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Review Based Book Chapter

FROM MONOGENIC MYTHS TO MULTIGENE FACTS: EXPLORING VARIABLE INHERITANCE AND THE EMERGENCE OF DIGENIC/OLIGOGENIC MODELS IN HUMAN DISEASES

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FROM MONOGENIC MYTHS TO MULTIGENE FACTS: EXPLORING VARIABLE INHERITANCE AND THE EMERGENCE OF DIGENIC/OLIGOGENIC MODELS IN HUMAN DISEASES

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Abstract

The conventional "one gene–one disease" template has shaped our understanding of human genetics. Still, cumulative evidence reveals that this approach is too simplistic for verifying the entire spectrum of clinical phenotypes. It has been examined that presumed monogenic disorders often exhibit variable expressivity, incomplete penetrance, and inexplicable diagnostic gaps, the challenges that accentuate the impact of modifiers, genetic background, and additional molecular contributors. Therefore, modern genomics has switched towards multi-gene models, underscoring the mechanistic underpinnings of digenic/oligogenic inheritance. These patterns reveal the interplay of interacting proteins, pathways, polygenic load, and buffering capacity that collaboratively determine disease onset and severity. This switching clinically redefines genetic counseling, diagnostic strategies, and the ethical outlook of genomic medicine, requiring consolidation of progressive functional and bioinformatic interpretation tools. With the evolution of precision medicine, the embracement of genetic complexity is not only a scientific necessity but a clinical imperative. Shortly, the omics era is one of

nuanced gene–gene interactions, interconnected networks, and redefined therapeutic horizons.

Keywords

Mendelian Concept, Monogenic Myths, Multigene Disorders, Variable Inheritance, Digenic/Oligogenic Models, Human Diseases

1. Introduction

The heterogeneity in clinical phenotypes, which is commonly seen with the same pathogenic variant within a family, has usually been explained by digenic or oligogenic inheritance or by the occurrence of genetic modifiers. It may lead to incomplete penetrance, where the clinical condition is not present even in the presence of a causative genotype or to variable expressivity, where there is variability in the extent and range of the phenotype. Definitions and context of classic genetic terminologies, such as digenic/oligogenic inheritance and genetic modifiers, need to be comprehended. Digenic inheritance is the phenotype resulting from variations in two genes that individually do not contribute to the expression of the phenotype, whereas oligogenic inheritance is characterized by three or more genes contributing to the expression of the phenotype. Nevertheless, recent evidence suggests that pathologic variants in novel disorders/differences in Sex Development (DSD) genes (e.g., *DMRT1, ZNRF3*) usually impact a comparatively small group of individuals. Consequently, as the number of genes linked to DSD is increasing, but there is no subsequent increase in the overall diagnostic yield. Exome studies on a large scale have drawn our attention to two areas of knowledge gaps: nearly half of all children with DSD are not yet diagnosed genetically, and even where a genetic diagnosis is known, there is still no easy way of predicting the variability in the clinical presentation [1].

Oligogenic (triallelic/modifier) inheritance in Bardet-Biedl syndrome (an oligogenic canonical disorder) has been estimated to range between <10-13% in informative families (increasing further to approximately 51% when putative modifier alleles are considered), indicating the strong influence of measurement procedure on reported rates [2]. Digenic complexes in familial hypercholesterolemia are rare but have been reported (one report has estimated this as around 1 in 564 for specific genetic combinations, around 0.18% in that cohort). General reviews and method papers point

to the fact that there are currently a few dozen of formally reported digenic diseases and that oligogenic structures are being discovered at an increasing pace due to large-scale sequencing (with disease-specific contributions varying from low single digits reaching large proportions in some cohorts based on detection approaches, phenotype, and involvement of modifier alleles) [3].

There are obvious practical barriers to diagnosis and treatment: the clinical sequencing pipelines and the rules of variant interpretation are programmable for a single-gene (monogenic) causative agent, so numerous variants interacting are frequently missed or misclassified, decreasing diagnostic accuracy and reproducibility; statistical evidence of interaction is difficult to obtain, and clinical evidence of interaction between variant pairs and disease is often absent. In therapy, oligogenic processes make targeted interventions complex due to (1) several pathways required to be modulated (2) the variability and context-sensitivity of penetrance and expressivity, and (3) the lack of standardized reporting/interpretation frameworks, so clinicians do not ready for action and directions for counseling/precision treatment. To address these issues, large well-phenotyped cohorts, databases that register multi-variant patterns, consensus standards related to reporting, and integrative functional studies are necessary for the transition from association to causation [4].

