The Genomics of Hearing Loss: A New Era for Clinical Practice

La génomique de la surdité : une nouvelle ère de la pratique clinique

KEY WORDS
GENETICS
INHERITED
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Abstract

Many aspects of audiological practice, from the choice of assessment protocols to the selection of intervention options for our hearing impaired patients, are guided by our understanding of the underlying auditory pathology.Biomedical science is undergoing a significant transformation that experts predict will continue at an exponential pace, altering the course of clinical practice for all health care professionals, including audiologists. As a consequence of the progress in genetics and genomics research, a revolution in our understanding of normal auditory function and disease has emerged during the last two decades. Genetic tests provide a window into the temporal bone, and have revolutionized our understanding of human cochlear structure, function and pathobiology. In this paper, we present a brief introduction to basic genetic concepts, and an overview of the recent advances in genetics and genomics relevant to hearing health care.

Abrégé

De nombreux aspects de la pratique de l'audiologie, à partir du choix des protocoles d'évaluation jusqu'à celui des options d'intervention pour nos patients malentendants, sont guidés par la compréhension que nous avons de la pathologie auditive sous-jacente. La science biomédicale est en voie de subir une transformation importante qui, selon les experts, va se poursuivre à une cadence exponentielle et va modifier le cours de la pratique clinique pour tous les professionnels de la santé, y compris les audiologistes. Grâce à la recherche génétique et génomique connaissant une croissance exponentielle, une révolution dans notre compréhension de la fonction auditive normale et de la maladie a émergé pendant les deux dernières décennies. Des tests génétiques ont été axés, entre autres, sur l'os temporal et ils ont révolutionné notre compréhension de la structure cochléaire humaine, de sa fonction et de sa pathobiologie. Dans cet article, nous présentons des concepts génétiques de base et un aperçu des récents progrès en génétique et en génomique qui ont rapport aux soins de santé relatifs à l'audition.

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Introduction

Many aspects of audiological practice, from the choice of assessment protocols to the selection of intervention options for our hearing impaired patients, are guided by our understanding of the underlying auditory pathology. We often counsel patients about the nature of hearing loss while explaining strategies for hearing loss prevention, or how treatment options vary depending on the type and location of auditory system damage. Yet, the details of an individual patient's specific etiology are often unresolved, and our elucidation of the underlying pathology is limited to a general categorization by location; sensorineural hearing loss, for example, is a deficit affecting the cochlea and/or auditory nerve. Imagine knowing the precise nature of your patient's lesion, involving a defective gene that causes a cochlear conductive sensorineural hearing loss because the tectorial membrane biomechanics are abnormal (Plantinga, Cremers, Huygen, Kunst & Bosman, 2007).Or, that you are counselling a young patient with a family history of early presbycusis, whose genomic testing reveals a neural receptor gene that confers vulnerability to age-related hearing loss (Friedman et al., 2009). Breakthroughs in genetics and genomics have revolutionized our understanding of human biology and disease; this is particularly true for the cochlea and the pathogenesis of hearing impairment. By studying how individual genes explain a particular phenotype or set of physical traits, scientists have come to realize that for some patients, their disease is due to a defect in a single gene. This is often the case for patients with inherited, early-onset hearing loss. A mutation in a single gene is responsible for their particular hearing loss phenotype. However, even when a single defect in one influential gene can cause disease, this genetic change must be considered in the context of genomics - in other words, an individual's entire genetic makeup, and also their environment. By studying genetics in this context of genomics, scientists and clinicians can tackle not only how interactions between multiple genes and the environment can influence the auditory deficit caused by a single gene of large effect (for example, why two siblings with the same genetic defect have different degrees of congenital loss), but also the etiology of complex, multifactorial impairments such as noise-induced hearing loss and presbycusis. In this review we provide an overview of the progress in genetics and genomics with implications for hearing health care, and introduce some basic concepts for understanding the genetics and genomics of hearing loss.

The New Molecular Era – A Vision for Personalized Health Care

Biomedical science is undergoing a significant transformation that experts predict will continue at an exponential pace, altering the course of clinical practice for all health care professionals, including audiologists. Because of the Human Genome Project (2011), and more recently the HapMap and 1000 Genomes Projects (The 1000 Genes Project Consortium, 2010; The International HapMap 3 Consortium, 2010), it is now recognized that genes contribute in some way to most diseases, a revelation that opens up new avenues for prevention and treatment. A new vision from representatives of the U.S. National Human Genome Research Institute illuminates the evolving science of genomic medicine, including the challenges and implications for human health, as researchers "navigate a course from the base pairs of the human genome sequence to the bedside of patients" (Green, Guyer, & National Human Genome Research Institute, 2011; p. 212). In the future, health care will become personal at a fundamental level, with disease prevention and management tailored to each patient's unique and entire genetic makeup.

However, early predictions for a rapid transition into the molecular era of personalized medicine have yet to be realized. To date, the impact of genetic and genomic science on the everyday clinical practice of most health care professionals has been negligible. Despite this, health, research and educational policy makers are preparing for the "genomics" era (CIHR, 2010; Green et al., 2011; NCHPEG, 2011;OBA, 2011).With public awareness and access to genetic information and services expanding, medical and allied health care providers in Canada (Carrol et al., 2009) and worldwide (Burke et al., 2002; EuroGentest, 2011; GenEd Project, 2011; Greendale & Pyeritz, 2001; HUGO, 2011; Metcalfe, Hurworth, Newstead, Robins, 2002; WHO, 2011) are being encouraged to acquire competencies in genetics and genomics. This is particularly relevant for those providing services to the deaf and hard-of-hearing, a patient population for whom gene discovery and the translation of related biomedical innovations into the clinical realm are outpacing those in most other clinical specialties (Shearer et al., 2010; Van Camp & Smith; 2011).

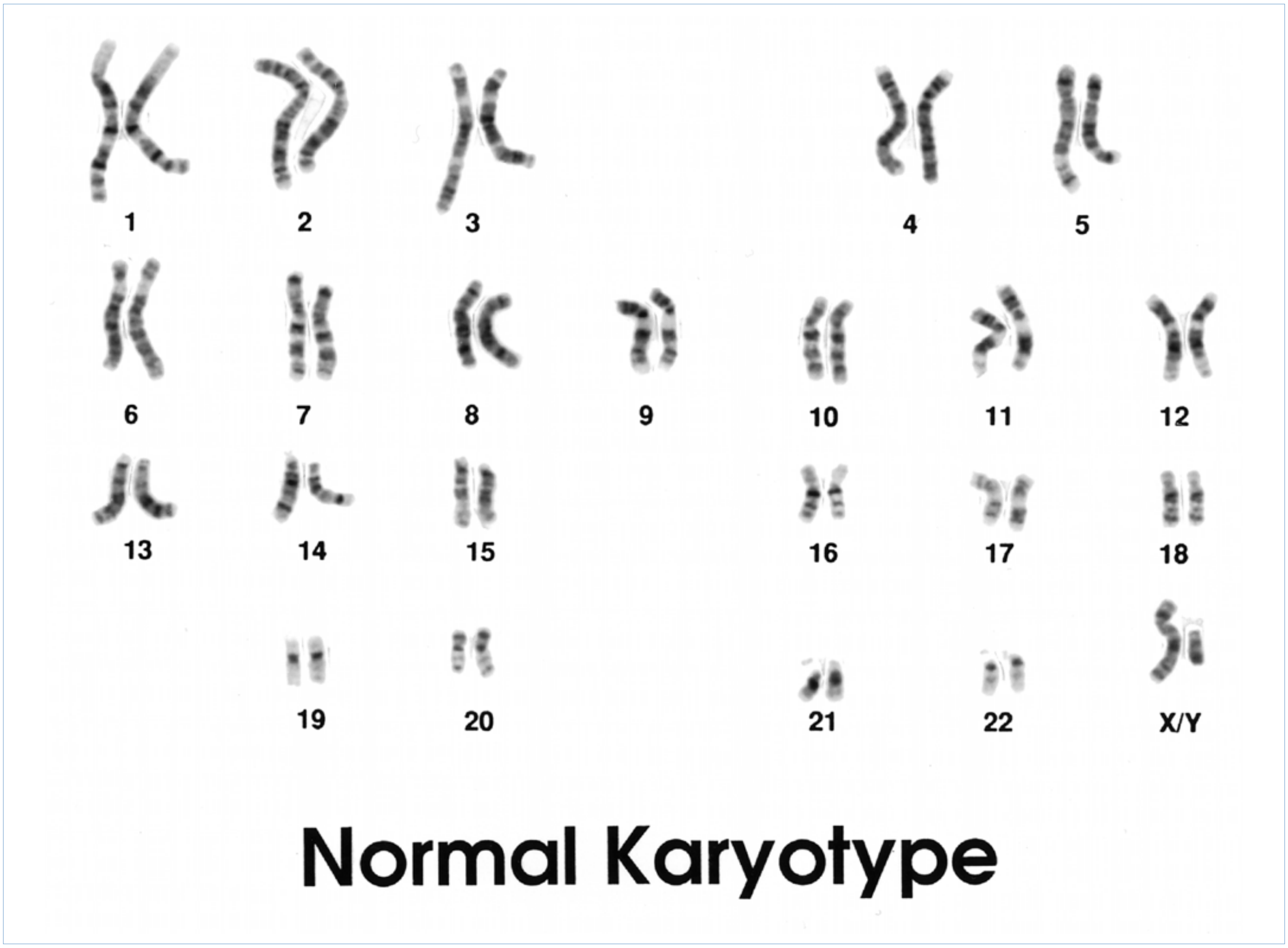
How Genetic Studies Have Evolved in the New "Molecular Era": Implications for Hearing Health Care.

