Special Article

Clinical Application of Forensic DNA Analysis: A Literature Review

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Polymorphic short tandem repeat (STR) analysis after polymerase chain reaction amplification is presently the most important analytical method of forensic DNA laboratory. Beside the forensic-purpose application, STR analysis is also necessary for chimerism testing after bone marrow or allogeneic stem cell transplantation. To increase success rate of the treatment and avoid adverse effect of the transplantation procedure, serial chimerism study has to be closely monitored. Many analytical techniques have been therefore developed to improve the accuracy and sensitivity. STR-PCR is currently the most commonly used analytical method for chimerism testing. Sensitivity of the method is about 3% of the minor DNA in a specimen. The method consumes a short period of time and is convenient due to availability of the commercial kits. High discriminative ability and well-validated interpretation procedure are the attractive characteristics of the method.

Keywords: *Chimerism testing, Forensic DNA analysis, Bone marrow, Allogeneic stem cell transplantation, STR analysis*

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Polymorphic DNA analysis in a forensic DNA laboratory is normally used for the purpose of personal identification, kinship analysis, and evidence-stain analysis. Short tandem repeat (STR) polymorphism genotyping is also necessary for diagnosis and monitoring of certain diseases. Chimerism testing is an important clinical application of forensic DNA analysis. It is one of the main workload of the Forensic Serology Division of Forensic Medicine Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Due to the rapid growth of the development of the science and technology in bone marrow and hematopoietic stem cell transplantation, an increasing number of hematologic malignancies and non-malignancy hematologic disorders have been treated with bone marrow and peripheral hematopoietic stem cell transplantation. At the Forensic Serology Division of the Faculty of Medicine Siriraj Hospital, Mahidol University, the requirement for chimerism testing has increased dramatically in the last few years. Only 20 and 84 chimerism analyses were done in 2007 and 2008 respectively, but there were already 462 analyses between 2010 and 2011. The final goal of the treatment of malignant hematological conditions is to completely eradicate the recipient's hematopoietic system and replace it with new donated bone marrow or stem cells. Major causes of the treatment failure are graft versus host disease (GVHD), graft rejection, and relapse of underlying conditions due to minimal residual disease (MRD). As a result, transplantation procedures have to be continually adjusted to increase efficacy of the treatment and to reduce mortality and morbidity. A sensitive and accurate analytical procedure is needed for monitoring therapeutic engraftment. In addition, appropriate medical procedures such as immunosuppression therapy or re-transplantation have to be implemented[1]. Chimerism analysis has been applied to monitor the ratio of blood components that originate from recipient and donor stem cells after bone marrow or allogeneic stem cell transplantation. In marrow/stem cell transplantation, post-transplantation individual will have the original DNA profile (recipient profile) in secretion and tissue except in all components of blood. In a successful transplantation, only the new DNA profile (donor profile) is detected in the blood. This condition will be interpreted as a complete chimerism. In contrast, if some recipient profile is present after the transplantation, this will be interpreted as a mixed chimerism profile. The lack of donor profile post transplantation will be reported as complete recipient chimerism (graft failure or rejection). There

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are two steps for DNA laboratory to perform a chimerism report after the transplantation:

1. Has the recipient DNA profile in peripheral blood been replaced with the donor profile?

2. What is the ratio of recipient/donor profile in a case of mixed chimerism?

Many analytical techniques have been used for chimerism testing such as conventional cytogenetics study, fluorescence *in situ* hybridization (FISH), immunocytochemistry, variable number tandem repeats (VNTR)-PCR and short tandem repeats (STRs)-PCR.

