Genes and environment in irritable bowel syndrome: one step forward

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Both low birth weight and genetic factors may be integral to the aetiological pathway in irritable bowel syndrome

The prototypic functional gastrointestinal disorder is irritable bowel syndrome (IBS) which affects approximately 10% of the population and causes considerable morbidity.¹ Traditionally, the pathogenesis of IBS has been simplistically conceptualised by applying the biopsychosocial model; this focuses on the interaction, via the brain-gut axis, of psychosocial processes with perturbations of gut sensory and motor dysfunction.² The model suggests that either genetic or environmental factors may alter central and peripheral physiology. However, how this occurs remains mysterious, few environmental factors have been linked to IBS and indeed whether or not genetics plays a part remains controversial.

There are clues that IBS is an inherited condition.³⁻⁵ In a family cluster study of 643 subjects from Olmsted County, Minnesota, those who reported having first degree relatives with bowel problems were significantly more likely to report IBS, adjusting for age, sex and the reporting of non-gastrointestinal somatic symptoms.³ Those who reported having a spouse with bowel problems were no more likely to report IBS.³ A study that directly surveyed relatives confirmed that there was nearly a threefold increase in IBS among the relatives of patients with IBS compared with the relatives of spouses.⁴ However, these results could all reflect a common intrafamilial environment rather than genes.

Two twin studies have suggested that there is a genetic component in IBS but clearly also indicate that the environment is key.^{6,7} Twins studies rely on the fact that monozygotic (identical) twins share 100% of their genes while dizygotic twins (like siblings) share only 50%. The first study to directly assess the potential role of genetics in IBS evaluated Australian twins.⁶ We found in this study that there was a 33% rate of concordance for a diagnosis of functional bowel disorder in monozygotic twins compared with only 13% in dizygotic twins. Structural linear modelling suggested that the additive

genetic variance for functional bowel disorder was 57%. We subsequently reported a smaller genetic contribution in a US twin registry; 17% of monozygotic twins were concordant for a self-reported diagnosis of IBS compared with 8% of dizygotic twins.⁷ The family environment was also important; we found that the best predictor of having IBS was a father with the condition, and this could not be explained by genetic factors alone.⁷ On the other hand, a well conducted twin study from the UK failed to detect any association of IBS with genetic traits which has led to controversy about the subject.⁸ This is one of the reasons why the report by Bengtson and colleagues⁹ in this issue of *Gut* is important (see page 1754). In an elegant study, young adult twins in Norway were mailed a postal questionnaire. The concordance for IBS was 22% in monozygotic twins compared with 9% in dizygotes; in women, the heritability of IBS was calculated to be 48%. Hence despite the negative data from the UK,⁸ a genetic component is likely to exist in IBS, at least in females.^{6,7,9}

So what genes are important? A number of studies have attempted to identify relevant candidate genes in IBS but here the data are really murky.^{5,10} Cytokines, for example, are under genetic control; some are proinflammatory while others are anti-inflammatory. Interleukin (IL)-10 is an anti-inflammatory cytokine and those who have a genetic predisposition to produce less IL-10 presumably have a greater probability of failing to downregulate inflammation after an infectious insult. A UK group evaluated IL-10 polymorphisms in IBS, and found that a high producer genotype (G/G) occurred significantly less frequently in IBS patients (21%) than in controls (32%).¹¹ A Dutch study suggested that possession of a high producer tumour necrosis factor α and a low producer IL-10 genotype were significantly more prevalent in IBS (9%) compared with controls (3%), and in diarrhoea (20%) compared with other IBS subtypes (<4%).¹² Hence genetic control of the inflammatory response

may be impaired in those with IBS, but based on these data this will be in the minority.