A few decades ago, clinical genetics was a medical specialty dealing with diseases caused by chromosomal or a few rare single gene defects, and genetic testing involved detecting changes in chromosome structure or number, for example Trisomy 21 causing Down Syndrome (see Figure 1). The genes responsible for most diseases were unknown, including those causing hearing loss, and clinical tests for single gene mutations were generally lacking (Korf, 2000). The evaluation of a hearing impaired child involved determining whether the hearing impairment was isolated, or accompanied by other features; in other words, a nonsyndromic or syndromic form of hearing loss. Epidemiological studies indicate that 70-85% of inherited

Figure 1. Human Chromosomes

A. Human karyotype

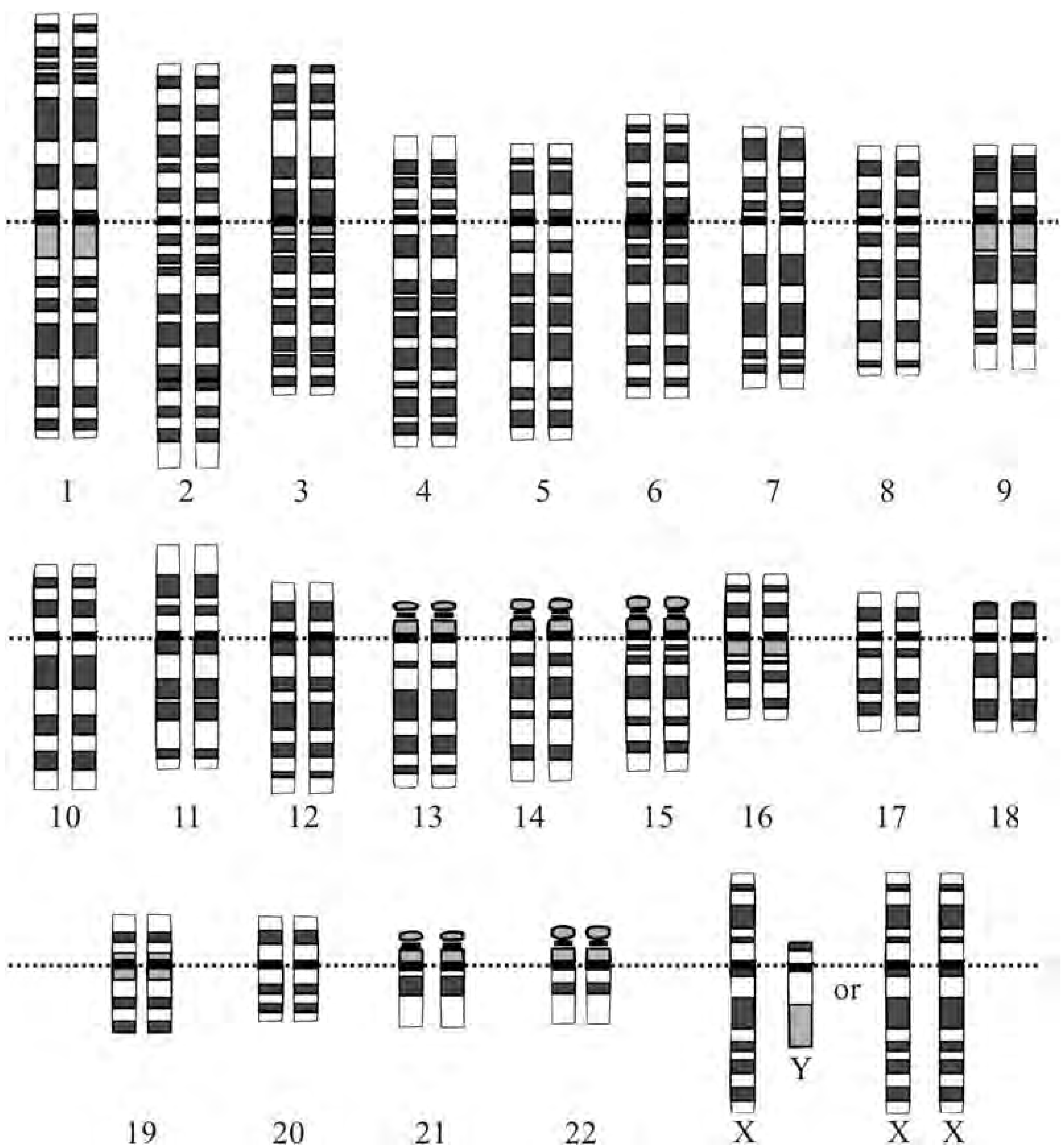
Microsopic images of human chromosomes are arranged in pairs and numbered according to size. Almost all human cells (except gametes and red blood cells) contain 46 chromosomes: 2 sex chromosomes, XX or XY depending on gender, and 22 pairs of matched, non-sex autosomes. For clinical purposes, a karyotype provides information about an individual's chromosome number and structure, their sex chromosomes, and any abnormalities. The karyotype shown is for a normal male: 46, XY.



Source: http://visualsonline.cancer.gov/details.cfm?imageid=2721

B. Ideogram: Normal

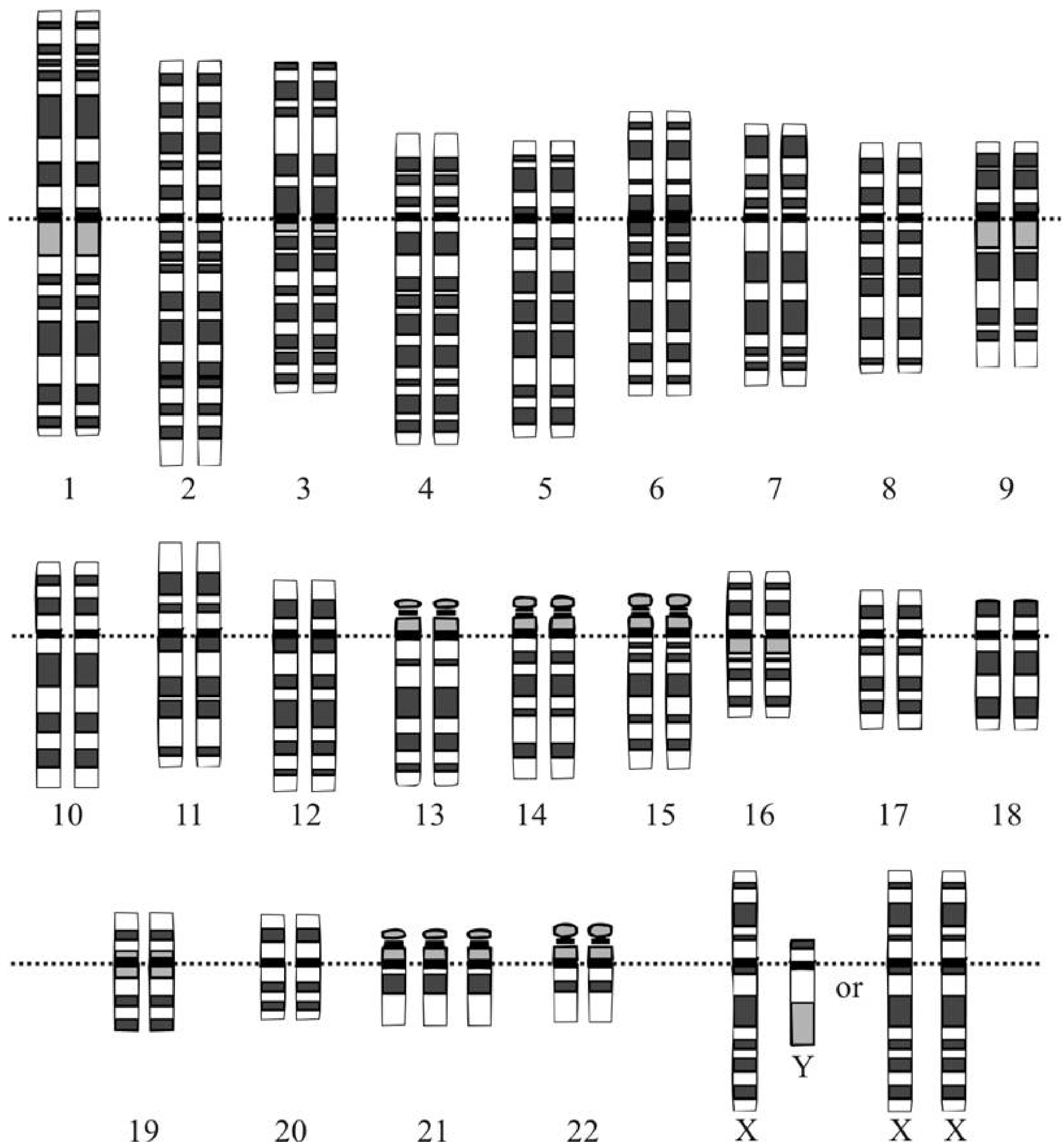
An ideogram is a diagram of the human chromosomes. Ideograms are arranged like the karyotype, with the chromosomes organized according to chromosomal number and relative size. The banding pattern is also shown for each chromosomes. These dark and light bands occur when chromosomes are prepared for microscopy, and are used to describe the location or "locus" of genes on each chromosome. This ideogram describes a normal female: 46, XX.



