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Audiology of the Future with Next Generation, Whole Human Genome Sequencing

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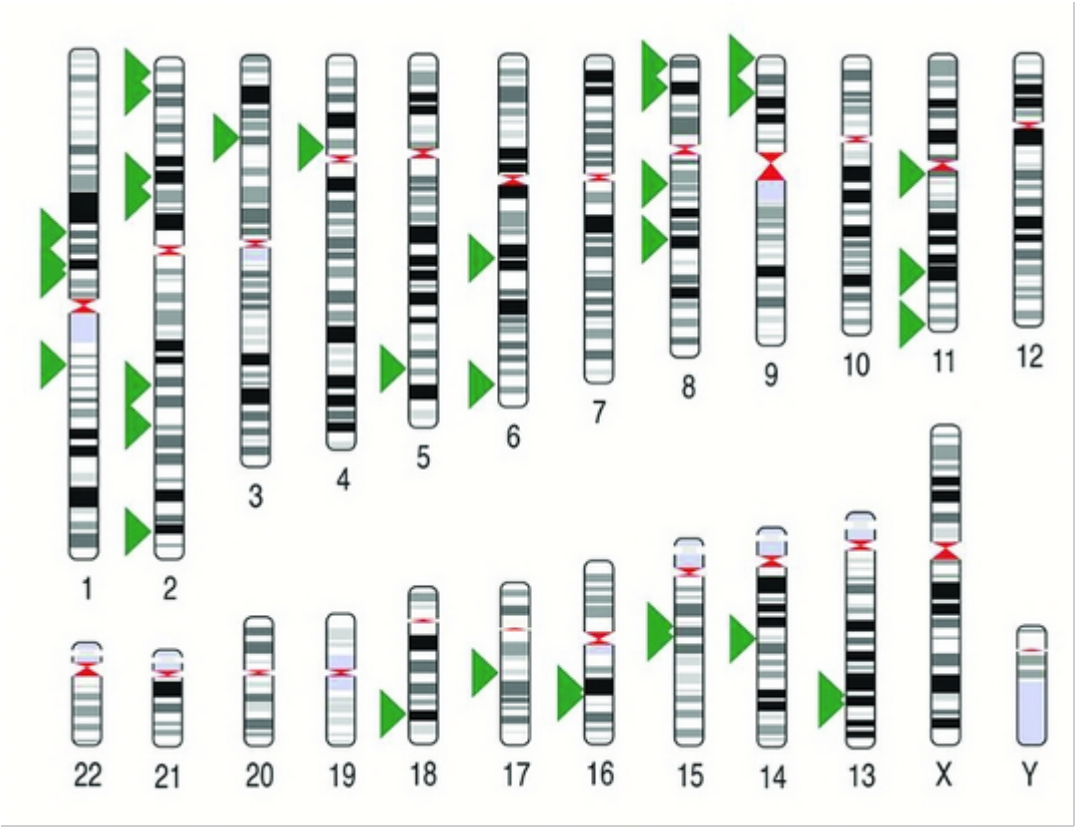
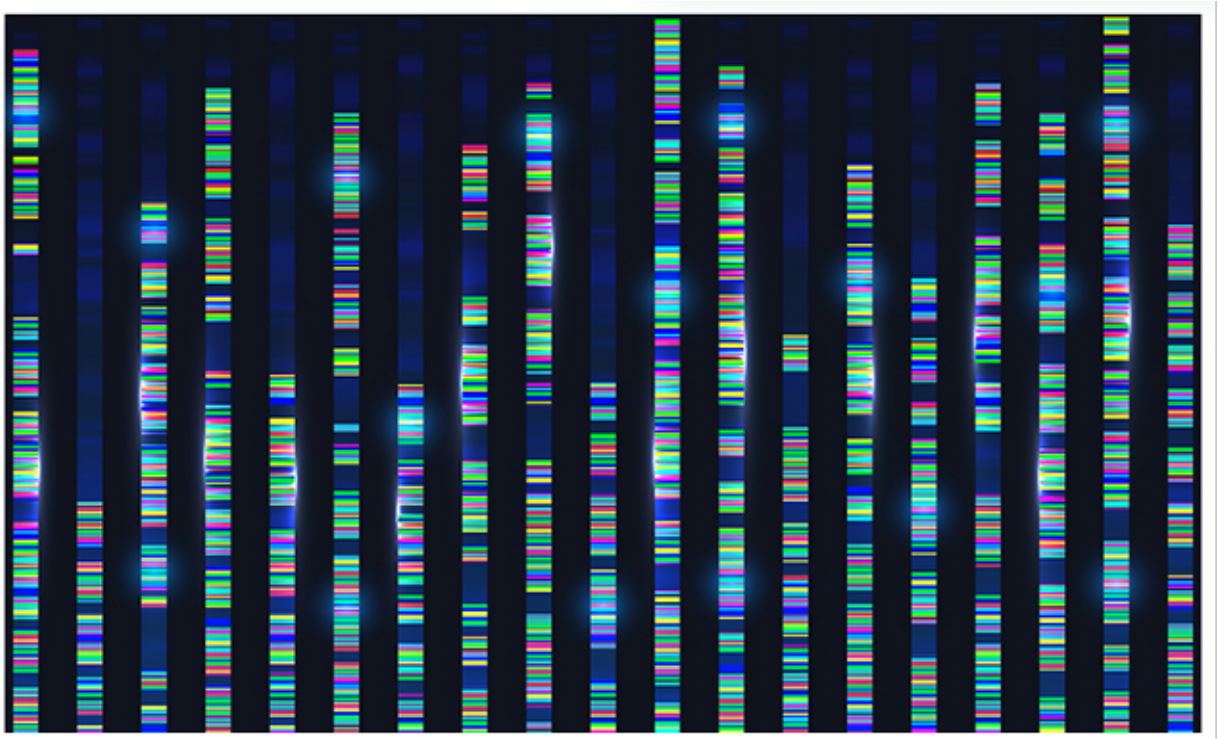
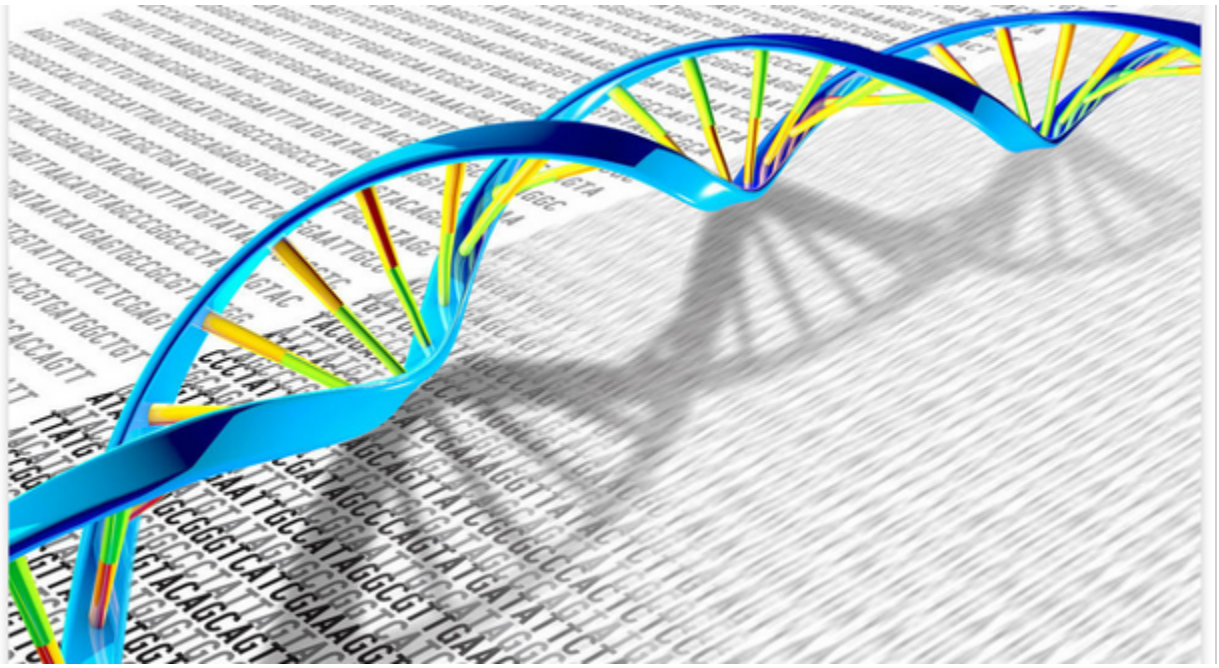
In my next few columns, I will explore new and exciting studies on using whole human genome sequencing as an emerging clinical tool for audiology. Imagine 20–30 years into the future when you might routinely order a whole genome sequence of a client, to provide an accurate diagnosis of a hearing or vestibular problem and guide optimal intervention. This will be the ultimate "personalized medicine" we hear so much about. I am convinced that the scenario above will come to pass. There are already many potential applications of whole genome sequencing in audiological areas such as neonatal screening, diagnosis of genetic causes of hearing loss, and determining risk factors (genetic disposition) for age-related hearing problems. I will discuss the current science around these and other audiological applications in future editions of *Canadian Audiologist*. But first, I want to get you up to speed today with a short overview of this exciting, emerging field.



