Meta Gene 5 (2015) 150–156

Contents lists available at ScienceDirect

Meta Gene

Mutation rate estimation for 15 autosomal STR loci in a large population from Mainland China

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ARTICLE INFO

Article history:
Received 5 May 2015
Revised 16 June 2015
Accepted 12 July 2015
Available online 26 July 2015

Keywords:
STRs
Mutation rate
China population
Parentage testing
Allele
Paternal mutation
Maternal mutation

ABSTRACT

STR, short tandem repeats, are well known as a type of powerful genetic marker and widely used in studying human population genetics. Compared with the conventional genetic markers, the mutation rate of STR is higher. Additionally, the mutations of STR loci do not lead to genetic inconsistencies between the genotypes of parents and children; therefore, the analysis of STR mutation is more suited to assess the population mutation. In this study, we focused on 15 autosomal STR loci. DNA samples from a total of 42,416 unrelated healthy individuals (19,037 trios) from the population of Mainland China collected between Jan 2012 and May 2014 were successfully investigated. In our study, the allele frequencies, paternal mutation rates, maternal mutation rates and average mutation rates were detected. Furthermore, we also investigated the relationship between paternal ages, maternal ages, area, the time of pregnancy and average mutation rate. We found that the paternal mutation rate was higher than the maternal mutation rate and the paternal, maternal, and average mutation rates had a positive correlation with paternal age, maternal age and the time of pregnancy respectively. Additionally, the average mutation rate of coastal areas was higher than that of inland areas.

1. Introduction

STRs are abundant in the human genome and highly polymorphic due to allelic variations in the number of repeat units of 2–5 base pairs. For the reason of susceptible slippage events during DNA replication, STR plays an important role as very useful genetic markers in the population genetics, linkage analysis, individual identification and parentage testing (Bar et al., 1997). As is well known, mutations of STR are relatively common in the human genome. Compared with some other mutations in the genome, the mutations of STR have higher genetic diversity. Therefore, the mutation rate of STR has been commonly used in the assessment of population mutation associated with age, times, geographic regions and so on.

Previously, some researchers have investigated the mutation of STR in some areas and districts of China (Yan et al., 2006; Sun et al., 2014; Lei et al., 2015; Meng et al., 2015; Yin et al., 2015), but the scale of data including the number of tested cases, scope and area is still limited. Meanwhile, there are limited data of human population genetics from STR mutation. In this study, mutations of fifteen autosomal STR loci (D8S1179, D21S11, D7S820, CSF1PO, D3S1358, TH01, D13S317, D16S539, D2S1338, D19S433, vWA, TPOX, D18S51, D5S818, FGA) commonly used in parentage testing were studied. We first studied the frequency of all alleles and mutation rates of STR locus. In addition, except for general analysis of average mutation rate, paternal mutation rate and maternal mutation rate, we further investigated the influence of repeat units of allele to the mutation of unit gains or losses. What's more, we also investigated the relationship between paternal age, maternal age, pregnancy time, area and gamete's mutation rate. Together, a total 19,037 trios were tested for the biological consistency of paternity and maternity through analyses of fifteen autosomal STR loci and according to the results of the parents, the mutation of the child was systematically calculated and analyzed. In our study, we finally observed a total of 678 mutations and to our best knowledge, so many numbers of STR mutation analyis are reported for the first time.

2. Material and methods

Blood samples of unrelated healthy individual from 2012–2014 in Mainland China were collected. These individuals include 42,416 DNA confirmed Chinese paternity testing cases and in which, there are 19,037 trios. In our study, the 19,037 trios were our research object. DNA from fresh blood was extracted and purified using PrepFiler™ Forensic DNA Extraction Kit (Applied Biosystems, Foster, CA, USA) and amplification of the STRs was performed using the AmpFlSTR® Identifiler® PCR

Abbreviations: SMM, step wise mutation model; STR, short tandem repeats; GD, genetic distance; UPGMA, unweighted pair-group method with arithmetic means.

