic recombination and some MII-derived trisomies; these are discussed in more detail in a later section.

Incidence of aneuploidy
The observed level of aneuploidy in humans varies enormously, depending on the developmental time point being examined (TABLE 1). Among newborns, ~0.3% of liveborns are aneuploid with the most common abnormalities being trisomy 21 and sex-chromosome trisomies (that is, 47,XXX, 47,XXY and 47,XYY chromosome constitutions). The incidence increases by an order of magnitude to ~4% among stillbirths (that is, fetal deaths occurring between ~20 weeks gestation and term), with the types of abnormality being similar to those identified among newborns. Among clinically recognized spontaneous abortions (that is, fetal deaths occurring between ~6–8 weeks and 20 weeks gestation), the incidence again increases tenfold, with ~35% of all such conceptions being trisomic or monosomic. Unlike stillbirths or livebirths, various different aneuploidies are represented among spontaneous abortions, including trisomies for nearly all chromosomes (TABLE 1). The most common specific abnormalities are sex-chromosome monosomy (45,X), accounting for nearly 10% of all spontaneous abortions, and trisomies 16, 21, and 22, which together constitute 50% of all trisomies identified in spontaneous abortions.

Results from these categories of conceptions — representing the three different classes of clinically recognized human pregnancy — allow us to estimate the minimal level of aneuploidy in humans. That is, using the above incidence figures and assuming that ~15% of recognized pregnancies spontaneously abort, 1–2% are stillborn and the rest are liveborn, we can estimate that at least 5% of all human conceptions are aneuploid.
This value, however, clearly underestimates the real incidence of aneuploidy in humans, because it does not include information from 'occult' pregnancies; that is, pregnancies that go undetected because they spontaneously abort during the first few weeks of gestation. Limited data on early pregnancies are available from studies of human pre-implantation embryos that were retrieved in association with human-assisted reproduction procedures, and these indicate that the real incidence of aneuploidy might be much higher than 5%. For example, Jamieson et al. (REF. 12) karyotyped 178 'spare' diploid embryos obtained from in vitro fertilization (IVF) or GAMETE INTRA-FALLOPIAN TRANSFER (GIFT) procedures, and found that nearly 20% were aneuploid. Consistent with this, fluorescence in situ hybridization (FISH) studies of IVF-derived pre-implantation embryos indicate possible rates of meiotic- and mitotic-derived aneuploidy of 20% or higher (for example, see REF. 10).

Furthermore, these results are consistent with cyto genetic analyses of human gametes. The FISH studies of human sperm during the past decade indicate chromosome-specific aneuploidy frequencies of ~0.1–0.2% (REF. 11); summing over the entire genome, this indicates that 2% or more of sperm might have missing or additional chromosomes. In oocytes, the value is much higher. Routine cytogenetic studies of over 1,000 oocytes obtained in IVF clinics have now been reported, with the largest studies indicating possible rates of aneuploidy of 20–25% (REF. 12). Furthermore, molecular cytogenetic analyses (for example, SPECTRAL KARYOTYPING) of human oocytes have yielded similarly high values (REF. 13). There has been considerable scepticism about the relevance of these observations to the in vivo situation — after all, IVF patients are unlikely to represent the general population of reproducing women, the oocytes come from ovaries that have been stimulated by exogenous hormones and, typically, the oocytes available for study are 'spares' that remained unfertilized after insemination. However, a recent study of 'control' oocytes indicates that the estimates might well be correct. That is, in FISH studies of 90 oocytes obtained from unstimulated ovaries, Volaric et al. (REF. 14) analysed M1 segregation of four chromosomes — 16, 18, 21 and the X — and identified ten abnormalities; extrapolating these results to the other chromosomes implies an overall rate of aneuploidy in excess of 20%.

Altogether, the combined results from clinically recognized pregnancies, pre-implantation embryos, and gametes indicate an extraordinary level of aneuploidy among human zygotes — at least 5% and possibly as high as 25%. So, for reasons that are as yet unclear, chromosome segregation in meiosis is surprisingly error-prone in our species.

**Origin of aneuploidy**

Over the past decade, DNA polymorphisms have been used to examine the origin of different aneuploid conditions. For monosomies, information is only available on the 45, X condition, as autosomal monosomies are apparently early embryonic lethals. Several studies of the origin of 45, X have now been conducted (for example, REF. 15), with an estimated 70–80% having a single maternally derived X chromosome; that is, it is the paternal X or Y that is lost, either in meiosis or in an early stage in embryogenesis. These results apply to both spontaneously aborted and liveborn 45, X conceptuses, which indicates that the parental source of the X chromosome does not influence the survival of the 45, X conceptus.

