Review Article

A brief clinical genetics review: stepwise diagnostic processes of a monogenic disorder—hypertriglyceridemia

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Abstract: The completion of the Human Genome Project and tremendous advances in automated high-throughput genetic analysis technologies have enabled explosive progress in the field of genetics, which resulted in countless discoveries of novel genes and pathways. Many phenotype- or disease-associated single nucleotide polymorphisms (SNPs) with a high statistical significance have been identified through numerous genome-wide association studies (GWAS), and various polygenic risk scoring (PRS) schemes have been proposed to identify individuals with a high risk for a certain trait or disorder. Meanwhile, medical education in genetics has lagged far behind, leaving many physicians and healthcare providers unprepared in the genomic era. Thus, there is an urgent need to educate physicians and healthcare providers with basic knowledge and skills in genetics. To facilitate this, some basic terminologies and concepts are discussed in this review. In addition, some important considerations in delineating and incorporating clinical genetic testing in the diagnosis and management of a monogenic disorder are illustrated in a stepwise fashion. Furthermore, the effects of disease-associated SNPs represented by a PRS scheme clearly demonstrated that even the phenotypes of a monogenic disorder due to the same pathogenic variant in family members are modulated by the polygenic background. In human genetics, despite these explosive advancements, we are still far from clearly deciphering the interplay of gene variants to effect unique characteristics in an individual. In addition, sophisticated genome or gene directed therapies are being investigated for numerous disorders. Therefore, evolution in the field of genetics is likely to continue into the foreseeable future. In the meantime, much emphasis should be placed on educating physicians and healthcare professionals to be well-versed and skillful in the clinical use of genetics so that they can fully embrace the new era of precision medicine.

Keywords: Clinical genetics; monogenic disorder; polygenic disorder; causal gene variant; single nucleotide polymorphism (SNP)

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Introduction

The field of genetics has experienced explosive progress after the completion of the Human Genome Project in 2003. The advent of next-generation sequencing (NGS) may be the greatest technological advance with its ability of massive parallel sequencing which enabled the analysis of the entire human genome. With the use of high-throughput technologies, many novel disease-causal genes and pathways in monogenic disorders have been discovered. At the same time, declining cost and widening availability have enabled NGS for clinical use.

Concomitantly, numerous disease- or phenotype-

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"associated" single nucleotide polymorphisms (SNPs) and their associated genes with a significant statistical significance have been successfully identified through numerous genome-wide association studies (GWAS). This astonishing genetic evolution was unfathomable prior to 2000 and brought the field of medical bioinformatics to the forefront of genetic research. Despite this impressive advancement in human genetics, we are still far from clearly appreciating the exact interplay of gene variants to effect individuals' unique characteristics because biological roles of many variants have not been deciphered.

Riding on this extraordinary wave of genetic transformation, "precision medicine" has become the future model of clinical medicine in which an individual's genetic make-up and lifestyle, along with the environment, are integrated in formulating management strategies, moving away from "one-size-fits-all" approach to minimize adverse consequences (1). The fields of oncology and pharmacology have already begun incorporating this innovative approach with favorable results (2), and others are following their leads.

In contrast, medical education has not kept up with the same rapid rate to prepare physicians and health care professionals with necessary knowledge and skills in genetics to fully embrace this new era of genomic medicine. With the availability of "direct-to-consumer" genetic testing, patients are now able to order tests by themselves. Furthermore, scarcity of genetic counselors and genetic professionals is expected to worsen, while the needs for such services are predicted to surge in the future. Since genetics and genomics are becoming an inseparable aspect in medicine, being well-versed in genetics will be indispensable skills for all healthcare professionals.

In this brief review, an overview of basic genetic terminologies and concepts is provided to promote awareness of clinical genetics. In addition, a stepwise diagnostic process of an often-misunderstood monogenic disorder is presented, while pointing out important considerations, and illustrating the interplay of monogenic causal variants and disease-associated risk SNPs.

Brief overview of basic genetics information (3,4) (supplementary file available at https://cdn.amegroups.cn/static/public/tp-24-131-1.pdf)

The human genome represents a complete set of DNA sequences (nucleotides) which contains about 20,000 protein-coding genes in an individual. Human DNA consists of two distinct types: nuclear DNA (nDNA) and often forgotten, but important, mitochondrial DNA (mtDNA).

About 3 billion pairs of nucleotides are packaged within 23 pairs of chromosomes (chr), consisting of 22 pairs of autosomes, and a pair of sex chromosomes (46, XX for female or 46, XY for male) in an orderly fashion. In a typical cell with some exceptions, one nucleus is present, maintaining a one-to-one relationship.

On the other hand, each mtDNA is a double-stranded circular structure of about 16,570 nucleotide pairs and is maternally inherited, unlike bi-parentally inherited nDNA (5). A various number of mitochondria are contained in each cell, depending on specific cellular energetic needs. Furthermore, one mitochondrion may contain about 2–10 mtDNAs.

In total, individual's DNA sequences in the genome are about 99.9% similar to that of another individual. The remaining culminative genetic variations, comprising less than 0.1% of the genome, make each of us uniquely different.

Genetic variants

SNPs, also known as genetic markers, are the most common variants, about 4 to 5 million in total, and each SNP is located at every ~1,000 nucleotides distributed throughout the genome. A polymorphism refers to the presence of two or more alternative nucleotides at a locus, with a frequency >1%, in a particular population or a group of individuals. Because many SNPs reside in genes' untranslated regions (UTRs), introns or intergenic loci, they are typically not translated into proteins. Therefore, many studies are ongoing to better understand whether any of them have a biological function (6,7). Copy number variants (CNVs), also known as structural variants, have a variable number of copies of particular gene or a locus, and their biological roles are also being investigated (8). Again, it is important to be reminded that not all genetic variants have identifiable or important functions (3,4).

The word "mutation" has often been used interchangeably with a "pathogenic variant", but the word itself describes an "event" that alters a nucleotide sequence. In addition, only germline variants are heritable to the next generation. Somatic mutations that often result in sporadic cancers are not heritable, but they are passed onto their somatic progeny. A post-zygotic mutation can result in somatic mosaicism which describes the presence of two or more genetically different sets of cells within a particular

organ system or population of cells. McCune-Albright syndrome is a great example of nonheritable genetic disorder due to mosaicism.

Monogenic disorders

Monogenic disorders are primarily caused by a variant(s) or certain allele(s) in a gene with a discernible inheritance pattern, and multiple family members may have similar conditions. In some instances, a "*de novo*" variant can arise in an individual (9). A familial condition often manifests earlier in life, during infancy or childhood, and a phenotype is typically severe than a sporadic type (10). In familial cancer syndromes, each member of a family may present with a different cancer type. In addition, bilateral presentation is more common in heritable cancers than sporadic types. Lastly, even monogenic disorders can be modulated by their polygenic background, the environment and/or lifestyle though much less than polygenic counterparts. Hence, a particular disorder can manifest differently in each member of a family, described as "variable expressivity".

Inheritance patterns

Autosomal dominant (parent-child, vertical) and autosomal recessive (children or siblings, horizontal) are common inheritance patterns in which a variant or variants are found in a gene on an autosome, typically without sex-predilection. Pathogenic alleles in autosomal recessive disorders are typically found in the trans-configuration or biallelic where both parental alleles are affected for disease manifestation.

Sex-chromosome disorders have unique inheritance patterns. Whereas disorders with X-linked dominant inheritance can manifest in both males and females, disorders with X-linked recessive inheritance typically manifest only in males. In rare instances, X-linked recessive disorders can manifest in females when skewed X-inactivation occurs or both X chromosomes are affected. Regardless, females, not males, pass on an X-linked disorder. Therefore, a mother who is heterozygous for a variant on one X chromosome may not have the condition, but her male child who inherits it at 50% (1/2) of the time, becomes hemizygous for the variant on the X chromosome will develop the condition.

