Chapter 7

Chromosomal Abnormalities in Preimplantation Embryos and Detection Strategies in PGD and PGS

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Additional information is available at the end of the chapter

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Abstract

Structural and numerical chromosomal abnormalities are common in early developing embryos, and these abnormalities may cause spontaneous abortions and implantation failure. The reproductive risk of carriers with structural chromosomal abnormalities depends on the breakpoint positions, the segregation patterns and the sex of the carrier. These carriers have a lower chance of producing normal or balanced gametes due to abnormal segregation of chromosomes at meiosis leading to repeated spontaneous abortions and infertility. Preimplantation genetic diagnosis (PGD) is offered to couples who have already been diagnosed with a single gene disorder or a chromosome imbalance to select an embryo free from the mutation or an embryo with a balanced karyotype prior to implantation and pregnancy. PGS is applied to patients experiencing repeated implantation failures or spontaneous abortions with normal karyotypes. Translocations are the most common type of structural chromosome rearrangement. Both reciprocal and Robertsonian translocations are phenotypically normal. PGD for translocations was initially performed by fluorescence in situ hybridization (FISH) at cleavage stage embryos. However, with the recent developments, many centers have opted for the use of array comparative genomic hybridization (aCGH), single-nucleotide polymorphism (SNP) arrays and next generation sequencing (NGS).

Keywords: chromosomal abnormalities, PGD, FISH, aCGH

1. Introduction

Preimplantation embryo development follows a series of critical events. These events start at gametogenesis and lasts until parturition. Gametogenesis is a process of gamete formation. Male and female gametes are derived from primordial germ cells (PGCs) by the processes of spermatogenesis and oogenesis, respectively. PGCs have unique properties of

gene expression, epigenetics, morphology and behavior. Once the PGCs undergo mitosis, spermatogenesis and oogenesis progress differently. In spermatogenesis, spermatogonia undergo mitosis starting at puberty until death, and each primary spermatocyte produces four spermatids at the end of meiosis. In oogenesis, PGCs differentiate into oogenia, and they enter meiosis and arrest until puberty. Unlike meiosis II in spermatogenesis, secondary oocyte and first polar body do not undergo meiosis II until fertilization. After fertilization, meiosis II starts and each oogenia produce a single viable oocyte [1].

At fertilization, the oocyte completes meiosis, and the fertilized oocyte is called the zygote. Oocyte and sperm nuclei fuse resulting in syngamy. The zygote undergoes series of cleavage divisions, forming 2-cell, 4-cell, 8-cell, morula and blastocyst stages [2]. During cleavage stage divisions programming of maternal and paternal chromosomes takes place to create the embryonic genome (embryonic genome activation, EGA) and to start the preimplantation embryo development. If the EGA fails, the development does not continue because of the inability of the embryo to have cellular functions [3]. This activation is initiated by degradation of maternal nucleic acids, specific RNAs stored in oocytes, proteins and other macromolecules [4]. Upon EGA, which starts at the 2-cell stage in mouse and 4–8-cell stage in human [5], remarkable reprogramming of expression occurs in the preimplantation embryo. These reprogramming events are controlled by DNA methylation, histone acetylation, transcription, translation and miRNA regulation [6].

Both conception and embryonic developments during pregnancy are vulnerable processes since a large number of the conceptions are chromosomally abnormal. Chromosomal imbalances, gains or losses of segments/whole chromosomes, are common in human, and they are observed in 1/380 live births [7]. Chromosomal imbalances have been observed in preimplantation embryos mostly in the form of aneuploidies and translocations, and they may lead to embryo death or development of an affected embryo [8, 9]. The incidence of chromosomally abnormal embryos increases vividly with advanced maternal age [10–12]. The main causes of spontaneous abortions and repeated implantation failure are these numerical and structural chromosomal abnormalities [13–17]. Therefore, in the last decades, a great focus has been put on detecting these chromosomal aberrations in preimplantation embryos. Preimplantation genetic diagnosis has been applied to patients with known structural chromosomal abnormalities as well as single gene disorders, whereas preimplantation genetic screening has aimed to detect aneuploid embryos and lower the risk of implantation failures and spontaneous abortions following in assisted reproductive technology treatments [18–20].