Unlike autosomal monosomies, most trisomic conditions are compatible with at least some fetal development and information is therefore available for several different trisomies (REF. 16–23). Results from studies of over 1,000 trisomic fetuses/liveborn individuals are summarized in Table 2, with two general principles emerging. First, there is remarkable variation among trisomies with regard to the parent and meiotic stage of origin of the additional chromosome. For example, paternal errors account for nearly 50% of 47, XXX and trisomy 2, but only 5–10% of most other trisomies, and they are rarely, if ever, the cause of trisomy 16. Similarly, the importance of M1 versus M2 errors varies among chromosomes. For example, among maternally derived trisomies most, if not all, cases of trisomy 16 seem to be due to M2 errors, but for sex-chromosome trisomies one-third of cases are associated with M1 errors, and for trisomy 18 most cases involve M2 non-disjunction. So, it seems likely that there are cis (chromosome-specific) effects that influence the patterns of non-disjunction.

However, overlying this chromosome-specific variation is at least one general theme. That is, maternal M1 errors predominate among almost all trisomies. This is perhaps not surprising, because the first division in females is initiated prenatally and is not completed until the time of ovulation (FIG. 1), and involves unique chromosome behaviours to segregate homologous chromosomes rather than sister chromatids. Indeed, the

### Table 1 | Incidence of aneuploidy during development

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>Sperm</th>
<th>Oocytes</th>
<th>Pre-implantation embryos</th>
<th>Pre-clinical abortions</th>
<th>Spontaneous abortions</th>
<th>Stillbirths</th>
<th>Livebirths</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1–2%</td>
<td>~20%</td>
<td>~20%</td>
<td>?</td>
<td>35%</td>
<td>4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>6–8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of aneuploidy</td>
<td>Various</td>
<td>Various</td>
<td>Various</td>
<td>?</td>
<td>45,X; +16; +21; +22</td>
<td>+13; +18; +21</td>
<td>XXX; XXY; XYY</td>
</tr>
<tr>
<td>Most common aneuploides</td>
<td>Various</td>
<td>Various</td>
<td>Various</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2**

<table>
<thead>
<tr>
<th>Chromosomes</th>
<th>Aneuploidies</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>+21; +22; +21</td>
</tr>
<tr>
<td>22</td>
<td>+21; +22; +21</td>
</tr>
<tr>
<td>16</td>
<td>+16; +13; +18; +13; +18; +21</td>
</tr>
<tr>
<td>18</td>
<td>+16; +13; +18; +13; +18; +21</td>
</tr>
<tr>
<td>21</td>
<td>+16; +13; +18; +13; +18; +21</td>
</tr>
<tr>
<td>X</td>
<td>45,X; +16; +13; +18; +13; +18; +21</td>
</tr>
</tbody>
</table>

**Notes**

SPECTRAL KARYOTYPING

Fluorescence in situ hybridization technique in which differentially labelled DNA probes to all chromosomes are used, making it possible to identify every chromosome in the complement in a single hybridization.

GAMETE INTRA-FALLOPIAN TRANSFER

(GIFT). Assisted reproduction technique in which oocytes and sperm are mixed and placed into the fallopian tubes, where fertilization might occur.

FISH

Fluorescence in situ hybridization technique in which differentially labelled DNA probes to all chromosomes are used, making it possible to identify every chromosome in the complement in a single hybridization.

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complexity of this division makes it clear that an understanding of the origin of human aneuploidy will require exhaustive analyses of the processes involved in starting, stopping and re-initiating MI in the human female.

**Recombination and non-disjunction**

Although there are now considerable data on the parent and meiotic stage of origin of different human aneuploidies, we know relatively little about the underlying non-disjunctural mechanisms. However, over the past few years the first molecular correlate of human aneuploidy, namely altered genetic recombination, has been identified and characterized.

**Lessons from model organisms.** Chiasmata, the physical manifestations of genetic recombination, have a crucial role in tethering homologous chromosomes during the first meiotic division. So, it is not surprising that, in all model organisms studied so far, disturbances in the recombination pathway are associated with abnormalities in chromosome segregation at MI. The most obvious effects involve mutations that reduce, or abolish, recombination: almost invariably, these mutations are associated with meiotic arrest, or with gross abnormalities in chromosome segregation or, at the very least, with increased levels of non-disjunction.

