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■ Review article ■

Genetic testing in clinical pediatric practice

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= Abstract =

Completion of the human genome project has allowed a deeper understanding of molecular pathophysiology and has provided invaluable genomic information for the diagnosis of genetic disorders. Advent of new technologies has lead to an explosion in genetic testing. However, this overwhelming stream of genetic information often misleads physicians and patients into a misguided faith in the power of genetic testing. Moreover, genetic testing raises a number of ethical, legal, and social issues. Diagnostic genetic tests can be divided into three primary but overlapping categories: cytogenetic studies (including routine karyotyping, high-resolution karyotyping, and fluorescent in situ hybridization studies), biochemical tests, and DNA-based diagnostic tests. DNA-based testing has grown rapidly over the past decade and includes pre- and postnatal testing for the diagnosis of genetic diseases, testing for carriers of genetic diseases, genetic testing for susceptibility to common non-genetic diseases, and screening for common genetic diseases in a particular population. Theoretically, once a gene's structure, function, and association with a disease are well established, the clinical application of genetic testing should be feasible. However, for routine applications in a clinical setting, such tests must satisfy a number of criteria. These criteria include an acceptable degree of clinical and analytical validity, support of a quality assurance program, possibility of modifying the course of the diagnosed disease with treatment, inclusion of pre-and postnatal genetic counseling, and determination of whether the proposed test satisfies cost-benefit criteria and should replace or complement traditional tests. In the near future, the application of genetic testing to common diseases is expected to expand and will likely be extended to include individual pharmacogenetic assessments. **(Korean J Pediatr 2010;53:273-285)**

Key Words : Genetic testing, DNA-based testing, Clinical application

Introduction

Recent progress in human genome research has accelerated the discovery of individual genes. This progress has also augmented our understanding of how genes work together and how genetic defects lead to the development of disease. Therefore, the possibility of analyzing individual genes and detecting the specific defects that are responsible for human genetic disorders has now reached the point where genetic testing is becoming an integral part of clinical practice. This increase in genetic information has been accompanied by a rapid evolution of diverse technologies for making accurate and efficient diagnoses. For instance, a number of platforms have been developed for detecting molecular defects, including sequencing technologies, multiplex ligation dependent probe amplification (MLPA), microarrays, oligonucleotide ligation assays, and triplet expansion assays. Methods for detecting structural chromosome abnormalities, such as fluorescent in situ hybridization (FISH) and array comparative genomic hybridization (CGH) are also available. Genetic testing is presently used to diagnose rare monogenic genetic disorders or chromosomal disorders, but will ultimately be extensively applied to assess the susceptibility to common multifactorial disorders or predict the response to a specific medication[1-3]. Because clinical practitioners are responsible for most day-to-day clinical care, including the initial assessment of medical problems, prevention, and long-term care, they will need to incorporate and effectively apply an exponentially increasing amount of information with regard to genetic testing and the clinical implications thereof. Notably, pediatricians are

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the first to encounter patients with genetic disorders or birth defects. This review will discuss the definition, classification, and evolving history of genetic testing and provide comments with regard to the clinical validity, utility, and limitations of such tests. The ethical, legal, and social implications of genetic testing will also be addressed.

Definition of genetic testing

Genetic testing is defined as the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites with the aim of detecting heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes [1]. A growing number of cytogenetic, molecular cytogenetic, biochemical, and DNA-based tests are being used to diagnose genetic disorders. Here, the focus of a vast majority of the discussion will be on DNA-based genetic testing with some consideration given to molecular cytogenetic testing.

Classification of genetic testing

1. Classification of genetic testing based on the purpose of the test[2]

1) Genetic testing for patients who have developed a disease: confirmatory diagnostic tests. Analysis of a disease-causing gene mutation or chromosome structure is carried out in patients with an established clinical diagnosis in order to confirm the clinical diagnosis. Examples include monogenic disorders (>1,500 diseases) and microdeletion syndromes, of which more than 20 are currently known.

2) Genetic testing for detecting carrier status: screening of an at-risk family member. When there is an affected patient with an autosomal recessive, X-linked recessive disorder, unbalanced chromosomal translocation, or chromosome microdeletion/duplication syndrome in a family, genetic testing is performed to determine whether examinees are carriers and whether the offspring may be affected by the same disorder.

3) Genetic testing to predict disorders. This includes presymptomatic testing that is almost completely predictive for the development of a genetic disorder caused by single gene defect. This type of testing includes susceptibility testing that evaluates the predisposition toward or risk of acquiring a multifactorial disease. Examples include adult-onset neurogenetic diseases, familial cancer syndromes, and Alzheimer's disease.

(1) Presymptomatic genetic testing. Testing for a disease where effective therapies or preventive methods are unavailable should not be offered in pediatric patients for ethical/legal reasons.

(2) Disease-susceptibility genetic testing. It should be established that analytical validity and clinical utility are at acceptable levels. Typical applications include insulin-dependent diabetes mellitus, obesity, hypertension, and hyperlipidemia.

(3) Genetic testing for familial cancer syndromes. Such testing should be approached cautiously, taking into account the possibility (or likelihood) that many diverse tumor-related genes are involved. Examples include retinoblastoma, osteosarcoma, breast cancer, and colon cancer.

4) Genetic testing for individual, differential drug responsiveness: pharmacogenetic testing. This includes the diagnosis of sensitivity to drugs by genetic testing based on polymorphisms in drug-metabolizing enzymes, receptors, or transporters that affect pharmacokinetics or pharmacodynamics (e.g., warfarin dosing and sensitivity to antiepileptic medications).

5) Prenatal genetic testing and diagnosis. Prenatal tests includes cytogenetic, biochemical genetic, and DNA-based tests using preimplantation diagnosis (PGD), chorionic villi sampling (CVS), amniocentesis, and cordocentesis (cord blood sampling), depending on the gestational age. An extremely cautious approach should be taken since these tests raise numerous ethical, legal, and social issues.