Source: National Human Genome Research Institute. http://en.wikipedia.org/wiki/File:Down_Syndrome_Karyotype.png#file

C. Ideogram: Trisomy 21

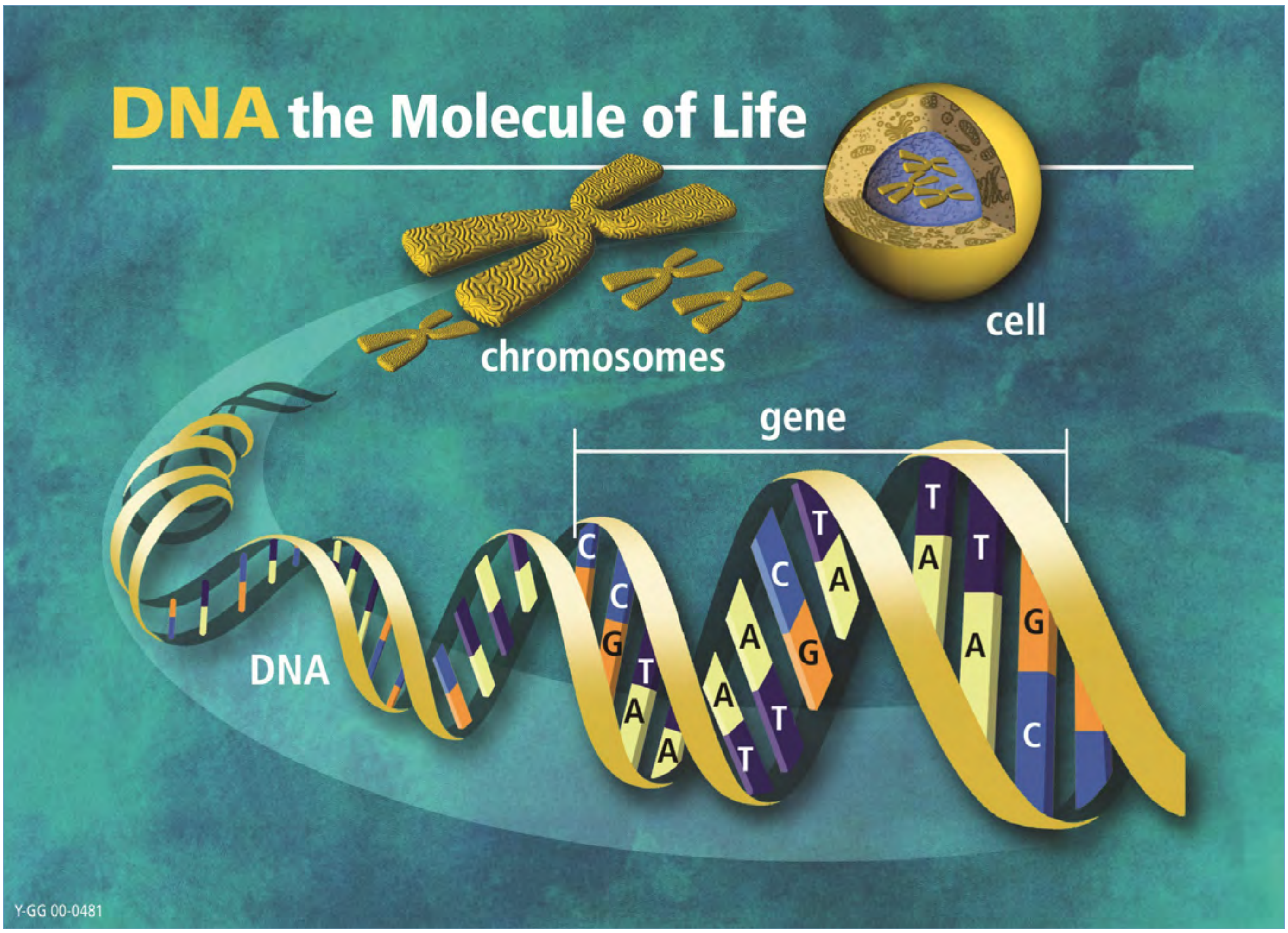
Major abnormalities include changes in the chromosomal number or in the gross structure of chromosomes. Extra or missing chromosomes, as well as breaks or rejoined chromosomes can be detected by microscopic examination and karyotype evaluation. Down syndrome is a chromosomal disorder and is often caused by an error in cell division that results in three copies of chromosome 21, also known as "trisomy 21". The human ideogram shown here represents trisomy 21 in a male: 47, XY, +21.



Source: National Human Genome Research Institute. http://en.wikipedia.org/wiki/File:Down_Syndrome_Karyotype.png#file hearing loss is nonsyndromic (Reardon, Toriello, Downs, 2004). For a child with nonsyndromic hearing loss and a potential genetic etiology, the clinician would estimate recurrence risk - or the likelihood that future offspring in the family would be hearing impaired - based on the family history. Determining etiology was challenging for many nonsyndromic, hearing impaired infants because the parents were often normal hearing with no other significant family history, and prior to universal newborn hearing screening, the identification of hearing loss was usually delayed, with the age of onset based on parent report.

The Human Genome Project, jointly led by the U.S. National Institutes of Health and the Department of Energy between 1990 and 2003 (Human Genome Project Information, 2011) accelerated deafness gene discovery exponentially and launched a new era in the genetic evaluation of hearing loss. The massive work undertaken to sequence the entire human genome immediately prompted the discovery of many disease-related genes, particularly monogenic diseases like hearing loss that are caused by a defect in only one gene (Green, Guyer, & National Human Genome Research Institute, 2011; Jimenez-Sanchez, Childs & Valle, 2001; OMIM, 2011; VanCamp & Smith, 2011). (See Figure 2).

Figure 2. Human Chromosomes: composed of DNA organized into Genes
Human DNA is combined with other molecules and arranged into 46 chromosomes. The DNA strand on each chromosome contains many genes. Each DNA strand is a large molecule containing repeating nucleotide bases: **A**denine, **T**hymine, **C**ytosine, **G**uanine (the four letters of the DNA code A, T, C, G). Each gene has a specific sequence of bases (A,T,C,G) that provide the cell with instructions on how to construct a protein.



