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Reviews

GENETIC MARKERS AND GENOME-WIDE ASSOCIATION STUDY IN PLANTS

***Tussipkan Dilnur[1], , Zhaoe Pan[2]**

[1]National Center for Biotechnolog, Plant Genetic Engineering Laboratory, 13/5, Qorghalzhyn road., Astana, 010000, Kazakhstan
[2]State Key Laboratory of Cotton Biology, Institute of Cotton Research, Chinese Academy of Agricultural Sciences, Anyang 455000, China
**tdilnur@mail.ru*

ABSTRACT

Due to the advanced sequencing technologies, breeders and researchers can use DNA markers to characterize various plants' genetic diversity, kinship, and population structures. This review describes four kinds of genetic markers. Among them, DNA-based molecular markers were discussed in types, basic mechanisms, advantages, and disadvantages in detail. Secondly, we summarize the whole process of a genome-wide association study, and its advantages and disadvantages. We hope that this review provides fundamental information that will be useful for understanding different markers, especially, DNA-based molecular markers, and genome-wide association studies.

Keywords: polymerase chain reaction (PCR) based marker, simple sequence repeats (SSRs), DNA-based molecular marker, single nucleotide polymorphisms (SNPs), genome- wide association study (GWS).

INTRODUCTION

GENETIC MARKERS

Identification of the genetic diversity present within and between various plant populations and phylogenetic, and evolutionary analyses can play an essential role in the efficient utilization of plants [1]. Genetic markers (markers) are used to study genetic diversity (reviewed in [2, 3], genomic organization [4], QTL analysis [5-7], and association analysis [8-10]. The genetic variations between the individual plant cultivars or species are referred to as genetic markers. Usually, markers do not act as genes themselves, but they are part of a gene. So they can serve as reference points to the location of the genes of interest. The present studies of genetic diversity are mainly reflected in four different markers: morphological markers, cytological markers, biochemical markers (monoterpenes, alloenzymes, and other protein markers), DNA based molecular markers [2, 11, 12].

Morphological marker. Basically morphological and physiological characteristics like flower structure, shape, color and pattern, seed size, growth habit etc. are used as visual markers for QTL studies in conventional breeding programs for more than centuries since the time of Mendel's discovery [12]. Morphological markers are controlled by genes and can be visualized in the form of phenotypes when they are prone to environmental stress. The environmental factors not only influence the marker expression but also lead to the false determination of linkage and gene action. Another disadvantage of morphological markers is that their development or application needs time [13], but they can be easily identified and are cost- effective.

Cytological marker. Cytological markers include the study of cytological characteristics like chromosome size, secondary constriction in chromosomes, the position of the centromere, arm ratio, constitutive heterochromatic patterns, banding characteristics, DNA content, total genomic chromosome length, chromosome volume, and meiotic behavior of chromosome, etc [2]. The cytological method has the characteristics of strong stability, but it can only provide limited information and has been very limited in genetic mapping and plant breeding [14].

Biochemical marker. A biochemical substance such as protein, lipids, and sugar can be used as a marker, but like morphological markers, biochemical markers are also limited in number [15]. Osmolytes such as proline, glycine betaine (GB), total sugars, and antioxidants such as catalase (CAT), peroxidase (POX), superoxide dismutase (SOD), glutathione, esterase (EST), malate dehydrogenase (MDH) and glutamate dehydrogenase (GDH) can be used as a biochemical marker for stress tolerance studies [16-18]. This is a rapid method of assessing diversity and requires a smaller amount of plant tissue as a sample. However, they are limited in number, affected by environmental fluctuations, and cannot be used to construct a complete genetic map [2].

