

GUEST EDITORIAL

Huntington's disease research and practice: reflections on the journey made and lessons learned

Knowledge about some of the rarer causes of dementia is now quite advanced (Lautenschlager and Martins, 2005), which can in turn inform other more common causes of dementia. Such is the case with the monogenic disorder of Huntington's disease (HD) when compared to, say, Alzheimer's disease (AD). HD is an autosomal dominant hereditary neurodegenerative disease, which involves the basal ganglia, its connections to the frontal lobe and related neural circuits. The onset of HD is typically in mid-life (but onset can range from childhood to old age), with motor, cognitive and neuropsychiatric symptoms. There is currently no cure for this devastating and inevitably fatal neurodegenerative disease, with current treatment approaches being solely symptomatic. The highest frequencies of HD are found in Europe and in those countries whose populations are of predominately European origin such as the USA and Australia (approximately 1 case per 10,000 people).

Research in HD has a long history of pioneering genetic breakthroughs, successful research collaborations, and effective and well thought-out person-centered service delivery and provision. This guest editorial discusses what we can learn from the HD journey, in the hopes of using this knowledge to guide the current and future clinical and research paths of the more prevalent types of neurodegenerative diseases, notably AD. Tackling the massive challenge of aging and dementia requires clinical and research partnerships and translational approaches, and the lessons learned from the HD journey can be valuable to illuminate other fields of dementia and the wider discipline of old age psychiatry.

A discussion about the issues raised in HD research and what we can glean from the long history of HD research is topical and timely given the current genetic testing revolution and also recent discussions regarding dementia classifications and pre-dementia AD stages and diagnosis (particularly because AD research is working towards characterizing the full spectrum of the illness from the earliest stages to confirmed dementia). Indeed, trends in the diagnosis of neurodegenerative diseases are moving towards earlier and earlier stages of disease. Mild cognitive

impairment (MCI) is now a well-used diagnosis of an intermediate stage, which involves cognitive problems greater than typical age-related changes. These changes do not yet show the pronounced decline of dementia, but they increase one's risk of developing dementia. As a result of increased public and professional interest in dementia over several decades, there are now more sensitive methods of detecting emergent cognitive impairment, which enable earlier diagnosis of MCI, AD and other forms of dementia (Almeida *et al.*, 2005). Additionally, distinctive and reliable biomarkers of AD are now available through structural magnetic resonance imaging (MRI), molecular neuroimaging with positron emission tomography (PET), and cerebrospinal fluid analyses, and researchers are well on the way to localizing the exact genes for AD. Knowing the genetic basis of the disorders raises the potential for early diagnosis, even before individuals become symptomatic. These issues will create great challenges for clinicians, especially in the future when assessing high risk individuals at a non-dementia stage (e.g. MCI stage) who want to know about their risks but who also have to live with that knowledge. The issues are also especially contentious as there is no current therapy shown to halt or reverse the underlying disease processes of most neurodegenerative disorders and treatment is symptomatic only.

A brief history of HD

After the death of her folk musician husband, Woody Guthrie, in 1967, Marjorie Guthrie founded the Committee to Combat Huntington's Disease (now the Huntington's Disease Society of America). Around the same time, Milton Wexler (psychoanalyst) formed the Hereditary Disease Foundation in 1968 after his wife and all three of her brothers were diagnosed with HD. In the 1970s and 1980s, HD was not a burgeoning field, with very few researchers interested. However, in the late 1970s, several significant converging, concurrent events occurred. In October 1979, the Hereditary Disease Foundation held a workshop, organized by David Housman (molecular biologist), which focused on how to use DNA markers to find the HD gene. Workshop participants ambitiously proposed

to map the entire human genome and then look for a marker that segregated with the HD gene – a process that could take over 100 years to accomplish, given the technology current at that time. Then, the world's largest family with Huntington's disease was discovered living in a poor rural fishing village on the shores of Lake Maracaibo, Venezuela. The original progenitor of this family had lived in the early 1800s and left around 18,149 descendants spanning ten generations, 15,409 of whom were still living (Wexler *et al.*, 2004). Since 1979, the US-Venezuela Collaborative Research Project, a team comprised of committed international doctors and scientists, led by Nancy Wexler of Hereditary Disease Foundation (psychologist daughter of Milton), travelled each year to Lake Maracaibo, keeping medical records, taking biosamples, and creating detailed genograms of disease transmission within families. The samples collected were sent to James Gusella (geneticist) at Massachusetts General Hospital, who, in 1983, discovered a DNA marker close to the Huntington's gene. The gene was localized near the top of chromosome 4, using then unknown techniques of recombinant DNA technology (Gusella *et al.*, 1983). Even though this followed almost a decade of wearisome research purgatory of failed experiments, false leads, and red herrings, the speed of this discovery was still astounding to the research world. This was the very first time that a gene was located using DNA markers when its address on a chromosome was unknown. This discovery was groundbreaking and proved that these new scientific techniques could work for finding genes. In contrast, it was not until 1987 that the first deterministic gene associated with AD was identified on chromosome 21.

