We are not alone, and are seeing more RED

Scientists have found more people have the genetic changes that underlie repeat expansion diseases, like HD, than previously thought. This new data tells doctors to consider expansion diseases more when diagnosing people with neurological symptoms.

By Dr Ray Truant | **November 18, 2024** | **Edited by Dr Rachel Harding**

A recent study published in Nature Medicine, looked at how common certain genetic diseases are within the population. The diseases they looked at are referred to as repeat expansion diseases and include Huntington's disease (HD). The researchers found that the genetic traits which underlie these diseases are more common than previously calculated. In this article, we will get into what the scientists found, and what this will mean for the HD community and beyond.

What are REDs?

HD is caused by an expansion of a repeating stretch of -C-A-G- DNA letters in the huntingtin gene. Everyone has these repeating CAGs but if you have too many, then you will develop HD if you live long enough.

DNA from over 82,000 people was randomly sampled from diverse populations worldwide. The entires genomes of each person were sequenced, mapping the precise letter code of every chromosome.

HD is not the only kind of disease caused by this type of genetic change. In fact, there is a whole family of genetic disorders referred to as Repeat Expansion Disorders, or REDs. These include diseases like spinocerebellar ataxias, some forms of ALS/Lou Gerhig's disease, Fragile X disease, Friedreich's ataxia, Myotonic Dystrophy, spinal bulbar muscular atrophy, and others.

Calculating how many people are affected by REDs

A long-standing issue in human genetics and the study of diseases like HD, is that most of our human data is limited to DNA samples from White populations in the west. This can lead to an inaccurate idea of how many people are affected by HD and can have real-world implications for how non-White people with HD can access healthcare and other resources.

We also only tend to genetically test folks who are symptomatic already or who we know to be at risk. This means if someone doesn't have a textbook series of symptoms, they might not have a genetic test and it's possible that their doctor might misdiagnose them.

These incidence numbers are also important when HD advocates and patient organisations appeal to governments worldwide to provide support for research and care for HD. Collectively, REDs tend to be referred to as rare, but with the limited data we have had to date, do we know this to be true?

Big data to answer big questions

A large group of researchers, anchored in University College London (UCL) in the UK, with Dr. Arianna Tucci, looked at a massive dataset of the entire genetic makeup of people to see how common REDs really are. This study used DNA from over 82,000 people randomly sampled from diverse populations worldwide. In these samples, a person's entire DNA was sequenced, not just one or two genes.

Armed with this huge set of genetic data, they asked a series of simple questions: looking across many regions and ethnicities without any bias for any disease, do we continue to see these REDs are mostly in White populations? Are these diseases that mostly affect Europeans and people of European ancestry?

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The answers from this study were profound in two aspects. First, REDs were seen in similar incidence across Europeans, Africans, Americans, East and South Asians. This challenges the status quo that REDs are primarily found in European populations, an assertion based on more limited historical datasets. In fact, they are represented in all broad populations.

The second surprise from this data was that the incidence of REDs was much higher than predicted in the past! The data show new incidence numbers of 1 in 283 for all REDs combined. From a different perspective, this means over 1.2 million people's DNA contain the genetic traits corresponding to REDs just in the USA. For HD alone, the incidence was seen at 1 in 4100, but with a variance from 1 in 2700 to 1 in 6300. Older statistics had this number around 1 in 10,000.

This finding tallies with some of the research talks we covered from theCHDI therapeutics meeting earlier this year. Sahar Gelfman from the Regeneron Genetics Center presented data from a study where they had looked at the HD gene from nearly a million peoples DNA. Although their samples did not include many people from outside Europe and North America, they did see that the genetic trait for HD was found in ~1 in 2000 people.