DNA-based molecular marker. The limitations of phenotype-based genetic markers led to the development of more general and useful direct DNA-based markers that are known as molecular markers [19]. Molecular markers are predominantly used marker nowadays, because it is easy to observe the genetic variations at the DNA level and provide a copious amount of genetic markers. They are DNA sequences that can be easily detected, moreover, whole inheritance can be observed through genome-wide identification of DNA polymorphism [12]. Molecular markers have numerous advantages as compared with the conventional methods: stable and environment insensitive; distributed throughout the genome, but require no prior information about the genome of an organism; non-tissue specific; phenotypically neutral, and with few pleiotropic and epistatic effects; small amounts of tissue and DNA samples is required; application methods are simple, quick and inexpensive; have linkage to distinct phenotypes; able to use identify the polymorphism between bi-parental population and natural population [9, 20-23]. On the basis of methodologies used for detection, DNA-based molecular markers are divided into three main classes according to the method of their detection (Figure 1).

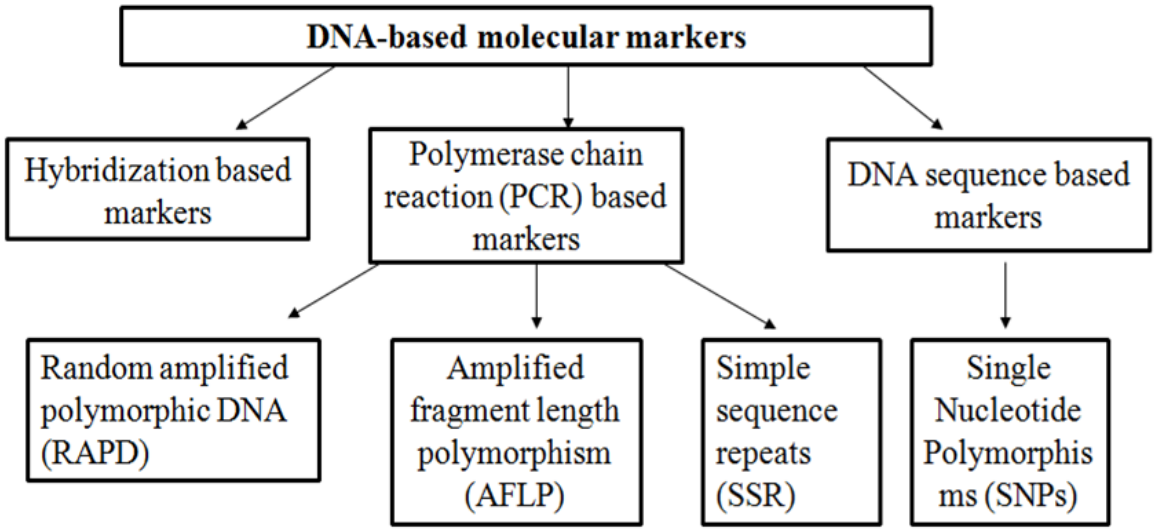

Figure 1 – The classes of DNA-based molecular markers

Hybridization-based maker. In the 1960s, Arber, Smith, and Nathans discovered and isolated DNA-cleaving enzymes from bacteria called restriction endonucleases. These enzymes, for example EcoRI and EcoRVetc recognize specific four, six, or eight base pair (bp) sequences in DNA, and found that it had the capability of cleaving DNA molecules at characteristic sites into pieces called restriction fragments [12, 24, 25]. The restricted pattern gives rise to variations in lengths that resulted from single nucleotide substitutions in the recognition sequence of the restriction enzyme, the basis of a new marker called the restriction fragment length polymorphisms (RFLPs) [26]. RFLP markers were first used in 1975 to identify DNA sequence polymorphisms for genetic mapping of a temperature-sensitive mutation of adenovirus serotypes [27]. It was then used for human genome mapping [28], and later adopted for plant genomes [29, 30]. A significant advantage of this marker system allowed researchers to assay genetic variation that occurred in the non-coding parts of the DNA sequence (unexpressed or silent) as well as in coding regions. Screening reveals three different types of banding patterns: a large band (homozygous), two smaller bands (restriction site occurs on both homologies), and all three bands (heterozygote) [26]. In addition, these markers are considered to be highly polymorphic, co-dominantly inherited, and highly reproducible. However, the RFLP technique is not very widely used, because it is time-consuming, involves expensive and toxic reagents, requires a large quantity of high-quality genomic DNA, and scans only one or a few loci with a single probe and restriction enzyme combination [31]. RFLP has been used for several purposes in a number of plants, including cotton despite some drawbacks. Meredith (1992) reported the first heterosis and varietal origins study in cotton using RFLP [32]. Reinisch, Dong [33] employ a detailed RFLP map to investigate chromosome organization and evolution in cotton and assembled 705 RFLP loci into 41 linkage groups. Wright, Thaxton [34] studied genes affecting the density of leaf and stem trichomes using a detailed RFLP map. Detailed RFLP maps of cotton with 31 and 17 linkage groups were developed by Shappley et al. (1998) [35] and Ulloa and Wrjr [36], respectively. Ulloa, Saha [37] developed RFLP join map into 15 linkage groups using four intraspecific kinds of cotton (*Gossypium hirsutum*) populations. Rashidismaelhag, Junichi [38] employed RFLP to study variations of the chloroplast DNA in three cultivated species of cotton.

