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Meiotic Behaviour of Chromosomes Involved in Structural Chromosomal Abnormalities Determined by Preimplantation Genetic Diagnosis

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1. Introduction

1.1 The origin of structural chromosomal abnormalities

Structural rearrangements can arise premeiotically, during meiosis or during postzygotic mitotic divisions. The main causes leading to chromosomal aberrations are illegitimate recombination due to chromosome misalignment and asymmetric pairing in meiosis and mitosis, defective DNA repair mechanisms and aberrant behaviour at the replication fork (Gardner and Sutherland, 2004).

Chromosome rearrangement breakpoints are not uniformly found throughout the genome (Lupski, 2004) and certain genomic regions, especially subtelomeric and pericentromeric regions (Shaw and Lupski, 2004) are more likely to be involved in a chromosomal rearrangement. This clustering of chromosomal rearrangements around hotspots creates considerable genomic instability (Shaw and Lupski, 2004). Such regions of genomic instability involve low copy repeats (LCRs).

LCRs act as substrates for non-allelic homologous recombination (NAHR), by erroneously facilitating different chromosome regions of the same or of different chromosomes to come together. Chromatin structure can also be involved in the generation of chromosomal aberrations, with areas which are less compacted being more accessible to double strand breaks and DNA damage (Shaw and Lupski, 2004).

There are also non-recurrent rearrangements, whose breakpoints are scattered around the genome and which often occur at unique sequences (Shaw and Lupski, 2004) but even in those cases the breakpoints often involve intronic motifs of smaller repetitive sequences which are usually involved in inducing susceptibility to double strand breaks (Toffolatti et al., 2002). Such rearrangements with unique breakpoints are created by non-homologous DNA end-joining (NHEJ), which is an error prone mechanism (Lieber et al., 2003) of repairing double strand breaks in multicellular organisms (Shaw and Lupski, 2005). NHEJ can result in genomic alterations by generating deletions or duplications through erroneously joining together the ends of double strand breaks from different chromosomes (Pfeiffer et al., 2004).

2. Structural chromosomal abnormalities and meiosis: Focussing on translocations

Structural chromosomal abnormalities involve chromosome breakage followed by the rejoining of chromosome parts into a different configuration. These structural rearrangements can be mainly categorised into translocations (reciprocal or robertsonian), insertions, inversions (pericentric or paracentric), deletions, duplications, ring chromosomes and isochromosomes. In the case of a structural rearrangement, each chromosome pair consists of a normal and a derivative chromosome.

Many structural abnormalities are associated with clinical characteristics, such as mental retardation, characteristic dysmorphic features and often other malformations and developmental delay. For example the cri-du-chat syndrome caused by a terminal deletion on chromosome 5, or the DiGeorge syndrome caused by a microdeletion on the long arm of chromosome 22. Duplication syndromes are also known to be associated with abnormal phenotypes, such as Charcot Marie Tooth disease Type I caused by a duplication in 17p12. Other structural aberrations such as inversions, translocations and ring chromosomes do not cause any abnormalities in balanced carriers when there is no gain or loss of genetic material, however these individuals are faced with reproductive problems.

The most common type of structural chromosomal abnormality in humans is translocation, most specifically reciprocal translocations that are seen in about 1 in 500 live births (Jacobs et al., 1992) and involve the exchange of genetic material between different chromosomes. In carriers of reciprocal translocations, each chromosome pair consists of a normal and a derivative chromosome, as shown in figure 1i. Carriers are phenotypically normal since there is no loss of genetic material unless the breakpoints disrupt important genes (Gardner and Sutherland, 2004). However they are faced with unfavourable meiotic segregation patterns when the chromosomes involved in the translocation pair up at prophase forming a quadrivalent (also known as pachytene) as shown in figure 1ii. The chromosomal status of the gametes produced by a carrier of a reciprocal translocation depends on the segregation pattern that took place in meiosis. As shown in figure 1iii, the chromosomes in the quadrivalent can segregate in a 2:2 mode, whereby each daughter cell will receive 2 chromosomes, in a 3:1 segregation mode, whereby one daughter cell receives 3 chromosomes and the other daughter cell receives just one or there might be complete non disjunction in a 4:0 mode of segregation.

Robertsonian translocations have a prevalence of 1 in 1000 and involve the centric fusion of two acrocentric chromosomes (in 75% of the cases chromosomes 13 and 14 are involved) and the loss of the short arms (Garner and Sutherland, 2004). As a result a derivative chromosome is formed as shown in figure 2i, which comprises of the two long arms of the chromosomes involved in the translocation and at meiosis the chromosomes pair up as shown in figure 2ii. The total chromosome number of carriers of Robertsonian translocations is 45. Although all acrocentric chromosomes have been found to be involved in Robertsonian translocations, rob(13q14q) and rob(14q21q) constitute around 85% of all Robertsonian translocations (Therman et al., 1989).

Balanced carriers of a structural chromosomal rearrangement are usually phenotypically normal since there is no loss of genetic material, unless the breakpoints are within important genes. They are however faced with unfavourable meiotic segregation patterns when the normal and derivative chromosome(s) involved in the abnormality pair up at meiosis I. Carriers therefore are at a high risk of producing unbalanced gametes and hence genetically

abnormal embryos that are associated with recurrent miscarriage, infertility as well as unbalanced offspring (Gardner and Surtherland, 2004).