Comparing genetic data to what is

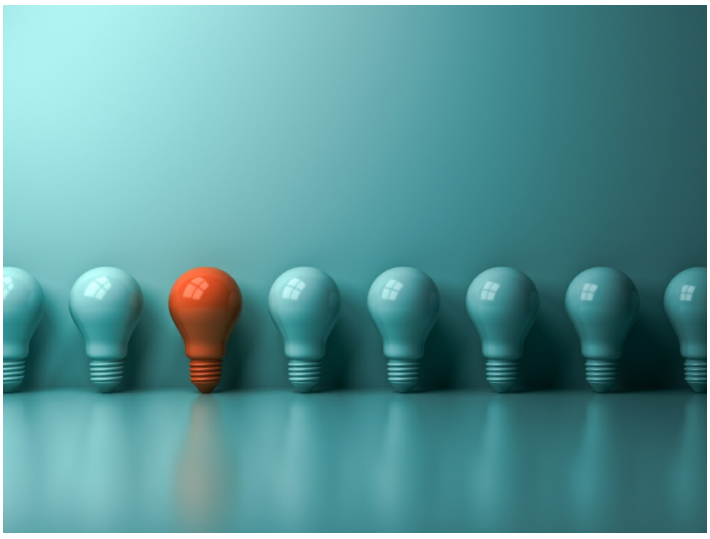
happening in the clinic

But does this mean that 1 in 283 people have these genetic diseases? Maybe not. The frequency of these genetic expansions does not match up with the number of people diagnosed by doctors to have REDs.

There could be two reasons for this. Firstly, many people may not yet have been properly diagnosed with a RED, or may be misdiagnosed with a different disease. Given how rare some of these diseases are thought to be, some non-specialist clinicians may have a hard time pin-pointing a diagnosis, especially if the presentation of symptoms is a little bit unusual or does not follow the textbook definition.

A second and more hopeful reason is that despite having a repeat expansion mutation in a known disease gene, some people will have very mild, limited, or no symptoms of these diseases. This is referred to in human genetics as reduced penetrance. This could be because of lifestyle factors or other genetic differences between people which can cause the disease onset to be delayed or progression of symptoms to be slowed down.

This has been an intense area of focus in HD research withGenome Wide Association Studies (GWAS). The hope is that we could design drugs to mimic the genetic traits which might cause someone to have disease later in life or a slower progression of symptoms. Now that we know even more people might have the HD gene but might not get sick as quickly, or at all, scientists could expand GWAS to include these folks, and maybe find new ideas for developing medicines.



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Take home messages

From this study, the message to doctors worldwide is that REDs are a lot more common than they were taught in their training in the past. This will hopefully empower them to test for these disorders with specific genetic tests when symptoms overlap with more common

diseases.

Often, diagnosing someone with a neurological disorder can be like solving a mystery, as symptoms can look and change differently in different people, symptoms between common and less common diseases can overlap, and family history is often not known. This may lead a doctor to test for certain common diseases, but not recognize a less common disease because they don't experience it often in their careers.

The study also gives us an idea of what the HD mutations look like in different ethnicities – this is important information to potentially tune therapeutics designed to specifically lower the expanded copy of huntingtin so that they're more effective in a broader range of people worldwide.

For example, the huntingtin lowering drug WVE003 from Wave Life Sciences currently in clinical trials, targets a genetic signature in the HD gene so that only the expanded toxic form of the HD protein is lowered. Current data suggests that the genetic signature they are targeting is found more commonly in people of European ancestry. Greater knowledge of the type of signatures found in different populations would help companies like Wave design drugs which might treat a more diverse pool of patients.

Importantly, this work will also be a message to governments and health agencies to rethink the term "rare" when it comes to these genetic diseases. Greater awareness of these diseases by policy makers and other stakeholders could help give communities, like ours, more resources and support to help affected families, provide appropriate healthcare, and develop new medicines.

The authors have no conflicts to declare. For more information about our disclosure policy see our FAQ...

GLOSSARY

therapeutics treatments

genome the name given to all the genes that contain the complete instructions for making a person or other organism