Polymerase chain reaction (PCR) based marker. PCR is one of the important discoveries in mid of the 1980s by Kerry Mullis [39]. It is a molecular biology technique for enzymatically amplifying small quantities of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence [40]. A basic PCR setup requires several components and reagents. The components include: a DNA template that contains the DNA region (target) to amplify; Taq polymerase, a DNA polymerase that is heat resistant, so that it can remain intact during the DNA denaturation process; Primers that are complementary to the DNA regions at the 3'and 5' ends of the DNA region; Deoxynucleoside triphosphates (dNTPs), the building-blocks from which the DNA polymerase synthesizes a new DNA strand; Buffer solution, providing a suitable chemical environment for optimum activity and stability of the DNA polymerase; Bivalentcations, magnesium or manganese ions; generally Mg^{2+} is used, but Mn^{2+} can be used for PCR-mediated DNA mutagenesis, as higher Mn^{2+} concentration increases the error rate during DNA synthesis; Monovalent cation potassium ions.

Random amplified polymorphic DNA (RAPD). RAPD was originally developed for mapping human genes [28]. In the agronomic field, the first RFLP map was constructed by Bernatzky and Tanksley [41] in tomatoes. RAPD technique uses a non-specific single primer (10 nucleotide length) and the PCR products come from many areas of the specimen sample of DNA without prior knowledge of the target gene.

The main advantages of the RAPD technology are that [42, 43]: It is suitable to work on anonymous genomes and only needs limited quantities of DNA; The process can be automated, so they are quick and also cost-effective; RAPD primers can easily be scored due to large size difference between fragments (as 1 for the presence of band and 0 for the absence of band); For detection method no need for a radioactive substance which is harmful to human health [44]. However, there are some disadvantages of using RAPD: the majority of the alleles segregate as dominant markers, and hence the technique does not allow identifying dominant homozy-

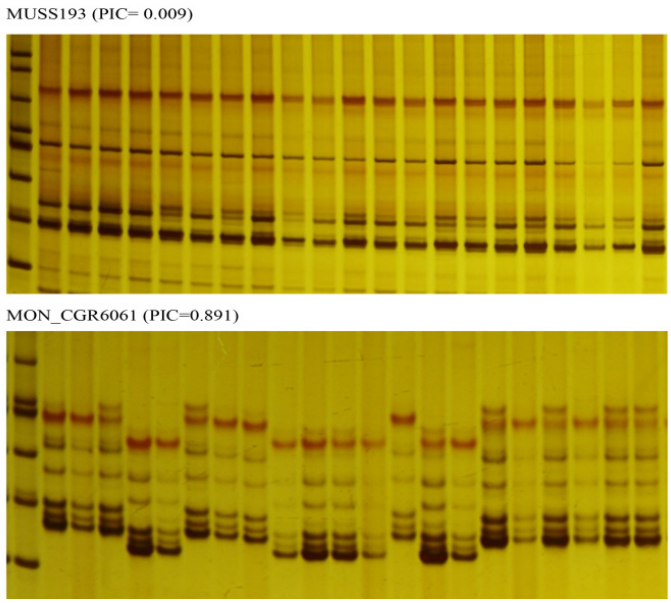

Figure 2 – SSR primers revealed the lowest (MUSS193) and the highest PIC (MON_CGR6061) polymorphisms in *Gossypium arboreum* [57].

