

All About Mutations

What it means to have a mutation and what role mutations play in Huntington's disease.

Figure Q-1: The Teenage
Mutant Ninja Turtles™



Although they were great for entertainment, these turtles helped cast a false conception of the word "mutation."

(TM, Mirage Studies USA)

With their sword-wielding, karate-chopping, and pizza-eating ways, the Teenage Mutant Ninja Turtles swept American children by storm in the early 1990s. Unfortunately, though they did get kids to sit still for 30 minutes each day, the turtles also contributed to a widely held public misconception about what it means to have a mutation. From watching their television program, one might think that people with mutations will grow green skin and begin a new life in the city's sewer pipes. In reality, though, there is nothing out of the ordinary about mutations. In fact, every person in the entire world has some sort of mutation in his or her DNA; in that sense, everyone is a mutant! Mutations are not just normal, they are important: evolution itself cannot occur without mutations.

While everyone has mutations, the location on the DNA of these mutations is different from person to person. For example, people who are albino have a mutation in the gene that codes for tyrosinase, an enzyme that is essential for providing skin coloration. The mutation inhibits the tyrosinase's normal function and results in the lack of coloration. As another example, the majority of people in the world cannot absorb lactose and thus become ill after drinking milk, but people who actually can absorb the lactose in milk are able to absorb it because of a mutation. It just so happens that people with Huntington's disease (HD) have a mutation that lies on the [Huntington gene](#) in the DNA. Since this gene codes for the [huntingtin protein](#), the mutant form of the gene creates an altered form

of the huntingtin protein, thus resulting in degeneration of the involved nerve cell and, in turn, the onset of the symptoms of HD. (For more information about HD symptoms, click [here](#).)

The following section seeks to answer some of the many questions about mutation and HD. The goal is to illustrate the role of mutations in HD and, in turn, to increase the understanding of the disease in general.

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- [What role does the environment play in mutation?](#)
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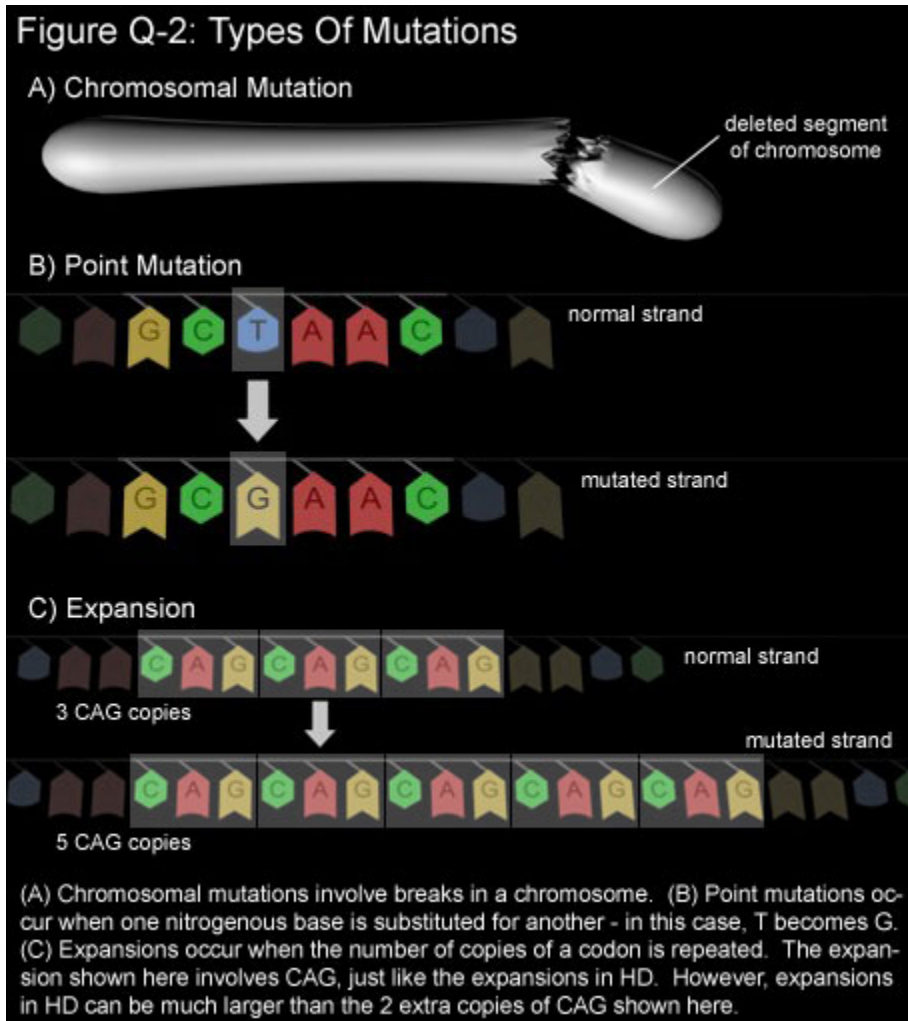
Part 1