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http://dx.doi.org/10.1016/j.mgene.2015.07.006

Amplification Kit (Applied Biosystems, Foster, CA, USA) according to the manufacturer's instructions. The kits include 15 STR loci (D8S1179, D21S11, D7S820, CSF1PO, D3S1358, TH01, D13S317, D16S539, D2S1338, D19S433, vWA, TPOX, D18S51, D5S818, FGA) and a sex determination gene (Amelogenin).

STR genotyping was done on the ABI PRISM® 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and analyzed using the GeneMapper ID 3.2 software (Applied Biosystems, Foster City, CA, USA). All experiments were carried out according to the kit control and laboratory internal control standards.

Null alleles were assumed and counted in cases of single discrepancies between a homozygous parent and a homozygous child at a locus when at least 12 other independent autosomal STR loci were consistent with paternity and/or maternity. Mutations were assumed and counted after excluding the null alleles in cases of single discrepancies between a parent and child at a locus when at least 12 other STR loci were consistent with paternity and/or maternity.

The experimental data was shown as the mean ± standard deviation. Statistical significance was evaluated with SPSS software. Experimental differences were analyzed using the two-tailed Student's t-test. P values < 0.05 were considered statistically significant.

2.1. Ethical compliance

Our research was prospectively reviewed and approved by a duly constituted ethics committee.

3. Results

3.1. Allele frequency and genetic diversity

We first investigated the frequencies of 15 autosomal STR loci and the results are shown in Fig. 1A and Supp. Table S1. In accordance with the previous reports of STR locus frequency, pairwise GD (genetic distance) values between the Chinese group and 8 neighboring groups (Romanian, Estonian, Iranian, Cayman Islander, South African, Brazilian, Libyan and Korean) were calculated and the data is shown in Supp. Table S2 (Lee et al., 2010; Aguiar et al., 2012; Khodjet-el-Khil et al., 2012; Hedjazi et al., 2013; Anghel et al., 2014; Lucassen et al., 2014; Sadam et al., 2014; Faris and Tanzillo-Swarts, 2015). Phylogenetic reconstruction was conducted to illustrate the genetic relationships and the UPGMA tree is shown in Fig. 1B. From our results, the shortest distance between the Chinese group and the other groups was 0.0073 (compared with Korean groups). The dendrogram can be divided into 2 main clusters: the first cluster was composed of the Romanian, Estonian, Iranian, Cayman Islander, South African, Brazilian, and Libyan groups; the second cluster consisted of the Chinese and Korean groups.

3.2. Mutation mode of STR loci

Generally, it is believed that the mutation of alleles occurs in the step wise mutation model (SMM) including single step mutation, double step mutation and multiple step mutation (Levinson and Gutman, 1987). In our analysis, we observed one to four step mutations and a total number of 518 gains of repeat units compared with 439 losses of repeat units across all loci. Among these mutations, there are 487 1-step mutations, 135 2-step mutations, 58 3-step mutations, 18 4-step mutations and 53 unequivocal mutations across all loci. The ratio of loss/gain repeat units of each allele of 15 STR loci are shown in Fig. 2. We found that along with the increases of repeat units, the ratio of loss/gain increases gradually especially in THO1, D7S820 and D13S317 although all gains of repeat units are higher than all losses. Overall, Fig. 2 not only presents a more detailed characterization of allele mutation of all loci, but also indicates the relationship between the length of repeat units and the losses or gains as well.