Types of variants

Point mutations are the most common type which can be categorized as silent or synonymous and nonsynonymous. Silent or synonymous variants normally do not result in phenotypic changes because no protein sequence changes occur. In rare instances, if a nucleotide replaces another nucleotide within a regulatory region or creates a new splicing pattern, a disorder may manifest such as seen in Progeria (11). A nonsynonymous mutation alters the peptide sequence, and the effect on the protein can vary depending on the location within the protein or the characteristics of the replaced amino acid.

Moreover, point mutations can be either nonsense or missense types. A nonsense mutation results in creating a novel or premature stop codon within a newly transcribed messenger ribonucleic acid (mRNA) that typically goes through a degradation process known as nonsense mediated decay (NMD) (12). Alternatively, when a truncated protein is generated, it is likely to be degraded quickly. These are protective mechanisms of the cell to remove unnecessary materials. A missense mutation results in a protein sequence change. The replaced protein can be a conservative or nonconservative change, with similar properties or with dissimilar properties, respectively.

Furthermore, more than one nucleotide may be deleted, duplicated, or inserted, which can alter protein sequences, and typically, in-frame (triplet codon), mutations are less deleterious than out-of-frame (non-triplet codon or shifting triplet codon) mutations where each amino acid is designated by specific triplet codons or three nucleotides.

Lastly, trinucleotide repeat (TNR) disorders are unique conditions that are caused by an expansion of certain TNRs, and a disease manifests once a certain threshold length is reached via elongation, often occurring in subsequent generations, by a phenomenon called "anticipation" (13). Fragile X (CGG) and Huntington disease (CAG) are well-known examples.

Specific types of disorders (more information listed in the supplemental file available at https://cdn.amegroups.cn/static/public/tp-24-131-2.pdf) (3,4,14,15)

Genomic disorders (Table 1)

Chromosomal syndromes are disorders with a different chromosome quantity or aneuploidies, typically due to non-disjunction, which is an error during a cell division in most cases. Down syndrome (47, XX, +21 or 47, XY, +21), or Turner syndrome, also known as monosomy X (45, X or 45,

Table 1 Genomic disorders

Disorder type	Underlying mechanism	Consequence	Well-known examples
Chromosomal syndromes[†]	Nondisjunction[†]	Aneuploidy[†] (abnormal chromosome number)	Down syndrome[‡]
			Turner syndrome[‡]
Segmental chromosomal syndromes[†] (microdeletion[†], duplication[†], insertion[†])	Recombination[†] occurring at segmental duplications	Segmental aneusomy[†], segmental CNV[†]	22q syndrome[‡]
			Williams-Beuren syndrome[‡]
Idiopathic segmental chromosomal disorders[†]	Sporadic and variable breakpoints[†]	Segmental deletion[†], segmental CNV	1p36 deletion syndrome[‡]
Uniparental heterodisomy[†] (including DMR[†])	Meiosis I error[†]	Two different chromosomes with DMR from one parent	Prader-Willi syndrome[‡]
			Angelman syndrome[‡]
Uniparental isodisomy[†] (including DMR[†])	Meiosis II error[†], post-zygotic chromosomal duplication	Two identical chromosomes with DMR from one parent	Prader-Willi syndrome
			Angelman syndrome
Imprinting disorders[†]	Abnormalities at DMR	Abnormal expressions of genes in DMR	Prader-Wcyndrome
			Angelman syndrome
			Beckwith-Wiedemann syndrome[‡]

[†], more information listed in the supplementary file (available at https://cdn.amegroups.cn/static/public/tp-24-131-1.pdf); [‡], more information listed in the supplementary file (available at https://cdn.amegroups.cn/static/public/tp-24-131-2.pdf). CNV, copy number variant; DMR, differentially methylated region.

XO), are well known chromosomal disorders.

Segmental chromosomal or segmental aneusomy disorders are due to deletion, duplication or insertion of a segment of chromosome and may result in altered chromosomal lengths. A translocation, an exchange of two segments within one chromosome or two chromosomes, can occur that can be either balanced with less effects or unbalanced with more significant consequences. Depending on the breakpoint loci, or the genes involved, phenotypic effects can vary tremendously.

Imprinting disorders

The most unique and confusing conditions may be uniparental disomic and genomic imprinting disorders. There are differentially methylated regions (DMRs) on specific chromosomes where methylation patterns of the genes within the loci differ by the parent-of-origin. This process results in differential tissue expressions in certain organs.

Uniparental disomic disorders can result when both chromosomes (e.g., chr 7, chr 11, or chr 15) or both alleles with a DMR are inherited only from one parent (16-18). Moreover, imprinting disorders can result due to a variant within the imprinting center (IC) or deletion of a DMR locus occurs. Prader-Willi and Angelman syndromes are great examples that display these unique properties of DMRs. A methylation analysis is the initial genetic test commonly recommended for imprinting disorders (19).

Primary mitochondrial disorders

Primary mitochondrial disorders may be the least known and most complicated disorders (5,20). Both nuclear and mitochondrial gene variants can cause primary mitochondrial disorders. Furthermore, primary mitochondrial disorders due to nuclear gene mutations can have any of the common inheritance patterns. On the other hand, only maternal mtDNA variants are commonly passed onto the next generation as noted earlier. Although each sperm carries a small number of mitochondria, they are mostly eliminated upon fusing with an ovum.

Moreover, mitochondrial disorders caused by mtDNA variants may manifest only when a certain threshold percentage of mutated mtDNA accumulates. Therefore, mtDNA mutants can be heteroplasmic (<100%) or homoplasmic (100%), depending on tissues or organs within the body. Organs which require high energy are particularly

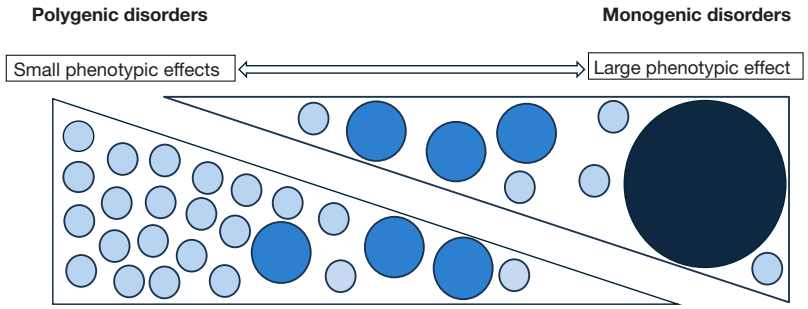

Figure 1 Spectrum of the phenotypic effects of variants in monogenic and polygenic disorders. Each circle represents the effect of a variant (larger size corresponds to a larger phenotypic effect).

vulnerable, such as the central nervous system and muscles.

Definitively diagnosing primary mitochondrial disorders is not straightforward. Metabolic analyses of blood and urine may be performed (21). Elevations of plasma lactate, fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15) may aid in screening, though they are neither sensitive nor specific for primary mitochondrial disorders (5,22). Proton magnetic resonance spectroscopy (MRS) of the brain may be used for the analysis of biochemical metabolites, and a high lactate peak is often identified in mitochondrial disorders (23). Unlike other disorders, blood may not be the best specimen for mtDNA analyses, and often, muscle biopsies or multiple specimens may be necessary.

MtDNA variants are classified into three distinct categories, including ancestral haplogroups, heritable pathogenic, and somatic variants. Ancestral haplogroups are population specific variants in mtDNA which arose as a result of adaptation to regional environmental change and determine baseline efficiency of the mitochondrial oxidative phosphorylation (24,25). In forensic science, mtDNA has been used extensively in investigation using hair, tooth and bone samples (26). Furthermore, it may not be well-known that mtDNA variants have been shown to modulate in the expression of nuclear genes, and they have been investigated extensively in various cancers (27-29). Details on mtDNA variants are not discussed further in this review.