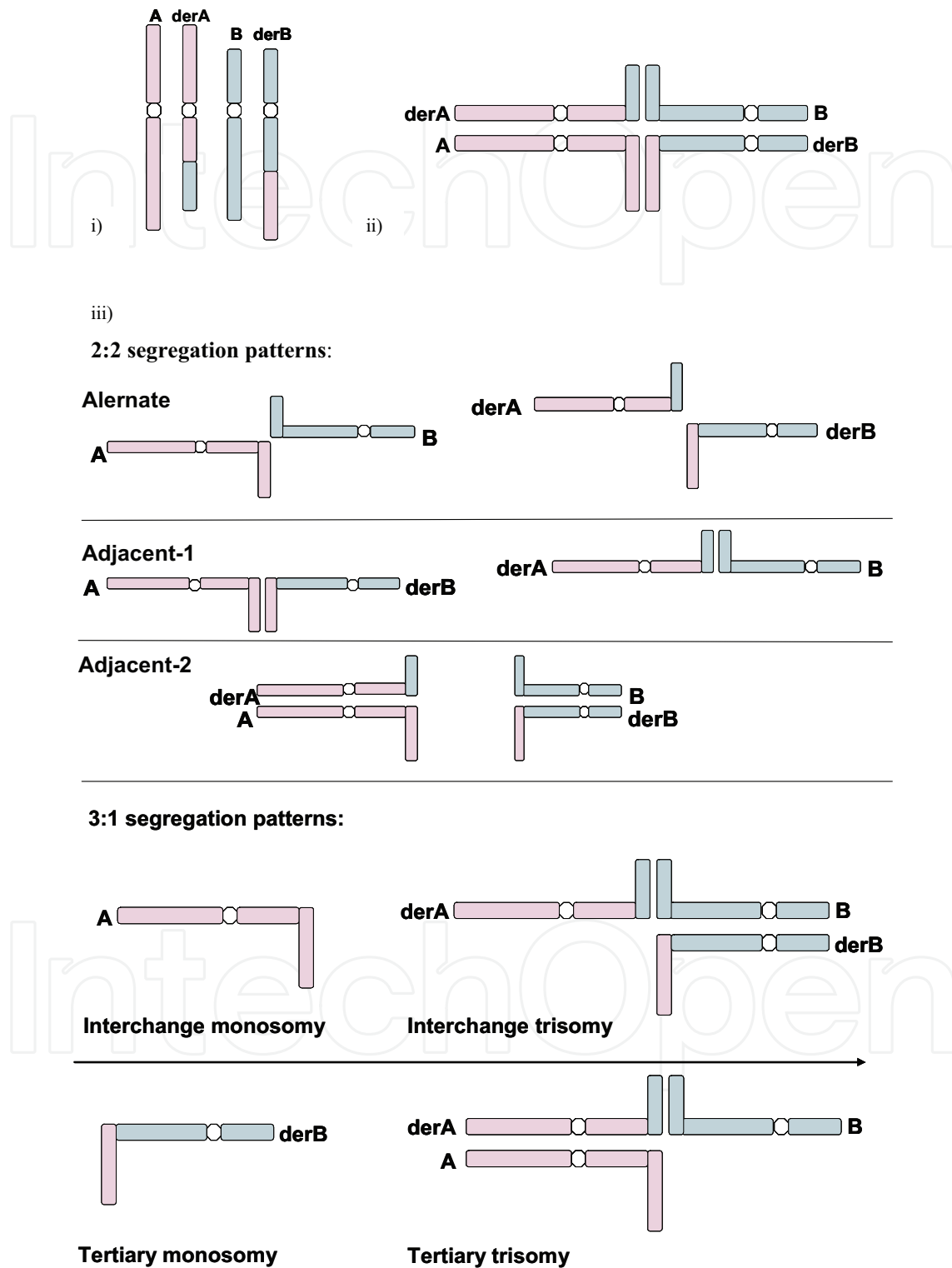


Fig. 1. i) Chromosomes in a cell of a carrier of a reciprocal translocation, ii) Pachytene configuration of the quadrivalent cross during meiosis in a carrier of a reciprocal translocation, iii) possible segregation modes seen at meiosis (4:0 segregants not shown here).

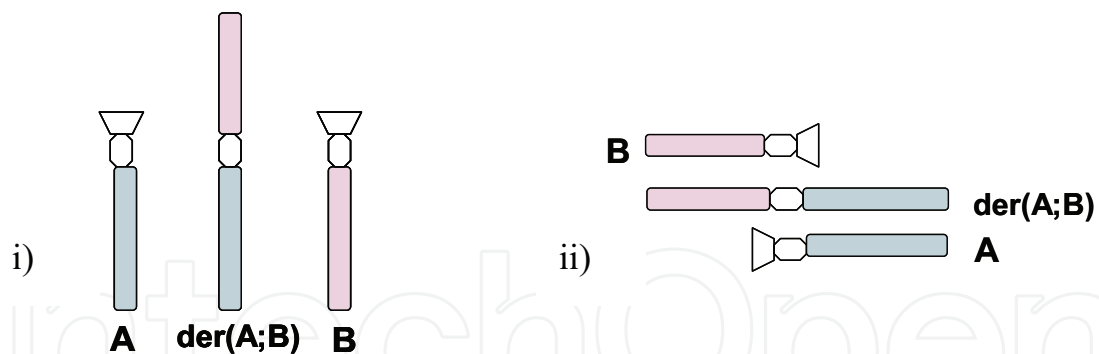


Fig. 2. i) Carrier of a Robertsonian translocation, ii) Pairing up of chromosomes, forming a trivalent during meiosis in a carrier of a Robertsonian translocation.

3. Preimplantation genetic diagnosis (PGD)

Preimplantation genetic diagnosis provides an alternative to prenatal diagnosis for couples at risk of having a child with a specific genetic or chromosomal abnormality. It involves the removal and testing of material from the oocyte or the developing embryo. First and second polar bodies for instance can be analysed in order to determine the genetic status of the oocyte (Verlinsky et al., 1990) or material can be biopsied from embryos generated through *in vitro* fertilization (IVF). In the case of embryo biopsy, one or two single blastomeres can be removed during the cleavage stage or material can be biopsied from the trophectoderm at the blastocyst stage (Dokras et al., 1990).

The biopsied material is then analysed by the polymerase chain reaction (PCR) for single gene disorders (Findlay et al., 1996) or fluorescent in situ hybridisation (FISH) for structural or numerical chromosomal abnormalities (Griffin et al., 1991, Coonen et al., 1998, Conn et al., 1998) whereas recently array comparative genomic hybridization (aCGH) has also been introduced (Alfarawati *et al.*, 2011). In this way unaffected embryos are selected and transferred to the uterus, aiming to establish an unaffected pregnancy.

Couples that are at risk of having a child with a specific single gene or chromosomal abnormality may opt to have PGD in order to avoid an affected pregnancy and to avoid having prenatal diagnosis which is associated with a 1% risk of miscarriage; moreover their decision to have PGD is often linked to the couple's view on pregnancy termination. At the same time other couples that seek PGD have difficulty achieving a pregnancy due to reasons of infertility or subfertility or are victims of repeated pregnancy loss.

