# Juvenile Huntington's Disease: The Cruel Mutation

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Jane Mervar and Karli

Looking back, signs that Jane Mervar's husband, Karl, had Huntington's Disease (HD) started about when their youngest daughter, Karli, began to have trouble paying attention in school. Karl had become abusive, paranoid, and unemployable due to his drunken appearance. The little girl, born in September 1996, was hyperactive and had difficulty following directions. When by age 5 Karli's left side occasionally stiffened and her movements slowed, Jane began the diagnostic journey that would end with Karli's diagnosis of HD, which had affected the little girl's paternal grandmother.

Soon Karli could no longer skip, hop, or jump. And new troubles emerged. "She had cold sweats, tachycardia, and chronic itching. She fell and suffered chronic pain. By age 6 she was losing her speech and became withdrawn," Jane recalls. Karli drooled and her speech became unintelligible. By age 7 her weight had plunged, and by 8 she developed pneumonia three times due to difficulty swallowing. By age 9 she required a feeding tube, suffered seizures, and would go long periods without sleep.

AN ADULT'S DISEASE IN A CHILD

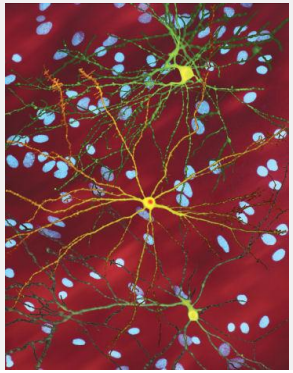
This isn't the way that a disease is supposed to run in families, striking child before parent. HD is regarded as a disease of adulthood, but in fact about 10% of people with the condition are under age 20 – they have juvenile Huntington's disease (JHD).

"Horse-and-buggy doctor" George Sumner Huntington first described HD in 1872. As a young man he'd accompanied his father and grandfather on house calls in East Hampton, Long Island, where a few local families had a mysterious movement disorder. The youngest Huntington recalled two very thin women gripped by constant contortions, and several men who staggered about as if intoxicated. He later described the symptoms intensifying "until the hapless sufferer is but a quivering wreck of his former self."


Folksinger Woody Guthrie lost a long battle with HD in 1967.

Dr. Huntington deduced the autosomal dominant inheritance pattern of HD. It affects both sexes, with each child of someone with the disease facing a 50:50 chance of sharing the fate. Loss of motor control typically begins in the late thirties, but behavioral and cognitive signs are often present years earlier, sometimes unrecognized. Folksinger Woody Guthrie put a famous face on HD 45 years ago, but the community today needs an Angelina Jolie.
HD symptoms in children differ from those in adults – Karli's problems in school and stiffness were classic — but inside cells, a similar crisis unfolds in a patient of any age.

The *Htt* gene encodes the protein huntingtin. The gene normally includes up to 35 copies of the DNA triplet CAG, just before the first exon (protein-encoding part). The disease arises when the gene grows – HD is the quintessential "expanding triplet repeat" disorder. Perhaps the enzymes that replicate DNA as sperm and egg form misalign while duplicating a short repeated sequence, like copying a line in a word document and introducing repeats of a word word word.



The orange dot in the center of the yellow striatal neuron is an inclusion body of abnormal huntingtin protein. (Dr. Steven Finkbeiner)

The triplet repeat somehow triggers a cascade of destruction, with its most profound effects in the "medium spiny neurons" in the movement centers of the brain.
The*Htt* gene with too many CAGs encodes a protein with too many glutamines. The protein can't fold properly, sticking to itself and to other proteins, blocking axons in neurons of the brain's striatum, preventing distribution of essential growth factors. The white matter of the brain shrinks.
Changes in behavior and thinking often precede the constant movements that fascinated the young Dr. Huntington. Irritability, loss of impulse control, and aggression are hallmarks. Jane's husband Karl spent wildly and threatened his family and others with guns. He spent his final years in a nursing home knowing that social services would take away his daughters otherwise.

AN UNUSUAL MUTATION
Karl was diagnosed six weeks after Karli in 2002. He was 35, she just 6. They died within weeks of each other in early 2010.

But the story gets worse. Karli's sister Jacey (who founded jhdkids.com), was diagnosed in 2004 at age 13, and her sister Erica in 2007 at age 17. The family history is so complex and unbelievable that even Jane has trouble recalling the chronology. All three girls inheriting the disease is probably just bad luck, but the repeat size for Karli echoes an unusual event.
In HD, gene size matters. Most adults have 40-60 repeats. Karl had 47 and his two older daughters have 47 and 49. But Karli inherited 99 CAGs, a consequence of DNA replication enzymes looping and doubling her father's 47. It's little wonder she got sick so fast — longer repeats mean earlier onset.

Karli and her dad.