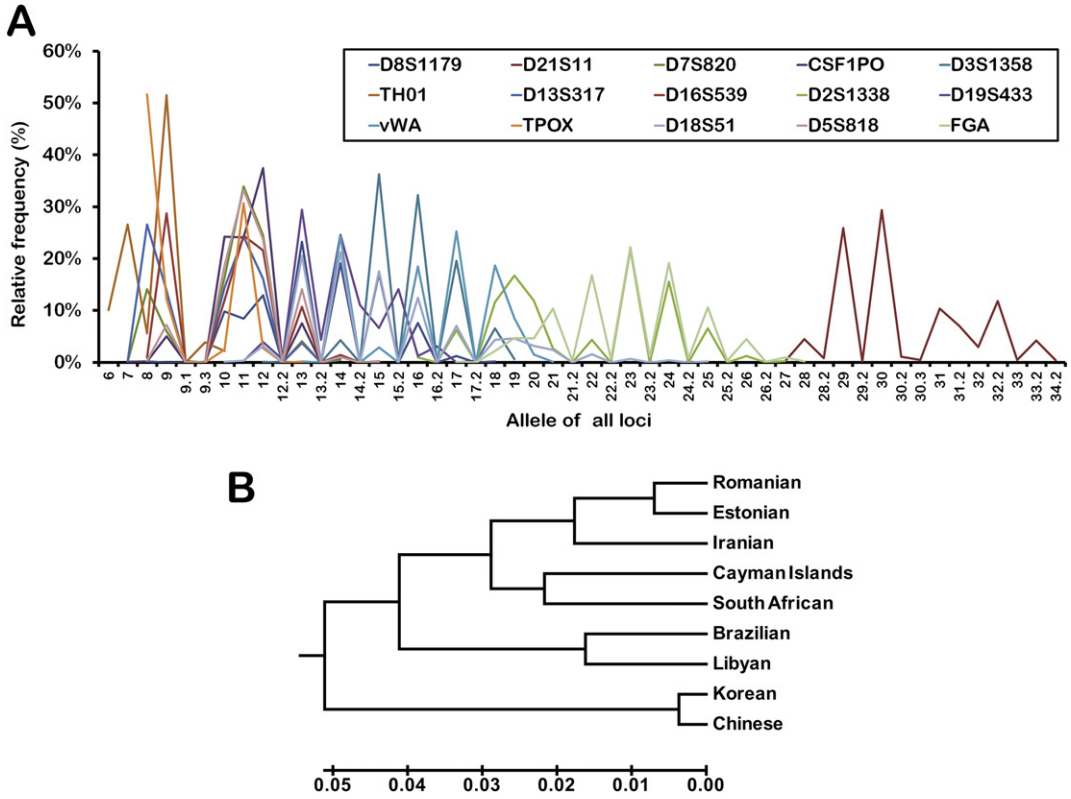

Fig. 1. (A) The distribution of allelic frequencies of 15 autosomal STR loci from Mainland China population. (B) Phylogenic tree of the Chinese group and 8 other groups constructed by the unweighted pair-group method with arithmetic means based on the STR loci.

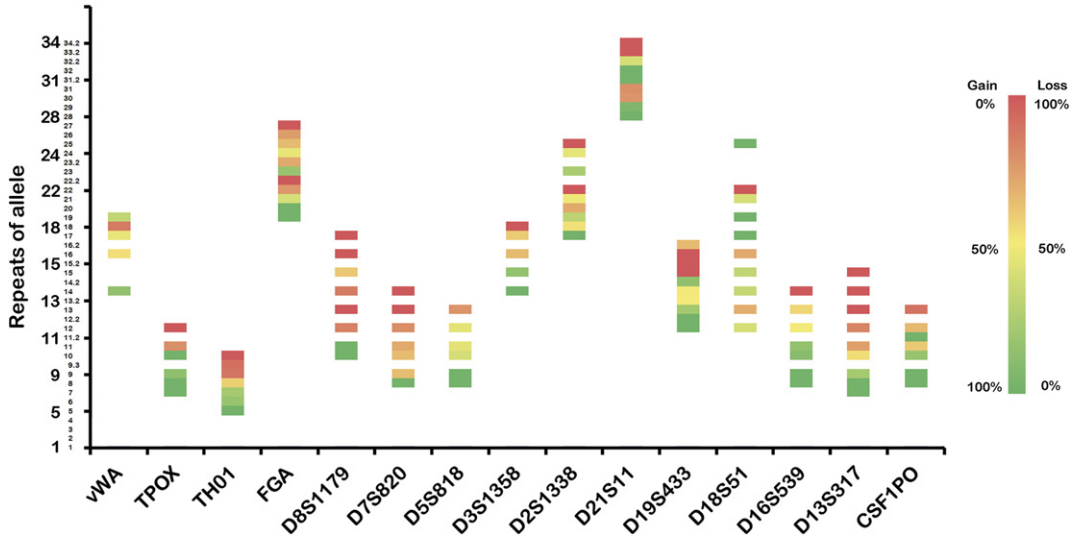

Fig. 2. The mutation changes of repeat gains or losses of all alleles in 15 STR loci. For each STR locus, the ratio of lost number/gained number of repeat units was calculated. The change of color represents the changes of ratio of loss/gain. Red: 100% of loss; green: 100% of gain.