4. PGD for structural chromosomal abnormalities: strategies and outcome

PGD provides a unique opportunity to investigate the meiotic behaviour of the chromosomes involved in a structural rearrangement. Until recently structural chromosomal abnormalities were tested for at PGD with FISH, using probes for the chromosomes involved in the translocation.

The main FISH probe strategies used in PGD for reciprocal translocations, involve the use of probes flanking the breakpoint in one of the chromosomes, in conjunction with another probe on the other chromosome. In this way on one chromosome one probe distal to the breakpoint (i.e. a subtelomeric probe specific to the segment that is translocated) and one probe proximal to the breakpoint (i.e. a centromeric probe of any other probe that will be

used for the enumeration of that chromosome) are used, together with another probe on the other chromosome, which can either be distal or proximal to the breakpoint on the second chromosome (Scriven et al.1998). So the main two strategies involve using two centromeric and one subtelomeric probe or one centromeric and two subtelomeric probes, where the subtelomeric probes will always be on the segments that are translocated. The aim of these probe strategies is to be able to detect all possible segregation patterns, so they need to be informative for both normal and both derivative chromosomes.

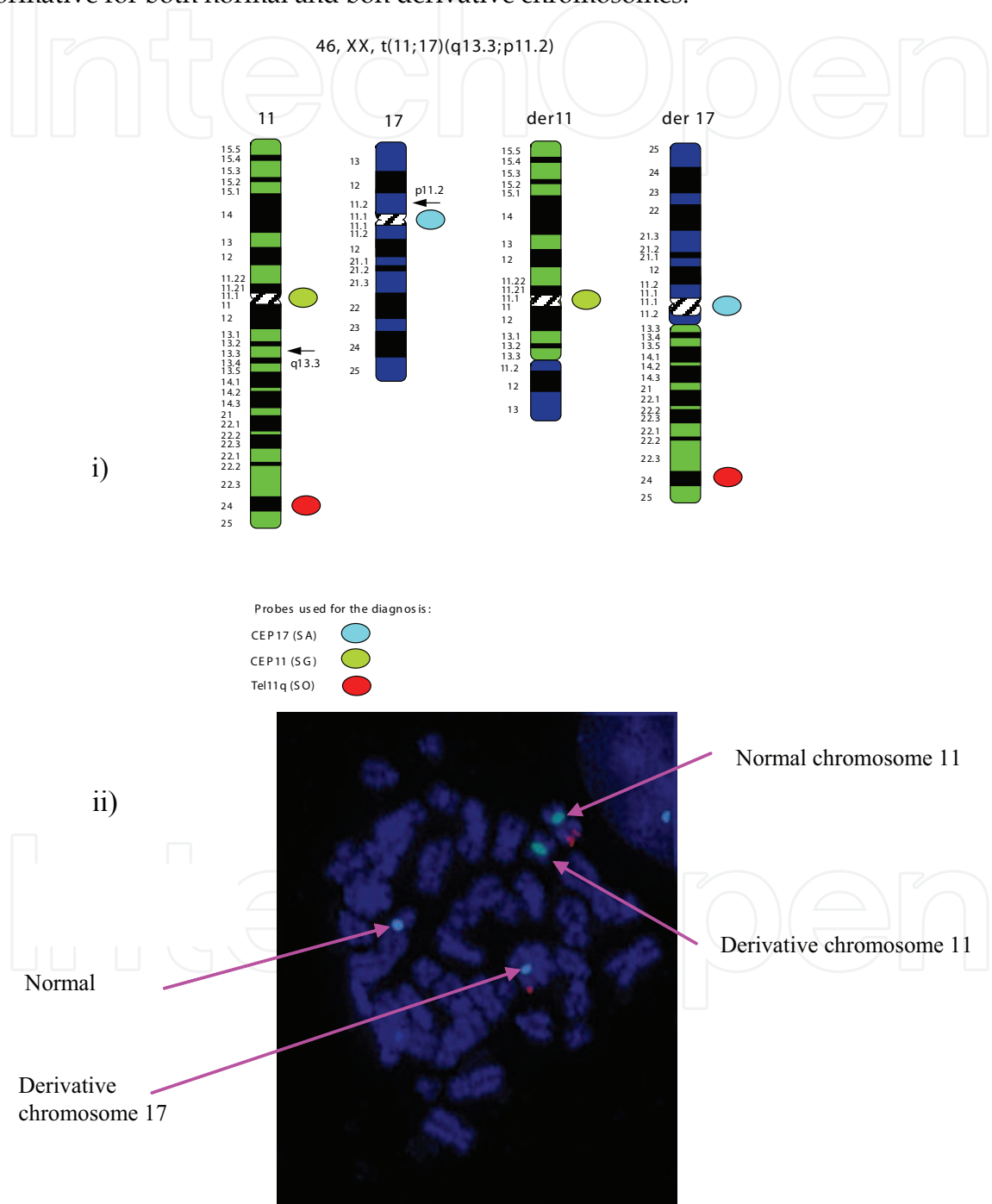


Fig. 3. i) Probe strategy for PGD for translocation 46, XX, t(11;17)(q13.3;p11.2), ii) Metaphase nucleus of the carrier of 46, XX, t(11;17)(q13.3;p11.2) after FISH with the probes for centromere of 11 and 17 and the telomere of 11q.

The probe strategy chosen for PGD for each structural abnormality case is tested prior to clinical application on control lymphocyte slides from the parents of the couple seeking PGD. For example figure 3 below shows an example of a translocation between chromosomes 11 and 17, carried by the female partner: 46, XX, t(11;17)(q13.3;p11.2).

The centromeric probe for chromosome 11 in spectrum green and the centromeric probe for chromosome 17 in spectrum aqua were used together with the subtelomeric probe for 11q in spectrum orange. The probes were tested on parental lymphocytes and in figure 3ii it is clear that the probes chosen pick up the abnormality and allow us to distinguish between the normal and derivative chromosomes on the metaphase spread.