6) Biochemical genetic testing: mass screening for newborns. These tests seek to identify affected newborns before the onset of symptoms in order to prevent detrimental consequences by appropriately treating or managing patients. Diseases suitable for mass screening should fulfill the following criteria: (i) the incidence should be relatively high, (ii) clinical diagnosis should be problematic prior to the onset of symptoms, (iii) effective screening tools with a reasonable economic burden and analytical validity should be available, and (iv) once diagnosed, measures should be available to prevent or treat the disease.

2. Classification of genetic testing based on choice of material to test[3] (Table 1)

1) DNA-based testing: two strategies—direct and indirect analyses—are available. Completion of the human genome

project has enabled the development of direct mutation analysis of most genetic disorders caused by a single gene defect. In cases where genetic homogeneity is predominant in the disease, mutation analysis can be targeted to a specific mutation or region of the gene instead of requiring sequencing of the entire gene. Indirect assessment using linkage analysis is useful if the disease gene has not yet been identified but has been mapped, or if the process of identifying mutations is problematic (e.g., because of extensive genetic heterogeneity or an extremely large gene size). However, this approach necessitates the presence of informative genetic marker (s) located near a disease gene, and the availability of specimens from additional family members. The technologies developed for such DNA-based genetic testing include polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP), DNA sequencing (including genomic and cDNA sequencing), microarrays, allele-specific oligonucleotide (ASO) hybridization, and MLPA.

2) Molecular cytogenetic testing. As new technologies such as array CGH, spectral karyotyping, and subtelomeric and multicolor FISH have developed, it has become clear that a subset of dysmorphic patients with developmental delay have microdeletions or structural rearrangements in chromosomes. Molecular cytogenetic testing progressed during the late 1980s with the introduction of FISH analysis, and has since evolved into what might be called the array CGH era. Recent advances in molecular cytogenetics are rapidly increasing the resolution of such analyses, providing insight into the dynamic nature of the human genome structure.

3) Cytogenetic genetic testing. Conventional chromosome analysis enables the detection of alterations in chromosome number and structure. Current routine cytogenetic analysis uses a banding technique to achieve a resolution of about 5 to 10 megabases of DNA. A metaphase chromosome spread will usually show 350-500 bands, and high resolution banding is able to show 500-850 bands.

4) Biochemical genetic diagnosis. These tests are carried out to screen or diagnose newborns affected by inborn errors of metabolism. Individual inherited metabolic disorders are rare, but in the aggregate, they have a major impact at the population level. Since Archibald Garrod introduced the concept of "inborn error of metabolism" or "chemical individuality," more than 600 such diseases have been identified that collectively affect approximately one in 500 newborns. Many sophisticated laboratory tests are available for the confirmatory diagnosis of each disease. This diversity poses a challenge to the general pediatrician, who must be knowledgeable about an array of biochemical metabolite assays based on high-performance liquid chromatography (HPLC) and tandem mass spectrometry as well as enzymatic assays.

3. Classification of genetic testing based on clinical utility and validity[4]

1) Clinical genetic testing. Clinical tests are defined by having specimens examined and results reported to the provider or patient for the purpose of diagnosis, prevention, or treatment of individual patients. Laboratories performing research testing are not subject to site visit inspections or regulations such as proficiency testing and registration. There is a charge for clinical tests, and costs vary according to the complexity of the test. Test results are reported in writing.

2) Research genetic testing. Research tests are those in which specimens are examined for the purpose of achieving a better understanding of a condition or developing a

Table 1. Classification of Genetic Testing Based on Purpose and Choice of Material to Test

Specimen Purpose	DNA-based genetic testing	Molecular cytogenetic testing	Cytogenetic testing	Biochemical genetic testing
DNA profiling	Paternity testing, individual identification (forensic medicine)			
Disease diagnosis (confirmatory, prenatal, presymptomatic)	Single gene Mendelian genetic disorders, mitochondrial disorders, familial cancer syndrome	Chromosome microdeletion/ duplication syndromes	Numerical & structural chromosome abnormalities	Inborn errors of metabolism
Disease prediction (susceptibility testing, pharmacogenetic testing)	Alzheimer's disease, hypertension, cancer, psychiatric disorder, coronary artery disease, prediction of drug response			Maternal serum biomarker screening

clinical test. Laboratories performing research testing are not subject to regulations. The cost of research testing is generally covered by the researcher. Test results are generally not given to patients or their providers, but are instead typically reported in peer-reviewed journals after removing patient identification information.

3) Investigational genetic testing. Investigational tests are tests that are perceived to have value, but that have not yet been scientifically validated or generally accepted by the medical community as accurate and useful. Test results may or may not be shared, and it may be a long time before results are made available.

A brief history of genetic testing

The first example of a genetic test was the analysis of chromosome number and structure, first reported in 1959 by Jerome Lejeune, who diagnosed Down syndrome as trisomy of chromosome 21 after determining that the correct human chromosome number was 2N=46 in 1956. In fact, routine cytogenetic studies were made possible by the advent of hypotonic treatment of dividing cells to spread the chromosomes and by the development of cell culture methods in the 1950s. In 1960, prenatal determination of sex became possible. In 1961, a biochemical screening method using a bacterial inhibition assay was invented to detect phenylketonuria and was applied in a population-based screen of newborns in Massachusetts in 1963. The first successful prenatal chromosomal analysis was reported in 1966, opening the door to prenatal genetic testing. Subsequently, maternal serum biomarker screening was initiated with a screen for α-fetoprotein in 1972. In the following year, an association between HLA type and disease was used to predict disease susceptibility. The first DNA-based genetic test for sickle cell anemia was successfully applied in 1978. Two major factors that greatly accelerated the expansion of DNA-based genetic testing were the discovery and subsequent widespread availability of a large variety of restriction enzymes in the late 1970s and the development of polymerase chain reaction (PCR) technology in the mid 1980s. Two advanced methods for DNA sequencing were reported simultaneously in 1977, for which Sanger and Gilbert shared the Nobel Prize in chemistry in 1980. Since then, the Sanger dideoxy method for DNA sequencing has remained the standard sequencing technology, although major advances in automation and other modification were made in the 1990s. During this time, molecular cytogenetic testing technology has also progressed. The FISH technique was introduced in the late 1980s. Multicolor FISH, spectral karyotyping, and CGH technologies subsequently became available to identify minute structural aberrations of chromosomes. Since the turn of the century, there has been explosive development of automation and high-throughput tools. Most recently, the next generation of technology based upon massively parallel DNA sequencing was invented[5-7].

