Genetics of Wilson Disease – 2013 ©

I'm sure many of you know a lot about the genetics of Wilson's disease (WD) already. Let me just remind you of two key aspects here:

- WD is inherited in so-called autosomal recessive fashion: We all have two copies of a relevant gene (one inherited from mum and one inherited from dad.) If a disease is recessively inherited, then this means that an individual has ended up with two damaged copies of a particular gene.
- The WD gene is called ATP7B; it is involved in the regulation of copper excretion and is located on chromosome 13.

I have recently participated in a large study on genetic aspects of WD which was completed in early 2013.***** Our study addressed two questions:

1. How useful is analysis of the WD gene ATP7B for the diagnosis of WD?

   Short answer – extremely useful. Modern techniques allow us to nail the diagnosis genetically in 98% of all WD patients. This does NOT mean that genetic testing should replace other, more conventional blood tests such as the measurement of caeruloplasmin or copper which can be done much more quickly and are also cheaper. However, our results confirm that genetic testing can be extremely helpful in those patients where the biochemical investigations are difficult to interpret. It's important to understand the limitations of genetics as well – the precise gene defects (or "mutations") will only ever tell you whether you've got WD or not. They will not tell you which symptoms you are likely to develop in the future, whether you will respond well to medication or not or anything else. Genetic testing is getting cheaper and cheaper – it is quite likely that more and more patients with definite or possible WD will be tested genetically in the future.

2. How common are ATP7B mutations in the UK?

   Old studies dating back to the early eighties suggested that there is one WD patient for every **30,000** people and that there is one ATP7B mutation carrier for every **90** people in the general population. However, these figures were at least partially based on guesses and predated the discovery of ATP7B as the WD gene. We therefore decided to analyse the entire ATP7B gene in 1000 controls to get a better idea of how common ATP7B mutations really are. Which controls did we choose? We used a little bit of dried blood spots from new-born babies. How did we do this? All new-born babies have a tiny little bit of blood taken so that certain illnesses can be detected and treated as early as possible.

   The results of our study actually suggest that WD may be as common as **1:7000** – much higher than the previous figure of **1:30,000,** and the incidence of carriers of about 1:40 rather than previous estimates of 1:90. However, it's really important to point out two limitations of our study:

   - It is likely that there is so-called reduced penetrance for at least some ATP7B mutations. This means that not everybody who carries two ATP7B mutations may develop WD.
   - It cost us a lot of money and took us several years of hard work to analyse ATP7B in 1000 controls. Nobody has ever attempted this before. However, it's still important to point out that 1000 controls is a comparatively small sample size when it comes to working out how common disease mutations such as ATP7B are in the general population. Just like any other study, our work needs to be repeated by others, ideally in many more controls still.

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***** '**A Genetic Study of Wilson's disease in the United Kingdom'** *Brain*, 2013 May; 136(Pt 5): 1476-87. doi: 10.1093/brain/awt035. Epub 2013 Mar 21. Coffey AJ, Durkie M, Hague S, McLay K, Emmerson J, Lo C, Klaffke S, Joyce CJ, Dhawan A, Hadzic N, Mieli-Vergani G, Kirk R, Elizabeth Allen K, Nicholl D, Wong S, Griffiths W, Smithson S, Giffin N, Taha A, Connolly S, Gillett GT, Tanner S, Bonham J, Sharrack B, Palotie A, Rattray M, Dalton A, Bandmann O.