What it means to have a mutation and what role mutations play in Huntington's disease.

What are mutations?

In the broadest definition of the word, a [mutation](#) is a change in the genetic composition of an organism. Many different phenomena fit this definition. For instance, [chromosomal mutations](#) (or [chromosomal rearrangements](#)) result from breaks in the chromosome. In these mutations, a segment of the chromosome is deleted, and may even attach onto another chromosome. Since chromosomes are made of millions of pieces of DNA all strung together, breaks in these chromosomes can mean the loss of many important genes, with very harmful results for the individual. (To learn more about chromosomes, click [here](#).) [Point mutations](#) are also potentially harmful. They occur when one

[nitrogenous base](#) is substituted for another (for example, when adenine (A) is substituted for thymine (T)). In some instances this can result in a [silent mutation](#), in which no noticeable change occurs. In others, however, the code alteration can disturb the gene, with the ultimate result of creating either an altered protein or no protein at all. Both of these results can be quite harmful to the individual.



Point and chromosomal mutations have been identified as the cause of many human diseases. With regard to HD, however, they do not appear to play a role. Instead, the mutation involved in HD is known as an [expansion](#). Expansion refers to the increase from one generation to the next (parent to child) in the number of copies of a certain [codon](#). This codon is normally repeated a certain number of times, composing what is called a [repeat region](#) of the DNA. When the mutation increases the number of copies of this codon, the length of the repeat region is expanded, hence the name "expansion." In HD, the codon involved is CAG and the repeat region is located on the [Huntington gene](#).

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What it means to have a mutation and what role mutations play in Huntington's disease.

If an expansion occurs, what is the effect on the child?

For a person to either develop HD himself or remain [asymptomatic](#) but have children with HD, the absolute minimum number of CAGs in the [repeat region](#) of the [Huntington gene](#) is generally recognized by researchers as 36. (See [Table A-1](#).) The consequences of [expansions](#) of the CAG repeat region (in the transmission from parent to child) depend on the number of repeats in the parents. We consider the three possibilities. The most common situation involves asymptomatic parents who both have fewer than 36 CAGs in the repeat region. Only very rarely does an expansion occur in this situation, and when one does, the children typically remain asymptomatic because the expansion is unlikely to be large enough to push the children over the 40 CAG mark. It is incredibly rare for a person to develop HD when his or her parents did not have at least 36 copies of CAG in the Huntington gene.

The second scenario involves people with between 36 and 40 copies of CAG. As mentioned in [The Basics of HD](#), these people may or may not have HD themselves. However, regardless of whether they have HD or not, they are at risk of having children with HD because expansion will likely result in the children having more than 40 CAGs, and more than 40 CAGs almost always means that the person will develop HD.

The third scenario involves people who themselves have HD. If expansion occurs in this situation, not only will the child likely have HD, but also the increased number of CAGs means that the child's symptoms will likely start showing at an earlier age than the parent's symptoms did. (Click [here](#) for more about early onset in children with HD.) This happens because generally the higher the number of CAGs in the repeat region of the Huntington gene, the earlier the age of onset. (To read about more about [juvenile HD](#), click [here](#).)

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Part 3

What it means to have a mutation and what role mutations play in Huntington's disease.

How do expansions occur?

This question has been the subject of a great deal of scientific research over the years. Although the exact cause is uncertain, two phenomena, [unequal crossing over](#) and [polymerase slippage](#), are the most probable mechanisms for [expansion](#) of the CAG codon.

