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Dissecting GI Phenotype – Genotype Relationships in GERD and Dyspepsia: An SNP Here and an SNP There!

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Abstract

It is known that the predisposition to human disease is a mixture of inherited susceptibility and acquired exposure to environmental factors. Understanding gastrointestinal disease has indicated that germline adenomatous polyposis coli mutations predispose with a 99% certainty to colorectal cancer, whereas squamous esophageal cancer is caused by a combination of environmental exposures (including alcohol consumption, cigarette smoke, ingestion of contaminated preserved food) and/or infection (specifically with human papilloma virus), in most cases. Until now, despite the reasonably strong evidence for genetic risk from monozygotic twin studies for gastroesophageal reflux disease (GERD), there have been no documented genetic targets in GERD. In this edition of the Journal, there is intriguing evidence that a common, single base-pair change in the secondary messenger gene *GNβ3* (i.e., a single-nucleotide polymorphism) may be important, perhaps through promoting abnormal perception of visceral pain in the esophagus. Other works link this genetic factor to functional dyspepsia, and these exciting preliminary lines of evidence are reviewed.

INTRODUCTION

Human disease is a mixture of inherited susceptibility and acquired exposure to environmental factors. The classical paradigm of inherited predisposition to gastrointestinal (GI) disease is familial adenomatous polyposis, in which adenomatous polyposis coli germline mutations are associated with a 99% rate of colorectal cancer by 40 years of age (1). On the other hand, squamous esophageal cancer appears to be due in most cases to a combination of environmental exposures (alcohol consumption, cigarette smoke, hot tea, ingestion of contaminated preserved food) and/or infection (specifically with human papilloma virus), in most cases (2).

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CONFLICT OF INTEREST

Potential competing interests: None.

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Gastroesophageal reflux (GERD) is reasonably strongly associated with genetic risk factors; thus, comparing monozygotic twins (who presumably have identical DNA) with dizygotic twins (who share 50% of their genes); about one-third of the predisposition to GERD is calculated to be genetic (3–5). The explanation for the potential inherited factors could be many, including inherited predisposition to a weak lower esophageal sphincter tone or increased transient lower esophageal sphincter relaxations, poor mucosal repair, altered acid or bile reflux composition, or inadequate refluxate clearance.

In this edition of the Journal, an entirely new mechanism is suggested, namely that enhanced perception of reflux events occurs in GERD as a consequence of increased sensory signal transduction that is partly genetically determined (6). The authors present data from a medium-sized case control study (363 Caucasian patients and 373 healthy controls) and test the association with a common polymorphism of the gene *GNβ3* that encodes the β3 subunit of the G-protein, key to secondary messenger function and thus signaling in the gut (Table 1). The polymorphism gives rise to three possible genotypes, i.e., CC, CT, and TT (one inherits a C or a T allele from each parent). The 825T allele within the TT or CT genotype causes different splicing of the gene and the formation of a truncated, but functionally active, splice variant. In general, the 825T allele is predictive of enhanced G-protein activation and, thereby, increased cellular or physiological responses (Figure 1). Homozygous 825C allele carriers (CC genotype) form only minute amounts of the β3 splice variant and thus are characterized by diminished signal transduction responses.

Polymorphisms in the 825T allele of the *GNβ3* gene may thus mediate an increased response to acid neurotransmitters (6). Intriguingly, those with more severe symptomatic reflux disease were more likely to have the CT functioning allele compared with those with Barrett's esophagus, implying that there may be a genetic predisposition to diminished perception of acid reflux events in the Barrett's esophagus group (6). Notably, the 825T allele has also been linked to functional dyspepsia (Table 1), a disorder characterized by disturbed gastroduodenal sensation in a subset (7–10).