gotes from heterozygotes. RAPD is extremely dependent on the experiential process such as the quality and concentration of template DNA, concentrations of PCR components, and sample contamination during the experiment [45]; If there are mismatches between the primer and the template DNA, they affect the total presence of PCR products. Thus, the RAPD results can be difficult to score and interpret [46].

Amplified fragment length polymorphism (AFLP). AFLP analysis is PCR-based technique, developed by Keygene BV, Wageningen [47]. This technique can analyze more than 50 independent loci simultaneously in a single PCR reaction [48]. The basic protocol for PCR is simple: first of all genomic DNA (about 500 ng) is treated with two restriction enzymes, a rare cutter (EcoRI) and a frequent cutter (Msel). These digested fragments were then modified with adapters. These modified restriction fragments are amplified with the help of selective primers which use adapter and restriction site sequence as target sites for annealing. Amplified fragments are further analyzed and scored through polyacrylamide gel electrophoresis [12, 49]. The markers have some advantages and disadvantages.

Advantages: The AFLP can give highly reliable reproducible results and it is easy to interpret the result. So, it has been reliably used for determining genetic diversity and phylogenetic relationship between closely related genotypes [47, 50]; AFLP markers do not require prior knowledge of the genomic composition [50]. Disadvantages: AFLP markers are generally dominant, which does not differentiate dominant homozygotes from heterozygotes [50]. Large amounts of DNA are required and a complicated methodology; is labor intensive and expensive to set up [51].

Simple sequence repeats (SSR). SSRs, also known as microsatellites are DNA-based molecular markers that have revolutionized molecular biology, molecular evolution, functional genetics, quantitative genetics, population biology, and evolutionary biology [52]. SSRs were first observed in 1981 in humans [53]. SSRs are tandem repeats of short DNA sequences, usually consisting of two to six bp nucleotides [54, 55]. They occur very commonly throughout the whole genome of an eukaryotic organism in both coding and non-coding regions, also present in prokaryotes but at low frequency [56]. The mutation rate of microsatellite loci is10^{-2} to$10^{}$events per locus per generation. The value of a marker for detecting polymorphism in a population is called polymorphic information content (PIC). Comparison of PIC value gives us a rough idea of the power of various markers. PIC depends on a number of alleles and their frequencies. For example, if a marker has 2 alleles of 0.6 and 0.4 frequencies then its PIC will be: PIC=1-[(0.6)2+ (0.4)2] = 0.48. (Figure 2)

Advantages of SSR marker: its abundance, high rate of polymorphism, co-dominant inheritance in nature, etc., frequently used in the studies of genetic diversity, genome mapping, and pedigree analysis [58]. SSRs provide multiple alleles that may be detected at a single locus using a simple PCR-based screen, very small quantities of DNA are required for screening, and analysis is amenable to automated allele detection and sizing [23]. It requires a small amount of DNA (10-100ng), is cheap, and is easy to run, so different research laboratories to produce consistent data for QTL mapping and association mapping can use them.

Disadvantages: If it needs to analyze a large population and a lot of makers, SSRs also have some disadvantages like they are time-consuming and laborious. PAGE and silver staining is used to visualize the polymorphism which is hazardous [59]. The presence of a lot of stutter bands becomes problematic even though sometime heterozygous may be confused with homozygous. Sequence information of the amplified region is needed [60]. Homologous loci are not always available which is also a problem in intra-genomic analyses [61].