Segregation mode in the gamete		Chromosomes present in the gamete of the carrier parent	FISH signals seen in the embryo	Outcome
2:2 segregation modes	Alternate	11 and 17	2xCEP11, 2xTel11p, 2xCEP17	Balanced
		Der11 and der17	2xCEP11, 2xTel11p, 2xCEP17	Balanced
	Adjacent-1	11 and der17	2xCEP11, 3xTel11p, 2xCEP17	Partial trisomy 11, partial monosomy 17
		Der11 and 17	2xCEP11, 1xTel11p, 2xCEP17	Partial monosomy 11, partial trisomy 17
	Adjacent-2	11 and der11	3xCEP11, 2xTel11p, 1xCEP17	Partial trisomy 11, partial monosomy 17
		17 and der17	1xCEP11, 2xTel11p, 3xCEP17	Partial monosomy 11, partial trisomy 17
3:1 segregation modes	3 →	11, der11 and 17	3xCEP11, 2xTel11p, 2xCEP17	Partial trisomy 11 and 17
	1 →	Der17	1xCEP11, 2xTel11p, 2xCEP17	Partial monosomy 11 partial monosomy 17
	3 →	11, der11, der17	3xCEP11, 3xTel11p, 2xCEP17	Trisomy 11
	1 →	17	1xCEP11, 1xTel11p, 2xCEP17	Monosomy 11
	3 →	Der11, 17, der17	2xCEP11, 2xTel11p, 3xCEP17	Trisomy 17
	1 →	11	2xCEP11, 2xTel11p, 1xCEP17	Monosomy 17
	3 →	11, 17, der17	2xCEP11, 3xTel11p, 3xCEP17	Partial trisomy 11, partial trisomy 17
	1 →	Der11	2xCEP11, 1xTel11p, 1xCEP17	Partial monosomy 11, partial monosomy 17

Table 1. Possible segregation patterns for the carrier of 46, XX, t(11;17)(q13.3;p11.2).

Once it has been established that a particular probe strategy is informative for the translocation chromosomes, the conditions of the FISH protocols are optimised and the couple can commence their stimulation to undergo their IVF cycle. The biopsied samples are then tested at PGD using the optimised protocol and embryos are diagnosed as balanced or unbalanced. Due to the fact that in the majority of cases of the nuclei of the biopsied cells during cleavage stage biopsy are in the interphase stage, it is not possible to distinguish between balanced embryos that will be balanced carriers of the structural aberration and normal embryos (Munne, 2005). By considering the FISH signals for each embryo it is then possible to determine the segregation pattern that took place in the gamete of the carrier parent, as shown in table 1, although crossing over events between the centromere and the breakpoint can complicate the situation further and affect the interpretation of the results (Hulten, 2011). Only biopsied samples with two signals for each probe used will be balanced as two signals indicate diploid status for the loci tested. Any other combination of signals is unbalanced for the translocation chromosomes due to chromosome malsegregation at meiosis.

Figure 4 shows another example of a reciprocal translocation between chromosomes 10 and 11, 46,XY,t(11;19)(q12.3;q13.1), the probe strategy used at PGD (figure 4ii) and images from single blastomeres that were biopsied on day 3 from cleavage stage embryos (figure 4ii).

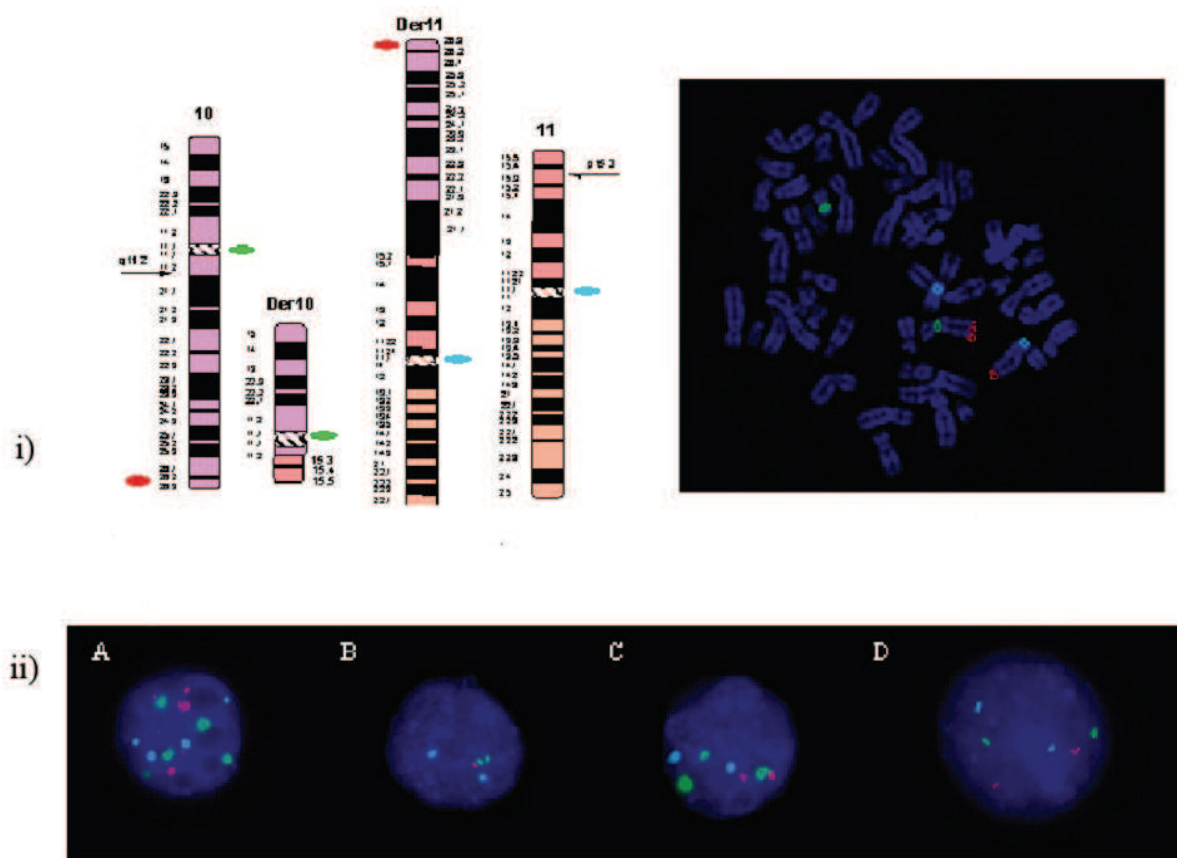


Fig. 4. Probe strategy for translocation 46,XY,t(11;19)(q12.3;q13.1) and FISH on the lymphocytes of the carrier parent and ii) images from the biopsied single cells from cleavage stage embryos at PGD. Only nucleus D is balanced for the translocation, whereas nucleus A is unbalanced and polyploid, nucleus B shows partial monosomy 10q and nucleus C shows partial trisomy 10.