Conventional cytogenetics study has been used to evaluate chimerism status after transplantation by the detection of recipient metaphases in the bone marrow. This karyotyping procedure needs a cell-culture laboratory, experienced personnel, and consumes more than 24 hours to obtain results[2]. Interpretation is dependent on microscopic observation of banded chromosome, which is not accurate and difficult to quantify the percentage of chimerism[3,4]. FISH is more sensitive than conventional cytogenetics study and is quantitative[5,6]. Use of FISH analysis for chimerism testing is limited to gender-mismatched transplantation pair[7-9] or in cases with clonal disease marker[10,11]. The technique uses single or multiple probes for the labeling of X and Y chromosome or other specific disease markers such as BCR/ABL gene in Philadelphia chromosome. Quantitative result is obtained by counting the different stained cells under a fluorescent microscope[12]. This technique has been used to examine the residual recipient hematopoietic cells and leukemic clones in bone marrow and peripheral blood samples. The advantage of this technique is the ability of morphological determination of recipient cells in a mixed chimeric sample. Morphological identification of the minor cellular population is possible when combining FISH analysis with other immunocyto-chemistry techniques[13]. This ability is very important when examining cases with a very small percentage of mixed chimerism. The residual host cells, which are not malignant, or non-hematopoietic cells such as osteoblast or stromal cell cannot be counted as minimal residual when present in bone marrow or peripheral blood sample. Residual host cells are firstly targeted with X and Y chromosome probes using FISH technique. X and Y probes are then removed from the slide and a second disease specific probe is applied to the targeted cell using FISH or immunocytochemistry technique to confirm their malignancy. Accordingly, the usage of this technique is limited only for diseases that have identifiable cellular characteristics. Most recently, sex-independent FISH probes were used in gender-match pair transplantation[14]. Instead of Y-chromosome, polymorphic deletion probe (PDP) genotype is assessed for chimerism estimation. At each PDP locus, there are only three possibilities for interpretation, null, homozygous, and heterozygous, according to the deletion/insertion variant. As a result, polymorphism rate of this genetic marker is lower than STR marker, in which more than eight possible alleles can be found in a single locus. A lack of sufficient numbers of potential PDP loci has impaired method sensitivity and discriminative ability of this method. It is not able to detect levels of chimerism below 5% of minor cell population. Moreover, its complicated and time consumed procedure is unsuitable for frequent repeated assays in clinical application.

DNA study was introduced for the evaluation of mixed chimerism since the 1980's[15-17]. Restriction fragment length polymorphism (RFLP) and Southern blotting techniques were firstly used to detect mixed chimerism status at above 10% of recipient/donor ratio[18]. DNA-based chimerism testing was then rapidly developed concurrently with cellular-based techniques, such as FISH and cytogenetic analysis. Microsatellite markers together with polymerase chain reaction (PCR) amplification technique had increased sensitivity of the analysis (less than 1% r/d ratio)[19]. VNTR, STR, and SNPs are the three major kinds of DNA sequences, which have been used for PCR-based chimerism analysis. Variable number tandem repeats (VNTRs) analysis had been commonly used for characterizing chimerism status after allogeneic stem cell transplantations due to its lower cost and easier procedure compared with STR and SNP analysis[20,21]. Sensitivity of the method has been claimed to be between 1 and 5% of r/d ratio[22]. However, use of this method has decreased due to its lower applicability compared with the other two DNA methods. Discriminative ability of VNTR analysis to distinguish recipient DNA from donor DNA is limited owing to the low number of alleles at each locus and the lack of worldwide population database, making it difficult to choose the proper loci for research and clinical applications[23,24].

To avoid the mortality of transplantation procedure due to GVHD, reduced-intensity stem cell transplantation or dose-reduced conditioning technique has been introduced for treatment of malignant and non-malignant hematologic diseases[25,26]. This

transplantation technique may result in mixed chimerism continuing over a time period. Serial chimerism study with a convenient, rapid and accurate method is therefore necessary for scheduling the appropriate intervention. Presently, STR polymorphism analysis is the most commonly used chimerism testing due to its multiple purpose usage and the availability of commercial kits[27-29]. The analysis can be completed within six hours in a well-organized forensic DNA laboratory and no extra instrument and personnel are required.

Human genomic DNA consists of more than 3.2 billion base pairs, which make it impossible to analyze the whole sequence individually. As a result, only some selected informative sequences have to be used as representative of an individual. A sufficient number of STR markers are needed in order to identify any single individual from the very close relatives. Fifteen autosomal STR loci and one amelogenin (gender) marker are usually used in forensic cases to identify an individual person. These 16 markers have been also applied for chimerism testing in post-transplantation patient[30]. Presently, there are several commercial kits available for STR analysis, which usually contain 13 international core loci (CODIS), an amelogenin locus and a few more additional loci. The use of a single commercial kit is recommended for serial chimerism testing in a transplantation pair. Discriminative ability of STR-PCR analysis is very high, and can be used in almost all recipient-donor pairs without any gender limitation. The only contraindication of this kind of chimerism testing is transplantation between a monozygotic twin pair.

The necessary information that have to be taken into consideration in order to calculate chimerism results using STR analysis are:

1. Pre transplantation DNA profile of the recipient and donor.
2. Post transplantation recipient DNA profile.
3. Stutter (artifact) peak information of the calculated loci.
4. Microsatellite instability in some hematologic disorders.

