

## REVIEW

## Etiopathogenetic Mechanisms in Diverticular Disease of the Colon

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## SUMMARY

This article reviews epidemiological evidence of heritability and putative mechanisms in diverticular disease, with greatest attention to 3 recent studies of genetic associations with diverticular disease based on genome-wide or whole-genome sequencing studies in large patient cohorts.

**This article reviews epidemiological evidence of heritability and putative mechanisms in diverticular disease, with greatest attention to 3 recent studies of genetic associations with diverticular disease based on genome-wide or whole-genome sequencing studies in large patient cohorts. We provide an analysis of the biological plausibility of the significant associations with gene variants reported and highlight the relevance of ANO1, CPI-17 (aka PPP1R14A), COLQ6, COL6A1, CALCB or CALCA, COL6A1, ARHGAP15, and S100A10 to colonic neuromuscular function and tissue properties that may result in altered compliance and predispose to the development of diverticular disease. Such studies also identify candidate genes for future studies. (Cell Mol Gastroenterol Hepatol 2020;9:15–32; <https://doi.org/10.1016/j.jcmgh.2019.07.007>)**

**Keywords:** Diverticulum; Diverticulitis; Diverticular Hemorrhage.

Colonic diverticulosis is the most common finding on screening colonoscopy in the United States,<sup>1</sup> and the prevalence of diverticulosis increases with age. Using national data from routine clinical colonoscopies, the prevalence of diverticulosis was 20% in individuals 40–49 years of age. The prevalence increased with every age group, reaching 75% in those 80 years of age and older.<sup>1</sup> In a U.S. colonoscopy-based study aimed at detecting diverticulosis,<sup>2</sup> the density, size, depth and distribution of diverticula also increased with age.

These false or pseudodiverticula are acquired with age and form when the colonic mucosa and submucosa herniate through vascular portals in the muscularis propria into the subserosa.<sup>3</sup> In contrast with the United States, colonic diverticulosis is less prevalent in African and Asian countries and, when present, is usually right-sided,<sup>4,5</sup> although left-sided diverticula are becoming more frequent as shown in a recent report from Yokohama, Japan.<sup>6</sup> African Americans in the United States are more likely to have right-sided diverticulosis.<sup>2</sup>

While diverticulosis is usually an incidental finding, some individuals with diverticulosis will go on to develop clinically significant complications.<sup>7</sup> The complications are morbid, sometimes fatal, and responsible for \$5.5 billion dollars in U.S. health care expenditures annually.<sup>8</sup> The 2 most common complications of colonic diverticulosis are acute diverticulitis and diverticular hemorrhage. Acute diverticulitis is characterized by inflammation localized to a diverticulum and the surrounding mucosa. Acute diverticulitis is usually a self-limited event but relapses unpredictably in more than 20% of cases.<sup>9</sup> In some cases of acute diverticulitis, the inflammation will lead to a phlegmon, abscess, bowel perforation, or peritonitis. Rarely, acute diverticulitis will become chronic or progress to a fistulizing or structuring disease. Chronic gastrointestinal symptoms are common after an episode of diverticulitis and attributed to postinflammatory visceral hypersensitivity.<sup>10–12</sup> In contrast, diverticular hemorrhage is the result of rupture of an artery in the base or neck of a diverticulum without associated inflammation. *Diverticular disease* is a nonspecific term often used to describe diverticulosis and all potential complications, but is sometimes used to only describe the complications of diverticulosis.<sup>13</sup> Most of the research to date has used the former. We used the term similarly in this review. When possible, we use more specific nomenclature (ie, diverticulosis and diverticulitis) because the mechanism by which colonic diverticula form may be entirely different from the mechanism by which diverticulitis or diverticular hemorrhage develops.<sup>14</sup> This review does not include discussion of symptomatic uncomplicated disease, a debated condition used to describe patients with diverticulosis without diverticulitis and chronic gastrointestinal symptoms.<sup>11,15–17</sup>

## Epidemiological and Twin Studies Support Genetic Contribution to Diverticular Disease

Emerging evidence suggests that genes contribute to the risk of developing colonic diverticular disease. Using data from the Swedish Twin Registry, the odds of developing

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2352-345X

<https://doi.org/10.1016/j.jcmgh.2019.07.007>

diverticular disease in siblings of index cases was 7-fold for monozygotic twins and 3-fold for dizygotic twins.<sup>18</sup> A population-based study in Denmark found that the risk of developing diverticular disease in siblings of index cases was 14.5-fold for monozygotic twins, 5.5-fold for dizygotic twins, and 3-fold for siblings.<sup>19</sup> The risk was significantly higher for siblings of cases with young-onset disease. Among twins, but not siblings, there was a marked difference in risk by sex, with strong evidence for a genetic effect in female twins, but not among male twins. Based on these 2 studies, the genetic contribution to diverticular disease is estimated at 40%–53%.

## Diverticulosis: Prevailing Hypothesis of Fiber Deficiency Questioned

Historically, colonic diverticulosis was attributed to a low fiber diet. In 1971, Painter and Burkitt<sup>20</sup> proposed that a low fiber diet resulted in smaller volume stool while the sigmoid colon would segment or functionally obstruct when the diet was deficient in bulk forming fiber.<sup>21</sup> Over time, the colon wall was thought to “rupture” from excessive pulsion forces with formation of diverticula.<sup>21</sup> The fiber hypothesis was based on ecologic observations—diverticulosis was rare in countries with high-fiber diets—and until recently, had never been formally studied. The fiber hypothesis was tested in 2 cross-sectional colonoscopy-based studies of well-characterized individuals (demographics, diet, and physical activity) presenting for a screening colonoscopy, thereby avoiding selection bias. In both studies, neither dietary fiber intake nor constipation was associated with an increased risk of colonic diverticulosis.<sup>22,23</sup> Measures of association were calculated with appropriate control for confounding variables. This work strongly challenged the hypothesis that diverticulosis is the result of a low fiber diet and created the space for alternative hypotheses.