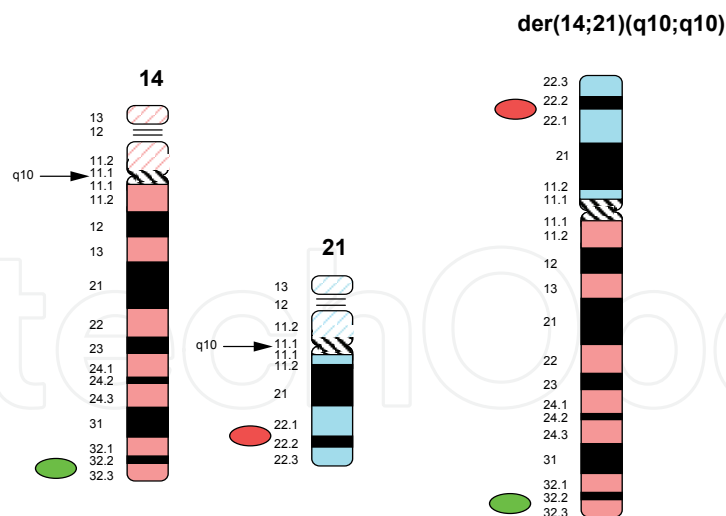


Fig. 5. Probe strategy for PGD for the Robertsonian translocation between chromosomes 14 and 21.

For Robertsonian translocations, the expected segregation patterns can also be worked out as shown in table 2. The resulting gametes are either nullisomic or disomic for either of the chromosomes involved in the translocation, resulting in monosomic or trisomic embryos (Scriven et al., 2001).

Segregation of the translocation chromosomes present in the gamete of the carrier parent	FISH signals seen in the embryo	Outcome
14, 21	2xTel14q, 2xLSI21	Normal
Der14/21	2xTel14q, 2xLSI21	Balanced
14, der14/21	3xTel14q, 2xLSI21	Trisomy 14
21	1xTel14q, 2xLSI21	Monosomy 14
14	2xTel14q, 1xLSI21	Monosomy 21
21, der14/21	3xTel14q, 2xLSI21	Trisomy 21

Table 2. Different possible segregation patterns at meiosis for the carrier of the Robertsonian translocation between chromosomes 14 and 21.

Since the first clinical PGD cases for carriers of translocations and structural abnormalities FISH was the method of choice for embryo testing in order to select those embryos that were balanced. A disadvantage of FISH however is that it only gives information for the chromosomes for which probes were used. Additional probes can be included in a subsequent round of hybridization for other chromosomes in order to test for the main chromosomes at risk of being aneuploid. Recently the application of aCGH has been reported in PGD for carriers of reciprocal or Robertsonian translocations as well as inversions (Alfarawati et al., 2011.) which allows the complete enumeration of all chromosome sets in a sample.

Results from PGD cycles for structural abnormalities using array CGH, have revealed aneuploidies for chromosomes other than those involved in the translocation, which could account for the poorer PGD outcome for women of advanced maternal age. Array CGH

can also be used for the detection of other structural abnormalities, provided that the smallest translocated segment is detectable by the resolution of the array platform used. Alternatively when the segments are small FISH can be used. In the case of other structural aberrations, such as inversions, insertions, duplications and deletions, FISH involves the use probes that are included in the segment that is inverted, inserted, duplicated or deleted and one or two other probes on either side (proximally and distally) of that segment in order to be able to detect all different meiotic outcome combinations. Figure 6 below shows examples of strategies used in PGD for an inversion and an intrachromosomal insertion.

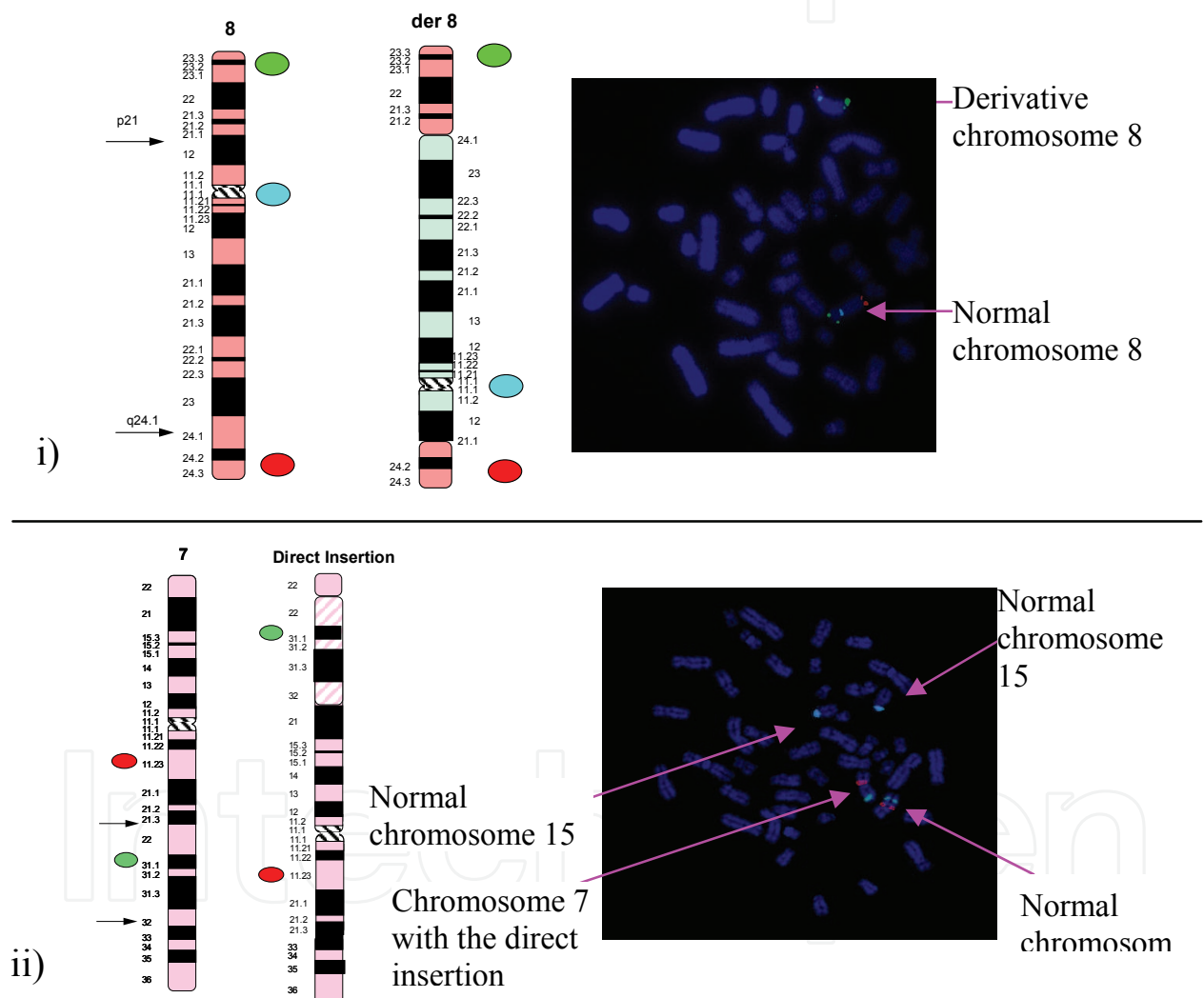


Fig. 6. i) Probe strategy for PGD for an intrachromosomal inversion, 46, XX, inv(8)(p21;q24.1) and FISH on the lymphocytes of the carrier parent, ii) probe strategy for PGD for an intrachromosomal insertion, 46, XY, dir ins (7)(p22q32q31.1) FISH on the lymphocytes of the carrier parent. An extra probe was used in this protocol for chromosome 15 to check for ploidy.

5. Evidence obtained from PGD treatment cycles relevant to the meiotic segregation of chromosomes involved in structural abnormalities

What is unique about studying preimplantation embryos is that all the products from all different modes of segregation from a structural aberration can be seen, which are not viable at later stages of development. Moreover in cases where the structural aberration involves a small segment, unbalanced forms are more likely to be tolerated until later stages of development.

For carriers of reciprocal translocations overall alternate segregation is reported as being the most common segregation pattern (Scriven et al., 2000), followed by adjacent-1 (25%), 3:1 (15%), adjacent-2 (10%) and 4:0 (2%), where most 3:1 segregations came from female carriers (Ogilvie and Scriven, 2002).

However each translocation is unique in terms of the position of the breakpoints and in terms of the length of the translocated segments. As a result different translocations will form different quadrivalents at meiosis I and in each case the configuration of the quadrivalent cross will be different. The quadrivalent configuration partly influences which spindle fibre gets attached to which centromere thus determining the way in which the translocation chromosomes will segregate (Gardner and Sutherland, 2004). The number and the position of chiasmata is also important (Scriven et al., 1998). Each translocation therefore behaves differently at meiosis (Conn et al., 1999) and hence for each translocation the frequency of each mode of segregation will be different and a particular segregation mode might occur at a higher frequency than others (Jalbert et al., 1980). In this way particular translocations will have a predisposition towards a specific mode of segregation. In order to confirm the meiotic segregation patterns seen on PGD, full follow up analysis is required on the untransferred embryos, which allows us to study the chromosomal ploidy status of those embryos.

For Robertsonian translocations sperm studies have shown that the most common segregation pattern in carriers of Robertsonian translocations is alternate segregation that results in normal or balanced gametes (Ogur et al., 2006), whereas an interchromosomal effect was also seen, as aneuploidy for other chromosomes that were not involved in the translocation were seen. This interchromosomal effect, referring to the translocation chromosomes affecting the recombination and segregation of other chromosomes was also suggested for reciprocal translocations by Estop et al. (2000), but it was not detected in later studies (Oliver-Bonet et al., 2004).

Follow up analysis on untransferred embryos has revealed that cleavage stage embryos show a high level of mosaicism, a situation whereby more than one different cell lines is present in the embryo (Munne et al., 1993, Harper et al., 1995, Delhanty and Handyside, 1995). An extreme form of mosaicism is chaoticism, whereby almost every nucleus present in the embryo will have a different chromosome constitution. Mosaicism has been reported not only in arrested or fragmented embryos but also in embryos of good quality (Delhanty et al., 1997) and has been observed in the embryos of both young and older women (Munne et al., 1995). Different factors are thought to be involved in the formation of mosaic embryos, such as the ovarian stimulation protocol used or the embryo culture conditions, as well as the fact that cell-cycle checkpoints are not fully functional at those early stages of preimplantation embryo development (Delhanty and Handyside, 1995).

A high level of mosaicism has been reported in embryos from reciprocal translocation carriers (Simopoulou et al., 2003), Robertsonian translocation carriers (Conn et al., 1998) as

well as other forms of structural abnormalities such as intrachromosomal insertions (Xanthopoulou et al., 2010). As far as the embryos from translocation carriers are concerned, Iwarsson et al. (2000) reported that the chromosomes involved in the translocation show an even higher degree of mosaicism when compared to control chromosomes. This suggests that the translocation chromosomes not only have a high risk of meiotic malsegregation leading to embryos with unbalanced genomes, but also have a predisposition to segregate unfavourably during the following postzygotic divisions and produce highly mosaic, chaotic embryos (Simopoulou et al., 2003). As a result errors in chromosome segregation during subsequent mitotic divisions can complicate the situation further (Conn et al., 1999). The chaotic nature of the chromosomes in the biopsied samples therefore might therefore produce signals that are not characteristic of a particular segregation pattern. Furthermore Delhanty et al. (1997) observed that there is a patient-related predisposition towards the production of chaotic embryos.

In addition to meiotic malsegregation and postzygotic errors resulting in mosaicism, recently testing embryos at PGD using aCGH has revealed a high level of abnormalities affecting other chromosomes apart from those involved in the structural aberration. More specifically Alfarawati et al. (2011) report that 28.9% of the embryos that were balanced for the aberration chromosomes had an aneuploidy for other chromosomes. Follow up analysis on the untransferred embryos can reveal whether there aneuploidies for other chromosomes are meiotic in origin. Figure 7 below shows results from aCGH PGD cases for reciprocal and Robertsonian translocations. In each case the karyotype of the carrier parent is shown together with the abnormalities detected at PGD. Figure 7i shows a normal, euploid profile, whereas the rest of the images show different abnormalities present, which are highlighted.

