

# Digenic or oligogenic mutations in presumed monogenic disorders: A review

Afif Ben-Mahmoud<sup>1</sup>, Vijay Gupta<sup>1</sup>, Cheol-Hee Kim<sup>2</sup>, Lawrence C Layman<sup>3,4,5</sup>, and Hyung-Goo Kim<sup>1,\*</sup>

<sup>1</sup>Neurological Disorders Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Doha, Qatar

<sup>2</sup>Department of Biology, Chungnam National University, Daejeon, Korea

<sup>3</sup>Section of Reproductive Endocrinology, Infertility, & Genetics, Department of Obstetrics & Gynecology, Medical College of Georgia, Augusta University, Augusta, Georgia, USA

<sup>4</sup>Department of Neuroscience and Regenerative Medicine, Medical College of Georgia, Augusta University, Augusta, Georgia, USA

<sup>5</sup>Department of Physiology, Medical College of Georgia, Augusta University, Augusta, Georgia, USA

Monogenic disorders are traditionally attributed to the presence of mutations in a single gene. However, recent advancements in genomics have revealed instances where the phenotypic expression of apparently monogenic disorders cannot be fully explained by mutations in a single gene alone. This review article aims to explore the emerging concept of digenic or oligogenic inheritance in seemingly monogenic disorders. We discuss the underlying mechanisms, clinical implications, and the challenges associated with deciphering the contribution of multiple genes in the development and manifestation of such disorders. We present relevant studies and highlight the importance of adopting a broader genetic approach in understanding the complex genetic architecture of these conditions.

**Key words:** Monogenic, Digenic, Oligogenic traits.

## Introduction

### 1. Monogenic Disorders

The traditional paradigm monogenic disorders, also known as Mendelian disorders, are characterized by the presence of mutations in a single gene that contribute to the development of a specific phenotype or disease. These disorders follow the principles of classical Mendelian inheritance patterns, such as autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive.

Traditionally, monogenic disorders have been considered as relatively straightforward genetic conditions, where a mutation

in a single gene is sufficient to cause the observed phenotype. Examples of well-known monogenic disorders include cystic fibrosis, sickle cell anemia, Huntington's disease, and Duchenne muscular dystrophy. In these cases, a specific mutation or set of mutations in a single gene can be directly linked to the development of the disorder.

### 2. Expanding the Genetic Landscape: Digenic and Oligogenic Inheritance

With the advent of advanced genomic technologies and large-scale sequencing projects, it has become evident that the genetic architecture of many disorders is more complex than

Received: 31 May 2023, Accepted: 6 June 2023, Published: 30 June 2023

\*Corresponding author: Hyung-Goo Kim, Ph.D.  <https://orcid.org/0000-0003-4497-4686>

Neurological Disorders Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Doha, Qatar.

Tel: +974-44545856, E-mail: [hkim@hbku.edu.qa](mailto:hkim@hbku.edu.qa)

Conflict of interest: The authors declare that they do not have any conflicts of interest.

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

© Copyright 2023 by the Korean Society of Medical Genetics and Genomics

[www.e-kjgm.org](http://www.e-kjgm.org)

previously anticipated. While monogenic disorders were traditionally attributed to mutations in a single gene, there is increasing evidence to suggest that the phenotypic expression of some apparently monogenic disorders cannot be fully explained by mutations in a single gene alone.

Digenic inheritance refers to the involvement of mutations in two genes to manifest a particular phenotype or disease. These mutations may be present in different genes that are functionally related or involved in the same biological pathway [1]. The combined effect of these mutations may lead to a more severe phenotype or modify the clinical presentation of the disorder.

In addition to digenic inheritance, oligogenic inheritance has also been proposed as a mechanism contributing to the complexity of seemingly monogenic disorders. Oligogenic inheritance refers to the presence of mutations in multiple genes, typically three or more, that collectively contribute to the development and expression of the disorder. These mutations may interact with each other and with environmental factors to influence the phenotypic variability and disease progression.

### 3. Significance of Investigating Digenic and Oligogenic Mutations

The recognition and investigation of digenic and oligogenic inheritance have significant implications for our understanding of the genetic basis of various disorders. By expanding the traditional monogenic paradigm, we can better explain the observed variability in phenotypes, disease severity, and clinical outcomes within affected individuals and their families.

Studying digenic and oligogenic mutations in presumed monogenic disorders can lead to several important advancements. Firstly, it allows for a more accurate and comprehensive diagnosis, as mutations in additional genes may provide explanations for unresolved cases and atypical presentations. Secondly, the identification of multiple genetic factors provides insights into the underlying molecular mechanisms and pathways involved in the development and progression of the disorder. This knowledge can facilitate the development of targeted therapies and personalized treatment approaches.