Others have looked at the genetic control of serotonin (or 5-hydroxytryptamine (5-HT)) reuptake. Serotonin appears to be a critical molecule for control of gut motor and sensory function; most of it is present in the gut in the enterochromaffin cells and is released on stimulating the gut, as occurs during migration of food.¹ The human serotonin transporter (SERT) reuptakes serotonin from the synapse and is under the control of a single gene; there is a functional promoter polymorphism present upstream from this serotonin transporter gene. Those who have the long SERT promoter polymorphism (L/L) have greater transcription, with greater activation of the transporter resulting in less serotonin in the synapses and, hence, potentially impaired peristalsis.⁵ The short polymorphism (S/S) is associated with lower transcription and these individuals should have peristalsis enhanced. However, the link between the SERT promoter polymorphism and IBS remains in dispute, with very inconsistent results in the literature.^{5,13-15} On the other hand, Gn β 3-C825T polymorphisms, first linked to functional dyspepsia,¹⁶ were similar in healthy controls and in patients with IBS.¹⁷ Other genes variably linked to IBS include polymorphisms of the 5HT_{2a} receptor gene,^{18,19} α_2 adrenoreceptor polymorphisms¹⁴ and the SCN5A channelopathy mutation.²⁰

For gene association studies across medicine, a failure of replication is the most common event, such that progress has been depressingly slow.²¹ In part, the inconsistency of the results probably reflects the issues of small sample sizes, patient heterogeneity (as even the Rome criteria probably do not identify a single form of IBS) and, of particular seriousness in case-control designs, population stratification (differing ethnic backgrounds in cases and controls resulting in spurious associations).²² Candidate gene studies have not evaluated any gene-environment interactions in IBS. Indeed, when tracking studies of human genes in the literature, it is clear that the emerging field of gene environment interactions represents a minority of studies.²³ Yet the environment is obviously key to IBS based on all of the twin data.⁶⁻⁹

Few environmental processes have been linked to IBS.²⁴⁻²⁶ Arguably the best established risk factor is bacterial gastroenteritis but there is more limited evidence that viral or protozoal gut infection can also lead to this syndrome in predisposed individuals.^{1,26,27} For

example, in Canada, there was a large outbreak of acute *Escherichia coli* 0157: H7 and *Campylobacter jejuni* gastroenteritis from contamination of a municipal water supply.²⁷ In this population, there was a nearly fivefold increased risk of developing IBS after experiencing bacterial gastroenteritis; 26% of the population who were exposed developed the syndrome.²⁷ Others have shown that those more likely to acquire post-infective IBS have underlying psychological comorbidity.^{26, 28} Does this indicate that there is a common genetic predisposition to both post-infectious IBS and anxiety or depression? Or could infection and the resulting inflammation alter brain function, inducing anxiety or depression in some cases?²⁹ Other potential environmental risk factors for IBS include childhood exposure to violence or sexual abuse,^{30, 31} and a higher childhood socioeconomic environment.²⁵ Exposure to certain foods has been supported by food elimination diet studies.³² However, in general, there have been only a handful of environmental exposures that have been consistently linked to IBS.

If unknown environmental factors are so important in IBS, as the twin studies suggest,^{6–9} one may ask exactly how they interact with the complex neural control mechanisms in the gut and brain to induce the symptoms we recognise as IBS? Also, why does not everyone exposed to bacterial gastroenteritis develop IBS? It is tempting to suppose that individual vulnerability to IBS may well in part be genetically controlled; this is the classical gene–environment paradigm.²¹ This paradigm hypothesises that the external environment causes IBS, but individual susceptibility is based on genetic makeup. However, to date, little has been done to directly test this hypothesis.