3.3. Mutation rate of 15 autosomal STRs in Mainland China

We assessed the mutation rates including the paternal mutation rate, maternal mutation rate and ambiguous. There are 289 mutations of paternal alleles, 191 mutations of maternal alleles and 198 ambiguous mutations (shown in Fig. 3 and Supp. Table S3). The mutation rate of 15 STR loci was 0.05% to 0.63% and the highest mutation ratio occurred in the D13S317 loci and the lowest ratio in TPOX loci. Interestingly, across all loci, the paternal mutation rate was distinctly higher than the maternal mutation rate except for D19S433 (the paternal mutation rate and maternal mutation rate are roughly equal; paternity: 0.08%; maternity: 0.09%) (Fig. 3A) and the average ratio of male/female is approximately 1.43:1 (Fig. 3B, $^{*}p < 0.01$). Sun et al. reported that the paternal mutations are more than the maternal mutations in Guangdong Province of China and even the average ratio of male/female mutations can reach 3.8:1 (Sun et al., 2014). Our results are consistent with her conclusion.

3.4. Influence of parental age and time of pregnancy on children's mutation rates

In accordance with the information of parental age, we further studied its effects on the children's mutation and the results are shown in Figs. 4 and 5. We found that there was a positive relationship between parental age and children's mutation rate. With the increase of parental age, the children's mutation rates have also increased (Fig. 4A and B, paternal age; Fig. 4C, maternal age) and especially with the increases of paternal age; When paternal age was over 31 years old, the mutation rate has a significant increase (Fig. 4A). The mutation rate of the research subjects with paternal age of ≥31 years is higher than that of 25–30 years and ≤24 years (Fig. 4B). Similarly, the influence of time of pregnancy on children's mutation was investigated too. The range of time of pregnancy in our investigated cases is from 1967 to 2013. According to the range of times trios were divided into four groups including a group for before 1996, group for 1997–2001, group for 2002–2006 and a group for after 2007. All loci mutation rates were analyzed and the data is shown in Fig. 5A. From the results, we found that if the pregnancy time is earlier, the mutation rate of the child is higher especially after 2002. Average mutation rate of all loci was calculated too and the results are shown in Fig. 5B. Being consistent with Fig. 5A, B characterized a positive relationship between time of pregnancy and mutation rates and moreover, the mutation rate rose apparently after 2002.

3.5. Area mutation rate in Mainland China

The studied population were located in Mainland China and distributed in most of the provinces. In accordance with the mutation events in