Polygenic disorders—important concepts

On the other side of genetic spectrum, polygenic disorders are thought to result from the culminative result of many gene variants (including SNPs), where each variant exerts a very small or negligible effect (*Figure 1*). Although "familial clustering" may be recognized, this should not be confused with a monogenic heritable pattern because neither discrete genotype nor specific inheritance pattern can be traceable within a family (30). Notable differences between polygenic and monogenic disorders are summarized in *Table 2*. Lastly, particular disease associated polygenic variants are likely to have a modifying effect on the overall phenotype of a monogenic disease, and this will be demonstrated in the case below.

Brief overview of clinical genetic testing

Many types of genetic testing are available in clinical genetics. Prior to the wide-spread availability of molecular testing, biochemical testing on the blood or urine has been a way to diagnose individuals with biochemical genetic disorders. However, more molecular testing is incorporated to definitively diagnose heritable metabolic disorders although biochemical testing is still used in conjunction for these disorders (31). In the field of cancer, additional testing such as gene expression studies may be performed on somatic cells obtained via biopsies (32,33).

In the field of molecular genetics, sequencing is the main way to identify a nucleotide sequence or nucleotide change. NGS is an automated massive parallel-sequencing or high-throughput sequencing method with which multiple genes or genetic regions can be covered simultaneously. NGS enabled sequencing of the entire human genome or exome (protein coding regions) by whole-genome sequencing (WGS) or whole-exome sequencing (WES), respectively, within a few weeks, and both are now available clinically. However, Sanger sequencing is still the gold standard although it can only cover a small genetic region at a time. Any genetic finding obtained using a NGS method should be verified by Sanger sequencing.

Table 2 Comparison of polygenic and monogenic disorders

Polygenic disorders	Monogenic disorders
A cumulative effect of multiple gene variants (each variant exerts a small or negligible effect)	A gene variant or variants with a large effect
No genotype traceable in pedigree	Genotype traceable in pedigree
Continuous trait/variation	Discrete trait/variation
Specific biological role may or may not be discernible	Specific biological role discernible
No discrete inheritance patterns Familial clustering may be observed	Discrete and discernible inheritance pattern
More likely to be influenced by lifestyle and environment	Less likely to be influenced by lifestyle and environment

Multi-gene panel sequence and single-site testing

A multi-gene panel test is appropriate for a disorder with multiple known causal genes. Single-gene or single-site testing is reserved for a disorder with only one known causal gene or one predominant genotype, respectively. A single-site testing can also be appropriate for family member screening with a known familial mutation or research result verification.

Historically, finding disease causal variants for a monogenic disorder had been laborious and often impossible. Linkage analysis is a causal gene hunting method often used for this purpose which incorporates a statistical analysis to determine whether two or more genetic markers or SNPs are co-segregated together or in linkage disequilibrium with a particular disease or trait. Even after potential loci are identified by linkage analysis, depending on the size of the regions, identifying the actual target variant(s) often took many years and required various methods including multiple sequencing attempts. Regardless, a large family with multiple family members with a particular disease was often necessary to be successful.

WGS and WES

Hence, the development of WGS and WES has revolutionized causal gene discovery process and facilitated the identification of many novel genes and variants for many disorders for which no causal genes had been identified. Integrating WGS and WES in clinical genetics has totally changed the landscape of rare disorders (34). Although WGS is more time consuming and laborious than WES, WGS is able to detect structural variants which cannot be detectable by WES.

More importantly, before employing these expansive genetic methodologies for clinical use, conducting a pre-testing discussion becomes extremely important because secondary or incidental findings are possible. Individuals can choose to be informed about incidentally identified genetic variants which are unrelated to the original inquiry. For this purpose, the American College of Medical Genetics and Genomics (ACMG) has published a list of genes and diseases for which specific interventions are available (35,36).

Chromosomal and CNV-testing

For chromosomal and large CNV-related disorders, sequencing is not appropriate. Traditionally, a karyotype with banding method which required living cells was the only method available to display individual's chromosome, from the largest (chr 1) to the smallest (chr 22) and sex-chromosomes.

A digital and colorful display of chromosomes, named spectral karyotyping (SKY), has been developed that uses fluorescent dyes to label each homologous pair of chromosomes with a specific color by fluorescence in situ hybridization (FISH) (37). It is very colorful and visually attractive, and each pair of homologous chromosomes can be easily identified.

For a segment of chromosome or CNV requires different methods, and each one has advantages and disadvantages (38). FISH with the use of a fluorescent probe of various sizes, has been used for detection which does not require living cells. Another method, multiplex ligation-dependent probe amplification (MLPA) is available which has a much better resolution to detect a CNV in smaller genetic regions such as several exons in a gene (39). Array comparative genomic hybridization (aCGH) is a high-resolution method for detecting CNVs across the entire genome, and this test is recommended as the first-tier test

Table 3 Comparison of CNV genetic testing [modified with permission (44)]

Analysis type	Resolution	Advantage	Disadvantage
Karyotype (GTG)	~10 Mb (45)	Whole genome analysis	Time consuming
		Detection of unbalanced and apparently balanced chromosomal rearrangements	Low resolution
FISH	30–100 kb (46)	Detection of unbalanced and apparently balanced chromosomal rearrangements and mosaicism	Time consuming
		Detection of small deletions and duplications	Low resolution, depending on the size of probe
MLPA	50–100 bases (47)	High throughput	Not whole genome analysis
		Simultaneous analyses of several samples	Sensitive to PCR inhibitors or contaminants
		Multiplex method to study several regions in the genome in a single reaction	
		Cost-effective	
CMA or aCGH	~20–200 kb (48)	Whole genome analysis	Unable to differentiate apparently balanced chromosomal rearrangements or mosaicism
		High resolution (up to 40 kb)	
WGS (CNV-detection)	>1 kb (short-read, depth-based algorithm) (49)	Whole genome analysis	CNV of unknown significance in clinic
		High resolution (all coding variants)	Expensive
		Single strand sequencing	

CNV, copy number variant; GTG, G-banding with Trypsin and Giemsa; FISH, fluorescence in situ hybridization; MLPA, multiplex ligation-dependent probe amplification; CMA, chromosomal microarray; aCGH, array comparative genomic hybridization; WGS, whole-genome sequencing; PCR, polymerase chain reaction.

for developmental delay, autism, and congenital anomalies in pediatric patients (40,41). The most appropriate CNV testing method should be employed depending on the size of targe regions (39,42,43). Advantages and disadvantages as well as its resolution of each method are summarized in *Table 3* (44-49).

A methylation analysis is recommended as the initial test for imprinting disorders to identify abnormal methylation patterns (45,50). Lastly, DNA microarray and SNP microarray are often used to detect specific variants or polymorphisms (SNPs), respectively, in the genome. A SNP-array has been used in many GWAS (51), but WGS can also be employed to identify SNPs.

It is important to choose the most appropriate type of genetic test for a particular purpose. Having accurate information on the testing targets and the limitations of each genetic test is important since a variant located outside of those regions or certain types of variants cannot be detected. In such case, the notation of "negative" does not mean no "variant" exists. As noted, sequencing is not the appropriate test for chromosomal abnormalities or structural variations. Moreover, some regions of the genome are still not analyzable by currently available methods due to a variety of reasons (52). Furthermore, each laboratory has a slightly different methodology or pipeline for analysis. Therefore, pre-testing discussion with laboratory personnel is helpful in choosing the most suitable test.

"Clinical" genetic testing

Only "clinical" genetic test results, never research results, can be revealed to patients and to be used for their clinical care in the United States (the US), and research genetic results have to be verified at a clinical laboratory because each "clinical" testing must meet certain performance standards, in terms of "analytical validity" and "clinical validity", as well as "clinical utility".

