An unchanging man faced with changing times

John Kurtzke’s dedication to the study of multiple sclerosis has not waned since the early 1950s. Neurologists are indebted to him for establishing the universally known eponymous Disability Status Scale which, since its introduction in 1955, has allowed patients with multiple sclerosis to be ranked according to impairment and disability (Kurtzke, 1955). The scale has well-identified limitations and has undergone refinement by creation of the ‘expanded’ scale (Kurzke, 1983), which was unwillingly endorsed by its author: ‘Personally, I would change my system only, perhaps, by returning to the DSS vice the EDSS. We have more steps, but I really wonder if the gain is worth [it]…’ (Kurtzke, 1989). In clinical metrics, more subtleties often result in less accuracy, precision and reproducibility. The scale has been exposed to an unceasing fire of repeated attacks during the Holy Grail-like search for an ideal clinical scale for multiple sclerosis (Amato et al., 1988; Willoughby and Paty, 1988). However, despite multiple assaults, the (Expanded) Disability Status Scale still stands alone, entrenched in the clinical consciousness of every specialist. And it is likely to remain so.

Providing further understanding of multiple sclerosis, John Kurtzke has previously studied two cohorts of the US army veterans, some of whom developed multiple sclerosis. The World War II/Korean Conflict cohort included 527 males with multiple sclerosis in army service at some point between 1942 and 1951. These studies led to the publication of many papers thoroughly and comprehensively describing the natural history of multiple sclerosis (Nagler et al., 1966; Kurtzke et al., 1977). By categorizing the veterans with multiple sclerosis by place of birth and location at service entry, the study demonstrated a north–south gradient in incidence of the disease and showed that the latitude-related risk of developing multiple sclerosis is set during infancy (Beebe et al., 1967). The so-called Vietnam and later cohort consisted of 4951 veterans who first entered military service between 1960 and 1994, and were ‘service-connected’ for multiple sclerosis (Wallin et al., 2012). With morbidity of white males as a reference population, the relative risk of multiple sclerosis was lower in black males (0.7) and significantly higher for females (3.0) regardless of race. This represented a significant increase compared with the World War II/Korean Conflict cohort, in which the relative risks for black males and white females were 0.4 and 1.8, respectively. The authors also noticed that the risk for natives of the northern United States was higher than for those from southern states, but this geographical differential had decreased by comparison with prior series. They concluded, ‘…such marked changes in geography, sex, and race in such a short interval strongly imply a primary environmental factor in the cause or precipitation of multiple sclerosis’ (Wallin et al., 2004).

In the present issue of Brain, Mitchell Wallin, with John Kurtzke and colleagues, present the first analysis of their third US army veteran nation-wide incident cohort, assembled from veterans who served between 1990 and 2007, during what they call the Gulf War era (Wallin et al., 2012). This Gulf War cohort represents 2691 patients with multiple sclerosis (66% males). Median age at onset is 30 years and not significantly different by race or sex. Average annual age-specific incidence rate per 100 000 is 9.6 for the entire cohort. It is 9.3 for Whites, significantly higher for Blacks (12.1) and non-significantly lower for Hispanics (8.2). It is significantly higher for females (24.7) compared with males (7.3), regardless of race. Lastly, incidence rates are similar in members of the Air Force (10.9), Army (10.6) and Navy (9.1), lower in the Coast Guard (7.9) and even more so in the Marines (5.3), a difference possibly driven (in my opinion) by the under-representation of females in these corps. As for the relative risk of multiple sclerosis, it is 3.5 for females compared with males in the entire cohort, with similar results whatever the race, and 1.2 for Blacks compared with Whites.

As do the previous cohorts, the Gulf War group inevitably suffers from several limitations. Composed solely of military personnel, the cohort is not representative of the general population and offers an over-representation of males, blacks, young people and probably, those with low socio-economic status and relatively limited education. However, with 33% females, the numbers are quite sufficient to compare the sex-related risk of multiple sclerosis in this population. And this cohort also has outstanding strengths, being nation-wide with an excellent ascertainment of multiple sclerosis cases through the military compensation and pension system.