Clinical utility and validity of genetic testing

1. Prerequisites for DNA-based genetic testing

1) For DNA-based testing of genetic disorders caused by a single gene defect, the structure or locus of the responsible gene and the function of the gene product must be known.

2) If the gene has not been cloned, an informative DNA marker linked to the gene should be available to track the segregation pattern of the marker in a family at risk.

3) Ideally, the defect of one gene leads to one genetic disorder (i.e., limited locus heterogeneity).

4) Genetic epidemiology data pertaining to the particular ethnicity of the examinee should be available and accessible.

5) Sufficient levels of analytical accuracy, clinical validity, and utility should be guaranteed.

6) Pre- and post-test genetic counseling should be provided.

7) The right of examinees to choose whether to be informed of test results should be respected and taken into account[1-3, 8, 9].

2. Technologies used for DNA-based genetic testing (Table 2)

This section describes methods used for mutation scanning include denaturing HPLC, DGGE (denaturing gradient gel electrophoresis), and two-dimensional gene scanning (TDGS). To date, genetic testing as a tool for diagnosing genetic disease has concentrated on identifying point mutations (including base substitutions and small deletions/insertions) by PCR and direct sequence analysis. However, it is difficult to identify large deletions and duplications by routine PCR gel-based assays, especially for genes with a heterozygous status. For the detection of large deletions

Table 2. Technologies Utilized for DNA-Based Genetic Testing

Allele-specific PCR/ARMS (amplification refractory mutation system)
Bead array
Invader chemistry
Mass spectrometry
Microarray technology
MLPA (multiplex ligation probe amplification)
Mutation scanning using dHPLC, SSCP, DGGE, TGGE, heteroduplex analysis, melting curve analysis
Oligonucleotide ligation assay (OLA)
PCR, bisulfite with methylation-specific primers
PCR, followed by capillary electrophoresis
PCR, followed by gel electrophoresis (agarose, polyacrylamide, etc.)
PCR, GeneScan fragment size analysis
PCR, followed by heteroduplex analysis
PCR, real-time with intercalating dye (e.g. SYBR Green)
PCR, real-time with allele-specific probe
PCR, melting curve analysis with intercalating dye (e.g. SYBR Green)
PCR, melting curve analysis with allele-specific probe
PCR, followed by RFLP assessment (restriction enzyme digestion)
PCR, followed by membrane transfer and probe hybridization
PCR, long distance
PCR, multiplex
PCR-based assay capable of differentiating methylated sites
PCR-based assay targeted at SNRPN gene expression
Pyrosequencing
Sequencing
Southern blot (without prior PCR amplification)
Southern blot using methylation sensitive restriction enzymes

or insertions, Southern blots or MLPA is needed. MLPA is a PCR-based method that can detect gene dosage. Since its introduction, it has been used to test a number of genes for large deletions or duplication mutations. By using MLPA to evaluate gene dosage, it is possible to detect large pathogenic deletion/duplications. In addition to detecting gene dosage, MLPA can be used to verify the methylation patterns of target genes, determine aneuploidy in prenatal diagnosis, and identify large deletions and duplications in applications related to cancer genetics. This simple method is advantageous because it requires only a small amount of template DNA and based on flexible principles that allow for multiple applications, including high-throughput applications. The disadvantages of MLPA include the possibility of false positives caused by poor template DNA quality, confounding of results due to SNPs being located within probe sequences, and complications associated with quantitative analysis[3, 10, 11].

3. Genetic testing in monogenic disorders (Table 3)

Clinical genetic tests are currently available for more than 1,600 rare genetic disorders[4]. Recently, there has been a veritable explosion in the application of DNA-based genetic testing for monogenic Mendelian disorders to confirm an existing diagnosis or for prenatal diagnostic purposes. While genetic testing might merely complement other tests, it is often more expensive because many of such tests are not reimbursed by insurance. Moreover, interpretations of test results may be problematic in some cases. Therefore, pre- and post-test genetic counseling should be provided to examinees. Physicians offering tests are required to fully understand the clinical and analytical validity as well as the pros and cons of genetic testing. The following list provides some examples of monogenic disorders where DNA-based genetic testing is justified[4, 11-13]:

1) Inherited metabolic disorders: urea cycle defects, Wilson disease, Gaucher disease, Tay-Sachs disease, glycogen storage disease (GSD) type Ia, hemochromatosis, fatty acid oxidation disorders, and cystic fibrosis

2) Skeletal dysplasia: achondroplasia and craniosynostosis syndrome

3) Neuromuscular disorders: progressive muscular dystrophy (DMD/BMD) and spinal muscular atrophy

4) Triplet-repeat expansion disorders: spinocerebellar ataxia, fragile-X syndrome, myotonic dystrophy, Kennedy disease, and Huntington's disease

5) Neurogenetic disorders: Canavan disease, adrenoleukodystrophy, and metachromatic leukodystrophy

6) Hematologic disorders: hemophilia, factor V Leiden, and prothrombin

7) Familial cancer syndromes: retinoblastoma (Rb), breast cancer, colon cancer, and ovarian cancer

8) Dysmorphic syndromes: Treacher-Collins syndrome, Rett syndrome, Waadenburg syndrome, Holt-Oram syndrome, Marfan syndrome, and Smith-Lemli-Opitz syndrome