With the DNA marker now known, the Hereditary Disease Foundation organized the "Gene Hunters," also an international, collaborative group to identify the HD gene itself. It took fully a decade, but in 1993, the Huntington's Disease Collaborative Research Group, an international consortium of over a hundred investigators isolated the actual Huntington's disease gene. Huntington's disease was found to be caused by the Huntington gene on chromosome 4. Also called HTT, it is the IT15 ("interesting transcript 15") gene, which codes for a protein called huntingtin. The mutation is an expanded trinucleotide repeat: unaffected individuals usually have 11 to 29 CAG triplet repeats, whereas those who eventually become symptomatic for HD generally have abnormal expansions of 36 to 112 (or more) triplet repeats, which is translated into an abnormal stretch of polyglutamines in the protein. In comparison, the first risk factor gene for AD was identified in 1993 (the APOE ϵ 4 gene on chromosome 19), but still

does not determine that a person who has it will develop the disease.

Collaboration is key

The localization and discovery of the HD gene provides a powerful model for collaborative biomedical research. The discovery of the location and then the HD gene represents a (regrettably) rare case of sustained scientific cooperation in which six laboratories in the USA, England and Wales willingly and openly shared their data, discoveries and ideas. The collaborative nature of HD research continued even after the gene was found. The Hereditary Disease Foundation launched the Cure Huntington's Disease Initiative in 1997 to accelerate progress from research to therapy, with the aim of stimulating and coordinating research in academia and private industry. Then, in 1998, the Huntington's Disease Array Group was formed, comprising 50 investigators from eight laboratories in the USA and Canada. The Group uses microarray chips in animal models and in human tissue to search for genes "turned on or off" in HD, and their findings initiated a therapeutic drug trial in mice. Even now, Huntington's Study Group (HSG, established 1993), funded by the National Institutes of Health (NIH) in the USA is an active collaborative research group, made up of more than 500 active investigators in the USA, Canada, Europe, Australia, New Zealand and South America, with approximately 90 research centers. The HSG has entered partnerships with pharmaceutical companies, private foundations, the NIH and the Federal Drug Agency (FDA) Orphan Drug Products Division in developing and conducting trials. HSG studies include the longitudinal worldwide multicenter 13-year PREDICT-HD study, and encourages HD families to engender real hope through participation. Throughout Europe, the European HD Network (EHDN) provides a platform for professionals and people affected by HD and their relatives to facilitate working together, and also provides infrastructure for close cooperation of basic scientists and clinicians for large-scale clinical trials on HD, facilitating natural history studies and interventional trials.

In AD research there are also more newly emergent, active ongoing collaborative groups comprised of both clinicians and researchers (such as the Alzheimer's Disease Neuroimaging Initiative, ADNI, in the USA, beginning in October 2004, and the Australian Imaging, Biomarkers and Lifestyle Study of Ageing collaborative group AIBL in Australia, launched in November 2006). These

collaborative groups, and the wider discipline in general, can learn much from the collaborative and open research style of HD research, which overtly combines and shares worldwide knowledge, skills, and expertise. HD research has had generally open and honest communication, with little delay in the communication of results amongst multidisciplinary members, from bench scientists to clinicians, with involvement from scientists, doctors, social workers, geneticists, psychologists and occupational therapists. Too often researchers can be overprotective of their research methods and data, particularly in the competitive world of academia and research. However, the huge discoveries in the HD field could not have been made without the spirit of contributory sharing and membership. Particularly in this internet age, with the ease of rapid transmission of information, there is potential to collaborate easily and efficiently with worldwide colleagues.

