Estimates of C9orf72 Statistics drawn from prior publications including estimated life expectancy for genetic carriers, estimated incidence of C9orf72 ALS and FTD, Estimated genetic carrier and at risk populations and others

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1)Introduction:

The discovery in 2011 of the *C9orf72* repeat expansion clarified the genetic cause of a significant subset of familial and seemingly sporadic Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) cases. Following the discovery, numerous studies have looked into *C9orf72*, the prevalence of repeat expansion in ALS and FTD cases, and the impact on carriers.

As a carrier myself, I realized there were significant issues that concerned me regarding *C9orf72,* which most treated as a mystery, including how many people carry the expansion? What is the impact on mortality when one has the expansion? How many people can be said to be experiencing the ALS or FTD disease process before diagnosis? Upon reflection, it became clear that by data-mining previously reported results, we could arrive at rough estimates for many of these missing data points. Here, I will describe my calculations, their outcome, and the potential implications for drug development, treatment, support, and related issues arising from these results.

2)Calculations

Total Incident *C9orf72* ALS and FTD Cases

Incidence of ALS and FTD: 1.7 per 100k for ALS[3], 2.9 per 100k for FTD[8]
Multiplied by
Prevalence of *C9orf72* Carriers in ALS and FTD[2]: 11% of ALS (7% Sporadic, 4% Familial) and 16% FTD (6% Sporadic, 10% Familial)

Total Population Of Presymptomatic Carriers

Investigations into the incidence and prevalence of rare diseases are often looked to as informative for future and past trends. Suppose we assume that roughly the same number of Incident *C9orf72* ALS and FTD cases develop each year. In that case, if we multiply that Incident finding by the disease's average age of onset, we will arrive at a rough estimate of the total population of carriers who will manifest disease in the future alive today.

Incidence of C9orf72 ALS and FTD
Multiplied by
Average age of Onset of C9orf72 ALS[5] and FTD[4] (58)

Total Population of non-manifesting *C9orf72* carriers.

There is a broad assumption that *C9orf72* is not fully penetrant, with the only calculations done to date to ascertain that rate proposing 90% penetrance (Murphy et al.). If this estimation is accurate, we can assume that, for each year's worth of Incident *C9orf72* ALS and FTD cases, there are 10% of that cohort that will never manifest. We can then extrapolate a rough estimate of the total living C9orf72 carriers who will not manifest disease before death by multiplying the 10% of yearly incidence by the average age of death.

Incidence of C9orf72 ALS and FTD
Multiplied by Estimation of Non-Penetrance (10%) [5]
Multiplied by Average age of Death for all people (77)

Total Population of *C9orf72* Carriers living with an ALS or FTD Diagnosis

By taking the incident number for *C9orf72* ALS cases and *C9orf72* FTD Cases and multiplying each by the estimated disease length for a *C9orf72* Carrier with that disease, and adding them together, we can estimate the total population of *C9orf72* Carriers living with an ALS or FTD diagnosis.

Incidence of C9orf72 ALS And FTD
Multiplied by their respective C9orf72 disease length
(3 Years C9 ALS[1], 7 Years C9 FTD [4])

Total Population of C9orf72 Carriers and those at risk.

Adding the estimates of the pre-manifest, non-manifesting, and currently diagnosed populations we can arrive at an estimate of the total population of C9orf72 Carriers. As predictive genetic testing is not standard, it is only practical to consider the population of those at risk of harboring the *C9orf72* expansion. For that, we can take the estimate of the entire population of carriers and multiply by 2 to capture the average of 50% of *C9orf72* carrier offspring that do not inherit the mutation.

Presymptomatic Population Estimate
+
Non-Manifesting Population Estimate
+
Diagnosed with ALS or FTD Population Estimate

X 2
At Risk Population

Number of *C9orf72* Carriers Experiencing Pre-Manifest Disease

Two studies from the Genetic FTD studies ALLFTD and Genfi have estimated the length of pre-diagnosis disease activity in *C9orf72* carriers. The first proposed 15 years, while the most recently published proposed 40 years, with a marked shift in excess neurodegeneration three years before diagnosis.