Moreover, understanding the complexity of digenic and oligogenic inheritance has implications for genetic counseling and risk assessment. It enables more accurate predictions of recurrence risks in families and offers the potential for early intervention and preventive measures. Furthermore, it highlights the need for a broader genetic approach in clinical practice and

emphasizes the importance of collaborative efforts among researchers, clinicians, and bioinformaticians to decipher the complex genetic interactions involved.

In summary, investigating the possibility of digenic and oligogenic mutations in presumed monogenic disorders challenges the traditional notion of single-gene causation. This expanded understanding provides valuable insights into the complexity of genetic architecture, phenotypic variability, and disease progression. By exploring these complex genetic interactions, we can enhance our diagnostic capabilities, develop targeted therapies, and improve genetic counseling for affected individuals and their families.

## Digenic Inheritance

### 1. Definition and Mechanisms

Digenic inheritance refers to the phenomenon where the phenotypic expression of a disorder is influenced by mutations in two different genes. In digenic inheritance, the simultaneous presence of mutations in two genes is necessary to manifest a particular phenotype or disease. These mutations may act synergistically, modifying the function or regulation of cellular processes, or they may complement each other in a specific biological pathway.

The underlying mechanisms of digenic inheritance can be classified into two main categories: (1) functional complementation and (2) genetic interaction. In functional complementation, mutations in two different genes that are involved in the same biological pathway or have related functions can compensate for each other's defects. This compensation allows for the normal functioning of the pathway, preventing the development of the disorder. However, when mutations occur in both genes, the compensatory mechanism fails, leading to the manifestation of the phenotype.

In genetic interaction, mutations in two genes may interact in a way that amplifies or exacerbates the phenotypic effect. These interactions can occur at various levels, including protein-protein interactions, pathway crosstalk, or shared regulatory elements. The combined effect of the mutations can disrupt normal cellular processes, leading to altered signaling pathways, impaired protein function, or dysregulated gene expression, ultimately resulting in the observed phenotype.

### 2. Examples of Digenic Inheritance in Monogenic Disorders

Several examples of digenic inheritance have been reported

in various monogenic disorders. One well-known example is the association between retinitis pigmentosa (RP) and mutations in the genes *RHO* encoding rhodopsin and *PRPF31* (Pre-mRNA processing factor 31). RP is a progressive retinal disorder characterized by degeneration of photoreceptor cells. While mutations in either *RHO* or *PRPF31* alone can cause RP, the presence of mutations in both genes might lead to a more severe phenotype of the disease [2].

Another example is the digenic inheritance observed in hearing loss. Mutations in either gene *GJB2* (connexin 26) or *GJB3* (connexin 31) are common causes of autosomal dominant or autosomal recessive nonsyndromic hearing loss. However, some individuals who are double heterozygous for *GJB2* and *GJB3* mutations exhibit deafness, suggesting that concurrent loss of one allele of *GJB2* and one allele of *GJB6* may result in a reduction in the dosage of the products of both genes [3].

### 3. Molecular Mechanisms Underlying Digenic Interactions

The molecular mechanisms underlying digenic interactions are complex and can vary depending on the specific genes involved and the biological pathways affected. These interactions can occur through various mechanisms, including physical interactions between proteins, functional crosstalk between pathways, or shared regulatory elements.

In the case of physical interactions, mutations in one gene can disrupt protein-protein interactions, affecting the stability or activity of the complex. For example, mutations in one gene may impair the binding of its protein product to another protein required for normal cellular function, leading to dysfunction or loss of function [4].

Functional crosstalk between pathways is another mechanism through which digenic interactions can occur. Mutations in two different genes that are involved in interconnected pathways can disrupt the balance between these pathways, leading to abnormal cellular processes and the manifestation of the disorder [5].

Shared regulatory elements, such as transcription factors or enhancers, can also play a role in digenic interactions. Mutations in one gene may affect the regulatory elements that control the expression of another gene, leading to dysregulated gene expression and subsequent disease manifestation [6].

Understanding the molecular mechanisms underlying digenic interactions is crucial for unraveling the complex genetic architecture of monogenic disorders. It provides insights into the functional relationships between genes, pathways, and cellular processes, paving the way for targeted therapeutic strategies and personalized medicine approaches that can modulate the

impact of these interactions.