SINGLE-NUCLEOTIDE POLYMORPHISMS

Mutations are rare; a polymorphism is essentially a “common” mutation (present in 1% or greater of the population). This study has looked at one single polymorphism by a simple measure, the beacon assay, which basically assesses the variation in the sequence of DNA between the two halves of chromosomes (alleles) we all inherit; one from each of our parents (e.g., in *GNβ3* the C or T allele). This variation in single base pairs between the two alleles is called a single-nucleotide polymorphism (SNP). Now more sophisticated techniques are being considered such as genome-wide association screening, whereby >10,000 polymorphisms can be tested in samples. In this regard, 2,000 Caucasian patients with Barrett's esophagus, as well as reflux controls, are undergoing genome-wide association screening analysis as part of the Aspirin Esome-prazole Chemoprevention Trial. Regardless of methods, how do we know when a particular SNP is likely to be important? One important clue can be if there is deviation of the Hardy–Weinberg equilibrium (HWE). This is a calculation of the expected genetic variation, such as a SNP, in the populations, both in cases and controls. If there is deviation from the HWE in the control groups, then the study is fundamentally flawed, which usually means genotyping errors or less likely inadvertent bias in patient selection. If the deviation from the HWE occurs in the case group, this suggests that perhaps the variation has a genuine disease association. Next is the effect size, and although relative risk is the most understandable way to measure altered risk, odds ratios approximate risk in case–control studies. In general terms, odds ratios < 20% (e.g., < 1.2) suggest a very subtle risk even if statistically significant, and may reflect unrecognized

bias. Finally, genetic association findings need replication by independent studies to show that the effect is generalizable to the same and different racial groups.

SNPS AND GI PRACTICE

The field of SNP analysis is likely to change practice. Perhaps a good example is inflammatory bowel disease, in which several SNPs have been shown to predict either ulcerative colitis or Crohn's disease (11). In total, 20 % of the diagnoses are unclear clinically and therefore, genetic assessment of these patients could augment management in the near future.

GN β 3 AND OTHER GI DISEASES

The only genetic association reported in functional dyspepsia is the link to *GN β 3* (12); this has been found in the United States (9), Europe (7,10), and Asia (8), although the sample sizes remain relatively small in all of these studies, which may account for some of the variability in the associations detected (Table 1). In other works, the 825T allele of the *GN β 3* gene was associated with lower fasting gastric volumes on ^{99m}Tc-SPECT scanning, which might account for postprandial symptomatology (13). deVries *et al.* found that GERD patients with concomitant functional GI symptoms had a weaker association with *GN β 3*, but this was a subanalysis, and the irritable bowel syndrome (IBS) was not able to be disentangled from functional dyspepsia. Indeed, no association between IBS and *GN β 3* has been detected in multiple studies (14–16).

CONCLUSIONS

This study is provocative but not large enough (6). Although the phenotypic characterization of the cases (to help create robust intermediate groups, or what are now called endophenotypes) is a step forward, it remains inadequately detailed; for example, although cases were all defined by abnormal esophageal pH testing, this will misclassify some cases (6). Furthermore, although body mass index was controlled for others, unknown confounders might still account for any association (16). Therefore, the link between GERD and this *GN β 3* polymorphism needs to be validated in much larger cohorts in both Caucasian and non-Caucasian populations, with well-characterized functional dyspepsia patients included as a potential control group, and IBS excluded. Still, the results remain potentially exciting in our field as, in a sense, this study has succeeded where others have failed to show a genetic predisposition in GERD (17).

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Figure 1.

Activation of G-proteins postsynaptically varies with C825T genotype in *GNβ*. 5HT (serotonin) and NE (norepinephrine) release is illustrated in this illustration. The heterotrimeric G-proteins are essential for stimulus-response coupling of receptors: TT is associated with increased signal transduction; CC with reduced signal transduction.

Table 1Association of *GN β* with gastrointestinal (GI) disease

<i>GNβ</i> association	Disease	Replication
No	IBS	Yes (no association confirmed)
Yes (825T allele)	GERD	No (future studies required)
Yes (825T allele, and homozygous 825C allele)	Functional dyspepsia	Yes (both associations supported)

GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome.