Hereditary Hearing Loss

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I would like to discuss something that you will find interesting and stimulating about a topic that sometimes people shy away from, particularly ENT surgeons. I'm going to introduce you to hereditary hearing loss (HHL), but looking at it from the context of the history of DNA, looking at the DNA timeline, have a look at the human genome project and at the future of genetics. Human beings as we know are complex organisms with feelings and emotions, but ultimately when we look at us under the microscope you can break us down into a four letter code. You may not believe it, but up to 36% of our DNA is shared with the humble fruit fly. 84% of our DNA we share with the Zebrafish. You may not realize that 98% of our DNA is in common with our closest ancestor, the chimpanzee.

Humans haven't been around very much in the history of the earth. We only account for 0.13% of the earth's history. Although you would think that we were around for a very long time when you look at the impact we have had on the earth over the last millennium. When things go wrong with genetics, they vary from very simple, very minor, sometimes silly things, but many people when thinking about genetics worry about things going really wrong, they worry about Orwellian-type scenarios.

So where does that leave us in the world of genetics and particularly in the world of hearing loss? Well, I am going to take you on a little journey that starts back in 1815 in Ireland. Sir William Wilde, father of noted author Oscar Wilde worked as an Eye and Ear surgeon in Dublin. He was one of the first people to look at the Irish population and documented through census reports that there was a very high incidence of congenital hearing loss in Dublin. He noted that congenital hearing loss was very common among families where there were first cousin unions or where there were consanguineous unions.

In 1858, Albrecht von Graefe was the first to describe three brothers with deafness, and retinitis-pigmentosa, and this went on to be known as Usher's syndrome as described by Charles Usher in 1914, an autosomal recessive disorder. Then we go on to the father of genetics, Gregor Mendel. Gregor Mendel was an Augustinian monk and he did 28 thousand tedious cross-breeding experiments in pea plants. Mendel discovered the difference between dominant and recessive genes. In 1866, Mendel published his treatise on plant hybrids. Many people like Mendel were before their time and the results weren't often appreciated during their lifetimes.

It wasn't until 1900 that Mendel's laws are rediscovered and reappreciated by Carl Correns, who's sometimes referred to as the father of genetics and that

probably was the beginning of genetics. Adam Politzer, a very famous otologist from Budapest, was another Physician who made very similar observations as William Wilde and as Mendel, particularly when you look at congenital deafness.

I think one of the fundamental things when looking at any family or looking at any group with hearing loss is accurate Pedigree Analysis – it's very important to take a proper pedigree. As you remember from your days of genetics, we've got 23 pairs of Chromosomes, 22 autosomes and a pair of sex chromosomes. Remember – chromosomes have telomeres and centromeres, very interesting structures.

Then we have to move right forward to the 1950's. It wasn't until the 1950's that Watson & Crick described the chemical structure of the DNA, followed by Fred Sanger, who was the first to sequence DNA. Later, in 1966, the genetic code was discovered and as you know, we've got a code of four letter that form triplets, which gives us 64 possibilities. Then in 1972 Paul Berg discovered Recombinant DNA. One of the biggest things that happened in the world of research in DNA was the discovery of PCR, the Polymerase Chain Reactions, this helped an awful lot by allowing us to do research and to sequence DNA. One of the biggest things that happened in PCR was the development, or the discovery of Taq Polymerase in 1986, this is a very important protein which allows scientists to speed up the process of sequencing DNA. It wasn't until 1980 that the first crime conviction occurred where DNA was used – and this involves using DNA fingerprinting in the United States.

In 1990 we saw the use of gene therapy, and it wasn't until 1990 that there was one of the most high profile cases, the one between President Clinton and Monica Lewinsky, where actual genetic material and genetic evidence was used, on a very famous case.

In 1990 the Human Genome project began. It's a very interesting project, between 1990 and 2000 there were two arms to it, there was the public funded side by Francis Collins, which was seen to be free, even though it costed 3 billion dollars to support. Then there was the private end by Craig Venture and his company, Celera Genomics, there was a competition between Celera and Francis Collins. The Human Genome project was a project to try and develop a high quality reference sequence of the 3.2 billion base pairs in the human genome. At that stage, they estimated that there were approximately 100 thousand genes in the human genome.

I was fortunate to be in Harvard in 2000 when Francis Collins came and presented their preliminary results, and when they had 90% of the human genome sequenced, both Collins and Venture, published their results that year in Nature and Science respectively.

But it wasn't until 2003 that this genome project was 100% complete. At that stage they sequenced the entire human genome, and it was 99.999% accurate. That's a phenomenal achievement. And that led to many discoveries, such as, we don't have 100 thousand genes, in fact we have 25 thousand genes. The genes account for the Human Proteome. And about 50% of our genetic DNA is junk

DNA. There is very little difference from human to human, only 0.2% separates us in the genetic tree. As I mentioned, there's only a 2% difference between us and chimpanzees. And the other big discovery from the Human Genome project was that nearly every chromosome that they looked at, they discovered genes that were involved in hereditary hearing loss. In May, 2007, Dr. James Watson was the first person who had his full genome sequenced and awarded to him.

You may not be aware, but the Human Genome project has progressed onto what they call the One Thousand Genomes Project. And the One Thousand Genomes Project was a project that started in January, 2008, and is a new map and they're trying to map the 6 trillion DNA building blocks from different people, from different parts of the world and the basis of this is to try and understand human disease and to try and come up with cures.

When we talk about genetic hearing loss or about hereditary hearing loss, 30% of hereditary hearing loss is syndromic - it involves other problems such as cranio-facial abnormalities. 70% and by far the majority of hereditary hearing loss is non-syndromic. About 80% is autosomal recessive, 15% is dominant, 2 to 3% is sex linked and just less than 2% is mitochondrial. And again, it wasn't until 1992, not that long ago that the first linkage analysis studies demonstrated the first autosomal dominant genes. The first gene that they discovered was the human diaphanous gene. And again, this was just the beginning. This was the beginning of an exponential growth in human research into the genetics of hearing loss. In 1994 the first autosomal recessive gene was discovered and this, as we all know, was the gap junction beta-2 (GJB-2) protein gene coding for Connexin 26. And this gene is very, very important - it accounts for 20% of all childhood congenital hearing loss. I included this slide to remind us of the importance of mice. Mice have been very important in the world of genetics, because the mouse genome is very similar to the human genome. Waltzer mice, Shaker mice, they've all been very important in understanding human genes, particularly those related to hearing loss.

There are a number of very good resources that you can check on the World Wide Web, The hereditary hearing loss homepage, and of course, OMIM, or Online Mendelian Inheritance in Man.

Genetic hearing loss, to understand it, we have to look at the cochlea. Each cochlea has 16 thousand specialized hair cells. These are lifelong cells with little ability to repair or regenerate. The molecular mechanisms that govern inner ear homeostasis are regulated by many genes.

Hereditary hearing loss affects one in one thousand children born per year. Approximately two to four children will delevope hearing impairment as they mature. And about 50% of childhood deafness is found to be caused by genetic defects. The other important thing to remember is that 95% of deaf children are born to parents with normal hearing.

In conclusion, ladies and gentlemen, our Auditory System is the basis of human communication. Over the last number of years our ability to unlock the human genome has allowed us to understand the nature and content of genetic material. And this has propelled us into a new millennium of molecular genetics.

Recommended readings

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10. Check Hayden, E. “Human genome at ten: Life is complicated.” Nature 2007, 464(7289): 664-7.