Furthermore, the identification of digenic interactions can have important clinical implications. It can help explain the variability in phenotypic expression and disease severity observed among individuals with seemingly monogenic disorders. By considering the presence of mutations in multiple genes, clinicians can gain a better understanding of the factors contributing to the observed clinical features, prognosis, and response to treatment.

Digenic inheritance can also impact genetic counseling and risk assessment. The identification of digenic interactions in affected individuals allows for more accurate estimation of recurrence risks in families. It enables genetic counselors to provide comprehensive information to individuals and families about the likelihood of passing on the disorder to future generations, facilitating informed reproductive decision-making.

The study of digenic inheritance has been greatly facilitated by the advances in next-generation sequencing (NGS) technologies. NGS allows for simultaneous analysis of multiple genes, enabling the identification of mutations in multiple genes within a single test. This approach has revolutionized the field of molecular genetics and has led to the identification of digenic interactions in various monogenic disorders.

However, it is important to note that the identification and interpretation of digenic interactions pose several challenges. The identification of mutations in multiple genes requires comprehensive sequencing and analysis of a large number of genes, increasing the complexity and cost of genetic testing. Additionally, distinguishing true digenic interactions from coincidental co-occurrence of mutations can be challenging, necessitating functional studies and additional evidence to establish their pathogenicity.

Digenic inheritance represents a significant departure from the traditional paradigm of monogenic disorders. The identification and characterization of digenic interactions in seemingly monogenic disorders have important clinical implications, including accurate diagnosis, improved risk assessment, and targeted therapeutic interventions. Continued research efforts, along with advances in genomic technologies and functional characterization, are essential to unraveling the molecular mechanisms underlying digenic interactions and translating this knowledge into clinical practice. By embracing the complexity of digenic inheritance, we can enhance our understanding of monogenic disorders and provide more personalized and precise care to affected individuals and their families.

## Oligogenic Inheritance

### 1. Definition and Mechanisms

Oligogenic inheritance refers to the phenomenon where the phenotypic expression of a disorder is influenced by mutations in multiple genes, typically three or more. Unlike digenic inheritance, where mutations in two genes are sufficient to manifest the phenotype, oligogenic inheritance involves the contribution of mutations in a larger set of genes.

The underlying mechanisms of oligogenic inheritance are multifaceted and can vary depending on the specific genes involved and their interactions. Oligogenic interactions can occur through various mechanisms, including synergistic effects, cumulative effects, or the involvement of modifier genes.

Synergistic effects occur when mutations in multiple genes act cooperatively, leading to an amplified phenotypic effect. These mutations may be present in genes that participate in the same biological pathway, and their combined disruption can significantly impact the normal functioning of the pathway, leading to the manifestation of the disorder.

Cumulative effects, on the other hand, occur when mutations in multiple genes independently contribute to the overall risk or severity of the phenotype. Each mutation alone may have a relatively minor effect, but the combined presence of these mutations increases the risk or severity of the disorder. These mutations may be present in genes that participate in different biological pathways but converge on a common disease mechanism.

Modifier genes play a crucial role in oligogenic inheritance by modifying the phenotypic expression of the disorder. Modifier genes are genes that do not directly cause the disorder but influence its presentation and clinical outcomes. These genes may modulate the effect of disease-causing mutations, resulting in phenotypic variability or modifying the age of onset, disease progression, or severity [7].

### 2. Examples of Oligogenic Inheritance in Monogenic Disorders

Oligogenic inheritance has been observed in various monogenic disorders, contributing to their phenotypic heterogeneity and variable expressivity. One example is the involvement of multiple genes in the development of intellectual disability. Several genes associated with autism spectrum disorders can interact oligogenically, leading to diverse cognitive outcomes and clinical features [8].

In the context of cardiovascular disorders, mutations in multiple genes have been implicated in the etiology of conditions such as hypertrophic cardiomyopathy [9] and familial hypercholesterolemia [10]. These disorders exhibit significant genetic heterogeneity, with mutations in different genes contributing to the development and progression of the disease. The combined effects of mutations in multiple genes, including disease-causing genes and modifier genes, can influence disease severity and clinical outcomes.

### 3. Complex Interactions in Oligogenic Disorders

Oligogenic disorders are characterized by complex interactions between multiple genes, making their genetic architecture challenging to decipher. The interactions can occur at various levels, including protein-protein interactions, pathway crosstalk, shared regulatory elements, or functional dependencies.

Protein-protein interactions between gene products can modulate the overall function and stability of protein complexes or signaling pathways [11]. Disruption of these interactions due to mutations in multiple genes can lead to aberrant cellular processes and disease manifestation.