"Analytical validity" refers to the ability of a test to identify the presence or absence of a particular gene or genetic change accurately as the test intended to detect. Clinical validity refers to the ability of a test result to determine the presence or absence of a particular disease

Table 4 Secondary causes of hypertriglyceridemia

Category	Causes
Lifestyle related	Excessive alcohol intake, dietary indiscretion, parental nutrition with excess lipids
Disorder related	Uncontrolled diabetes mellitus (DM), obesity/metabolic syndrome, untreated hypothyroidism, chronic liver disease, chronic kidney disease, nephrotic syndrome, glomerulonephritis, multiple myeloma, systemic lupus erythematosus (SLE)
Physiological	Pregnancy (third trimester)
Medications	
Hormonal	Oral estrogen, tamoxifen, raloxifene, retinoids, glucocorticoids
Immunological	Cyclosporine, tacrolimus, sirolimus, cyclophosphamide, interferon
Other	Beta-blockers, thiazides, selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics, rosiglitazone, bile acid sequestrants, L-asparaginase, protease inhibitors (PIs)

as the test intended to conclude. Clinical utility refers to the usefulness of a test result to improve the health of the patient with the condition being tested.

In order to standardize clinical testing, the Clinical Laboratory Improvement Amendments (CLIA) ensure the analytical validity of each clinical genetic test in the US. In addition, the College of American Pathologists (CAP) Laboratory Accreditation Program (LAP) monitors to ensure that accredited clinical laboratories are conforming to certain standards.

There are several federal agencies that are responsible for regulating clinical genetic tests in the US: the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), and the Federal Trade Commission (FTC). CMS is responsible for regulating the analytical validity of clinical genetic tests, but currently, there is no strict oversight of the clinical validity or clinical utility of most genetic tests. However, more uniformity in the quality of clinical genetic tests may be achieved in the future with more experience. Regardless, each genetic testing laboratory has its own protocol for reporting their genetic test results.

Lastly, individuals' genetic information is protected by the Genetic Information Nondiscrimination Act (GINA) that was enacted in 2008. GINA protects individuals from being discriminated against based on their genetic information for obtaining health insurance coverage and in employment. Although some states may have additional protection, it does not cover life, disability or long-term care insurance coverage at this time.

Clinical case—evaluating individuals with hypertriglyceridemia (HTG)

HTG is common, and most cases of HTG are polygenic, especially in adults. However, HTG is becoming more prevalent in children and adolescents because of the epidemic of obesity, type II diabetes mellitus (T2DM) and metabolic syndrome. Therefore, every healthcare professional should understand the differences between monogenic, polygenic or secondary HTG and its associated clinical consequences because each type of HTG requires a tailored management strategy.

Secondary causes of HTG

The most important process in an evaluation of HTG is to identify secondary causes of HTG (*Table 4*). Although secondary HTG may be less concerning in infants or children, they should be identified and mitigated if feasible. Regardless, modifying secondary causes of HTG is the key to overall effectiveness of therapies. The presence of offending agents such as medications with propensity to cause HTG in susceptible individuals should be discontinued or replaced with another agent without such side effect.

For secondary HTG such as due to T2DM or obesity, the main focus is to manage these underlying conditions. Involvement of a nutritionist is imperative so that the most appropriate and practical diets which provide essential nutrients for growth and development can be recommended,

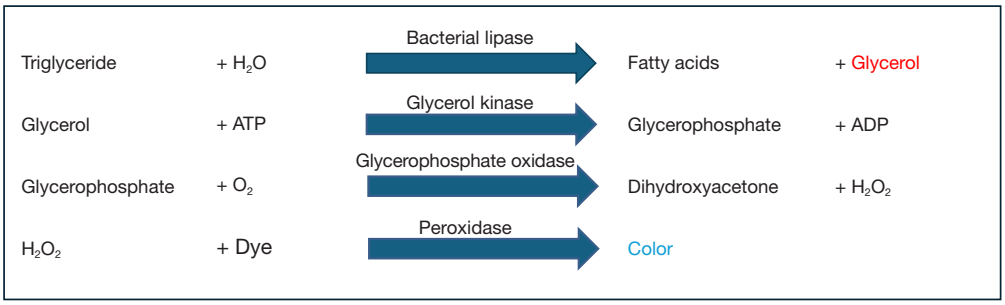

Figure 2 Commonly used laboratory triglyceride analysis. ATP, adenosine triphosphate; ADP, adenosine diphosphate.

especially in children. By managing the primary conditions, triglyceride (TG) levels are likely to stabilize.

Although newer diabetes mellitus (DM) medications, glucagon-like pepetide-1 (GLP-1) agonists have gained popularity for weight loss in addition to DM management, considering lifestyle modifications to result in healthy weight and weight maintenance should always be considered first and be the mainstay of therapy, especially in children and adolescents. Although the FDA has approved GLP-1 agonists, such as semaglutide and liraglutide, in individuals older than 12 years old, the pros and cons of these agents should be discussed with a healthcare provider.

Glycerol kinase deficiency (GKD)

One important, but less well-known information about HTG laboratory values is that the commonly used TG analysis method quantifies the backbone "glycerol" as "TG-surrogate", after releasing the three fatty acid side chains by a bacterial lipase (*Figure 2*). Therefore, measured "glycerol levels" are reported instead for TG measurements. Currently, pretreatment with glycerol-blanking is only performed at designated reference laboratories due to an extra cost in the US. Regardless of the availability of newer instruments, it is still important to keep this information in mind.

This detail becomes particularly important when measuring TG levels in individuals with an X-linked recessive contiguous deletion syndrome known as GKD (OMIM: 307030), in which baseline glycerol is elevated. A large deletion can include the *DMD* gene for Duchenne muscular dystrophy (DMD), and the *NR0B1* gene for adrenal hypoplasia congenita (AHC) in addition to the glycerol kinase (*GK*) gene for GKD. Depending on the size of deletion, clinical features are tremendously variable.

Patients with the late-onset or isolated GKD may have a variant in *GK* alone, and elevation in plasma and urinary glycerol are the only discernible features that can be identified as mild-to moderately increased HTG or pseudo-HTG (53). Depending on the availability of glycerol-blanking, GKD should be considered whenever a "male" patient presents with HTG without any other feature and less responsive to TG-lowering medications.

Non-lipoprotein disorders with HTG as a feature

Another group of conditions to pay attention is monogenic, but non-lipoprotein disorders with HTG as a clinical feature. Some examples are genetically and clinically heterogeneous inherited lipodystrophy and autosomal recessive glycogen storage disease type I and type III. The presence of other unique clinical features may be helpful in delineating the correct diagnosis.

Transient infantile HTG or also known as transient infantile HTG and hepatosteatosis, due to biallelic mutations in the glycerol-3-phosphate dehydrogenase 1 (*GPD1*) gene is another monogenic cause of HTG often presents with vomiting and failure to thrive in infancy, associated with hepatomegaly, fatty liver and liver function abnormalities. This condition tends to resolve in many patients as they grow older. However, because it is extremely rare, its clinical spectrum is still not well understood.

Monogenic HTG disorder

This is a case of three siblings, including fraternal twins who came to the clinic seeking a second opinion for the management of recurrent pancreatitis due to severe and unrelenting HTG. Although this case has been reported previously (54), many aspects of this case are worth highlighting and revisiting.