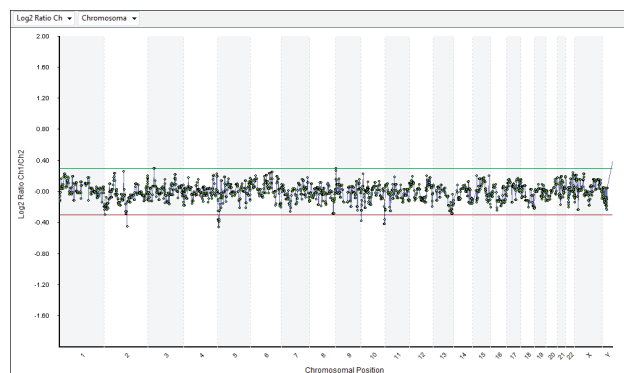


Fig. 7i. Normal euploid aCGH profile of a male embryo

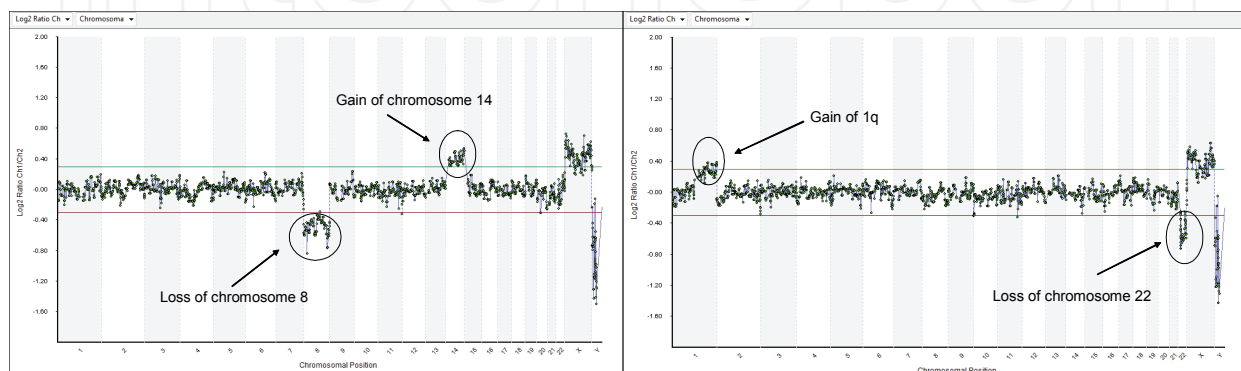


Fig. 7ii. aCGH profiles from cleavage stage embryos from 45, XX, der(13;14)(q10;q10)

The image on the left shows a female embryo with a gain of chromosome 14 as a result of the translocation, but also a loss of chromosome 8. The image on the right shows a female embryo that is balanced for the translocation chromosomes but has a gain of 1q and a loss of chromosome 22.

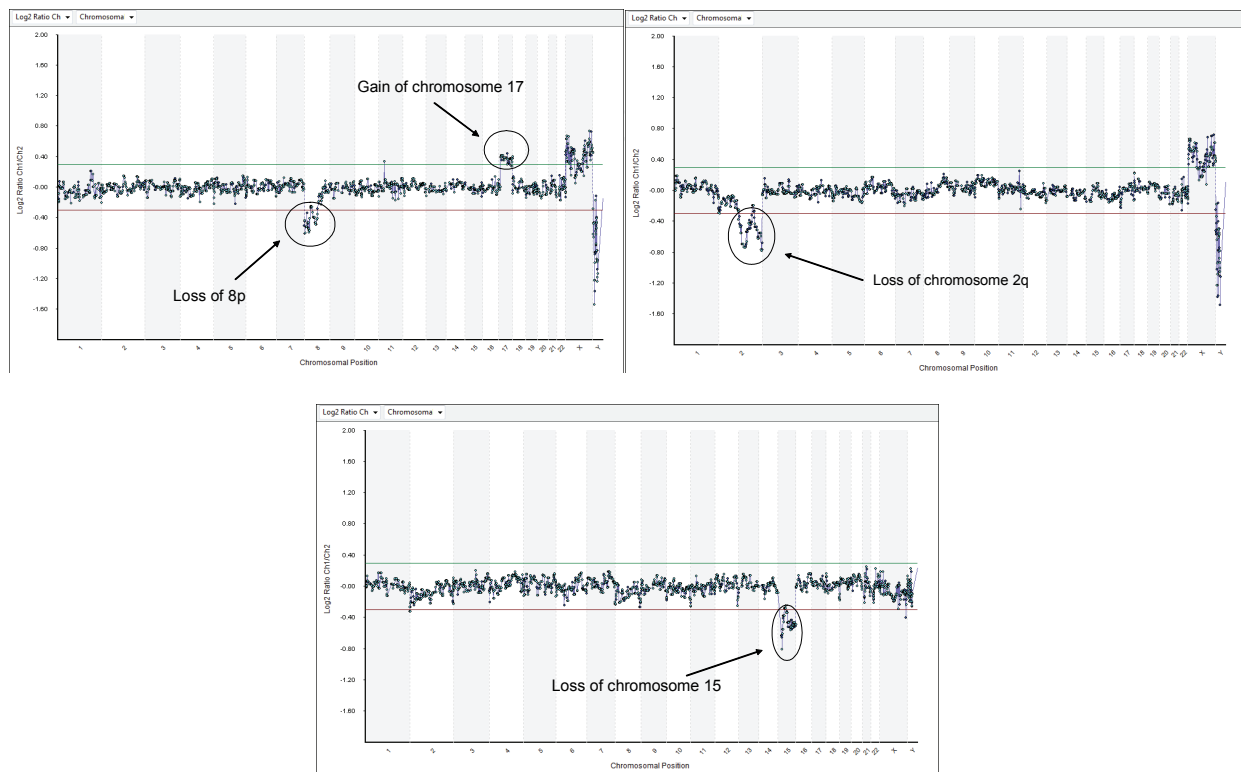


Fig. 7iii. aCGH profiles from trophectoderm after blastocyst stage biopsy for the reciprocal translocation 46, XX, t(8;17) (q21.1;p11.2).