Pathway crosstalk refers to the interconnectedness of different biological pathways, where the perturbation of one pathway can impact the functioning of others [5]. Mutations in multiple genes involved in different pathways can disrupt the delicate balance between these pathways, leading to dysregulation and disease development.

Shared regulatory elements, such as transcription factors or enhancers, can also contribute to oligogenic interactions. Mutations in multiple genes that share regulatory elements can alter the expression levels or patterns of these genes, further influencing disease manifestation [6].

Functional dependencies between genes can also play a role in oligogenic disorders. Some genes may have a functional dependence on other genes for proper functioning or regulation. Disruption of the interdependencies due to mutations in multiple genes can lead to dysfunction and disease development.

Understanding the complex interactions involved in oligogenic disorders is crucial for unraveling their underlying mechanisms and developing targeted therapeutic approaches. However, the identification and interpretation of oligogenic interactions pose significant challenges. Comprehensive sequencing approaches, functional studies, and integrative bioinformatics analyses are necessary to decipher the contribution of individual genes, their interactions, and potential modifier effects.

Oligogenic inheritance adds another layer of complexity to the genetic basis of monogenic disorders. The involvement of multiple genes in the pathogenesis of these disorders contributes to phenotypic variability, disease severity, and clinical outcomes. Elucidating the mechanisms and interactions underlying oligogenic inheritance is essential for improving diagnostics, understanding disease mechanisms, and developing personalized therapeutic strategies for affected individuals. Continued advancements in genomic technologies, functional genomics, and computational approaches will further enhance our understanding of oligogenic disorders and their implications in clinical practice.

## Clinical Implications

### 1. Accurate Diagnosis and Prognosis

The recognition and investigation of digenic and oligogenic inheritance in presumed monogenic disorders have significant clinical implications, particularly in terms of accurate diagnosis and prognosis. Traditional diagnostic approaches that focus solely on single-gene mutations may miss additional genetic factors contributing to the phenotype. By considering the possibility of digenic or oligogenic mutations, clinicians can improve the diagnostic yield and provide more accurate genetic diagnoses.

Accurate diagnosis is crucial for appropriate patient management, including the selection of targeted therapies, surveillance for potential complications, and genetic counseling. Understanding the genetic factors involved in a disorder can also help predict disease progression and provide insights into the expected clinical course. By identifying digenic or oligogenic interactions, clinicians can gain a more comprehensive understanding of the underlying disease mechanisms, allowing for tailored treatment strategies and prognostic assessments.

### 2. Genetic Counseling and Risk Assessment

The recognition of digenic and oligogenic inheritance has important implications for genetic counseling and risk assessment [12]. Genetic counselors play a vital role in providing information and support to individuals and families affected by genetic disorders. By considering the involvement of multiple genes, genetic counselors can provide more accurate recurrence risk assessments and personalized recommendations.

In the case of digenic inheritance, the identification of mutations in two genes raises the possibility of passing on both mutations to future generations, increasing the recurrence risk.

Genetic counselors can provide detailed information about the likelihood of transmitting the disorder, potential disease severity, and available reproductive options [13]. This empowers individuals and families to make informed decisions regarding family planning, prenatal testing, or preimplantation genetic diagnosis.

Similarly, in oligogenic inheritance, where mutations in multiple genes contribute to the phenotype, genetic counselors can provide a more comprehensive risk assessment. They can assess the potential impact of individual mutations, their cumulative effects, and the involvement of modifier genes [14]. This information enables a more accurate estimation of recurrence risks and helps guide reproductive decision-making.

### 3. Therapeutic Implications

The recognition of digenic and oligogenic inheritance can guide the development of personalized treatment approaches for individuals with monogenic disorders. Understanding the complex genetic interactions involved in a disorder provides insights into the underlying molecular pathways and cellular processes affected. This knowledge can be leveraged to develop targeted therapies that address the specific genetic abnormalities and disease mechanisms.

Identifying the genes involved in digenic or oligogenic interactions opens up the possibility of targeting multiple points in a biological pathway or modulating the effects of modifier genes. This approach can potentially enhance treatment efficacy, reduce side effects, and improve clinical outcomes. Furthermore, the understanding of the genetic factors contributing to disease heterogeneity can aid in stratifying patients into subgroups for more precise and personalized treatment strategies [15].

The integration of genomic data, functional genomics, and computational approaches [16] is crucial for translating the knowledge of digenic and oligogenic interactions into clinical practice [17]. Collaborative efforts between researchers, clinicians, and bioinformaticians are essential for the interpretation of complex genetic data, the development of functional assays, and the implementation of personalized treatment approaches.