9) Mitochondrial disorders: MELAS (Mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms), MERRF (Myoclonic Epilepsy with Ragged Red Fibers), LHON (Leber's hereditary optic neuropathy), and Kearn-Sayers syndrome

10) Endocrine disorders: multiple endocrine neoplasia, adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, growth hormone (GH) deficiency, and GH resis-

tance syndrome

11) Renal disorders: polycystic kidney disease and Alport syndrome

12) Immune disorders: agammaglobulinemia and chronic granulomatous disease (CGD)

4. DNA-based genetic testing for epigenetic disorders (Table 4)

Epigenetics is a newly emerging field of human genetics. Epigenetic change is characterized by the alteration of gene expression without a permanent change in the genetic information. Several mechanisms to account for epigenetic changes have been elucidated, including DNA methylation at CpG dinucleotides in the promoter region of the gene, histone modification by acetylation/deacetylation, and non-coding microRNA interference at the transcription level. Epigenetic changes have been shown to contribute to several genetic disorders through genomic imprinting. Genomic imprinting is caused by differential expression of a gene depending on whether it is inherited maternally or paternally (otherwise known as the so-called "parent-of-origin effect"). DNA-based genetic testing of genomic imprinting associated with differential methylation is based on bisulfite treatment of DNA, followed by amplification and differential digestion with restriction enzymes. As shown

Table 3. Single Gene Disorders and Responsible Genes Where DNA-Based Genetic Testing is Offered by the Medical Genetics Clinic & Laboratory, Asan Medical Center Children's Hospital (Continued)

Category	OMIM	Disease	OMIM	Gene	Location
Cancer disease	#175200	Peutz-Jeghers syndrome	*602216	*STK11*	19p3.3
	#193300	Von Hippel-Lindau Syndrome	*608537	*VHL*	3p26-p25
	#194070	Wilms tumor, WT1-related	*607102	*WT1*	11p13
	#192500	Long QT syndrome	*607542	*KCNQ1*	11p15.5
	+152427	Long QT syndrome	+152427	*KCNH2*	12p11.1
	#603830	Long QT syndrome	*600163	*SCN5A*	3p21
Cutaneous disease	#176670	Familial lipodystrophy	*150330	*LMNA*	1q21.2
	#308300	Incontinentia Pigmenti	*300248	*NEMO (IKBKG)*	Xq28
	#275210	Restrictive dermopathy	*606480	*ZMPSTE24*	1p34
	#275210	Restrictive dermopathy	*150330	*LMNA*	1q21.2
Dysmorphic syndrome	#118450	Alagille syndrome	+601920	*JAG1*	20p12
	#105830	Angelman syndrome	*182279	*UBE3A*	15q12
	#207410	Antley-Bixler syndrome	*124015	*POR*	7q11.2
	#208085	ARC syndrome	*608552	*VPS33B*	15q26.1
	#300419	ARX-related disorders	*300382	*ARX*	Xp22.13
	#130650	Beckwith-Wiedemann syndrome	*600856	*H9*	11p15.5
			*103280	*LIT1*	
			*604115	*IGF2*	
	#214800	CHARGE syndrome	*608892	*CHD7*	8q12.1
	#613013	Central hypoventilation syndrome	*603851	*PHOX2B*	4p12
	#176450	Currarino syndrome	*142994	*HLXB9*	7q36
	#109400	Goltz-Gorlin syndrome	*601309	*PTCH*	9q22.3
	#142900	Holt-Oram syndrome	*601620	*TBX5*	12q24.1
	#154700	Marfan syndrome	*134797	*FBN1*	15q21.1
	#608967	Marfan syndrome II	+190182	*TGFBR2*	3p22
	#610380	Marfan syndrome II	*190181	*TGFBR1*	9q22
	#162200	Neurofibromatosis 1	*613113	*NF1*	17q11.2
	#101000	Neurofibromatosis 2	*607379	*NF2*	22q12.2
	#163950	Noonan syndrome	#163950	*SOS1*	2p22-p21
	#163950	Noonan syndrome	*176876	*PTPN11*	12q24.1
	#151100	LEOPARD syndrome			
	#310600	Norrie disease	*300658	*NDP*	Xp11.4
	#176270	Prader Willi syndrome	*182279	*SNRPN*	15q12
	#180849	Rubinstein Taybi syndrome	*600140	*CREBBP*	16p13.3
	#270400	Smith-Lemli-Opitz syndrome	*602858	*DHCR7*	11q12-q13
	#154500	Treacher Collins syndrome	*606847	*TCOF1*	5q32-q33.1
	#193500	Waardenburg syndrome	*606597	*PAX3*	2q35

Table 3. Single Gene Disorders and Responsible Genes Where DNA-Based Genetic Testing Is Offered by the Medical Genetics Clinic & Laboratory, Asan Medical Center Children's Hospital (Continued)

