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The specialist neurologist and the "new genetics"

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ABSTRACT

- The "new genetics" will require specialist physicians to deal with an increasing number of genetic issues.
- Huntington disease (HD) is a rare single gene adult-onset fatal neurodegenerative disorder. It provides a model to illustrate the role of the specialist physician in the new genetics.
- DNA testing options in HD include diagnostic DNA tests to confirm a provisional diagnosis, and predictive or presymptomatic DNA tests to determine whether disease will develop in an at-risk individual.
- The specialist physician is well positioned to interact with the genetics services by providing in-depth knowledge of the clinical implications. This will become particularly relevant as the more complex multifactorial disorders (eg, Alzheimer disease) are understood at the DNA level.
- For optimal use of the new genetics, a team approach is essential to ensure that all areas of expertise are covered.

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FIFTY YEARS AGO, Watson and Crick's discovery of the double helical structure of DNA[1] marked the beginning of the "new genetics". Medical practitioners are now faced with the prospect of an escalating number of disease-causing genes being identified. The sequencing of the human genome will only accelerate our knowledge of human genetic disorders.[2]

Advances in molecular genetics are presently being utilised in the clinical setting through the powerful tool of genetic (DNA) diagnosis. This allows the confirmation of a diagnosis in clinically affected individuals, and the preclinical determination of genetic status in those at risk of genetic disease, long before signs and symptoms develop. In both these activities, the specialist physician, who has an intimate knowledge of the clinical implications, will play a key role.

Ten years ago the Huntington disease (HD) mutation was identified.[3] Much of our subsequent approach to the diagnosis of genetic diseases, particularly in adults, has been influenced by our experience with HD. This model will be used to illustrate current and future practice developments relevant to specialist physicians. An understanding of the HD model is useful for adult-onset genetic disorders in other internal medicine disciplines.

Disease pathogenesis

New disease classifications based on DNA findings are appearing. One novel class of human genetic disorders is known as the triplet repeat diseases. These diseases result from increases in the number of triplet units in a DNA triplet repeat. Triplet repeats are scattered throughout our genome, but it is only when the number of repeating units in a particular gene reaches a critical number that gene function becomes impaired.[4] Triplet repeat diseases include spinocerebellar ataxias and HD. These involve expansions of a CAG repeat. In HD, the normal number of CAG repetitions is $\leqslant 26$. People with 40 or more repetitions will develop HD. The clinical significance of triplet repeats between these two values is more difficult to interpret: repeats of 27–35 triplets represent risk factors for the individual's children. Repeats of 36–39 triplets may be associated with reduced penetrance for developing clinical disease. Spinocerebellar ataxias illustrate the complexities arising from the new genetics, with 23 subtypes presently identified, some of which are only definitely distinguishable by DNA testing.

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Increased knowledge from DNA testing has produced new insights into disease phenotypes. For example, except for early-onset rigid forms, all cases of HD were believed to be associated with chorea. It was also thought that HD would not arise *de novo* (ie, in the absence of a family history) or develop in people over 60 years old. We now know that HD can present without chorea, and very elderly people can develop HD.[5] Furthermore, hereditary and senile chorea, previously regarded as benign, may be accompanied by the HD mutation. This finding has implications for family members.[6,7] Finally, new mutations resulting in HD do arise. These cases occur when intermediate CAG repeats, not long enough to cause disease, are unstable and expand to the disease range on transmission to a child. The complexities inherent in these neurological disorders would not have been unravelled without input from both geneticists and specialist neurologists. A similar team approach is needed in the clinical setting.

Diagnostic testing

DNA testing can mean certainty of diagnosis even in the absence of a family history. This is relevant in HD, with the potential for some CAG triplet repeats to be unstable and so produce HD without a preceding family history. Expensive investigations (assuming that these are even available) can be deferred if there is a diagnostic DNA test for the genetic disorder. In the example of HD, it is no longer necessary to consider a long list of differential diagnoses for chorea if the mutation known to produce HD is detected by a straightforward DNA test.

A specialist physician with experience in the disorder can make or confirm the diagnosis. The clinical assessment will include the appropriate investigations to make a definitive diagnosis, as well as to establish disease subtype and stage, impact on function, and ultimate prognosis. As part of the assessment, genetic testing would be discussed and the implications of the result — medical and other (eg, insurance) — both for the patient and for the family would be addressed. Psychosocial support from a social worker, counsellor, psychologist or appropriately trained nurse should be offered, but not forced on the individual.

Predictive or presymptomatic testing

Individuals at risk of a genetic disease may be identified when a relative is diagnosed or when the individual's family history is taken. For these people, predictive or presymptomatic DNA testing allows their risks of developing a disease to be accurately defined, and in some cases early interventions can be implemented. For example, the predisposition to inherited cancers such as familial adenomatous polyposis (FAP)[8,9] can be assessed by DNA testing of at-risk family members. People shown to have the FAP mutation can be monitored more effectively with this knowledge, and treatment (colectomy) can be instituted earlier during the inevitable progression of polyps to colon cancer.

Because of privacy considerations, the doctor has to work through the patient (if competent; otherwise, the next of kin) to contact at-risk family members to give them the opportunity to be tested. For individuals at risk through family relationship, the DNA test can detect those with the relevant mutation. The risk can then be converted into a more definite "disease" risk. For example, in a young adult shown to have a CAG triplet repeat of 41 units in the HD gene, there is 100% certainty that the person will develop HD. Fewer CAG units in HD indicate lower levels of certainty. Individuals who carry the mutant gene but have no signs of illness, and may not develop any clinical features for some time, represent a new group of "not yet" patients.