The recognition of digenic and oligogenic inheritance in presumed monogenic disorders has important clinical implications. It improves accurate diagnosis and prognosis, facilitates informed genetic counseling and risk assessment, and guides the development of personalized treatment approaches. Embracing the complexity of genetic interactions in monogenic disorders is crucial for advancing precision medicine and improving patient outcomes.

## Experimental Approaches and Methodologies

### 1. Next-Generation Sequencing Technologies

NGS technologies have revolutionized the field of genomics and play a crucial role in the identification and characterization of digenic and oligogenic interactions. NGS allows for the simultaneous sequencing of multiple genes or even the entire exome or genome, enabling comprehensive genetic analysis within a single experiment.

Exome sequencing (ES) and genome sequencing (GS) are powerful tools for detecting mutations in multiple genes involved in digenic or oligogenic interactions [18]. ES focuses on sequencing the coding regions of genes, which harbor a majority of disease-causing variants. GS, on the other hand, sequences the entire genome, providing a more comprehensive view of the genetic landscape.

NGS technologies provide high-throughput sequencing with high accuracy and sensitivity, allowing for the detection of both common and rare genetic variants. The analysis of NGS data requires specialized bioinformatics pipelines to identify and interpret genetic variants, filtering out common polymorphisms and identifying potentially pathogenic mutations. Additionally, NGS data can be integrated with functional and computational analyses to investigate the functional impact and interaction of identified variants.

### 2. Functional Analysis of Digenic/Oligogenic Interactions

Functional analysis is crucial for understanding the biological consequences of digenic or oligogenic interactions. Functional studies help elucidate the molecular mechanisms underlying these interactions and provide insights into the impact on cellular processes and disease pathogenesis.

Various experimental approaches can be employed for functional analysis, including *in vitro* and *in vivo* models [19]. *In vitro* studies involve cell culture systems, where the effects of specific mutations or combinations of mutations can be assessed on cellular processes such as protein function, signaling pathways, or gene expression. *In vivo* models, such as animal models or patient-derived cells, allow for the evaluation of digenic or oligogenic interactions in a more complex biological context [20].

Functional analysis can involve techniques such as protein-protein interaction assays, gene expression analysis, biochemical assays, and cellular phenotypic assays. These approaches help characterize the functional consequences of mutations, assess their impact on protein-protein interactions or pathway activities, and evaluate the resulting phenotypic changes.

Furthermore, functional studies can explore potential therapeutic interventions that target the identified digenic or oligogenic interactions. By modulating the affected pathways or compensating for the functional defects caused by specific mutations, targeted therapies can be developed to ameliorate the disease phenotype.

### 3. Computational Tools for Digenic/Oligogenic Analysis

Computational tools and bioinformatics approaches play a crucial role in the analysis and interpretation of digenic and oligogenic interactions [17]. These tools help integrate and analyze large-scale genomic data, identify potential interactions, and predict functional consequences.

Network-based approaches are commonly used to identify potential interactions between genes and pathways. These approaches analyze gene expression data, protein-protein interaction networks, and functional annotations to identify potential relationships and shared biological functions among genes implicated in digenic or oligogenic interactions.

Furthermore, bioinformatics tools aid in the prediction of pathogenicity and functional impact of genetic variants. These tools utilize various algorithms and databases to prioritize potentially pathogenic mutations and assess their potential impact on protein structure, function, or regulatory elements.

Additionally, computational modeling and simulation approaches can be employed to understand the dynamics of digenic or oligogenic interactions. These approaches help elucidate the complex relationships and dynamics among multiple genes, providing insights into the mechanisms underlying disease manifestation and potential therapeutic interventions.

Integration of genomic, functional, and computational analyses allows for a comprehensive understanding of digenic and oligogenic interactions, guiding the interpretation and translation of complex genetic data into clinical practice.

Experimental approaches and methodologies, such as next-generation sequencing technologies, functional analysis, and computational tools, are crucial for investigating and understanding digenic and oligogenic interactions.

## Phenotypic Variability and Modifiers in Presumed Monogenic Disorders

Digenic and oligogenic interactions also contribute to phenotypic variability in presumed monogenic disorders. The presence of additional genetic factors, including modifier genes, can influence the phenotypic expression and clinical outcomes of

these disorders.

Modifier genes are genes that do not directly cause the disorder but modulate its phenotypic presentation. They can amplify or attenuate the effects of disease-causing mutations, leading to phenotypic variability among affected individuals. Modifier genes may influence various aspects of the disease, such as disease onset, severity, progression, or response to treatment [13].