Bengtson *et al* evaluated a novel environmental risk factor and assessed whether there might be a gene–environment interaction.⁹ After confirming that genetic factors are relevant, they went on to test whether low birth weight influenced the risk of development of IBS in later life. Intriguingly, they found that low birth weight was a risk factor for IBS, with the critical birth weight appearing to be under 2500 g. It was also notable that the onset of bowel symptoms was earlier in those of lower birth weight. There is good evidence that the nervous system of the gut is deranged in IBS based on sophisticated studies of motor and sensory function.^{1, 2} They speculated that inadequate maturation of the enteric and central nervous system (as manifest by low birth weight) may predispose to an abnormally hardwired gut nervous

system in these children. Early life events have been shown in animal models to be of potential relevance. For example, neonatal maternal separation in rats has been associated with the onset of colorectal hyperalgesia.³³ Certainly, low birth weight has many causes and may be a measure of maternal illness or drug use, or poverty³⁴; even *Helicobacter pylori* has been implicated.³⁵ While Bengtson *et al* could nicely control for genetic factors in their study, environmental confounders of interest could not be adequately considered, although local intrauterine factors may in fact be most relevant.³⁴

There were other limitations of the Bengtson study,⁹ as there often are with any genetic epidemiological research. The phenotype used to define IBS was based on a self-reported diagnosis rather than the Rome criteria. It is notable that the UK study that was negative for an association of IBS with genetic factors in twins used the Rome II criteria⁸ in contrast with all of the other studies.^{6, 7, 9} This might seem perplexing but raises the hypothesis that the current Rome II or III criteria themselves may identify a non-genetic type of IBS while those who have abdominal pain and bowel disturbance that do not necessarily fit the Rome criteria may be more likely to have a genetic predisposition. Work needs to be done to unravel this issue. Another concern is the generalisability of twin data on fetal growth to the rest of the population. Indeed, twins generally have a lower birth rate, and factors such as variable placental sharing may be of specific relevance.³⁴ Finally, low birth weight is uncommon and if causal probably only accounts for a small minority of IBS cases.

In future gene-association studies, it will be important to ensure there is adequate study power; some have argued that assuming genetic associations are modest (odds ratios under 2), at least 1000 cases will usually be needed (in addition to a similar number of controls).³⁶ This is well above the numbers in all the studies on the topic combined.⁵ For this reason, it may be better to use endophenotypes rather than the classical symptom based IBS criteria in future studies.²¹ Endophenotypes are constituents of a disorder that have a more objective biomarker associated. For example, one potential endophenotype in IBS may be neurophysiological changes in the brain after balloon distension in those with gut hypersensitivity.^{1, 37} Circulating serotonin levels and minor inflammatory changes in the colon in IBS are other potential endophenotypes.¹ The concept here is that these end points are likely to have simpler genetic associations, which

may make gene association studies more robust and interpretable. However, it is notable that most of the potential biomarkers in IBS identified to date have not held up to close scrutiny. For example, Naliboff and colleagues³⁷ applied a rigorous rectal distension protocol, and measured perceptual ratings and activation of the central pain matrix using positron emission tomography over a 12 month period. They noted that while perceptual ratings normalised over the follow up period, symptoms of IBS did not change, while activity in the limbic, paralimbic and pontine regions of the brain decreased. Hence although there are abnormalities demonstrable in the brain in IBS, there may be a disconnect between adverse stimuli from the gut and brain activation. Could such abnormalities in central pain activation still be causal? Perhaps if one could show that brain activation was dependent on genotype, this would suggest cause rather than effect, and such work deserves close attention.

The introduction of studies of gene–environment interactions, such as that by Bengtson and colleagues,⁹ may be essential for unlocking the aetiopathogenesis of IBS and other related conditions. The data implicate early life factors as being possibly critical in the development of a disorder that typically has its onset in adulthood. Assuming the results are replicated, it now appears that both low birth weight and genetic factors are integral to the aetiological pathway. Further work in gene–environment interactions may lead us to uncover why women are more likely to develop IBS than men, why only a minority who are exposed to gastrointestinal pathogens later develop IBS and how psychosocial exposures can permanently alter neurological gut function that leads to this syndrome. There is now fertile ground for testing new aetiological hypotheses in IBS following this important work.

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Competing interests:
Declared (the declaration can be viewed on the *Gut* website at <http://www.gutjnl.com/supplemental>)

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