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I’m a Huntington’s disease gene carrier at age 60, so why haven't I developed symptoms yet?

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At Risk for Huntington's Disease

HD is a genetically caused brain disorder that causes uncontrollable bodily movements and robs people's ability to walk, talk, eat, and think. The final result is a slow, ugly death. Children of parents with HD have a 50-50 chance of inheriting the disease. There is no cure or treatment.

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WEDNESDAY, FEBRUARY 12, 2020

I'm a Huntington's disease gene carrier at age 60, so why haven't I developed symptoms yet?

Huntington's disease struck my mother in her late 40s, turned her into a debilitated, mere shadow of herself by her late 50s, and took her life at 68. I inherited from her the same degree of genetic mutation. Last December, I turned 60. So, doomed to suffer this inevitable and untreatable disease, why don't I have any apparent symptoms yet?

Of course, I am *thrilled* to have avoided the dreadful scenario I imagined for myself after my mother's diagnosis in 1995 and my positive test for the mutated, expanded gene in 1999. I did not believe that, by age 60, I would still be able to work, write, and not become a burden for my family. Indeed, in January, I marked fifteen years as a Huntington's disease blogger.

I have written about my broad range of strategies for keeping healthy, including swimming, neurobics (exercising the brain) and blogging, and taking supplements, some of which were ultimately proved ineffective. I stretch daily to keep limber, and I eat a healthy diet (no alcohol, sodas, or red meat; minimal processed foods; and lots of fish and fresh fruits, vegetables, and salads). I also consult a psychotherapist, meditate, and practice spirituality.

I also have the benefit of a stable, solid-paying job and a close relationship with my wife and daughter. I cannot be sure whether any of these things help avoid HD, but they generally bolster health.

As Robert Pacifici, Ph.D., the chief scientific officer for the nonprofit, HD-focused CHDI Foundation, Inc., pointed out in a major interview last year, "lifestyle" is potentially very important. Evidence from at least one animal study suggests this, he said, although no scientific data yet prove this for HD in humans (click here to read more).

However, extensive, pathbreaking research based on humans has provided a new understanding of the genetics of Huntington's and why people with the same size of gene mutation – the same CAG count, as explained below – can experience widely different ages of onset. A Huntington's Disease Society of America (HDSA) webinar, presented by James Gusella, Ph.D., on November 19, 2019, explained the main points of this research and its relevance for HD families.

"You can relatively easily find people who've developed symptoms maybe 20 or more years later than you'd expect from the average, or 20 or more years earlier than you'd expect, and you can find people all along that range," said Dr. Gusella, who titled his presentation "New Insights on Huntington's Disease Age of Onset from Genetic Studies of HD Families."

Dr. Gusella is the Bullard Professor of Neurogenetics at Harvard Medical School and the director of the Center for Human Genetic Research at Massachusetts General Hospital. He helped lead the efforts that narrowed the search for the

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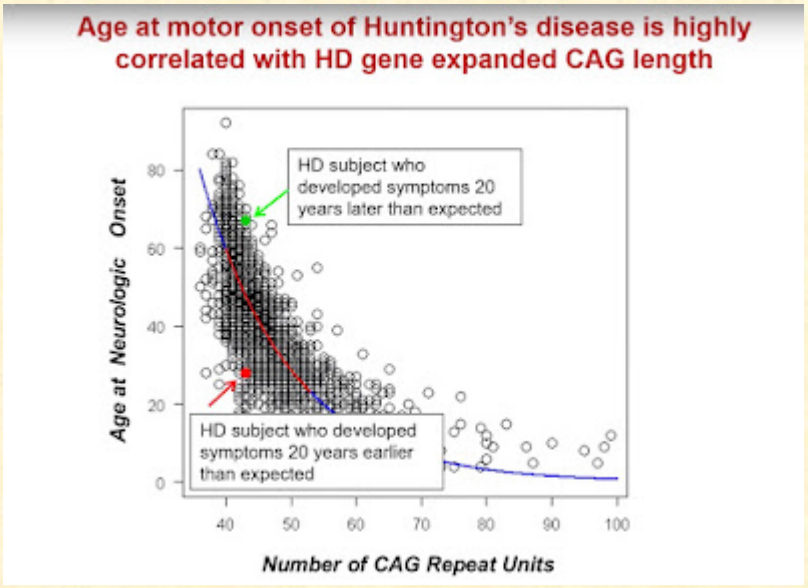
huntingtin gene to chromosome 4 in 1983 and the discovery of the gene in 1993 (click here to read more). Since then, he and his collaborators have continued to make important discoveries about HD.