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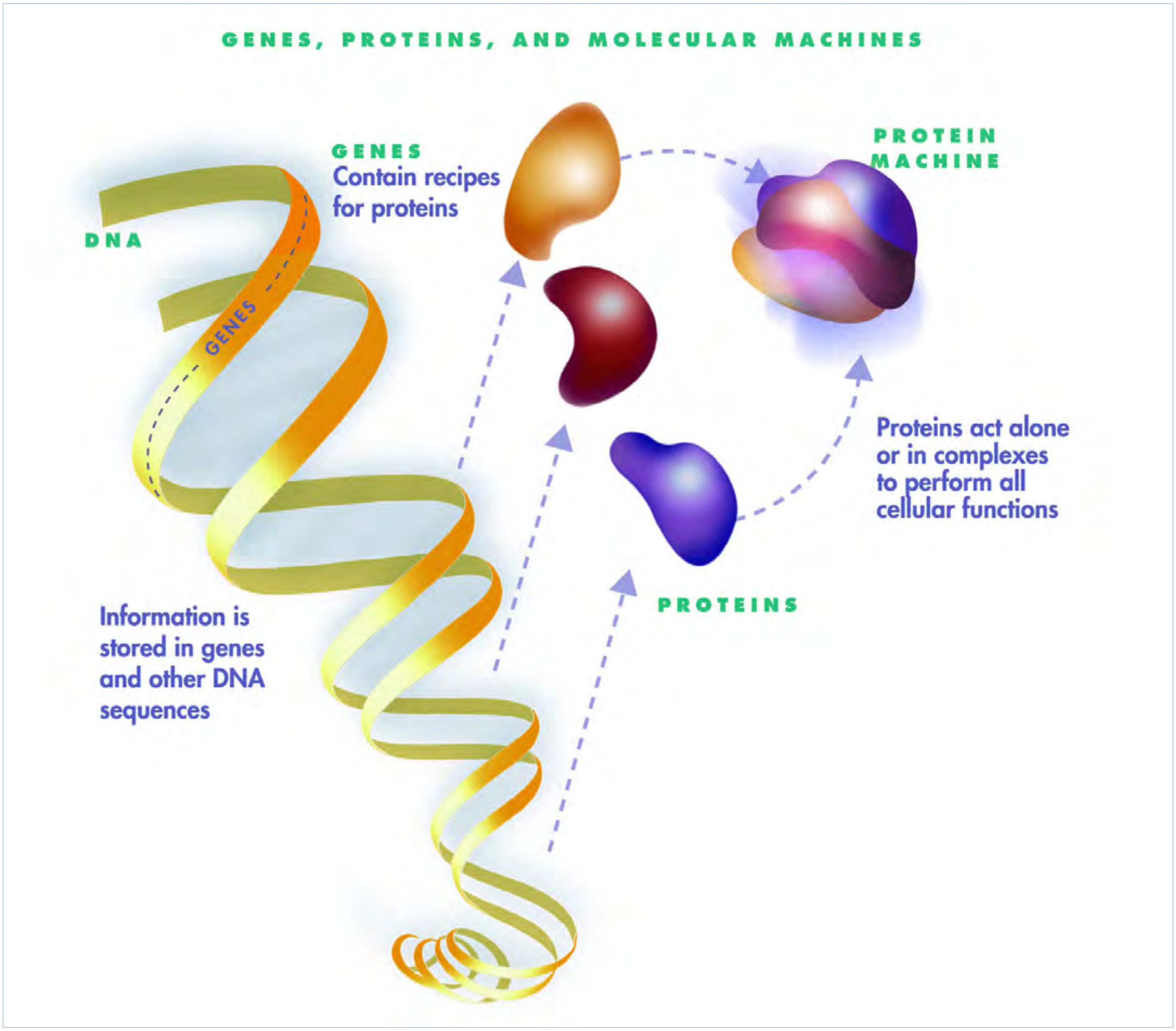
Office of Biological and Environmental Research of the U.S. Department of Energy Office of Science. http://science.energy.gov/ber/
Prepared by: The Biological and Environmental Research Information System, Oak Ridge National Laboratory. http://genomicscience.energy.gov/ and http://genomics.energy.gov/

Following the sequencing of the human genome, genetic linkage analysis was a key strategy for deciphering which of the 22-25,000 human genes was responsible for hearing loss, a technique still used for deafness gene discovery today. Genetic linkage analysis is accomplished by mapping genetic variance in large families affected by the disease of interest. First, the chromosome which houses the responsible gene is identified by comparing DNA between normal hearing and deaf family members, and the location of the suspect gene is narrowed down to a specific region, or 'locus" on this chromosome. Candidate genes residing within this chromosomal "address" are then explored (see Figures 3 to 6) by searching for DNA nucleotide changes – differences in the DNA nucleotide "letter" code - within the locus. A DNA coding change must then be evaluated to determine if it is actually linked to the presence of disease in the affected family members. Consider the example of a large family with inherited hearing impairment: once

Figure 3. Genes, Proteins and Molecular Machinery

Humans, like other living organisms are composed largely of proteins. Proteins provide the structural elements of cells and tissues, and enzymes for essential cell functions. Proteins are large, complex molecules made up of amino acid subunits organized into a chain. A gene contains the instructions for organizing amino acids into a sequence to form a protein.



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Office of Biological and Environmental Research of the U.S. Department of Energy Office of Science. http://science.energy.gov/ber
Genomes to Life Program Roadmap, April 2001, DOE/SC-0036, U.S. Department of Energy Office of Science. http://genomicscience.energy.gov/
Prepared by: The Biological and Environmental Research Information System, Oak Ridge National Laboratory. http://genomicscience.energy.gov/ and http://genomics.energy.gov

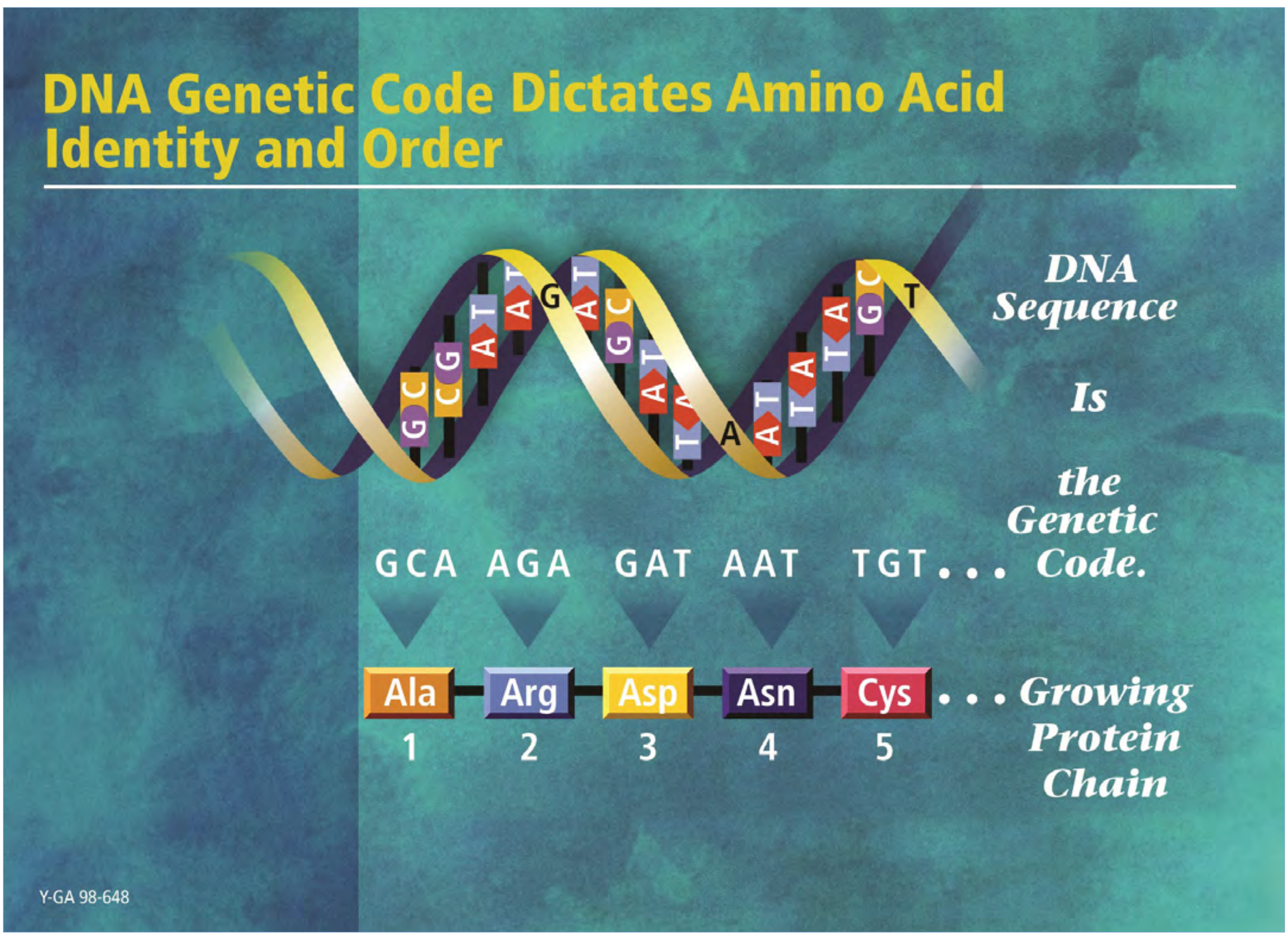
a potential deafness gene locus is identified, the specific DNA sequence of family members with hearing loss is compared to those with normal hearing (Young et al., 2001). Changes in a gene's DNA sequence that are only present in affected individuals may alter the genetic code in a way that changes the protein produced by the gene (see Figures 4 and 5). If this is the case, and the altered protein product is detrimental to human biology, disease may ensue.

This exclusively genetic approach, focusing on individual genes and disease caused by their mutations, was painstakingly slow and insufficient to identify the cause of multifactorial traits, or to account for the interaction of genes. Genomics, the study of an organism's entire set of genes in the context of their environment, opens a new frontier in human biology that will facilitate the exploration of how genes interact with each other and with other factors such as environmental exposure. Now, in addition to the discovery of disease-causing single gene defects, many new techniques such as genome-wide linkage and association studies are used to examine the entire genome in a family or population of interest (Chial, 2008). With this revolution in molecular genetics, the number of diseases suitable for genetic testing continues to grow.

Deafness Gene Discovery and Hearing Health Care – Where Are We Now?