Below we discuss two proposed models:

- [The Unequal Crossing Over Model](#)
- [The Polymerase Slippage Model](#)

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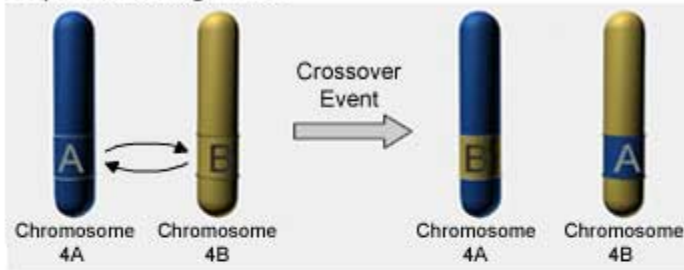
Part 4

What it means to have a mutation and what role mutations play in Huntington's disease.

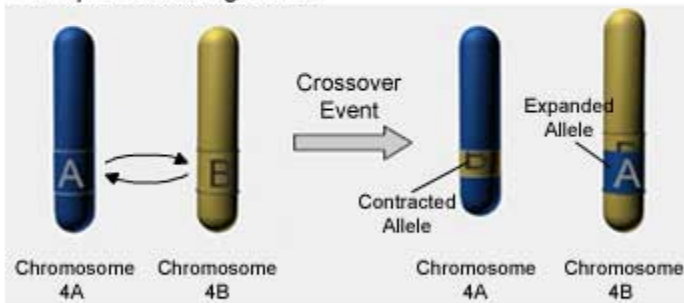
The Unequal Crossing Over Model

Figure Q-3: The Unequal Crossing Over Model

Equal Crossing Over:



Unequal Crossing Over:



In equal crossing over, the entire segment of allele A switches places with the entire segment of allele B. But in unequal crossing over, only part of B switches places, leaving the rest behind to add to the length of B. The result is a shorter (contracted) segment B on chromosome 4A and a larger (expanded) segment comprised of all of A and part of B on chromosome 4B.

Sperm and egg cells reproduce by a process called [meiosis](#). During meiosis, [homologous chromosomes](#) line up, enabling alleles to switch places between the chromosomes in an event described as [crossing over](#). During [equal crossing over](#), the alleles are exchanged equally. For instance, say that originally allele "A" is on chromosome "4A" and allele "B" is on chromosome "4B." During equal crossing over, if allele A and allele B were to switch places, then allele A would move to chromosome 4B, while allele B would move to chromosome 4A. However, during [unequal crossing over](#), the position switching of allele A and allele B might not be quite so smooth. Instead of whole alleles switching places, only a certain segment of each may switch, leaving the rest behind to act as a neighbor for the new inhabitant (the allele coming from the other chromosome). In the case of HD, the segments being cut unequally are often the repeating CAG regions of each Huntington allele. After the crossover, one of the chromosomes will have a Huntington allele with fewer CAGs than before. This is the "contracted allele" due to the contraction of the number of CAGs. The other chromosome will have a Huntington allele with more CAGs than before. This [expansion](#) results in the "expanded allele."

Once meiosis is complete, the two homologous chromosomes are split apart. In males, one of the chromosomes goes to one sperm, and the other chromosome goes to a different sperm. In females, one of the chromosomes goes to one egg, and the other to a different egg. The end result is that, should a baby be created from an egg or sperm with a chromosome housing the contracted Huntington allele, then the baby will have a reduced

number of CAGs on his or her [Huntington gene](#) (in comparison to the parent). If the baby's number of CAGs is below threshold for HD (see [Table A-1](#) for the rough threshold numbers), the baby is unlikely to develop HD. However, should the expanded Huntington allele be present, then the baby will have a greater number of CAGs than the parent. If there are enough CAGs (again, see [Table A-1](#) for the rough threshold numbers), then the child will develop HD. (For a general discussion of the probability of passing HD to one's children, click [here](#). For more about how expansion affects passing HD to one's children, see [Part 2](#) of this chapter.)

The [unequal crossing over model](#) does not perfectly represent the expansion mechanism in HD. Its most important flaw is that it suggests that expansion occurs during meiosis, which happens before sperm and eggs are developed. In reality, however, researchers have found little evidence of expansion during meiosis. Instead, they believe that expansion happens during mitosis, which takes place in the developing embryo after fertilization (when a mature sperm and a mature egg have fused together). Another phenomenon that is unexplained by the unequal crossover model is that in real life, expansion occurs much more often than contraction. One study demonstrated that 52.1% of parent-child transmissions of HD result in expansion, compared to only 18% for contraction. Say the unequal crossing over happens in the father's body: According to the model and our discussion of homologous chromosomes, his child should have a 50% chance of being made from a sperm with chromosome 4A and a 50% chance of being made from a sperm with chromosome 4B. If one of these chromosomes has an expanded Huntington allele and the other has a contracted Huntington allele, then the chances of expansion and contraction should be 50/50, like calling heads or tails with a coin. The same argument can be made for a mother and her eggs. With a 50/50 prediction and 52.1/18 results, the model clearly is not a perfect fit for what actually occurs to cause expansion in HD. This certainly does not mean that the model plays no role in expansion; it simply suggests that, if the model does play a role, there are also others players involved.