In this chapter, the applications of preimplantation genetic diagnosis for translocations and preimplantation genetic screening for aneuploidy testing will be discussed. Translocations are the most common type of rearrangements that we come across in fertility clinics. Different techniques that are being used currently will be thoroughly evaluated. Finally, different aspects of preimplantation genetic screening will be evaluated.

2. Structural chromosomal abnormalities in human embryos

Majority of conceptus with chromosomal abnormality aborts spontaneously with <1% of abnormal conceptus resulting in term pregnancy. Chromosomal abnormalities can arise at

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three stages during human development, gametogenesis, fertilization and embryogenesis. Analysis of chromosomes in human gametes and embryos has become available with the development of artificial reproductive (ART) technologies developed to treat infertility.

Balanced structural chromosome rearrangements are common in human. Approximately 1/500 to 1/1000 live births carry a balanced translocation [21]. Translocations are formed due to rearrangements of nonhomologous chromosome segments. They can be caused by abnormal DNA repair, chromosome breakage, centric fission followed by malsegregation of that chromosome or through the formation of isochromosomes or terminal deletion accompanied by a duplication of the rest of the chromosome [22]. Translocations are grouped in two categories: reciprocal, the most common form, and Robertsonian. Reciprocal translocations occur due to an exchange of two ends of nonhomologous chromosomes. Robertsonian translocations involve rearrangement of two acrocentric chromosomes (chromosomes 13, 14, 15, 21 and 22) with the loss of the short arms occurring in 1/900 live births [7]. The most common Robertsonian translocation involves chromosomes 13 and 14 [23].

Although the carriers of both reciprocal and Robertsonian translocations are phenotypically normal, the reproductive risk of balanced carriers varies depending on the chromosomes involved, breakpoint positions, the segregation patterns and the sex of the translocation carrier [24]. However, they generally have a lower chance to produce normal or balanced gametes due to abnormal segregation of chromosomes at meiosis leading to repeated spontaneous abortions and infertility [21, 25]. At pachytene stage of meiosis I, chromosomes with reciprocal translocation rearrangements form quadrivalent. At the end of meiosis I, these chromosomes can segregate in four different ways: alternate (2:2), adjacent (2:2), 3:1 and 4:0 (**Figure 1a**). Alternate segregation either leads to a normal or a balanced rearrangement, and therefore, it results in a viable birth. Studies suggest that the most common segregation pattern of gametes produced by the carriers of reciprocal translocations is alternate (balanced) segregation [26]. In the case of an adjacent segregation, homologous chromosomes cause a monosomy for one centric center and trisomy for the other centric center. Studies suggest that adjacent two segregation pattern is rather uncommon [26] and may rise in cases of maternal meiotic errors [21]. Three to one segregation leads to a tertiary trisomy/monosomy or interchange trisomy/monosomy. This type of segregation can be viable. If the chromosomes fail to segregate, it leads to 4:0 segregation resulting in double trisomy or double monosomy. In case of a Robertsonian translocation, one normal with one derivative chromosome or single chromosomes of derivative or the single chromosomes of the normal chromosome can segregate resulting in an abnormal gamete (**Figure 1b**). The only way of a Robertsonian carrier can produce a normal gamete is if the two normal chromosomes segregate together at meiosis I [27].

Insertions can be classified as a type of translocations, and these are uncommon rearrangements. The simple insertion involves three breaks where the first two removes the part of the chromosome, and the segment is reinserted within the third break. The conceptus with a smaller insertional segment has a potential to be viable [28]. The insertions, especially the small ones, may be passed on from generations to generations without being detected. However, with the use of newer technologies, such as microarrays, more patients with insertions are likely to be detected [29]. Insertions are one the rearrangements with the highest reproductive risk, in such approximately 32% of male and 36% of female carriers are having a chromosomally abnormal child [30].