## Alternative Hypotheses for Diverticulosis: Altered Tissue Integrity, Sex Hormones, the Microbiome, and Inflammation

Diverticula form when colonic mucosa and submucosa herniate through the perivascular connective tissue envelope that surrounds the intramural vasa recta (Figure 1).<sup>14</sup> As such, there is potentially a role for dysfunctional connective tissues, best illustrated by association of diverticulosis with both acquired<sup>24</sup> and inherited connective tissue disorders including Marfan, Ehlers-Danlos, Coffin-Lowry, and Williams syndromes, reviewed by Reichert and Lamert,<sup>25</sup> and aging (Figure 1). Dysfunctional connective tissues may predispose colonic mucosa and submucosa to herniate into the subserosa, and alter colonic compliance. There is lower compliance of the sigmoid compared with the transverse colon,<sup>26</sup> which has similar compliance to the ascending colon.<sup>27</sup> These observations might explain the higher prevalence of distal diverticulosis in Western populations. Collagen accounts for mechanical stability of connective tissues, and is altered in patients with a history of recurrent diverticulitis, as a reaction to chronic

inflammation.<sup>28–30</sup> In diverticulosis without diverticulitis, there is evidence for higher expression of matrix metalloproteinase-1 (ubiquitously expressed interstitial collagenase) and altered connective tissues.<sup>31–35</sup> While dysfunctional connective tissues or compliance contribute to the risk of distal diverticulosis, right-sided diverticulosis in Asian individuals<sup>4,5</sup> may suggest a genetic contribution.

Endogenous sex hormones may be associated with diverticulosis risk. In a prospective study of patients undergoing screening colonoscopy, diverticulosis was less prevalent in premenopausal age women compared with similar aged men.<sup>36</sup> The prevalence of diverticulosis in men and women was the same after 50 years of age. This finding suggests that ovarian steroid hormones in premenopausal women may reduce the risk of diverticulosis, potentially via favorable effects of steroid hormones on collagen or elastin.<sup>37,38</sup> In the same study, general obesity increased the risk of diverticulosis in women, but not men.<sup>36</sup> The increased risk was limited to women before the age of 60. Premenopausal obesity may increase the risk of diverticulosis in women by decreasing circulating estrogen and increasing free testosterone.<sup>39</sup>

The development of colonic diverticulosis is unlikely to be related to an aberrant microbiota, based on absence of significant alterations in a careful study.<sup>40</sup> Mucosal inflammation is also unlikely to play a role; in a colonoscopy-based study, there was no association between markers of chronic mucosal inflammation and diverticulosis.<sup>16</sup>

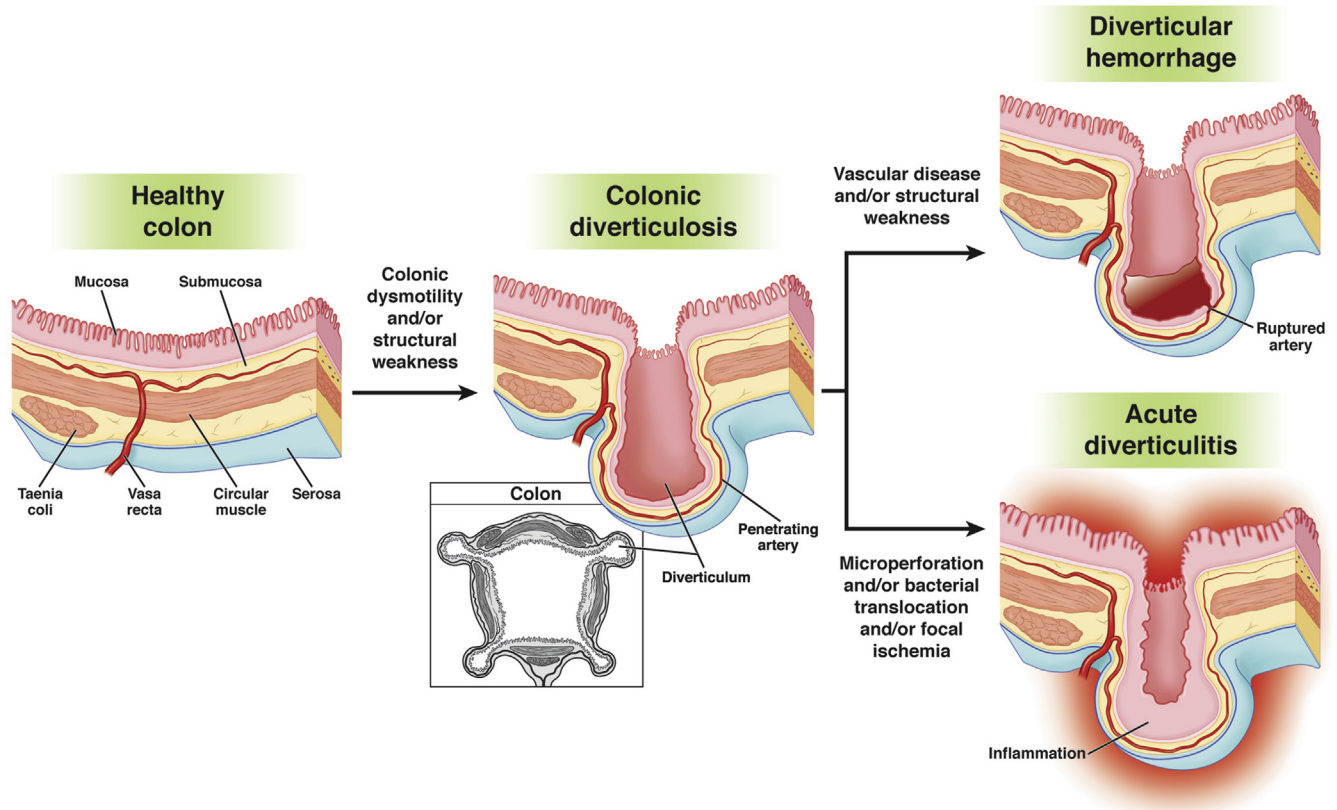
## Diverticulosis and Motility: Neuromuscular Mechanisms and Receptors

Studies utilizing full-thickness human sigmoid colons with diverticulosis have found significant alterations in enteric smooth muscle in noninflamed regions. Such studies documented severely reduced spontaneous motility and enhanced neutrally mediated sigmoid colon tissue responses,<sup>41</sup> multiple molecular alterations involved in smooth muscle contractile functions,<sup>42</sup> increased ratio of connective tissue within the longitudinal muscle layer, or increased thickness of the circular and longitudinal muscle layer, structural alterations of smooth muscle cells, and decreased expression of functionally relevant myofilament types.<sup>33</sup> One study reported downregulation of 5-hydroxytryptamine receptor 4 receptors (which are involved in stimulation of peristalsis) in colons with diverticulosis.<sup>43</sup>

Descriptive motility studies suggested compartment formation in sigmoid colons with diverticulosis,<sup>21,23</sup> leading to elevated segmental pressures. These provocative studies did not formally compare motility measurements in healthy subjects, and may have involved selection, age or sex bias. There are no contemporary studies of colonic motility in patients with diverticulosis without such biases.<sup>44</sup>

