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Searching for Grendel: origin and global spread of the C9ORF72 repeat expansion

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Abstract

Recent advances are uncovering more and more of the genetic architecture underlying amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative condition that affects ~6,000 Americans annually. Chief among these was the discovery that a large repeat expansion in the C9ORF72 gene is responsible for an unprecedented portion of familial and sporadic ALS cases. Much has been published on how this expansion disrupts neuronal homeostasis and how gene-based therapy might be an effective treatment in the future. Nevertheless, it is instructive to look back at the origins of this important mutation. In this opinion piece, we attempt to answer three key questions concerning C9ORF72. First, how many times did the expansion occur throughout human history? Second, how old is the expansion? And finally and perhaps most importantly, how did the expansion spread throughout Europe? We speculate that the expansion occurred only once in the past, that this event took place in the Finnish population and that the Vikings and their descendants were responsible for disseminating this mutation throughout the rest of the continent.

Introduction

Amyotrophic lateral sclerosis (ALS) has long been considered a mysterious disease. However, in recent years, advances in our understanding of the genetic architecture of this disorder have led to new insights into ALS. The discovery of each new disease-associated gene represents a milestone in ALS research, as it provides a unique view into the cellular processes that underlie motor neuron degeneration. In addition, genetic discoveries have allowed for the development of animal and in vitro models, and provided targets for the development and testing of rational therapies for this devastating neurodegenerative condition. Thus far, the genes responsible for two-thirds of familial ALS and approximately 10 % of the more common sporadic form of disease have been discovered [30].

Chief among the genetic advances was the recent discovery of a pathogenic repeat expansion at the start of the gene C9ORF72 [7, 31]. In carriers of this mutation, neurodegeneration is the result of a six base pair segment of DNA on the short arm of chromosome 9 that is repeated up to several thousand times. Several groups have since replicated this finding [4, 9, 11, 33] and it has generated tremendous excitement in the ALS research community for several reasons. First, the C9ORF72 repeat expansion is the most common cause of ALS identified to date, accounting for approximately 40 % of all familial cases of ALS in European and North American populations. Second, this mutation underlies about 8 % of sporadic ALS in the same populations [21]. Although a genetic etiology had long been postulated for sporadic ALS, this represented the first time that a genetic cause had been identified in a substantial percentage of individuals with this more common form of disease. Third, the C9ORF72 repeat expansion is an equally common cause of Frontotemporal Lobar Degeneration (FTLD), thereby effectively merging these two clinically disparate neurodegenerative syndromes. There were longstanding clinical, epidemiological and pathological data to suggest that ALS and FTLD formed a continuum of disease, but this was the first time that a single mutation had been found in a large percentage in both diseases.

Finally, and perhaps most importantly, the repeat expansion nature of the mutation means that it might be amenable to gene therapy designed to halt disease progression. Even though the C9ORF72 expansion was only described 2 years ago, there is already speculation that antisense oligonucleotide therapy targeting the repeat may be effective in reversing the effects of the underlying mutation [8]. If such a therapy did work, it would mean an effective treatment for one in ten ALS patients and would represent an excellent example of the power of personalized medicine.

The odyssey that led to the discovery of the pathogenic mutation has been documented elsewhere [37]. But genomic data can also help us delve deeper into the C9ORF72 locus. For example, what is the origin of the C9ORF72 repeat expansion and how it might have spread across the globe?

How many times did the repeat expansion occur?

A key question to ask about the C9ORF72 mutation is whether the repeat expansion occurred on a single occasion in human history with subsequent spread throughout the population or whether the locus itself is inherently prone to expansion, allowing these events to occur again and again. Other repeat expansion diseases show that both mechanisms exist. For example, the repeat expansion in the AR gene that causes Kennedy's disease is known to have occurred spontaneously on many occasions [20]. In contrast, the strong linkage disequilibrium surrounding the intronic repeat expansion responsible for myotonic dystrophy type 1 suggests that the expansion event occurred only once or twice in the past [13, 18, 24].

So what is the evidence for the origins of the C9ORF72 repeat? The obvious first step might be to compare the length of the repeat expansion across populations in hopes of observing sub-groups among carriers. However, the repeat length is highly variable from carrier to

carrier and even between different tissues of the same individual [1], so this property of the expansion does not provide useful information on its origins.

In the search for the origin of the repeat, then the next evidence to turn toward is the original disease-associated haplotype. The Finnish population, which was used in the original genome-wide association study (GWAS) that identified the C9ORF72 locus, is ideal for a genomic study of ALS for two reasons. First, the conserved nature of the population decreases allelic and genetic heterogeneity, thereby making it easier to find genes, and second, Finland has one of the highest incidence rates of ALS in the world [5, 23]. The original GWAS capitalized on these aspects of the Finnish population and identified a strong association signal in the 9p21 region. Examining the data more closely, all of the patients contributing to this signal were found to also carry a 232-kb haplotype that greatly increased the risk of developing ALS [19]. Dense genotyping of SNPs in this region allowed for the identification of this risk haplotype and narrowed the search for the causal mutation to just a small area of the genome. This was an essential step toward the identification of underlying mutation and highlights the important contributions that GWAS have made to our understanding of ALS genetics [32, 37].

Once the underlying mutation was identified in 2011, the question was whether non-Finnish patients carrying the repeat expansion also carried the Finnish risk haplotype. Surprisingly, every single patient who carried this repeat expansion carried the haplotype to a greater or lesser extent [21]. Subsequent data from other investigators have largely confirmed that there is a single haplotype associated with the expansion [14, 15, 17, 25, 29, 33, 38]. Notably, this association between the expansion and the risk haplotype holds across the globe including in the Chinese and Japanese ALS populations.

The one dissenting publication from Beck et al. [1] suggests that multiple haplotypes exist across the locus. However, these conclusions are based on microsatellite data, which are known to be much less stable over several generations compared to SNPs [26]. More importantly, the short tandem repeat markers analyzed in that publication are much further away from C9ORF72 (10 markers over 13.1 Mb surrounding the gene) than the original Finnish risk haplotype, and as such, provide little or no information about the C9ORF72 locus. Thus, the bulk of current data points to a single risk haplotype existing across the repeat expansion locus.

That is not the end of the story, however. Even if there is a single haplotype, it remains possible that the haplotype is “permissive”. In other words, some intrinsic aspect of the Finnish risk haplotype might have allowed recurrent repeat expansion events to occur at several time points in human history. The SCA8 locus provides the best example of this particular genetic mechanism [12]. In the case of C9ORF72, epidemiology and knowledge of European history provide additional clues to unraveling the origins of the locus.

How old is the C9ORF72 repeat expansion?

Genetic data can provide an estimate of the age of the mutation within a given population. Assuming that this was a single event that occurred in Finland, genome-wide genotype data from Finland can be used to estimate how long ago this occurred. The statistical calculations

surrounding this are complex and depend somewhat on an arbitrary selection of variables that can push estimates to be older or younger, but in essence the methodology involves analyzing the haplotype structure surrounding the C9ORF72 gene. This analysis shows that the C9ORF72 repeat expansion first appeared in the Finnish population ~100 generations ago with an interquartile range of 58–128 generations [21]. The word “appeared” is important in this context as it allows for the possibility that the repeat expansion arose somewhere else and then was “transported” into the Finnish population 100 generations ago.

A different study that used the same statistical methodology (albeit with slightly different starting population parameters) generated older estimates [lower estimate was 157 generations (95 % CI 134–196) and an upper estimate was 479 generations (95 % CI 419–550)] using samples drawn from the Swedish, United Kingdom and Italian populations [33]. Assessments of mutation age tend to be imprecise owing to the necessity of making assumptions about population parameters in the model. Nevertheless, it is reassuring that the estimates based on different genomic datasets are not completely dissimilar. If a generation equates to 15 years, then the mutation occurred around 500 A.D., which is roughly the same time as the fall of Rome (410 A.D.) and at the beginning of Viking invasions of Europe.

How did C9ORF72 spread around Europe?

If the expansion really did occur on one occasion in Scandinavia about 1,500 years ago, how did it end up elsewhere in Europe? One theory is that the C9ORF72 expansion was spread across Europe during the time of the Viking conquests [22]. It should be recognized that this is a speculative interpretation of the data and that it will be nigh on impossible to conclusively prove or disprove this “Viking horde” theory. Nevertheless, the geographical distribution of C9ORF72 and the Viking conquests are strikingly similar (Fig. 1).

Prior to discovery of the repeat expansion, there appeared to be a North–South gradient in the Finnish risk haplotype in Europe. However, other groups have failed to detect a gradient (apart from the obviously higher rate of C9ORF72 in Scandinavia) [38]. In light of new data that has become available since the finding of the underlying mutation, it is opportune to revisit and extend this theory as to how the expansion might have spread. The key to understanding the current distribution of C9ORF72 in Europe lies in the fact that the Vikings were a seafaring people who primarily confined their military activities to the coastline (with the occasional foraging parties sailing up major rivers). There is firm historical evidence that they traveled as far as the Mediterranean Sea and established settlements on several islands in that region; in this context, it is interesting to note that a high rate of C9ORF72 has been observed on Sardinia [2, 21]. Furthermore, the direct descendants of the Vikings, the Normans, were active in the First Crusades, which may explain the occurrence of C9ORF72 expansions in the modern day Israeli population [21].

The geographical distribution of C9ORF72 within Europe provides additional support for the “single event” theory concerning the genesis of the expansion. If the expansion arose on several occasions during human history, multiple areas of high disease frequency around the world would be expected. Indeed, there is a group of more than 30 monogenic diseases that are common in Finland and a single founder has been identified for most of them [16, 27].

This ‘so-called’ Finnish genetic heritage provides a clear template for the ‘Out of Finland’ C9ORF72 expansion hypothesis.

In the centuries since the Vikings roamed Europe, increasing globalization has ensured the repeat expansion’s continued spread to more distant populations, which explains the presence of the Finnish haplotype in East Asian carriers of the mutation.