The convergence of universal newborn hearing screening with extensive research following hearing impaired families,

Figure 4. DNA and the Genetic Code
The sequence of nucleotide bases (A,T,C,G) provides the code which a cell uses to produce a protein. Proteins are composed of subunits, called amino acids, which are arranged in a sequence like beads on a string. Within every gene, each specific sequence of three DNA bases (codons) directs the cell to add specific amino acids and manufacture the gene-specific protein product. The DNA base sequence specifies the number and order of amino acid subunits that form the final protein.



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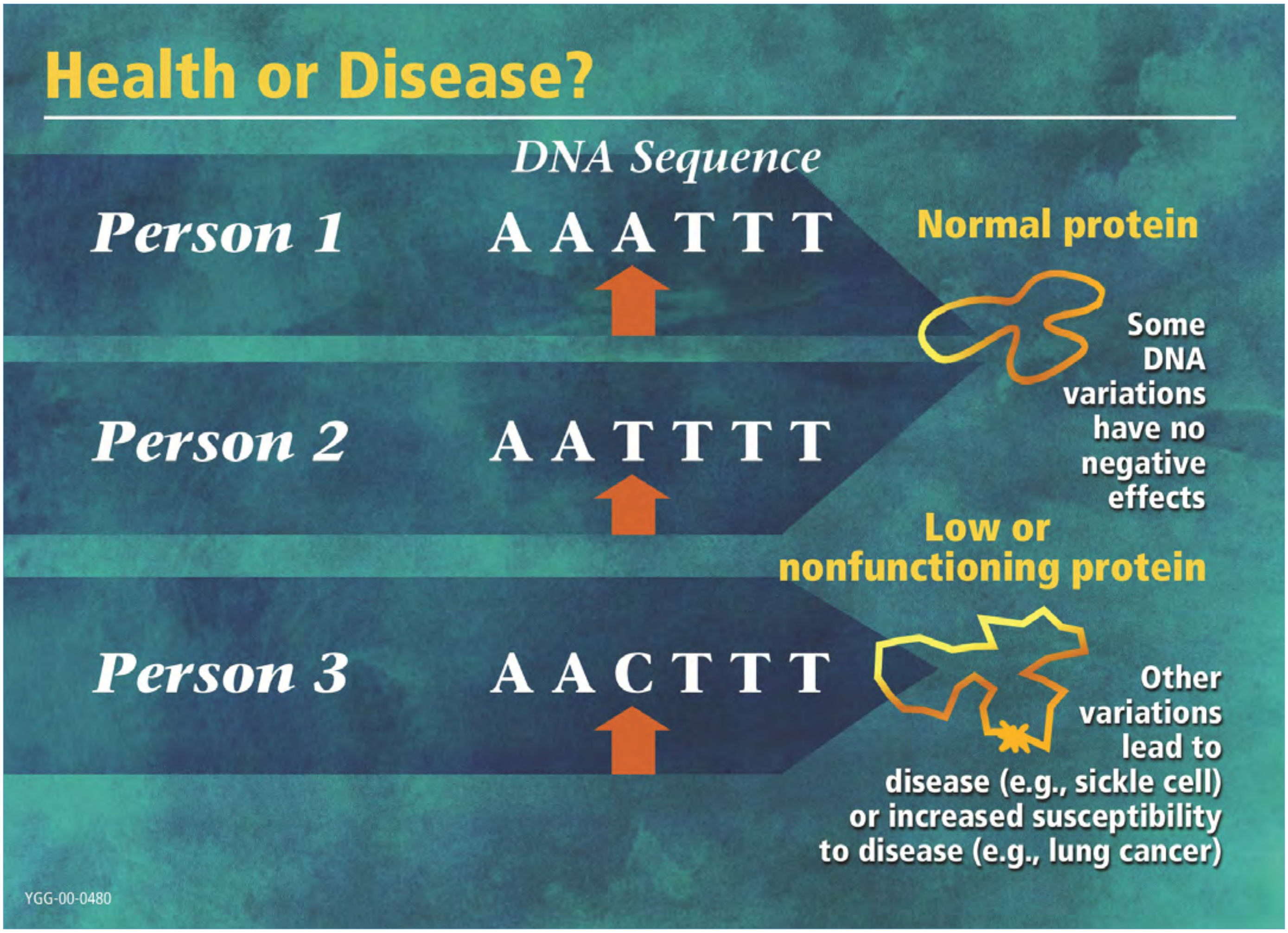
Office of Biological and Environmental Research of the U.S. Department of Energy Office of Science. http://science.energy.gov/ber/
Prepared by the Biological and Environmental Research Information System, Oak Ridge National Laboratory. http://genomicscience.energy.gov/ and http://genomics.energy.gov/

Figure 5. Variations in DNA Sequence Cause Normal Variation and Disease
An individual's genome is their complete set of DNA. Most variations in DNA are subtle and require a close analysis of the DNA molecule to find changes in the nucleotide bases and their related codons – the "letters" and "3-letter words". Many of these subtle changes are considered normal variation and have little or no effect on the protein that is produced. Others cause different proteins that account for the normal variation in our physical traits or phenotype (e.g. hair colour). However, some variations in the genetic code cause changes in a protein which then causes a specific disease or leads to an increased susceptibility to a disease. Hereditary hearing loss often results from a subtle change in the genetic code of just one gene. There are many different types of hereditary hearing loss, each with its own specific gene defect, making this a heterogeneous group of monogenic disorders.



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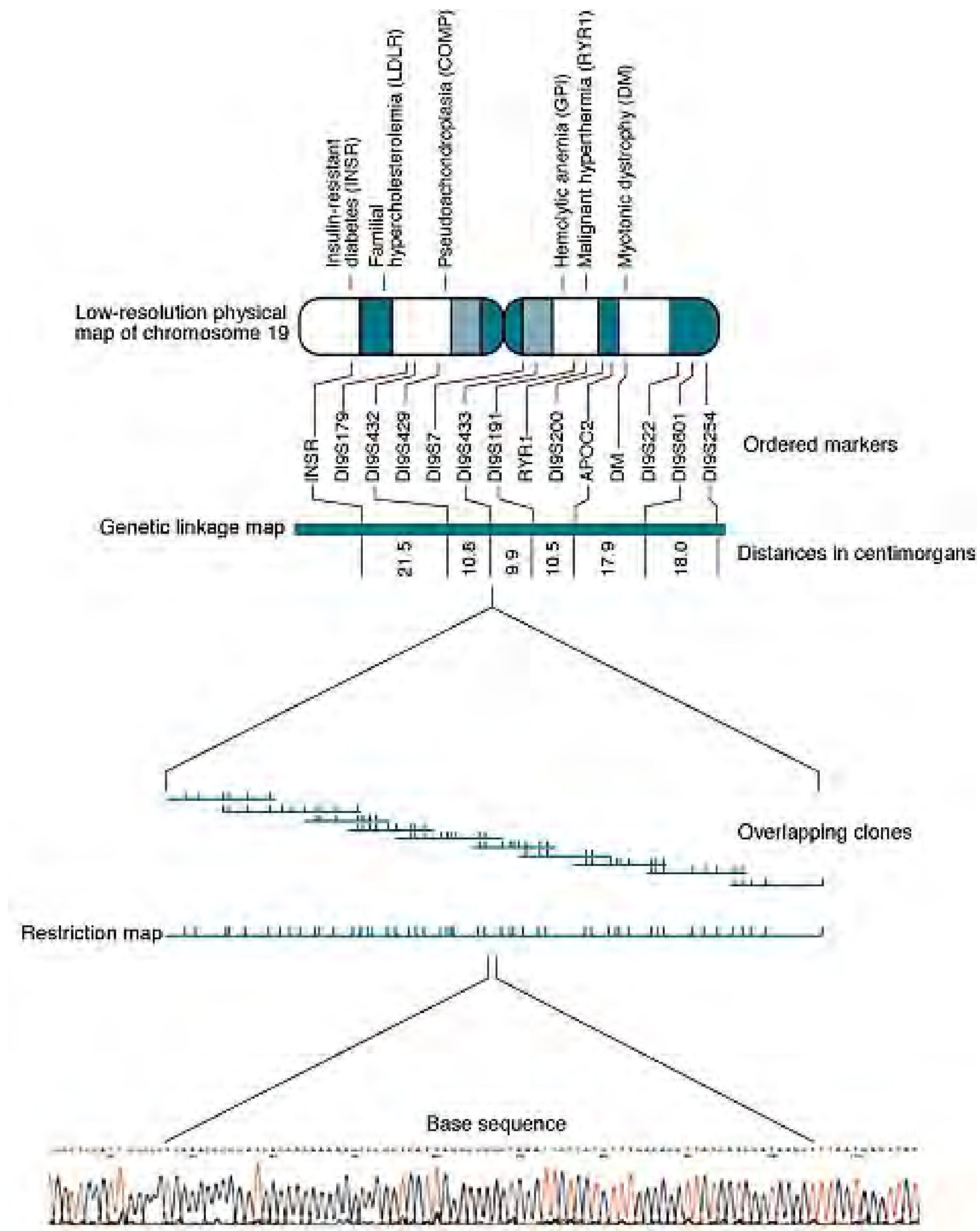
Office of Biological and Environmental Research of the U.S. Department of Energy Office of Science. http://science.energy.gov/ber/
Prepared by: The Biological and Environmental Research Information System, Oak Ridge National Laboratory. http://genomicscience.energy.gov/ and http://genomics.energy.gov/