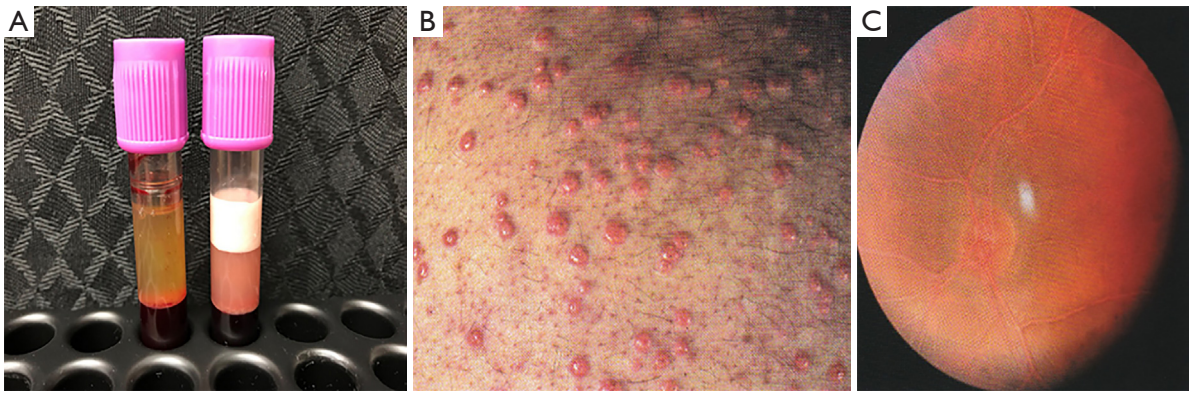

Figure 3 Chylomicronemia associated clinical features. (A) Lipemic blood (right) with chylomicrons floating on top of plasma. (B) Eruptive xanthomas. (C) Lipemia retinalis. Reproduced with permission from Wiley and Sons (55): *Journal of Internal Medicine* 2020;287(4):341.

Unlike an autosomal dominant disorder such as familial hypercholesterolemia (FH), identifying an autosomal recessive disorder is often difficult because family history may be lacking initially until one family member develops the condition. Furthermore, the main therapeutic goal in FH is to prevent or to delay the development of atherosclerotic cardiovascular disease (ASCVD), which is similar to polygenic or common hypercholesterolemia, albeit with differing timing and severity.

In HTG disorders, however, the therapeutic goals are different between monogenic and most other polygenic HTG. This may be due to having two distinctly different exogenous and endogenous pathways which also differ in associated clinical consequences. When severe HTG is noted, HTG is likely chylomicronemia with exogenous and dietary TG. An opaque and turbid appearance of fasting plasma (*Figure 3A*) indicates increased chylomicrons (TG >1,000 mg/dL or >11.3 mmol/L) with an elevated risk of pancreatitis, not ASCVD as often considered with HTG. Thus, delineating the monogenic form is essential.

Severe HTG—familial chylomicronemia syndrome (FCS)

FCS is the only monogenic lipoprotein-associated disorder with severe HTG, and ideally, FCS should be diagnosed earlier in life to prevent the first episode of acute pancreatitis which can be life-threatening, as well as unnecessary abdominal procedures in children (55-57).

Two brothers in the case were diagnosed with HTG (TG >1,000 mg/dL) during a routine lipid test in their late teens. Unfortunately, the female twin was not diagnosed until age 20 during her first pregnancy when she was hospitalized with pancreatitis due to HTG (>2,000 mg/dL).

Upon questioning, the twins had been to the National Institutes of Health (NIH) in their early 20's. The clinical diagnosis of the Frederickson classification or the World Health Organization (WHO), "type I hyperlipoproteinemia", now known as FCS, was provided when molecular testing was unavailable, and a low-fat diet was appropriately recommended.

However, perhaps due to the unfamiliarity of FCS in their home community, a low-fat diet was discontinued. Instead, a low-carbohydrate diet which is typically recommended for common HTG was implemented, and this misinformation began their long struggle. In fact, when the twins decided to seek a second opinion in their 50's, they were having multiple pancreatitis, up to 4 times per year, due to poorly managed HTG with their maximum TG levels as high as 5,000 mg/dL. Their lipid profiles at the time of visit are listed in Table S1.

Any heritable condition has a variable time of onset with a wide spectrum of clinical presentations. Nevertheless, when multiple family members have a similar condition, especially identified before adulthood, an inherited disorder should be suspected.

In infants, common features are failure to thrive, irritability, and colic. In children and adolescents, initial presentation may be quite variable, from nagging abdominal discomfort to debilitating pain, due to smoldering pancreatitis. Often, these episodes may be mistaken as viral illnesses, childhood complaints, or worse, these bouts may prompt unnecessary procedures before arriving at the correct diagnosis.

With some probing, the twin sister revealed that

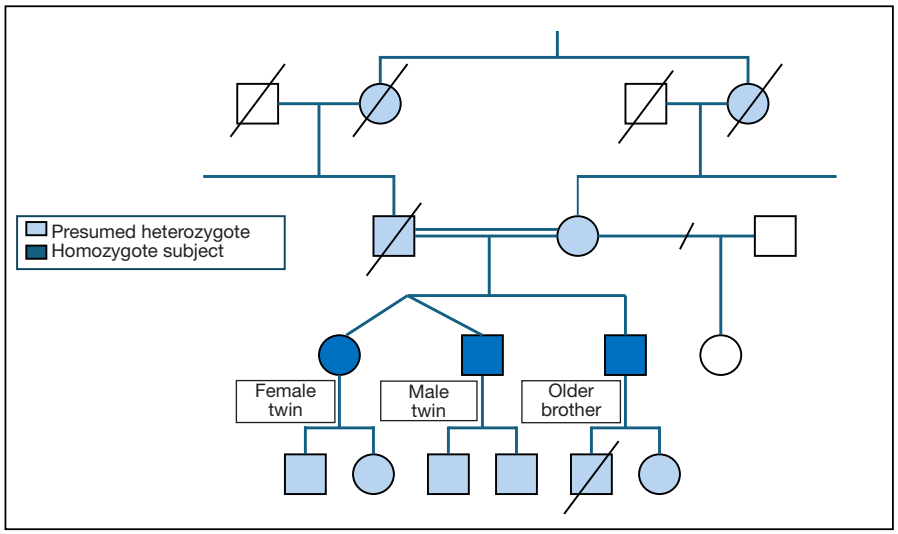

Figure 4 Family pedigree. Presented with permission from *Annals of Internal Medicine* (54).

she frequently complained of "stomachaches" during childhood. However, instead of suspecting pancreatitis or HTG, these complaints might have prompted procedures that she did not need, though no records were available. She had an appendectomy at age 15 and a unilateral oophorectomy at age 18. Finally, HTG was identified when she was hospitalized with acute pancreatitis during her first pregnancy which is a well-known secondary HTG susceptible state.

FCS-associated clinical features

When FCS diagnosis is suspected, associated clinical manifestations should be noted carefully although not everyone develops all of them, and they are typically reversible. Eruptive xanthomas (*Figure 3B*) are small white-yellowish and non-pruritic dermatological papules with erythematous base of about 3–5 mm. They are due to the accumulation of TG in subcutaneous macrophages, mostly noted on the torso, elbows, or buttocks. Lipemia retinalis (*Figure 3C*) describes milky lipid-filled retinal vessels that can be observable via fundoscope. Engulfment of TG-rich lipoproteins (TRL) by macrophages in the reticulo-endothelial cells results in hepatosplenomegaly. In rare instances, patients with FCS may present with a transient ischemic attack (TIA) or complain of memory issues, presumably due to the turbidity of plasma, resulting in sluggish circulation and poor oxygenation.

Newer instruments have mostly eliminated issues such as pseudo-hyponatremia (58), and abnormal coagulation studies with the use of optical analyzer due to the opacity of plasma. However, these issues may still surface depending on the availability of newer instruments (59).

Lipemia retinalis was the only FCS feature noted in the twins. Their family history with a pedigree (*Figure 4*) revealed the three siblings were the only children of their parents who were first cousins, which is a well-known risk factor (consanguineous marriage) for unmasking an autosomal recessive disorder. Their father who died with a brain aneurysm reportedly had HTG without a history of pancreatitis, and their mother was never diagnosed with HTG, but their records were unavailable. Although the siblings did not have all the features of FCS, the available information was enough to make the clinical diagnosis of FCS.

