**Is gene silencing aiming to be a cure for HD?**

HDYO has more information about HD available for young people, parents and professionals on our site:

www.hdyo.org

**Q. I have been following the HD ‘gene silencing’ or ‘lowering’ clinical trials this year but does this represent a genuine ‘cure’ or does it, at best, represent a delay - if its the latter how many years would it delay the onset of HD?**

Ashok, Young Adult, UK

**A. Dear Ashok,**

Thanks for this very important question. I will attempt to answer it comprehensively. I hope you find my explanation useful.

At the present time, there are no known treatments that modify disease progression by in some way preserving either vulnerable neurones or brain function (they may not be the same thing). That is, all we can do at present is imperfectly relieve symptoms for some time.

As a single gene disorder HD should potentially be amenable to treatments that ‘modify disease progression’. I prefer this term to cure. From my point of view, cure in the context of HD would imply permanently excising or inactivating the expanded gene rather than suppressing the gene or preventing downstream effects of the abnormal gene with ongoing treatment that might be for the life of the person.

If you look at the possible range of disease modifying treatment options, they might include any of the following:

1. preventing neuronal loss & brain damage for an individual’s entire life (i.e. they die of old age without ever getting HD). I guess this might be considered to equal a cure.
2. delaying symptomatic disease onset for many years (for example delaying the age of onset to old age rather than in early adulthood)
3. not delaying or preventing disease onset but either slowing down the rate of disease progression or preventing specific symptoms such as dementia from appearing

None of these possibilities is necessarily mutually incompatible. Perhaps we might get a variety of different treatments acting in different ways in a complimentary fashion. A cocktail rather than a single drink if you like.

Silencing or blocking the expanded gene, for example with anti-sense mRNA, is a very attractive option as the mutant gene is the ultimate HD bad guy. It seems to be intuitively obvious that blocking the bad gene without knocking out the good normal gene offers the best hope for patients. The animal gene silencing trials are very exciting & the fact that a preliminary trial in humans is about to start is very hopeful, but there might also be other therapeutic options in the future.

One of the striking features of HD is that the size of the expanded gene (i.e. the size of the gene fault) doesn’t fully explain the variability in the age of onset of HD or why HD affects different people differently. This implies that there must be other factors that influence how the HD gene behaves. There is substantial evidence that other genes which interact with the HD gene might influence the age of onset at least. These ‘genetic modifiers’ are being studied very intensively at present. Another therapeutic option might be to exploit these genetic modifiers in some way to modulate or reduce brain damage in HD.

It might also be that lifestyle (environmental) factors such as how much alcohol a person drinks could also influence how the HD gene causes brain damage, but we know little about these at present.

Blocking or eliminating the toxic protein that is made from the abnormal HD gene is another potential treatment modality.

To summarise, there might be a variety of ways which we can ultimately protect the brain of someone with the HD gene.

Lastly, I want to briefly outline why we need to do drug trials in humans.

The metabolism of mice or other experimental animals with the human HD gene might be very different from
that of humans. For that reason we need to do trials in people as we can’t assume that a drug that works in
one species works in us. This makes it impossible to say in advance how effective this gene silencing agent
or any future treatment will be in humans. To put it another way, until we do human trials it is impossible to
be certain if that treatment will either prevent the disease from appearing or, if it delays symptom onset by
how much.

We also might find that there will only be a useful therapeutic effect if people with the HD gene get a cocktail
of treatments rather than a single treatment alone.

For these reasons, members of the HD community might find that over the next few years:

1. there will be many trials (good)
2. that some hopeful treatments in animals don't live up to their early promise (bad)
3. that it will be a few more years before the full potential of gene silencing and other treatments is
   understood & successfully exploited (frustrating)
4. that the combination of high quality laboratory science and well designed drug trials hopefully leads to
effective disease modifying treatments that allow people with the HD gene to lead long happy &
healthy lives (the ultimate goal),

Andrew

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