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Original Article

Application of short tandem repeat (STR) genotyping in partial hydatidiform mole

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Abstract: Objective: The short tandem repeat (STR) technique, which is currently the most extensively applied genetic marker, works mainly due to the differences in DNA repeats, resulting in a rich population polymorphism and high genetic stability. This paper primarily investigated the application of STR genotyping in partial hydatidiform mole (PHM). Methods: The clinical data of 31 PHM patients and 23 hydropic abortion patients diagnosed in the Pathology Department of Beijing Tsinghua Chang Gung Hospital from 2017 to 2022 were collected and retrospectively analyzed. The histomorphological features of H&E sections were observed. Immunohistochemical staining was performed to determine p57 protein levels. STR polymorphisms (STRPs), including 15 polymorphic loci and 1 sex recognition gene locus, were detected in tissue specimens, and the role of STR in the differential diagnosis of PHM was analyzed. Results: In PHM cases, each STR locus of the PHM contained one maternal allele and two paternal alleles. Decidual tissue showed alleles of biparental origin. According to the Kappa's consistency test, the diagnosis made by STR showed good consistency ($\kappa = 0.925$, $P < 0.001$). Conclusions: STR genotyping is of great value in the diagnosis of PHM.

Keywords: Short tandem repeats, genotyping, immunohistochemistry, partial hydatidiform mole

Introduction

Hydatidiform mole (HM), a common placental proliferative disease that can be detrimental to female reproductive health, is characterized by the proliferation of trophoblast cells (TBs) after pregnancy, leading to high levels of edema in the villous stroma, and the formation of clusters of blisters of different sizes resembling grapes [1]. HM is classified as either partial hydatidiform mole (PHM) or complete hydatidiform mole (CHM) [2, 3]. This disease presents a high risk of developing persistent trophoblastic diseases (invasive HM, choriocarcinoma, etc.), with CHM patients (15-20%) experiencing a greater disease progression rate than PHM patients (< 4%) [4, 5]. PHM refers to the degeneration of some placental villi and the proliferation of local trophoblasts. In most cases, visible embryo and fetal tissue are present, but the fetus has died [6]. Thus, it is of great clinical implications to distinguish HM from non-molar hydropic abortion (HA) and to further distinguish CHM from PHM.

PHM and CHM can be detected early in pregnancy as ultrasound technology advances, but they two are highly similar to HA, which is difficult to distinguish by histomorphology [7]. Early CHM is often misdiagnosed by clinicians and pathologists as HA or normal pregnancy. While the diagnosis of PHM is more problematic in clinical practice, with the phenomena of both under- and over-diagnosis [8, 9]. Over-diagnosis of a non-molar pregnancy as a HM can lead to adverse clinical consequences, including unnecessary follow-up, contraception, and psychological burden.

Histopathological examinations, including cytology and histology, are direct and reliable approaches for the identification of HM from normal cases. In addition, p57 protein expression has been reported to be of great value in

identifying HM [10]. The p57 gene is located on chromosome 11p15.5 and is expressed maternally by paternal imprinted genes. Given that CHM does not contain maternal nuclear DNA, and both PHM and HA have DNA from both parents, p57 gene expression can be used to identify molar pregnancies [11, 12]. Furthermore, due to the unique genetic background and mechanisms, the pathogenesis of moles has gradually been clarified. The p57 immunohistochemical (IHC) test cannot distinguish between maternal allele-containing trophoblastic diseases, such as diploid HA, PHM, triploid digynic-monoandric gestations, and trisomy [13]. Short tandem repeat (STR) is a type of DNA repeat with a length of 2-7 nucleotides, which is abundant in the non-coding region of the human genome and with high genetic stability [14]. STR polymorphism (STRP) analysis is currently the most accurate method for individual identification in forensic medicine [15]. The identification of excess paternal genome is considered to be the "gold standard" for the final diagnosis of HM [16]. Based on the same principle, the genetic components of both parents in the HM can be obtained by analyzing the STRPs of the pregnant and corresponding maternal tissues, which can assist in clarifying the diagnosis and typing of moles. STRP analysis has been confirmed to be the most accurate and practical method for HM diagnosis and classification. In recent years, some large medical institutions have accurately diagnosed and typed HM through STRPs of multiple specific loci [17, 18]. Therefore, this study used tissue samples from the clinical pathology department to analyze the application value of the 16-locus STR analysis in the differential diagnosis of PHM.