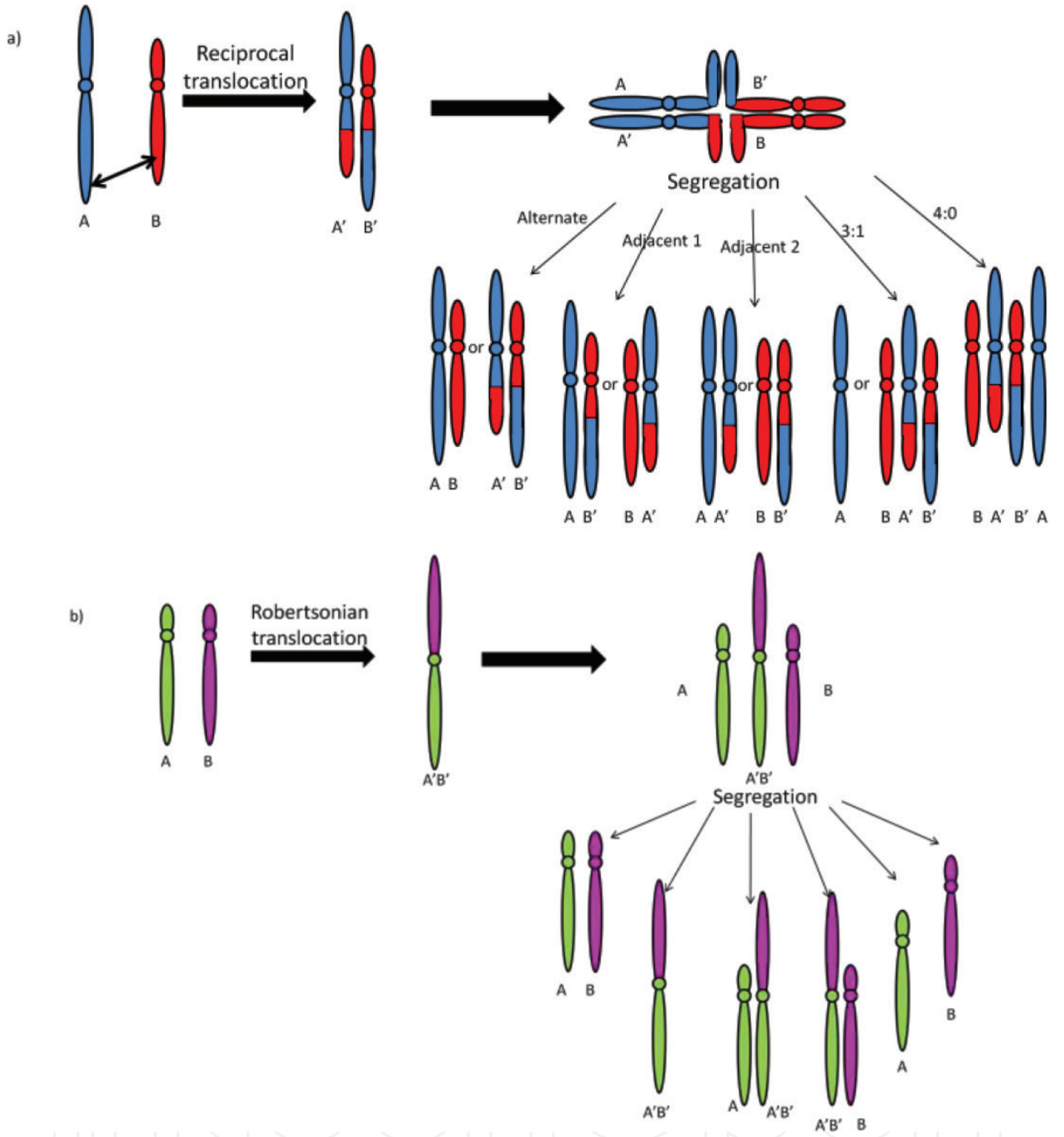

Figure 1. Segregation patterns of translocation carriers (a. Reciprocal and b. Robertsonian translocation carriers) during meiosis.

Another example of chromosomal rearrangements is inversions. These are intrachromosomal structural rearrangements. The simple inversion involves two break points within the same chromosome where the intercalcary segment gets rotated and reinserted. The inversions can be subcharacterized as pericentric, where the inverted segment involves the centromere, and paracentric, where the inverted segment is reinserted on the same chromosome arm. It is very rare that an inversion, especially pericentric inversions, would cause infertility [31]. However, abnormal synapsis of a chromosome pair may cause the development of an abnormal embryo

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due to malsegregation of chromosomes during gametogenesis. Depending on the break point, whether it involves genes or not, the size of the inversion could result in detrimental effects. Therefore, the risk of an inversion carrier varies among couples, and each has their own risk. The risk estimate can be performed by family studies, literature with similar inversion break points and gamete (sperm) analysis. Sperm studies have shown that during spermatogenesis, inversions with larger segments could result in spermatogenic arrest [32].