Category	OMIM	Disease	OMIM	Gene	Location
Endocrine disease	#202110	17 hydroxylase deficiency	*609300	*CYP17A1*	10q24.3
	#176410	46, XY, DSD	+152790	*LHCGR*	2p21
	#264600	5 alpha reductase deficiency	*607306	*SRD5A2*	2p23
	#202200	ACTH Resistance	*607397	*MC2R*	18p11.2
	#607398	ACTH Resistance	*609196	*MRAP*	21q22.1
	#612965	Adrenal failure	+184757	*NR5A1(SF1)*	9q33
		Adrenocortical dysplasia	*609377	*ACD*	16q22.1
	#300068	Androgen insensitivity syndrome	*313700	*AR*	Xq11-q12
	#415000	Azoospermia		*AZF*	Yq11.2
	#262600	Combined pituitary hormone deficiency	*601538	*PROP1*	5q
			*173110	*POU1F1*	3p11
			*601802	*HESX1*	3p21.2-p21.1
			*600577	*LHX3*	9q34.3
			*602146	*LHX4*	1q25
			*313430	*SOX3*	Xq26.3
	+201910	Congenital adrenal hyperplasia	+201910	*CYP21A2*	6p21.3
	#300200	Congenital adrenal hypoplasia	*300473	*NR0B1*	Xp21.3-p21.2
	#275200	Congenital Hypothyroidism	+603372	*TSHR*	14q31
	#218700	Congenital Hypothyroidism	*167415	*PAX8*	2q12-q14
	#201710	Congenital lipoid adrenal hyperplasia	*600617	*STAR*	8p11.2
	#145980	Hypocalciuric hypercalcemia	+601199	*CASR*	3q13.3-q21
	#146110	Hypogonadotropic hypogonadism	*138850	*GNRHR*	4q21.2
	+308700	Kallmann syndrome 1	+308700	*KAL1*	Xp22.3
	#125850	MODY1	*600281	*HNF4A*	20q12-q13.1
	#609734	Monogenic obesity	*176830	*POMC*	2p23.3
	+131100	Multiple endocrine neoplasia type 1	+131100	*MEN1*	11q13
		Multiple endocrine neoplasia type 2A,B	+164761	*RET*	10q11.2
	#606176	PHHI, Neonatal DM	*600937	*KCNJ11*	11p15.1
		PHHI, Neonatal DM	*138130	*GLUD1 (GDH)*	10q23.3
		PHHI, Neonatal DM	*138079	*GCK*	7p15-p13
		PHHI, Neonatal DM	*600509	*SUR1*	11p15.1
	#103580	Pseudohypoparathyroidism 1a	+139320	*GNAS*	20q13.2
	#603233	Pseudohypoparathyroidism 1b			
		SRY sequencing	*480000	*SRY*	Yp11.3
	#607200	Thyroid dyshormonogenesis	*606759	*DUOX2*	15q15.3
	#274500	Thyroid dyshormonogenesis	*606765	*TPO*	2p25
	#188570	Thyroid hormone resistance	*190160	*THRB*	3p24.3
	#601410	Transient neonatal diabetes mellitus	*606546	*HYMA*	6q24
	#304800	X-linked nephrogenic DI	*300538	*AVPR2*	Xq28
Gastrointestinal disease	#613217	Congenital tufting enteropathy	*185535	*EPCMA*	2p21
	#167800	Hereditary or familial pancreatitis	+276000	*PRSS1*	7q35
			*167790	*SPINK1*	5q32
			*601405	*CTRC*	1p36.21
	#601847	PFIC II	*603201	*ABCB11*	2q24
Hematologic disease	#603553	Familial hemophagocytic lymphohistiocytosis	*170280	*PRF1 (MUNC13-4)*	10q22
	#612304	Protein C deficiency	*612283	*PROC*	2q13-q14
	+275350	Transcobalamin II deficiency	+275350	*TCN2*	22q11.2-qter
Immune disease	#300755	Bruton's agammaglobulinemia	*300300	*BTK*	Xq21.3-q22
	#306400	Chronic granulomatous disease	*300481	*CYBB*	Xp21.1
	#304790	IPEX syndrome	*300292	*FOXP3*	Xp11.23-q13.3
	#300400	Severe Combined Immunodeficiency, X-linked	*308380	*IL2RG*	Xq13
	#301000	Wiskott Aldrich syndrome	*300392	*WAS(IMD2)*	Xp11.23-p11.22

Table 3. Single Gene Disorders and Responsible Genes Where DNA-Based Genetic Testing Is Offered by the Medical Genetics Clinic & Laboratory, Asan Medical Center Children's Hospital (Continued)

Category	OMIM	Disease	OMIM	Gene	Location
Metabolic disease	#250950	3-Methlyglutaconic aciduria 1	*600529	*AUH*	Chr.9
	#210200	3-Methylcronylglycinuria	*609010	*MCCA*	3q25-q27
			*609014	*MCCB*	5q12-q13
	#143890	AD familial hypercholesterolemia	*606945	*LDLR*	19p13.2
	#300100	Adrenoleukodystrophy	*300371	*ABCD1*	Xq28
	+107400	Alpha-1 Antitrypsin deficiency	+107400	*SERPINA1*	14q32.1
	#207800	Arginase deficiency	*608313	*ARG1*	6q23
	#207900	Arginino-succinyl Lyase deficiency	*608310	*ASL*	7cen-q11.2
	#237300	Carbamoylphosphate synthetase I deficiency	*608307	*CPS1*	2q35
	#212140	Carnitine deficiency	*603377	*SLC22A5*	5q31.1
	#255110	Carnitine palmitoyltransferase II deficiency	*600650	*CPT2*	1p32
	#219700	CFTR-related disorders	*602421	*CFTR*	7q31.2
	#605814	Citrin deficiency	*603859	*SLC25A13*	7q21.3
	#215700	Citrullinemia	*603470	*ASS*	9q34.1
	#220100	Cystinuria	*104614	*SLC3A1*	2p16.3
	#177000	Erythropoietic protoporphyria	*612386	*FECH*	18q21.3
	#301500	Fabry disease	*300644	*GLA*	Xq22
	#162000	Familial hyperuricemia	*191845	*UMOD*	16p12.3
	#227810	Fanconi Bickel syndrome	*138160	*SLC2A2*	3q26.1-q26.3
	#230400	Galactosemia	*606999	*GALT*	9p13
	#230200	Galactosemia type 2	*604313	*GALK*	17q24
	#230350	Galactosemia type 3	*606953	*GALE*	1p36-p35
	#256540	Galactosialidosis	*613111	*PPGB*	20q13.1
	#230800	Gaucher disease	*606463	*GBA*	1q21
	#231670	Glutaricacidemia type 1	*608801	*GCDH*	19p13.2
	#231680	Glutaricacidemia type 2	*608053	*ETFA*	15q23-q25
			*130410	*ETFB*	19q13.3
			*231675	*ETFDH*	4q32-qter
	#232500	Glycogen storage disease type IV	*607839	*GBE1*	3p12
	+232200	Glycogen storage disease type Ia	+232200	*G6PC*	17q21
	#232220	Glycogen storage disease type Ib	*602671	*SLC37A4*	11q23
	#232400	Glycogen storage disease type III	*610860	*AGL*	1p21
	#234500	Hartnup disease	*608893	*SLC6A19*	5p15.33
	#229600	Hereditary fructose intolerance	*612724	*ALDOB*	9q22.3
		HFE-associated hereditary hemochromatosis	+235200	*HFE*	6p21.3
	#238970	HHH syndrome	*603861	*ORNT1*	13q14
	#236250	Homocystinuria	*607093	*MTHFR*	1p36.3
	+236200	Homocystinuria	+236200	*CBS*	21q22.3
	+309900	Hunter syndrome	+309900	*IDS*	Xq28
	#607014	Hurler syndrome	*252800	*IDUA*	4p16.3
	#259900	Hyperoxaluria type 1	*604285	*AGXT*	2q36-q37
	#239500	Hyperprolinemia 1	*606810	*PRODH*	22q11.2
	#307800	Hypophosphatemic Rickets,	*300550	*PHEX*	Xp22.2-p22.1
	#602390	Juvenile hemochromatosis	*608374	*HJV*	1q21
			*606464	*HAMP*	19q13
	#245200	Krabbe disease	*606890	*GALC*	14q31
	#609016	LCHAD deficiency	*600890	*HADHA*	2p23
			*143450	*HADHB*	2p23
	#300322	Lesch-Nyhan syndrome	*308000	*HPRT1*	Xq26-q27.2
	#309000	LOWE syndrome	*300535	*OCRL*	Xq26.1
	#222700	Lysiuric protein intolerance	*603593	*SLC7A7*	14q11.2
	#248600	Maple Syrup Urine disease	*238331	*DLD*	7q31-q32
			*248610	*DBT*	1p31
			*608348	*BCKDHA*	6q14
			*248611	*BCKDHB*	19q13.1-q13.2

