Proceedings of the Nutrition Society (2009), **68**, 122–126 doi:10.1017/S0029665109001074
 First published online 26 February 2009

A Meeting of the Nutrition Society, hosted by the Irish Section, was held at the O'Reilly Hall, University College Dublin, Dublin, Republic of Ireland on 18–20 June 2008

Symposium on 'The challenge of translating nutrition research into public health nutrition'

Session 3: Joint Nutrition Society and Irish Nutrition and Dietetic Institute Symposium on 'Nutrition and autoimmune disease' Recent advances in genetic understanding of coeliac disease

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Over the past 20 years major advances have been made in the diagnosis and understanding of pathogenic mechanisms relating to coeliac disease. Recently-identified genetic markers support the immunological–inflammatory nature of the disease. It is hoped that these newly-identified genes will assist further dissection of the inflammatory pathways in coeliac disease and give insight into why certain individuals develop intolerance to dietary gluten.

Coeliac disease: Genetic markers: Inflammatory pathways

Coeliac disease is a common disorder, thought to affect approximately 0·5–1% of the population in Northern Europe. In the early 1950s, through the seminal observations of a Dutch paediatrician, Willem Dicke, the cause of coeliac disease was identified as dietary gluten[(1)]. This finding led to a highly-specific treatment for coeliac disease, the gluten-free diet. Initially, coeliac disease was considered to be a relatively rare disorder, affecting only one in 1000 or smaller numbers in the population. An exception to this estimate was found to be the west of Ireland, where the prevalence of coeliac disease was calculated to be one in 300[(2)]. This finding led to the incorrect perception that coeliac disease was uniquely common in Ireland, especially in the western seaboard region. With better diagnostic tests and case ascertainment it is now appreciated that coeliac disease has a high prevalence in many regions of the world[(3)].

Early in the study of coeliac disease an increased incidence of this condition was noted in families, and the potential that genes contribute to the disease mechanism was considered[(4)]. An association with genes that code for molecules of the MHC was quickly established and MHC genes located on chromosome 6 have been confirmed as the major genetic influence on coeliac disease[(5)].

Advances in the diagnosis of coeliac disease

Following identification of the histological lesion in coeliac disease the diagnosis of the disorder was primarily based on examination of small intestinal biopsies, with evidence that the lesion remits after institution of a gluten-free diet. Measuring anti-gliadin antibodies in serum was used as an adjunct to biopsy and, although useful, the test lacks specificity and is only moderately sensitive[(6,7)]. An assay for the detection of anti-endomysial antibodies was reported in the early 1980s[(8)] and deployment of this test became widespread in the following decade. Evidence shows that the presence of endomysial antibodies is virtually 100% specific for coeliac disease, with a reported sensitivity of 87–89%[(9,10)]. Several large population studies were subsequently performed that employed the endomysial antibody assay. A high prevalence of coeliac disease was revealed by all studies, ranging from one in

Abbreviations: HLA, human leucocyte antigen; IL-18R, IL-18 receptor; SH2B, Src homology-2-B; SNPs, single-nucleotide polymorphisms.

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140 in Northern Ireland[11], one in 200 in Italy[12] and Sweden[13] and one in 250 in the USA[14].

The development of the endomysial antibody test as a highly-specific serological diagnostic assay for coeliac disease represented a major breakthrough in the investigation of this disorder. In 1997 the target auto-antigen of endomysial antibodies was identified as the enzyme tissue transglutaminase[15]. This finding continues to have major implications for on-going coeliac research. It is now possible, using an ELISA system, to measure antibodies to tissue transglutaminase, and raised levels of these antibodies correlate strongly with detection of endomysial antibodies[16,17]. ELISA-based assays have several advantages, which include enabling a large throughput of patient samples and providing more stringent data on antibody levels.

Advances in understanding the pathogenesis of coeliac disease

Many studies have subsequently been undertaken to investigate a potential role for tissue transglutaminase in the pathogenesis of coeliac disease. It has been demonstrated that the interaction of gluten proteins (gliadins) with the enzyme enhances the *in vitro* immunogenicity of these gliadin peptides[18,19]. This effect is attributed to deamidation of certain glutamine residues in gliadin, thereby converting these residues to glutamic acid[20]. This deamidation process is not a random event but highly selective for the position of glutamine amino acids relative to nearby proline residues in a gliadin peptide sequence[21]. Furthermore, it has been demonstrated that this glutamic acid modification in the peptide sequence enhances its binding to human leucocyte antigen (HLA)-DQ2 molecules, thereby increasing the immunogenicity of gliadin[21]. Currently, this mechanism is considered to be the principal manner in which tissue transglutaminase contributes to coeliac disease pathogenesis. However, since tissue transglutaminase is a multi-functional enzyme it may play a role through a diverse range of other effects, including its ability to activate the cytokine transforming growth factor β[22].

