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Genetic risk factors for diverticular disease – emerging evidence

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Introduction

Despite its high incidence, the pathophysiology of diverticulitis remains incompletely understood. Although diverticulitis is classically described and currently understood as an environmental disease, accumulating evidence suggests that genetics play a substantial role. Twin studies estimate 40–53% of individual disease susceptibility stems from genetic factors, suggesting that diverticulitis, like most common diseases, is a complex trait with both environmental and genetic risk factors. The genetic architecture of diverticulitis has been defined in the past three years through genome wide association studies, revealing genes, biological pathways, and cell types of interest. These novel data present multiple opportunities for discovery in diverticulitis, a disease which, despite its commonality, is understudied and lacking in basic research.

Epidemiology

Diverticulitis is one of the most common colorectal diseases treated by primary care providers, surgeons, and emergency room physicians. Diverticulitis causes more than 200,000 inpatient admissions annually in the United States resulting in billions of dollars in cost and thousands of surgical interventions¹. A review of the literature would suggest that diverticulitis confounds clinicians. Antibiotics, routine colectomy, traditional dietary recommendations, and surgical approaches have all been seriously questioned in the past decade, suggesting there is much more to learn about this disease clinically, surgically, and at a molecular level.

In European-ancestry populations, diverticulosis is ubiquitous in the sigmoid colon of older individuals. More than 60% of individuals over 50 undergoing screening lower endoscopy are found to have diverticula in North America and Europe². Historical trends demonstrate increasing incidence over time, historically attributed to industrialization³. However, even in the modern era incidence is increasing rapidly, especially among Americans <40 years of

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age⁴. The triggers that produce diverticulitis in <5% of patients with diverticulosis are unknown, but environmental and individual risk factors have been identified. Within industrialized nations, incidence of diverticulitis is higher in Northern latitudes, and a seasonal trend in admissions persists across the hemispheres⁵. Outside of geography and season, well-phenotyped cohort studies have demonstrated associations of diverticular disease with low physical activity, obesity, and unhealthy diet^{6–8}, but whether these associations are causal or only correlative is unknown.

Globally, diverticulosis demonstrates striking geographic variation. This epidemiologic observation led to early and lasting etiologic hypotheses. Working in Uganda in the 1960s, Burkitt observed the high fiber diet, bulky stools, and decreased disease prevalence in Sub-Saharan African compared to Northern European populations⁹. From these observations he developed Burkitt's hypothesis that attributed diverticular disease and multiple other diseases of Western society, hernias, appendicitis, diabetes, varicose veins, colon cancer, and arteriosclerosis, to low fiber consumption¹⁰. Fiber intake continues to be recognized a risk factor in these diseases¹¹. Global variation remains high. In Sub-Saharan Africa where Burkitt studied, lack of routine screening endoscopy continues to be a barrier to determining true incidence of diverticulosis, but modern reported colonoscopic series of symptomatic patients report diverticulosis at 2–15%^{12,13}. Given that these symptomatic patients are likely to be enriched for pathology, the true incidence of diverticulosis in the population as a whole is likely very low. Nonetheless, clinical diverticular disease is increasingly seen in African hospitals¹⁴.

In Asia, diverticular disease is likely more prevalent than in Africa, but less so than in Europe and North America. Diverticulosis in Asian populations is also anatomically distinct, demonstrating a strong right sided predilection. For example, a series of >62,000 colonoscopies performed in China demonstrated <2% of the population had diverticulosis, but >85% was right-sided¹⁵. Similar studies from Korea and Taiwan have demonstrated higher prevalence, 13–15%, with preserved right-sided dominance^{16,17}. The underlying biology behind the anatomic variation is unknown, but right-sided diverticulosis intuitively seems less likely to be due to constipation and mechanical stress, given the liquid nature of stool in the right colon.