## Diverticulitis: Compelling Evidence that Diet and Lifestyle Contribute to Risk

In addition to the genetic contribution described previously, there is strong evidence that age, female sex, diet, and



**Figure 1.** Colonic diverticula form when mucosa and submucosa herniate through the envelope that surrounds the intramural vasa recta; colonic dysmotility or structural weaknesses likely contribute to this pathology. Diverticular hemorrhage is an arterial bleed in an uninfamed diverticulum, with vascular disease or structural weakness likely playing a role. Acute diverticulitis is inflammation localized to a diverticulum and the surrounding mucosa triggered by microperforation or bacterial translocation, or focal ischemia.

lifestyle contribute to the risk of diverticulitis.<sup>45</sup> Similar to diverticulosis, diverticulitis risk increases with age.<sup>46</sup> Likewise, premenopausal age women are protected from diverticulitis compared with similar-aged men.<sup>46</sup> Unlike diverticulosis risk, the risk of diverticulitis increases significantly in women after the age of menopause and is greater in women over 60 years of age compared with similar-aged men.<sup>46</sup> Menopausal hormone therapy increases the risk.<sup>47</sup> In well-characterized prospective cohort studies, obesity, a Western diet (including low dietary fiber and high red meat intake), physical inactivity, and smoking increase the risk of diverticulitis.<sup>45,46,48–52</sup> Regular use of nonsteroidal anti-inflammatory drugs doubles the risk,<sup>53</sup> and chronic immunosuppression<sup>54</sup> is also a risk factor for diverticulitis and the more serious complications, such as abscess and perforation.

### Diverticulitis Pathophysiology: Dysmotility, the Microbiome, and Inflammation

Similar to diverticulosis, the etiopathogenesis of diverticulitis is poorly understood. Some authors have hypothesized that diverticulitis is the result of inspissated stool eroding through the diverticular wall (Figure 1).<sup>55</sup> It has

also been suggested that peridiverticular submucosal blood vessels can become compromised causing local ischemia and inflammation.<sup>14</sup> There is a theory that a narrow necked diverticulum does not empty well and that increased exposure time to stool facilitates translocation.<sup>14</sup> Finally, the fundus of the diverticulum (with only a serosal covering) may become distended to the point of microperforation.<sup>14</sup>

There are a number of factors that may contribute to diverticulitis pathogenesis. Dysmotility may play a role in the pathogenesis of diverticulitis. In preliminary work, more frequent bowel movements at baseline were associated with diverticulitis risk.<sup>56</sup> Studies utilizing full-thickness human sigmoid colons electively resected for diverticular disease (usually diverticulitis) found hypoganglionosis of the enteric nervous system,<sup>57</sup> altered GDNF/Ret signaling in the myenteric plexus,<sup>58</sup> altered expression of the homeobox transcription factor Phox2b<sup>57</sup> and abnormalities in longitudinal muscle relaxation.<sup>59</sup> Recurrent diverticulitis may induce changes in the enteric nervous system or these factors may be associated with diverticulosis pathogenesis but not progression to diverticulitis. In a single multigenerational family with early onset diverticulitis, whole exome sequencing was performed and identified a variant in the *LAMB4* gene. This protein plays a role in the function of the enteric nervous system.<sup>60</sup>

If the fecalith or distended diverticulum hypotheses are true, dysfunctional connective tissues may not only predispose to diverticulosis pathogenesis, but may also contribute to diverticulitis. In diverticulitis, there is evidence for diffuse alterations in concentrations of matrix metalloproteinases and tissue inhibitors of metalloproteinases<sup>61</sup> and elastosis.<sup>62</sup> Because connective tissue is changed by chronic inflammation, it is difficult to determine whether these changes occurred before the development of diverticulitis.

The gut microbiome may play a role in the pathogenesis of diverticulitis.<sup>13,63</sup> Gut dysbiosis is associated with mucosal barrier defects and local immune dysfunction and these derangements may contribute to the mucosal inflammation of diverticulitis. This hypothesis is based on evidence that aging, smoking, obesity, a Western diet, and physical inactivity are associated with dysbiosis and diverticulitis risk. Antibiotics use also leads to an unbalanced microbial community, and there are preliminary data that chronic antibiotic use is associated with developing diverticulitis.<sup>64</sup> Previous studies of the microbiome in patients with diverticulitis are based on small cohorts that assessed the microbiome after diagnosis and antibiotic exposure, which may cause dysbiosis.<sup>65–68</sup> Because the majority of individuals with diverticulosis have multiple colonic diverticula and diverticulitis is a focal disease, the contribution of dysbiosis is likely in addition to other factors. The gut microbiome is modifiable, which makes understanding how the microbiota contributes to the inflammatory cascade of diverticulitis an important next step in understanding diverticulitis pathogenesis.

Chronic inflammation is suspected to contribute to diverticulitis risk based on the evidence that obesity, a Western diet, and physical inactivity are risk factors.<sup>13</sup> Likewise, statins reduce the risk, albeit this evidence is limited.<sup>69</sup> There is preliminary evidence that plasma levels of inflammatory (C-reactive protein and interleukin-6) biomarkers are elevated before a diagnosis of diverticulitis, which more directly supports a role for chronic, systemic inflammation.<sup>70</sup> There are multiple inflammatory pathways that could plausibly increase the risk of diverticulitis. Several trials of anti-inflammatory and immunosuppressive drugs for inflammatory bowel disease did not reduce the risk of recurrent disease, which suggests that these diseases do not share a common inflammatory pathway.<sup>9</sup> Additionally, corticosteroids and nonsteroidal anti-inflammatory drugs increase, not decrease, diverticulitis risk.

Chronic inflammation plays a role in cardiovascular disease. Diverticulitis and cardiovascular disease share several risk factors including obesity, physical inactivity, a Western diet, smoking, and chronic corticosteroid use, and among women, being postmenopausal. In a large population-based study, incident diverticular disease was associated with development of acute myocardial infarction, stroke, venous thromboembolism, and subarachnoid hemorrhage. This risk remained even after excluding the first year of follow-up.<sup>71</sup> This study raises the question of whether vascular disease contributes to diverticulitis risk similar to heart disease. Given the shared risk, factors this is a feasible hypothesis.