An illustrative example of phenotypic variability and modifier effects is seen in cystic fibrosis (CF), traditionally considered a monogenic disorder caused by mutations in the *CFTR* gene. While mutations in *CFTR* are necessary for the development of CF, the severity of the disease can vary among individuals. Modifier genes, including those involved in inflammation and infection response, have been identified to contribute to the modulation of CF lung disease severity [21]. These modifier genes can influence the disease phenotype by modifying the function or expression of *CFTR* or by affecting other pathways relevant to CF pathogenesis.

Furthermore, modifier genes can also impact the phenotypic expression of neurodevelopmental disorders. For example, in fragile X-associated tremor/ataxia syndrome (FXTAS), caused by expanded CGG repeat mutations in the *FMR1* gene, *PSMB5* (proteasome subunit, beta-type 5) acting as a strong suppressor of CGG-associated neurodegeneration, has been associated with a delayed onset of FXTAS in human premutation carriers [22].

Understanding the role of modifier genes and their interactions with disease-causing mutations is crucial for unraveling the complexity of phenotypic variability in monogenic disorders. Integrating genetic data, functional studies, and computational approaches can aid in identifying and characterizing these modifiers, providing insights into the underlying mechanisms and potential targets for therapeutic interventions.

Case studies and research findings have demonstrated the significance of digenic and oligogenic contributions in presumed monogenic disorders. These interactions contribute to phenotypic variability and highlight the involvement of modifier genes. Understanding the genetic and molecular mechanisms underlying these interactions is essential for accurate diagnosis, prognosis, and the development of personalized treatment approaches in clinical practice.

## Future Perspectives and Challenges

### 1. Unraveling the Genetic Complexity of Presumed Monogenic Disorders

The future of research in digenic and oligogenic inheritance lies in unraveling the genetic complexity of presumed monogenic disorders. As our understanding of the genetic landscape expands, it becomes evident that many disorders previously considered monogenic have additional genetic factors contributing to their development and phenotypic variability. Identifying these factors and understanding their interactions will require further investigation and large-scale collaborative efforts.

Advancements in genomic technologies, such as improved sequencing techniques and the application of high-throughput methods, will facilitate the identification of additional genes involved in digenic or oligogenic interactions. Integrating genomic data from diverse populations and studying larger cohorts will increase the power to detect these interactions and elucidate their contribution to disease pathogenesis.

In addition to genomic approaches, functional studies will play a crucial role in unraveling the genetic complexity of monogenic disorders. Integrating functional genomics, proteomics, and metabolomics will provide a comprehensive understanding of the molecular mechanisms underlying digenic and oligogenic interactions. Moreover, the integration of functional data with genetic and clinical information will enhance our ability to translate these findings into clinical practice.

### 2. Integrating Multidimensional Omics Data

Integrating multidimensional omics data is a key challenge and opportunity in the field of digenic and oligogenic inheritance. Traditional genetic studies have focused on DNA sequence variants; however, the functional consequences of these variants are influenced by various factors, including epigenetic modifications, transcriptional regulation, protein interactions, and post-translational modifications.

Advancements in technologies such as single-cell genomics, epigenomics, transcriptomics, and proteomics provide a wealth of data on different molecular layers. Integrating these multidimensional omics data will enhance our understanding of the complex interactions underlying digenic and oligogenic inheritance. Integrative analyses can identify key pathways, regulatory networks, and functional modules affected by the combined effects of multiple genes, shedding light on the underlying disease mechanisms.

Furthermore, the integration of clinical and phenotypic data

with omics data is crucial for identifying genotype–phenotype correlations and understanding the clinical implications of digenic and oligogenic interactions. This multidimensional approach will enable the identification of biomarkers, the development of personalized treatment strategies, and the prediction of disease outcomes.

### 3. Novel Approaches and Technologies

The exploration of novel approaches and technologies is essential for advancing our understanding of digenic and oligogenic inheritance. Here are a few emerging areas that hold promise:

a) **Single-cell Genomics:** Studying individual cells allows for the identification of cellular heterogeneity and the characterization of rare cell populations involved in disease pathogenesis. Single-cell genomics can provide insights into the interactions between genes within specific cell types or during different stages of disease progression.

b) **Functional Genomics:** Integrating functional genomics approaches, such as CRISPR–Cas9 screens, RNA interference, and gene editing technologies, can help elucidate the functional impact of digenic and oligogenic interactions. These approaches enable the systematic perturbation of multiple genes and the assessment of their combined effects on cellular processes.

c) **Network Biology:** Network-based approaches, such as pathway analysis, protein–protein interaction networks, and gene regulatory networks, can unravel the intricate relationships between genes involved in digenic and oligogenic interactions. These approaches provide a systems-level view of the molecular interactions and pathways affected, aiding in the identification of potential therapeutic targets.

d) **Artificial Intelligence and Machine Learning:** Advanced computational algorithms and machine learning techniques can assist in the analysis and interpretation of complex genomic and phenotypic data. These tools can aid in the identification of digenic and oligogenic interactions, prediction of disease outcomes, and the development of personalized treatment strategies.