2. Historical Foundation: From “One Gene-One Disease” to Genetic Complexity

The classical concept of “one gene-one disease" originated with early clinical examinations of inborn errors of metabolism. Building on this, Beadle and Tatum introduced the one gene-one polypeptide concept and enforced molecular genetics towards the identification of single causative genes for several Mendelian disorders [5]. After the mid-20th century, positional cloning, linkage analysis, and gene sequencing interpreted that paragon of diagnostic successes (for instance, cystic fibrosis, PKU and Huntington's), affixing monogenic patterns in medical genetics. However, recently large-scale studies and genomic sequencing have revealed major exceptions, including incomplete penetrance, variable expressivity, documented digenic/oligogenic contributions, and modifier loci, redirecting a route for reclassification of some monogenic disorders as oligogenic/multi-factorial [1].

3. Limitations of the Classical Mendelian View in Explaining Variable Phenotypes

Even for monogenic disorders, the real findings often fail to match Mendelian expectations:

Variable expressivity

Individuals with the same mutation can reveal variability in severity, e.g., Marfan syndrome, depending on *FBN1* expression, which shows differences in symptoms [6].

Incomplete penetrance

In some carriers of the disease-causing mutation, the symptoms do not appear. This makes the counseling and clinical prediction difficult [7].

Influence of modifiers and genetic background

In some diseases (rare), additional modifiers are responsible for alterations in phenotypes. Examinations in Mendelian conditions reveal that genetic modifiers/variants in the genome can either decrease/increase the disease presentation [8].

Diagnostic gaps

Despite advancements in genetic testing (for example, exome sequencing), the majority of the Mendelian disorders remain unidentified, suggesting the absence of complexities like atypical inheritance mechanisms/interacting genes [9].

4. Rise of Multi-Gene Models: Moving Beyond Mendel

As clinical examinations continuously exposed the limitations of single gene analysis, especially due to variable expressivity and incomplete penetrance, the area switched towards multigene interactions vital in several "monogenic" disorders. However, digenic inheritance in which two variants of a pathogen are required for expression of disease has more recognition with databases, e.g, DIDA systematizing above 250 digenic combinations in 54 conditions [3]. Expanding this, oligogenic inheritance is a condition affected by a small number of genes and acts as an intermediate between monogenic and polygenic inheritance patterns [10]. These models illuminate the scenarios where primary mutation may be responsible for disease in isolation, but its severity and penetrance are shaped by a modifier gene, which is consistent with both theoretical genetics and clinical observations [11].

However, there is increased emphasis on epistasis in which the influence of one gene relies on the occurrence of variants in another gene, showing complex genetic

and non-additive interactions [11]. This concept has fundamental importance in comprehending clinical heterogeneity, for example, in certain immunodeficiency diseases, a pathogenic variant *TCF3* shows the entire disease phenotype only in the presence of *TNFRSF13B/TACI* variant, as well as exhibiting the true digenic epistatic model [11].