Another model, polymerase slippage (also known as "DNA slippage"), is the one that is receiving the highest amount of attention with regard to HD mutation research. We discuss this model next.

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Part 5

What it means to have a mutation and what role mutations play in Huntington's disease.

The Polymerase Slippage Model

Most cells reproduce by a process called [mitosis](#), in which a cell copies (or [replicates](#)) its DNA and then splits into two identical [daughter cells](#), each containing a complete copy of the original DNA. If a cell divided during mitosis without undergoing DNA replication first, the two daughter cells would each have a serious deficiency of DNA. This deficiency of essential information would have catastrophic results for the organism involved. Thus, DNA replication is essential not only for creating identical cells, but also for the organism as a whole. [DNA polymerase](#) (we will call this just "polymerase" for short) is the enzyme that replicates the DNA. Working with other compounds, it takes each of the two initial strands in the double helix and uses it as a template for creating a new strand. The polymerase elongates this new strand by attaching new nitrogenous bases to the template bases. For instance, if the template strand has an adenine (A), polymerase attaches its partner, a thymine (T); if the template strand has a guanine (G), polymerase attaches a cytosine (C). This matching of corresponding bases occurs on both of the initial strands in the double helix, with the result that polymerase pairs each initial strand with a new strand. While polymerase is working, another enzyme, [helicase](#), unwinds the initial double helix, thus releasing the initial strands from each other's grasp. As the initial strands are paired with their respective new strands, what began as one double helix ends up as two identical double helices.

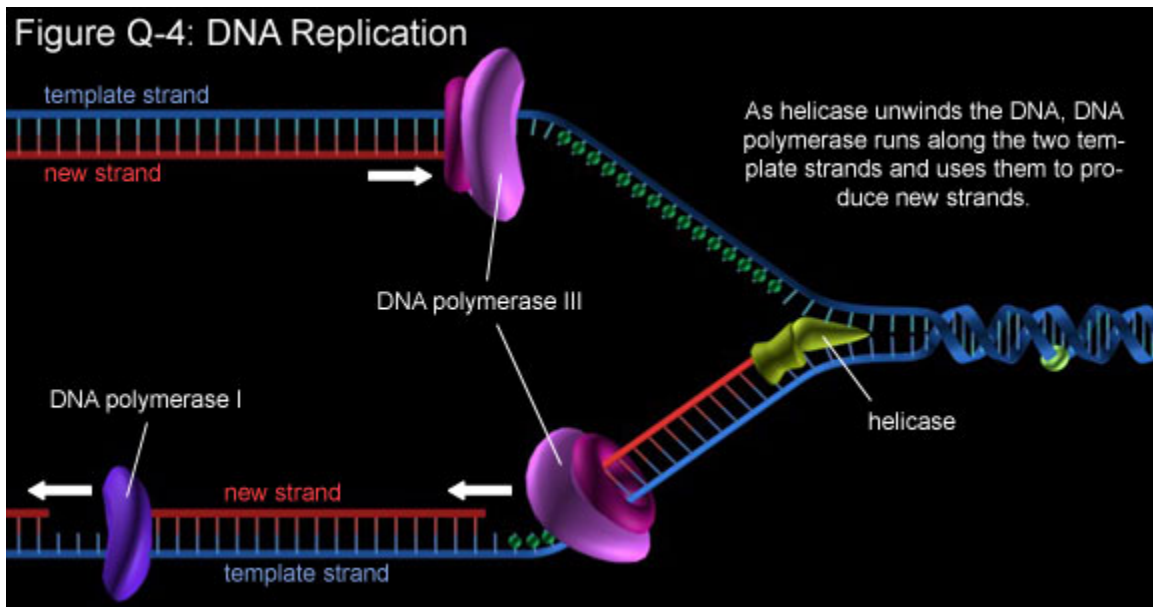
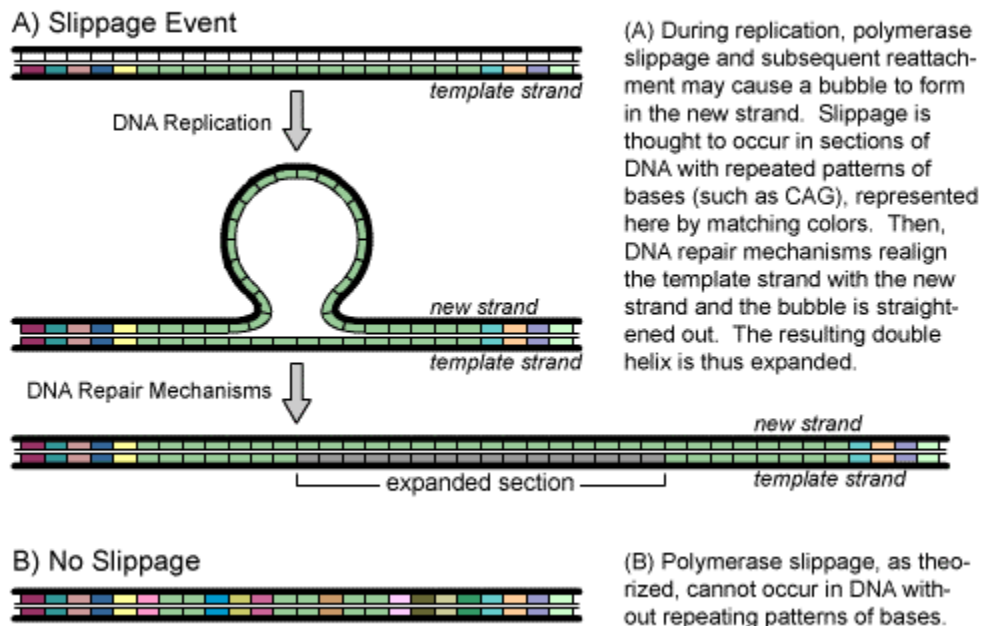