Why did the C9ORF72 expansion spread so far?

An ancillary question to ask concerning the C9ORF72 repeat expansion is how did the expansion spread so far and become so frequent in the general population, especially if the mutation causes a rapidly fatal neurological disease? The most parsimonious answer is that the C9ORF72 mutation is associated with reduced penetrance. Reduced penetrance is not unique to C9ORF72 and, by definition, is a feature of any late-onset disease. While the mechanism of this reduced penetrance is unknown, it is a source of ongoing research.

Patients seldom develop overt symptoms before 40 years of age meaning that the mutation does not typically manifest at a time that would interfere with reproduction of an individual carrier. The net result is that the C9ORF72 repeat expansion had the opportunity to spread without coming under pressure from natural selection. Genetic drift (driven by purely random events) has also clearly played a role in the high frequency of C9ORF72 in Finland and Sardinia, just as in any other relatively frequent mutation.

But there may be more to the story than simply reduced penetrance. Much of the success of Vikings as a conquering nation can be attributed to their bellicose nature. Similarly, the religious fervor of the Normans was a driving force in rallying support for the Crusades. It is interesting to speculate then, that the behavioral disinhibition and lack of social empathy associated with FTLN caused by the C9ORF72 expansion may have contributed to the war-like characteristics of some of the Vikings and their descendants. Perhaps, repeat expansion carriers were the most uninhibited in their enthusiasm for conquest. It is also interesting to note that psychosis is a central feature of the FTLN symptoms associated with C9ORF72 in both FTLN [35] and in ALS [34].

Other FTLN mutations provide anecdotal, though credible, support for the hypothesis that possession of the expansion and its predisposing clinical phenotype may have contributed to the pressures to leave local environs, and establish new communities in distant and less populated regions of the world. For example, the +16 exon 10 splice mutation of MAPT is a common cause of FTLN in the UK population, but is also seen in the British colonies of Virginia, British Columbia and Australia [28]. Again history may provide us with clues. This mutation is believed to have arisen in North Wales, a geographically isolated region of the United Kingdom, at least 500 years ago [3]. The mutation is still common in North Wales, but is also widely prevalent within the Northwest region of England, within the major conurbations of Manchester and Liverpool. During the Industrial Revolution, many individuals migrated from the country to urban areas in search of work. In this context, we could speculate that individuals showing personality or behavioral changes commensurate with FTLN might have been stigmatized and shunned by local communities, prompting

migration to cities where work was possible, and personality and behavioral issues might be more tolerated.

The United Kingdom also deported religious objectors and criminals to America in large numbers before 1776 [6], and transported criminals to Australia during the late 1700s and early 1800s (Deportation. December 11, 2013 In Wikipedia Retrieved December 28, 2013, from <http://en.wikipedia.org/wiki/Deportation>). Such forced emigration was more likely to fall on those appearing in front of the courts due to behavioral/unsocial/criminal behavior, thereby facilitating the spread of the mutation geographically. There are likely parallels with other FTLT associated mutations such as p.Pro301Leu, which is the most common MAPT mutation in France and Belgium (Flanders), and is prevalent in French-, but not English-speaking parts of Canada [36].

Lastly and more recent, peaceful, ‘Viking migrations’ to North America have resulted in C9ORF72 expansions being more prevalent within the Midwest region of the United States than elsewhere [10]. Again, the need to make a new start in life away from native lands could have prompted this second wave of spread of the C9ORF72 expansion.

Where do we go from here?

It is amazing how much data has been published on C9ORF72 in the two short years since its discovery. In many ways, this reflects the transformative advances in technology that have accelerated the pace of genetic discovery, allowing us to move beyond the (deeply flawed) candidate gene approach into the era of genomics. These genome-wide data can be pieced together to act as a primitive time machine to look back at how the C9ORF72 mutation may have arisen and then spread throughout the globe. But it can also be used to turn the tide of this mutation’s spread. Knowledge of the repeat expansion’s origins may help to reclassify diagnosed “sporadic” carriers as part of a large C9ORF72 family. In addition, understanding the disease-associated haplotype may be important in developing genetic treatments for the disease. Beyond this, much still remains to be learned about this important neurodegenerative locus. Newer technologies that allow for long range single molecule reads will enable sequencing across the entire repeat. Such a transformative technology would more accurately measure expansion size and identify interruptions in the repeat sequence, either of which might influence phenotype of the patient.

The C9ORF72 repeat expansion has likely had a tumultuous history that led to its spread across the globe. But hopefully its story will continue by aiding in the identification of the cellular mechanisms of motor neuron degeneration, and by leading to the first effective treatment for ALS. In that case, as Beowulf said to Grendel in the halls of Heorot, “your bloodletting days are finished, demon”.

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Figure 1.

The left panel shows the extent of Viking expeditions across Europe, the Atlantic and the Mediterranean from the eighth to eleventh centuries (Image retrieved from <http://en.wikipedia.org/wiki/File:Vikings-Voyages.png>). The right panel shows modern day distribution of the C9ORF72 repeat expansion across Europe (based on data published in reference 21)