Genetics in Parkinson's Disease

Who gets Parkinson's disease? Is it genetic?

Age is the most prominent risk factor for the development of Parkinson's disease. We like to tell people that if the neuroscientists realize their dream and make everyone live forever, we may all end up with Parkinson's disease.

The simple truth is that anyone can get it, and even though the worldwide average age is in the mid-fifties to early sixties, it can occur at any age. Men are more likely than women to come down with Parkinson's disease.

Parkinson's disease is probably not one disease. It is likely a syndrome with multiple diseases that share common clinical symptoms (tremor, stiffness, slowness, non-motor features). There are now several families that have been identified as having a single gene as the responsible factor for their Parkinson's disease. These single gene defects, or abnormalities in the DNA (DNA is the word we use to refer to each person's individual genetic makeup) to date account for less than 10% of all cases. The most common and publicized gene defects include LRRK2 and PARKIN(Klein 2001; Klein and Schlossmacher 2006; Bonifati 2007; Klein and Lohmann-Hedrich 2007; Klein and Schlossmacher 2007; Wider and Wszolek 2007; Biskup, Gerlach et al. 2008). Gene tests are not in wide commercial use, and those people and families who choose to have a gene test should meet with a genetic counselor. The implications of knowing that you are gene positive for a disease that may strike at any age can result in serious and life changing implications. In Huntington's disease, where ½ of all children with one parent carrying the disease will become afflicted/affected, following genetic counseling only (approximately) one half of patients will ask for a genetic test. The most widely publicized recent case was Segey Brin, the co-founder of Google. After learning his mom had Parkinson's disease, he and his mom were both tested, and Sergey himself was gene positive. Though he doesn't have symptoms, there is a high likelihood at some point in is future he will develop Parkinson's disease. He has dedicated much of his time and resources to preventing and treating a disease he will eventually personally suffer from.

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The new paradigm in thinking about genetics is that it is more than just the abnormality in the DNA. There is likely a complex interaction between the gene and the environment. Some experts have playfully referred to this as the gene loading the gun and the environment pulling the trigger.

There is an outstanding lay review of Parkinson's disease genetics on the website called genetics Home Reference and it is produced by the National Library of Medicine. On this site they detail information such as the gene mutations that seem to cause Parkinson's disease, "LRRK2, PARK2, PARK7, PINK1, and SNCA," as well as genes associated with Parkinson's disease, "GBA, SNCAIP, and UCHL1." The home reference notes that how genes cause disease is unknown but they offer the following insight, "some mutations appear to disturb the cell machinery that breaks down (degrades) unwanted proteins. As a result, un-degraded proteins accumulate, leading to the impairment or death of dopamine-producing neurons. Other mutations may involve mitochondria, the energy-producing structures within cells. As a byproduct of energy production, mitochondria make unstable molecules, called free radicals, that can damage the cell. Normally, the cell neutralizes free radicals, but some gene mutations may disrupt this neutralization process. As a result, free radicals may accumulate and impair or kill dopamine-producing neurons."

So far we believe that LRRK2 and SNCA only require the parent to pass one copy of the gene to the child for inheritance (autosomal dominant). Two copies (one from each parent) seem to be required for PARK2, PARK7, and PINK1 (autosomal recessive). We are still researching inheritance patterns of genetic forms of Parkinson's disease(Klein and Schlossmacher 2006; Klein and Lohmann-Hedrich 2007; Klein and Schlossmacher 2007).

What are the risk factors for the development of Parkinson's disease?

There is a branch of medical research called epidemiology. In epidemiological studies, scientists will often go door to door to identify how many people in a population do and do not have a disease. They will then assemble lists of disease characteristics and potential risk factors for a particular disease or syndrome. Parkinson's disease seems to be more common in men than women, but is similar in incidence across many continents, races, and ethnicities. There

may be a lower prevalence of Parkinson's disease among African Americans and this is a point under intensive study.

Risk factors associated with the development of Parkinson's disease (and parkinsonism) include such things as well water, rural living, herbicides/pesticides, trauma, drugs and exposure to chemicals such as tetrahydroquinolone (found in foods such as Barbeque). Head trauma, welding, and several other controversial risk factors have been debated by the experts. The herbicide rotenone has been used to develop animal models of Parkinson's disease as has the accidentally discovered recreational drug compound referred to as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Some studies have pointed to protective factors against the development of Parkinson's disease such as caffeine, nonsteroidal anti-inflammatories, and smoking(Langston and Ballard 1983; Langston, Irwin et al. 1984; Tanner and Langston 1990; Tanner 1992; Tanner and Goldman 1996; Tanner, Ottman et al. 1999; Tanner and Aston 2000; Tanner, Goldman et al. 2002; Tanner 2003; Alves, Forsaa et al. 2008).

It is important that people suffering from Parkinson's disease understand that risk factors are just risk factors, and once you have been diagnosed with Parkinson's disease, modification of your lifestyle will likely have no impact in these areas. Also, it is important to realize that there are many epidemiological studies and sometimes there are conflicts in findings. These conflicts can sometimes be explained by study design, biases (e.g. cultural, racial, gender, geographical, etc.), and other factors.

Excerpt from NPF website Forum/May 2009 - Michael Okun MD