DNA SEQUENCE-BASED MARKERS

Single Nucleotide Polymorphisms (SNPs). SNPs are often abbreviated to SNP as a variation in a single nucleotide that occurs at a specific position in the genome [62] and is one of the most popular markers to identify genetic polymorphisms at the DNA level [63]. SNPs are estimated that the most common genetic variant found in all individuals, one

SNP occurs every 100–300bp in any genome, so SNPs markers have higher polymorphism than that of SSRs and other molecular markers [62] SNPs have been well characterized since the beginning of DNA sequencing in 1977, but the ability to genotype SNPs rapidly in large numbers of samples was not possible until the application of high-throughput Microarray technology (gene chip) in the late 1990s [64]. SNPs are widespread [65] throughout the genome. There are three different categories of SNPs: transitions (C/T or G/A), transversions (C/G, A/T, C/A, or T/G), and small insertions/deletions (indels) [23]. SNP could be divided into non-coding region SNP and coding region SNP (cSNP). The non-coding region of the genome contains many important regulatory elements including promoter, enhancer, and insulator, any kind of change in this regulatory region can change the functionality of that protein [66].

Advantages of SNP markers: this type of marker is a co-dominant marker and helps to discriminate between the homozygous and heterozygous stage of an individual. SNPs are found abundantly throughout the genome. They are highly reproducible and loci-specific [67]. They are more abundant and have greater potential for automation [68].

Disadvantages of SNP markers: Compared with multi-allele microsatellites, SNP markers have a low value of polymorphic information content (PIC), because they have been regarded as bi-allelic (nucleotide substitution as either transition (C/T or G/A) or transversion (C/G, A/T, C/A, or T/G). In addition, they need sequence information and are also very costly. SNP genotyping is challenging because of the requirement for specialized equipment and expertise [67].

SNP markers were widely used in plant genetics and breeding because of their excellent genetic attributes and suitability for genetic diversity analysis and evolutionary relationships, understanding of population substructure, detection of genome-wide linkage disequilibrium, and association mapping of genes controlling complex phenotypic traits [69]. It has been used in different crop genetics, including rice [70-73], barely [74], soybean [75, 76], maize [77], wheat [78-82], pea [83-85] and cotton [9, 86-88]. For example, Dilnur et al. reported nine SNP-rich regions analysis revealed 143 polymorphisms that distributed 40 candidate genes and significantly associated relative fresh weight, relative stem length, relative chlorophyll content, relative water content, and comprehensive index of salt tolerance in Asiatic cotton (Gossypium arboretum) [9].

GENOME-WIDE ASSOCIATION STUDY (GWS)

The fundamental aim of genetics is to connect genotype to the heritable phenotype. The identification and characterization of genes associated with agronomical important traits are essential for both understanding the genetic basis of phenotypic variation and efficient crop improvement [9]. Traditionally, QTL mapping has been used as a methodology to understand the genetic control of polygenic traits and identification of genes underlying agronomic quantitative trait loci (QTLs) [89], however QTL mapping presents limitations, such as low mapping resolution and limited genetic diversity between the mapping population parents. For example, only two allelic variations are analyzed (one per parent) in a biparental population, which means that various alleles occurring in other plants are missed [90]. These limitations of linkage mapping in dissecting QTL have been improved with the use of association mapping or LD mapping (Ross-Ibarra et al. 2007). Association mapping has also been referred to as "association genetics," "association studies," "Genome-wide association study (GWS)" and "linkage disequilibrium mapping" in different studies.

Historically, association mapping was first successfully used for the identification of alleles at loci contributing to susceptibility to human diseases. Nowadays, association genetics is a multidisciplinary field, involving components of genomics, statistical genetics, molecular biology, and bioinformatics, which together form the basis for selecting, evaluating, and associating genomic regions for correlation with trait variation.