During the diagnostic process, some calculated laboratory parameters may be helpful in supporting FCS diagnosis. In HTG, chylomicronemia can be suspected with the calculated value of TG/TC ratio >5 (mg/dL)/(mg/dL) or >2.2 (mmol/L)/(mmol/L) in untreated patients. In addition, the TG/apolipoprotein B (apoB) ratio ≥8.8 (mg/dL)/(mg/dL) or ≥10 (mmol/L)/(g/L) (60,61), with a low (<75 mg/dL or 0.75 g/L) or low normal apoB value, can be a good indicator of FCS.

Apolipoprotein B (apoB-100 or apoB-48) measurements

One way to distinguish chylomicronemia from other types

Table 5 Proteins important in LPL function and FCS causal genes

Gene	FCS	OMIM	Role in LPL activity
LPL	X	609708	Main enzymatic protein which catalyzes the hydrolysis of TG molecules in chylomicrons and VLDLs, releasing non-esterified FAs and glycerol for tissue utilization
APOC2	X	608083	Essential activating co-factor of LPL
LMF1	X	611761	Chaperone protein of LPL, required for maturation and transport
GPIHBP1	X	612757	Protein important in LPL anchoring, dimerization, and stabilization to endothelium
APOA5	X	606368	Stabilizing co-factor of LPL and apoC-II, and also a modulator of hepatic TG metabolism
APOC3		107720	Interferes with apoC-II reducing LPL lipolysis, reduces TRL clearance, enhances TRL secretion
ANGPTL3		604774	Attenuator of LPL and endothelial lipase activities, reduces TRL clearance

OMIM®: an online catalog of Human Genes and Genetic Disorders (https://www.omim.org/) (15). X: FCS causal genes. LPL, lipoprotein lipase; *APOC2*, apolipoprotein C-II (apoC-II); LMF1, lipase maturation factor 1; *GPIHBP1*, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein; APOA5, apolipoprotein A-V; *APOC3*, apolipoprotein C-III; ANGPTL3, angiopoietin-like 3; FCS, familial chylomicronemia syndrome; TG, triglyceride; VLDL, very-low-density lipoprotein; FA, fatty acid; TRL, triglyceride-rich lipoprotein.

of HTG is to assess apolipoprotein B-100 (apoB-100 or typically measured apoB) levels, carried in very-low-density lipoprotein (VLDL) particles, different from apoB-48, which is the product of mRNA editing of apoB-100 that occurs in the intestine and package in chylomicrons. High levels of apoB or VLDL are associated with a high risk of ASCVD, whereas low or normal apoB levels are associated with a high risk of pancreatitis due to chylomicronemia.

Genetic causes of FCS

Molecularly, bi-allelic pathogenic variants in the gene encoding lipoprotein lipase (*LPL*) gene are the most common (60–80%) cause of FCS, and currently, over 250 disease-causing variants have been reported in the Human Gene Mutation Database (HGMD; www.hgmd.cf.ac.uk). In addition, bi-allelic pathogenic variants in apolipoprotein C-II, (apoC-II; *APOC2*), lipase maturation factor 1 (*LMF1*), and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein (*GPIHBP1*), or apoA-V (*APOA5*), all of which have a role in LPL and its lipolytic function, are additional (20–30%) causes FCS (*Table 5*) (62-64).

Genetic testing in FCS

With expanding availability and declining cost, patients who are suspected of having FCS, an FCS-causal gene panel is recommended for definitive diagnosis. A single-gene or single-site testing is reserved for patients with a known familial variant.

In all siblings, a "novel" homozygous missense variant, c.617T>C, p.V206A in the *LPL* gene was identified using a FCS-gene panel (65), and this variant was later confirmed at a CLIA compliant laboratory.

Variant classification

The next step is to classify the identified variant(s), as "pathogenic", "likely pathogenic", "likely benign", "benign" or "variants of unknown significance (VUS)". Although many US-based clinical laboratories follow the guidelines published by the ACMG (66,67), each laboratory usually has its own procedure. In addition, various websites [Appendix 1 (68-74)] may be helpful in determining its classification.

Using the ACMG criteria, this variant, c.617T>C, p.V206A in the *LPL* gene could be categorized as "likely pathogenic" in terms of functional data, population data, and *in-silico* computational prediction analyses. The variant is "non-truncating" (missense), but it is "non-synonymous" and located in a well-established "mutational hot spot". In addition, the variant is found at a very low frequency in a large population database, such as the Genome Aggregation Database (gnomAD), and a deleterious effect on its protein function is predicted via several computational prediction tools.

Functional analyses of LPL

Nonetheless, for a novel variant, it is always prudent

to perform functional studies if feasible. Historically, LPL enzyme analysis was the method to diagnose LPL deficiency which is tedious and only available at specialized centers. Moreover, no standardized LPL activity assay is commercially available, and results often do not correlate well with clinical features. However, results can be helpful in supporting the pathogenicity of the variant.

LPL activity can be assessed by collecting two sets of plasma, before and after an intravenous heparin bolus injection (60 U/kg body weight) to release LPL tethered to the endothelium into the circulation. Absent or a markedly reduced LPL function, after excluding hepatic lipase (HL) activity, in the post-heparin plasma is diagnostic for LPL functional deficiency (57). Then, apoC-II deficiency can be delineated by restoration of LPL activity, upon addition of apoC-II or "normal" plasma (75).

In the three siblings, reduced LPL functional activities were reported by multiple methods, corroborating the pathogenicity of the variant (Table S2) (76-78). Therefore, the *LPL*, c.617T>C, p.V206A variant could be reported as the causal variant in FCS. Finding additional unrelated individuals with FCS with this genotype can solidify its pathogenic role in FCS. Once these steps are completed, the classification of the novel variant can be reported with confidence.

Beside the process described above, several diagnostic algorithms of FCS have been published (79-81). In FCS, although it is a familial condition, family history may not be helpful until one individual presents with the condition, due to the nature of autosomal recessive disorder. However, despite each child only has a 1/4 (25%) chance of inheriting both parental pathogenic alleles, and the chance of 1/64 seems very minuscule for all three children to inherit the same alleles, it is not uncommon to have multiple family members to have the same autosomal recessive condition.

Clinical management in FCS

Lastly, the most important reason for having the definitive diagnosis in a monogenic disorder is to determine the appropriate treatment strategy. For FCS, "medical nutrition therapy" with a low-fat diet is recommended for lowering TG levels to minimize or to prevent the risk of pancreatitis.

As the twins experienced, a low-carbohydrate diet is not appropriate for patients with FCS. For this reason, the definitive diagnosis of FCS is critically important. Whereas FDA-approved TG-lowering medications are effective in VLDL-HTG disorders, they are minimally effective in FCS, albeit they are still prescribed as adjuncts. Therefore, less-responsiveness to the TG-lowering medications may also suggest the diagnosis of FCS (82).

A low-fat diet in FCS is to restrict dietary fats to ≤15% of total energy intake, ideally to maintain TG <500 mg/dL for preventing pancreatitis (57,82-85). Medium-chain triglycerides (MCTs) are not packaged into chylomicrons so they can be used to supplement energetic needs (86). Regardless, life-long adherence to an extreme low-fat diet is challenging and patients often require continual encouragement.

Thankfully, for the twins, after implementing a low-fat diet, a stable reduction in TG levels and pancreatitis episodes has been achieved. In order to appropriately provide a special dietary recommendation, it is always important to involve a dietician who has expertise in rare disorders with special dietary needs. After receiving a definitive diagnosis and understanding the rational for therapeutic strategy, patients and their families usually become more compliant.