To calculate the ratio of mixed chimerism in a post-transplantation patient, peak areas or peak heights of every informative locus are considered according to the pattern of heterozygosity of the alleles[31-33]. Averaged ratio of mixed chimerism is finally reported as the percentage of recipient DNA in a mixed chimerism profile. Accuracy of the result is most often interfered by the presence of stutter peak in the post-transplantation profile. Stutter or artifact peak can occur during PCR amplification due to strand mispairing and may lead to misinterpretation of the chimerism results. An understanding of stutter behavior is required in order to ensure the accuracy of the results of chimerism testing[34-36]. In addition, instability of STR marker due to slippage error during DNA replication in some diseases has to be taken into consideration in certain cases[37]. The limit of detection of multiple markers in STR analysis for residual recipient's DNA is reported at about 3%[38-42]. As a result, this method is not able to detect minimal residual DNA in the early stages of leukemic relapse or graft rejection. Therefore, other analytical methods have been developed to enhance the sensitivity. Real-time PCR amplification of DNA polymorphisms allows for a more sensitive quantitative assessment of mixed chimerism. The method uses single nucleotide polymorphisms (SNPs) as genetic markers or other types of genomic polymorphisms, such as Indel or Y-chromosome specific sequences[43-46]. The detection limit of real-time PCR chimerism testing is found to be as low as 0.1%, which is able to detect the occurrence of malignancy relapse earlier than STR-PCR analysis. A major disadvantage of the method is the limited applicability due to its lower discriminative ability compared with STR analysis[47]. From 10 to 19 SNP loci are able to discriminate recipient from donor DNA in only 90 to 93% of the cases, whereas all cases except identical twin pairs can be discriminated by 11 loci of STR. Real-time PCR process usually has a complicated procedure and sophisticated equipment is required[48]. Moreover, according to the lack of commercial kit and well-organized population database, this method is not able to replace the classical STR analysis for routine chimerism testing[49,50].

Potential conflicts of interest

None.

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การประยุกต์ใช้นิติพันธุศาสตร์ในทางคลินิก

ชัยรัตน์ มานะเสถียรกิจ, ชัชวิน ระงับภัย

การตรวจวิเคราะห์หน่วยซ้ำทางพันธุกรรม (short tandem repeat) เป็นวิธีการตรวจวิเคราะห์ที่สำคัญที่สุดของห้องปฏิบัติการทางนิติพันธุศาสตร์ เพื่อบรรลุวัตถุประสงค์ทางนิติเวชศาสตร์ และนอกจากนั้นยังมีความจำเป็นอย่างยิ่งสำหรับการตรวจวิเคราะห์ chimerism ในผู้ป่วยหลังการปลูกถ่ายไขกระดูก หรือ เซลล์ต้นกำเนิดเม็ดเลือดอีกด้วย การตรวจติดตามภาวะ chimerism อย่างใกล้ชิดส่งผลอย่างยิ่งต่อผลการรักษา และการป้องกันผลข้างเคียงอันไม่พึงประสงค์ของกระบวนการรักษา เทคนิคการตรวจวิเคราะห์หลายวิธีการจึงได้รับการพัฒนาขึ้น เพื่อเพิ่มความละเอียดและแม่นยำของผลการวิเคราะห์ภาวะ chimerism การตรวจวิเคราะห์ภาวะ chimerism ด้วยเทคนิคการตรวจ STR เป็นวิธีการที่นิยมมากที่สุดในปัจจุบัน เนื่องจากมีความสะดวกรวดเร็วและสามารถตรวจติดตามซ้ำได้บ่อย ๆ อันเป็นผลมาจากการที่มีชุดตรวจสำเร็จรูปอย่างแพร่หลาย โดยความละเอียดของผลการตรวจ (sensitivity) มีค่าประมาณร้อยละ 3 ของ DNA ส่วนน้อยที่อยู่ในสิ่งส่งตรวจ คุณสมบัติอันโดดเด่นของวิธีการตรวจวิเคราะห์แบบนี้คือ การที่สามารถประยุกต์ใช้ได้ในเกือบทุกกรณีของการปลูกถ่าย ถึงแม้จะเป็นการปลูกถ่ายระหว่างเพศเดียวกันหรือในเครือญาติใกล้ชิด นอกจากนั้นกระบวนการแปลผลการวิเคราะห์ยังได้รับการศึกษาและปรับปรุงในระดับนานาชาติมาอย่างดีอีกด้วย