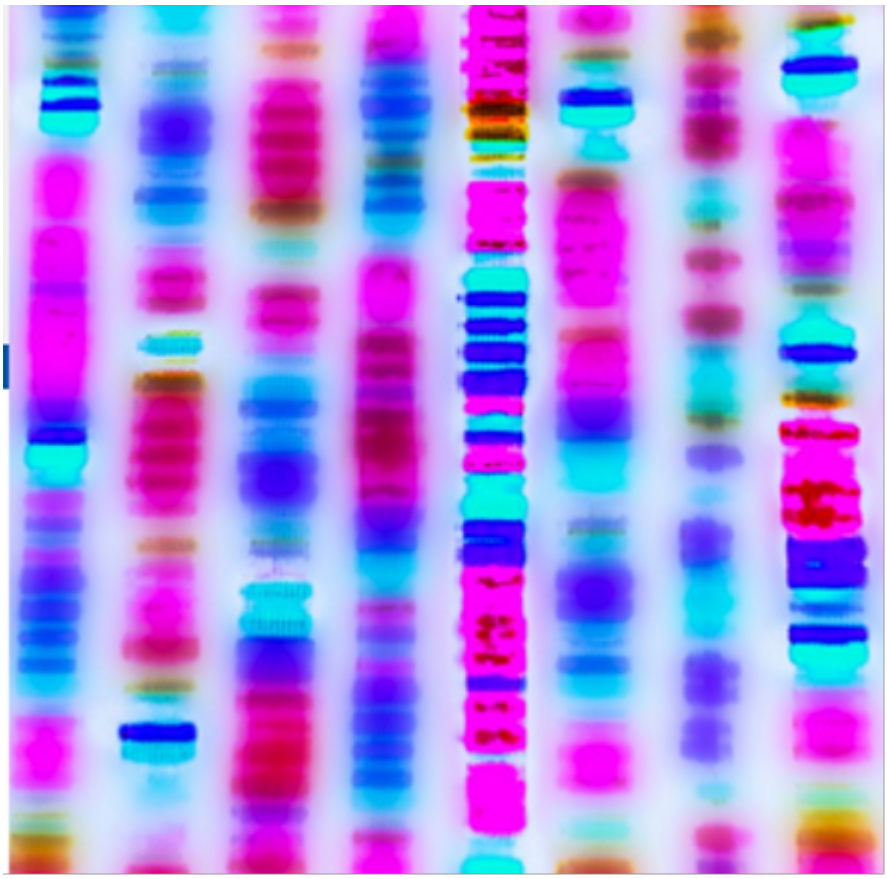




The original methodology for whole genome sequencing was invented by Frederick Sanger in 1975, and originally applied to sequencing bacterial DNA.[1,2] This technique is usually referred to as Sanger sequencing.

The total cost of generating the first human genome sequence[3] was many billions of dollars (yes, billions!). The US funding contribution alone was $3 billion. Within a decade, and with improved technology, the cost of an individual, high-quality genome sequence fell to $14 million by 2006. Ten years later (2016) the cost was down to a few thousand $, but data processing times were lengthy - days to weeks even with highly automated methods. More recently, “new generation sequencing” methods and shortcuts have been developed to reduce time and costs. For example, pieces of DNA (exons) that provide instructions for making proteins make up a small percentage of the whole genome and can be sequenced rapidly. It is thought that most (but not all) mutations that