Above, Dr. James Gusella (left) during an interview with Gene Veritas (aka Kenneth P. Serbin) at the 7th Annual Huntington's Disease Therapeutics Conference, sponsored by CHDI, in 2012. Below, a slide from Dr. Gusella's HDSA webinar presentation illustrating the average age of HD onset correlated with the CAG count.



The CAG count

Focusing on the discovery of so-called "modifier genes" for HD, Dr. Gusella delved into the reasons for the wide variations in onset – and the potential this research has for producing HD treatments.

As Dr. Gusella explained in the webinar, the human genome has 3 billion "letters," or base pairs, which make up our DNA. The four letters that make up the bases of DNA are A (for adenine), C (cytosine), G (guanine), and T (thymine).

Like all genes, the huntingtin gene is made of a string of "three-letter words," sequences from those four letters. Within the gene is a segment in which the word "CAG" is repeated a number of times. Normal genes have 10-25 CAG repeats. Repeat lengths of 26-34 do not ordinarily cause HD,

but the repeat number can increase as the gene is passed to a child, leading to HD in the offspring. HD can occur in people with 35-39 repeats, and genes with 39 or more repeats "almost always" cause the disease, Dr. Gusella stated.

"CAG repeats" is the lingo of the HD community. Tested gene carriers like me usually know our repeats, and those of our affected parent and relatives. I have 40, as did my mother.

The "CAG count," as it's also known, became critical in my wife's and my decision to conceive, especially because males (we were told) had a greater tendency to pass on a larger number of repeats. What if our child had a few more repeats or even more?

The CAG count has long factored heavily in genetic counseling and even in people's decisions about moral dilemmas like abortion.

In general, the more repeats, the earlier the onset, leading even to juvenile HD – although, as Dr. Gusella emphasized, the age of onset varies widely.

New thinking about HD genetics

Since the discovery of the HD gene, scientists have published thousands of papers on HD, many of them based on studies in non-human organisms such as flies, mice, sheep, and primates – some of these organisms genetically modified (before birth) to later develop HD-like symptoms. However, because HD occurs only in humans, ultimately our species provides the best model for understanding and treating the disease, scientists say.

Scientific advances and the advent of clinical trials have made deeper research in humans more widespread and easier to carry out.

"We're firm believers that, if you're going to study a human disease, you're best to study it first in people, rather than in trying to recreate it in other animals," Dr. Gusella stated. "People really give you the information for what the disease is."

Assessing genetic data collected over decades in more than 9,000 people affected by HD, Dr. Gusella and the Genetic Modifiers of HD (GeM-HD) Consortium have made discoveries that have changed standard thinking about Huntington's genetics.

This type of broad-ranging study is known as GWAS, genome-wide association study.

As Dr. Pacifici stated in 2015, human data are "precious" because they enable Huntington's drug hunters to design and run better clinical trials, which are crucial for developing treatments.

Dr. Robert Pacifici (photo by Gene Veritas)

Explaining onset

In the webinar, Dr. Gusella detailed the research on CAG repeats and onset. A correlation definitely exists, he stated. However, other key factors come in into play.

"The inherited CAG length accounts for about 60 percent or so of the variation in age of onset, but there is a lot of variation" at each CAG count, he said.

"Just measuring the CAG repeat doesn't give you an accurate prediction of when any given individual is going to have onset," he emphasized. Research in thousands of people produces an average, "but it really doesn't tell you much specifically about a given individual that would be useful diagnostically."

However, the mass CAG data can help scientists explain why individuals diverge from the average, he stated.

Forty percent of the reason for onset must be due to factors other than the CAG count, Dr. Gusella continued. From their research, the GeM-HD Consortium concluded that 20 percent is due to other genes, that is, modifier genes "that are influencing when you have onset."

Environmental factors 'hard to study'

"The other 20 percent remains unexplained," Dr. Gusella said. "It could be anything. It could be chance. It could be environmental factors."

Environmental factors "are very hard to figure out and study," he added. In answer to a webinar question about environment, diet, and exercise, Dr. Gusella could point to no study on the topic, although he noted that such research falls outside his expertise.