Table 3. Single Gene Disorders and Responsible Genes Where DNA-Based Genetic Testing Is Offered by the Medical Genetics Clinic & Laboratory, Asan Medical Center Children's Hospital (Continued)

Category	OMIM	Disease	OMIM	Gene	Location
Mitochondrial disease	#256000	Leigh syndrome	+516060	*MTATP6*	
	#256000	Leigh syndrome	*185620	*SURF1*	9q34
	#535000	LHON	*516003	*MTND4*	
	#540000	MELAS	*590050	*MTTL1; MTND5*	
	#545000	MERRF	*590060	*MTTK*	
	#580000	Nonsyndromic hearing loss, mitochondrial	*561000	*MTRNA1; MTTS1*	
Muscular disease	#310200	Duchenn muscular dystrophy	*300377	*DMD*	Xp21.2
	#300376	Becker muscular dystrophy			
	#310300	Emery-Dreifuss Muscular dystrophy	*300384	*EMD*	Xq28
	#160900	Myotonic dystrophy type 1	*605377	*DMPK*	19q13.2-q13.3
	#602668	Myotonic dystrophy type 2	*116955	*CNBP*	3q13.3-q24
	#310400	Myotubular myopathy type 1	*300415	*MTM1*	Xq28
	#253300	Spinal muscular atrophy	*600354	*SMN1*	15q12.2-q13.3
Neurologic disease	#125310	CADASIL	*600276	*NOTCH3*	19p13.2-p13.1
	#116860	Cerebral Cavernous Malformation	*604214	*CCM1*	7q11.2-q21
			*607929	*CCM2*	7p13
			*609118	*CCM3*	3q26.1
	#118220	Charcot-Marie-Tooth neuropathy type 1A	*601097	*PMP22*	17p11.2
	#302800	Charcot-Marie-Tooth neuropathy type X	*304040	*GJB1*	Xq13.1
	#128230	Dopa-responsive dystonia	*600225	*GCH1*	14q22.1-q22.2.
	#125370	DRPLA	*607462	*DRPLA*	12p13.31
	#128100	Early-onset torsion dystonia	*605204	*TOR1A*	9q34.
	#300624	FMR1-related disorders	*309550	*FMR1*	Xq27.3.
	#229300	Friedreich Ataxia	*606829	*FRDA*	9q13.
	#143100	Huntington disease	*613004	*HD*	4p16.3
	#312750	MECP2-related disorders	*300005	*MECP2*	Xq28
	#254800	Myoclonic epilepsy, Unverricht and Lundborg	*601145	*CSTB*	21q22.3
	#121200	Neonatal epilepsy 1	*602235	*KCNQ2*	20q13.3
	#234200	Pantothenate kinase-associated neurodegeneration	*606157	*PANK2*	20p13-p12.3
	#600116	Parkinson disease	*602544	*PARK2*	6q25.2-q27
	#312080	Pelizaeus-Merzbacher disease	*300401	*PLP1*	Xq22
	#182600	Spastic paraplegia type 3A	*606439	*SPG3A*	14q11-q21
	#182601	Spastic paraplegia type 4	*604277	*SPG4*	2p22-p21
	#600363	Spastic paraplegia type 6	*608145	*SPG6*	15q11.1
	#313200	Spinal and bulbar muscular atrophy	*313700	*AR*	Xq11-12.
	#164400	Spinocerebellar ataxia type 1	*601556	*ATXN1*	6p23.
	#603516	Spinocerebellar ataxia type 10	*611150	*SCA10*	22q13
	#604326	Spinocerebellar ataxia type 12	*604325	*SCA12*	5q31-q33
	#607136	Spinocerebellar ataxia type 17	*600075	*SCA17*	6q27
	#183090	Spinocerebellar ataxia type 2	*601517	*ATXN2*	12q24.1.
	#109150	Spinocerebellar ataxia type 3	*607047	*MJD*	14q32.1.
	#183086	Spinocerebellar ataxia type 6	*601011	*CACNA1A*	19p13.
	#164500	Spinocerebellar ataxia type 7	*607640	*SCA7*	3p21.1-p12.
	#608768	Spinocerebellar ataxia type 8	*603680	*SCA8*	13q21
	#191100	Tuberous sclerosis complex	*605284	*TSC1*	9q34
			*191092	*TSC2*	16p13.3
Ophthalmologic disease	#106210	Aniridia	*607108	*PAX6*	11p13
	#607541	Corneal dystrophy, avellinotype	*601692	*TGFB1*	5q31
	#133780	Exudative Vitreoretinopathy type 1 (EVR1)	*604579	*FZD4*	11q14-q21
	+312700	Retinoschisis, X-linked	+312700	*XLRS1*	Xp22.2-p22.1
	#153700	Vitelliform macular dystrophy	*607854	*VMD2*	11q13
Otologic disease	#220290	Nonsyndromic deafness, Cx26	*121011	*GJB2*	13q11-q12