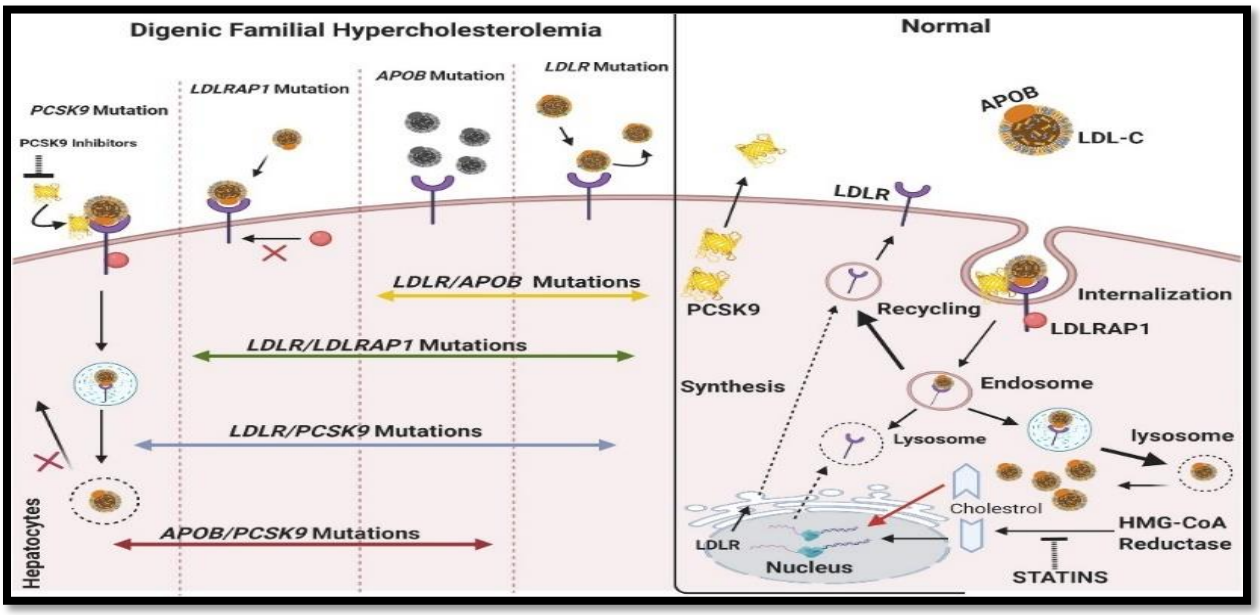

Figure 1: Mechanistic overview of digenic familial hypercholesterolemia illustrating how combined mutations in *LDLR, APOB, PCSK9, and LDLRAP1* disrupt LDL-C uptake and clearance as compare to normal cholesterol metabolism [12].

Recent trials utilizing genome and exome sequencing data have transfigured the understanding. For example, disorders of sex development have shown that above 11% patients possess multiple/likely pathogenic variants, depicting the more common evolution of digenic or oligogenic models than previously thought. Moreover, methods of statistical frameworks are emerging for the identification of digenic combinations in large sequencing datasets. All illustrated the progressing landscape from oligogenic configurations to Mendelian-plus-modifier models speculate the regard for the entire biological context: while single gene mutations may commence the disease, the phenotypic expression results from non-additive effects, genetic background, network of

gene interactions, organizing the movement from Mendelian genetics towards realistic and integrative models of inheritance [13, 3,14].

Table 1: Representing the definitions along with examples of basic terminologies for the comprehension of the Post Mendelian Era

Term	Definition	Example
Digenic	Disease requires a two-gene interaction	In retinitis pigmentosa, *PRPH2* + *ROM1*
Oligogenic	Together, variations in a small number of genes contribute	Triallelism, or Bardet-Biedl syndrome
Epistasis	One gene can obscure or alter the impact of another.	In Hirschsprung disease, *RET* and *EDNRB*
Modifier gene	Changes the primary gene's penetrance and severity	In cystic fibrosis, *TGFB1* modifies *CFTR*

Table 2: Disorders with Multi-Gene Models

Disorder	Genes involved	Model
Retinitis pigmentosa	*ROM1* + *PRPH2*	Digenic
Bardet–Biedl syndrome	BBS genes (at least three alleles)	Oligogenic
Kallmann syndrome/HH	*PROKR2* + *FGFR1* (others)	Digenic
Deafness	*GJB2* plus *GJB6*	Digenic
Ciliopathies (NPHP, JBTS)	Numerous ciliary genes	Oligogenic
Cystic fibrosis	*TGFB1* and *MUC* genes are modifier genes for *CFTR*	Modifier

5. Why Single-Gene Models Sometimes Fail

5.1. Negative Genetic Test Despite Clinical Phenotype

Even with the significant progress in next-generation sequencing (NGS), especially exome sequencing, nearly half of the clinically diagnosed Mendelian cases cannot be explained genetically. This diagnostic gap reveals the drawback of the traditional short-read sequencing, which is not always able to identify structural variants, repeat

expansions, deep intronic mutations, or other complicated rearrangements outside of the captured exonic loci. As an example, the repeat expansion disorders, e.g., *FMR1*-related fragile X syndrome or *C9orf72*-related amyotrophic lateral sclerosis, remain unnoticed without dedicated tools like Expansion Hunter or long-read sequencing systems (PacBio, Oxford Nanopore). The recent combination of multiple techniques has identified the cryptic pathogenic variants that were previously unnoticed, and it is imperative to note that the monogenic assumptions can be overly simplistic in their view of disease complexity. Hence, the unresolved cases tend to point towards the multi-locus or oligogenic contributions, which cannot be covered by the conventional one-gene models [15].

