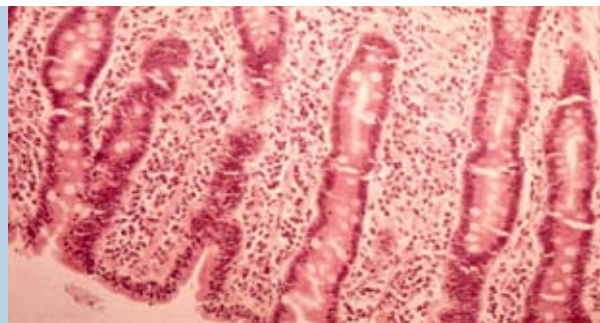


Gut feeling: Dissecting the genetic basis of coeliac disease

SUMMARY

Coeliac disease is an autoimmune disease of the small intestine. For decades, only one genetic region was known to be linked to the disease. Now, Professor David van Heel and colleagues have identified eight further genetic regions, and have begun to explore how the function of the immune system is altered in coeliac disease. Their research could contribute to the future development of novel diagnostic markers for the disease, and possibly immune-based therapies.



Background

Coeliac disease – an autoimmune disease of the small intestine – is thought to affect 1 in 100 adults in the UK, although only 1 in 8 people with the condition has been diagnosed. The disease is caused by a reaction to the protein gluten, found in wheat, rye and barley. When somebody with coeliac disease eats gluten their immune system attacks the mucosa of the small intestine, preventing them from absorbing nutrients normally.

The only known treatment for coeliac disease is a gluten-free diet, which is both extremely difficult and inconvenient. Not only is gluten found in foods made from cereals (such as bread, pasta, pastry and cakes), but also it can be present in many other things, including sauces, sausages, beer and even ice cream.

The disease runs in families, and the involvement of one particular gene, *HLA-DQ2*, has been known for several decades. Until recently, the genetic basis of the disease was poorly understood beyond this.

Advance

Professor David van Heel, now working at Barts and The London School of Medicine and Dentistry, London, and colleagues have used the latest large-scale techniques for genetic association studies to find genetic regions implicated in coeliac disease.

The team carried out the first ever genome-wide association study for coeliac disease, the results of which were published in *Nature Genetics* in 2007. Comparing people with coeliac disease and healthy controls, the researchers identified variants in the region of the genome that contains the genes for interleukin-2 and interleukin-21, cytokines that control how T cells function in the immune system.

The link between immune system genes and coeliac disease risk was strengthened in a further *Nature Genetics* paper, published by Professor van Heel's group in 2008.

The researchers identified seven further genetic regions linked to coeliac disease risk, of which six contained genes involved in the control of the immune system.

This work has helped researchers to understand which biological systems are disturbed in coeliac disease, and has revealed that many of the factors linked to the disease also seem to be factors linked to type 1 diabetes.

In 2008, the Trust awarded Professor van Heel a £1 million project grant to complete a more in-depth genome-wide association study to identify further risk factors for coeliac disease. The team will work in conjunction with Professor Cisca Wijmenga from Groningen University in The Netherlands, Dr Ross McManus from Trinity College Dublin and Dr Panos Deloukas from the Wellcome Trust Sanger Institute, Cambridge. The team is also looking at the previously identified genetic regions associated with coeliac disease, to try to pinpoint the specific disease-causing factors within them.

How it's making a difference

Professor van Heel's work has transformed the way researchers think about coeliac disease. Eventually, he and his colleagues hope to identify causative markers for the disease, which could be used to devise novel diagnostic tests. His research could also contribute to the development of new immune-based therapies for coeliac disease.

Wellcome Trust funding, in the form of a Clinician Scientist Fellowship between 2002 and 2006, gave Professor van Heel the chance to develop a career in academic medicine, which has already resulted in his appointment as Professor of Gastrointestinal Genetics at Barts and The London School of Medicine and Dentistry in 2006.

Professor van Heel has developed a website to freely share information with other researchers and patients with coeliac disease (<http://vanheelgroup.googlepages.com>). He regularly presents lectures to local and national patient groups from Coeliac UK (www.coeliac.co.uk), a UK-wide charity for those with coeliac disease that has also supported Professor van Heel's research. His work has attracted coverage in UK national newspapers.

References

Hunt KA et al. Newly identified genetic risk variants for celiac disease related to the immune response. *Nat Genet* 2008;40(4):395–402.

van Heel DA et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. *Nat Genet* 2007;39(7):827–9.

Other key publications by Professor van Heel can be found at www.icms.qmul.ac.uk/Profiles/Gastro/van%20Heel%20David.htm.