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Recent Inventions in Concepts, Tools, and Applications of Classical Genetics: A Review

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ABSTRACT
Classical genetics, traditionally founded on Mendelian principles of inheritance such as segregation and independent assortment, has witnessed a robust revival through the integration of advanced molecular, genomic, and computational technologies. Traditional approaches—including phenotypic segregation analysis, linkage mapping, and complementation tests—formed the historical foundation of gene discovery but are now reinforced by high-throughput genotyping and next-generation sequencing (NGS). Recent methodological advances, notably mapping-by-sequencing, dense single-nucleotide polymorphism (SNP)–based linkage maps, and CRISPR–Cas-mediated functional validation, have transformed the field into a high-precision analytical framework. These tools enable rapid identification of causal mutations and definitive confirmation of genotype–phenotype relationships across plants, animals, and microorganisms. This review synthesizes the evolution of genetic tools, discusses current methodological limitations, and highlights future prospects in single-cell genomics and artificial intelligence–assisted analysis. Modernized classical genetics therefore remains central to understanding gene function, trait architecture, and evolutionary processes in the post-genomic era.
Keywords: *Classical genetics; Mendelian inheritance; linkage mapping; QTL analysis; CRISPR–Cas9; forward genetics*

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INTRODUCTION

Classical genetics constitutes the conceptual cornerstone of modern biological sciences and originates from the pioneering work of Gregor Mendel on *Pisum sativum*, which established the laws of segregation and independent assortment [1]. These discoveries provided the first quantitative explanation of hereditary transmission and were later extended through chromosomal theory and linkage analysis [2]. Throughout the twentieth century, phenotype-based segregation analysis, complementation testing, and cytogenetics remained fundamental tools for gene discovery [3].

With the emergence of molecular genetics and genomics, classical approaches were often viewed as limited in resolution. Traditional forward genetics depended on random mutagenesis, extensive mapping populations, and labor-intensive fine mapping, often requiring several years to identify a single causal mutation [8]. However, recent technological progress—particularly next-generation sequencing—has revitalized classical genetics and enabled rapid inheritance-based gene discovery [8,10].

Mapping-by-sequencing now integrates classical crossing strategies with whole-genome sequencing to bypass slow marker-based mapping procedures, thereby accelerating mutant gene identification [13]. Similarly, dense molecular marker systems such as SNP arrays, RAD-seq, and genotyping-by-sequencing (GBS) have dramatically improved linkage resolution and QTL detection [11,13]. Functional confirmation of candidate genes is further strengthened by CRISPR–Cas genome editing, which enables targeted knockouts and allelic replacement to establish causal genotype–phenotype relationships [14,15,35].

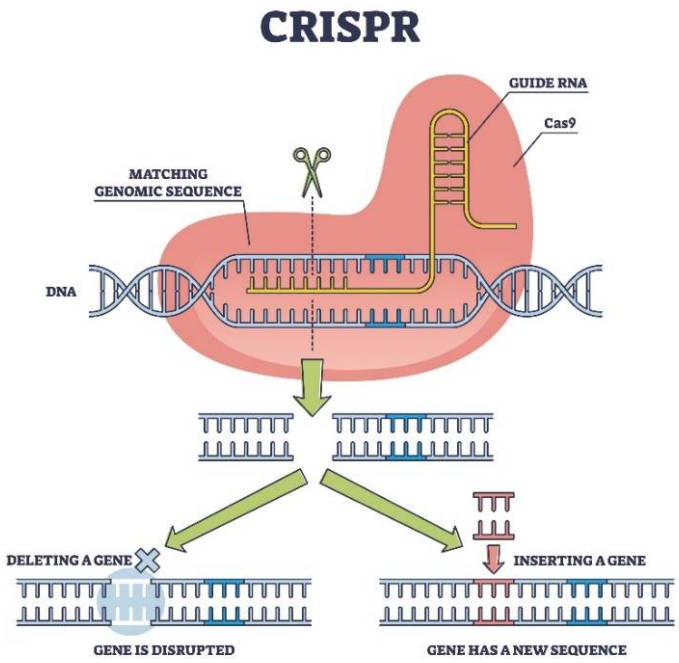

Fig.1. CRISPR–Cas9 Gene Editing Mechanism

This review examines the modernization of classical genetics from early linkage mapping theory [16,17] to contemporary genomic and genome-editing technologies, highlighting applications across plant, animal, and microbial systems.

CORE PRINCIPLES OF CLASSICAL GENETICS

The framework of classical genetics is rooted in Mendelian inheritance, including dominance, segregation, and independent assortment [1]. Integration with chromosomal theory demonstrated that genes occupy defined linear positions on chromosomes and can therefore be mapped through recombination frequency analysis [2].

Linkage and Recombination

Genes located in close proximity on the same chromosome exhibit linkage and are inherited together more frequently than expected by independent assortment. Recombination frequency provides the basis for estimating genetic distance, while mapping functions developed earlier correct for multiple crossover events [16,17]. These classical principles remain foundational for modern high-density linkage mapping.