## Diverticular Hemorrhage: Pathophysiology and Epidemiology

The second-most-common complication of colonic diverticulosis is diverticular hemorrhage, an arterial bleed from the base or neck of an uninflamed diverticulum. Diverticular hemorrhage is the most common cause of lower gastrointestinal bleeding, but is difficult to diagnosis and is most commonly a presumed diagnosis, making research difficult.<sup>72</sup> Diverticula proximal to the splenic flexure are more likely to bleed compared with diverticula in the descending and sigmoid colon.<sup>14</sup> Some authors have hypothesized that diverticular hemorrhage is the result of inspissated stool causing trauma (Figure 1).<sup>14</sup> Mechanical vulnerability has also been proposed.<sup>14</sup> Diverticular hemorrhage is most common in U.S. adults over 60 years of age and African Americans.<sup>73</sup> Obesity, physical inactivity, hypertension, diabetes, and vascular disease increase the risk.<sup>51,52,74</sup> Regular use of nonsteroidal anti-inflammatory drugs is also a risk factor.<sup>75</sup> Recurrent hemorrhage is common with 15% risk recurrence in 5-year follow-up.<sup>76</sup>

## Multiple Genetic Association Studies Identify Possible Loci

Genome-wide association studies (GWASs) aimed at discovery of variants associated with diverticular disease have implicated several novel genes. These studies are summarized in Table 1, which provides information at the discovery and replication stages. To date, at least 35 loci are associated with diverticular disease. In contrast with other works,<sup>77,78</sup> the tumor necrosis superfamily 15 gene was not identified in GWASs.

## Biological Plausibility of Suggested Gene Variants in Diverticular Disease

Given the identification of these genetic loci (Table 2), we have evaluated the biological plausibility of a role in development of diverticular disease, based on the actions of the genes themselves and the impact of the gene variants. The reported variants can be classified into 5 groups (Table 2) based on association with altered smooth muscle or nerve functions, connective tissue function, possible association with other bowel functions (eg, epithelial or immune), biological or clinical relevance unrelated to bowel function, and uncharacterized single nucleotide polymorphisms (SNPs) or unnamed single nucleotide variants (SNVs) of unclear biological or clinical significance.

Among gene variants associated with altered smooth muscle or nerve functions, the prime candidates of interest appear to be *ANO1*, *CPI-17* (aka *PPP1R14A*), *COLQ6*, *COL6A1*, and *CALCB* or *CALCA*. Thus, *ANO1* influences Ca<sup>2+</sup>-activated Cl<sup>-</sup> channels in the pacemaker ICCs, downregulation of *CPI-17* causes sustained muscle contraction, and downregulation of *COLQ* reduces acetyl cholinesterase. *P2RY12* and *CALCB* or *CALCA* affect afferent nerves, microglia, or calcium balance, and may indirectly affect neuromuscular function. Other genes, *COL6A1*, *ARHGAP15*, and *S100A10*, potentially impact the structure, tensile strength, or

**Table 1.** Extensive Genome Studies of Association Diverticular Diseases

Discovery Stage			Replication Stage			Combined Analysis	
Population	Sample Size	Genome-Wide Significant Loci	Population	Sample Size	Genome-Wide Significant Loci	Genome-Wide Significant Loci	Reference
Icelandic population	5426 cases diverticular disease <sup>1</sup> 2764 cases diverticulitis <sup>a</sup> 245,951 controls	3	Danish National Biobank	5970 cases diverticular disease <sup>b</sup> 3020 controls	3	3	88
UK Biobank	27,444 cases diverticular disease <sup>c</sup> 382,284 controls	40	Michigan Genomics Initiative	1854 cases diverticulosis <sup>d</sup> 718 cases diverticulitis 28,649 controls	8	NA	89
UK Biobank	31,964 cases diverticular disease <sup>e</sup> 419,135 controls	48	Germany, Austria, Lithuania, and Sweden	3893 cases diverticular disease <sup>f</sup> 2829 diverticula-free controls	27	35 (meta-analysis using Michigan data from ref. 89)	85

<sup>a</sup>Diverticular disease included individuals with diverticulosis and any potential complication. Cases of diverticular disease were defined as an individual with an International Classification of Diseases-Ninth Revision (ICD-9) code 562.1-2 or International Classification of Diseases-Tenth Revision (ICD-10) code K57.2-9. Patients who came to the hospital for diverticulitis complications or if the diagnosis was coupled to a resection of the left colon or sigmoid colon were classified as diverticulitis.

<sup>b</sup>Diverticular disease included individuals with diverticulosis and any potential complication. Cases were defined as an ICD-9 code 562.1-2 or ICD-10 code K57.2-9.

<sup>c</sup>Diverticular disease included individuals with diverticulosis and any potential complication. Cases were defined as an individual with any ICD-10 K57 code.

<sup>d</sup>Diverticulosis cases were defined by individuals with ICD-9 562.10 or 562.12 code. Diverticulitis cases were defined by individuals with an ICD-9 562.11 or 562.13 code.

<sup>e</sup>Diverticular disease included individuals with diverticulosis and any potential complication. Defined as an individual with an ICD-9 code 562 or ICD-10 K57 in the UK Biobank dataset for primary, secondary, and self-reported diverticular disease diagnosis.

<sup>f</sup>Diverticular disease included individuals with diverticulosis and any potential complication. The German and Lithuanian samples were phenotyped by review of colonoscopy reports, hospital admissions, and ambulatory clinic records to identify cases with diverticulosis and diverticulitis, and diverticula-free controls. The Austrian samples were phenotyped by review of colonoscopy and clinical data. The Swedish samples were phenotyped based on colonoscopy reports to identify cases with or without diverticulosis.

