Polymorphism of autosomal Alu- insertions

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Abstract: The polymorphism of mitochondrial DNA and Y chromosomes gives us the characteristics of male and female populations in the gene pool. Alu- repeats got their name due to the fact that most of them contain tetranucleotide AGCT (170 bp repeat from the beginning), which can be cleaved with the restriction enzyme Alu I. Alu- repeats influence the composition, organization, and expression of the genome. Alu- repeats are widely used as a genetic markers for genome mapping in clinical diagnosis and characterization of genomic rearrangements. Thus, in this article, we summarize the data on the origin and evolution of Alu-repeats, and the mechanisms of their retroposition which are used as genetic markers in genetics of populations.
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INTRODUCTION

Over the last decade the picture of the population spread throughout the globe was practically solved. Lately the work related to refining demographic and evolutionary history of individual regions and ethnic groups has become more urgent.

If prior to the 90s of XX century population studies were largely based on analysis of polymorphism and serum immunological markers of blood proteins, currently the study of the gene pool structure of individual populations and phylogenetic relationships between them is traditionally done by the analysis of polymorphism loci of nuclear and mitochondrial genomes. At the moment it is generally accepted that mitochondrial DNA, Y- chromosome polymorphism, and autosomal Alu- insertions are the most convenient molecular genetic marker systems for the study of the gene pool structure of individual populations. Usage of these systems allows obtaining genetic portraits of individual ethnic groups and reconstructing their evolutionary pasts [Batzer, 1996; Stoneking, 1997].

Alu- repeats in the human genome

The polymorphism of mitochondrial DNA and Y chromosomes gives us the characteristics of male and female populations in the gene pool. Thus, the study of autosomal Alu- insertions polymorphism makes it possible to determine some features of the human genome diversity in the population as a whole. The advantage of Alu- insertions is that, unlike other biallelic systems, the initial and final states (states before and after Alu insertions) of the element are always known [Stepanov et al. 2002; Levy S., 2007]. It has appeared relatively recently that in human evolutionary genetics the usage of those Alu-insertions coincides with the continent where this human is settled. Some of the loci containing Alu-elements were highly informative markers of differentiation of populations in Europe and Asia - Ya5NBC148, PV92, TPA25 and Ya5NBC27 [Khusnutdinova et al. , 2006].

Repetitive DNA (a substantial portion of the eukaryotic genome) was found in the laboratory in the middle of the 60s by Britten [Waring M., Britten RJ, 1966]. It suggested that the amount of DNA repeats is proportional to the genetic complexity of the organism. For *Caenorhabditis elegans* this amount is ~ 17 % of the DNA, for *Nicotiana tabacum* - 67 % [Smit AF, 1996], and for man - more than 50 % of the genome [International Human Genome Sequencing Consortium, 2001]. Currently there are five major classes of repetitive elements in the human genome identified: repeats arising from transposons; partially inactive gene copies; simple repeats ($(A)_n$, $(CA)_n$, $(CGG)_n$); segment duplications (10-300 m.bp); blocks tandem repeat sequences [International Human Genome Sequencing Consortium, 2001].

Most of these repeats in human genome belong to the first class repeats – those arising from transposons (45 %) [Batzer MA, Deininger PL, 2002]. In almost all mammals transposons are of four types: short (SINE), long (LINE) dispersed repetitive elements with long terminal repeats (LTR-transposons), and DNA transposons [International Human Genome Sequencing Consortium, 2001]. The SINE class is common in mammals. Some types of the SINE class, such as Alu, developed only in humans and primates. It originated from 7SL RNA gene [Ullu E., Tschudi C., 1984].

The structure and origin of Alu- elements

Alu- repeats got their name due to the fact that most of them contain tetranucleotide AGCT (170

bp repeat from the beginning), which can be cleaved with the restriction enzyme Alu I. Alu- repeats consist of two tandems - arranged forms of the ancient Alu-monomer FAM (left (FLAM) and right (FRAM) monomers) [Quentin Y., 1992]. In primates FLAM-FRAM dimerization occurred about 60 million years ago [Zietkiewicz E. et al., 1998]. Ancient Alu-monomer derived from the 7SL RNA gene by deletion of 141 bp and the derivation of a poly-A region at the 3'-end [Ullu E., Tschudi C., 1984; Han K., 2005].

