The life expectancy of Stephen Hawking, according to the ENCALS model

Stephen W Hawking, one of the most famous physicists, died on March 14, 2018, at the age of 76 years. Although he was best known for his remarkable work on black holes and quantum gravity, he was also a famous patient with amyotrophic lateral sclerosis (ALS). His long survival (of more than 50 years) after diagnosis has been a source of speculation. Through our population-based registries for amyotrophic lateral sclerosis, we have followed more than 11,000 patients with amyotrophic lateral sclerosis over the past 20 years. Our data show that amyotrophic lateral sclerosis is a heterogeneous disease and survival can be exceptionally long in some cases. We have examined Professor Hawking’s clinical phenotype using our recently validated predictive model of survival (the ENCALS survival model), which is based on eight predictors. The model was designed to generate survival probabilities on the basis of a composite endpoint, which we defined as death, tracheostomy, or dependency on non-invasive ventilation for at least 23 h a day. Using publicly available data, we examined whether Professor Hawking’s survival was as rare as his intellectual performance, or if it could have been predicted solely on the basis of his disease characteristics at diagnosis in 1963.

We found that he had a 10-year survival probability of 94% at disease onset. The interquartile range for his predicted survival lay between 1981 and 2011 (figure). By mid-1985, which is within this interval, the endpoint was reached because he had a tracheostomy. Then, the model predicts that he had a 20% probability of surviving, to the time of his death some 33 years later. According to the ENCALS survival model, Professor Hawking’s young age of onset was the most important factor for his long survival. However, more than half of his disease duration (ie, after tracheostomy) can be attributed to the benefits of the combined use of invasive ventilation and intensive supportive care.

The model predictions are in stark contrast to the life expectancy of 2 years that was given to him after his diagnosis in 1963, which would be the median disease duration for people with ALS at that time. Although estimation of exact survival times remains difficult, our data show that prediction models can be useful in the provision of realistic information for patients and in selecting individualised care paths.

Professor Hawking was an exceptional man, whose prolonged survival was consistent with current knowledge of disease progression, showing that, as he said, “one need not lose hope”. A-C reports other financial relationships with Mitsubishi-Tanabe Pharma, Chronos Therapeutics, Orion Pharma, Cytokinetics Inc, and Treeway, outside the submitted work. OH reports personal fees from Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration journal and grants from Science Foundation Ireland outside the submitted work. LHvdB reports grants from ALS Foundation Netherlands, The Netherlands Organization for Health Research and Development (Vici scheme, SOPHIA, STRENGTH, ALS-Care project; the latter three of which are funded through the EU Joint Programme-Neurodegenerative Disease Research), and personal fees from Shire, Biogen, Cytokinetics, and Treeway, outside the submitted work. H-JW and TPAD declare no competing interests.

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Top research priorities for stroke genetics

Cerebrovascular diseases are the leading cause of adult disability worldwide and a major contributor to dementia.1 The collaborative efforts of the International Stroke Genetics Consortium (ISGC) enabled the combination of multiple independent studies, leading to the identification of genetic associations underpinning cerebrovascular disease. A large meta-analysis2 gathering data from the vast majority of genome-wide association studies has been completed. Through parallel, collaborative genome-wide association studies, additional loci have been identified that are associated with risk of intracerebral haemorrhage,3 less common but well characterised causes of stroke such as cervical artery dissection4 and intracranial aneurysm,5 and MRI-defined changes, specifically white matter hyperintensity burden.4 Efforts are also underway to unravel the genetic underpinnings of other MRI markers caused by presumed vascular brain injury, and of acute and long-term stroke recovery.

On behalf of the ISGC, we present the research priorities for stroke genetics that we have identified using the Delphi method.6 Augmenting this process, we used the James Lind Alliance Approach, which includes four stages: gathering research uncertainties, checking existing research evidence, interim prioritisation to identify the priorities of relevant individuals or stakeholders, and final consensus to reach agreement.7

To implement the process, the ISGC first held discussions at a workshop in Hamilton (Ontario, Canada) in November, 2015. From this initial feedback, an anonymous open-ended survey was developed to request topics for research priorities. The ISGC includes a wide variety of professionals from different disciplines, including neurology, neurosurgery, cardiology, epidemiology, statistical genetics, genetic epidemiology, and molecular biology. These open-ended research priorities obtained from the survey were then organised into topical categories, which were reviewed by the working group (the authors). For example, we categorised suggestions on phenotyping, lacunar stroke, and intracranial hemorrhage as deep phenotyping. These larger categories were then reviewed for existing research evidence by experts in the working group and subsequently presented at a workshop held in Milan (Italy) in November, 2016, for interim prioritisation. The final list of research priorities was then reached by consensus of the working group and after final approval by the ISGC General Assembly on November 3, 2017, in Utrecht, Netherlands.

Through the course of the effort, 6 pical areas were suggested, which were then combined by common themes or overlapping topics. Our priority list (panel) is ranked according to the number of topics that were proposed.

Our top priority will now be to focus on implementing cohorts of sufficient sample size to genetically characterise stroke subtypes. The identification of novel associations in a race or ethnic group might have benefits for all groups. As an example, the identification of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a drug target for cholesterol lowering was based on the data obtained from African Americans with an uncharacteristically low low-density lipoprotein.8 The translation of the genetic findings into therapeutics naturally follows the identification of these novel risk associations. A priority of drawing the available resources already collected, both data and tissue samples, into a readily accessible central library might greatly facilitate the number and types of analyses that can be done with greater statistical power. The Cerebrovascular Disease Knowledge Portal has been developed to this end. However, further resources are needed to address the limitations of the Portal, and to improve quality control and statistical tools.

A recent publication of the ISGC describes an effort to evaluate genetic associations with improved stroke outcomes, as assessed by the modified Rankin scale approximately 3 months after stroke onset.9 A crucial priority is to combine biosample collection with detailed outcome assessment, including functional, motor, behaviourual, and cognitive outcomes. A wide variety of outcome measures are available in the literature, and careful selection to maximise their utility and feasibility will be needed.

The application of novel techniques might also require large-scale sample collection. Most genetic research has been done on DNA obtained from blood, but there is a marked paucity of samples stored with an RNAse inhibitor, which would be a requirement for techniques investigating the transcriptome. Similarly, storage of plasma for evaluation of metabolites and the manner in which samples are collected might not permit reliable proteomic or metabolomics research, unless such collection is carefully pre-planned and coordinated with...