Figure 6. Gene Discovery and Gene Mapping

Genetic mapping is a method used to identify the chromosome that contains the gene and determine precisely where it lies on that chromosome.Genetic maps have been used successfully to find the single gene responsible for many forms of inherited hearing loss. To produce a genetic map, researchers collect blood or tissue samples from family members where a certain disease or trait is prevalent. Unique patterns of DNA bases, seen only in family members with hearing loss, are used as markers to guide the search. Before researchers can identify the gene responsible for the hearing loss, they must hone in on the approximate location of the suspect gene. DNA markers are used to find the general location of the gene – which chromosome and roughly where the gene is located on the chromosome. If a particular gene is close to a DNA marker, the gene and marker usually stay close together on the chromosome, as the DNA is passed from parent to child. So, if each family member with hearing loss also inherits a particular DNA marker, it is likely that the gene responsible for the hearing loss lies near that marker. In this way the gene is located, and the DNA sequence of the gene is identified.



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Office of Biological and Environmental Research of the U.S. Department of Energy Office of Science. http://science.energy.gov/ber/
Human Genome Program, U.S. Department of Energy, Human Genome Program Report, 1997. http://web.ornl.gov/sci/techresources/Human_Genome/publicat/97pr/index.shtml
Prepared by: The Biological and Environmental Research Information System, Oak Ridge National Laboratory. http://genomicscience.energy.gov/ and http://genomics.energy.gov/

and publication of The Human Genome Project outcomes, has radically changed our understanding of inherited hearing loss. These combined efforts have fueled the golden age of "deafness" gene discovery, and revolutionized hearing science by elucidating the structure and function of the normal and impaired cochlea on a molecular level. Hearing impaired patients and their health care providers are one of the largest groups to directly benefit from these scientific advances in genetics during the past few decades (Hilgert, Smith & Van Camp, 2009a; Korf, 2000; Matsunaga, 2009; Morton & Nance, 2006; Nance, 2003; Petit, 2006).This is because permanent childhood hearing loss is a common sensory disorder, with genetic causes accounting for more than half of the pediatric population, and because only one gene, from a long list of potential causative genes, is largely responsible for an individual's hearing loss. This genetic heterogeneity of hearing loss was discovered via revolutionary genetics and genomics techniques, and now, despite this genetic heterogeneity, clinical tests are available which evaluate 74 "deafness" genes in order to identify the gene responsible for a given patient's hearing impairment (Eppsteiner, Shearer, Hildebrand, Taylor, et al., 2012;Eppsteiner, Shearer, Hildebrand, Deluca et al., 2012). Although such clinical testing is currently expensive, costs are declining rapidly.

In industrialized nations with modern health care, the environmental causes (e.g. infection) of congenital hearing loss are reduced, with genetic causes responsible for more than half (50 - 68%). Prevalence estimates of genetic hearing loss vary with the criteria used to define hearing loss, genetic methods used to define the etiology, the age range considered, and other characteristics of the study population such as country of origin (Cryns & Van Camp, 2004; Kochhar, Hildebrand, Smith, 2007; Morton and Nance, 2006; Reardon et al., 2004; Smith & Taggart, 2004; Van Camp, Willems & Smith, 1997). Furthermore, individuals with a specific form of genetic hearing impairment (autosomal dominant – see below) typically present with delayed onset and/or progression, and are not accounted for in most prevalence estimates derived from prelingually hearing impaired populations. In Canada, the incidence of hearing loss in the newborn population has not been studied, and prevalence estimates of genetic hearing impairment are limited; the only patient population studies evaluating the genetics of nonsyndromic hearing loss have focused on the cochlear implant population (Hochman et al., 2010; Propst, Stockley, Gordon, Harrison, & Papsin, 2006).

Deafness related genes and loci are named according to their Mendelian Inheritance pattern.

Many different deafness genes have been identified, and Mendelian inheritance patterns for nonsyndromic hearing losses have been classified for each gene locus (Van Camp & Smith, 2011). (Note that genetics researchers coined the term "deafness" genes: this convention is observed throughout the paper, but the term refers to all types and degrees of hearing loss associated with genes and gene loci). Although inheritance patterns can be complex, particularly in isolated populations (Young et al., 2001) or in the Deaf community (Blanton et al., 2010), typical patterns of autosomal recessive, autosomal dominant, X-linked, Y-linked and mitochondrial inheritance of hearing loss have been delineated. Autosomal recessive hearing loss is frequently congenital or prelingual, and accounts for the majority (59-77%) of children with nonsyndromic permanent hearing loss. Two copies of the defective gene, one from each parent, must be inherited for hearing loss to be expressed in the individual, meaning that each parent, with only one mutated copy of the culprit gene, is unaffected. A smaller, but significant proportion (22-36%) of children with a genetic hearing loss inherit a single defective gene from one of their parents, who is most often hearing impaired too. In this situation a normal version of the gene, or normal allele, inherited from the other parent, is not sufficient to support normal hearing. This form of hearing loss is therefore considered dominant, and also autosomal, because the aberrant gene is located on one of the non-sex chromosomes. Autosomal dominant hearing losses are often progressive. Postlingual onset is considered typical but it should be noted that documented age of onset and progression of early hearing loss is often based on parental report rather than hearing threshold measurements. Universal newborn hearing screening and early diagnostic programs combined with genetic research will provide invaluable documentation of the natural course of early hearing loss with different genetic etiologies. The remaining <5% of the population affected with permanent hearing loss are accounted for by rare X-chromosome, Y chromosome, and mitochondrial genes with more complex inheritance patterns (Cryns & Van Camp, 2004; Hilgert, Smith & Van Camp, 2009a; Hilgert, Smith & Van Camp, 2009b; Morton & Nance, 2006; Van Camp et al., 1997).

A few deafness genes are relatively common and clinical genetic testing is available in Canada. In the late 1990s, the discovery that mutations in one gene, *GJB2*, are a frequent cause of nonsyndromic recessive hearing loss prompted the development and implementation of cost-efficient clinical testing that was serendipitously feasible because screening for mutations and full sequencing were relatively inexpensive for this small gene with only 2 exons. Diagnostic testing in conjunction with early detection and intervention programs for hearing impairment were proposed by Morton and Nance in 2006, and new predictions suggest that universal newborn genetic screening could be implemented by the next decade (Hochman et al., 2010; Propst, Stockley et al., 2006). Because mutations in GJB2 are fairly common worldwide, affecting between 30-50% of those with nonsyndromic hearing loss, clinical tests are now available in most clinical genetics facilities (GeneTests., 2011). Canadian audiologists may be quite familiar with genetic testing for hearing loss caused by abnormal connexin 26 proteins that form cochlear gap junction channels, but less so with a related type of hearing loss caused by another gap junction protein, connexin 30. The terms “connexin 26 gene” and “connexin 30 gene” are commonly used, even by geneticists, but are imprecise – the correct terminology for these connexin genes are *GJB2* and *GJB6*, respectively. Genetic testing protocols for both genes are available in Canada. Clinical testing is also available at selected facilities for a small subset of additional deafness genes because they are also relatively common (e.g., *SLC26A4* related to Pendred syndrome and Enlarged Vestibular Aqueduct), or involve a syndrome which is difficult to diagnose and/or progressive (e.g., Usher Syndrome) (GeneTests, 2011; Hilgert, Smith,Van Camp, 2009a). Genetic testing can improve clinical efficiency; for example, the early diagnosis of a genetic etiology can streamline the process, with fewer specialty referrals and laboratory tests, and provide early detection and management for patients with late-onset or progressive syndromes (eg. Usher or Pendred). With respect to genetic counseling, genetic testing can improve recurrence risk estimates (Cryns & Van Camp, 2004; Matsunaga, 2009; Morton, 2002; Morton & Nance, 2006). Knowledge of specific auditory deficits and characteristic phenotypes associated with specific mutations can be translated to improved clinical care, including early detection in at-risk relatives, and greater predictability of onset, progression, and efficacy of various treatment strategies. Furthermore, understanding the genetic etiology caninform prognosis, especially for families with GJB2 nonsyndromic recessive hearing loss or mutations in other genes expressed in the sensory structures of the cochlea. Cochlear implantation has proven to be successful for most children, especially those with a “cochlear” genetic etiology, whereas poorer outcomes may relate to a primarily neural dysfunction induced by a defective gene expressed primarily in the spiral ganglion (Eppsteiner, Hildebrand, Taylor et al., 2012; Fukushima et al.,2002; Propst, Papsin, Stockley, Harrison, & Gordon, 2006).