The results provided by this cohort are important per se: the annual incidence rate per 100 000 for multiple sclerosis in this population is currently high (9.6 in the entire cohort); the relative risk for multiple sclerosis is three times higher for females and increased for blacks compared with white people. But the results are even more impressive when seen in the context of the two prior cohorts, thus spanning more than 65 years of direct
observation. Using white males as the reference shows a significant and steady rise in the risk of multiple sclerosis among blacks and females. Indeed, compared with whites, the relative risk of multiple sclerosis for black men was 0.4 in the World War II/Korean conflict, 0.7 in the Vietnam and later cohort and 1.2 in the Gulf War veterans. In other words, from initially showing only half the risk, this is now slightly higher compared with that of white males. Similarly, in white females, the relative risk for developing multiple sclerosis was 1.8 in the World War II/Korean conflict, 3.0 in the Vietnam and later cohort and now 3.5 in the Gulf War veterans. Put another way, during the whole study period, the relative risk of developing multiple sclerosis has always been higher for females than for males, but exhibits striking temporal changes, as it doubles for white females, and even triples for black females.

These observed changes in the US veteran cohorts are outstandingly consistent with the three major temporal trends in the epidemiology of multiple sclerosis that have been observed over the last decades in other large series. First, the incidence of multiple sclerosis is increasing. This is likely to be so in the veterans’ series, considering the high annual age-specific incidence rates for multiple sclerosis observed in the Gulf War cohort, although not formally demonstrated since incidence rates are not available for the two prior cohorts. That said, such an increasing incidence in multiple sclerosis is obvious in many countries (Alonso and Hernán, 2008). Second, the female-to-male ratio as assessed at the time of the diagnosis is clearly increasing in the US veterans throughout the study period. A similar result was observed by year of birth over a 50-year period in a population of 27 074 Canadians with multiple sclerosis (Orton et al., 2006). This has also been observed by year of birth and date of disease onset in the Observatoire Français de la Sclérose en Plaques (OFSEP) cohort of over 35 000 persons with multiple sclerosis in France (C. Confavreux, manuscript in preparation). Third, the latitudinal gradient in the frequency of multiple sclerosis is decreasing, as shown by the comparison of the first two veteran cohorts. A similar conclusion has been drawn in France where near disappearance of the gradient has been noticed in a recent survey (Fromont et al., 2010). This has also been observed over a 50-year period in a population of 27 074 Canadians with multiple sclerosis (Orton et al., 2006).

The observed changes in these veteran cohorts are robust, wide-ranging and convincing. They provide clues to the identification of susceptibility factors in multiple sclerosis. Changes are major over a rather limited timescale that, in an otherwise relatively stable population, makes it hardly conceivable that they could result from anything other than changes in the environment, namely ‘westernization’ of the populations in the modern era. Untangling the problem is anything but simple. It is already known that several and probably many environmental factors play a role in the changing risk of multiple sclerosis. We have also to understand and explain how these environmental changes lead to variations in the incidence of multiple sclerosis, with a sex- and race-related differential effect. We may anticipate interplay between genetic risk and the environment. Lastly, we have to be aware of possible confounding factors. A nice illustration of that is provided by two recent nation-wide studies conducted in France with apparently contradictory results. Analysis of the regional prevalence of multiple sclerosis in 2003 in the farming population, which is affiliated to a specific health insurance system (4 098 477 affiliates), showed a marked geographical gradient with a 2-fold increase in prevalence from South–West to North–East (Vukusic et al., 2007). In contrast, a similar analysis in 2004 of the general population (farmers excluded), which is affiliated to the general system of public health insurance (52 359 912 affiliates), was unable to show any gradient (Fromont et al., 2010). The explanation could be that, in the first case, the population under study was rather old and, for professional and familial reasons, unlikely to change residence, contrasting, in the second case, with a much younger and geographically more mobile population. In this respect, it is significant to note that in the second study the only regions in which the prevalence of multiple sclerosis was found to be significantly lower than the national average were Ile de France and Côte d’Azur, where the cost of living is higher, whereas in all other French regions the incidence of multiple sclerosis was found to be comparable to the national average (Fromont et al., 2010). The ‘modern way of life’ is not only changing the risk of developing multiple sclerosis, it also clouds the issue for investigators.

Clearly, there is a long way to go before we can decipher the nature of the environmental changes that underlie the fluctuating epidemiology of multiple sclerosis. But Professor Kurtzke and his group must be applauded for collecting the facts with great precision. Times change; but Professor Kurtzke remains unfailingly productive and talent, all command admiration. So, from his many friends and admirers, hats off to Mr Kurtzke!