Association mapping is a study aiming to detect linkage between genetic polymorphisms and phenotypic variations in existing germplasm. In general, the following six procedures are outlined for association mapping study in the structured population: (i) to choose a diverse population such as exotic accessions, wild relatives, and elite cultivars and landraces. This strategy can be used to detect many natural allelic variations simultaneously in a single study; (ii) Although it is so important to select the phenotypic diversity of agronomic traits such as yield, stress tolerance or quality-related traits and multiple repeats like years/environments; (iii) the genotypes are then scanned with suitable molecular markers (AFLP, SSRs, SNPs), mostly SNP makers were performed over association mapping; (iv) population structure and kinships are determined to avoid false positives followed by (v) quantification of LD extent using different statistics like D, D' or r^2. (vi) Finally, genotypic and phenotypic data are correlated using appropriate statistical software for finding maker-trait associations. After then, it is chosen –Log P value high SNPs related traits and candidate genes. Consequently, these tagged genes were verified by Quantitative real-time PCR (qPCR), transgenic method, genome editing systems, and annotated for a precise biological function [91, 92]. The whole process of genome-wide association study and candidate gene analysis was illustrated simply in Figure 3.

The advantages of association mapping over conventional QTL mapping are due to (i) a powerful tool for the identification of genes associated with agronomic traits and can be used to detect many natural allelic variations simultaneously in a single study; (ii) Recent advances in high-throughput sequencing technologies have enabled rapid and accurate sequencing of a large number of genomes, so these technologies make GWS timesaving and cost-effective [90]; (iii) likelihood for a higher resolution mapping because of the utilization of majority recombination events from a large number of meiosis throughout germplasm development history; and (iv) possibility of exploiting historically measured trait data for association [93-95].

On the other hand, the limitations of this approach are also obvious (i) the hypothesis of population homogeneity in association studies, particularly case-control studies, can identify both false negative (Type II error) and false positive (Type I error) errors. False negative (Type II error) is a state of lack of marker-trait association when in fact it exists and false positive (Type I error) is a state when there is a marker-trait as-

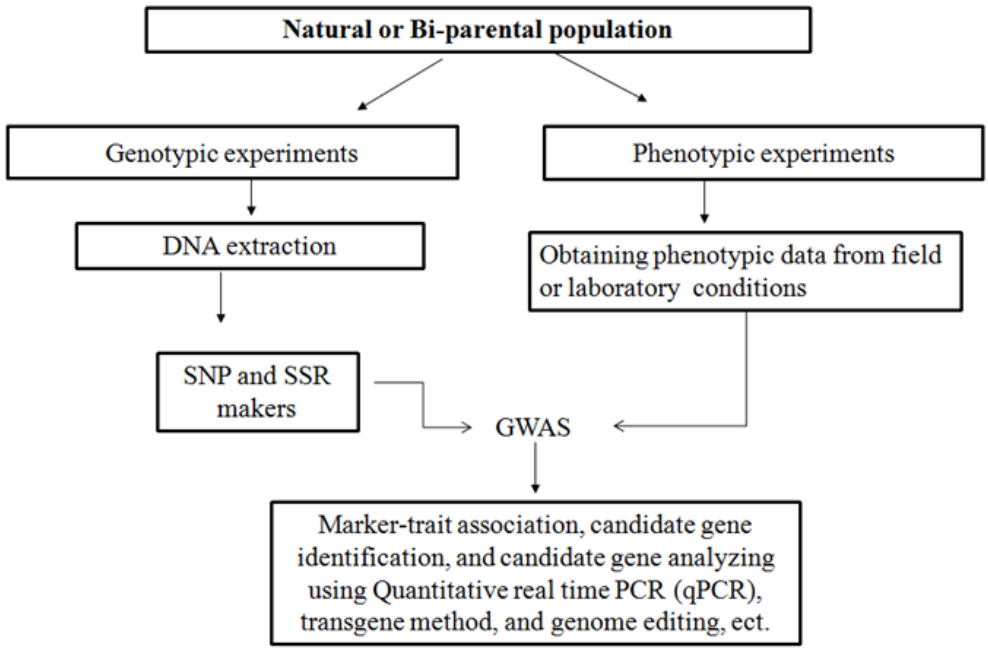

Figure 3 – Whole process of genome-wide association study and candidate gene analyzing