Materials and methods

Clinical data

The clinical data of 31 PHM patients and 23 HA patients were collected from the Department of Pathology of Beijing Tsinghua Chang Gung Hospital from 2017 to 2022 for this retrospective analysis. Inclusion criteria: (1) Patients were 18 years old or more; (2) Patients mainly presented with abdominal pain after amenorrhea, vaginal bleeding, and post-abortion hemorrhage, or came for early pregnancy examination; (3) Urine pregnancy tests were all positive; (4) B-ultrasonography suggested embryo growth arrest or a cardiac fetus, but it was not able to differentiate between HA or HM in the early stage; (5) All patients were treated by routine curettage; (6) Patients had IHC results; (7) Patients left complete clinical files and tissue specimens.

Exclusion criteria: (1) Patients were younger than 18 years old; (2) Urine pregnancy tests were negative; (3) Patients did not undergo B-ultrasonography; (4) Patients were not treated by routine curettage; (5) Patients had incomplete IHC results or clinical files. Patient data were collected, including pregnancy age, gestational weeks, gravidity, and serum human chorionic gonadotropin (hCG) levels. This study has been reviewed and approved by the ethics committee of Beijing Tsinghua Chang Gung Hospital.

Histological examination

All tissue specimens were neutral formaldehyde (4%)-fixed, paraffin-embedded, routinely sliced and hematoxylin-eosin (H&E)-stained. Each specimen was evaluated by three senior pathologists specializing in obstetrics and gynecology. Histomorphological observations were made on the H&E sections, including the presence or absence of embryonic tissue (or nucleated fetal red blood cells and other fetal components), villi size, villous edema degree (light, medium, or heavy), pool formation (more than 50% area of the villi), and TB proliferation degree (light, medium, or heavy). We also evaluated whether there were sufficient and qualified villi and decidua tissues in each specimen to facilitate tissue separation, so as to ensure a smooth STR analysis. The primary outcome was to determine the diagnostic consistency between STR and pathological confirmation.

p57 IHC staining

Following antibody instructions and laboratory specifications, p57 protein expression was measured by the PV-9000 two-step immunohistochemistry kit (Beijing Zhongshan Goldenbridge Biotechnology Co. Ltd, China) after diaminobenzidine and hematoxylin counterstaining, with antibodies supplied by Beijing Zhongshan Goldenbridge Biotechnology Co. Ltd. The p57 protein was located in the nucleus and was found to be brownish-yellow. Five visu-

Table 1. Comparison of patients' clinical data

Groups	Partial hydatidiform mole group (n = 31)	Hydropic abortion group (n = 23)	χ^2/t/Z	P
Age (years old)	26.8±2.9	26.6±4.4	0.201	0.841
Gestational age (weeks)	8.7±1.4	8.4±1.7	0.711	0.481
Gravidity (n)			0.273	0.601
First pregnancy	21	14		
Two or more pregnancies	10	9		
hCG before curettage (IU/L)	112890 (7063-267490)	137760 (6707-251520)	-0.883	0.377

Notes: hCG, human chorionic gonadotropin.

al fields (100 cells/visual field) in different parts were selected to count the proportion of colored cells, with a proportion of colored cells > 30% being positive and a proportion ≤ 30% being negative. As CHM lacks a maternal genomic component, it is not expected to express imprinted genes that are normally expressed by the maternal allele, so IHC analysis for p57 is a valuable tool in the diagnosis of CHM [19].

STR genotyping

The distribution of villi and decidual tissue was determined based on morphological observations. A sterilized surgical blade was used to separate villi and decidual tissue after they were marked by H&E staining. DNA was isolated using the SimplexOUPTM FFPE DNA Extraction Kit (T), as per the reagent instructions. After extraction, DNA specimens were sent to Triplex International Biosciences (China) Co., Ltd. for PCR analysis of 15 loci and amplification of one sex identification locus. The alleles at each STR locus were compared to identify abnormal paternal alleles in the villi.