5.2. Variable Expressivity

Variable expressivity is the variability of clinical manifestations of individuals infected with the same pathogenic variant. The occurrence of such a phenomenon is due to various biological factors, such as the type of mutation (missense vs. truncating), tissue-specific thresholds, modifier genes, environmental effects, and heteroplasmy of mitochondria. For instance, *LMNA* gene variants may show clinical effects between muscular dystrophy and cardiomyopathy depending on the effects of modifier genes, as well as the level of tissue-specific expression. Likewise, mutations in mitochondrial DNA e.g., *m.3243A>G* in *MT-TL1*, may result in diabetes to MELAS. These trends are evident that even single-gene mutations can actually be more complex genomic and cellular phenomena with variable effects that cannot be considered deterministic according to the paradigm of classic Mendelian inheritance [16].

5.3. Incomplete Penetrance

Incomplete penetrance is a genetic condition in which people with a pathogenic variant do not show the expected phenotype, and this means that the presence of a mutation is not necessarily the development of a disease. A well-documented example is Long QT syndrome (LQTS), in which the penetrance ranges between 25 and almost 100 percent even within carriers of the same *KCNQ1* or *SCN5A* mutation. This variability can be explained by polygenic background, epigenetic control, and environmental modifiers that regulate gene expression and disease risk. For example, the common

variants in cardiac ion channel genes together produce a polygenic threshold effect on arrhythmic susceptibility [17].

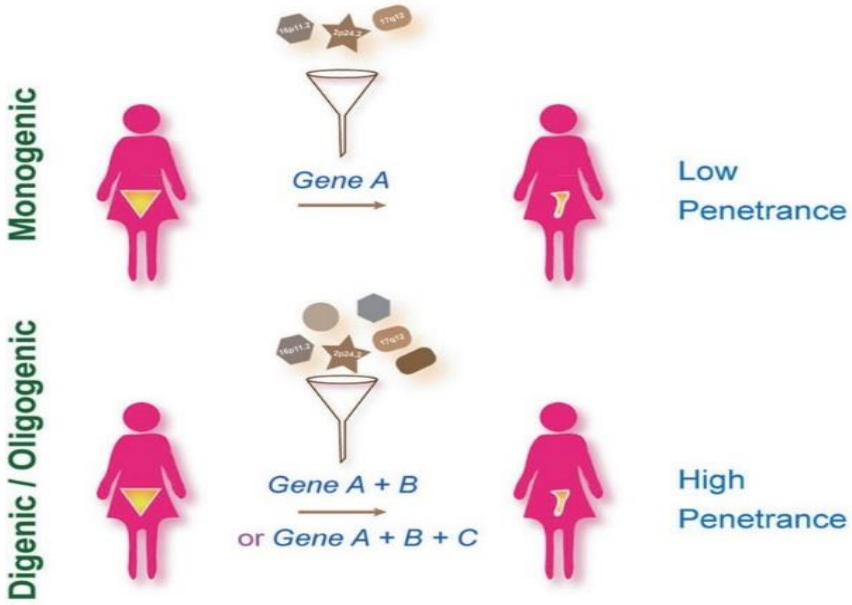

Figure 2: Difference of monogenic and digenic/oligogenic inheritance, depicting how additional gene variants enhance disease expression and penetrance

5.4. Additional Genetic contributors

The term oligogenic and digenic contributions implies that not one, but multiple genetic alterations interact in the process of causing (or exacerbating) a disease, such as in some cases of idiopathic hypogonadotropic hypogonadism (IHH). Instead of a single disease-causing gene being responsible, there are two or more pathogenic changes that are interacting. Several pairs and small combinations have been well-documented in the case of IHH, including *CCDC141* along with *PROKR2* and *SEMA3A* in combination with *SPRY4*, indicating how the combination of two hits can interfere with reproductive development [18]. Recent cohort studies indicate that oligogenicity can be a significant fraction of some rare endocrine diseases than previously thought (estimates of IHH have ranged between 10-20 percent in older studies to claims of up to 70 percent in selected series), and the prevalence estimates are highly dependent on

how the patients are selected and tested. Mechanistically, some combinations are "true oligogenic" events that require all variants to be present to cause disease, while other combinations are due to a principal pathogenic variant that has been altered by other minor-effect (polygenic) variants that alter severity or penetrance [19]. Lastly, ascertainment and testing bias (what type of genes are on panels, which have been sequenced) have a great impact on reported rates; that's why new analytic approaches and careful family studies are needed to distinguish between true digenic/oligogenic and by chance co-occurrence of variants [20].