Inherited hearing loss is a heterogeneous disorder and an important public health issue in Canada. Although mutations in *GJB2* are a relatively common cause of genetic hearing loss worldwide, this gene still accounts for only 20-30% of individuals with nonsyndromic hearing loss (equivalent to 30-50% of those with autosomal recessive hearing loss). Collectively, defects in the many other rare “deafness” genes account for the remaining 70-80% of the population with non-syndromic hearing loss, making this an extremely heterogeneous sensory disorder. Over 65 genes for non-syndromic hearing loss with different inheritance patterns have now been identified, and 50 additional non-syndromic “deafness” gene loci have been mapped, with the specific genes yet to be identified. Together the known deafness genes and loci (>130 total for both syndromic and non-syndromic hearing loss) extend across all 22 human autosomes and both the X and Y sex chromosomes. For many of these genes, different mutation-specific types of change in the DNA sequence can occur within the same gene. Like other monogenic diseases, a mutation in any one of these genes is generally rare, with any single “deafness” gene accounting for a small proportion of the hearing impaired population (Hilgert, Smith & Van Camp, 2009a; Shearer et al., 2010; Van Camp & Smith, 2011).

Scientific advances associated with gene discoveries in hearing and deafness research are now recognized as having major public health significance internationally (NIDCD, 2011) and in Canada (CHR, 2011). Gene mapping, linkage studies and gene mutation studies have led to “deafness” gene discoveries in Canada, with relevance to the clinical management of multiethnic and historically isolated populations in the country (Young et al., 2001; Propst, Stockley et al., 2006). Despite this exponential progress in research, changes in hearing health care service delivery have been modest to date because clinical tests for most of these rare genes are not routinely performed or widely available (GeneTests, 2011; Hilgert, Smith,Van Camp, 2009a). Currently, routine clinical genetic protocols and technology require that genes be analyzed individually and sequentially, requiring significant time and cost. The choice of gene(s) to be tested becomes critical, and is usually guided by the clinical phenotype and ethnicity of the individual. Canada is similar to most industrialized nations, in that only a few clinical genetic tests for the most common deafness genes are routinely available through clinical molecular genetic laboratories. Genetics services are still provided almost exclusively by specialists, medical geneticists and genetic counselors, with very limited involvement by primary care or allied health providers. Thus access togenetic testing depends on the availability of specialized clinical services which involve a medical genetic evaluation, interpretation of the genetic test results, and genetic counselling for patients and their families. Rapid advances in deafness gene discovery have caused an explosion of information about the genetic bases of hearing loss, and it is difficult for clinicians, even geneticists and hearing health care specialists, to keep up (Burton et al., 2006; Korf, 2000).

Deafness Gene Discovery – Implications for the Future of Hearing Health Care in Canada

Genetic tests have revolutionized our understanding of human cochlear structure, function and pathobiology.

The cochlea, buried within the temporal bone, has until recently been inaccessible for detailed analysis in living humans. With genetic tests we now have a non-invasive molecular toolbox which opens a window into the temporal bone, allowing us to probe the cells and molecules of the inner ear and auditory system of our patients. Molecular techniques allow us to define the nature and site of an auditory system lesion at the cellular-molecular level in patients with a positive genetic test result. Permanent hearing loss is currently defined by the clinical features, or phenotype - as conductive, mixed or sensorineural, for example. We now realize that hearing loss, particularly inherited sensorineural loss, is not a homogeneous disorder, but rather a collection of different ear pathologies caused by many rare genes. What does this mean for genetic test outcomes for our patients? The majority of individuals with an inherited nonsyndromic loss harbour a rare gene mutation affecting a single gene which is not identified by clinical tests. This is because routine clinical genetic tests evaluate only the most common deafness genes (eg. *GJB2*).Unfortunately, most patients do not have a common genetic defect; a wide array of rare deafness genes must be considered, and the DNA subjected to multiple gene-specific tests, in order to pinpoint each individual patient's specific gene defect. At present, patients with such rare gene mutations are usually identified through clinical research centres specializing in genetics and deafness (Harvard Medical School Centre for Hereditary Deafness, 2011; University of Iowa, 2011).

When the precise genetic etiology has been identified for a patient, knowing the defective gene and the type of mutation can provide a detailed appreciation of their underlying pathology. Genes that are active in the cochlea express a wide variety of protein products that together form unique molecular structures necessary for normal inner ear function; these include structural molecules that support and connect the hair cell stereocilia, many types of channels for transduction and cell-cell communication, motor molecules in hair cells, to name just a few. Consequently, a person harbouring a mutation in one of these critical genes may produce a defective protein molecule, or no protein at all, which in turn disrupts the structure or function of cells and tissues critical for hearing (cochlear cells and/or auditory neurons) (Friedman and Griffith, 2003; Hilgert, Smith & Van Camp, 2009b; Matsunaga, 2009; Morton, 2002; Morton & Nance, 2006; Petit, 2006; Shearer et al., 2010; Van Camp & Smith, 2011).Table 1 provides some examples of known deafness-causing genes expressed in the cochlea, and the associated cochlear functions that are disrupted by the faulty proteins produced as a consequence of these gene mutations. A comprehensive, regularly updated list of deafness genes and loci, categorized by inheritance pattern, and a diagram of where these genes are expressed in the cochlea, can be found at http://hereditaryhearingloss.org. Several excellent reviews are also available to the reader interested in different genetic etiologies and the underlying pathophysiologic mechanisms (Ealy & Smith, 2010; Hilgert et al., 2009b; Manchaiah, Zhao, Danesh, & Duprey, 2011; Richardson, de Movel, Petit, 2011).

Genetic testing technologies are evolving rapidly, allowing for simultaneous testing of multiple deafness genes.

Experts predict that genome-based approaches will improve the early detection, diagnosis and prevention of many diseases. In this future genomics era, clinical care will be guided by each patient's unique molecular biology in addition to their phenotype, and their diseases classified according to the underlying pathobiology. Genomic testing - analyzing an individual's entire genetic makeup - will not make significant inroads into daily health care practice until at least the next decade. However, the ability to test a subset of multiple genes simultaneously rather than consecutively is now available in specialized clinical research centres. New genetic testing protocols, employing rapidly evolving high-throughput technologies, will make simultaneous testing for multiple deafness genes feasible and cost-effective in the relatively near future, and long before genome-wide testing becomes commonplace (University of Iowa Health Care, 2011). Clinical protocols for testing a wide spectrum of deafness genes in the same patient will revolutionize the diagnostic assessment of hearing impairment. Technological advances can foster radical shifts in the diagnostic protocols used in audiology. Consider the detection of retrocochlear lesions, first with the advent of the Auditory Brainstem Response (ABR), and again as magnetic resonance imaging became widely available. Likewise, the application of otoacoustic emission techniques in the clinic was instrumental in the identification of a new category of hearing loss: auditory neuropathy spectrum disorders. In the future, the genetic etiology of hearing loss and site of lesion classification will be greatly refined as testing for all known "deafness" genes becomes cost-effective and more widely accessible. A revised classification system for patients with inherited hearing loss will be feasible with the implementation of these new methodologies. Apatient's site of lesion may be defined as a defect in the transducer or ion channels of the hair cell stereocilia (Schultz et al.,2005) or a pathology causing cochlear conductive hearing loss due to aberrant biomechanical properties of the tectorial membrane (Plantinga et al., 2007). Re-categorization based on the causative genetic etiology and underlying pathophysiology is now within reach, with inherited hearing loss falling into many different subgroups based on

Table 1. Nonsyndromic Hearing Loss Genes: Protein Products and Function

Gene & Locus Names	Protein Product	Chromosome Location	Protein Function: Cochlear Expression
Electrical & Metabolic Coupling in the Cochlea			
GJB2 DFNB1	connexin 26	13q12.11	Along with other connexins, Cx26 proteins form cochlear gap junction channels that connect adjacent cell membranes. Gap junctions allow transportation and recycling of small molecules and ions through nonsensory epithelial and connective tissue cell networks in the cochlea.
Inner & Outer Hair Cell Structure & Function			
WHRN DFNB31	whirlin	9q32	The α-tectorin protein is an important, non-collagenous component of the tectorial membrane, a structure overlying the hair cell stereocilia.
MYO7A DFNB2	myosin 7A	11q13.5	Myosin VIIA is an unconventional myosin involved in different cell functions including stereociliar development and stability, as well as vesicle trafficking and endocytosis in the hair cell body.
Inner Hair Cell-Auditory Afferent Synapse			
OTOF DFNB9	otoferlin	2p23.3	Together with other molecules, the otoferlin protein facilitates the release of neurotransmitter at the synapse connecting the hair cell and auditory neuron.

For detailed information about individual genes, mutations and related hearing disorders see the Hereditary Hearing Loss Homepage http://hereditaryhearingloss.org.