Alu-repeat structure (Fig.1.) [Batzer MA, Deininger PL, 2002] is characterized by several features. The left half (FLAM) with the length of 140 bp is coupled via the poly-A with the longer right half (FRAM), which additionally contains 31 bp [Quentin Y., 1992]. Variation in length between the right and left monomers is defined by the deletion which occurred during their evolution from the FAM [Quentin Y., 1992; Jurka J., Zuckerkandl E., 1991; Hormozdiari F, 2011].

Left monomer contains two promoter elements for the RNA polymerase III, the block A and the block B, each of which has a length of approximately 10 bp [Jurka J., Zuckerkandl E., 1991]. A and B portions are located at positions 10-25 and 70-90 respectively [Knight A. et al., 1996; Novick GE et al., 1996]. Promoter initiates transcription from position A, and block B defines the accuracy of the transcription initiation. It is believed [Batzer MA, Deininger PL, 2002] that only unit B is required for transcription, as members of Ya5 (HS) subfamily have much greater homology observed in this unit.

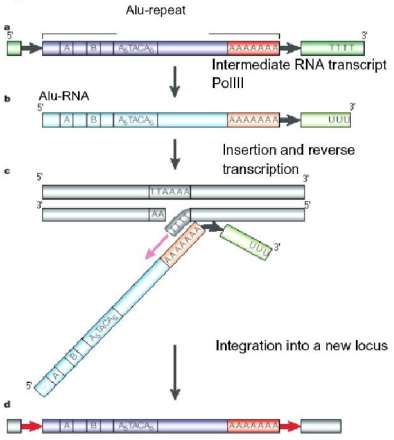

Fig.1. Alu- repeat structure of the human genome and its mechanism of retroposition. a) The structure of a typical Alu- repeat (explanation in the text); b) Intermediate RNA Pol -III- transcript; c) Example of reverse transcription (direction of transcription is shown by pink arrow); d) A copy of the Alu- repeat in the new section of the genome [Batzer MA, Deininger PL, 2002].

Localization and distribution in the human genome

There are 1.09 million copies of Alu-repeats in the human genome, which represents 10.6% of the human nuclear DNA [International Human Genome Sequencing Consortium., 2001]. Alu-sequence is spread with high frequency within the noncoding regions (intergenic regions, introns, etc.) [Batzer MA et al., 1990]. Significant proportion of them is concentrated in the R-segments of chromosomes, where mainly tissue-specific genes are located [Blinov VM, et al, 1998]. Moreover, it was suggested that Alu-elements preferably integrate in regions rich in AT repeats [Bailey AD, Shen CK, 1993]. Analysis of the Alu-repeats organization suggests that they are preferably located in GC-rich regions; these "selfish" elements are possibly favorable for the host (human) [International Human Genome Sequencing Consortium., 2001].

High concentration of Alu-repeats in the saturated regions of the genes of the chromosome allows duplicating portions of the genome between the Alu, their elimination, and chromosomal rearrangements. Perhaps the rapid evolution of primates is associated with a sharp increase in genetic diversity through the recombination Alu-repeats [Blinov VM et al , 2001].

ALU repeats are arranged separately, in pairs, and in direct and inverted orientations [Batzer MA et al., 1991; Wang J., 2006; Hormozdiari F, 2011].

Options Alu - elements

Alu- repeats influence the composition, organization, and expression of the genome. These elements can enhance transcription of neighboring loci due to the promoter or enhancer activity [Vansant G., Reynolds WF, 1995; Britten RJ, 1997; Deininger PL, Batzer MA, 1999]. In addition the presence of internal promoters can activate previously "dormant" sequences [Novick GE et al., 1996; Vansant G., Reynolds W.F., 1995]. Alu-repeats may also reduce the transcriptional activity of neighboring regions by promoting the assembly of nucleosomes in this area [Englander EW, Howard BH, 1995]. Furthermore, Alu-repeats promote surrounding loci methylation, thus providing another mechanism for control over gene expression [Heller H. et al., 1995]. Although the effect of methylation is typically inhibitory, there are cases in which methylation of Alu-repeats increases transcriptional activity. For example, methylated CpG sites located within two Alu-repeat loci GPHA (α-subunit of the glycoprotein hormone) stimulate expression of this gene [Cox GS et al., 1998].

Alu-repeats allow creation of a variety of secondary and tertiary structures due to triplex, cruciform and other non-canonical DNA structures [Blinov VM, et al, 1998]. It can be assumed that this possibility can build three-dimensional structure by

binding proteins of chromosomes and creating local spatial structure - convenient operation for the genes and/or regulation of their activity. Another possibility is that the Alu-repeats delete linear DNA structures of a sufficient distance from each other to form a space between the complexes which may lead to compaction of DNA in the chromosome [Blinov VM et al, 2001].

The transcription is also regulated by the secondary structure of DNA Alu-repeats [Hanke, JH, Hambor JE, Kavathas P., 1995]. For example, the locus of the human CD8-α comprises two Alu repeats that can be linked together to form a cruciform conformation which inhibits transcription. Alu elements contained within introns (as well as 5 'and 3 ' untranslated regions (UTR)) may affect the pre-mRNA processing and play a leading role in changing the gene product [Mitchell GA et al., 1991; Knebelmann B. et al. 1995]. Alu-repeats can also inactivate or alter the function of gene products by creating alternative splicing sites or interfering with their mechanisms.

These changes, which often result in serious genetic effects, can cause point mutations in the pre-existing Alu elements and insertions formed de novo [Bailey AD, Shen CK, 1993 ; Knebelmann B. et al . 1995]. The presence of Alu repeats, as well as other retropositioning elements (B1, B2, Mir, LINE) in a pre-mRNA transcript may affect polyadenylation and affect the efficiency of translation [Harendza CJ, Johnson LF 1990; Smit AF, Riggs AD, 1995; Schmid CW 1996].

The presence of Alu-repeats in exons can affect gene expression [Berquin IM, Ahram M., Sloane BF, 1997; Szmulewicz MN, Novick GE, Herrera RJ, 1998]. Insertion in a coding or regulatory region of a gene can lead to the development of the disease. There are three pathogenetic mechanisms associated with Alu- repeats [Miki Y., 1998; Zhang W., 2011]: retroposition Alu-repeats in the genes de novo; insertion Alu-repeats in mRNA splicing; homologous recombination between the Alu-repeats, which leads to chromosomal rearrangement. The most common of these mechanisms is apparently the first.

The insertion of the Alu- repeat de novo was found in exon 5 of clotting factor IX from a patient with hemophilia B [Vidaud D. et al., 1993]. The Alu-repeat with the length of 322 bp is located in the coding region; it terminates the reading frame of glutamic acid protein Factor IX, resulting in a premature stop codon. The nucleotide sequence of the built - ALU repeat is different from Ya (HS) Alu-family only by one additional adenine residue, flanked by direct repeats (15 bp), and it contains the poly-A 78 -bp region at the 3' – end. While the direct repeats contain almost no adenine and thymine, the surrounding sequence repeats consist predominantly of T and A - residues.

The Alu-repeat insertion which is embedded in exon 2 ChE was found in a patient with acholinesterasemia. Alu- repeat with the length of 342 bp comprised poly– A-38 -bp region. It was flanked by target site duplications (15 bp) from both sides. In the initial sequence of the gene ChE mutation is absent. Alu-repeat sequence had 93% homology with the evolutionarily youngest Alu- subfamily of human appearance suggesting that the insertion in this case was a result of the mechanism of retrotransposition [Muratani K., 1991].

A similar mechanism of gene inactivation was found in some other diseases, including neurofibromatosis type 1, hyperparathyroidism newborn, Huntington's disease, familial hypercalcemia. Other Alu- repeat insertions de novo in the districts of potential oncogenes and tumor suppressor genes can trigger the process of carcinogenesis. In particular, it is shown that one of the pathogenic mutations of B- lymphoma cells is an integration of Alu- repeat locus Mlvi- 2.

Deletions in genes due to homologous recombination between the Alu- repeat loci have been found in low-density lipoprotein receptors for familial hypercholesterolemia in a gene of alpha chain; in beta - hexosaminidase and in adenosine deaminase genes with severe combined immunodeficiency; in C1 inhibitor gene for hereditary angioedema Eden, and in some other hereditary diseases and chromosomal rearrangements [Miki Y., 1998].

The mechanism associated with the insertion of Alu- repeat in the mRNA during splicing is rare enough. There are only several disease states which are caused by splicing-mediated integration of Alu-repeat in the mRNA. Such an insertion was found in 142 nucleotides of the junction of exons 3 and 4 of the gene in mRNA -D- ornithine aminotransferase (OAT). Lined sequence in 3' -terminal portion of Alu- repeat was present in the normal gene intron 3 OAT. CG transversion in Alu- repeat has led to a new splice donor site within the Alu - element activation of cryptic acceptor site and splice -mediated insertion of Alu- element in the mature mRNA of OAT [Mitchell GA et al., 1991].

Evolution of subfamilies

As a result, the study of sequence of Alu-repeats revealed that they have a large number of point mutations that consistently occur during evolution. Today, there are at least 14 major subfamilies [Kapitonov V., Jurka J., 1996 ; Batzer MA, Deininger PL, 2002 ; Roy-Engel AM, 2002], which can be grouped into three groups: young, intermediate, and ancient, given the initial

retroposition. [Deininger P.L. et al., 1992; Kapitonov V., Jurka J., 1996].

Recent studies have shown that two oldest subfamilies Jo and Jb occurred about 81 million years ago [Kapitonov V., Jurka J., 1996; Sela N., 2007], which corresponds to the time of appearance of detachment in primates. Subfamilies S (Sx, Sp, Sq, Sc) are intermediaries by age (48-35 million years ago) and are of CpG- composition. It is suggested that differences in the sequence of Alu-repeats in Sp and Sc subfamilies is due to their derivation from two different ancestral sequences [Jurka J., Milosavljevic A., 1991; Roy-Engel AM et al., 2001]. The speed of Alu-repeats amplification decreased significantly, and now it is a rare event that occurs only in the group of young subfamilies (Y, Yc1, Yc2, Ya5, Ya5a2, Ya8, Yb8, Yb9) [Shaikh TH, Deininger PL, 1996].

Two models were proposed to explain the origin of the families of Alu- modified RNA transcript 7SL RNA gene: the transposon model and the master gene. Transposon model suggests that many SINE-elements are capable of generating new ones that have transposon activity [Novick GE et al., 1996].

According to the master gene model [Deininger PL et al., 1992], most SINE derived from one or more active regions of the genome. This model assumes a linear amplification rate, which is controlled by a master gene. Mutations in master genes generate new subfamilies and are the main reason for the differences in the rate of amplification.

Alu- repeats as a genetic marker

Alu- repeats are widely used as a genetic markers for genome mapping in clinical diagnosis and characterization of genomic rearrangements. They are effective genetic markers due to the widespread dissemination of the human genome [Mnukova-Fajdelova M.et al., 1994; Toda Y., Tomita M., 1997; Stewart C., 2011].

Several properties of polymorphic Alu-repeats make them very comfortable genetic markers. These properties include high stability of Alu-repeats, low insertion de novo, and absence of a specific mechanism for the removal of the locus. These characteristics allow a high degree of reliability in considering insertion Alu- repeat loci in each case as an independent event that happened only once. Furthermore, the nature of movement Alu- repeats can uniquely identify initial and final states of the allelic loci. Finally, genotyping of polymorphic Alu-repeats stands out because of its methodological simplicity [Novick GE et al., 1996; Stoneking M. et al., 1997; Stewart C., 2011].

Currently polymorphic Alu- repeats (along with other genetic markers (microsatellites, mtDNA, Y- chromosome, SNP)) are widely used for the analysis of the phylogeny and evolution of human populations. Research on genetic diversity of human populations using Alu-repeats is maintained in several centers in the U.S., Europe, and in Russia [Stepanov VA et al, 2001; Hitrinskaya IY et al, 2001; Batzer M.A. et al., 1996; Stoneking M. et al., 1997; Stewart C., 2011].

Polymorphism analysis of several Alu-repeats in the population of the world has shown that the data of the distribution of Alu-repeats in populations is consistent with the hypothesis of African origin of modern man [Batzer MA et al., 1996; Stoneking M. et al., 1997]. Genetic diversity of African populations is higher than that of populations from other continents. The separation of African and non-African populations (according to Alu- repeats) corresponds to 137,000 ± 15,000 years.

Thus, in this article, we summarize the data on the origin and evolution of Alu-repeats, and the mechanisms of their retroposition which are used as genetic markers in genetics of populations. Alu-repeats continue to generate genomic diversity, and their amplification leads to the formation of the largest family of transposable elements in the human genome. Exactly these polymorphic Alu- repeats are convenient genetic markers to study the interaction between populations of origin.

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