The image on the top left shows a female embryo with a loss of 8p and a gain of chromosome 17 as a result of the translocation, whereas the image on the top right shows a female embryo that was balanced for the translocation chromosomes but had a loss of 2q. The image in the middle shows a male embryo that was balanced for the translocation chromosomes but had loss of chromosome 15.

As a result, apart from unfavourable meiotic segregation, mosaicism and postzygotic errors contribute to the reproductive challenges faces by couples carrying structural abnormalities. Array CGH therefore might be a more appropriate method for PGD for those patients as it allows screening of all chromosomes and therefore aids in choosing those embryos that are viable.

6. Other factors affecting chromosome segregation at meiosis in carriers of reciprocal translocations

6.1 Sex of the carrier parent and segregation mode at meiosis

For couples treated with PGD for reciprocal translocations the overall number of balanced embryos does not seem to be different between male and female carriers (Xanthopoulou et al., 2011). Munne et al. (2000) reported that the meiotic segregation patterns found at female

carriers of Robertsonian translocations were different from those described in male carriers, with females showing a higher level of unbalanced gametes, however this observation was not confirmed by later studies (Munne, 2005). However for one family with an intrachromosomal insertion there seemed to be an effect of the sex of the carrier parent on the mode of segregation (Xanthopoulou et al., 2010).

Chromosomal insertions are rare forms of structural chromosomal abnormalities, that involve breakpoints on the same chromosome and they can be interchromosomal or intrachromosomal depending on whether the material that is broken off from one chromosome is inserted at another site within the same chromosome or is inserted on another chromosome. Moreover insertions can be direct or inverted depending on whether the orientation of the inserted segment is the same or changes with relation to the centromere. An example of an intrachromosomal insertion and the way that chromosomes can segregate at meiosis is shown in figure 8.

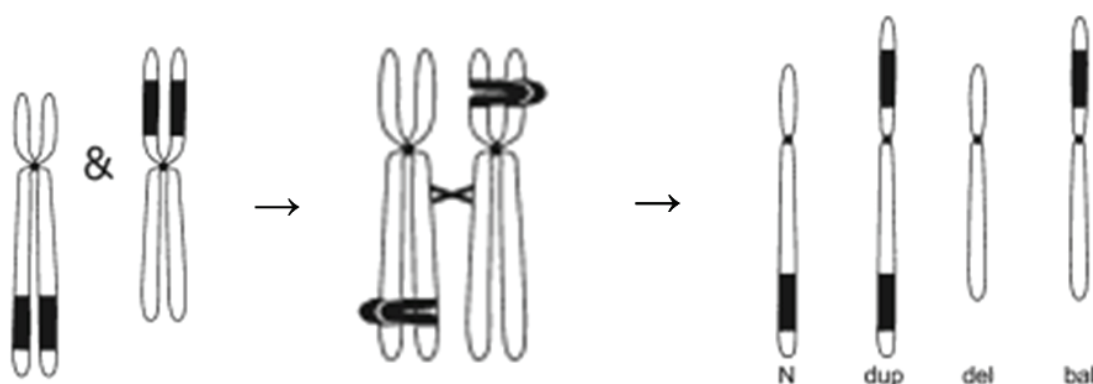


Fig. 8. Chromosome segregation in a carrier of an intrachromosomal insertion at meiosis. Key: N: normal, dupl: duplication of the inserted segment, del: deletion of the inserted segment, bal ins: balanced chromosome that carries the insertion

Balanced carriers of direct intrachromosomal insertions are phenotypically normal but are at risk of unbalanced meiotic segregation due to crossing over. At PGD it is possible to study all possible segregation modes, which might not be viable in later stages of development.

Full follow up analysis on 22 untransferred embryos from a female carrier and 19 embryos from a male carrier of the same intrachromosomal insertion, indicated that the female carrier produced far more balanced embryos (45% versus 16%, Xanthopoulou et al., 2010).

6.2 Maternal age

Advanced maternal age has long been associated with an increase in the rate of aneuploidy, for example trisomy 21, whereas preimplantation embryos from women of advanced maternal age referred for Preimplantation Genetic Screening (PGS) also seem to have an increased level of meiotic errors (Mantzouratou et al., 2007).

Ogilvie and Scriven (2002) reported a higher percentage of 3:1 segregation modes in female carriers of reciprocal translocations, resembling aneuploidy non-disjunction, but no maternal age associations were made. Advanced maternal age is not considered to increase levels of aneuploidy for the chromosomes involved in a structural abnormality in embryos.

However women of advanced maternal age referred for PGD for reciprocal translocations have reduced chances of achieving a pregnancy (Xanthopoulou et al., 2010) due to the high level of meiotic aneuploidy for chromosomes other than the ones involved in the aberration as well as due to malsegregation of the aberration chromosomes.

7. Conclusion

PGD provides a unique opportunity to study the behaviour of chromosomes involved in structural abnormalities during meiosis. At those early stages of human preimplantation development all the different modes of meiotic segregation which might not be viable at later stages of development can be seen. As described above carriers of structural chromosomal abnormalities face a high risk of malsegregation at meiosis.

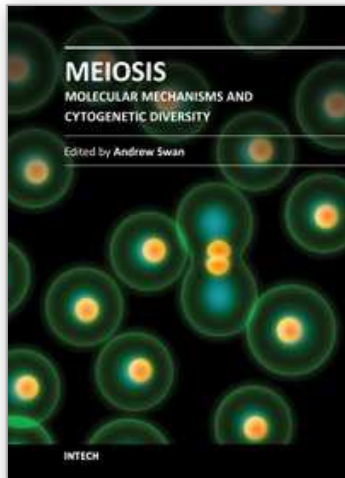
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Meiosis, the process of forming gametes in preparation for sexual reproduction, has long been a focus of intense study. Meiosis has been studied at the cytological, genetic, molecular and cellular levels. Studies in model systems have revealed common underlying mechanisms while in parallel, studies in diverse organisms have revealed the incredible variation in meiotic mechanisms. This book brings together many of the diverse strands of investigation into this fascinating and challenging field of biology.

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