Novel therapeutics in FCS

For many rare genetic disorders, gene replacement therapy is considered the ultimate therapeutic approach, and this was also considered for FCS, or more specifically for LPL deficiency. Alipogene tiparvovec is an adeno-associated virus type I (AAV1) as a vector that contains the human *LPL* gene with a "gain-of-function" variant or with enhanced lipolytic function. It was originally approved by the European Medicines Association (EMA) in 2012, but then, it was withdrawn from the market in 2017, mainly due to the high cost ($1 million per therapy) and lack of demand. In the US, Alipogene tiparvovec was never approved by the FDA.

Fortunately, antisense oligonucleotide (ASO) agents, or RNA interfering (RNAi) biologics, olezarsen and plozasiran, which target the *APOC3* mRNA are being investigated for treatment of HTG. Now, olezarsen has been approved for a "compassionate use" to treat patients with unrelenting pancreatitis due to severe HTG, even in FCS (87-89).

ApoC-III can modulate TG metabolism via LPL-dependent and LPL-independent mechanisms. ApoC-III has been shown to interfere with the attachment of LPL to the endothelial surface and to compete with its essential cofactor apoC-II (90). In addition, apoC-III has been shown to hinder the attachment of triglyceride-rich lipoproteins (TRLs) to the hepatic low-density lipoprotein-related protein 1s (LRP1s), their receptors for clearance, as well as interfering with the function of hepatic low-

Table 6 HTG polygenic scores of the siblings. Modified with permission from *Annals of Internal Medicine* (54,95)

#	SNP	Chr	Gene 1	Gene 2	Change	Locus and type	Female twin	Male twin	Older brother
1	rs10889353	1	*DOCK7*	*ANGPTL3*	A†->C, T	Intron variant	CA†	A†A†	CA†
2	rs7557067	2	*LINC02850*	*APOB*	A†->G	Regulatory region variant	A†A†	A†A†	GG
3	rs1260326	2	*GCKR*	–	T†->C	Missense variant	CC	CC	T†C
4	rs714052	7	*BAZ1B*	*MLXIPL*	A†->G	Intron variant	GA†	GA†	GG
5	rs7819412	8	*XKR6*	–	G->A†, T	Intron variant	A†G	A†G	A†G
6	rs328	8	*LPL*	–	C†->G	Stop gain	C†C†	C†C†	C†C†
7	rs12678919	8	*RPL30P9*	*LPL*	A†->G	Intergenic variant	A†A†	A†A†	A†A†
8	rs2954029	8	*TRIB1*		A†->T	Polymorphic variant	A†A†	TA†	TT
9	rs174547	11	*FADS2*	*FADS1*	T->C†	Intron variant	C†T	C†T	TT
10	rs964184	11	*ZPR1*	–	G†->C	3-prime UTR variant	CC	G†C	CC
11	rs3135506	11	*APOA5*	–	G->C†, A	Missense variant	GG	GG	GG
12	rs662799	11	*LNC-RHL1*	*APOA5*	G†->A	Intergenic variant	AA	G†A	AA
13	rs17216525	19	*PBX4*	*CILP2*	C†->T	Intergenic variant	C†C†	C†C†	C†C†
14	rs7679	20	*PCIF1*	*PLTP*	T->C†	3-prime UTR variant	C†T	C†T	C†T
Polygenic risk score	–	–	–	–	–	–	15/28	17/28	10/28

†, HTG-risk allele. #: SNP number in polygenic risk scoring. *DOCK7*, dedicator of cytokinesis 7; *ANGPTL3*, angiopoietin-like 3; *Linc02850*, long intergenic non-protein coding RNA 2850; *APOB*, apolipoprotein B; *GCKR*, glucokinase regulatory protein; *BAZ1B*, bromodomain adjacent to zinc finger domain, 1B; *MLXIPL*, MLX-interacting protein-like; *XKR6*, X Kell blood group precursor-related family, member 6; LPL, lipoprotein lipase; *RPL30P9*, ribosomal protein L30 pseudogene 9; *TRIB1*, tribbles pseudo-kinase 1; *FADS2*, fatty acid desaturase 2; *FADS1*, fatty acid desaturase 1; *ZPR1*, ZPR1 zinc finger protein; *APOA5*, apolipoprotein AV; *LNC-RHL1*, lincRNA regulator of hepatic lineages 1; *PBX4*, PBX homeobox 4; *CILP2*, cartilage intermediate layer protein 2; *PCIF1*, phosphorylated CTD interacting factor 1; *PLTP*, phospholipid transfer protein; HTG, hypertriglyceridemia; SNP, single nucleotide polymorphism; Chr, chromosome; UTR, untranslated region.

density lipoprotein receptors (LDLRs) (91-93). Therefore, inhibiting the synthesis of apoC-III, in turn, has positive effects by diminishing these regulatory functions.

Beside the process described above, several diagnostic algorithms of FCS have been published (91-93). In FCS, although it is a familial condition, family history may not be helpful until one individual presents with the condition, due to the nature of autosomal recessive disorder. However, despite each child only has a 1/4 (25%) chance of inheriting both parental pathogenic alleles, and the chance of 1/64 seems very minuscule for all three children to inherit the same alleles, it is not uncommon to have multiple family members to have the same autosomal recessive condition.

PRS

Through GWAS, many traits and disease-susceptibility or -associated SNPs have been identified, and much effort has been devoted in establishing a PRS system for risk assessment for a variety of conditions. Nevertheless, the utility of each PRS should be carefully vetted prior to clinical implementation (94).

Although PRS is intended for disease risk assessment in individuals without manifesting a particular condition, an individual's polygenic background, represented by a PRS, may be informative in appreciating a monogenic disease phenotype.

Currently, underlying biological mechanisms by which FCS clinical features are modified have not been elucidated. However, one plausible influential factor may be HTG levels. Among the siblings, the male twin's clinical history had been the worst with severe HTG with multiple episodes of pancreatitis and hospitalization. On the other end, the older brother's clinical history had been the least severe with less TG fluctuations with only two lifetime episodes of pancreatitis.

Using 14 non-weighted HTG-risk alleles, a PRS was determined in each sibling (95). The lowest risk score of 10/28 (1st percentile) was identified in the older brother, while the highest risk score of 17/28 (95th percentile) was identified in the male twin. The female twin had the intermediate risk score of 15/28 (65th percentile) as shown in *Table 6* (54).

Intriguingly, the siblings' HTG-risk scores corresponded well with the severity of HTG and clinical phenotypes. The results seem to demonstrate the modulatory effect of the polygenic background on a monogenic phenotype in individuals with the same genotype, even within a family, and this is an example of variable expressivity as mentioned earlier (3,4).

Case summary

Stepwise diagnostic processes using genetic testing were presented to illustrate key considerations in the evaluation of a monogenic severe HTG disorder. Based on the preliminary evaluation with the medical and family history, the diagnosis FCS was suspected. A novel homozygous variant was identified in *LPL*, with the use of FCS-causal gene panel. The ACMG variant classification scheme, corroborated by the results of multiple LPL functional studies, determined that *LPL*, c.617T>C, p.V206A could be classified as the causal gene variant for FCS in the three siblings.

After implementing the most suitable therapy of a low-fat diet, a reduction in their TG levels as well as in pancreatitis episodes has been achieved. The phenotypic differences among the siblings could be partially explained by their HTG PRS values, illuminating the interplay between the monogenic genotype and the variable polygenic background.

More importantly, this case exposed multiple instances of missed opportunities to identify a monogenic disorder and unfortunate situations that failed to minimize the serious clinical consequences. The presence of multiple family members (the male siblings) with the diagnosis of HTG and the repeated abdominal complaints of the female twin in childhood should have been a red flag to investigate further for a familial disorder. If more people had been knowledgeable about FCS and its specific dietary therapy, several decades of their lives might have been different.