sociation when in fact it does not exist [91]. To control false associations, several statistical methods have been used such as the general linear model (GLM) incorporates the Q-matrix only and the mixed linear model (MLM), also the kinship matrix [96]. (ii) there is a lack of linkage disequilibrium information among the markers identified for significant associations [97]. (iii) Unbalanced allele frequency in the population. (iv) It is not efficient for the detection of rare alleles, and it requires large population sizes. (v) association could be caused by population structure, and thus an efficient control of the population structure is needed [98].

CONCLUSION

During the last two decades, there has been resurgence in molecular methods and the development of second generation advanced molecular techniques. These advancements in molecular biology have greatly facilitated research in many disciplines like taxonomy, phylogeny, ecology, genetics, and plant breeding. Nowadays, whole-genome sequence data of a lot of plants are available in public databases. This provides a platform for genetic improvement, including molecular research and genetic engineering research of different useful traits in plant science.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ГЕНЕТИКАЛЫҚ МАРКЕРЛЕР ЖӘНЕ ГЕНОМДЫҚ ҚАУЫМДАСТЫҚТЫ ЗЕРТТЕУ

***Түсіпқан Ділнұр[1], Чжаоэ Пан[2]**

[1]Ұлттық биотехнология орталығы, Өсімдіктердің генетикалық инженериясы зертханасы, Қорғалжын көшесі 13/5, Астана, 010000, Қазақстан
[2]Мақта биологиясының мемлекеттік негізгі зертханасы, Мақта зерттеу институты, Қытай ауыл шаруашылығы ғылымдары академиясы, Аньян 455000, Қытай
**tdilnur@mail.ru*

ТҮЙІН

Дамыған секвенирлеу технологияларының көмегімен, селекционерлер мен зерттеушілер әртүрлі өсімдіктердің генетикалық алуан түрлілігін, туыстық және популяциялық құрылымдарын сипаттау үшін ДНҚ-маркерлерін қолданады. Бұл мақалада генетикалық маркерлердің төрт түрі сипатталады. Олардың ішінде ДНҚ негізіндегі молекулалық маркерлердің түрлері, негізгі механизмдері, артықшылықтары мен кемшіліктері талқыланды. Екіншіден, геномдық қауымдастықты зерттеудің артықшылықтары мен кемшіліктері, және жалпы процесстері қысқаша сипатталды.

Негізгі сөздер**:** полимеразды тізбекті реакцияға (ПТР) негізделген маркер, қарапайым реттілік қайталануы (SSR), ДНҚ негізіндегі молекулалық маркер, бір нуклеотидтік полиморфизмдер (SNPs), жалпы геномды қауымдастықты зерттеу (GWS).

ГЕНЕТИЧЕСКИЕ МАРКЕРЫ И ПОЛНОГЕНОМНОЕ АССОЦИАТИВНОЕ ИССЛЕДОВАНИЕ

***Түсіпқан Ділнұр[1], Чжаоэ Пан[2]**

[1]Национальный Центр Биотехнологии, лаборатория генетической инженерии растений, Кургальжинское Шоссе 13/5, Астана, 010000, Казахстан
[2]Государственная ключевая лаборатория биологии хлопка, Институт исследований хлопка, Китайская Академия сельскохозяйственных наук, Аньян, 455000, Китай
**tdilnur@mail.ru*

АБСТРАКТ

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Ключевые слова: маркер на основе полимеразной цепной реакции (ПЦР), повторы простых последовательностей (SSR), молекулярный маркер на основе ДНК, однонуклеотидные полиморфизмы (SNP), полногеномное ассоциативное исследование (GWS).