Genetic breakthroughs

The *New York Times* called the HD gene the most “coveted treasure in molecular biology.” During the ten-year search for the gene, 14 new technologies were discovered and used in subsequent investigations to find other disease genes, including mapping genes for many of the neurodegenerative disorders. The genetic bases of many of the neurodegenerative disorders are now better known, including the rarer autosomal dominant inherited early onset familial form of AD, which is associated with mutations of the presenilin 1, presenilin 2, and amyloid precursor protein (APP genes) (Sherrington *et al.*, 1995). Parkinson's disease also has a substantial genetic component, with alpha synuclein (SNCA, also implicated in dementia with Lewy bodies), parkin (PARK1–8 and DJ-1), mutations in the PTEN Induced Kinase (PINK1) gene identified (Polymeropoulos *et al.*, 1997; Groen *et al.*, 2004). Even familial Creutzfeldt-Jakob Disease (CJD) has been associated with mutations in the PRNP gene on chromosome 20912-pter (Ladogana *et al.*, 2001), and recent work on the frontotemporal dementias (FTDs) has found the existence of at least three genetically distinct groups of inherited FTD: FTDP-17, FTD linked to chromosome 9, and FTD linked to chromosome 3, and tau on chromosome 17 (Yancopoulos *et al.*, 2003). Many of the techniques developed in finding the Huntingtin gene were also critical for the successful completion of the Human Genome Project – the massive international effort from 1990 to 2003 to map and identify the 20,000–25,000 genes in the human body. It is significant that

Francis Collins, a member of the collaborative HD group, presided over the Human Genome Project.

Genetic testing

HD provided the framework for genetic testing guidelines, counseling requirements and possible therapies for other genetic diseases that have the potential to be genetically tested. Progress toward a treatment or cure could be instrumental in finding ways to treat other illnesses with more complex genetics. However, the genetic breakthroughs and advances in HD have also resulted in several novel problems. Wexler (1985) asked the poignant and relevant question at the beginning of the DNA testing era: Would this new genetic knowledge be life enriching or destructive?

As the Huntingtin gene was one of the first disease genes to be found, its discovery resulted in several novel and contentious issues regarding genetic testing. Based on his study, Gusella introduced a test that was 96% accurate in detecting whether an individual bears the HD gene. For the first time, a simple blood test could assist people in planning their lives. However, this has also resulted in concerns regarding the consequences of having a predictive genetic test that could forecast future health status, particularly for an incurable disease.

In Australia, genetic testing is available for more than 400 different complex diseases including hereditary breast, stomach, and bowel cancer, heart disease, deep vein thrombosis, melanoma, diabetes, liver disease, kidney disease, cystic fibrosis, amyotrophic lateral sclerosis, various inherited neuropathies and several of the dementias. AD differs from HD in that it is probably a polygenic disorder with multifactorial etiologies, where having the mutation means increased risk, but not a certainty; by contrast, HD is a monogenic dominantly inherited disorder with complete penetrance. For AD, the gene APOE ϵ 4 on chromosome 19 is the gene linked to a greater risk of susceptibility for developing the more common late-onset AD. Although there is a blood test available that can identify which APOE ϵ 4 alleles a person has, it is not yet proved possible to predict who will or will not develop AD, as APOE ϵ 4 is only a risk factor and is neither necessary (people without APOE ϵ 4 can develop the disease) nor sufficient (not all people with APOE ϵ 4 develop AD).

The HD experience has taught that a genetic test result can have a profound and unanticipated impact on patients and their families. Testing can bring relief from uncertainty and more control over the future (Duisterhof *et al.*, 2001), and increased genetic testing can help in the development of

more effective (even curative) treatments, can help in early diagnosis, and gives people at risk the opportunity to take more responsibility and control over their lives, health, and future, including the implementation of preventive management options. Although one's core genetic makeup is predetermined, lifestyle modifications may help reduce the potential effects of having abnormal genes: which can include eating a healthy diet, exercising and staying mentally active.

Predictive testing raises many distinctive and contentious issues including the confidentiality of the genetic information, challenges regarding identity, responsibility, what it means to live with information that predicts future health status, and also the potential for stigmatization and genetic discrimination (particularly by employers and insurance companies). Other important issues involve patient rights, privacy, childbearing decisions, interpersonal relationships and the mental health of the recipient and family members. Genetic tests also reveal information to other family members, who may not want to know their risk. Genetic risk information may, additionally, lead to genetic determinism or fatalism, where patients believe that the genotype completely determines the phenotype, and that there is no way to avoid genetically predetermined outcomes, no matter what they do or what happens to them.