Current state of gene and molecular therapy in rare diseases

Although gene therapy did not become available for FCS, the FDA has approved over 35 gene therapies in the US prior to 2024, and over 500 gene therapies are currently in the pipeline waiting for approval. Therefore, more patients with rare diseases are likely to benefit with a gene replacement therapy in the near future (96).

In addition, an incidental finding of unusual repetitive sequence in *Escherichia* coli, which later named as, clustered regularly interspaced short palindromic repeat (CRISPR)-CRISPR-associated protein 9 (Cas9), has been adopted for the use in human genome. This cutting-edge genome editing technology utilizes a bacterial immune defense system which can introduce or correct mutations by cutting DNA at specific nucleotides and replacing them with desired nucleotides. The FDA has recently approved the use of CRISPR-Cas9 in the hemoglobin-beta (*HBB*) gene for the treatments of sickle cell disease (SCD) and transfusion-dependent beta thalassemia (97,98). The therapeutic technology using CRISPR-Cas 9 may be the most sophisticated example of precision medicine.

However, there are certain ethical concerns with the use of genome editing. Although most genome editing is done on somatic tissues and localized to certain tissues which are not passed onto the next generation. In the US and some other countries, it is illegal to perform gene editing in germline cells (ova or sperm) or embryos because of the concerns about ethics and safety (99). However, if this technology is used in embryos, changes can be passed onto future generations. This creates a situation where the human genome could be manipulated to improve or to gain some "desirable" traits. Hence, more in-depth discussions and debates involving international authorities to set strong guidelines for the responsible use of this amazing technology in humans.

Genetic counseling

For any genetic evaluation, providing pre-genetic counseling is essential. Positive and negative aspects of genetic testing should be presented so that the patients (and their family) can make informed decisions (*Table 7*). Potential psychological effects of various scenarios should be presented. Some patients may dread having a condition which may not be curable, while the others may be relieved to have a name to their condition and to learn that they were not at fault for having it. They may also be glad that they can make informed plans about their life.

In post-genetic counseling, genetic test results and management plans will be the focus, as well as identifying

Table 7 Pros and cons of clinical genetic testing

Pros
Relief of having a definitive diagnosis
Not at fault for having the condition
Better understanding of health status and risks
Screening for other clinical manifestations
Making informed medical and lifestyle decisions
Participation in clinical trials if available
Identification of other at-risk family members
Cons
"Positive" may not provide clear prognosis
"Negative" means "Not, all-clear"
"Inconclusive" or "Uncertain" results are possible (added frustration and worries)
Result may alter quality of life (QOL) such as medication, diet, lifestyle restrictions, for lifetime
Psychological effects of having a potentially incurable condition
Parental guilt about passing on a gene mutation
Burden of notifying other at-risk family members
Financial burden

additional family members who may also be at risk of developing the same condition. Disclosure of genetic test results can become complicated when no variant is identified, or the identified variant is reported as a VUS.

Possible reasons for a negative result are: (I) the patient does not have the condition for which the test was performed; (II) the patient has the condition, but a variant/variants resides/reside on the outside of targeted regions; (III) a variant is a large structural variant which is undetectable with the method used, and another method such as MLPA or FISH analysis may be required; (IV) the patient has the condition, but a variant/variants resides/reside on another, yet to be identified gene and another method such as WES or WGS may be needed; (V) the condition is a phenocopy of the genetic condition tested, such as the presence of antibodies; and lastly, (VI) a mistake in test processing occurred, either at collection or at the testing laboratory. If the test result is negative, it is important to have a discussion with laboratory personnel so that the accurate information can be passed onto the patients. If a newer technology becomes available in the future, it may be possible to identify a variant/variants.

When a variant is reported as a "VUS", it is neither a "negative" finding nor a causal variant. The notation of VUS indicates that a variant is identified, but its classification cannot be determined with the currently available data. It may be helpful to perform functional studies if feasible. Alternatively, it may require national or international inquiries for additional patients with the same genotype-phenotype, or periodic follow-ups to monitor a change in its classification, as more information becomes available.

Preconception and prenatal counseling

Another important service that genetic counselors provide is pre-conception counseling for individuals who are planning to become pregnant or prenatal counseling for individuals who are already pregnant. The main goal is to promote healthy pregnancy and to minimize adverse effects for the mother and the fetus. Providing a risk assessment is an important component. Prenatal screening and diagnostic tests are listed in *Table 8*.

The ACMG recommends screening for autosomal recessive conditions with the carrier frequency ≥1/200 and X-linked recessive conditions with the carrier frequency >1/40,000 (100,101). On the other hand, the American College of Obstetricians and Gynecologists (ACOG) recommends screening for conditions with the carrier frequency of 1/100 (102,103).

Furthermore, genetic counselors can inform individuals who may have additional risk factors beyond the general population. The risk of having a heritable condition is increased in founder populations and in a consanguineous marriage. The founder effect describes an increase in certain heritable conditions observed due to a reduction in genetic diversity when a few individuals from a large population settle in a new location to establish a community. Consanguinity refers to the marriage of individuals who are closely related by ancestry. Therefore, children of consanguineous parents are at risk of having an autosomal recessive condition, due to a high homozygosity by decent (HBD).

The case of the family with FCS had both of these risk situations so that it was not surprising that this family had three children with FCS due to a novel homozygous variant.

Summary

The completion of the Human Genome Project and

Table 8 Types of prenatal testing (screening and diagnostic)

Type of testing	Screening *vs.* diagnostic	Timing	Method	Conditions tested
Carrier testing	Screening	Preconception or prenatal	Blood or saliva	Autosomal recessive conditions
NIPT (cfDNA)	Screening	9–10 weeks of gestation	Placental cells in maternal blood	Aneuploidies
First trimester screening	Screening	10–14 weeks of gestation	PAPP-A, beta-HCG, nuchal ultrasound	Aneuploidies
Quad testing	Screening	15–21 weeks of gestation	Beta-HCG, AFP, inhibin, uE3	Aneuploidies, neural tube defects
CVS (invasive)	Diagnostic	10–14 weeks of gestation	Placental biopsy	Aneuploidies
Amniocentesis (invasive)	Diagnostic	>16 weeks of gestation	Cells in amniotic fluid	Aneuploidies

NIPT, non-invasive prenatal testing; cfDNA, cell-free DNA; CVS, chorionic villus sample; PAPP-A, pregnancy associated plasma protein A; AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; uE3, unconjugated estriol.

tremendous advances in genetic technologies have facilitated explosive progress in the field of genetics. Despite all, we are still far from deciphering how all genetic variants work together to effect unique features in individuals. Therefore, significant evolution is still expected in the foreseeable future.

For successful integration of precision medicine in clinical practice, physicians and healthcare providers should be well-versed in the basic knowledge in genetics. As presented, monogenic and polygenic disorders are two major, but distinctively different genetic disorders. Although monogenic disorders are thought to be extremely rare, collectively, an estimated 25 to 39 million individuals are known to have a rare disorder (104). Hence, all healthcare providers should be able to delineate and to manage monogenic disorders appropriately.

Moreover, the concept and availability of a PRS is appealing to predict the risk of developing a condition or trait because individuals' gene variants are accessible anytime in their lifetime. However, before any PRS can be implemented, its clinical utility should be carefully assessed and validated through randomized clinical trials.

Finally, this topic has not received much attention, but in-depth dialogue on ethical implications of genotype- or genomics-driven clinical assessment and therapy, especially with the use of PRS and genome editing technology with CRISPR-Cas 9, respectively, should be scrutinized extensively. An international agreement on the responsible practice of genomic medicine should be advocated and instituted (105,106).

Conclusions

In this review, some basic genetic concepts and terminologies were discussed to increase the awareness of clinical genetics. Going forward, various venues should be employed to familiarize and to educate physicians and healthcare professionals with necessary knowledge and skills in clinical use of genetics so that they would be able to fully embrace the era of genomic medicine.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related

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