Indeed, in my more than two decades as an HD advocate and participant in numerous research studies, I've not been aware of any such study for presymptomatic gene carriers like me. The closest was PREDICT-HD, which collected samples of blood, urine, saliva, and cerebrospinal fluid from presymptomatic gene carriers. It also had them undergo a motor coordination exam and brain MRI scan and perform a battery of cognitive and mood tests. (Click here to read more).

Dr. Gusella added that the unexplained factors could also include "simply the diagnostic uncertainty, because you're dealing with a motor onset."

Motor onset marks the start of the involuntary movements typical in HD. Doctors have long used it as the standard way of diagnosing the disease, as opposed to other, initially often more subtle symptoms such as depression or cognitive difficulties.

However, as Dr. Gusella noted, diagnosing motor onset can be "a little bit subjective" on the part of the patient, the family, and the physicians. They all might also lack certainty about the exact time of onset.

Modifier genes influence age of onset

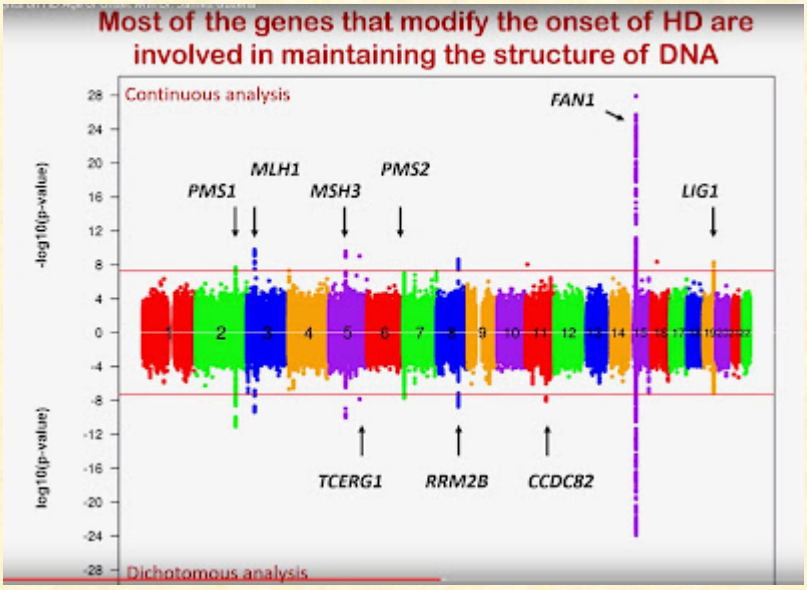
For the 20 percent of onset determined by modifier genes, the GeM-HD Consortium has hard evidence from the genetic studies of the 9,000-plus individuals.

It is "clear" that genetic variations "account for the differences" in age of onset for people with the same CAG count, Dr. Gusella said.

Everybody has genetic differences such as hair and eye color, and the overall number of differences among people is very large, he explained. By studying thousands of people, and using two methods of analysis, the scientists have detected 23 genes that influence the onset of HD.

Modifiers can come from both the affected and non-affected parent, Dr. Gusella pointed out.

As with many other genes, researchers have assigned these modifiers with very long, scientific names, which they have abbreviated to terms like FAN1. Delay in onset from the average varied from one to 20 years. FAN1 and most of the other modifiers are involved in the maintenance and repair of DNA, which, in general, helps cells remain healthy, he noted.



A slide from Dr. Gusella's presentation illustrating the location on the chromosomes of some of the currently identified Huntington's disease modifier genes

Dr. Gusella stressed that the GeM-HD research had not yet resulted in new types of genetic tests for individuals to discover whether they have favorable or unfavorable modifier genes. The research correlates to

observations in thousands of people, but does not allow for prediction of age of onset in any given individual.