Below is the detail of some variable inheritance genetic patterns:

5.4.1. Oligogenic inheritance

The oligogenic form of inheritance is characterized by requiring more than one gene (usually 2–4) that is harmful to express the disease, instead of a single causative gene. The individual variants might not be sufficient alone, but when combined, they drive the same biological pathway beyond some threshold, resulting in the disorder. For example, in congenital hypogonadotropic hypogonadism (CHH / IHH), numerous patients have mutations in two or more CHH genes; previous studies showed that approximately 10-20% of cases were digenic/oligogenic, whereas recent cohorts (selected by sequencing method) have a much higher proportion [21].

5.4.2. Digenic/trigenic interactions

If two genes interact with each other, it is referred as digenic interaction, and if three, it is referred as trigenic interaction. The interaction may be either additive (each variant adding risk), or synergistic (joint effect greater than the sum of parts). Such combinations frequently deal with those genes in the same pathway (developmental or signaling). For example, *CCDC141* + *PROKR2* is reported to be a digenic combination involved in incomplete penetrance of hypogonadotropic hypogonadism; other documented combinations are *SEMA3A* + *SPRY4* as well as *FGFR1*, *KAL1*, and *PROK2*, etc. The definitions of these were based on family studies, functional assays, and in-silico digenic predictors [22].

5.4.3. Polygenic modifiers

In cases where a rare high-impact variant is found, there may be a wide range of common variants throughout the genome (with small effects each) that modulate the

severity of the disease or its occurrence at all. These typical variants create a polygenic background that changes expressivity and penetrance. Examples, Recent studies indicate that polygenic scores and common-variant burden can increase or decrease the severity of developmental and other conditions (i.e. a monogenic diagnosis may be partially influenced by the common-variant history of the individual themselves). This is one of the reasons why individuals experiencing the same rare mutation may exhibit quite different clinical presentations [17].

5.4.4. Ascertainment bias: phenotype-first vs genotype-first and effect on penetrance/expressivity

When you begin with individuals already having a robust clinical phenotype (phenotype-first) then you will exaggerate the probability that a genetic variant will result in severe illness. When you initiate with population sequencing (genotype-first), you will often spot several carriers with weaker or no symptoms. Reported penetrance and expressivity are altered by this difference (ascertainment bias).

High digenic/oligogenic rates or high penetrance reporting studies may indicate selection of severe cases; in genotype-first population studies, lower penetrance and more variable expressivity can be observed. The recent reviews and empirical research are directing to follow the approach of combining both methods for unbiased interpretation [23].

Table 3: Representing the genetic factors that contribute for the failure of single gene models

Contributing Factors	Why Single-Gene Testing Fails
Hidden variants (SVs, STRs, non-coding)	They are missed by standard sequencing [24]
Exome interpretation limits	Unknown genes, gaps in variant classification, and inadequate coverage [25]

Contributing Factors	Why Single-Gene Testing Fails
Regulatory, 3D chromatin impacts	Regulation outside of coding regions is changed by non-coding SVs. [26]
Expressivity variability	Heteroplasmy, organ compensation, mutation type, and modifier genes [27]
Incomplete penetrance	Variant reclassification, polygenic context, and asymptomatic carriers [27]
Oligogenic inheritance	The disease phenotype requires multiple variants. [28]
Digenic/trigenic combinations	Gene interactions that work in concert intensify the severity [29]
Ascertainment bias	Penetrance estimates are impacted by cohort selection [30]

6. Mechanistic Insights of Digenic/Oligogenic Inheritance

6.1. Interacting Proteins and Pathways

Genetic synergy evolves when components of the same pathway/interacting proteins jointly get rattled. In such conditions, the combined impact surpasses the effect of a single defect, thrusting the system beyond its functional threshold e.g., double perturbations in photoreceptor disc-rim proteins i.e., *ROM1* and *PRPH2* (RDS) cause a comparatively severe retinal degeneration than either gene alone. Same mechanisms support digenic effects in connexin-mediated gap-junction assembly and developmental signaling (for example, *FGFR1* with neuronal resettling genes [31].