The carriers with a chromosomal rearrangements have the option to pursue pregnancy without seeking for any medical help and wish for a chromosomally normal child. Some of these carriers may have had an abnormal child due to the chromosomal abnormalities, and some of these carriers, especially translocation carriers, may have experienced repeated spontaneous abortions. Therefore, these patients may choose to seek for different options to avoid such experiences. These couples may opt for donor gametes, prenatal diagnosis or preimplantation genetic diagnosis.

3. Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) is offered to couples who have already been diagnosed with a single gene disorder or a chromosome imbalance to select an embryo free from the mutation or an embryo with a balanced karyotype prior to implantation and pregnancy [9]. The first application of PGD was performed for a couple with X-linked recessive disorder almost a quarter century ago by Handyside and colleagues [33].

PGD is a highly invasive technique that requires IVF and biopsy of the polar body of the mature oocyte or the developing embryo (cleavage stage or blastocyst stage). Polar body biopsy involves biopsying the first only or the first and the second polar bodies. Neither the first polar body nor the second polar body is required for fertilization or a normal embryonic development [34]. Polar body biopsy is advantageous since it provides sufficient time for analysis. First polar body biopsy alone only allows analysis of meiotic errors (maternal origin only), and it does not give any information on the mitotic errors. Although the biopsy of both polar bodies provides information on both the meiotic and mitotic errors, it is still limited to detect the maternal errors only [35].

Biopsy at the cleavage stage on day 3 postfertilization provides more complete diagnosis than polar body biopsy and with enough time to finish the diagnosis before the embryo transfer [36, 37]. However, mosaicism (presence of at least two cell lines) at this stage is a major issue for PGS. In mosaic embryos, one or two cells may not represent the rest of the embryo due to different cell types in every cell [38–43].

Blastocyst biopsy has been applied more frequently in PGS in the last years. Biopsy of trophectoderm cells provides more number of cells for diagnosis and therefore overcomes the trouble of the single cell diagnosis [44]. Even though some studies report mosaicism at the blastocyst stage [45–47], due to the activation of cell cycle control points by the 8-cell stage embryo, many mosaic embryos are arrested or are repaired [48]. The lower rates of mosaicism in addition to analysis of several cells instead of just one provide less diagnostic errors. Conversely, blastocyst stage biopsy is limited before the procedure can even begin as it depends on the development of the embryo into a blastocyst [49].

4. Numerical chromosomal abnormalities in embryos and preimplantation genetic screening

Since the initial applications of PGD for sex-linked disorders and monogenic diseases, the indications have been expanded to aneuploidy screening by preimplantation genetic screening (PGS). PGS is applied to patients with advanced maternal age, recurrent miscarriages, repeated in vitro fertilization (IVF) failures or male infertility. Unlike PGD, patients undergoing PGS do not carry a genetic disorder and they have a normal karyotype. The main goal of PGS is to test embryos for aneuploidies that arise spontaneously in human gametogenesis, more prevalent in female meiosis, or early embryonic development [50, 51]. Aneuploidy is a common feature in preimplantation embryos causing the low success rates and high miscarriage rates in assisted reproductive technology (ART) treatments [52, 53]. Although embryos with autosomal monosomies are mainly lethal; embryos with some trisomies (13, 18 and 21) have higher chances of survival with the risk of developing genetic disorders [54], and some trisomies (15, 16 and 22) can cause embryonic developmental arrest or implantation failures [55, 56]. Therefore, selecting an embryo with a normal chromosomal complement helps to improve the implantation rates and increases the chances of birth of a healthy child.

