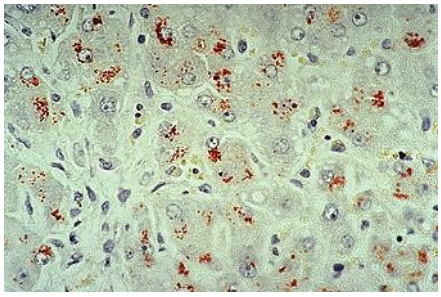
Healthcare industry BW

# Rare diseases – the long road to correct diagnosis and treatment

**Rare diseases are conditions that are too often neglected by research, industry and medicine. Here we use Wilson's disease as an example to illustrate the particular problems associated with research into and treatment of rare diseases and to provide information on measures that can be taken to improve the situation of people with rare diseases. These measures include central treatment and care institutions and programmes like the Wilson's disease programme in Heidelberg, which work closely with patient organisations.**



Wilson's disease is a condition in which copper accumulates in the liver.


In Germany, a disease is considered rare when it affects less than one person in 2,000. According to this definition, approximately 7,000 to 8,000 of the around 30,000 known diseases are classified as rare diseases. An estimated 4 million people suffer from a rare disease in Germany. Although the public at large is barely aware of them, rare diseases are not as rare as it seems and affect quite a large number of people.

Patients with rare diseases have long been neglected and, in contrast to common diseases, little is yet known on how they can be treated. A cooperative project funded by the German Ministry of Education and Research (BMBF) entitled "Development of innovative healthcare concepts for rare diseases" (EiVE) is aiming to come up with solutions to improve the situation and reduce the dismally long road to correct diagnosis and therapy where they can. The German Alliance for Chronic Rare Diseases (ACHSE), a grouping of more than 100 member organisations, is an important partner in the project. In 2010, ACHSE, the BMBF and the German Ministry of Health established the National Action League for People with Rare Diseases (NAMSE), in which 24 German organisations (including the German Research Foundation, medical and university hospital organisations, health insurance companies and the pharmaceutical and diagnostic industries) work together with the aim of "coordinating measures for improving the health situation of people with rare diseases and initiating model projects and other action in the field of rare diseases" (Joint Declaration of 8th March 2010).

It has since become obvious that interest in rare diseases is growing. However, there is still a long way to go on the road towards the effective improvement of the situation of patients with rare diseases. Wilson's disease is used below to illustrate the challenges associated with the diagnosis and treatment of rare diseases.

## Wilson's disease

The disease, which bears the name of the British neurologist S. A. Kinnier Wilson, is an autosomal recessive disorder in which copper accumulates in tissues. The disease affects around 30 people in a million and is therefore classified as a very rare disease. It is estimated that only 800 people in Germany suffer from this particular disease. It can therefore be safely assumed that the vast majority of general practitioners (who have an average of around 1,000 patients each) will never come into contact with the disease. The lack of experience, as well as the minor role assigned to rare diseases in medical curriculums and the training of medical doctors, has the consequence that the symptoms of Wilson's disease often go unrecognised.

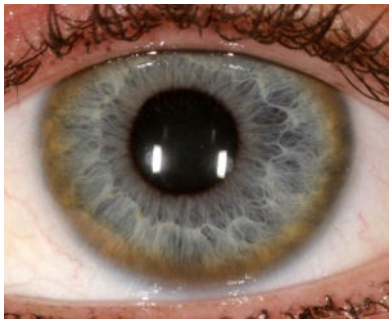
The disease is inherited in an autosomal recessive pattern; in order to inherit, both parents of an affected individual must carry a mutated ATP7B gene. The parents might be carriers of the abnormal gene without developing disease symptoms themselves. Children with the abnormal gene develop abnormalities in copper metabolism, i.e. Wilson's disease. The ATP7B gene encodes a specific copper-binding ATPase, an enzyme located in the plasma membranes of liver cells that controls the transport of copper into bile and incorporates it into ceruloplasmin. Mutations in the ATPase gene cause copper to accumulate in the liver (and later also in other organs such as the eyes and the central nervous system) rather than being eliminated with the stool. Liver damage can already be apparent in children affected by this disease and can develop into hepatitis and liver cirrhosis. Adolescents and young adults often present with central nervous system disorders, including movement disorders, slurred speech, tremor and difficulties to swallow, to name just some of the many symptoms. Some Wilson's disease patients also have psychiatric disorders. A characteristic symptom of the disease is the accumulation of copper in the eye, which is associated with so-called Kayser-Fleischer rings, greenish-brown rings that encircle the iris. These rings tend to appear only in the advanced stages of disease and cannot therefore be used in the diagnosis, i.e. exclusion of Wilson's disease.