6.2. Genetic Background and Polygenic Load

The genomic background strongly influences the appearance of monogenic variants. Both rare modifiers and polygenic variants can modulate expressivity and penetrance. For instance, carriers of high penetrance alleles in hereditary breast cancer, Lynch syndrome and familial hypercholesterolemia show commonly variable disease possibilities depending on polygenic context. Current studies in developmental disorders also depict that rare-variant and polygenic burden shape the onset and severity [31].

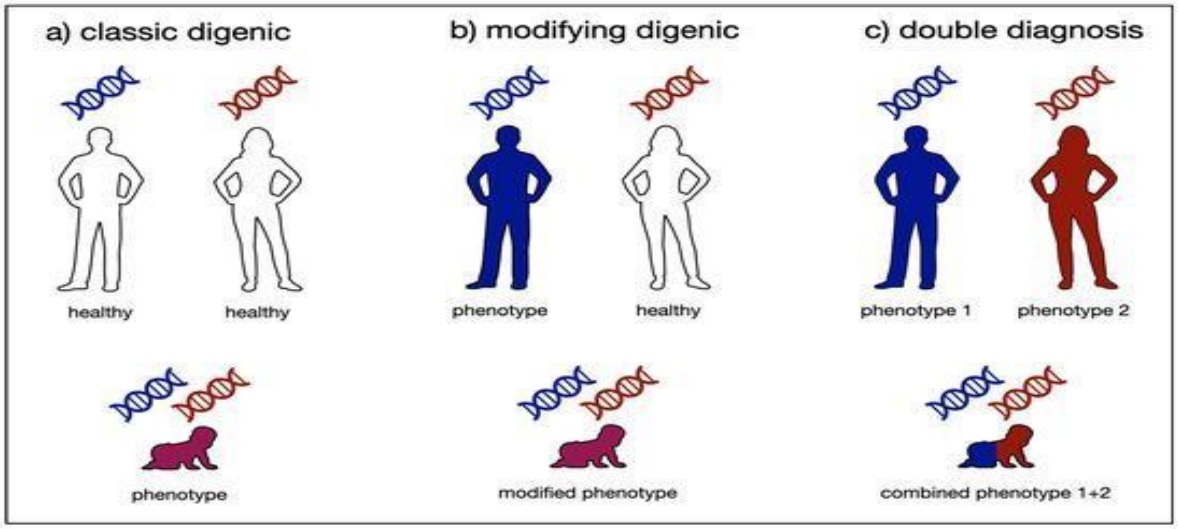

Figure 3. Diagrammatic depiction of inheritance patterns involving two genes with harmful variants. (a) Classic digenic inheritance: A child who inherits both mutations develops a disease phenotype as a result of the interaction between the two variants. Each unaffected parent carries a mutation in a different gene. (b) Modifying digenic inheritance: If a child inherits both variants, the phenotype will be different from that of the affected parent, which is changed by the second mutation. One parent has a mutation that alone causes disease, while the other parent carries a mutation in a different gene but is symptom-free. (c) Double diagnosis: When both pathogenic variants are passed on, the child exhibits a blended phenotype that incorporates traits from both conditions. Each parent has a distinct monogenic disorder [32].

6.3. Partial Loss of Gene Dosage or Buffering capacity

Variants involved in reducing functions of two genes, mildly buffering the same phenomena (for instance, a large structural protein and kinase in muscle), collectively cause a functional collapse (e.g *TTN* + *SRPK3* in digenic myopathy). This illustrates why

some apparently recessive/dominant disorders show incomplete penetrance/atypical severity when other loci maintain net response [33].