Figure Q-5: The Polymerase Slippage Model



Sometimes the polymerase slips from the template strand during replication. It is this event, called [polymerase slippage](#), that many researchers believe holds the key to codon [expansions](#). According to the [polymerase slippage model](#), if the polymerase slips, it causes the new strand to unpair (release) from the template strand. If the slip occurs at the template's codon [repeat region](#) of the [Huntington gene](#), then when the new strand tries to reattach to the template strand, it will have many identical copies of the codon to choose from. With so many identical codon copies to reattach to, the new strand may reattach to the template at the wrong copy, usually one more distant than the copy that was adjacent to the polymerase before it slipped. As a result of this misplacement, the new strand forms a bubble of unpaired bases, which represents the expansion of the new strand. Once DNA replication is complete, an unknown mechanism allows the template strand to realign with the new strand and bring the bases from the bubble back into line with the template strand. The bases are then paired with their corresponding partner bases (cytosine (C) to guanine (G); adenine (A) to thymine (T)). In the end, the brand new double helix of DNA contains more CAGs in the repeat region of the Huntington gene than existed before. Polymerase slippage has caused expansion.

Like the [unequal crossing over model](#), the polymerase slippage model also has its flaws. One criticism rests on the fact that, of all the codons in DNA, very few of them have been known to expand in human disease. According to the polymerase slippage model, the codon GGA should be just as likely to expand as CAG. However, in reality, we see no evidence of GGA expanding and the model cannot explain why. Another criticism of the polymerase slippage model is its inability to explain why some expansions are quite large. Small codon expansions (say, less than 5 copies of CAG) require little energy and are easily accounted for by the slippage model. However, many of the expansions that researchers see are quite large, sometimes in the hundreds of repeats. Slippage as the