Diverticulitis and Mendelian Traits

Diverticulitis is occasionally observed in association with rare Mendelian connective tissue traits including Ehlers-Danlos Syndrome, Marfan Syndrome, polycystic kidney disease, and Williams Syndrome^{18–20}. These occurrences, although rare, have raised the hypothesis that connective tissue degeneration is involved in the development of diverticular disease. Further support for this hypothesis is provided by clinical associations between diverticulitis and other common degenerative conditions such as rectal prolapse, aortic aneurysm, and incisional hernia¹⁸.

Occurrence of early onset, severe diverticular disease in otherwise healthy families has been noted and has led to the discovery of associated variants in the genes *LAMB4* and *TNFSF15*^{21,22}. The exact role of these genes in diverticulitis is unknown, but both are

involved in pathways that seem logically linked to diverticular disease. *LAMB4* encodes a member of the laminin protein family, critical structural proteins in the extracellular matrix. *TNFSF15* is a member of the tumor necrosis factor family implicated in inflammation. These processes, connective tissue integrity and infection/inflammation are critically linked in our concept of the disease as a super-infection/inflammation of an acquired degenerative precursor lesion. Outside of these rare syndromes and families however, diverticulitis typically occurs sporadically in otherwise healthy patients. However, even among typical diverticulitis patients, family history is an independent risk factor for disease recurrence and diverticular complications²³.

Twin Studies of Diverticular Disease

At the population level, twin studies are classic and powerful for tools for analyzing the relative contributions of genetic and environmental risk factors to disease development. Monozygotic twins, dizygotic twins, and siblings share different proportions of DNA, but experience similar environmental risks. Two twin studies for diverticular disease have been performed in large, well-defined European populations. First, a population-wide Danish study found a relative risk of 2.92 for diverticular disease in siblings as compared to the general population. The relative risk was 14.5 for monozygotic twins²⁴. Second, a population-wide Swedish study found an odds ratio for disease concordance of 7.15 in monozygotic and 3.20 in dizygotic twins²⁵. Taken together the increased disease concordance in monozygotic twins allows estimations that 40–53% of individual risk of diverticular disease is due to heritable factors. Genetic risk factors are more prominent in severe disease. Relative risk for disease concordance was 2.92 for siblings with uncomplicated diverticulitis, but 5.37 for siblings who had surgery for diverticulitis²⁴.

Diverticulitis as a Complex Trait: Genome-Wide Association Studies

It is clear that outside of some rare families, diverticulitis not a Mendelian phenotype. However, family histories and twin studies provide evidence that like coronary artery disease, atrial fibrillation, common cancers, and indeed most common diseases, diverticulitis is a complex trait with both genetic and environmental risks. The underlying genetic architecture a complex trait is not that of Mendelian phenotypes like sickle cell anemia or cystic fibrosis. Rather than a single deleterious mutation driving the disease, in a complex trait the individually small contributions of thousands of genetic polymorphisms combine to create an individual genetic risk profile that interacts with environmental factors to produce disease. Unlike most environmental risk factors, like diet or smoking, the genetic background does not change. It can be considered an individual's first and most constant risk factor for disease.

The genetic architecture of diverticular disease has been defined in the past three years with genome wide associations studies (GWASs). GWASs use whole genomic sequencing to identify single nucleotide polymorphisms (SNPs) associated with a phenotype. Given the immense size of the human genome, GWASs require the statistical power of large, genotyped populations to identify genome-wide significant SNPs ($p < 10^{-8}$) even for common traits like diverticulitis.

The first GWAS for diverticular disease was performed in an Icelandic population and validated in a Danish population, each including approximately 5,500 cases of diverticulitis. The study identified three genome-wide significant SNPs in the genes *ARHGAP15*, *FAM155A*, and *COLQ*²⁶.

Our group followed this initial work in the much larger United Kingdom Biobank (UKBB), an incredible resource including 500,000 middle-aged British individuals. Whole genome sequencing data are linked to detailed phenotypic data including morphometrics, questionnaires, and inpatient medical admissions. Within the UKBB, approximately 27,500 participants had an inpatient admission for diverticular disease (ICD-10 K57)²⁷. We performed a GWAS for associated genetic variants that identified 39 novel SNPs and replicated the 3 SNPs from the prior GWAS. We mapped these variants to 99 nearby genes and validated many of them in the much smaller Michigan Genomics Initiative.