Incidence of C9orf72 ALS and FTD Cases
Multiplied by
Estimation of Pre-Diagnosis Disease Activity Length

Average Lifespan of *C9orf72* Carriers

Since we know the estimates for the average age of onset and the average disease length for *C9orf72* ALS and FTD [4,5], we can arrive at the life expectancy for *C9orf72* Carriers with those diseases. Additionally, as we have an estimation for the carriers who will not develop the disease, we can estimate their lifespan as the average lifespan. The next question is how to balance the three to arrive at a lifespan estimate for all carriers? It is often assumed it is an even split[8] and provide a 45% weight to the *C9orf72* ALS lifespan, a 45% weight to the *C9orf72* FTD Lifespan, and a 10% weight to the non-penetrant carriers. Combining these will arrive at an average lifespan for all carriers.

Weighted Average Assuming Equal Distribution of ALS and FTD
45% C9 ALS Life Expectancy
45% C9 FTD Life Expectancy
10% Non Manifesting C9 Carrier Life Expectancy

However, the widely assumed even distribution between ALS and FTD in *C9orf72* is not corroborated when looking at the annual Incidence of *C9orf72* ALS and *C9orf72* FTD. Due mainly to a much higher calculated rate of incidence for FTD, the number of Incident *C9orf72* FTD cases is nearly double the estimated *C9orf72* ALS incident cases. While it is highly likely that the incidence of ALS we rely on is too low and the incidence estimate for FTD is too high, this data cannot be ignored. To account for this, we can re-weight the life expectancy calculation using that distribution (25.84% for ALS and 64.16% for FTD) for the 90% of penetrant cases keeping the 10% non-penetrant cases.

Weighted Average using our Incidence Finding
25.84% C9 ALS Life Expectancy
64.16% C9 FTD Life Expectancy
10% Non Manifesting C9 Carrier Life Expectancy

3) Results

Prevalence Of C9orf72 Carriers in the US

Incidence of C9 ALS and FTD: 0.187 per 100k for ALS and 0.464 for FTD, totaling 0.651 Per 100k
0.651 per 100k in the US, with a population of 332,400,000, is 2163 people diagnosed with C9orf72 ALS or FTD each year.

Premanifest ALS and FTD Population: 125,454

Non Penetrant C9orf72 Population: 16, 632

C9orf72 Carriers living with an ALS or FTD Diagnosis:
1863 C9orf72 Carriers living with an ALS diagnosis
10,794 C9orf72 carriers living with an FTD Diagnosis
Combined C9orf72 Carriers living with an ALS or FTD Diagnosis = 12657

Premanifest, Non-Penetrant, and C9orf72 Carriers living with an ALS or FTD Diagnosis combined equals 154,743 total C9orf72 carriers in the US or 46.55 per 100k. The At-Risk Population is estimated at 309,486 or 93.1 per 100k.

Average LIfespan For C9orf72 Carriers

Assuming an Equal Distribution between FTD and ALS:
45% of carriers who will be diagnosed with ALS will live on average 61 years - Age of Onset (58) + average disease length (3 years) = 61
45% of Carriers who will be diagnosed with FTD will live on average 65 years - Age of Onset (58) + average disease length (7 years) = 65
10% of Carriers who will not manifest ALS or FTD and will live on average 77 years - The average life expectancy for all in the US is 77.

Doing a weighted average of 45% 61, 45% 65 and 10% 77 equals 64.4

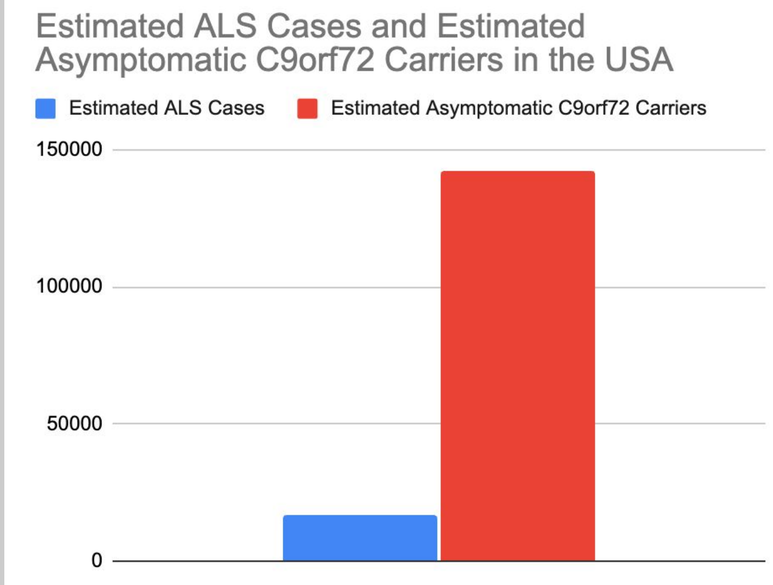
Assuming the greater incidence of C9 FTD is correct:
25.84% of carriers who will be diagnosed with ALS will live, on average, 61 Years
64.16% of carriers who will be diagnosed with FTD will live, on average, 65 Years
10% of Carriers who will not manifest ALS or FTD will live on average 77 years.
Doing a weighted average of 25.84% 61, 64.16% 65 and 10% 77 equals 65.16.