Most HD kids with very expanded mutations inherit them from their fathers, and this may be due to the different timetables of sperm and egg production. A female at puberty has about 400,000 eggs, each halted on the brink of completing meiosis, when the slippage that expands the gene could happen. But a male shoots out a quarter of a billion sperm with each ejaculation – many chances over a reproductive lifetime for the gene to be miscopied and grow.

WHEN, AND IF, TO TEST

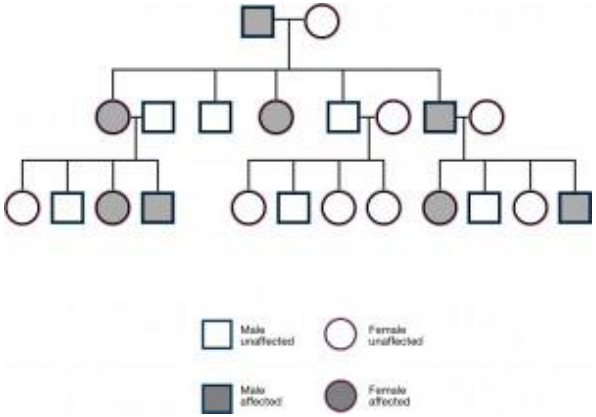
A test to count CAG repeats is essential to confirm a clinical diagnosis of HD. When genetic testing first became available in the mid 1990s, following a decade of using a less-predictive marker test, concern was that people finding out they have the mutation before symptoms begin would freak out. That hasn't happened. Nor has testing found many takers. Most "at-risk" individuals, those who know they have one affected parent, choose not to be tested.

Because testing raises complicated psychosocial issues, and because onset is usually in the fourth decade, it's generally not recommended for those under 18. But when the young person has symptoms, it's a different story.

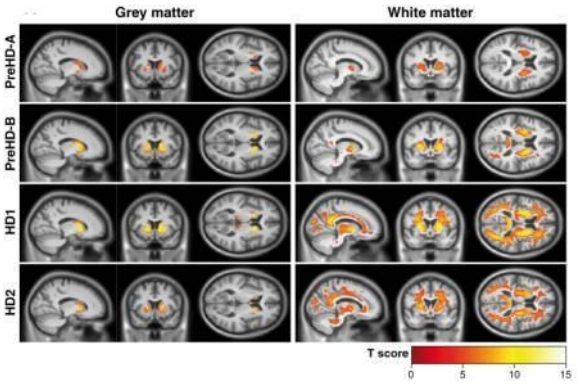
Martha A. Nance MD, medical director of the Struthers Parkinson's Center and the director of the HD Center of Excellence at Hennepin County Medical Center, both in Minneapolis, and author of "The Juvenile HD Handbook," explains the nuances. "It's important to distinguish *diagnostic* testing in a child who is having problems from *presymptomatic* testing in a child whose parent has HD or is at-risk for HD but has no neurologic or psychiatric symptoms."

Presymptomatic testing doesn't make much sense, Dr. Nance says. "No treatment hinges on getting an early test result, and the things that people do are probably a good idea whether you have the abnormal gene or not, or at least won't hurt, such as exercising and eating right." For children and teens, Dr. Nance says, the psychosocial repercussions of learning test results when there aren't symptoms can be huge. "The parent who tests his asymptomatic 10-year-old because of guilt, concern, or a desire to plan, removes that child's freedom to choose. There's a 90% chance that child, if able to decide for himself, wouldn't want to be tested."

Another problem is that it can be very hard to tell when symptoms start, and if they indicate HD or something else. Does a teen who can no longer multi-task at a restaurant job have the family legacy? Is anxiety or irritability due to HD?




The multi-generational nature of the disease complicates matters. “We’re hesitant to diagnose HD in a 13-year-old from a challenging home environment, usually an affected father who probably isn’t working and may have bizarre behavior. The last thing we want to do is take a kid who is profoundly depressed or acting out, whose father is dying of HD, and do a gene test that shows he has a mutation of a size that generally causes symptom onset in a person’s 40s. Then we have just done a predictive test in an unstable 13-year-old,” Dr. Nance explains. Very few physicians are trained to recognize JHD. Specialists in movement disorders work with older adults, such as those with Parkinson’s disease, and pediatricians rarely encounter HD. “So a child with HD symptoms will either be seen by a pediatric neurologist who knows little about HD, or by an HD neurologist who knows little about kids,” Dr. Nance says. Diagnosis typically takes 2-7 years as physicians await obvious motor symptoms, or a clear decline in cognitive function. This is too long for families to wait. Dr. Nance and others are working to find better tools to determine when a child’s challenging behavior is just “being a teenager” or some other problem, and when it is due to the onset of HD.




A range of new clinical, functional, and neuroimaging tests developed by researchers in the Department of Neurodegenerative Disease at University College London (UCL) make it possible to track the progression of Huntington’s disease long before noticeable symptoms appear.

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