STR result determination: this study detected 15 commonly used STR loci (CSF1P0, D7S820, D8S1179, D21S11, D2S1338, D3S1358, D13S317, D16S539, TH01, D18S51, D19-S433, TPOX, vWA, D5S818, and FGA) and 1 sex recognition gene loci (Amelogenin). If there were two paternal and one maternal alleles at each STR locus, it was considered a PHM [20]. HA was indicated by the presence of a balanced biallele phenotype from both parents [21]. The secondary outcome was to determine the diagnostic performance differences between STR and pathological confirmation.

Statistical methods

Data analysis was performed using SPSS 22.0 software. Measurement data were represented by mean ± standard deviation or median (minimum and maximum), and comparisons were conducted by independent t tests or nonparametric tests. Comparisons of count data (expressed as percentages) were carried out using Chi-square tests or Kappa consistency tests. Differences were considered significant when *P*-values were lower than 0.05.

Results

Patient clinical information

The 23 HA patients, including 14 patients with their first pregnancy and 9 with two or more pregnancies, were aged 26 on average (range: 20-35 years old), with a mean gestational age of 8.4±1.7 weeks, and a median serum hCG of 137,760 IU/ml (6,707-251,520 IU/L). The 31 PHM patients, including 21 patients with their first pregnancy and 10 patients with two or more pregnancies, had a mean age of 26 years (range: 22-32), a mean gestational age of 8.7±1.4 weeks, and a median serum hCG value of 112,890 IU/ml (7,063-267,490 IU/L). The basic data were not statistically different between the two patient cohorts (P > 0.05, **Table 1**).

Histopathological features and p57 IHC expression

PHMs were histopathologically characterized by slight edema of villous stroma with pools, formation of trophoblast inclusions, and mild or moderate proliferation of TBs (**Figure 1A**). While the major histomorphological manifestations of

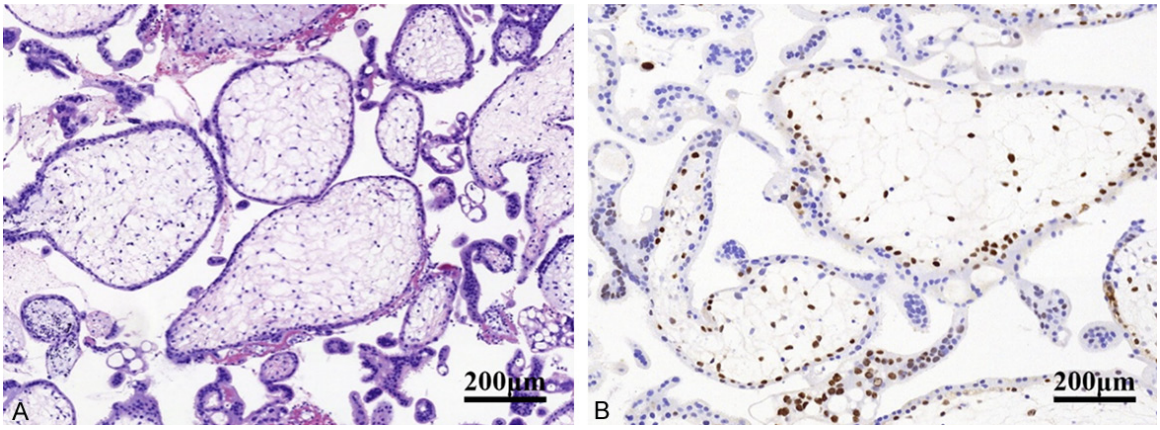

Figure 1. H&E staining and immunohistochemical staining. A: Histomorphological characteristics of partial hydatidiform mole cases; B: Immunohistochemical staining of p57 protein in partial hydatidiform mole cases.

