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Frontotemporal dementia often strikes young people. Can this insidious disease be explained by our genes?

Destiny does not only lie in the genes

Recently the Norwegian Broadcasting Association reported the case of a 38-year-old man who had been diagnosed with frontotemporal dementia (1). For a long time his wife had not realised he was ill since he functioned well at work and his memory was not affected. But he had changed: whereas before he had liked black, he suddenly liked white, and he switched from enjoying detective series to watching children's TV. In addition he stopped going out with friends.

It can be difficult to identify the early symptoms of dementia, particularly among young people (2). Patients with frontotemporal dementia can appear ungrateful towards their relatives and health professionals because they do not realise they are ill and need help. Many of those who have a mother or a father with this serious disease are also worried about getting it themselves.

Frontotemporal dementia affects between four and 15 persons per 100 000 under the age of 65 (3) and is currently considered as an umbrella term for several different diseases (2). The most common symptoms are cognitive impairment and personality changes. Language ability can be affected, producing varying degrees and types of aphasia. Since the symptoms can vary and can be complex, it is often difficult and time-consuming to make the diagnosis (4). Phenotypically, frontotemporal dementia can be roughly divided into three subgroups: a behavioural variant, a semantic variant and an aphasia variant (3). Other subgroups are also described. The symptoms of the different versions of the disease can bring to mind the changes seen in psychiatric disorders, other forms of dementia and neurological conditions – for example amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis is a motor neuron disease that occurs in two forms – one that is hereditary and one that is sporadic. The clinical picture is largely characterised by the loss of motor function; however, it has become clear in the past few years that many of the patients also have a number of cognitive and behavioural symptoms such as poor insight into their illness, irritability and an obsessive personality (5). The symptoms may be similar to those of frontotemporal dementia. The article by Gjerde & Tysnes in this issue of the Journal of the Norwegian Medical Association (6) gives an account of the clinical and genetic similarities between frontotemporal dementia and amyotrophic lateral sclerosis. But the question is whether a genetic and clinical comparison of this type achieves a deeper general understanding of the conditions. Can any common genetic basis explain sporadic cases of the disease? In the final analysis, the key question for the clinician is whether such genetic similarities are clinically relevant.

A few years ago, patients with frontotemporal dementia were roughly divided into groups based on a histopathological classification with findings of the proteins tau or ubiquitin. This classification has proved to be inaccurate (7). Another protein, called FUS, was later considered to be a common denominator for frontotemporal dementia and amyotrophic lateral sclerosis, but the connection is not clear (8). In 2011 a mutation in the *C9orf72* gene was recognised as the most common genetic mutation that these diseases had in common (9).

Gjerde & Tysnes' article does not always make a clear distinction between the use of hereditary and sporadic forms. It may be tempting to believe that the hereditary and sporadic forms of these diseases have the same genetic basis. This does not always have to be the case, since a distinction must be made here between correlation and causality. It is obvious that there are genetic *correlations* that give predisposed persons a greater risk of developing amyotrophic lateral sclerosis and frontotemporal dementia. On the other hand, genetic mutations on their own are with few exceptions the main cause of a dementia disease, and it is often difficult to show clear causal connections between genetic defects and illness. It is enough to bear in mind that researchers hold the view that mutations in three known genes cause less than 1 % of all cases of Alzheimer's disease (10).

So how much do genes explain the occurrence of frontotemporal dementia? Opinions are divided and the results differ substantially. Although some studies reveal that 10–20 % of patients with frontotemporal dementia show signs of an autosomal dominant inheritance pattern with mutations in known genes (3), the findings are difficult to interpret. One study showed that up to 42 % of patients with frontotemporal dementia have at least one family member with the same condition, while only 10 % have a clear autosomal dominant inheritance pattern (11). Many cases will therefore be regarded as sporadic (8).

A genotype does not necessarily produce one specific phenotype. Doctors treat patients, not genes. Even though there are some common clinical and genetic traits between subgroups of frontotemporal dementia and amyotrophic lateral sclerosis, it is difficult to define the clinical relevance of this. Children and other relatives of patients with frontotemporal dementia should always be offered a consultation with a doctor or another health professional on the heritability of the disease. The importance of genetics remains unclear (8).

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