Some of the 99 identified genes have known roles in processes with logical relevance to diverticulitis such as inflammation, intestinal membrane transport, intestinal motility, and extracellular matrix formation. For instance, the top hit *ARHGAP15* is a negative regulator of neutrophils and could therefore be implicated in the immune response to diverticulitis²⁸. *ANO1* is a calcium-activated chloride transporter critical to intestinal pacemaker function of the interstitial cells of Cajal²⁹. *ELN* encodes the key extracellular matrix component elastin, which has been found to be altered in diverticular colon³⁰ and is among the genes deleted in Williams Syndrome, which frequently manifests with diverticular disease²⁰. Deleterious mutations in *SPINT2* cause a hereditary sodium-wasting diarrhea which can be fatal³¹. However, many identified genes have no known function, or a function not obviously relevant to diverticular disease. Interestingly, genes previously identified in severely afflicted families and many of the genes known to cause connective-tissue syndromes were not identified in our GWAS, suggesting that these unusual cases represent the exception rather than the rule in genetic diverticular risk.

We performed follow-up analyses including tissue/cell enrichment, pathway analysis, and a phenome-wide association study (PheWAS). We found gene enrichment in mesenchymal stem cells and many connective cell and tissue types. Enrichment of our genes of interest was identified in known biological pathways including mesenchymal development, vascular biology, and the extracellular matrix. PheWAS performed in the UKBB found that our identified SNPs also associated with multiple types of hernias, female genital prolapse, arterial and venous vascular pathology, and morphometric traits such as BMI and waist/hip ratio. Other common colorectal conditions such as inflammatory bowel disease, appendicitis, and colon cancer were not associated with diverticulitis-SNPs on PheWAS.

A subsequent GWAS including overlapping UKBB data but a distinct European validation population also confirmed the majority of correlated SNPs³² identified in our study.

The GWAS approach identifies fascinating genetic correlations but has important limitations. First, as with many genomic analyses, conclusions are limited to the European ancestry participants. Second, enrollment in UKBB was limited to 40–60 year-old individuals, potentially excluding younger patients with the most severe disease or older

patients with distinct pathophysiology. Third, the de-identified nature of large biobanks prevents the creation of detailed medical phenotypes. Therefore, although we considered inpatient admission a marker for diverticular disease rather than an asymptomatic precursor, it is possible that our identified variants are more closely correlated with diverticulosis than diverticulitis.

Future Directions

Changing the paradigm of diverticulitis from a purely environmental disease to a complex trait provides an avenue for scientific discovery. The genes, pathways, and tissue types identified in genomic research provide multiple future areas for research including mechanistic studies of individual variants in model organisms, investigation of pleiotropy in the associated traits, and further study of genomic associations in smaller databases permitting more detailed sub-phenotyping, such as institutional biobanks and clinical trial repositories.

However, detailed mechanistic understanding is time consuming and not a prerequisite for clinical utility. In other complex traits, such as coronary artery disease and diabetes, genomic data have been harnessed to create polygenic risk scores. These scores have demonstrated early promise in clinical risk stratification for screening and treatment and become rapidly commercially available³³. A similar approach in diverticulitis, providing individualized risk prediction, could improve elective surgical decision-making and inform patient counselling.

Our understanding of the molecular pathophysiology of diverticulitis is still developing. Much critical work remains to be done including developing animal models, increasing our knowledge of non-European ancestry populations, and assembling well-phenotyped patient cohorts for longitudinal study. These studies and more may help science finally disentangle the complex interactions of gene and environment in this common and morbid disease. Finally, the relatively lagging pace of scientific discoveries in a common surgical disease like diverticulitis compared to other medical illnesses speaks to the critical need for increased surgical involvement in basic research.

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