Table 2. Comparison of p57 positive rate between the two groups of patients

Groups	Number of positive cases	Positive rate (%)	χ^2	P
Partial hydatidiform mole group (n = 31)	27	87.1	3.205	0.073
Hydropic abortion group (n = 23)	23	100		

HAs were slight edema in the villous stroma and no significant TB proliferation. The p57 protein was positively expressed in villi interstitial cells and cytotrophoblasts on the villous surface, showing pale yellow and brownish-yellow granules (**Figure 1B**). p57 was positive to varying degrees in the villi of 23 cases of HA and 27 cases of PHM. In PHM group, 27 cases tested positive for p57, with a positive rate of 87.1%. All the 23 cases (100.00%) of HA tested positive for p57. The p57 positive rate was not statistically different between PHM and HA patients (χ^2 = 3.205, P = 0.073), as shown in **Table 2**.

STR genotyping test results

All specimens were analyzed for STRPs at 9 loci, using maternal decidual tissue as a control. Two HA cases and two PHM cases failed to be detected. The remaining 21 HA samples contained one allele each of paternal and maternal origin at each STR locus. The histological diagnosis of HAs was consistent with the STR analysis. In the 29 successfully detected PHM cases, each STR locus contained one maternal allele and two paternal alleles (D3S1358 and TH01 loci showed two identical paternal alleles, D18S51 locus showed two different paternal alleles, and D21S11 locus showed the same alleles as maternal alleles, one from the mother and two from the father). Biparental alleles (**Figure 2**) were found in decidual tissue.

Consistency of STRP diagnosis in the diagnosis of HM

The genotyping results of STR in 29 cases of PHM and 23 cases of HA were consistent with the STRP diagnosis, with a coincidence rate of 93.5% and 100%, respectively. The Kappa consistency test revealed good consistency of the methods (κ = 0.925, P < 0.001), as shown in **Table 3**.

Discussion

At the genetic level, HM pregnancies are characterized by abnormal paternal chromosome components and an excess of paternal genomes that are key genetic factors involved in the pathogenesis of CHM and PHM [22]. The genetic essence of PHMs is triploid diandric and monogynic gestations. They come from an egg with a haploid nucleus fertilized by two sperm at the same time, or from an egg with a haploid nucleus that is fertilized by one sperm. Subsequently, paternal chromosome doubling occurs due to meiosis failure, resulting in a triploid pregnancy with diandric diploid (paternal) and haploid maternal origin [23].