Quantitative and Complex Inheritance

Many biological traits are polygenic and influenced by environmental factors. Quantitative genetics provides statistical tools for estimating heritability and predicting breeding values [19]. QTL analysis enables dissection of complex traits such as yield and disease resistance, while epistatic interactions further shape phenotypic expression [21,22].

RECENT INVENTIONS ENHANCING CLASSICAL GENETICS

High-Throughput Forward Genetics and Mapping-by-Sequencing

Mapping-by-sequencing combines classical mutagenesis and crossing with whole-genome sequencing to rapidly identify causal mutations [15]. Mutagenesis approaches integrated with NGS enable efficient mutation discovery and high-throughput screening [4]. Large-scale mutant libraries and pooled screening strategies further extend forward genetics in microorganisms and model systems [22, 34].

Advanced Linkage Mapping and QTL Analysis

High-density molecular markers—including microsatellites, SNP arrays, RAD-seq, and GBS—have substantially improved the resolution of linkage and QTL mapping [11,13]. Integration of linkage mapping with genome-wide association studies enhances detection of loci underlying complex traits [23]. Nevertheless, genotyping errors and population structure can distort recombination estimates and reduce mapping accuracy [24].

CRISPR–Cas Systems as Functional Extensions

CRISPR–Cas genome editing enables direct validation of genes identified through classical mapping by generating targeted knockouts, base edits, or allelic substitutions [24, 25]. High-content CRISPR screening platforms further enable genome-wide functional analysis across biological systems [15,26]. In agriculture, CRISPR-assisted validation accelerates crop improvement and trait engineering [27].

APPLICATIONS OF MODERNIZED CLASSICAL GENETICS

Plant Genetics and Crop Improvement

Classical inheritance principles remain fundamental to crop breeding. Marker-assisted selection and genomic selection rely on linkage relationships between markers and traits [28]. Studies of domestication genes and natural variation continue to inform crop improvement strategies [31]. CRISPR-mediated validation further accelerates development of climate-resilient cultivars [27].

Animal and Human Genetics

Controlled crosses and QTL mapping in animal models elucidate the genetic architecture of growth, behavior, and disease [32]. In humans, pedigree analysis combined with whole-genome sequencing enhances identification of Mendelian disease genes and improves diagnostic precision [2].

Microbial and Experimental Genetics

Model organisms remain essential for pathway discovery and epistasis analysis [1]. Genome-wide mutant libraries and CRISPR-based functional screens allow systematic mapping of gene function in microbes [22,26].

NON-MENDELIAN AND EPIGENETIC EXTENSIONS

Classical Mendelian genetics has progressively expanded to incorporate diverse mechanisms of non-Mendelian inheritance, particularly epigenetic regulation and parent-of-origin–dependent gene expression. Epigenetic modifications—including DNA methylation, histone modification, and non-coding RNA–mediated regulation—can generate heritable changes in gene expression without alteration of the underlying DNA sequence. Evidence from plants, animals, and humans demonstrates that **transgenerational epigenetic inheritance** can contribute to stable phenotypic variation across generations, thereby extending the traditional genotype–phenotype framework beyond strictly sequence-based determinants (18,20). Another key departure from Mendelian expectations is **genomic imprinting**, in which allelic expression depends on the parental origin of the gene. Imprinting plays essential roles in embryonic development, growth regulation, and metabolic processes, and its disruption is associated with developmental disorders and disease syndromes in mammals (12,35, 36). Together, epigenetic inheritance and imprinting underscore the multilayered regulation of heredity and highlight the need to integrate chromatin biology, developmental context, and environmental influence into modern genetic theory.

METHODOLOGICAL CHALLENGES AND LIMITATIONS

Despite rapid technological advances in genomics and molecular breeding, several methodological and practical challenges continue to constrain progress. Limited population sizes in mapping populations or association panels substantially reduce statistical power for detecting loci with small phenotypic effects, thereby biasing quantitative trait locus (QTL) discovery toward major-effect variants (5, 29). In addition, genotyping errors, missing data, and cryptic population structure can inflate recombination estimates and generate spurious marker–trait associations, ultimately compromising the reliability of linkage and genome-wide association analyses (30,31).

Environmental heterogeneity further complicates the interpretation of genotype–phenotype relationships, particularly for complex traits governed by low heritability and strong genotype-by-environment interactions, which may obscure true genetic signals and reduce predictive accuracy in breeding programs (6,7). Moreover, ethical, biosafety, and regulatory considerations continue to shape the application of genome-editing technologies such as CRISPR–Cas systems, especially in humans and food-producing livestock, where societal acceptance, off-target effects, and governance frameworks remain critical concerns (9,26).

Collectively, these limitations highlight the need for larger, well-structured populations, rigorous quality-control pipelines, multi-environment phenotyping, and transparent regulatory oversight to ensure robust and responsible implementation of modern genetic technologies.

CONCLUSION

Recent inventions have successfully transformed classical genetics from a traditional low-resolution inheritance discipline into a high-precision analytical framework. By integrating foundational Mendelian

principles with modern genomic, computational, and genome-editing technologies, the field continues to provide robust and essential insights into gene function, trait architecture, and evolutionary processes.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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