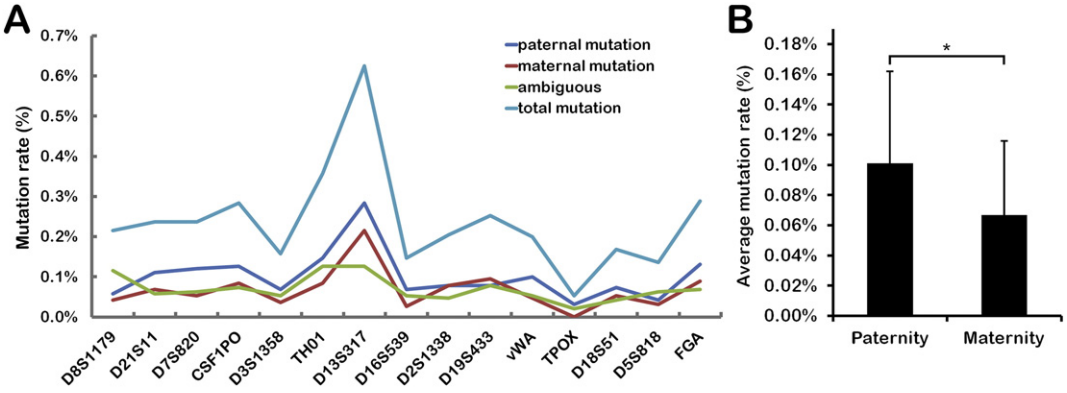

Fig. 3. Mutated source analysis of children's mutation in 15 STR loci. Observed mutations from 19,037 trios were divided into paternal mutation, maternal mutation and ambiguous according to the mutation source. (A) The rate of paternal mutation, maternal mutation, ambiguous and total mutation at each STR locus. (B) The average mutation rate of all STR loci from paternity and maternity.

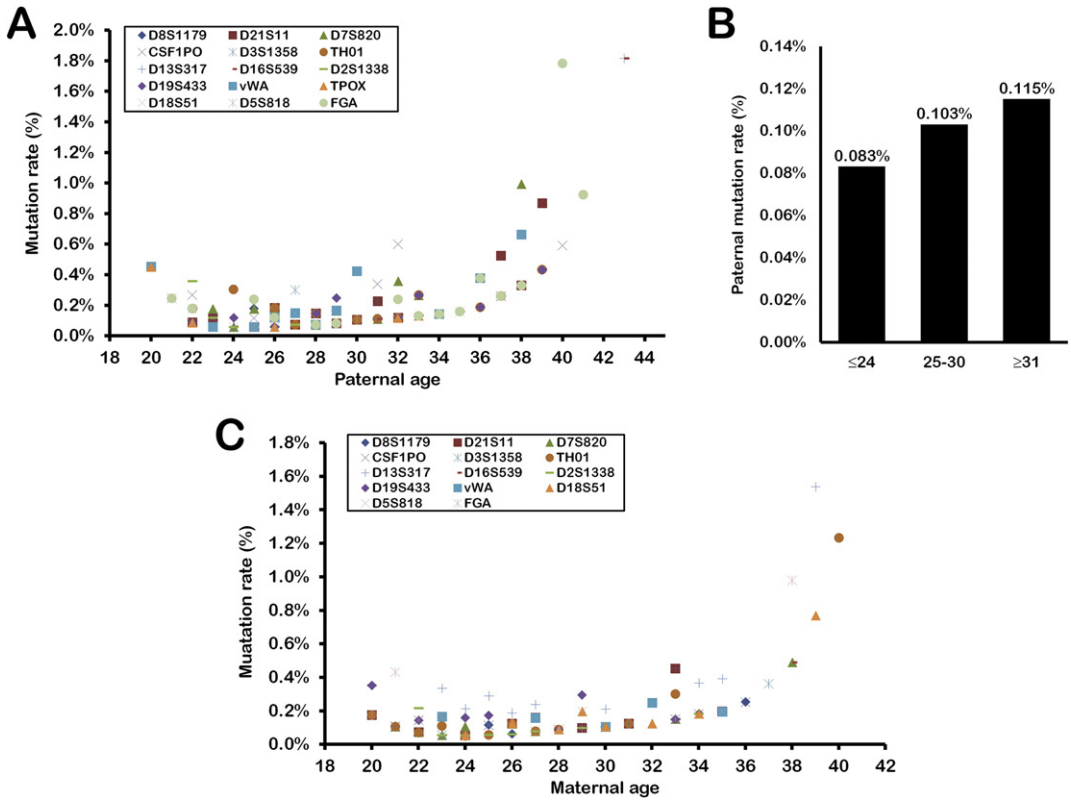

Fig. 4. The relationship between parentage age and mutation rate. The average mutation rate of all loci at a certain age of paternity and maternity was analyzed. (A) The relationship between paternal mutation rate and paternal age. (C) The relationship between maternal mutation rate and maternal age. (B) All paternal mutation events were divided into three groups according to paternal age including the group ≤24, the group of 25–30 and the group of ≥31 and the average mutation rate of each group is calculated.