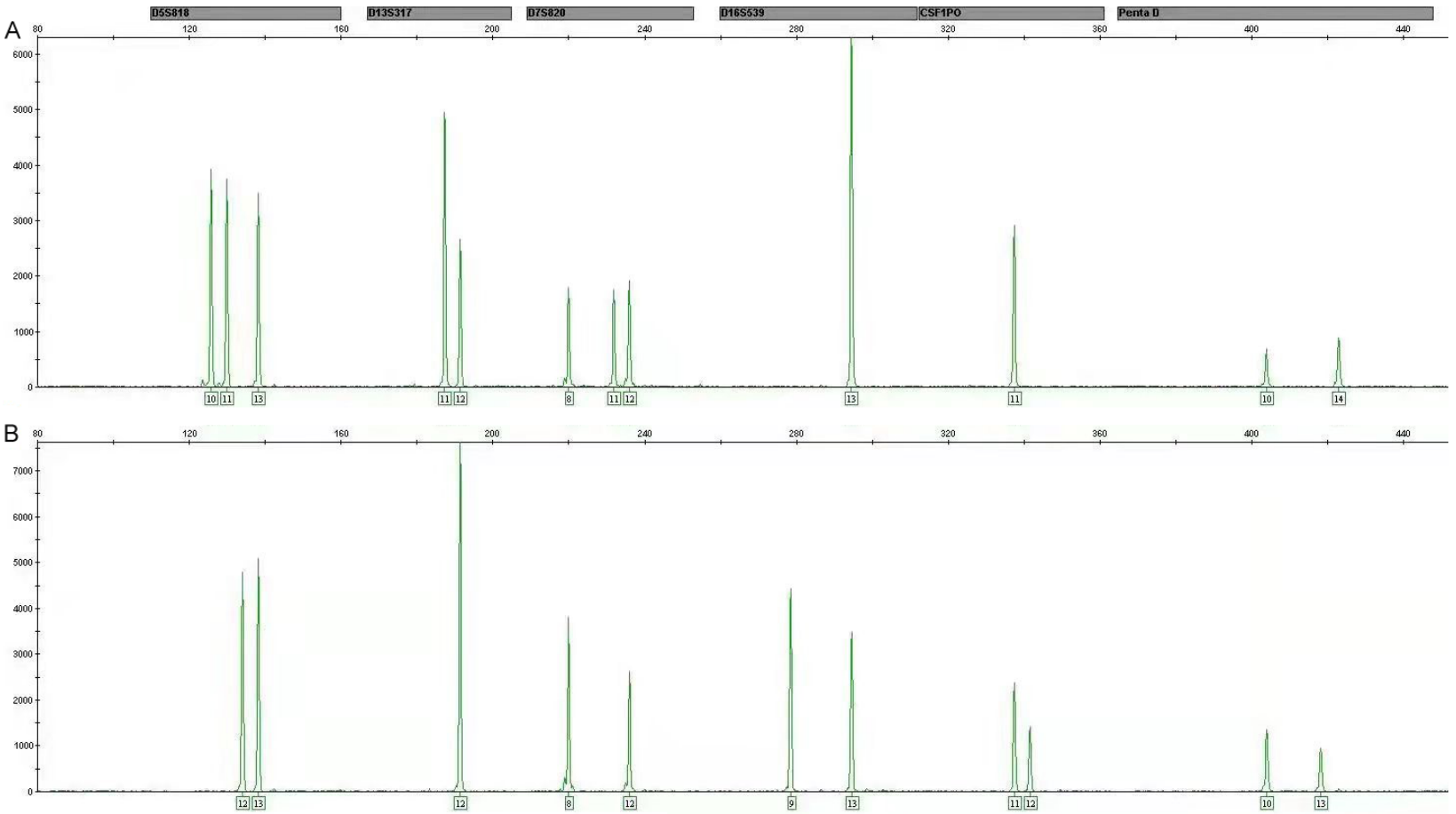

Figure 2. STR genotyping of heterozygous partial hydatidiform moles. A: It harbors diandric heterozygous paternal alleles in addition to one maternal allele at every locus; B: Normal biallelic profiles seen in the maternal endometrium.

Table 3. Genotyping results of short tandem repeats

Diagnosis	Pathomorphism diagnosis		Kappa	P
	Partial hydatidiform mole group (n = 31)	Hydropic abortion group (n = 23)		
Partial hydatidiform mole	29 (93.5)	0 (0.0)	0.925	< 0.001
Hydropic abortion	2 (6.5)	23 (100.0)		

Approximately 0.5 percent of PHMs have progressed to aggressive molar pregnancy, choriocarcinoma, and other trophoblastic tumors [24]. However, due to the insufficient villi development of early pregnancy abortion and nonspecific histomorphological characteristics, a large number of cases may be missed if routine pathological examination was performed without the assistance of other auxiliary detection modalities. Early CHM is often misdiagnosed by clinicians and pathologists as HA or normal pregnancy. In practice, the diagnosis of PHM is more problematic, with the phenomena of both under- and over-diagnosis. Also, the expression of the p57 gene can be used for the identification of HM. Meanwhile, HMs are not equally divided into CHM and PHM histopathologically, and the rates of missed diagnosis and misdiagnosis of each type of HM are not stratified at the level of CHM and PHM [25]. Hence, determining the number of paternal chromosomes in a triploid pregnancy is important in diagnosing PHM.