Table 3. Single Gene Disorders and Responsible Genes Where DNA-Based Genetic Testing Is Offered by the Medical Genetics Clinic & Laboratory, Asan Medical Center Children's Hospital (Continued)

Category	OMIM	Disease	OMIM	Gene	Location
Renal disease	#300009	Dent's syndrome	*300008	*CLCN5*	Xp11.22
	#256100	Nephronophthisis 1	*607100	*NPHP1*	2q13
	#220150	Renal hypouricemia	*607096	*SLC22A12*	11q13
Skeletal disease	#100800	Achondroplasia	*134934	*FGFR3*	4p16.3.
	#114290	Campomelic dysplasia, sex-reversal	*608160	*SOX9*	17q24.3-q25.1
		FGFR2-related craniosynostosis	*176943	*FGFR2*	10q26.
		FGFR3-related craniosynostosis	*134934	*FGFR3*	4p16.3.
	#146000	Hypochondroplasia	*134934	*FGFR3*	4p16.3.
	#166200	Osteogenesis Imperfecta	+120150	*COL1A1*	17q21.31-q22
			*120160	*COL1A2*	7q22.1
	#215100	Rhizomelic chondrodysplasia punctata type 1	+601757	*PEX7*	6q22-q24
	#183900	Spondyloepiphyseal dysplasia	+120140	*COL2A1*	12q13.11-q13.2
	#107480	Townes Brocks syndrome	*602218	*SALL1*	16q12.1

Table 4. Genetic Disorders Associated with Imprinting Defects

Genetic Disorder	OMIM#	Chromosome	Gene(s)	Imprinted
Angelman syndrome	105830	15q11-13	*UBE3A*	Pat
Prader-Willi syndrome	176270	15q11-13	*SNRPN*	Mat
Beckwith-Wiedemann syndrome			*Others (MKRN3, NDN)*	Mat
	130650	11p15.5	*H19*	Pat
			IGFII	Mat
Silver-Russell syndrome			*CDKN1C*	Pat
	180860	11p15.5	*H19*	Pat
		7p11.2-p13	*GRB10*	Mat
AHO/PHP 1a, pPHP	103580	20q13.3	*GNAS1*	Pat

in Table 4, Prader-Willi/Angelman syndromes (PWS/AS) are prototypes of such epigenetic disorders. To date, at least six disorders are known to be caused by epigenetic changes: PWS/AS, Beckwith-Wiedemann syndrome (BWS), Silver-Russell syndrome (SRS), Albright hereditary osteodystrophy (AHO)/pseudohypoparathyroidism (PHP), and transient neonatal diabetes mellitus[10] (Table 4).

5. Pharmacogenetic DNA testing

Pharmacogenetic DNA testing is an example of a genetic test that offers the potential of predicting the response to a particular drug by an individual patient. This enables precise tailoring of drug dosages for maximum efficacy, reduction of adverse reactions and identification of drugs that should be avoided altogether. In pediatric practice, pharmacogenetic tests for sensitivity to mercaptopurine, a drug used for acute childhood leukemia, is one example. In this case, the activity of the enzyme thiopurinemethyltransferase (TPMT) varies among individuals due to a variant of the TPMT gene. Pharmacogenetic testing will be increasingly used in clinical practice in the near future. However, many different genes involved in the pharmacokinetics and pharmacodynamics of drug metabolism should be extensively analyzed simultaneously to enhance the sensitivity and specificity of prediction[14-17]. The following currently used pharmacogenetic tests have demonstrated clinical utility and validity:

1) Warfarin genotyping: cytochrome P450 enzyme 2C9 (CYP2C9) and vitamin K oxide receptor complex-1 (VKORC1)

2) Slow/rapid acetylator genotyping: N-acetyl transferase 2 (NAT2) gene

3) Thiopurine drug (6-MP, 6-thioguanine, azathioprine) metabolism genotyping: thiopurine methyltransferase (TPMT) gene

6. SNP-based disease-susceptibility genetic testing

The use of SNP-based disease-susceptibility tests tends to be clinically justified because the disease categories covered include more common disorders that represent a greater socio-economic burden to the health care system. However, the clinical and analytical validity of such tests

do not reach a level that warrants their recognition as bona fide clinical tests. Obtaining clinically significant genetic data in certain ethnic groups using SNP-based disease-susceptibility tests requires a collective analysis of numerous genes and SNPs in both normal and patient populations. As statistical genetics and new technologies continue to rapidly develop, SNP-based disease-susceptibility genetic tests can be expected to play a growing role in the management of more common diseases in a clinical practice setting, although this increasing use will also raise tremendous ethical, legal, and social issues. The following currently used tests have demonstrated a degree of clinical utility and validity in specific populations[18-20]:

1) Thrombophilia panel: factor V Leiden, prothrombin (factor II) and MTHFR (methylenetetrahydrofolate reductase) genes