The immune response to gliadin is considered to be the central pathogenic event in the development of coeliac disease[23]. Although over the past two decades much has been learned about gliadin stimulation of T lymphocytes, the final pathways that result in histological damage to the small intestine have not been fully elucidated. It is known that gliadin peptides can migrate across the epithelial cell barrier and, after modification by tissue transglutaminase, bind strongly to MHC class II molecules, in particular HLA-DQ2 molecules, which are found on antigen-presenting cells and in this setting are able to activate host T-cells. These T-cells then set in train an inflammatory response that results in tissue damage to the intestine. As such, coeliac disease has many features that resemble a classic auto-immune disorder, including the presence of a highly-specific auto-antibody (the endomysial antibody), being more common in females and associated with a specific immune response to gliadin, the antigen that is responsible for inciting the disease.

Advances in genetics of coeliac disease

As already mentioned, genes that code for MHC class II molecules are the strongest genetic influence on coeliac disease pathogenesis. In northern European populations with coeliac disease approximately 95% of patients are HLA-DQ2-positive and the majority of the remaining 5% are HLA-DQ8-positive. The genes that code for these DQ molecules are considered to account for approximately 35% of the genetic contribution to coeliac disease.

Recent studies have focused on determining the identity of the remaining contributing genes.

Many of these initial studies were based on the finding of linkage regions in family studies that identify commonly inherited regions among patients. These regions are usually large ones containing many genes. These genes were subsequently assessed as candidates and further analysed by fine mapping or sequencing. Alternatively, candidate genes could be selected for study based on their known functions. Both these approaches are constrained to a greater or lesser extent by current knowledge, and the functionality of many or even most gene products is incompletely understood.

Considering the disadvantages of these approaches, the application of novel analytical tools to the genetics of complex disease has had a profound effect on disease gene discovery. As with any mapping strategy, these methods benefit from being hypothesis-free. In essence, these methods use dense maps of genetic markers to look for regions that are more commonly found in patients with the disease compared with those without the condition. This field has been made possible by the precise cataloguing of genetic variation throughout the genome, which has been carried out by the International HapMap consortium and others. The most-commonly-used variants are termed single-nucleotide polymorphisms (SNPs), which exist as a natural element of population diversity and evolution and in the latest iteration of the HapMap (HapMap II) there are $>3{\cdot}8\times10^6$ SNPs genotyped, one SNP per 700 bases on average[24].

To date, one genome-wide association study of patients with coeliac disease has been carried out using >300 000 SNP markers on a UK patient cohort. Significantly-associated SNPs were re-analysed in independent UK, Dutch and Irish patient cohorts[25]. In addition to reconfirming the strong association between coeliac disease and the HLA class II DQ loci, this study has revealed a novel association with a genomic region (on chromosome 4q27) encoding four genes, notably including the IL-2 and IL-21 loci (Table 1). Following genotyping in the replication cohorts, this locus has shown a highly significant association with coeliac disease susceptibility for a range of SNPs and haplotypes (several SNPs with $P<10^{-10}$). This highly significant statistical result is also important from a functional standpoint, given the currently-accepted view of the role of T-cells in coeliac disease pathogenesis. It is not currently possible to distinguish which gene in this region is responsible for the association and no SNPs with

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Table 1. Summary of genome-wide association study findings in coeliac disease to show the chromosomal regions associated with the disease