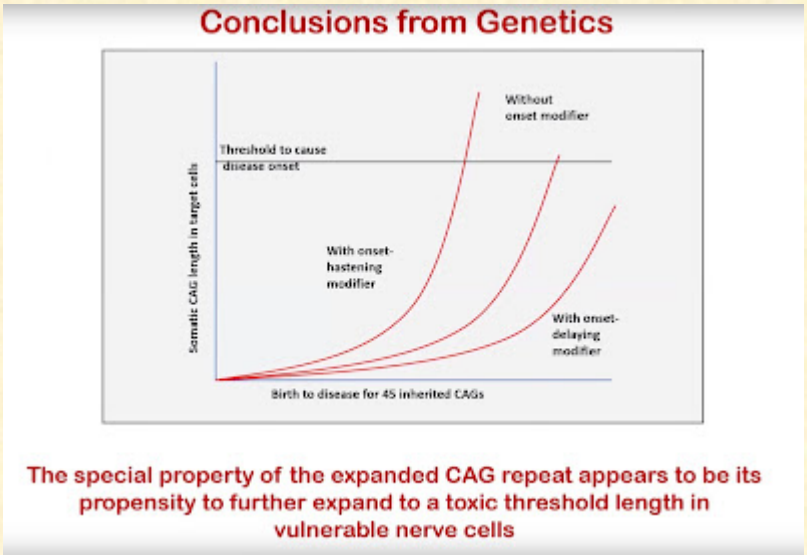
The GeM-HD findings have shed light on other genetic aspects of the disease critical for families and family planning. When an affected parent passes on an abnormal CAG repeat, the count can increase or decrease, usually by one to three repeats, with a slight tendency to go up, and with a greater tendency for increases in CAG count when the gene is passed on by males, Dr. Gusella stated.

However, because of the action of modifier genes and the larger overall variation in onset, any attempt to "to predict onset from relatives" could "easily be wrong."

So, Dr. Gusella asked, if such findings cannot directly inform individuals and their families, what are they good for?

Researchers can seek to investigate the "mechanism" by which the modifiers affect the "disease process" and then, based on that knowledge, design treatments to influence that process "in a much, much stronger fashion" than any of the modifiers does individually.

"Imagine if we had a drug that could delay onset of motor symptoms by 40 years!" Dr. Pacifici exclaimed, commenting on the discovery of the modifier genes. "My gosh, that would be fantastic. Nature's kind of done that experiment for us. It's told us that it is possible to modulate the disease."



A slide from Dr. Gusella's presentation illustrating how age of disease onset is influenced by modifier genes, as shown in the different curves

The defective protein

Another key finding of the GeM-HD studies has also changed standard thinking in the HD field. This discovery involves the protein made by the huntingtin gene, also called huntingtin.

Each 3-letter "word" in the DNA encodes an amino acid to put into the protein the cell is making. There are 20 different amino acids; proteins are made of long chains of hundreds or thousands of amino acids, which are then folded, linked, or otherwise modified to create the final product. Dr. Gusella described proteins as the "workers in the cell." Cells are assisted in this process by RNA, which acts as a messenger to carry instructions from the DNA in the making of proteins.

In the case of huntingtin, there is a particular location in the gene where the word CAG appears many times in a row, as noted above. This leads to the creation of a protein that includes the amino acid glutamine many times in a row.

Since the discovery of the gene, scientists have assumed that HD onset occurred because of too many glutamines in the protein, supposedly resulting in cumulative damage to brain cells by the faulty protein, Dr. Gusella observed.

"This assumption is actually not correct," he reported.

The gene drives onset

The GeM-HD researchers found that, after the string of CAG repeats in the gene, there is usually the "word" CAA and then another CAG, Dr. Gusella explained. The DNA "words" CAG and CAA both mean "glutamine" to the cell's protein-making apparatus.

"The vast, vast majority of Huntington's disease individuals have that structure," he continued.

However, in less than one percent of people with HD, there is *no* extra CAA-CAG – or there are *two* CAA-CAG combinations.

These genetic differences affect the measurement of the CAG count, making the actual section of the gene shorter or longer than the laboratory would measure using usual test methods, Dr. Gusella explained. Detecting these very small variations in DNA sequence in a small number of patients is difficult and costly. Also, as with modifier genes, getting tested for these differences would not benefit HD patients in any way, he added.

However, these uncommon variants in the DNA sequence permitted researchers to do something very important: to distinguish the effect of the CAG from the effect of the glutamine.

"It's not glutamine that's driving the time of onset," Dr. Gusella explained. "It's some property of the CAG repeat itself, some property of the DNA where the consecutive CAG that's not interrupted by anything is determining roughly the time of onset."