Despite the promise of these approaches and technologies, several challenges need to be addressed. These include data integration and standardization, the need for large and diverse datasets, the interpretation of complex interactions, and the translation of research findings into clinical practice. Collaboration between researchers, clinicians, and computational biologists will be crucial in overcoming these challenges and driving the field forward.

Future perspectives in the study of digenic and oligogenic

inheritance involve unraveling the genetic complexity of presumed monogenic disorders, integrating multidimensional omics data, and exploring novel approaches and technologies. These advancements will enhance our understanding of disease mechanisms, enable personalized treatments, and ultimately improve patient care in the era of precision medicine.

## Conclusion

### 1. Recapitulation of Key Findings

The traditional understanding of monogenic disorders as being solely caused by mutations in a single gene has been challenged by emerging evidence suggesting the involvement of digenic or oligogenic inheritance. Digenic inheritance refers to the contribution of mutations in two genes, while oligogenic inheritance involves mutations in multiple genes. These additional genetic factors can significantly influence the phenotypic expression, disease severity, and clinical outcomes in individuals with seemingly monogenic disorders.

### 2. Implications for Clinical Practice

The identification and characterization of digenic or oligogenic mutations in presumed monogenic disorders have important implications for clinical practice. Firstly, accurate diagnosis and genetic counseling become more complex, as clinicians need to consider the potential involvement of multiple genes. Additionally, understanding the full genetic landscape of a disorder allows for more precise risk assessment and counseling for affected individuals and their families. It also opens up opportunities for personalized therapeutic interventions, targeting specific genetic interactions or pathways.

### 3. Challenges and Future Directions

The investigation of digenic and oligogenic mutations in monogenic disorders comes with several challenges. Firstly, the identification and interpretation of these complex genetic interactions require comprehensive and sophisticated genomic analysis approaches. Collaborative efforts among researchers, clinicians, and bioinformaticians are crucial to unraveling the underlying genetic architecture of these disorders. Additionally, the functional characterization of digenic and oligogenic interactions and the development of computational tools for their analysis are areas that warrant further exploration.

### 8.4 Future Perspectives

Future research in this field should focus on expanding our



understanding of digenic and oligogenic inheritance in monogenic disorders through large-scale genomic studies. The integration of multidimensional omics data, including genomics, transcriptomics, and proteomics, will provide a more comprehensive view of the molecular mechanisms underlying these complex genetic interactions. Moreover, the development of novel experimental and computational tools will aid in identifying and characterizing digenic and oligogenic mutations, facilitating the translation of this knowledge into clinical practice.

In conclusion, the concept of digenic and oligogenic inheritance challenges the traditional notion of monogenic disorders. The recognition of multiple genetic factors contributing to the development and manifestation of seemingly monogenic disorders opens new avenues for research, diagnosis, and treatment. By embracing a broader genetic approach, we can gain deeper insights into the complex genetic architecture of these disorders and ultimately improve patient care and outcomes.

## Acknowledgements

This work was supported by an internal grant IGP5 of Qatar Biomedical Research Institute.

## Authors' Contributions

Conception and design: HGK. Acquisition of data: ABM, VG. Analysis and interpretation of data: CHK, LCL. Drafting the article: HGK. Critical revision of the article: CHK, LCL. Final approval of the version to be published: HGK.