**Table 2.** Functions of Gene Variants Associated with Diverticulosis, Diverticular Disease, or Diverticulitis

Nearest Gene	Full Name	Functions of Genes	SNP/SNV	Associations With Colon Functions	Mechanistic Effects of Variants	Discovery Reference(s)	Mechanism Reference(s)
<b>Gene variants associated with altered smooth muscle or nerve function</b>							
<i>FADD</i> or <i>ANO1</i>	<i>FADD</i> = Fas associated via death domain; <i>ANO1</i> = Anoctamin 1, aka trans-membrane protein 16A (TMEM16A)	<i>FADD</i> associated with colon cancer and Crohn's disease; <i>ANO1</i> related to gastrointestinal pacemaker activity	rs875107 rs72945112	DD and D-osis (89); DD (85) Hirschsprung disease and functional constipation	Intronic SNP of UNCS; <i>ANO1</i> Influences Ca <sup>2+</sup> -activated Cl <sup>-</sup> channel in epithelia and ICCs	85,89	90–92
<i>ARHGAP15</i>	Rho GTPase activating protein 15	Negative regulator of neutrophil functions; affects the architecture and function of hippocampal inhibitory neurons and causes cognitive deficits	rs4662344 rs6734367	DD (85,88) Hirschsprung in Mowat-Wilson syndrome DD and D-osis (89)	Intronic SNP of UNCS; Overexpression results in an increase in actin stress fibers and cell contraction Intronic SNP of UNCS	85,88 89	93–95 96 97
<i>COLQ</i> or <i>METTL6</i>	COOH-terminal collagen Q; Methyltransferase like 6	Collagen-like tail subunit of asymmetric acetyl-cholinesterase; controls postsynaptic differentiation at neuromuscular junction	rs7609897	DD (88) DD and D-itis both borderline significant (89) DD (85)	<i>COLQ</i> affects acetylcholinesterase; Congenital myasthenic syndrome	85,88,89	98 99 100 101
<i>PPP1R14A</i> (aka <i>CPI-17</i> ) or <i>SPINT2</i>	protein phosphatase 1 regulatory inhibitor subunit 14A or serine peptidase inhibitor, Kunitz type 2	<i>CPI-17</i> is a phosphorylation-dependent inhibitory protein for smooth muscle myosin phosphate (including colon); Downregulation of <i>CPI-17</i> expression causes sustained contraction in colonic muscle; <i>CPI-17</i> may cause reduced contraction in aging rat colon	rs11667256	DD and D-osis borderline significant (89) DD (85)	SNP of UNCS; however, mutations in <i>SPINT2</i> result in congenital sodium diarrhea	85,89	102–104
<i>P2RY12</i>	purinergic receptor P2Y12	Critical role in platelet function and microglia neuronal function	rs3732760	DD (85)	Intronic SNP of UNCS;	85	105 or 106
<i>CALCB</i> , or <i>CALCA</i>	calcitonin related polypeptide beta	Afferent nerve function and calcium balance, vasodilators with signaling mechanisms in vascular endothelium and smooth muscle	rs575909118 or 12293535 or 12293178	D-itis > D-osis (85)	SNVs of UNCS	85	107
<i>COL6A1</i>	collagen type VI alpha 1 chain	Association with muscular dystrophies/ myopathies and ossification of ligaments; Collagen VI regulates peripheral nerve myelination and function; Lack of collagen VI promotes neurodegeneration	rs7281388	DD (85)	Intronic SNP of UNCS; a <i>COL6A1</i> mechanism associated with Hirschsprung disease by interfering with colonization of the bowel by enteric neural crest cells	85	108–112 113 114

Table 2. Continued

Nearest Gene	Full Name	Functions of Genes	SNP/SNV	Associations With Colon Functions	Mechanistic Effects of Variants	Discovery Reference(s)	Mechanism Reference(s)
<b>Gene variants with conceivable associations with other bowel functions (eg, epithelial or immune)</b>							
<i>PHGR1</i> or <i>DISP2</i>	<i>PHGR1</i> proline, histidine and glycine rich 1 or <i>DISP2</i> dispatched RND transporter family member 2	Epithelial dysfunction, high expression in colon and small intestine	rs71472433	D-itis > D-osis (85)	Intronic SNP of UNCS;	85	115
<i>ABO</i>	<i>ABO</i> , $\alpha$ 1-3-N-acetylgalactosaminyl-transferase and $\alpha$ 1-3 galactosyl-transferase	Gene encodes proteins related to blood group system, ABO; Expression in colon, small bowel	rs582094	DD and D-itis (89) DD (85)	Intronic SNP of UNCS	85,89	116
<b>Gene variants associated with altered connective tissue</b>							
<i>S100A10</i>	S100 calcium binding protein A10	Regulates the remodeling of the extracellular matrix	rs61814883	D-itis > D-osis (85)	Intronic SNP of UNCS;	85	117
<i>BMPR1B</i>	bone morphogenetic protein receptor type1B	Protects neurons against kainic acid-induced neurodegeneration	rs1544387	DD and D-itis (89); DD (85)	Intronic SNP of UNCS;	85,89	118 119
<i>ELN</i> or <i>L1MK1</i>	Elastin gene and LIMK1 (ELASTIN) LIM domain kinase 1	Extracellular matrix protein responsible for arterial resilience and skin integrity; Associated with aneurysms (eg, Marfan) and cutis laxa	rs3823878	DD and D-osis (89) DD (85); abnormalities in longitudinal muscle relaxation and content of elastin in uncomplicated DD	Intronic SNP of UNCS;	85,89	59
<i>EFEMP1</i>	Epidermal growth factor-containing fibulin-like extracellular matrix protein 1	extracellular matrix protein associated inguinal hernias and varicose veins, carpal tunnel syndrome, and biliary atresia; association with risk of glioma in Chinese	rs1802575	DD (89)	Not found in gene, genome, OMIM, or PubMed databases	85	120
<b>Gene variants with biological or clinical relevance, but unrelated to bowel functions</b>							
<i>SLC35F3</i>	solute carrier family 35 member F3	Gene involved in hypertension and thiamine transport	rs43333882	DD and D-osis (89) DD (85)	Intronic SNV of UNCS	85,89	121
<i>GPR158</i>	G protein-coupled receptor 158	Gene involved in cognition	rs7086249	DD and D-itis (89) DD (85)	Intronic SNV of UNCS	85,89	122 123 associated with obesity in Pima Indians