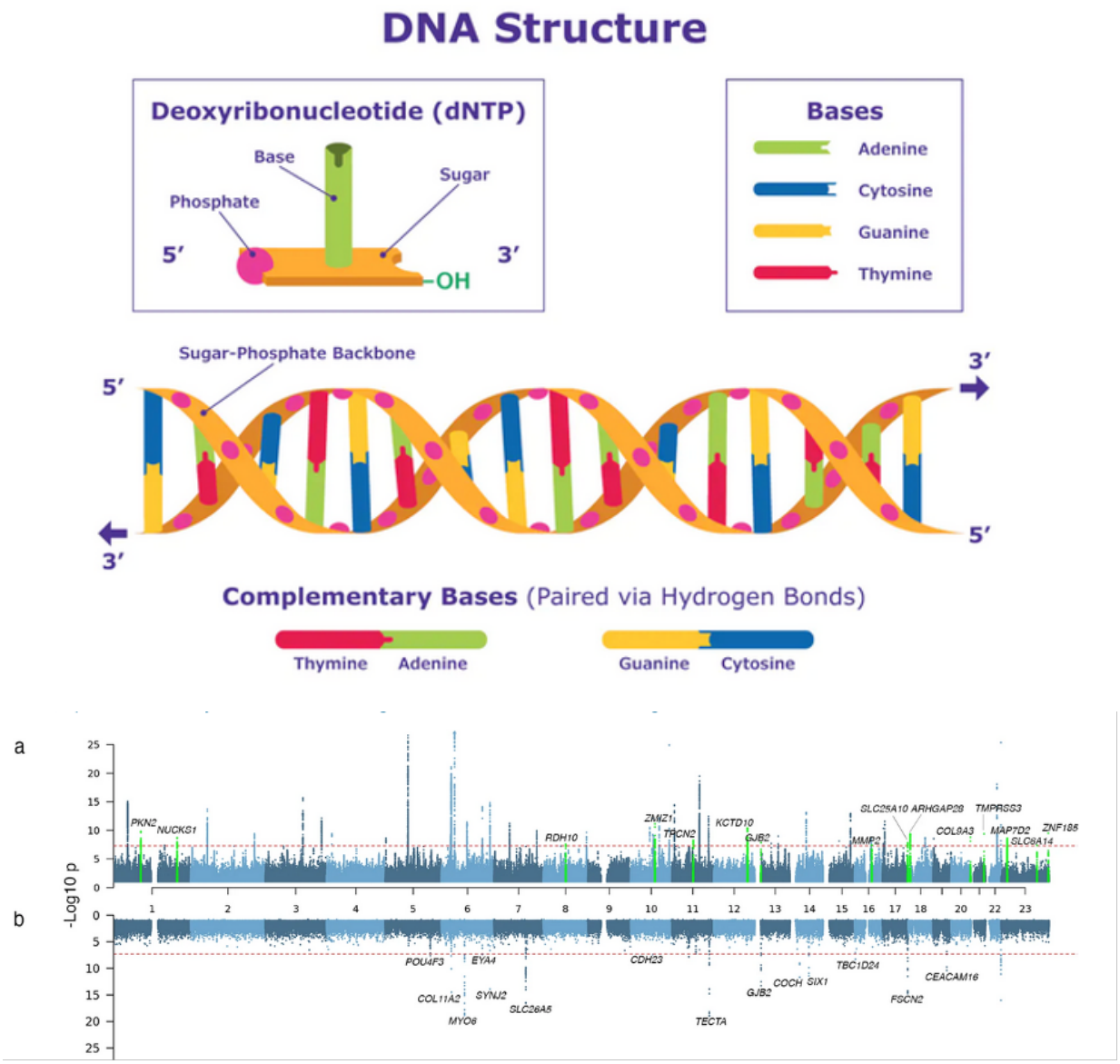
cause disease occur in exons, so whole exome sequencing can efficiently identify mutations that cause disease. Today, such whole exome sequencing costs a few hundred dollars and takes about 5 hours. These costs/times now make whole genome sequencing an affordable research tool and convenient for potential clinical applications.



There is no doubt that the ability to map the human genome has the promise of a new era in healthcare. The earliest clinical applications were in detecting unknown, disease-causing gene mutations. In some cases, identification of the genes (genotype) and their biological function (phenotype) has led to successful treatment to restore normal function. Our accumulation of knowledge about the genes mutations responsible for various diseases has provided us with gene panels that can be used in genetic screening for individual patients. We are all familiar with certain types of congenital, genetically related hearing problems in audiology, and we presently use genetic screening panels to identify ***known*** gene mutations. However, hundreds (if not thousands) of rare and unknown gene mutations (single or multiple) are linked to hearing loss; these can be potentially revealed by whole genome sequencing.

With the potential low cost and availability of whole genome mapping, we might well see this used for UNIVERSAL neonatal screening to complement our hearing screening.[4,5] This will more immediately help to define the etiology of a hearing problem and inform optimal intervention. Further to genome mapping for congenital hearing loss, we could move to whole genome mapping in later life to determine genetic risk factors for developing hearing loss, tinnitus, or balance problems related to noise exposure or aging.[6-9] Regarding another audiology application, I recently heard a conference presentation on whole genome sequencing of a large cohort of patients with Meniere's disease. As we know, this grouping is very much a "mixed bag," and the study's intent was to define genetic subtypes with distinctly different etiology and pathological features. Such a sub-classification could be useful to finally understand the causes of the disease and define

treatment options. Perhaps the same methods can be used to subdivide the spectrum of disease in ANSD.Clearly, human genome sequencing has much to offer the field of audiology. In future columns we will further discuss these potential applications.



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