## Access to appropriate diagnosis and treatment

Samuel Alexander Kinnier Wilson, M.D., D.Sc., F.R.C.P. (1878-1937), British pathologist after whom Wilson's disease is named.


As the disease is so rare and associated with a broad range of different symptoms, there is often an erroneous diagnosis and long, ineffective courses of treatment – a rather typical fate of patients suffering from other rare genetic diseases, including Marfan syndrome (a genetic disorder of the connective tissue) or epidermolysis bullosa (a connective tissue disease that causes blisters in the skin).

In such cases, attempts are undertaken to diagnose patients and find an appropriate therapy in specific centres that have been established in many German cities. However, this depends on the existence of well-informed general practitioners who can refer patients to such centres. Self-help groups such as the "Morbus Wilson e.V." association, the "Epidermolysis bullosa" network or "Marfan Hilfe" work with doctors and provide information and advice to people with rare



Copper deposits in the eye of a Wilson's disease patient: a typical Kayser-Fleischer ring develops.


diseases. The integration of self-help groups into an umbrella organisation such as ACHSE contributes to rare diseases receiving greater attention from politicians and healthcare providers.

Left untreated, Wilson's disease becomes progressively worse and is eventually fatal. However, there are some effective therapies available that help remove copper or prevent the absorption of copper from a person's diet. Those affected have a good prognosis if the disease is detected and early treatment is initiated and continued for the rest of a patient's life. One possible therapy is the administration of chelating agents; they form water-soluble complexes with copper and are flushed out through the urine. In Germany, the chelating agent D-penicillamine is the first-line treatment of the disease. Patients who do not tolerate penicillamine and develop severe adverse effects to the drug can be given trientine, which is associated with fewer adverse effects and is the first-line treatment in the USA for counteracting the accumulation of copper in tissues.

## Heidelberg has a special focus on diagnosis and treatment of Wilson's disease

A study led by Dr. Karl-Heinz Weiss from the Department of Gastroenterology, Infectious Diseases and Intoxication at the Heidelberg University Hospital (medical director: Professor Dr. Dr. h.c. Wolfgang Stremmel) has shown that chelating agents have a more reliable effect in the majority of Wilson's disease patients than drugs that inhibit the absorption of copper. The researchers have also discovered new markers that provide information on the inefficiency of therapies.

Research and treatment of Wilson's disease have for quite some time been a major priority of the Heidelberg University Hospital which is home to the largest specialist outpatient clinic in Europe. This clinic treats more than 200 Wilson's disease patients in Germany; the Wilson's disease consultation clinic is run by Dr. Weiss. This specialist outpatient clinic, which offers diagnostic and therapeutic measures as well as genetic examinations and consultation, works closely with the German Morbus Wilson e.V. association; Professor Stremmel is scientific advisor of the association.

At a symposium on research into rare diseases held on 23rd March 2012 as part of the EiVE project, Dr. Mark Schäfer, another Morbus Wilson e.V. advisory board member and gastroenterologist from Heidelberg, talked about the interest that Wilson's disease patients take in their own treatment and presented drawings done by Wilson's disease patients to illustrate how patients cope with the disease. Among the exhibits was a particularly moving one drawn by a nine-year-old girl after she had been taken off the drug trientine (which she had previously been given and tolerated well) because the insurance company refused to pay for it any more. Everyone who saw it and the other drawings cannot have doubted for a second that improvements in the medical treatment of rare diseases require the involvement of those who suffer from them. The patients are often the experts in such cases.