Table 2. Continued

Nearest Gene	Full Name	Functions of Genes	SNP/SNV	Associations With Colon Functions	Mechanistic Effects of Variants	Discovery Reference(s)	Mechanism Reference(s)
<i>FAM155A</i>	family with sequence similarity 155 member A	Mainly expressed in hypothalamus and pituitary gland with low expression in colon	rs67153654	DD (88)	Intronic SNP of UNCS	85,88	124,125
			rs9555371	D-itis > D-osis (85)			
			rs9520344				
			rs11619840	DD and D-osis (89)	Intronic SNP of UNCS	89	
			rs9520339	DD (85)	Intronic SNP of UNCS	85	
<i>SHFM1</i> or <i>CLSTN2</i>	<i>SHFM1</i> split hand/foot malformation (ectrodactyly) type 1; <i>CLSTN2</i> calyntenin 2	<i>CLSTN2</i> with human memory, Alzheimer's disease, neural development	rs3113037	DD and D-osis (89)	Upstream variant	85,89	126,127 128
<i>CTAGE1</i>	cutaneous T-cell lymphoma-associated antigen 1	Expression of <i>CTAGE-1</i> restricted to normal testis or most tumors	rs9960286	DD (85)	Intergenic; SNP of UNCS	85	129
<i>GTPBP1</i>	GTP binding protein 1	Upregulated by interferon gamma and encodes a protein that is a member of the <i>AGP11/GTPBP1</i> family of GTP-binding proteins	rs138699	DD and D-osis (89)	Intronic SNP of UNCS	89	130
<i>ISL2</i> or <i>ETFA</i> or <i>SCAPER</i>	<i>ISL2</i> ISL LIM homeobox2; <i>ETFA</i> electron transfer flavoprotein subunit $\alpha$ ; <i>SCAPER</i> S-phase cyclin A associated protein in the Endoplasmic Reticulum	<i>ISL2</i> transcription factor essential for motor neuron development; <i>SCAPER</i> involved in cell cycle progression	rs2056544 rs10519134	DD borderline significant (85); DD and D-osis (89) <i>ETFA</i> variant: susceptibility to glioma; <i>SCAPER</i> variant: Bardet-Biedl syndrome, retinitis pigmentosa, Parkinson's	Intronic SNP of UNCS;	85,89	131,132
<i>TNRC6B</i>	trinucleotide repeat containing adaptor 6B	Involved in RNA interference machinery; Associated with prostate cancer, leiomyoma	rs5995842	DD (85)	Intronic SNP of UNCS;	85	133
<i>SNX24</i>	sorting nexin 24	Involved in endocytosis and protein trafficking; Gene variant associated with coronary aneurysm in Kawasaki disease	rs34126945	DD (85)	Intronic SNP of UNCS;	85	134
<i>C1QTNF7</i> (aka <i>CTRP7</i> )	C1q and tumor necrosis factor- $\alpha$ -related protein 7	Gene related to adiponectin gene and induces AMP-activated protein kinase phosphorylation, increased glycogen accumulation, and fatty acid oxidation	rs4515160	DD (85)	Intronic SNP of UNCS; variants in <i>C1QTNF7</i> gene associated with conduct disorder in childhood	85	135,136



Table 2. Continued

Nearest Gene	Full Name	Functions of Genes	SNP/SNV	Associations With Colon Functions	Mechanistic Effects of Variants	Discovery Reference(s)	Mechanism Reference(s)
<i>PIAS1</i>	protein inhibitor of activated STAT 1	Protein inhibitor of activated STAT proteins are multifunctional nuclear proteins operating in immune system; Associated with Huntington's and other neurodegenerative disorders	rs387505	DD (85)	Intergenic; SNP of UNCS	85	137
<i>HLX</i>	H2.0 like homeobox	Involved in hematopoiesis and fetal growth; Candidate gene for anomalies associated with congenital diaphragmatic hernia, short bowel, and asplenia or childhood asthma	rs2784255	DD (85)	Intergenic; SNP of UNCS	85	138–140
<i>FBXL13</i> or <i>FAM 185A</i>	<i>FBXL13</i> F-box and leucine rich repeat protein 13; <i>FAM 185A</i> family with sequence similarity 185 member A	Possible association with success at smoking cessation	rs10257317	DD (85)	Intronic SNP of UNCS;	85	141
<i>LINC01082</i>	long intergenic non-protein coding RNA 1082	Associated with alveolar capillary dysplasia	rs2280028	DD (85) (borderline)	Intergenic (downstream); SNP of UNCS	85	142
<i>DISP2</i>	dispatched RND transporter family member 2	Described in drosophila, zebrafish and gastric cancer	rs71472433	DD (85) (borderline)	Intronic SNP of UNCS	85	143
<i>CACNB2</i>	calcium voltage-gated channel auxiliary subunit beta 2	<i>CACNB2</i> is 1 of 4 homologous genes coding for the auxiliary Cav $\beta$ subunits, which are important modulators of the Ca <sup>2+</sup> channel activity; <i>CACNB2</i> gene linked to 5 mental, 3 cardiovascular diseases	rs1888693	DD (85) (borderline)	Intronic SNP of UNCS	85	144
<i>NOV</i>	Nephroblastoma overexpressed gene	<i>NOV</i> encodes a secreted cysteine-enriched multimodular protein that acts as a localized multivalent signal integrator; highly expressed in the nervous system, especially in the spinal cord and in the dorsal root ganglion during development	rs60869342	rs1381335	DD (89)	rs60869342:SNV of UNCS rs1381335 Not found in gene, genome, OMIM, or PubMed databases	85,89
<i>EDEM 1</i>	ER-degradation-enhancing alpha-mannosidase-like protein-1	<i>EDEM 1</i> associated with the development of hepatocellular carcinoma	rs7624168	DD (85)	Intergenic SNV of UNCS	85,89	145

Table 2. Continued

Nearest Gene	Full Name	Functions of Genes	SNP/SNV	Associations With Colon Functions	Mechanistic Effects of Variants	Discovery Reference(s)	Mechanism Reference(s)
<i>LYPLAL1-AS1</i>	lysophospholipase like 1 antisense RNA 1	Association with hypertension, obesity and nonalcoholic fatty liver disease	rs61823192	DD (89)	Not found in gene, genome, OMIM, or PubMed databases	85	
<i>SLC25A28</i>	solute carrier family 25 member 28	nuclear-encoded transporters embedded in the inner mitochondrial membrane (specifically mitoferrin 2 which is ubiquitous (heart, liver, kidney)	rs7098322	DD (89)	Not found in gene, genome, OMIM, or PubMed databases	85	146
<i>SLC4A1</i>	solute carrier family 4 member 1	Associated with renal tubular acidosis and RBC senescence	rs8074740	DD (85)	Intergenic SNV of UNCS	85	147
<i>CWC27</i>	spliceosome associated cyclophilin	Associated with retinal degeneration, brachydactyly, craniofacial abnormalities, short stature, and neurological defects	rs10471645	DD (85,89)	Intronic SNV of UNCS	85	148
<b>Uncharacterized SNPs or unnamed SNVs of unclear biological or clinical significance</b>							
<i>LOC101927314</i>	Uncharacterized		rs4839715	DD (Euro) (borderline)	Intronic SNP of UNCS;	85	
<i>unnamed</i>			rs11619840	DD and D-osis	Intronic SNV of UNCS	89	
<i>unnamed</i>			rs72945112	DD and D-osis	SNV of UNCS	89	
<i>unnamed</i>			rs10519134	DD and D-osis	Intronic SNV of UNCS	89	

D-itis, diverticulitis; D-osis, diverticulosis; DD, diverticular disease; ICC, interstitial cells of Cajal; OMIM, Online Mendelian Inheritance in Man; RBC, red blood cell; SNP, single nucleotide polymorphism; SNV, single nucleotide variant; UNCS, unknown clinical significance.

biomechanical properties of the colon. Despite their biological plausibility, the SNPs or SNVs themselves are mostly intronic and are of unclear clinical significance.