The first PGS was performed by fluorescence in situ hybridization (FISH) in polar bodies and cleavage stage embryos in 1995 [57–59]. Up until recently, FISH was the preferred method of analysis in cleavage stage embryos [60]. As discussed earlier, although at cleavage stage, both maternal and paternal errors can be analyzed, it is complicated by high levels of mosaicsism. Mosaicsism is rare for monogenic diseases; however, it is very common for aneuploidies in the embryos at cleavage stage. There are more than ten randomized control trials showing that cleavage stage biopsy and FISH analysis does not improve the delivery rates [61–71]. In 2010, European Society of Human Reproduction and Embryology (ESHRE) reported that cleavage stage biopsy using FISH is not recommended for PGS [72]. The majority of the aneuploidies in the embryos affecting the pregnancy rates are believed to occur in the oocyte, and therefore, polar body (PB) biopsy may have an added advantage in PGS, especially since PBs are not affected by mosaicim arising in mitosis [73]. However, biopsy of the first PB does not provide a complete aneuploidy screening since biopsy of first PB only gives errors occurring in meiosis I, and it does not reveal any information about meiosis II. Therefore, performing both PB I and PB II biopsies are recommended for better analysis. Biopsy of PBs is considered less invasive than biopsy of a blastomere or trophectoderm, and the use of aCGH in PB biopsy was shown to have improved implantation rates [74]. Furthermore, the multicenter randomized control trial set by the ESHRE Task force reported that PGS using the first and the second PB by aCGH increases the delivery rates significantly in patients with advanced maternal age [75]. One of the pitfalls of polar body biopsy is that oocytes diagnosed as aneuploid may actually form a euploid embryo due to a chromatid predivision error in MI with a balanced segregation at MII [75, 76]. Moreover, Geraedts and colleagues (2011) reported that at least 1 in 10 oocytes biopsied do not provide a diagnostic result [75]. Therefore, embryos with no diagnostic results and developed normally are either discarded or biopsied at a later stage. This increases the labor for both embryology and genetics teams, and it causes an added economical burden to the patients.

With the recent improvements in IVF laboratories, blastocyst biopsy has become the preferred method for PGS. In the past, one of the main problems of performing blastocyst biopsy was the limited time allowed for the diagnosis since the embryonic cells are either biopsied on day 5 or on day 6 for the slow developing embryos. With the use of vitrification, high embryo survival rates were reported [77–80], and many centers have opted performing PGS at blastocyst stage [81]. Furthermore, vitrifying embryos provide chance of an embryo transfer during an unstimulated cycle that was shown to result in high pregnancy rates [82–84]. In good prognosis patients, a pilot randomized clinical trial showed that trophectoderm biopsy and use of aCGH for PGS increases the implantation and ongoing pregnancy rates [85]. The pitfall of trophectoderm biopsy is that some embryos may not reach to the blastocyst stage in vitro that may be viable in utero [86]. As an added evaluation of aneuploidy screening, mitochondrial DNA (mtDNA) copy number has been investigated in euploid embryos showing that high mtDNA copy number indicates lower embryo viability and implantation [87, 88].

In addition to the array comparative genomic hybridization (aCGH) platforms, validation and the initial applications of single-nucleotide polymorphism (SNP) arrays [22, 76, 89–91] and next generation sequencing (NGS) platforms [92–96] showed promising results for their use in PGS. With the use of SNP arrays, the aneuploidies including monosomies or partial deletions as well as parental origin of any chromosomal abnormality can be identified [97].

Although PGD is widely accepted and applied throughout the world, there is still an ongoing debate on whether PGS is beneficial to infertile couples due to variable success rates depending on the maternal age, the technique used and the time of biopsy. Therefore, more and more studies are being developed for indirect aneuploidy assessment of the embryos.

5. PGD for translocations

Up until recently, the most common technique used to detect translocations in PGD was FISH. Polymerase chain reaction (PCR), which has been widely used to detect monogenic disorders, has also been used to detect translocations in PGD [98]. Other techniques that have been introduced to detect translocations in PGD are aCGH and more recently SNP arrays and NGS platforms.

5.1. PGD for translocations by FISH

FISH is a cytogenetic technique that had been used to detect structural chromosome analysis for patients with translocations and X-linked disorders. FISH is based on the hybridization of interphase chromosomes on specific DNA probes [99]. Although FISH is a rapid and accurate technique, it is limited as only a few chromosomes can be examined in a single cell. Moreover, it is restricted to analyze only the regions known to have imbalances. Signal interpretation is very important for correct diagnosis since the hybridization efficiency with each successive round could be lowered due to signal splitting and signal overlap. Additionally, loss of micronuclei during fixation of the blastomere causes difficulties in diagnosis [100].