Genetic discrimination is the denial of rights, privileges, or opportunities or other adverse treatment based solely on genetic information (including family history). There has been much recent focus on the issues of genetic discrimination in the legal and healthcare literature and in the media. Unfortunately, empirical assessment and quantification of the perception and experience of genetic discrimination has not caught up, even in the domain of HD. The need for empirical evidence regarding genetic discrimination to inform policy and law has been identified in Australia (Australian Law Reform Commission, 2003). A study we conducted in Australia (together with the HSG; Goh *et al.*, 2010) revealed that many in the HD community had experienced adverse genetic discrimination, and there were reports of feeling pressured to reveal results in order to obtain life insurance, income protection, mortgage insurance, and some superannuation funds that include life insurance. There were concerns about insurers increasing premiums, denying coverage, or offering a shorter period of cover. Here in Australia, Australian *health* insurers cannot set premiums according to individual risk factors, but life insurance companies can, and often demand that a prospective customer release the results of a genetic test if they have had one, or the policy is deemed

null and void. Analyses also revealed a concerning lack of knowledge of legal rights and avenues regarding genetic discrimination. Fears of genetic discrimination lead many to shun genetic tests, even though some can be used to prevent some diseases (such as diabetes, heart attacks and some cancers).

Genetic tests are likely to become increasingly part of future routine health care, and these issues are especially timely given our current climate of genetic revolution. Consumer personalized genetic tests are now purchasable over the internet, but results are given without medical opinion or counseling support for high incidence disorders such as cancer (breast, prostate, colon, lung for example), heart disease, arthritis, psychiatric disorders and many more. Some consumer companies even claim to give the percentages of predisposition to avoid errors, being addicted to heroin, having a sweet tooth, and sensitivity to smelling body odor (see Docker, 2010, who reports on having his own DNA tested by US-based genetics company "23andme").

In his original description of the disease, George Huntington (1872) himself referred to HD as "that form of insanity that leads to suicide." As early as 1986, there was research into suicide and attempted suicide in HD, and the implications for preclinical testing of persons at risk. Of the 4,527 persons worldwide undergoing testing in the study by Almqvist and colleagues (1999), there were five completed suicides, 20 suicide attempts, and 18 psychiatric hospitalizations. In Victoria, over the past 18 years, genetic counseling has been mandated before predictive testing, which focuses on careful education about the test process, the disease, and the potential implications and test outcomes (both if the test returns positive and if it returns negative). All are given the option not to proceed with the test. As far as we know, there have been no known Australian suicides as a direct consequence of HD genetic testing. There is stringent regulation of laboratories, regulation of tests, regulation of genetic counselors, and assurance of patient safety – including that of privacy and emotional welfare. There are also strict US protocols for testing in HD which are compliant with the Huntington Disease Society of America's Guidelines for Genetic Testing for HD (e.g. the University of Iowa's protocol for presymptomatic testing for HD, which requires a minimum of three in-person visits). Such protocols also exist in other countries, including Europe.

There is much concern about the burdens engendered by widespread utilization of genetic tests, particularly given that ongoing future analyses of the human genome will lead to testing for even more disorders (and more highly sensitive and

specific techniques). Additional issues are raised in the domain of AD because APOE ϵ 4 is neither sufficient nor necessary for the development of disease. Many at-risk people would have seen loved ones suffer and die with the illness. The HD experience teaches us that thorough psychological assessment of at-risk persons and extensive patient (and family) support systems must be integral components of any genetic testing program.

Understanding more about the genetic underpinnings of the neurodegenerative disorders will help researchers and clinicians answer questions about disease mechanisms, gene-gene interactions, and lifestyle or environmental factors that affect risk. It will also help in the early identification of high-risk people, and focus on novel prevention and treatment approaches. However, clearly, stringent guidelines are required to monitor genetic testing, and HD can help to provide the backbone and history. Currently, the scientific progress of gene testing, its application to industry, and the ensuing economic pressure for its use have outpaced legal and ethical frameworks that protect the individual. Some authors fear that an uncontrolled use of the tests may lead to a revival of social policies based on eugenics (Kevles, 1985). Ongoing research into the significance and varieties of genetic discrimination is essential to inform future guidelines and policy, and to ensure the ethical and appropriate use of genetic testing, now and in the future. In the coming years, the prior examinations and lessons learned from HD research will become invaluable as the issues regarding genetic testing, counseling, and discrimination will come to the forefront.

Innovative service delivery: the Melbourne experience

One of us (EC) established the world's first HD Clinic at the Royal Melbourne Hospital in 1972 in the Department of Psychiatry, The University of Melbourne. This HD Clinic is still running, under the auspices of the Neuropsychiatry Unit (directed previously by John Lloyd and now Dr Dennis Velakoulis, and one of us (AG) is now the clinic coordinator). In addition to the Clinic, Betty Teltscher, as a social worker/advocate, determined that a family organization should be established. Thus, the Victorian HD Association (now Huntington's Victoria) was formed in 1973, and other HD Associations then followed in other Australian states. To date the Huntington's Associations in Australia are very strong advocates for the HD community and are members of the International Huntington's Association (IHA), which actively promotes international collaboration