Because diverticular disease is a heterogeneous grouping, the relative genetic effect of 27 replicating loci on diverticulitis vs diverticulosis risk was assessed in the European cohort of the Schafmayer et al study. Four loci showed stronger effects for diverticulitis compared with diverticulosis (*PHGR1*, *FAM155A-2*, *CALCB*, and *S100A10*). Again, the gene *CALCB* is associated with afferent nerve function and calcium balance, which supports a role for dysmotility in diverticulitis pathogenesis. The gene *S100A10* regulates the remodeling of the extracellular matrix, which also suggests dysmotility or potentially structural weakness in the diverticulum leading to diverticulitis. The gene *PHGR1* may conceivably increase risk of diverticulitis as it causes epithelial dysfunction and could conceivably increase the likelihood of bacterial penetration to induce inflammation.

Of note, with rare exception (*FADD*) there was little overlap with genes associated with inflammatory bowel disease. Specifically, the genetic studies in diverticulosis and diverticulitis have not identified associations with HLA genes, or genes involved in regulation of innate or adaptive immune responses, defense responses, or responses to biotic stimuli or organisms, which have been described as factors determining susceptibility or outcome in patients with Crohn's disease.<sup>79</sup> Similarly, there was no overlap with 38 susceptibility loci for inflammatory bowel disease identified across populations.<sup>80</sup>

Diverticular hemorrhage is the result of an arterial rupture in the base or neck of a diverticulum. While less frequent than diverticulitis, cases of diverticular hemorrhage would have been captured under the umbrella of diverticular disease in the GWASs described here. There are several genes in the GWASs that could be implicated in the pathogenesis of diverticular hemorrhage. The genes *ELN*, *BMPR1B*, and *EFEMP1* are associated with connective tissue function, and laxity in a diverticulum may predispose to shearing of the culprit artery. There are also several genes associated with vascular disease. The *ABO* gene encodes proteins related to the ABO blood group system. In addition to red blood cells, ABO carbohydrates are expressed on the surface of many tissues and cells, including epithelial cells, sensory neurons, platelets, and vascular epithelium, and are associated with risk of thrombosis and hemorrhage.<sup>81</sup> ABO antigens and blood group type has been associated with risk of gastrointestinal bleeding.<sup>82</sup> While *P2RY12* has a role in neural development, this gene also has a role in platelet function, which may impact hemorrhage risk. *CALCB* has a role in vascular endothelium, *SLC35F3* in hypertension, and *CACNB2* in Ca (2+)-channel activity. If the hypothesis that vascular disease drives diverticulitis risk is true, these same genes may play a role in diverticulitis. However, the mechanism whereby a vascular mechanism results in diverticulosis is still unclear.

While the approach used in our appraisal of the genetic associations with diverticular disease have been based on prior biological knowledge, there are algorithms and tools

for inferring and scoring regulator networks upstream of gene-expression data (eg, based on large-scale causal network derived from the Ingenuity Knowledge Base) or to predict downstream effects on biological functions and diseases, within Ingenuity Pathway Analysis (<http://www.ingenuity.com>). Thus, causal analytics tools are available to appraise upstream regulator analysis, mechanistic networks, causal network analysis, and downstream effects analysis.<sup>83</sup> However, the pathway analysis is usually applied to tissue gene expression or transcriptomics and may identify tissue processes such as inflammation and immune response, cytokine signaling, cellular growth, and movement in addition to processes more directly related to specific functions such as nerve regeneration following nerve injury.<sup>84</sup>

Schafmayer et al<sup>85</sup> used 2 gene set and pathway analysis approaches (MsigDB)<sup>86</sup> and VEGAS2Pathway<sup>87</sup> to determine if the polygenic signal measured in the diverticular disease associated genes clustered in specific biological pathways. VEGAS2Pathway analysis pointed to processes involved in cell and organ differentiation and extracellular matrix among the top 5 identified pathways: negative regulation of cell differentiation, extracellular matrix, negative regulation of developmental process, muscle organ development, and regulation of cell differentiation. These relatively nonspecific pathways contrast with the identified individual genes that affect neuromuscular mechanisms or connective tissue in the study by Schafmayer et al<sup>85</sup> such as *ANO1* (intestinal motility), *COL6A1/A2* (connective tissue), and *GDNF* and *BDNF* (neurotrophic factors). These are all mechanisms that are plausibly related to the development of diverticular disease.

## Future Research

This analysis provides insights into the genes and mechanisms that might be prioritized for further mechanistic, phenotypic measurements (eg, colonic diameter, transit, pressures, and compliance), as well as association studies with gene variants that are more closely aligned to colonic function. Such hypothesis-based research would require smaller sample size and should ascertain the contributions of abnormal motor physiology and genetics to the development and natural history of diverticular disease.

## References

1. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. *Gastroenterology* 2009;136:741–754.
2. Peery AF, Keku TO, Martin CF, Eluri S, Runge T, Galanko JA, Sandler RS. Distribution and characteristics of colonic diverticula in a United States screening population. *Clin Gastroenterol Hepatol* 2016; 14:980–985.e1.
3. Ye H, Losada M, West AB. Diverticulosis coli: update on a "Western" disease. *Adv Anat Pathol* 2005;12:74–80.
4. Sugihara K, Muto T, Morioka Y, Asano A, Yamamoto T. Diverticular disease of the colon in Japan. A review of 615 cases. *Dis Colon Rectum* 1989;27:531–537.