Cytogenic location	Candidate genes in associated regions	Potential role of selected candidate genes	OR*	95% CI
1q31	*RGS1*	RGS1 is a GTPase-activating protein that regulates signalling pathways causing transcriptional activation in response to chemokines	0·71	0·63, 0·80
2q11–2q12	*IL1RL1, IL18R1, IL18RAP*	*IL18R1* and *IL18RAP* encode the two proteins that form the IL-18 receptor. IL-18 signalling leads to up-regulation of T-cell Th1 response and IFN-γ production. IL-1RL1 is a member of the IL-1 receptor family.	1·27	1·15, 1·40
3p21	Chemokine gene cluster (*CCR* genes)	Components of chemoattractant mechanism allowing immune cell homing to sites of inflammation	1·21	1·10, 1·32
3q25–3q26	*IL12A*	Encodes IL-12p35 protein subunit. IL-12 IL-12 is a dimer encoded by *IL12A* and *IL12B* and causes up-regulation of Th1-cell responses and IFN-γ production	1·34	1·19, 1·51
3q28	*LPP*	LPP is a smooth muscle protein involved in cell–cell interaction; transcription activator	0·82† 1·21†	0·76, 0·90 1·11, 1·31
4q27	*IL2, IL21*	IL-2 and -21are determinants of T-cell function, particularly Th1 subtype	0·71	0·63, 0·80
6p21	*HLA-DQA1, HLA-DQB1*	Antigen presentation molecules; present gliadin and related molecules to T-cells	7·04	6·08, 8·15
6q25	*TAGAP*	T-cell-activation Rho GTPase-activating protein is thought to be associated with regulation of T-cell activation by turning on Rho GTPases (negative regulators of cell signalling)	1·21	1·11, 1·31
12q24	*SH2B3 (LNK)*	A member of the SH2-B family; component of signalling cascades activated by binding of T-cell and cytokine receptors	1·19	1·10, 1·30

RGS1, regulator of G-protein signalling 1; IL-1RL1, IL-1 receptor-like 1; Th, T-helper; IFN, interferon; LPP, lipoma preferred partner; SH2-B, Src homology-2-B.
*A measure of the risk of developing the disease in the presence of these variants. In practice, many single-nucleotide polymorphisms (SNPs) may be associated in any given region; only the most significant values are shown for clarity.
†SNPs causing both reduced and increased risk are found in the region encoding *LPP*, implying that some variants of *LPP* may decrease risk of developing coeliac disease while others increase the likelihood of developing the disorder.

obvious functional consequences have been identified. Of the remaining two genes found in this region, one is testis specific and the other encodes a protein with unknown function and broad tissue expression patterns. However, both IL-2 and IL-21 represent excellent candidates for a role in an immune-mediated inflammatory disease.

As a follow on from this initial study approximately 1500 SNPs were selected for further investigation. Of the selected SNPs 1000 were found to be the most strongly associated SNPs from the initial genome-wide association study. The remainder comprised non-synonymous SNPs (i.e. SNPs that change the amino acid sequence of a gene or protein) showing some extent of association in the genome-wide association study, and further SNPs were chosen in genes based on their function. These SNPs were genotyped in all three population samples and significant novel disease associations for a further seven genomic regions were revealed[26]. It is encouraging to note that six of these regions encode one, or in some instances, several genes with clear roles in the immune system (Table 1), including genes in the chemokine gene cluster (the *CCR* genes) on chromosome 3p21, and genes for the IL-18 receptor (IL-18R) subunits (*IL18R1* and *IL18RAP*; 2q11) and *IL12A* (3q25), *RGS1* (1q31), *TAGAP* (6q25), *SH2B3* (12q24). *LPP* is the exception to this trend since it does not appear to be expressed in cells of the immune system but rather in smooth muscle.

The *CCR* genes comprise several genes that function in the homing of lymphocytes to sites of immune activity. The region encoding the IL-18R subunits IL-18R-α (encoded by *IL18R1*) and IL-18R-β (encoded by *IL18RAP*) also harbours members of the IL-1 receptor cluster. However, *IL18RAP* is considered the best candidate in this region, since one of the most-strongly-associated coeliac disease SNPs in the area (denoted rs917997) is also associated with altered IL-18Rβ expression in peripheral blood lymphocytes from patients treated for coeliac disease[26]. IL-18 signalling is highly relevant given its critical upstream regulatory role in the production of interferon-γ, which is produced in abundance in the coeliac lesion and is a hallmark of the disease[27].

IL12A codes for the IL-12p35 subunit of IL-12, which is an important immune regulator, promoting natural killer and T-cell activity and, with particular reference to coeliac disease pathogenesis, T-helper type 1 lineage differentiation[28]. IL-12 also strongly promotes interferon-γ expression, emphasising its credentials as a strong functional candidate.