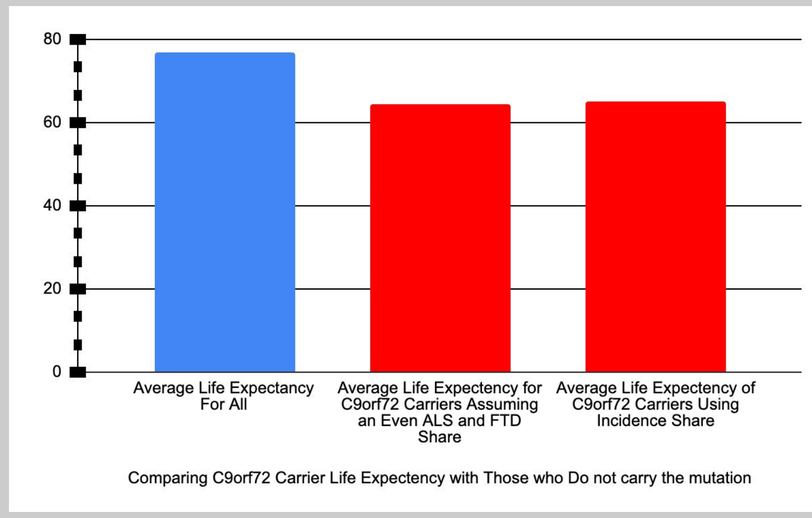
A C9orf72 Carrier's Life Expectancy is estimated at 64.4 if there is an equal distribution between ALS and FTD cases and 65.16 if the distribution is 25.84% ALS and 64.16% FTD.

The population of C9orf72 Carriers Experiencing Pre-Manifest Disease

Incidence of ALS and FTD (2163) multiplied by pre-symptomatic disease length (40 years broadest, 15 years medium, three years most acute) = 86,520 at 40 years pre-manifest disease activity length, 32,445 at 15 years, and 6,489 at three years.

The population of C9orf72 Carriers experiencing pre-manifest disease is 86,520 if it is 40 years, 32,445 if it is 15 years, and 6,489 if it is three years.





4) Discussion

The population of *C9orf72* carriers in the US is large. As most individuals at risk of genetic ALS do not pursue predictive testing, it is only practical to consider the full population of those at risk for the gene, which is even larger. This is the same size or larger than the population in the US that carry the expansion repeat responsible for Huntington's disease or are at risk for it.

When considering possible drugs for the treatment or curing of ALS or FTD, we must consider that the population of those who have a compelling reason to be administered treatment or cure includes the full pre-symptomatic population. Looking just at *C9orf72*, this more than quadruples the number of people with an ALS diagnosis today. Suppose we are to be more conservative and only provide a treatment or cure after the disease process has begun. In that case, we can see that it is still a very large population of between 86,520 at a most expansive definition and 6,489 at a conservative definition. Keeping this in mind has implications for the market; and increases the strategies available for drug development and intervention and multiple stages of the diseases.

Knowing one is at risk of ALS and FTD and is likely to have a much-shortened lifespan is a hard position to be in. We must consider what resources are available to this pool of people. Through hard work and compassion, we can see that the Huntington's Disease Community has amassed many resources for those at risk, led perhaps most ambitiously by the Huntington's Disease Youth Organization. Those of us at risk of genetic ALS and FTD do not have anything so well organized. But we have started to address this with the Familial ALS Team at I AM ALS. However, as we build these support systems, the clinical and impacted communities must work together closely.

Sometimes people attempt to downplay the situation of a *C9orf72* carrier regarding reduced mortality. They lean on the fact it is likely not fully penetrant. We can see in the life expectancy that, even factoring in a reduced penetrance, any *C9orf72* carrier will live, on average, 12.6 - 11.84 years less than an unaffected person. That rises to 14.39 to 13.63 less for a female C9orf72 carrier. These are meaningful differences, so it would be prudent and reasonable for a *C9orf72* carrier to embrace any possible attempt to prevent the worst of the disease.

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