Here is an example: a typical person with HD might have a huntingtin gene with 42 CAGs followed by a CAA and another CAG. Because both CAA and CAG lead to glutamine, the gene test would say that he had 44 CAG repeats, and his huntingtin protein would have 44 glutamines in a row. But the testing in Dr. Gusella's laboratory would show that there were only 42 CAG repeats before the CAA "interruption." Another person might have 44 CAG repeats without a CAA interruption. Her gene test would show that she has 44 CAG repeats, the special test would show 44 repeats, and the protein would have 44 glutamines in a row. The first patient, however, who has a smaller actual number of CAG repeats before the interruption, would have a later onset age than the second patient.

This finding "makes a big difference for how you think about the disease and how you might go about trying to intervene in it," Dr. Gusella concluded.

Dr. Gusella with long-time collaborator Marcy MacDonald, Ph.D., a member of the GeM-HD team (HSDA photo)

The CAG can expand over time

Another "special property" of the expanded CAG repeat is that the longer it starts out, the more likely it is to increase in size over time, Dr. Gusella said.

According to Dr. Pacifici, this so-called somatic expansion could be related to the appearance of symptoms. In this theory, brain cell damage and death occurs as CAG repeat lengths within the cell increase from 40-50 to 100 or more.

Several of the 23 modifier genes identified by the GeM-HD team appear to influence somatic expansion of the CAG; some modifiers seem to make it go faster, leading to early symptom onset, while others seem to slow somatic expansion, leading to a later onset of symptoms.

Onset (start of the disease) is different from progression (how the disease worsens over time).

Dr. Gusella cautiously answered a question from a webinar participant about whether a later onset could slow or hasten "progression" of the disease. He observed that the HD field has not yet established a clear definition of progression, with much debate on the matter. Clearly, as the GeM-HD data demonstrate, there's a "lesser influence" of the CAG count on the changes in symptoms "than there was on getting there in the first place, of starting to have them."

Implications for potential treatments

Taken together, the GeM-HD findings have helped to specify – over a large number of people – a number of genetic factors determining HD onset, and to show that it's not a "cumulative damage as a result of the huntingtin protein," Dr. Gusella summarized.

"The mechanism of toxicity is uncertain – it might involve huntingtin protein or might act by another mechanism involving the DNA or RNA of the HD gene," he said.

The search for other modifier genes continues in the quest to clarify how the cells are being harmed, he said. Researchers are also examining how rapidly certain measures of health change before onset, how the disease

changes after onset, and the differences in how the disease develops in people with very similar CAG length.

Dr. Gusella addressed the potential implications of the GeM-HD research for clinical trials in progress that seek actually to reduce the amount of the huntingtin protein in brain cells. Run by Roche, the first of these so-called huntingtin-lowering trials, GENERATION HD1, entered a critical and final Phase 3 in early 2019 (click here for the latest update on the trial).

"Those therapies are being applied at a point in time where you're right around onset or after onset, which means that the expansion of the repeat that is leading to damage has gotten to the point where enough cells are damaged that you are close to or showing symptoms," Dr. Gusella said. "If you now knock down the huntingtin [protein], if the huntingtin is the mechanism by which the expanded repeat ultimately kills the cell, then it should work. If it's the RNA, it may work, depending on what the effect of the treatment is on the RNA level."

However, Dr. Gusella emphasized that the GeM-HD findings do not address when a huntingtin lowering therapy should be given, or whether or how they work.

"I certainly hope that it does," he added.

Other paths to drugs

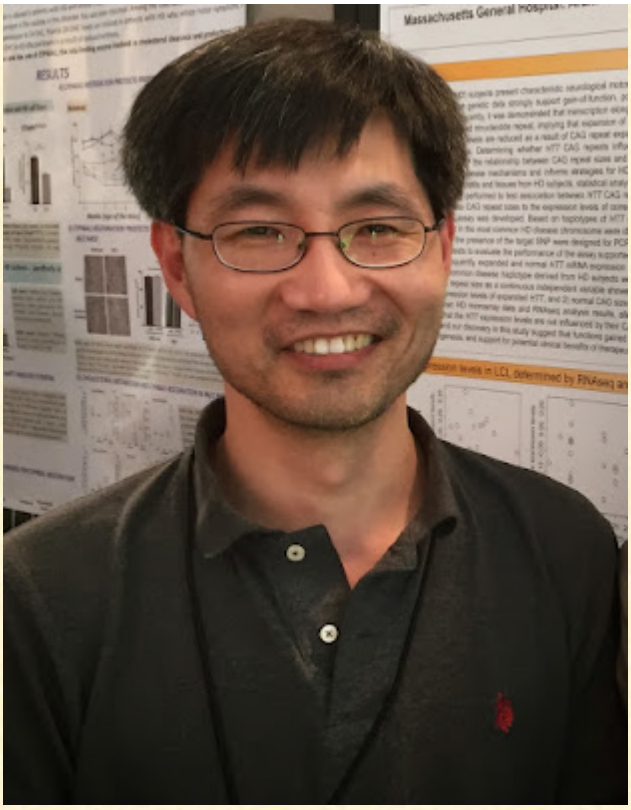
Dr. Gusella addressed other ways in which the new understanding of HD genetics might help in the search for treatments. One possibility would be to interfere with the characteristic of the CAG repeat that is seen as driving onset, he said. Another approach could involve the modifiers engaged in DNA maintenance and repair – by manipulating them with drugs, suppressing them, or by activating them.

