Genetics and neurology

Our understanding of neurological diseases has exploded in recent decades owing to genetic approaches. Investigations from our laboratory exemplify the power of genetics in the analysis of a wealth of diseases of the nervous system

The analysis of monogenic neurological disorders aims at the identification of genes mutated in given diseases (disease genes) and the analysis of their (ab)normal function. This facilitates prenatal and differential diagnosis as well as – in late onset disorders – predictive testing. Although monogenic neurological disorders are rare, they can serve as models for the more common 'sporadic' variants in which both genetic and environmental factors contribute to disease. Furthermore direct analysis of 'sporadic' neurological diseases by association studies provides a direct approach to their molecular dissection. The following gives examples of the genetic analysis of movement disorders both monogenic and 'sporadic', primary degenerative dementia, and hereditary tumours of the nervous system.

Movement disorders

Movement disorders cause abnormal voluntary and involuntary movements. Our laboratory studies dystonias, parkinsonism (syndromes), and spinocerebellar ataxias (SCAs). Investigation of an X-linked form of dystonia, the X-linked dystonia-parkinsonism syndrome (XDP), resulted in the identification of molecular changes within the complex transcript system *TAF1/DYT3*.[1] The mutation(s) cause altered expression of genes involved in vesicular transport, dopamine metabolism, synapse function, Ca^{2+} metabolism, and oxidative stress.[2] Dysregulation of these genes may also contribute to more common forms of dystonia and Parkinson's disease.

A 'sporadic' atypical parkinsonism syndrome, progressive supranuclear palsy (PSP), was analysed in a genome-wide association study (GWAS). As contributing causative factors, the study identified genes involved in vesicle-membrane fusion at the Golgi-endosomal interface, the endoplasmic reticulum unfolded protein response, coding for Tau, and a myelin protein.[3] The investigation of SCAs resulted in the identification of the gene *KCNC3,* coding for a voltage-gated potassium channel that when mutated causes previously not described SCA, type 13 (SCA13).[4] Further, molecular diagnosis was refined for SCA17.[5] Finally, molecular studies showed that two clinically distinct forms of SCAs, i.e. SCA3 and Machado-Joseph disease, are genetically identical.[6]

Alzheimer's disease

AD is the most common cause of primary dementia. About 100 million people worldwide are expected to be affected by 2050. AD can be divided into early onset (less than 65 years of age, EOAD) and late onset (LOAD) forms. The latter make up the majority of cases (95%). While most forms of AD are 'sporadic', about 2% (mostly EOAD variants) are inherited as autosomal dominant traits. We routinely test the three known genes *(PSEN1, 2, APP)* for mutations in suspected autosomal dominant cases of the disease. This resulted in the identification of novel pathogenic gene mutations. Unaffected mutation carriers can enter the dominantly inherited Alzheimer's disease network (DIAN) that offers experimental treatments in the hope of delaying disease onset. Interestingly, the first case of AD was a rare autosomal dominant, early onset variant caused by a mutation in the gene *PSEN1.*[7]

Neuronal tumours

Various tumour syndromes of the nervous system are inherited as monogenic traits. Hereditary paragangliomas (PGLs)/pheochromocytomas (PCC) are tumours of the sympathetic and parasympathetic paraganglia, and are inherited as autosomal dominant traits. We identified *SDHC* as the gene mutated in PGL3.[8] *SDHC* codes for subunit C of complex II of the respiratory chain. It functions as a tumour suppressor gene in PGL3. Tumour formation occurs according to Knudson's classic two-hit model. In carriers of a germ line mutation of *SDHC* (first hit), total or severe inactivation of SDHC activity occurs in tumour cells by loss of the wild-type allele (second hit). Tumour formation is probably triggered by chronic hypoxia in paraganglia.

Summary

In summary, the examples demonstrate that genetic approaches greatly contribute to an understanding of pathological mechanisms in neurogenetic disorders. Such understanding is the basis for the development of causative therapies. At this stage the findings allow prenatal, differential, and predictive diagnosis in monogenic neurogenetic disorders. Predictive identification of a mutation in a gene causing late-onset disease is a prerequisite for offering patients experimental treatments in order to delay or entirely prevent disease onset.

References

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