Regulator of G-protein signalling 1 and T-cell-activation Rho GTPase-activating protein are both GTPase-activating proteins expressed in cells of the immune system and likely to attenuate cell signalling events. Regulator of G-protein signalling 1 is expressed by both T-cell αβ receptor-positive and γδ-positive intraepithelial lymphocytes in contrast to splenic and thymic T-cells, in which it does not appear to be expressed[26]. *Rgs1*-knock-out mice show increased B-cell and dendritic migration[29,30]. T-cell-activation Rho GTPase-activating protein is expressed in activated T-cells, in which it is believed to be involved in cytoskeletal changes[31]. Interestingly, *TAGAP*

https://doi.org/10.1017/S0029665109001074 Published online by Cambridge University Press

is one of a number of immunological genes recently reported to show reduced expression in children with Down's syndrome[32], in whom an increased prevalence of coeliac disease is known to occur[33,34].

Src homology-2-B (SH2B) 3 (also termed LNK) is one of three members of the SH2B family and is expressed in epithelial cells and a variety of immune cells including monocytes, dendritic cells and lymphocytes[35,36]. SH2B3 is an adaptor protein with the capacity to negatively regulate growth factor and cytokine-induced signalling pathways in immune cells[37,38] and has been shown to attenuate the ability of TNF to induce adhesion factor expression by vascular endothelial cells[39]. SH2B3 is an established susceptibility factor for type 1 diabetes[40]. rs3184504, the coeliac-associated SNP, is the most strongly associated SNP in diabetes, which may be a causative association given that it results in a non-synonymous Arg262Trp amino acid alteration to the pleckstrin homology domain. SH2B3 is expressed in small intestinal biopsies from patients with coeliac disease and individuals who are unaffected[26].

LPP, as mentioned earlier, is present in smooth muscle rather than cells of the immune system. The protein, lipoma preferred partner, appears to play a role in influencing cell migration and functions by linking the cytoskeleton to the cell membrane at adhesion sites and also as a transcription factor[41]. Activation of its transcriptional functions may be induced by changes in cell adhesion, and there is substantial evidence indicating that dysregulation of lipoma preferred partner can contribute to oncogenesis, principally by means of its transcriptional activities[41]. How it might promote coeliac disease is unknown, but its potential role in regulating cell adhesion and motility could indicate a structural role, e.g. in barrier function.

The observation of shared susceptibility loci with type 1 diabetes is not unexpected given that coeliac disease is more common in patients with diabetes and vice versa[42,43]. Indeed, at least three loci show some evidence of being involved in both diseases, these loci being the *IL-2* and *IL-21*, the *CCR* genes and the *SH2B3* regions. Previous studies show the 2q33 region encoding *CTLA4* (but also *CD28* and *ICOS*) to be associated with both diseases[44–46]. Other shared genes are likely to emerge with greater patient and control samples providing improved power to detect these associations. The *IL-2* and *IL-21* region is also implicated in several other diseases, including rheumatoid arthritis and psoriasis[47,48], whilst *IL18RAP* is associated with inflammatory bowel disease[49], providing support for the theory that many of these diseases share common pathways.

Previous studies using linkage analysis and candidate-gene studies have implicated regions on chromosome 11q21 and 5q33 as harbouring genes that predispose to coeliac disease[50,51]. Similarly, several studies have implicated *CTLA4* (designated the *COELIAC2* locus) as being linked to coeliac disease[45,46]. However, these findings were not replicated in the genome-wide association study. The reasons for this result are unclear, but besides the obvious possibility that they represent false positive associations, another possibility is that they may relate to more complex genetic associations involving haplotypes rather than single SNPs. This latter explanation may apply in the case of *CTLA4*, for which individual SNPs are less strongly linked to disease than an extended haplotype[46]. Interestingly, this disease-associated haplotype appears to be under positive selection pressure in Caucasian populations[52] and carries three genes (*CD28*, *CTLA4* and *ICOS*) with complimentary activities in regulating the extent and duration of T-cell activation. This finding indicates that in some instances the co-inheritance of variants in more than one gene may be of greater importance than the inheritance of any individual variant; this effect will not be identified without extended haplotype analysis. Larger studies and more in-depth analysis (complex because of the enormous volume of data generated) are likely to be required to resolve these questions.

Acknowledgements

The authors declare no conflict of interest. Funding was provided by the Health Research Board, Science Foundation Ireland, the Higher Education Authority PRTLI and the Wellcome Trust. Both authors contributed equally to this review.

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