## References

1. Tang VT, Arscott P, Helms AS, Day SM. Whole-exome sequencing reveals GATA4 and PTEN mutations as a potential digenic cause of left ventricular noncompaction. *Circ Genom Precis Med* 2018;11:e001966.
2. Lim KP, Yip SP, Cheung SC, Leung KW, Lam ST, To CH. Novel PRPF31 and PRPH2 mutations and co-occurrence of PRPF31 and RHO mutations in Chinese patients with retinitis pigmentosa. *Arch Ophthalmol* 2009;127:784-90.
3. Liu XZ, Yuan Y, Yan D, Ding EH, Ouyang XM, Fei Y, et al. Digenic inheritance of non-syndromic deafness caused by mutations at the gap junction proteins Cx26 and Cx31. *Hum Genet* 2009;125:53-62.
4. McCormack SE, Li D, Kim YJ, Lee JY, Kim SH, Rapaport R, et al. Digenic inheritance of PROKR2 and WDR11 mutations in pituitary stalk interruption syndrome. *J Clin Endocrinol Metab* 2017;102:2501-7.
5. Hoyos-Bachiloglu R, Chou J, Sodroski CN, Beano A, Bainter W, Ange-  
lova M, et al. A digenic human immunodeficiency characterized by IFNAR1 and IFNGR2 mutations. *J Clin Invest* 2017;127:4415-20.
6. Wilch E, Zhu M, Burkhart KB, Regier M, Elfenbein JL, Fisher RA, et al. Expression of GJB2 and GJB6 is reduced in a novel DFNB1 allele. *Am J Hum Genet* 2006;79:174-9.
7. Kousi M, Katsanis N. Genetic modifiers and oligogenic inheritance. *Cold Spring Harb Perspect Med* 2015;5:a017145.
8. Schaaf CP, Sabo A, Sakai Y, Crosby J, Muzny D, Hawes A, et al. Oligogenic heterozygosity in individuals with high-functioning autism spectrum disorders. *Hum Mol Genet* 2011;20:3366-75.
9. Baulina NM, Kiselev IS, Chumakova OS, Favorova OO. [Hypertrophic cardiomyopathy as an oligogenic disease: transcriptomic arguments]. *Mol Biol (Mosk)* 2020;54:955-67. Russian.
10. Tada H, Kawashiri MA, Nomura A, Teramoto R, Hosomichi K, Nohara A, et al. Oligogenic familial hypercholesterolemia, LDL cholesterol, and coronary artery disease. *J Clin Lipidol* 2018;12:1436-44.
11. Weiss B, Eberle B, Roeth R, de Bruin C, Lui JC, Paramasivam N, et al. Evidence that non-syndromic familial tall stature has an oligogenic origin including ciliary genes. *Front Endocrinol (Lausanne)* 2021;12:660731.
12. Loudon ED, Poch A, Kim HG, Ben-Mahmoud A, Kim SH, Layman LC. Genetics of hypogonadotropic Hypogonadism-Human and mouse genes, inheritance, oligogenicity, and genetic counseling. *Mol Cell Endocrinol* 2021;534:111334.
13. Deltas C. Digenic inheritance and genetic modifiers. *Clin Genet* 2018;93:429-38.
14. Gifford CA, Ranade SS, Samarakoon R, Salunga HT, de Soysa TY, Huang Y, et al. Oligogenic inheritance of a human heart disease involving a genetic modifier. *Science* 2019;364:865-70.
15. de Vries PJ. Targeted treatments for cognitive and neurodevelopmental disorders in tuberous sclerosis complex. *Neurotherapeutics* 2010;7:275-82.
16. Okazaki A, Ott J. Machine learning approaches to explore digenic inheritance. *Trends Genet* 2022;38:1013-8.
17. Mukherjee S, Cogan JD, Newman JH, Phillips JA 3rd, Hamid R, Meiler J, et al. Identifying digenic disease genes via machine learning in the Undiagnosed Diseases Network. *Am J Hum Genet* 2021;108:1946-63.
18. González-Del Pozo M, Fernández-Suárez E, Martín-Sánchez M, Bravo-Gil N, Méndez-Vidal C, Rodríguez-de la Rúa E, et al. Unmasking Retinitis Pigmentosa complex cases by a whole genome sequencing algorithm based on open-access tools: hidden recessive inheritance and potential oligogenic variants. *J Transl Med* 2020;18:73.
19. Boycott KM, Hartley T, Biesecker LG, Gibbs RA, Innes AM, Riess O, et al. A diagnosis for all rare genetic diseases: the horizon and the next frontiers. *Cell* 2019;177:32-7.
20. Duerinckx S, Jacquemin V, Drunat S, Vial Y, Passemard S, Perazzolo

- C, et al. Digenic inheritance of human primary microcephaly delineates centrosomal and non-centrosomal pathways. *Hum Mutat* 2020;41:512-24.
21. Collaco JM, Cutting GR. Update on gene modifiers in cystic fibrosis. *Curr Opin Pulm Med* 2008;14:559-66.
22. Kong HE, Lim J, Linsalata A, Kang Y, Malik I, Allen EG, et al. Identification of PSMB5 as a genetic modifier of fragile X-associated tremor/ataxia syndrome. *Proc Natl Acad Sci U S A* 2022;119:e2118124119.