

## **The Search for Genetic Modifiers**

The age of onset varies widely in Huntington's Disease, from infancy to old age. Statistical analysis of large samples of patients shows that the single most important factor influencing age of onset is the CAG count, explaining about two-thirds of the variance. The higher the count, the earlier the average age of onset. Although this relationship is very clear on the aggregate level, there are significant variations among individuals and it is possible for two people with the same count to have onsets a decade or more apart.

Analyses of data collected from Lake Maracaibo, Venezuela where there is a high percentage of individuals with the Huntington's Disease gene shows that both environmental and genetic factors play a role in producing these variations. The environmental factors are not clear but it is reasonable to suppose that good health practices may make a difference.

Some progress has been made in finding genetic modifiers and there is good reason to look for them. The HD protein causes numerous pathological processes in the brain and it is difficult to determine which targets should be prioritized for drug development. If a variation in a gene associated with a process that is impaired in HD results in an anticipation or a delay in the age of onset, then this is a good indication that this is an area in which treatments should be developed because they are likely to be effective. Further, since the modifier is affecting onset, it involves an early pathology rather than one later in the disease process.

The latest genetic modifier study was conducted by researchers in the Department of Neuroscience at the University of Pisa in Italy. They found that a variation in the DNA repair gene, hOGG1, is associated with higher CAG repeats and earlier onset. The polymorphism reduces OGG1 activity and increases 8-oxoG formation, oxidized damage to the DNA. This finding makes sense in that other researchers led by Dr. Cynthia McMurray found that somatic expansion of the CAG count occurs as a result of the process of removing oxidized base lesions, and is dependent on a single base excision repair enzyme, 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1).

Two Coalition for the Cure researchers, Dr. James Gusella and Dr. Marcy MacDonald have reviewed the genetic modifier studies in a new journal article and noted some limitations. First, the studies have small numbers of participants which makes it hard to find the modifiers and get statistical significance. Some of the studies which found a probable genetic modifier failed to be replicated in a subsequent study.

Second, there have been methodological problems. Multiple hypothesis testing needs to be corrected for statistically. When a researcher is doing exploratory work and testing for a number of possible variables, the probability goes up that an association will be found which has actually only been produced by chance and not causation.

Third, some of the studies have not linked the genetic variation to a specific mechanism. For example, two separate studies have found that a polymorphism in the PPARGC1A gene is associated with delayed onset but it's not clear what that variation actually does.

Fourth, by only looking at genes thought to have some connection to aggravating or mitigating a known HD pathology, researchers may be overlooking other possible genetic modifiers. Drs. Gusella and MacDonald have concluded that the potential of this type of research can be expanded by doing genome wide analyses on large human samples and by taking an unbiased approach as opposed to the candidate approach. In the candidate approach, a researcher looks at genetic variations in a protein thought to be involved in HD pathology. For example, loss of brain derived neurotrophic factor (BDNF) appears to be a major pathology in HD so researchers have looked at variations in the BDNF gene to see if they are associated with earlier or later than expected onset. No associations have been found, suggesting that the loss of BDNF is not a factor leading to onset as it has been classically defined, as the onset of motor symptoms, and continues to be so defined for the purpose of these studies.

In the unbiased approach, no hypotheses or assumptions are made. By looking at the entire genome in a very large sample, researchers should be able to find previously unsuspected genetic modifiers if they are present and resolve the questions raised by the studies of smaller patient population. Thanks to volunteers around the world who have donated samples for DNA analysis, it should soon be possible for researchers to conduct such studies. The results are likely to be very helpful in directing the development of new treatments.

## References

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- *Marsha L. Miller, Ph.D., October 29, 2009*