In addition to an effect of the number of recombination events, the location of the exchanges also seems to be important. For example, in meiotic studies that use yeast artificial chromosomes (YACs) or derivatives of budding yeast natural chromosomes, Dawson and co-workers observed that exchanges in different chromosomal intervals had differing abilities to properly segregate chromosomes. Specifically, chromosomes with a single distally located exchange were more likely to non-disjoin than those with more proximally positioned exchanges. By contrast, Sears et al. observed a high frequency of MI segregation errors (either PSSC or non-disjunction) in YACs in which pericentromeric exchange events had occurred. So, these results indicate that exchanges can either be too near or too far from the centromere, and that both situations impart a risk for non-disjunction.

**Table 2 | The origin of human trisomy**

<table>
<thead>
<tr>
<th>Trisomy</th>
<th>No. of cases</th>
<th>Paternal MI</th>
<th>Paternal MII</th>
<th>Maternal MI</th>
<th>Maternal MII</th>
<th>Post-zygotic mitosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>18</td>
<td>28</td>
<td>-</td>
<td>54</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
<td>-</td>
<td>15</td>
<td>76</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>104</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>143</td>
<td>-</td>
<td>-</td>
<td>33</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>21</td>
<td>642</td>
<td>3</td>
<td>5</td>
<td>65</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>22</td>
<td>38</td>
<td>3</td>
<td>-</td>
<td>94</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>XXY</td>
<td>142</td>
<td>46</td>
<td>-</td>
<td>38</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>XXX</td>
<td>50</td>
<td>-</td>
<td>6</td>
<td>60</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>

(MI, meiosis I; MII, meiosis II.)

(Adapted from REF. 6.)

In flies, also, there seems to be a link between the location of meiotic exchanges and the likelihood of non-disjunction. For example, in an analysis of spontaneous X-chromosome non-disjunction in Drosophila females, Koehler et al. observed an increase in BIVALENTS with a single distally located exchange in MII errors, and an increase in extremely proximal exchanges in MII errors. So, as in yeast, exchanges too close to or too far from the centromere seem to increase the risk of non-disjunction. The link between distal crossovers and mal-segregation has also been supported by mutational analyses. That is, several mutations that cause non-disjunction of non-exchange bivalents in Drosophila females (for example, nod (no distribution), Axs (Abnormal X segregation), Dub (Double or nothing) and ncd (non-derailed disjunction)) also increase non-disjunction of exchange chromosomes; in virtually all these cases, single crossovers are distally positioned (for example, REFs 28,29, and R. S. Hawley, personal communication), which indicates that such bivalents might be more susceptible to non-disjunction than are those with more proximally located chiasmata.

Altogether, the data from these and other model organisms (for example, REFs 30,31) indicate that absent or reduced levels of recombination, or suboptimally positioned recombinational events, increase the likelihood of non-disjunction. So, an obvious question is whether or not these effects also apply to humans.

**Human non-disjunction.** By using genetic mapping techniques to study the inheritance of DNA polymorphisms in trisomic conceptuses, it is possible to recapitulate the recombinational events that occurred in the trisomy-generating meioses. During the past decade, several laboratories have used this approach to study the relationship of recombination and human non-disjunction, by comparing the frequency and distribution of meiotic exchanges in trisomy-generating meioses with those from chromosomally normal meioses (for example, REFs 17,18). Several general principles have emerged from these analyses and are discussed in the following paragraphs.

Significant reductions in recombination are a feature of all MI-derived trisomies so far studied. This includes paternally derived cases of trisomy 21 and Klinefelter syndrome (47,XXY), and maternally derived cases of trisomies 15, 16, 18, 21, and sex-chromosome trisomies (47,XXX) and Klinefelter syndrome (47,XXY; FIG. 3). The magnitude of the effect is variable, the most pronounced reduction is observed for paternally derived XXYS, in which the genetic map of the XY pairing region is decreased four- to fivefold, from ~50 cM in normals to ~10–15 cM in trisomy-generating meioses. For others (for example, trisomy 15), the effect is subtler; nevertheless, it seems likely that diminished recombination is a correlate of all human trisomic conditions.

Conceptually, either of two processes might be responsible for the reduced map lengths of the different trisomic conditions. First, a proportion of cases might involve chromosomes that failed to recombine;
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