Yet another way would be to block the somatic expansion of the huntingtin gene, Dr. Gusella continued. Researchers could also use the new techniques developed for manipulating DNA and perhaps even change the number of repeats. Also, huntingtin-lowering drugs (if and when they are developed) could be used in combination with as yet undiscovered modifiers, he said.

Would more genetic information be helpful?

In addition to the Dr. Gusella's 2019 webinar – his first such presentation for HDSA – I've also watched talks at scientific conferences by him, his long-time collaborator Marcy MacDonald, Ph.D., and Jong-Min Lee, Ph.D. According to Dr. Gusella, Dr. Lee "in particular has helped drive these studies."

People in the HD community often speculate as to what "triggers" the disease. The GeM-HD research provides a partial but important answer with its discovery of modifier genes and other genetic factors that influence the age of onset.



Dr. Jong-Min Lee at the 2015 HD Therapeutics Conference (photo by Gene Veritas)

For many years, I have speculated about my age of onset, almost always referencing my mother's situation. However, as the GeM-HD research now shows, that is not very helpful because of the great variation in age of onset.

Thus, as I've watched the research progress, I have wondered: could one or more modifier genes inherited from my parents have acted to delay my HD onset well beyond my mother's?

I've also thought about somatic expansion: perhaps my mother's 40 CAG repeats expanded to a much higher number more quickly than mine. Perhaps the other genetic factors outlined by Dr. Gusella have had an impact.

For now, at least, I can't be tested for the modifier genes or these other factors. As Dr. Gusella indicated, even if I could, it's not clear how predictive they would be, nor how helpful such knowledge would be.

From 1995 to 2000, my family went through three CAG tests: my mother's, mine, and our daughter's. Luckily, our daughter tested negative in the womb, but my wife and I waited for three agonizing months to learn her status.

After those difficult experiences, would I really want to go through *more* tests? If I *could* know my genetics to a more precise level, including moment of onset and how the disease would develop, would I really want such information?

Because of the lack of an effective treatment, most at-risk untested individuals decline testing for the CAG count. As Gene Veritas – the person who wanted to know the "truth in his genes" – I'm an outlier.

However, I cannot predict my feelings about further genetic testing until actually facing that possibility. I would only know at the moment they

became available.

HD in the vanguard, but still highly complex

A decision to get tested again and my feelings about it would also depend on the availability of effective treatments. With the potential success of the Roche drug and others, doctors and HD clinics are preparing for the likely boom in testing for the CAG mutation, as people seek to learn their status before taking a drug.

As Dr. Gusella pointed out, HD stands in the vanguard of the attempt to apply protein-lowering and other cutting-edge techniques because, unlike the other major neurological disorders, it is monogenetic: it has a single genetic cause.

The critical GeM-HD discoveries could perhaps bolster the effectiveness of these other approaches or even result in unique medicines.

However, the new genetic research also underscores another reality of HD. Despite its monogenetic status, it is complex and features subtle genetic nuances. Huge challenges remain in developing treatments.

For HD-impacted individuals and their families, in the near term much will remain a mystery.

(For further background on the GeM-HD research, click here for the 2019 CHDI presentation "Genetic Modifiers" by Dr. MacDonald. Click here for the 2015 CHDI presentation by Dr. Lee.)

Posted by Gene Veritas at 11:08 PM

Labels: CAG repeats , CHDI , environmental factors , GeM-HD Consortium , genetic testing , genetics , HDSA , human data , huntingtin , huntingtin lowering , Huntington's disease , James Gusella , modifier gene , onset , symptoms

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