Herein, we first performed IHC staining of p57 protein on tissue samples from included patients. Twenty-seven PHM cases and 23 HA cases tested positive for p57, with the positive rates being 87.1% and 100.00%, respectively, showing no significant difference between the two patient groups. p57 is a cyclin-dependent kinase inhibitory protein that inversely modulates cell cycle and suppresses proliferation [26]. In the placenta, paternal p57 is an imprinted gene that cannot be expressed, while maternal p57 alleles are expressed. Therefore, nuclear p57 protein expression can be used as a marker of maternal genes in placenta [27]. PHMs are triploid due to the maternal expression of p57, which is expressed because one of them is from the maternal line. Given that HA also contains maternal genes, the clinical detection of p57 expression is still challenging to distinguish PHM from HA [7]. Meanwhile, there were 3 negatives, which may be due to operating process errors or slice quality. We then selected 9 loci and performed STR tests on tissue specimens. In the successfully detected 30 cases of PHM, each STR locus contained one maternal allele and two paternal alleles (D3S1358 and TH01 loci showed two identical paternal alleles, D18S51 locus showed two different paternal alleles, and D21S11 locus showed the same alleles as maternal alleles, one from the mother and two from the father), consistent with the histological diagnosis results. As STR genotyping can determine genetic differences among different members of the same species, it is possible to identify whether each haploid genome in a HM comes from the father or the mother [28]. By comparing the alleles of each STR locus, the abnormal paternal alleles in villi were identified. A diagnosis of CHM can be determined if the STR profile of the villous tissue contains paternal alleles in at least two loci [17]. If two paternal and one maternal allele are present at each STR site, a PHM can be identified. Having a balanced biallele phenotype from both parents is a nonmolar pregnancy, i.e., a diploid HA. Furthermore, we found that STR genotyping can further improve diagnosis accuracy. The extremely rare CHM of parental origin (single spermatozoon-egg) is a potential trap for the STR gene detection of HM. Despite the presence of maternal chromosomes, the abnormal gene imprinting makes its histological performance highly similar to that of a CHM. However, because this HM has both paternal and maternal sex chromosomes, STR genotyping shows a balanced biallelic phenotype. At this time, p57 IHC detection often indicates abnormal imprinting of maternal genes (no p57 nuclear expression in cytotrophoblast cells and villus interstitial cells). Integrating the patient's medical history, clinical manifestations and genetic mutation detection is helpful for the diagnosis of such rare genetic diseases [16]. A study examined 481 patients with suspected HMs using traditional pathology methods and STR analysis, and found that the histopathologic diagnoses in 84 patients were not in agreement with STR analyses, proposing that STR polymorphism analysis is a rapid, simple,

and accurate method that could be utilized for the diagnosis of early HMs and HAs [29]. STRs are present throughout the entire human genome, abundant in non-coding regions and genetically stable. Its loci have the advantages of small repeat units, short fragments and easy amplification, allowing for multiple loci amplification simultaneously, which is conducive to improving work efficiency and saving time for differential diagnosis [30]. DNA can be extracted from fresh villous tissue or parental blood, or using formalin fixed paraffin-embedded villous and decidual tissue samples, as the latter can be stored for longer periods of time and is easier to obtain [31]. By calculating the ratio of peak height or peak area of the two types of alleles, the alleles in the stripped chorionic villi were compared with those in the maternal tissue [15]. This technique is effective, with its sensitivity and specificity confirmed by numerous studies, similar to the "diagnostic truth" of all HM cases [32]. Thus, STR genotyping should be recommended for PHM patients. Although STR genotyping is a promising approach, it is still uneconomical and difficult to generalize. Also, there are some interpretative challenges and unusual situations. For example, when using formalin-fixed paraffin-embedded tissues, maternal contamination is one of the most common problems. Unfortunately, in general, the father's DNA is not available, which may complicate the analysis [33]. Also, the genomes of biparental CHMs exhibit maternal and paternal contributions at all loci, which could be misinterpreted as non-molar pregnancies. In this case, it is important to relate these findings to morphological and IHC staining results.

To sum up, the STR genotyping technique is of great value in diagnosing PHM. But this research still needs further improvement. First, due to the lower incidence of PHM than that of CHM, the PHM cases included in this study are limited. Furthermore, this paper focuses on distinguishing PHM from HA, and CHM samples were not included. Therefore, multi-center studies with a larger sample size of PHM, CHM, and non-molar cases are needed in combination of STR analysis for clear diagnosis and classification.

Disclosure of conflict of interest

None.

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