Table 4: Representing the mechanistic insights of multigene models

Mechanistic Basis	How Synergy Arises	Examples	Key Insight
Protein–protein interaction defects	Double hits cause essential complexes to become unstable or stop assembling	BBSome subunits (Bardet–Biedl), *PRPH2–ROM1* (retina)	Partial defects become additive or multiplicative due to physical interdependence [34]
Pathway cascade perturbation	Downstream dysfunction is caused by variations at various stages of a signaling pathway	*FGFR1* + migration genes in development, hedgehog/ciliary genes in ciliopathies	Signaling deficiencies are exacerbated by sequential disruption [35]
Shared-module burden	Accumulated hits in a single biological module overload function across several genes	Deafness connexins and ciliary transport genes	Together, dispersed minor flaws surpass the functional threshold [36]
Polygenic background modulation	Modifier alleles that are common and uncommon change the expressivity and penetrance of monogenic variants	Lynch syndrome, FH, *BRCA1/2* breast cancer, and developmental disorders	Genetic "context" is a prerequisite for monogenic causation [37]
Stoichiometric imbalance	In multi-subunit assemblies, variations alter dosage ratios	Photoreceptor disc complexes and gap-junction proteins	Proper stoichiometry is essential; dysfunction is made worse by imbalance [38]

Mechanistic Basis	How Synergy Arises	Examples	Key Insight
Compensatory pathway failure	Single hits are concealed by redundancy, but buffering is eliminated by dual perturbation	Connexins and parallel ciliary trafficking genes	Reveals networks' hidden buffering [39]
Epistasis and threshold effects	Beyond additive risk, non-linear outcomes are driven by interactions between variants	Oligogenic ciliopathies and digenic retinitis pigmentosa	Only when the total genetic load surpasses a certain threshold does disease risk become apparent [40]

7. Clinical and Research Implications of Digenic/Oligogenic Inheritance

7.1. Genetic Counseling and Diagnostic Yield

The acknowledgment that a single gene variant may not be responsible for the phenotype of the patients raises the significance of imparting the patterns of inheritance archetype during genetic counseling. However, families in history assured by negative single-gene tests are still at risk if there is the presence of additional variants in interacting genes, which changes the calculations of renewal risk and advice for family planning. The emergence of whole-exome and whole-genome sequencing, as well as multi-gene panels, has significantly advanced diagnostic capability. These avenues not only capture the primary causative mutation but also secondary variants in related pathways, opening the way for the detection of digenic/oligogenic patterns that were previously neglected [41]. However, for rare disorders, only 30 to 50% cases are explained by monogenic models, emphasizing that multi-locus contributions are unexplained [41, 42].

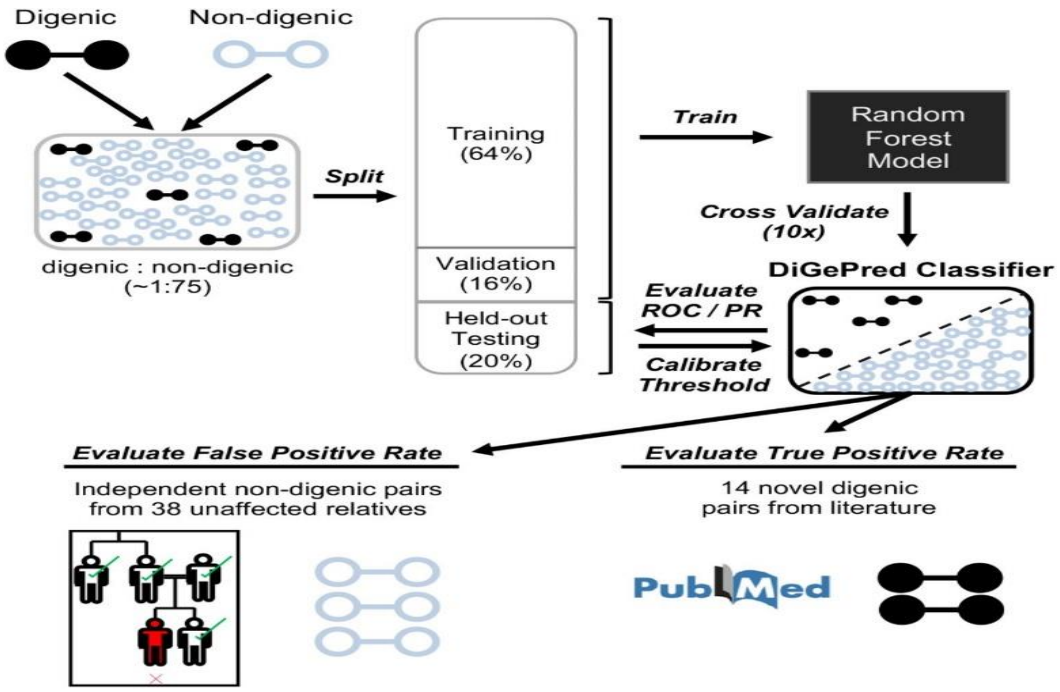

Figure 4: Basic work strategy of DiGePred classifier: both digenic as well as non-digenic gene pairs are divided into training, validation, as testing sets to generate a random forest model to evaluate and calibrate true and false positive population [43].