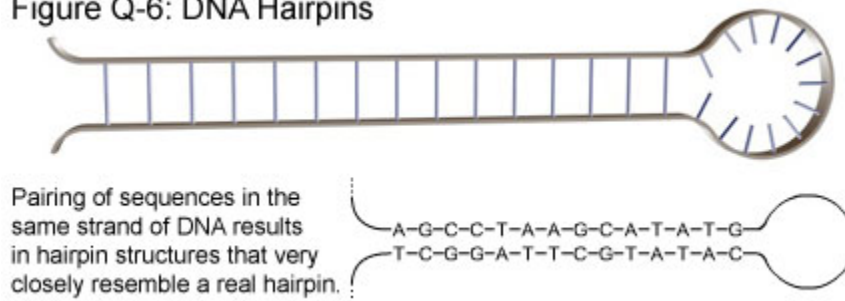
cause of these large expansions would be energetically unfavorable. This simply means that for the DNA, the energy costs of long-range slippage far outweigh the energy benefits. Since nature always seeks the "easiest route," an inefficient mechanism like this should either not occur, or it should continue with the aid of other events that make it more energetically efficient. In the case of polymerase slippage, most researchers believe that the latter is true: Polymerase slippage does play a role in codon expansion but it requires something else to make it happen. That something else appears to be what researchers call hairpins, which we will discuss next.

All About Mutations Part 6

What it means to have a mutation and what role mutations play in Huntington's disease.

What is a hairpin and how does it affect mutations?

Figure Q-6: DNA Hairpins



When a single strand of DNA curls back on itself to become [self-complementary](#), the result is a partial double helix with a bend in it. The structure is called a [hairpin](#), and as you can see from Figure Q-6, it looks just like one.

Hairpins may be the missing piece in the mutation puzzle. The reason researchers are so intrigued by hairpins is that they only form in the codon [repeat regions](#) of diseases in which [expansion](#) is seen (HD, of course, is one of these diseases). This specificity suggests that hairpins play a role in expansion. The big question is exactly how they do this. While many explanations have been put forth, the most popular one seems to be that hairpins aid in polymerase slippage.

Below we discuss a proposed model:

- [The Hairpin-Mediated Polymerase Slippage Model](#)

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What it means to have a mutation and what role mutations play in Huntington's disease.

The Hairpin-Mediated Polymerase Slippage Model

As mentioned in [Part 5](#), the polymerase slippage model by itself could not explain why some [expansions](#) in HD are so large (sometimes in the hundreds of codon repeats); slippage this long-range is energetically unfavorable. However, hairpins are helpful in the polymerase slippage model because they produce [hydrogen bonds](#) that would not otherwise be present, and these bonds help compensate for the energy lost due to long-range slippage. As a result, hairpins have the unique ability to minimize the energy difference between the normal double helix and the double helix where slippage has occurred. The [hairpin-mediated polymerase slippage model](#) is energy efficient and it thus provides an effective answer to the main criticism of the regular polymerase slippage model. Although the hairpin-mediated model is very enticing, more research is necessary to clearly determine just how big of a role hairpin-mediated polymerase slippage actually plays in expansion.

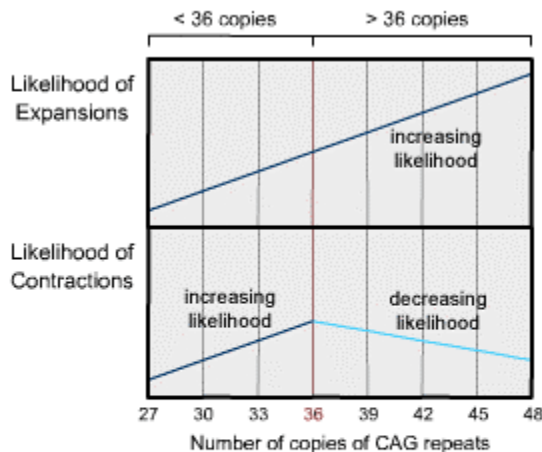
All About Mutations

Part 8

What it means to have a mutation and what role mutations play in Huntington's disease.

HD has repeat expansions, but shouldn't repeat contractions occur as well?

Figure Q-7: Likelihood of CAG Expansion



As the number of CAGs increases from 0 to 36, there is an increasingly high frequency of both expansions and contractions. Beyond the threshold of 36, expansions continue to be more frequent with increasing number of repeats; however, contractions actually become less frequent.