5.2. PGD for translocations by PCR

PCR, a technique to amplify DNA by in vitro enzymatic replication, is mainly used to detect monogenic disorders [37] and recently, to detect translocations [98]. PCR is a technically demanding procedure, especially single cell PCR for PGD. The most important issues with PCR are the high risk of contamination, allele dropout (ADO) and amplification failure. ADO, which occurs when one of the alleles fails to amplify in a heterozygote cell for that particular region and is usually caused by a low amount of DNA in single cell PCR procedures, incomplete lysis or imperfect denaturation temperature [101], could lead to a misdiagnosis [101]. Fluorescent-PCR and multiplex PCR, which are more sensitive than conventional PCR, can be used to lower the ADO risk and amplification failure [102]. Although PCR has its limitations, it has the potential to conquer the drawbacks of FISH in detecting translocations.

Quantitative fluorescent PCR (QF-PCR) has been incorporated to the analysis of chromosomal imbalances. Studies have shown that QF-PCR is a sensitive, rapid and accurate technique that has been applied to study chromosomal abnormalities in spontaneous miscarriages [103] and in prenatal diagnosis [104]. Not only the parental and meiotic origin of aneuploidy can be detected by QF-PCR by using semi/fully informative short tandem repeat (STR) markers, but also the possible recombination events can be analyzed using informative STR markers. QF-PCR results of this study are preliminary, and more studies must be carried out.

5.3. PGD for translocations by array comparative genomic hybridization

aCGH, which is a similar technique to metaphase CGH, is used to determine total or partial aneuploidy by detecting chromosomal gains and losses of the entire genome [105]. Manual identification of chromosomes is not required with aCGH, and this technique has higher sensitivity and specificity for small genomic changes [106]. aCGH not only is used in prenatal diagnoses for identification of translocations [107, 108] and being reported as a rapid technique to detect de novo chromosome imbalances [109] but also is used to detect translocations in PGD clinically [110–112].

The comprehensive chromosome screening using aCGH has an added advantage to FISH in detecting aneuploidies and interchromosomal effect. Interchromosomal effect is the phenomenon known as the interference of chromosomes involved in rearrangement with the segregation of the structurally normal chromosomes [113–115]. Twenty-four chromosome aneuploidy screening revealed that segregation errors occur at high frequency even for the chromosomes not tested by FISH [8, 9, 20, 100, 116–120]. Furthermore, aCGH can detect copy number differences more precisely compared to FISH and PCR analyses since these methods are at much lower resolution than aCGH [121]. However, one of the limitations of aCGH is its inability to detect ploidy [122].

The methodology of aCGH is similar to metaphase-CGH, such that the only difference is that aCGH does not require metaphase chromosomes, and it can use target DNA for hybridization from cloned DNA segments, such as PCR-generated sequences, bacterial artificial chromosome (BAC) and cDNA clones [49]. More importantly, aCGH is much faster technique

compared to metaphase CGH in detecting chromosomal abnormalities within less than 1 day [123]. The test and reference DNA are labeled with green and red fluorochromes, respectively. After hybridizing the labeled test and reference DNA on the array covered with BAC/cDNA clones or PCR-generated sequences, an array scanner captures the scanned image and computer systems are used to analyze the ratio of green to red fluorescence. If the test DNA is normal, the ratio of green to red signal should be 1:1. If the test DNA is monosomic, the green labeled chromosome will be less compared to the red labeled, and therefore, the ratio of green to red ratio is decreased and vice versa [124].

One of the most important advantages of aCGH is that it requires a small amount of genomic DNA for hybridization, as low as 2–4 μg [44]. However, in PGD/PGS, WGA, a technique used to amplify the whole genome for molecular analysis using small amounts of DNA [125], is fundamental. This technique can abolish DNA as being a limiting factor for genetic analysis by generating large quantities of DNA from starting material as small as 6pg, such as from a single blastomere [126]. Multiple WGA techniques have been used in the past, such as primer extension preamplification [127], linker-adaptor PCR [128], degenerate oligonucleotide primed-PCR [9, 129–131] and multiple displacement amplification [132–134].