Gene expression in cochlear structures can also be viewed at http://hereditaryhearingloss.org/main.aspx?c=.HHH&n=86597

For excellent reviews of genetic hearing disorders and "deafness genes" see: Hilgert et al., 2009a; Manchaiah et al., 2011; Smith et al., 2010.

the auditory structures and cells where the defective gene is expressed and exerting a detrimental effect (Hilgert, Smith and Van Camp, 2009a; Hilgert, Smith and Van Camp, 2009b; Shearer et al., 2010; University of Iowa Health Care, 2011).

Common, acquired types of hearing loss, associated with aging, noise, or other types of disease, also have a genetic component. Mapping human genetic variation involves evaluating the entire genetic makeup, or genome, of many healthy individuals across different human populations (The 1000 Genes Project Consortium, 2010; The International HapMap 3 Consortium, 2010). Information about more common gene variants is supplementing the growing database of rare gene mutations associated with human disease. Through these efforts investigators have learned that most diseases have a genetic component. Common diseases are more complex than rare monogenic disorders, often involving one or more genes interacting with environmental triggers. Genome Wide Association Studies (GWAS) are now addressing these multifactorial disorders, including complex systemic conditions like diabetes that increase the risk for developing sensorineural hearing impairment (Green et al., 2011; The 1000 Genes Project Consortium, 2010; The International HapMap 3 Consortium, 2010). Many forms of acquired hearing loss are in fact common, multifactorial disorders that involve predisposing genes. Genetic susceptibility to aging and ototoxins like noise is well established, but for humans, the contributing genes are for the most part unknown (Davis et al.,2001; Davis, 2003; Frisina, 2009; Konings, Van Laer Van Camp 2009; Van Eyken, Van Camp, Van Laer, 2007). Gene identification and investigations of complex gene-gene and gene-environmental interactions are progressing at a rapid pace in humans and animal models (Johnson, Zheng, Noben-Trauth, 2006; McHugh, Friedman 2006; Schultz et al., 2005;

Yan & Liu, 2010). Now on the scene are human genome-wide studies, investigating nuclear genes, and also maternally inherited mitochondrial genes, that confer vulnerability to multifactorial auditory system diseases; some are bearing fruit, such as GMR7 associated with presbycusis (Friedman et al.,2009; Raimundo et al., 2012). Complex communication disorders affecting speech, language and acquired hearing are most often multi-factorial, and genomics approaches will be especially useful to their investigation. Advances in our understanding of acquired hearing loss, and the complex interactions between genetic and environmental contributions to pathobiology, are expected with genome-wide linkage and association studies.

How Will Audiological Practice Evolve in the New Molecular Era?

Many clinicians question whether a new assessment procedure, including genetic test protocols, is justified if the clinical outcomes are not altered by the test results. This is a valid concern. The translation of knowledge from the research laboratory into general clinical practice can involve many stages, and input from clinicians is essential in this process. As new deafness genes and mutations are identified, deep phenotyping – detailed profiling of behavioural, physiological, and imaging measures of auditory structure and function – will be critical to our understanding of how gene mutations affect human audition. Much can be gleaned from animal models, particularly mice, with similar gene defects, but ultimately, the pathophysiological repercussions of the molecular lesion caused by a specific gene mutation must be confirmed in humans. This is a crucial step in the translation of knowledge into the clinical realm, and one in which audiologists can play a key role.

A clear understanding of the causative molecular mechanisms will continue to streamline the diagnostic process and improve the early detection of progressive syndromes and nonsyndromic hearing loss as more genes are discovered and added to routine genetic testing protocols. Although not yet cost-efficient, universal screening and/or diagnostic testing of multiple genes and mutations, and incorporation of such protocols into early hearing detection and intervention programs will most likely be realized during the next decade (Linden Phillips et al., 2013; Wu et al., 2011). Furthermore, as genetic contributions to common diseases (e.g., presbycusis, noise-induced hearing loss, diabetes) are delineated, genetics-based care will become increasingly relevant to hearing health care practitioners, including audiologists. However, biomedical breakthroughs are the most dramatic when they lead to innovative new treatments for disease. Understanding the pathogenesis of hearing disorders will foster the development of molecular-level treatments and specialized biomedical devices, with implications for the treatment of both monogenic and more complex, acquired forms of hearing loss. Most audiologists would agree that patients with the same audiogram vary considerably in other respects, including their response to intervention. Armed with new insights into how genes affect different cochlear and auditory system structures and interact with environmental stressors to modify hearing loss, scientists can now investigate these inter-individual differences in clinical presentation. The links between an individual's genetic defect and specific underlying pathobiology and their responses to medication, amplification or cochlear implantation can now be explored. Pharmacogenomics may identify individual risks for ototoxicity, guide the development of preventative and treatment medications and modify the prescription process, with drug selection and dosage based on an individual patient's genotype (Green et al, 2011; Matsunaga, 2009). New gene-based therapies are now available for treating diseases like blindness, and pharmaceutical treatments influenced by genetic variation are under investigation for auditory disorders in animal models (Bainbridge et al., 2008; Davis et al.,2007). Eventually, this translational research will lead to a more tailored intervention process, and stimulate innovative and complementary modes of therapy in humans (e.g. gene delivery combined with neural prostheses) (Di Domenico et al., 2011; Hildebrand et al. 2008; Jan, Pereira, Turner, & Kotov, 2011).

With these advances on the horizon, the disadvantages of genetic and genomic testing and barriers to knowledge translation must be addressed. Before we can harness the power of genomics and translate this knowledge into meaningful clinical interventions that improve quality of life, genotype-phenotype relationships must be explored and the impact of these findings on the individual, their family, and society at large must be explored. We have at present a superficial knowledge of how hearing-related gene mutations influence human physiology, behaviour, and clinical presentation. The ethical issues of identifying unaffected gene mutation carriers, or those with a causative genotype who are asymptomatic at the time of genetic screening or testing must be confronted (Linden Phillips L, et al., 2013; Schimmenti et al., 2004; Wu et al., 2011). For genomic testing, the management of incidental findings – identifying mutations in genes not related to hearing loss – is critical for the patient and their family members. How will vulnerable groups or an individual's rights be protected with respect to the provision of health insurance? Could the identification of a gene mutation for hearing loss limit future vocational opportunities, for instance? With respect to knowledge translation, scientists, clinicians, and governments face an exciting but immense challenge (Zwart & Nelis, 2009). As genomic technologies continue to evolve, genotyping is outpacing the comprehensive phenotyping of newly identified genes and mutations, and the social, legal, and ethical implications of these discoveries.

Summary & Concluding Remarks

In this paper, we present a brief introduction to basic genetic concepts, and an overview of the recent advances in genetics and genomics relevant to hearing health care. Personalized medicine, where each patient receives customized health care based on their unique genetic make-up, is the main goal of translational genomics, but more than a decade away (Green et al., 2011). However, as a consequence of the exponential progress in genetics and genomics research, a revolution in our understanding of normal auditory function and disease has emerged during the last two decades. Multiple deafness gene testing protocols are now available at clinical research sites, and rapidly evolving high-throughput technologies will continue to improve their time- and cost-efficiency (Shearer et al., 2010; University of Iowa Health Care, 2011). Noninvasive clinical tests for detecting mutated genes and their defective gene products – the proteins – will enable a precise molecular level definition of auditory system defects in an ever-increasing proportion of our patients.

Over the next few decades, genetics-based care will evolve beyond the domain of medical geneticists and genetic counsellors. As research advances are translated into the clinic, genetic specialists will eventually be overwhelmed by the demand for services and the breadth of disease-specific knowledge encompassed by the "new genomics". As multidisciplinary models become the standard for genetic service delivery, the translation of genomics breakthroughs into the clinical realm will depend on the acquisition of genetic competencies by the health care community (Bottorff et al., 2005; Burke et al. , 2002; Canadian Nursing Association, 2005; Carrol et al., 2009; Gurwitz, Weisman, Rehavi, 2003; Harvey, Stanton, Garrett, Neils-Strunjas & Warren, 2007; OBA, 2011). Recognized by government, research and professional agencies as a crucial issue, joint efforts have led to the development and implementation of health professional and public educational programs worldwide, including Canada, Europe, and the United States (e.g., EuroGentest, Core competencies for health professionals in Europe, 2011; GenEdProject, 2011; Genetics Education and Training, 2011; Genetics in the Practice of Speech Language Pathology and Audiology, 2011; HUGO, 2011; NCHPEG, 2011; OBA, 2011; WHO, 2011).

Supported by two decades of deafness gene discovery and rapidly evolving technology, hearing researchers and clinicians are poised to evaluate these molecular genetic innovations in the clinic. As the promises of personalized medicine are realized, the diagnosis, treatment and counseling of hearing impaired patients and their families will evolve accordingly. Eventually, genetics-related principles will infuse everyday clinical practice, affecting all health care professionals, including audiologists. Those who understand the genetic basis of hearing impairment will be well prepared to embrace these new developments, able to understand new diagnostic protocols and treatments, make appropriate referrals, and provide (re)habilitation and counseling to patients with concerns about the genetic basis of their hearing loss and implications for other family members.

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