It seems that for every one thing in life, there always exists an opposite: For black there is white, for truth there are lies, and for rain there is sun. It makes perfect sense, then, to assume that [expansions](#) in HD should also have an opposite, [contractions](#). While contractions do in fact occur, they are less common than one might expect. As discussed in [Part 4](#), one real-life study of HD showed that 52.1% of parent-child transmissions result in expansion, compared to only 18% for contraction. The big discrepancy between the two phenomena may be explained by the number of CAGs in the repeating region of the parent's [Huntington gene](#): A study of a large group of adults with 36 or fewer CAG repeats in the Huntington gene showed that both expansions and contractions became more frequent with increasing numbers of CAGs. For example, an individual with 35 CAGs had a higher chance of causing an expansion or a contraction than an individual with 30 CAGs. However, beyond 36 CAGs, while expansions continued to be more frequent with an increasing number of repeats, contractions became less frequent. For instance, while the DNA of someone with 70 CAGs is more likely to undergo an expansion than the DNA of someone with 40 CAGs, the DNA of the person with 70 CAGs is actually less likely to undergo a contraction than the DNA of a person with 40. These data suggest that parents with more than 36 CAGs may help account for the higher number of expansions than contractions in the real-life data.

It is unclear why exactly there appears to be a barrier for contraction at 36 CAGs. It is interesting to note, however, that 36 is also the number of CAGs that places a person at the bottom of the intermediate range for risk of HD (If a person has between 36 and 40 copies of CAG, he may or may not develop HD. See [Table A-1](#).) Of the people without HD, those in the intermediate range (with 36 to 40 CAGs) are more likely to have children with expansions than are people who have fewer than 36 CAGs.

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Part 9

What it means to have a mutation and what role mutations play in Huntington's disease.

Why is it that the longer a parent's CAG repeat region is, the higher the likelihood of expansion?

In order to know the exact answer to this question, we must know the exact mechanism of [expansion](#). Since researchers are not yet completely sure what this mechanism (or combination of mechanisms) is, we can only hypothesize from the probable mechanisms why more CAGs correspond to a greater likelihood of expansion. The most probable mechanism for expansion, the [hairpin-mediated polymerase slippage model](#), offers two explanations for why longer CAG [repeat regions](#) correspond to a greater likelihood of expansion. First, the longer the CAG repeat region is, the more slippage sites there are. Thus, more CAGs mean an increased chance of slippage and therefore an increased chance of expansion (if indeed this model is the true one). Second, the longer the repeat region, the larger, more stable, and more probable hairpin formation becomes. Since hairpins help stabilize the energy change in the DNA that is caused by slippage, larger, more stable, and more probable hairpin formation may lead to a greater likelihood of slippage and thus a greater likelihood of expansion. However, it should again be emphasized that, although this model is a popular theory, it has not been proven as the exact mechanism of expansion. Thus, although it explains the relationship well, this does not mean that it is necessarily the 100% true answer to the question.

As for the unequal crossing over model, it does not appear to offer any reasonable answer to the question.

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Part 10

What it means to have a mutation and what role mutations play in Huntington's disease.

Is expansion more likely to come from the mother or the father?

A variety of studies have produced overwhelming evidence suggesting that expanded CAG [repeat regions](#) in the [Huntington gene](#) originate in the father more often than in the

mother. The strongest evidence seems to come from studies of juvenile HD. Typically in HD, the longer the CAG repeat region in the Huntington gene, the earlier the person will start to experience the symptoms of the disease. For example, a person with 90 copies of CAG will likely start to experience the symptoms of HD earlier than a person with only 50 copies. If the person has enough CAGs, he or she may have [juvenile HD](#) and experience symptoms as early as childhood. (For a more in-depth discussion of juvenile HD, click [here](#).) What the studies have found is that fatherly (paternal) transmission of juvenile HD is much more common than motherly (maternal) transmission. In many cases, if the juvenile HD arose from an [expansion](#), researchers are able to prove that this expansion originated in the father. Thus, since juvenile HD often results from very long expansions and seems to arise more frequently from fatherly transmission, the studies provide sound evidence that expansion comes from the father. For more information on the inheritance of HD, click [here](#).

Another research group performed a very interesting study on mice with HD. The study looked at the CAG repeat size in sons and daughters of the same father mouse. What the study found was that the sons predominately had an expanded number of CAGs (compared to the father), while the daughters had a contracted number (fewer CAGs than the father). These results are quite intriguing because, for the first time, they appear to imply that the gender of the baby has an effect on expansion. Because of this, the researchers suggested that, although the HD allele is known to reside on chromosome 4, there may also be X chromosome or Y chromosome factors at work in determining expansion. They also suggested that this gender dependence in the baby may explain why expansion occurs through the fatherly line. While this study is quite interesting, it must be noted that not only is it very new research, but it was also performed using mice, not humans. Thus, while it may present wonderful new breakthroughs, we cannot be sure of this until more research is done, especially research on humans.