Many diseases detectable by DNA testing are serious and incurable. HD is one example, as are many of the other neurological illnesses, which can be complicated by coexisting dementia.[4,6,10,11] In these circumstances, information from preclinical testing can, in itself, lead to further distress for patients and their families. Thus, pre- and post-test counselling and ongoing support is important. Because of the complex issues involved and the lack of clinical interventions, preclinical DNA testing for HD is not available for children.

Specialist physicians and genetics services

The interaction between the specialist physician and genetics services (clinical and laboratory) is essential in both diagnostic and predictive DNA tests. In neurological disorders it is particularly relevant, as some diseases are associated with normal cognition (eg, familial motor neurone disease), while others include cognitive impairment (eg, HD and Alzheimer disease). Although this article focuses on HD, a rare genetic disorder, a greater challenge will come with the more common multifactorial disorders, such as Alzheimer disease and other dementias. For the present, the genetic basis of Alzheimer disease remains poorly understood and is predominantly of research interest, except for rare cases in which there is a strong family history and testing for known mutations is possible.[12]

The first priority in delivering a test result is to avoid misinformation and confusion for the patient and family. Therefore, if the specialist physician has little knowledge of the disorder, and particularly the ramifications of any gene result, it is essential, before conveying the test result to the patient, to discuss it with the molecular geneticist or another specialist who has particular expertise in the disorder and its genetic basis. Physicians must regularly update their knowledge, as information in the new genetics is constantly changing. All GPs and physicians need to be aware of two excellent free online sources of information: Online Mendelian Inheritance in Man (OMIM; www.ncbi.nlm.nih.gov/omim/) and Gene Clinics (www.geneclinics.org/). Doctors also need to realise that patients returning for a gene test result may have searched the Internet and gathered information about the disorder — another change for the practising physician this past decade.

The alternative to the specialist physician ordering the DNA test is to refer the patient to a clinical genetics service that will also provide information about the genetics of the disorder, and the risks to family members. A decision to involve the clinical genetics service will be influenced by the frequency and perceived severity of the disorder. Thus, relatively common genetic illnesses (eg, haemochromatosis), particularly if mild, are more likely to be managed by the physician or GP.

As DNA testing becomes available for common multifactorial diseases, such as Parkinson disease, Alzheimer disease and related dementias, clinical genetics services may have difficulty coping with the demand for testing. Furthermore, although clinical genetics services can provide accurate genetic information related to modes of inheritance and risks and options available during pregnancy, they are likely to be limited in the diagnosis of complex disorders and the in-depth knowledge of day-to-day management or prognosis in the longer term. Subspecialisation and special interest is now well established in specialist physician practice but, with the exception of cancer genetics, clinical geneticists remain generalists. This is potentially a problem with the increasing scope of genetic illnesses. The challenge might only be met by specialist physicians in each discipline who have also developed skills in genetics. This is particularly relevant now that genetic knowledge is providing explanations for pathophysiology that will increasingly be linked to management. Such specialisation is starting to occur: neurogenetics is a well-established subspecialty in the United Kingdom and the United States,[11] and oncologists are developing skills in genetics.[8]

Dealing with neurogenetic diseases is further complicated when there is cognitive change associated with poor insight into disease, and eventually dementia. A patient may present

for a predictive test not realising that the disease is already established, and may not want medical attention, or to hear that he or she has a disease, or to consent (or be able to consent) to a DNA test. In this setting, the specialist physician can still offer a clinical diagnosis, stage the illness, treat the symptoms and work with the patient and family over time, with assistance from the GP, social workers and others to develop acceptance, if possible. This building of rapport can take months or years.

A team approach

Experience in predictive DNA testing has led to the issuing of best practice guidelines. These conclude that a team approach between many disciplines, including geneticists, specialist physicians and support organisations,[13-16] is essential for delivering optimal care. Isolated general genetics clinics do not fit this model, and the future genetics input for many of the common or complex genetic problems is likely to be provided through an integrated clinic dealing with specific disciplines such as neurology, oncology, and gastroenterology and their associated genetic issues.

The specialist physician's role in the new genetics is to establish whether there are signs of the disorder (symptoms are unreliable, particularly in the inherited dementias).[17] In the case of HD, the initial physician contact and subsequent follow-up helps the patient with the HD gene mutation through reassurance that the disease has not yet developed. Review is also encouraged, as many genetic diseases are insidious and so cause damage to relationships, particularly within the family. Once treatment or preventive measures are available, the at-risk group will most likely present initially to the physician or GP.

Presently, clinical genetics services are best equipped to carry out the counselling process. This allows informed, optimally timed choices to be made about tests that will have major impacts. The clinical genetics service can also support the patient through the predictive DNA testing period.[13] Just as specialist physicians must work within their particular skills and counselling resources, clinical geneticists and counsellors must avoid overinterpretation of a result or giving clinical information that is not accurate. They may face decisions that are difficult to make without specialist physician, psychiatrist or GP input,[11,18] such as the appropriateness of delivering a test result to a patient with severe depression. Sometimes clinical monitoring for signs by the specialist physician may be a better option than the certainty of a predictive test result.

What patients and families want most are medical practitioners willing to take an interest in the long term. Over this time, the most accessible healthcare professional will be an interested and trained GP, possibly a general physician (this will be influenced by location) with close liaison with an experienced specialist physician. From the patient's perspective, once treatment is under way, it matters very little that a disease is inherited. Depending on the problems encountered, it may be necessary to call on the expertise of a social worker, psychiatrist, rehabilitationist, neuropsychologist, physiotherapist, speech pathologist, occupational therapist, dietitian, skilled community health workers, or palliative and chronic care nurses. All may contribute to patient management and support, which, in inherited disease, extends to the carer and family.

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