5.4. PGD for translocations by single nucleotide polymorphism arrays

SNP arrays consist of oligonucleotide probes and most of them examine between 10,000–500,000 SNPs with high accuracy and reproducibility. SNP arrays utilize an approach similar to metaphase-CGH, such that the labeled test sample is hybridized separately on a different area of the array than the reference sample that is analyzed in parallel. The alleles detected at each SNP locus for the embryo are compared with the SNPs detected for the parents, and then, fluorescence intensities obtained for the test (embryo) and reference samples are analyzed by the brightness of the signals obtained. Brighter signals of the test sample indicate excess of that chromosome and *vice versa* [135].

The main advantage of SNP arrays is that they can determine the inheritance of genes that can allow simultaneous analysis of monogenic diseases and chromosome rearrangements, such as translocations including the balanced translocations unlike aCGH or FISH [100]. The drawback of SNP arrays is their high susceptibility to noise and bias, especially with the amplified single cell samples. SNP arrays cannot detect duplications. When SNP arrays are used in PGD/PGS, vitrification of embryos is necessary to enable enough time to complete the procedure [135].

SNP arrays have been applied in research to detect total aneuploidy and structural chromosomal imbalances to identify disease risks such as for type-2 diabetes, prostate cancer, glaucoma and some cardiovascular conditions [136]. SNP arrays were shown to analyze the copy number differences and chromosomal instability in studies following WGA of cells from cell lines [100] and amplified blastomeres from human cleavage-stage embryos [22, 137, 138]. Clinical applications of SNP arrays have been reported for several cancers [139] and for Gaucher disease and Marfan syndrome following blastomere biopsy [140]. SNP arrays have also been clinically applied in PGD and PGS [141–143].

5.5. PGD for translocations by next-generation sequencing

NGS is a technology that is used to sequence the nucleotides in a massively parallel manner. With the use of NGS, higher throughput data with lower cost can be obtained in a faster way compared to Sanger sequencing. Furthermore, for NGS platforms, bacterial cloning procedures are not required. On the other hand, NGS technologies require complex alignment algorithms in order to assemble and map the genome using short reads [144]. Up until this year, three main NGS platforms have been introduced, Roche (454), Life technologies and Illumina. Roche (454) generates 700 base pair fragments of approximately 1 million reads [145]. With the Life Technologies platform, semiconductor-sequencing technology has been used with solid-state pH meter. In this platform, proton generates up to 200 bp fragments of about 60–80 million reads. This technology generates up to 10 Gb of sequence in every run [145]. Illumina's platform generates up to 150 bp fragments of about 6 billion reads with approximately 1.8 Tb of sequence in each run over a period of 3 days [145]. Since NGS has become cost-effective, this comprehensive analysis has been applied in assessment of numerical and structural chromosomal abnormalities in PGS and PGD [96, 141, 146–149].

6. Conclusion

One of the most important reasons of the development of PGD was to avoid termination of pregnancy or avoid a severe congenital abnormality. Soon after the PGD implications have developed; PGS has been introduced aiming to select a euploid embryo to improve the implantation rates and avoid spontaneous abortions. However, PGD is not an easy reproductive option especially since there is no guarantee of pregnancy or even an embryo transfer in cases where all the embryos have the mutation or chromosomal imbalance [72]. Complex and multidisciplinary approaches are required for a successful PGD cycle combining the expertise of geneticists, embryologists and fertility doctors. Each PGD cycle starts with genetic counseling, fertility assessment, hormonal ovarian stimulation, development of embryos in vitro, biopsy of these embryos and preimplantation genetic testing of the embryonic samples. Initial studies were performed by a molecular cytogenetic technique, FISH, with some limitations including problems with fixation of the nucleus, hybridization problems and intensity of the fluorescence of the probes. As the newer technologies have been introduced, the fields of PGD and PGS have also improved. In the last past few years, with the development of aCGH, SNP arrays and NGS technologies, precise and reliable results have obtained from embryo biopsies with improvements in the implantation and take home baby rates.

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