All About Mutations

Part 11

What it means to have a mutation and what role mutations play in Huntington's disease.

There are many safeguards against mutation. Why don't these safeguards stop the codon expansion before it becomes harmful?

DNA interacts with many compounds that act as safeguards to repair any mutations that may occur. However, sometimes the safeguards miss the mutation, allowing it to elicit a change in the organism involved. Hundreds of millions of years ago, the safeguards missed the mutations that allowed the first animals to have lungs that could breathe air. These mutations allowed life to emerge from the sea and onto land. The safeguards also missed the mutations that allowed the first humans to stand upright, as well as the

mutations that allowed people to develop the tools necessary for speech. These amazing feats would never have been achieved if the mutations would have been repaired by the safeguards. But the safeguards can also miss mutations that can have harmful results. For instance, it appears that in people with HD, the expansion mutation in the Huntington gene is not repaired by the safeguards.

One of these safeguards is called [MSH2](#). MSH2 is what is known as a [mismatch repair enzyme](#): it guards against bases matching up with incorrect partners (for instance, it stops adenine (A) from pairing with cytosine (C) or guanine (G)). In addition, MSH2 also repairs unpaired regions of DNA (such as bubbles resulting from [polymerase slippage](#)) and it stops [hairpins](#) from forming. Researchers believe that the problem with MSH2 in regards to HD is either that MSH2 itself becomes altered or the compounds that are essential to its effectiveness become altered. Either way, MSH2 cannot perform its normal duties and thus it cannot properly safeguard against expansion. The only problem with this model is that MSH2 only seems to be involved in stopping small-scale (usually less than 5 copies of CAG) expansion. It seems, then, that other proteins are involved in avoiding large-scale expansion. Like MSH2, if they become altered or are in some way unable to perform their normal duties, then the safeguard breaks down and expansion occurs.

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Part 12

What it means to have a mutation and what role mutations play in Huntington's disease.

What role do environmental substances play in expansion?

Substances in the environment that cause mutations are called [mutagens](#). Cancer causing agents (called [carcinogens](#)) are often harmful because they are either mutagens themselves or are turned into mutagens in the body. However, as of this writing (January 2002), research on Huntington's disease has shown that, unlike the case in many cancers, mutagens do not appear to play a role in HD.

However, it does deserve to be noted that very rarely, HD "appears" in a person whose family had no history of the disease. Although these cases of HD might seem to imply that environmental substances (and not genes) are at work, this is probably not true. Instead, there is a more likely explanation: a person who has a [non-HD allele](#) with a borderline number of repeats (typically between 36 and 39 copies of CAG) may produce a sperm or egg cell that contains a slightly expanded [allele](#). Sometimes, these few extra copies of CAG may be just enough to cause the child inheriting the allele to have an abnormal [codon repeat](#) number (40 CAGs or above). One researcher speculated that about 10% of HD cases are caused by such changes in repeat number. Thus, although

environmental substances might appear to cause these rare cases of HD, small [expansions](#) of already borderline alleles provide the more likely explanation.

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Part 13

What it means to have a mutation and what role mutations play in Huntington's disease.

Another Theory...

It was mentioned in [Part 3](#) that most researchers believe that [expansion](#) occurs during [mitosis](#) instead of [meiosis](#). However, a very recent study suggests that expansion does not occur in either of these settings. The study found that instead, expansion occurs in sperm while they reside in the male [epididymis](#), which is where the sperm undergo their final maturation. Thus, instead of during mitosis or meiosis, the researchers believe that expansions occur in the final maturation of sperm. However, this is very new research and it will take many more studies before the research community is convinced that sperm maturation, rather than mitosis, is when expansion occurs.

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What it means to have a mutation and what role mutations play in Huntington's disease.

A Final Note

The discussions of the previous questions have included many citations of very intriguing research. Some of the studies produced results that are contradictory to others. Still more studies are so cutting-edge that they lack the test of time to see if in fact their results are substantiated. Though they shed light on so many different aspects of HD, the common thread in each of the studies is that they have shown how incredibly devoted researchers are to getting to the bottom of this disease. Hopefully, this devotion and the world of ingenuity in the research community will continue to allow the development of better and better treatments for HD. One day, they may even find the cure.

-M. Stenerson, 1-31-02

For further reading:

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