7.2. Functional & Bioinformatic Interpretation Tools

The detection of co-occurring variants is inadequate - evaluation requires functional authentication and computational interpretation. Digenic Diseases Database (DIDA) as well as OLIDA both control digenic/oligogenic cases and establish confidence scores contemplating the evidence strength. Platforms like ORVAL (incorporating VarCoPP) as well as its newer repetition VarCoPP2.0 utilize machine learning for the prediction of possibly pathogenic combinations with a lower rate of false positive analysis and enhanced performance when instructed on high-standard OLIDA data. Recent AI models like diVas refine this phenomenon by integration of patient phenotypes and decipherable AI to prefer causative combinations responsible for digenic inheritance with high rank accuracy, 73% sensitivity, approaching 0.81 sensitivity in several published digenic cases [19, 44].

7.3. Ethical and Counseling Challenges

The distribution of oligogenic findings is a difficult task. Sometimes problems are created only when a genetic mutation combines with another one, making it complicated to illustrate. Counselors must show integrity and should be supportive, since inconsistent analysis can be stressful.

Screening programs both for the general population and carriers also face new problems: How and when should doctors make people aware about the possibilities that rely on more than one gene? The old view of "one gene–one disease" is replaced by the vision that health is affected by a network of genes. It means clear guidelines, new rules, and careful methods to include results in medical judgment are needed [29].

8. Future Prospects

Table 5. Representing the prospects regarding the post-Mendelian era for the intervention of current challenges

Future Prospect	Explanation
Improved Diagnosis	Complex inheritance patterns can be more accurately detected by using network-based techniques, exome/genome sequencing, and multi-gene panels
Personalized Counseling	By taking into account multilocus risk instead of single-gene models, genetic counselors will offer more individualized guidance
Refined Risk Prediction	Functional assays and sophisticated bioinformatics will be used to forecast how variant combinations affect disease
Updated Clinical Guidelines	In clinical practice, new guidelines for the reporting and interpretation of oligogenic results will be developed
Ethical Frameworks	To prevent needless anxiety when reporting uncertain or multilocus results, clear policies will be required
Therapeutic Strategies	Novel therapies that target pathways rather than individual genes may result from an understanding of gene–gene interactions
Population Screening	Programs for screening newborns and carriers may be expanded to take into consideration the contributions of multiple loci to disease risk

9. Conclusion

The transition from Mendelian simplicity to genomic complexity reveals a fundamental fact that genetic disorders rarely result from the involvement of a single gene. The shortcomings of the monogenic framework, demonstrated in variable phenotypes, inconsistent test results and missing heritability, have triggered the standard shift towards digenic/oligogenic (multigene) models. By exploring the interplay of modifier genes, interacting pathways and polygenic contributions, we now acknowledge disease expression as a versatile product of genetic networks instead of linear inheritance. This approach broadens diagnostic accuracy, upgrades genetic counseling and makes new avenues for site-specific therapies while simultaneously lifting interpretive and ethical challenges. Foreseeing the fusion of computational biology, high-throughput sequencing and systems genetics ensures a future where mechanistic clarity, tailored interventions, and individualized risk prediction converge. While unfolding the post-Mendelian era, we adopt the complexity that clarifies human biology along with the potential to redesign modern medicine.

Author Contributions

Design, data analysis, writing, results interpretation, editing, original draft preparation, visualization and final approval, H.S; Writing & data analysis, F.M; Conceptualization, visualization & final approval, S.I; Data Analysis, visualization & final approval, M.F.N & S.H; Writing, S.G, L.R, A.K, B.G, K.M,M.A, A.N, A.L, R.K & S.S; Data Analysis & Visualization, H.F & A.S.

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Conflicts of interest

All authors declare no conflict of interest.

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