in the search for a cure for HD in 39 countries. The urgent need for quality residential care for those with HD was a major concern to Chiu and Teltscher as people requiring such care had nowhere to go but to mental hospitals (which held over 80 HD patients in 1980). When the Wesley Central Mission received a large windfall of money from land sales that became available for use in community projects, Chiu and Teltscher were able to persuade the Wesley Board, under the leadership of Reverend Arthur Preston, to take on a project to establish residential care for HD patients. The Arthur Preston Residential Centre was officially opened in 1980 as the only such center in the world for HD patients and their families, and today remains a world leader in this area of care. In 1982 Chiu committed himself to the discipline of Old Age Psychiatry and served as the President of the International Psychogeriatric Association (1999–2001). In 1985, Chiu and Teltscher wrote a handbook for "Caring in HD", and noted the goal of providing the best possible care for HD, which could be translated to a model for the caring of related brain disorders and services for the elderly.

The Huntington's Research Group Victoria (HRGV) was established in 2004 and represents a local collaboration of scientific and clinical investigators from academic, clinical and research centers that are committed to the cooperative planning and implementation, analysis and reporting of research studies aimed at improving the understanding and treatment of Huntington's disease and related disorders. This group will take the HD research agenda forward in the coming years.

Looking to the future

The HD field can also benefit from the research focusing on other neurodegenerative disorders. In the next several decades, HD research must turn to the domains of therapeutic trials, including drug trials, which have been successful in the domain of AD. This is particularly important as the first large clinical drug trial to focus on the cognitive aspects of HD, the HORIZON trial of investigational drug dimebon (latrepirdine, conducted by the HSG and EHDN), found that dimebon did not improve cognition in HD. Despite the negative findings, the HORIZON study was reviewed by regulatory agencies in the USA and European Union, and was conducted on a global basis without difficulty. This study will lay the foundation for future global investigations of promising new treatments for cognition and other aspects of HD. The field of AD research also informs the need for research into the behavioral and psychological symptoms of HD,

akin to the behavioral and psychological symptoms of dementia (BPSD).

Summary

Despite being a relatively rare disease, HD has been crucial in the genetic revolution of the past few decades. As a result of the gains in HD research, the scope for genetic testing is now extended to include predictive testing for monogenic and multifactorial diseases, and impacts upon personal risk reduction – with far reaching effects – from families to large sections of the ostensibly healthy population. HD is now a leader in the field of molecular genetics and proteomics, and has attracted considerable research interest. It has contributed greatly to our understanding of neurodegeneration, neurogenesis and neuroplasticity, and is also unique and invaluable in the field of neurodegenerative disorders as the only disorder for which definitive, valid, and reliable predictive diagnostic genetic testing is currently possible. Overall, HD research over the past 40 years has been both groundbreaking and provocative, with huge leaps in knowledge and technologies in the field of HD research, which has in turn informed the general neurodegenerative and old age psychiatry research field. It has laid down crucial building blocks for our future, and has furthered dementia understanding and research in general.

Looking to the future, HD and most other cerebral degenerative conditions (including AD, FTD, and dementia with Lewy bodies) have as their central pathology a “gain of function” in abnormal proteins (huntingtin, beta-amyloid, tau, synuclein) that wreak neural havoc. HD can be used as a useful “model” in neurodegenerative research in general because: (1) it can be definitely diagnosed clinically; (2) it has a known offending protein in Huntington; (3) the gene is identified and is responsible for the disease, (4) it is predictive of clinical outcome in gene expression; (5) the gene and its product protein can be (although not yet totally) characterized; (6) reliable and valid predictive testing is available; and (7) it allows study in a definite pre-clinical and pre-dementia phase.

The journey for old age psychiatry as a major contributor to the understanding and management of neurodegenerative disorders has been a challenging one, and the HD journey may provide historical and practical lessons for our discipline. We now have the tools, the equipment, and, with the technology of the internet, the ability to collaborate easily internationally, to combine our knowledge from the cellular domain, the genetic domain, the psychological domain, the clinical domain, and the social science domain

to understand and integrate fundamental and applied insights. Over the coming decades, the trend of leaps and bounds in knowledge is likely to continue, particularly in dementia and AD research, with active ongoing collaborative groups, increased genetic technologies, and more research into the issues of individuals having a known predisposition or known gene for a genetic disorder. We look forward to a future that reveals fruitful and rewarding international research and clinical collaborations in the field of neurodegenerative disorders, and which results in new therapies that can stop aberrant gene expression and delay the onset and/or even reverse the symptoms of the currently incurable neurodegenerative diseases.

Conflict of interest

None.

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