different province, we calculated the average mutation rate in Mainland China area and the data is shown in Fig. 6. We divided the map of mainland china into six regions including Northeast China, East China, North China, South China, Southwest China and Northwest China and analyzed the mutation rates respectively in above regions (Fig. 6A). We found that the mutation rates of Northeast China, East China, North China and South China were higher, but the mutation rates of Southwest China and Northwest China were lower. Mutation presents a tendency that the population of the east area has a higher mutation rate, but the population of the west area has a lower mutation rate. The average mutation rate of the east area, midland area and west area of Mainland China was investigated too and the result was consistent with Fig. 6A (Fig. 6B).

4. Discussion

Due to the high genetic polymorphism, STR has been used in human population studies as a genetic marker. In our study, we assessed the mutation model and mutation rate of 15 autosomal STR through a large cohort (19,037 trios). Based on the large scale population, all allele frequencies and genetic diversity were studied and analyzed.

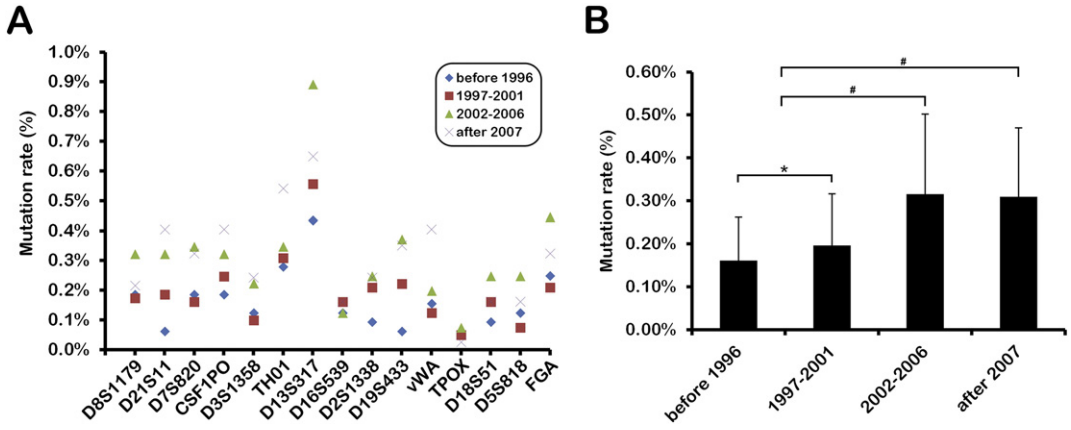

Fig. 5. The relationship between time of pregnancy and mutation rate. All mutations of 15 STR loci were divided into four groups according to the time of pregnancy and for each locus, the average mutation rate of each group was calculated (A). (B) The average mutation rate of all loci is shown in the certain range of years.