2) Coronary heart disease: lipoprotein (Lp(a), apoE), coagulation factor, and MTHFR genes

3) Hypertension: angiotensin-converting enzyme (ACE) gene

4) Insulin-dependent diabetes mellitus: HLA genes

5) Cancer disease: BRACA1, BRACA2, Rb, adenomatosis polyposis coli (APC), and N-myc, BCR-ABL genes

6) Hemochromatosis: HFE gene (population screening in Caucasians)

7) Alzheimer's disease: Apo E gene

8) Neural tube defect: MTHFR gene

7. Chromosome microdeletion syndrome (Table 5)

Molecular cytogenetic testing has progressed since the late 1980s with the advent of new molecular biology techniques. One such technique is FISH, in which purified single-stranded DNA sequences labeled with a fluorescent dye are hybridized to target complementary single-stranded chromosomal DNA sequences in the interphase or metaphase state. The resolution of FISH is limited by the size of the probes required to generate detectable fluorescence. FISH testing can be undertaken to diagnose microdeletion/duplication syndrome in cases where there is a high clinical suspicion of such a condition. Subtelomeric FISH is usually recommended for assessing patients with developmental delay or failure to thrive. Recently, arrayed CGH using dense SNP chips have allowed the detection of minute chromosomal structural aberrations at extremely high resolution and led to the discovery of new dysmorphic syndromes caused by chromosome microdeletion/duplication. However, copy number variations can exist that have uncertain clinical significance, and therefore, the results of such analyses should be interpreted with caution. Table 5 summarizes microdeletion syndromes that are diagnosed by FISH[10, 21].

Table 5. Microdeletion Syndromes Diagnosed by FISH

Syndromes	Deletion of chromosome locus
1p deletion	1p36
Soto	5q35
Williams	7q11.23
WAGR	11p13
Jacobsen	11q24.1-qter
Prader-Willi	15q11-q13 (pat)
Angelman	15q11-q13 (mat)
Rubinstein-Taybi	16p13.3
Smith-Magenis	17p11.2
Miller-Dieker	17p13.3
Alagille	20p12
DiGeorge/Velocardiofacial	22q11.2

8. Direct-to-consumer (DTC) genetic testing

The term "direct-to-consumer" genetic testing has been used variously to refer to both the advertising and sale of genetic tests. The best known and most controversial example is Myriad's advertising campaign in the United States for its BRACAnalysis test, which predicts predisposition to hereditary breast and ovarian cancers. DTC genetic tests may be made available in one of two ways. In the first, the availability of the test is advertised to the public, but the test must be prescribed by a healthcare provider, who also receives the test results. Alternatively, genetic tests may be advertised and directly marketed to the consumer, who can initiate the purchase of genetic tests/services and receive the results without involvement of a health care provider. The most common access to direct-marketed tests is via the Internet. Numerous commercial laboratories offer tests for trait and disease susceptibility of unproven clinical and analytical validity. In Korea, the government has implemented legislation to prohibit DTC genetic tests by law. However, there should be a serious government policy discussion of the clinical validity of DTC genetic tests as well as their potential for benefit or harm. Equally important are considerations of who has the right to make the decision to purchase DTC genetic tests, who regulates or supervises these tests, and how they are administered. In fact, the DTC genetic testing market is rapidly expanding and is becoming a business model of the

future. Many DTC genetic testing companies are flourishing, offering susceptibility testing for common diseases and ancestry testing (23 and Me); for cancers, diabetes and heart disease (deCODE); for risk analysis for more than 20 common diseases, including prostate cancer and diabetes (Navigenics); and for diverse pharmacogenetic testing (Genelex). The American College of Medical Genetics issued the following statement on DTC genetic testing: "A knowledgeable professional should be involved in the process of ordering and interpreting a genetic test. The consumer should be fully informed regarding what the test can and cannot say about his or her health. The scientific evidence on which a test is based should be clearly stated. The clinical testing laboratory must be accredited by applicable accrediting agencies. Privacy concerns must be addressed"[21-23].

Ethical, legal, and social implications of genetic testing

Genetic testing raises complex ethical, legal, and social issues. The health care providers involved with genetic testing must take extreme care to respect the human rights of tested individuals and their relatives. Maximal efforts should be made to protect the genetic privacy of those tested against possible discrimination in job opportunities, education, or insurance based on genetic information. Informed consent should be obtained via pretest genetic counseling that covers the following elements: purpose, methods, implications, diagnostic limitations (accuracy), alternatives to genetic testing, cost of the test, accurate information on any harm or medical risks associated with the test, and the necessity of post-test counseling to explain the clinical significance of the results. A decision on whether to undergo genetic testing should be made freely and autonomously by the examinee. The physicians must explain the individual's right not to be tested, to withdraw at any time, and to refuse disclosure of data after testing. The examinee should be fully informed that test results might not be used to improve treatment modalities. In pediatric cases, where the patient is incapable of autonomous decision-making, the consent of a surrogate representative must be sought. Pediatric genetic testing for adult-onset genetic diseases where no effective preventive or therapeutic options exist should be avoided. The right of examinees to know or not to know the results should be equally respected. Genetic counseling must be non-directive, and designed to maximize patients' benefits and minimize harm. Genetic testing for the characterization of traits should not be recommended for reasons of uncertain scientific validity as well as ethical concerns. Discretion should be applied in recommending SNP-based DNA testing for predisposition to common diseases[21, 24-28].

Conclusion

Genetic testing has rapidly progressed during recent decades and has already become incorporated into daily routine clinical practice. Pediatricians increasingly face issues involving genetic testing. Therefore, it is very important that physicians have a basic understanding of the range of possible tests, indications for their utility, and pitfalls in their interpretation. In the near future, the application of genetic testing to common disorders is expected to expand, and such tests will likely be extended to include individual pharmacogenetic assessments. Awareness of the pros and cons of genetic testing by the public and health care professionals should be enhanced by continuing education.

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