Christian Confavreux1,2
1 Université Claude Bernard Lyon 1, Hospices Civils de Lyon, Lyon, France
2 Hôpital Neurologique Pierre Wertheimer, Service de Neurologie, A59 boulevard Pinel, 69677 Bron, France

Correspondence to: Christian Confavreux
E-mail: christian.confavreux@chu-lyon.fr
doi:10.1093/brain/aws135

References

The advent of next-generation sequencing technologies available at an increasingly affordable price is revolutionizing the discovery and diagnosis of human disease genes. We are without doubt, witnessing the dawn of a new era of disease gene discovery that will radically impact the field of human genetics. Next-generation sequencing technologies are already having a significant impact on neurological disorders, with huge further potential for improved clinical service delivery.

In late 2010, *Brain* first published a paper (Wang et al., 2010) detailing the identification of a disease gene for spinocerebellar ataxia by sequencing the exomes of four affected family members. An exome comprises ~1% of the entire genome, encompassing all coding and coding-flanking regions, and is estimated to account for ~85% of all disease-causing mutations. Notably, Wang et al. (2010) demonstrated that when they allied linkage data with their exome sequencing results, exome data from only one affected individual were sufficient to find the mutation.

There have been further illustrations of the power of next-generation sequencing technologies in the past 2 years. Combining linkage and exome sequencing data was again effectively harnessed to identify mutations for familial amyotrophic lateral sclerosis (Johnson et al., 2010), a dominant form of limb girdle muscular dystrophy with a vacuolar pathology (Harms et al., 2012b), and paroxysmal kinesigenic dyskinesias (Wang et al., 2011). Homozygosity mapping in consanguineous families can also be partnered with exome sequencing for successful gene discovery, for example, for an autosomal recessive spinocerebellar ataxia (Doi et al., 2011), and also in the mammotrophic efforts of Najmabadi et al. (2011), who studied 136 consanguineous families leading to identification of 50 novel genes for intellectual disability or related neurological disorders. Targeted capture and next-generation sequencing of the transcriptome of a linkage region revealed the genetic cause of a dominant spinal muscular atrophy (Harms et al., 2012a), whereas sequencing of all X chromosome transcripts (Tsurusaki et al., 2011), or the entire mitochondrial genome (Kaufman et al., 2012), have also successfully been exploited. In the absence of multiple affected individuals from one family, small cohorts of unrelated patients diagnosed with the same disease have been studied together (Lee et al., 2012).

Reports such as these, and others using whole-genome sequencing [e.g. Lupski et al. (2010) to identify a Charcot–Marie–Tooth disease gene] are enticing examples of the ability of the application of next-generation sequencing to a small number of patients to find novel disease genes. Additionally, exome sequencing has indicated genetic association, such as rare CYP27B1 variants in multiple sclerosis (Ramagopalan et al., 2011).

This issue of *Brain* highlights the benefits of next-generation sequencing, in particular for large genes. Two teams apply exome sequencing, each to a cohort of three families with hereditary (cytoplasmic) myopathy with early respiratory failure (HMERF; Online Mendelian Inheritance in Man #603689; also known as hereditary inclusion body myopathy with early respiratory failure (Chinnery et al., 2001]). Ohlsson et al. (2012; page...) and Pfeffer et al. (2012; page...) identify the same disease-causing mutation g.274375T>C in exon 343 (p.C30071R) in the giant gene titin, TTN, as the cause of the disease. The p.C30071R amino acid substitution is at a highly conserved residue in a myosin-binding fibronectin-III domain of A-band titin. TTN codes for a protein >1 μm in length, which spans from the M-line to the Z-disc in the sarcomere, and its sheer massive size (363 exons; complementary DNA >100 kb) has been a serious impediment for screening using traditional methods. Mutations have previously been identified in TTN, including a p.R279W mutation in three families with HMERF (Lange et al., 2005), but the current studies are the first to exploit exome sequencing effectively to screen TTN for mutations. The current reports are vital examples of how next-generation sequencing can deal easily with the largest human gene and therefore potentially other large genes causing neuromuscular diseases (e.g. nebulin and the ryanodine receptor).

Ohlsson et al. (2012) sequenced 50 Mb captured exomes for two affected and two unaffected family members. Pfeffer et al. (2012) initially sequenced two exomes from affected individuals using a 38 Mb capture system, which gave poor coverage of TTN, so they subsequently sequenced a further exome from a different affected individual using a 62 Mb capture system. This sequenced 99.8% of the TTN coding region, at a minimum 10-fold coverage, and mean depth of 105-fold. After filtering and analytical steps revealed the TTN variant as a likely disease-causing candidate.