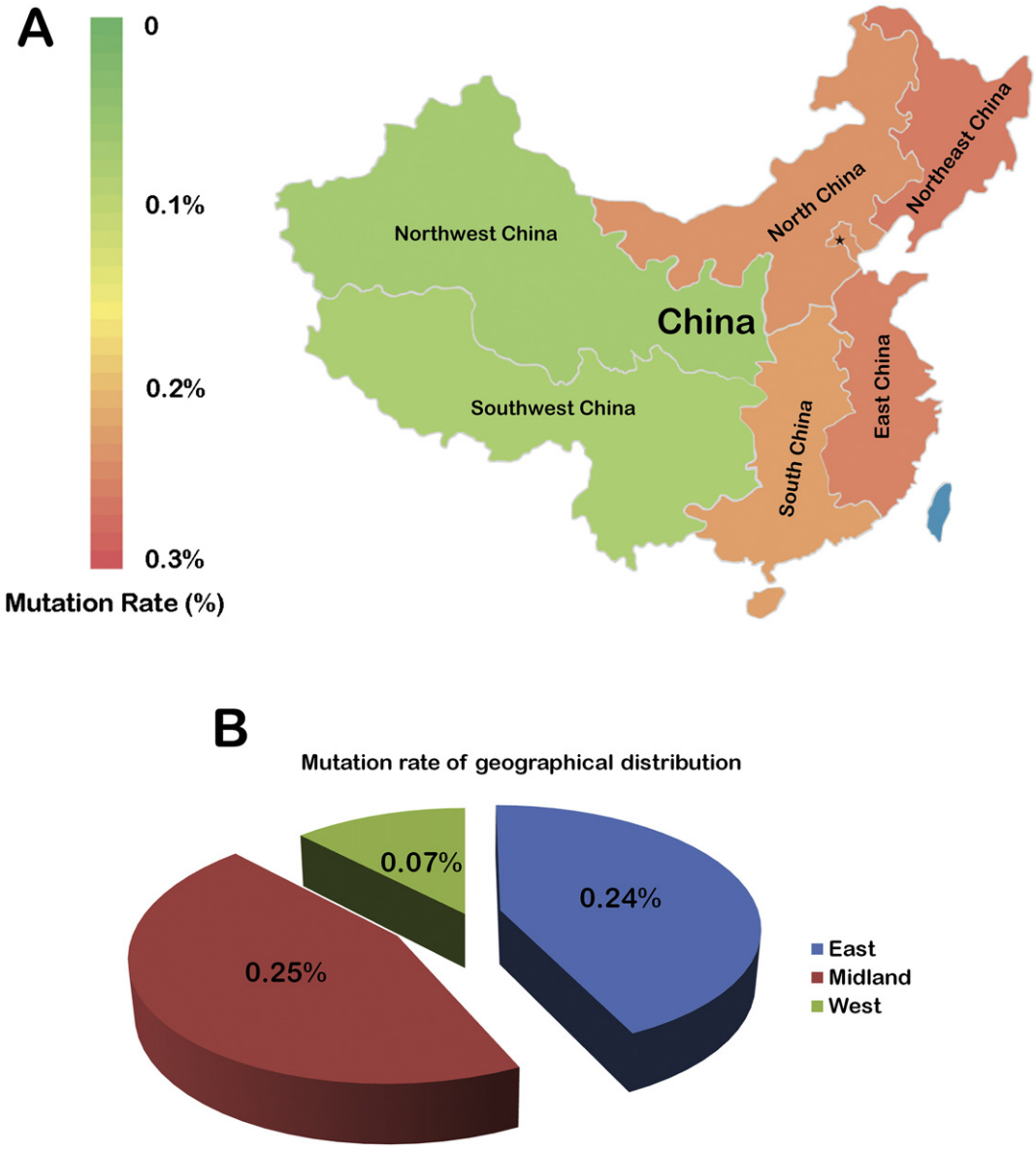

Fig. 6. Distribution of mutations in the Mainland China population. The area of Mainland China was divided into six regions and included the regions of Northeast China, East China, North China, South China, Northwest China and Southwest China respectively. All mutations of above regions were investigated and the average mutation rate is shown (A). Red: high mutation rate; green: low mutation rate. (B) The mutations of the east, midland and west areas were respectively investigated and the mutation rates are shown.

In our study, we focused on the mutation model and we found that the mutation model of STR loci was mainly through repeat unit gains or losses. It is now generally accepted that replication slippage is the major mechanism causing STR allele mutation (Levinson and Gutman, 1987). In our research, four types of allele mutation (1, 2, 3, 4-step mutation) including 698 mutated individuals were observed and these mutations accounted for about 93% of total mutations and our findings were in accord with the stepwise mutation model. Besides, 53 unequivocal mutations were also observed and these mutations presented nonholonomic gain or loss of repeat units. These findings confirmed and expanded the mutation model of autosomal STR loci. What's more, a significant positive correlation existed between repeat losses and the number of repeat units. Along with the increases of the repeat unit's length, the ratio of loss/gain increased too indicating that in the case of more numbers of repeat unit, the repeat unit was easier to lose. To our best knowledge, the effects of repetitions on lost mutation are first reported.

Taking the mutation source, paternal age and maternal age, all mutation events were analyzed. Our results showed that the paternal mutation is higher than the maternal mutation and the parent's age could increase the mutation rate on the children's STR loci. As we know, with the increases of mitosis the probability of mutation also increases (Fleming, 1988; Riparbelli et al., 2004; He et al., 2005). In humans, the sperm mitosis is far more frequent than egg mitosis, and therefore the paternal mutation should be higher in theory and our results could also be illustrated by this point. In addition, it has been reported that estrogen plays an important role in the antioxidant activity against free radicals, mitochondria protection and anti-aging compared with androgen (Leal et al., 1998; Stirone et al., 2005; Ruan et al., 2014; F. Wang et al., 2014; H.D. Wang et al., 2014; Zetterberg and Celojevic, 2015) indicating that estrogen might have a stronger protection in the genetic mutation. Fortunately, the present findings across our studies were consistent with these theories.

From our results, we found that the average mutation rate of children from older parents is higher than that of children with younger parents, especially after 38 years (paternal age or maternal age). As is well known, telomerase play a crucial role in maintenance of telomere length and the stability of chromatin structure. Some reports showed that with age, the enzyme activity of telomerase decreased and the

telomerase gene might even mutate and then these effects influenced the length of the telomere, induce mutation and cause tumorigenesis (Aubert and Lansdorp, 2008; Labussiere et al., 2014; Liu et al., 2014; Dai et al., 2015; Hosen et al., 2015). Our findings about mutations mediated by age were consistent with these reports. Moreover, we also found that the influence of paternal age is stronger than that of maternal age in children's mutation. We considered that these differences might be due to men and women having disparate lifestyles, living environments and stress states.

The genetic polymorphism in some provinces of Mainland China have been investigated (He and Guo, 2013; Hou et al., 2013; Wang et al., 2013; Weng et al., 2013; Gao et al., 2014; Sun et al., 2015; F. Wang et al., 2014; H.D. Wang et al., 2014; Zhang et al., 2015) and the mutations have also been analyzed by some researchers (Brinkmann et al., 1998; Yan et al., 2006; Zhao et al., 2007; Weng et al., 2013). However, little is known about population genetics and mutations of the whole Mainland China. Our present work has firstly described the average mutation rate of 15 autosomal STR loci in Northwest China, East China, North China, South China, Southwest China, Northwest China area. Additionally, we have also investigated the relationship between the time of pregnancy and average mutation rate. China's economy has been growing rapidly and the living standards have constantly improved after the reforms and opening-up policy. From the point of view of area and time, the economy of the east costal area is better than that of the west inland area; moreover, China has entered into the phase of primary product manufacturing after 1995 and entered into early industrialization after 2004 (Liu et al., 2004; Xu and Li, 2006; Fu and Huang, 2008; Qi et al., 2013). Nevertheless, unlike economic development the environmental pollution and the chance of toxic exposure have increased more indicating that the incidence of mutation might also increase. Combined with our results, we considered that the results of different mutation rates in different areas or from different times could be explained through the development of China's economy and the deterioration of the living environment.

5. Conclusion

In this study, we have firstly investigated the genetic polymorphisms, mutation mode and mutation rate of 15 autosomal STR loci in mainland china. Based on the large population, our results indicate that the mutation is mainly through repeat unit losses or gains and furthermore, with the increases of repeat units, the ratio of loss/gain increases gradually. According to the mutation analysis, we found that the paternal mutation rate was higher than the maternal mutation rate and there was a positive correlation between the mutation rate and paternal age, maternal age, and time of pregnancy and furthermore, the average mutation rates of coastal areas were higher than those of inland areas. Taken together, we hope that these findings of genetic polymorphism and mutation in this Chinese population could contribute to the analysis of its genetic diversity for the purpose of forensic testing or population genetic research.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgment

We are grateful to Tianjin Jinshi Forensic Center for providing the supporting data. This work was financially supported by Tianjin CIQ Science and Technology Project (TK049-2013).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.mgene.2015.07.006.

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