5. Lohsiriwat V, Suthikeeree W. Pattern and distribution of colonic diverticulosis: Analysis of 2877 barium enemas in Thailand. *World J Gastroenterol* 2013;19:8709–8713.
6. Terao K, Sekino Y, Nonaka T, Iida H, Inamori M, Nakajima A, Maeda S, Natsumeda Y, Ikegami T, Ohshige K. Recent trends in colonic diverticulosis in Yokohama City: a possibility of changing to a more Western profile. *Intern Med* 2015;54:2545–2550.
7. Shahedi K, Fuller G, Bolus R, Cohen E, Vu M, Shah R, Agarwal N, Kaneshiro M, Atia M, Sheen V, Kurzbard N, van Oijen MG, Yen L, Hodgkins P, Erder MH, Spiegel B. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. *Clin Gastroenterol Hepatol* 2013;11:1609–1613.
8. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, Jensen ET, Shaheen NJ, Barritt AS, Lieber SR, Kochar B, Barnes EL, Fan YC, Pate V, Galanko J, Baron TH, Sandler RS. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. *Gastroenterology* 2019;156:254–272.e11.
9. Strate LL, Peery AF, Neumann I. American Gastroenterological Association Institute technical review on the management of acute diverticulitis. *Gastroenterology* 2015;149:1950–1976.e12.
10. van Dijk ST, Daniels L, de Korte N, Stockmann HB, Vrouwenraets BC, J Consten EC, B van der Hoeven JA, Faneyte IF, W Dijkgraaf MG, Boermeester MA. Dutch Diverticular Disease (3D) Collaborative Study Group. Quality of life and persistent symptoms after uncomplicated acute diverticulitis. *Dis Colon Rectum* 2019;62:608–614.
11. Strate LL, Modi R, Cohen E, Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. *Am J Gastroenterol* 2012;107:1486–1493.
12. Cohen E, Fuller G, Bolus R, Modi R, Vu M, Shahedi K, Shah R, Atia M, Kurzbard N, Sheen V, Agarwal N, Kaneshiro M, Yen L, Hodgkins P, Erder MH, Spiegel B. Increased risk for irritable bowel syndrome after acute diverticulitis. *Clin Gastroenterol Hepatol* 2013;11:1614–1619.
13. Strate LL, Morris AM. Epidemiology, pathophysiology, and treatment of diverticulitis. *Gastroenterology* 2019;156:1282–1298.e1.
14. Wedel T, Barrenschee M, Lange C, Cossais F, Böttner M. Morphologic basis for developing diverticular disease, diverticulitis, and diverticular bleeding. *Viszeralmedizin* 2015;31:76–82.
15. Scarpignato C, Barbara G, Lanas A, Strate LL. Management of colonic diverticular disease in the third millennium: Highlights from a symposium held during the United European Gastroenterology Week 2017. *Therap Adv Gastroenterol* 2018;11:1756284818771305.
16. Peery AF, Keku TO, Addamo C, McCoy AN, Martin CF, Galanko JA, Sandler RS. Colonic diverticula are not associated with mucosal inflammation or chronic gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 2018;16:884–891.e1.
17. Järbrink-Sehgal ME, Rassam L, Jasim A, Walker MM, Talley NJ, Agréus L, Andreasson A, Schmidt PT. Diverticulosis, symptoms and colonic inflammation: A population-based colonoscopy study. *Am J Gastroenterol* 2019;114:500–510.
18. Granlund J, Svensson T, Olén O, Hjern F, Pedersen NL, Magnusson PK, Schmidt PT. The genetic influence on diverticular disease—a twin study. *Aliment Pharmacol Ther* 2012;35:1103–1107.
19. Strate LL, Erichsen R, Baron JA, Mortensen J, Pedersen JK, Riis AH, Christensen K, Sørensen HT. Heritability and familial aggregation of diverticular disease: a population-based study of twins and siblings. *Gastroenterology* 2013;144:736–742.e1:quiz e14.
20. Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. *Br Med J* 1971;2:450–454.
21. Painter NS, Truelove SC, Ardran GM, Tuckey M. Segmentation and the localization of intraluminal pressures in the human colon, with special reference to the pathogenesis of colonic diverticula. *Gastroenterology* 1965;49:169–177.
22. Peery AF, Sandler RS, Ahnen DJ, Galanko JA, Holm AN, Shaukat A, Mott LA, Barry EL, Fried DA, Baron JA. Constipation and a low-fiber diet are not associated with diverticulosis. *Clin Gastroenterol Hepatol* 2013;11:1622–1627.
23. Peery AF, Barrett PR, Park D, Rogers AJ, Galanko JA, Martin CF, Sandler RS. A high-fiber diet does not protect against asymptomatic diverticulosis. *Gastroenterology* 2012;142:266–272.e1.
24. Broad JB, Wu Z, Clark TG, Musson D, Jaung R, Arroll B, Bissett IP, Connolly MJ. Diverticulosis and nine connective tissue disorders: epidemiological support for an association. *Connect Tissue Res* 2019;60:389–398.
25. Reichert MC, Lammert F. The genetic epidemiology of diverticulosis and diverticular disease: Emerging evidence. *United European Gastroenterol J* 2015;3:409–418.
26. Ford MJ, Camilleri M, Wiste JA, Hanson RB. Differences in colonic tone and phasic response to a meal in the transverse and sigmoid human colon. *Gut* 1995;37:264–269.
27. Steadman CJ, Phillips SF, Camilleri M, Haddad AC, Hanson RB. Variation of muscle tone in the human colon. *Gastroenterology* 1991;101:373–381.
28. Mimura T, Bateman AC, Lee RL, Johnson PA, McDonald PJ, Talbot IC, Kamm MA, MacDonald TT, Pender SL. Up-regulation of collagen and tissue inhibitors of matrix metalloproteinase in colonic diverticular disease. *Dis Colon Rectum* 2004;47:371–378: discussion 378–379.
29. Pantaroto M, Lopes Filho Gde J, Pinto CA, Antico Filho A. Comparative study of collagen deposition in the colon wall of patients operated for sigmoid diverticular disease. *Acta Cir Bras* 2015;30:715–719.
30. Stumpf M, Cao W, Klinge U, Klosterhalfen B, Kasperk R, Schumpelick V. Increased distribution of collagen type III and reduced expression of matrix metalloproteinase 1 in

- patients with diverticular disease. *Int J Colorectal Dis* 2001;16:271–275.
31. Wess L, Eastwood MA, Wess TJ, Busuttill A, Miller A. Cross linking of collagen is increased in colonic diverticulosis. *Gut* 1995;37:91–94.
  32. Thomson HJ, Busuttill A, Eastwood MA, Smith AN, Elton RA. Submucosal collagen changes in the normal colon and in diverticular disease. *Int J Colorectal Dis* 1987;2:208–213.
  33. Hellwig I, Böttner M, Barrenschee M, Harde J, Egberts JH, Becker T, Wedel T. Alterations of the enteric smooth musculature in diverticular disease. *J Gastroenterol* 2014;49:1241–1252.
  34. Altadill A, Eiró N, González LO, Junquera S, González-Quintana JM, Sánchez MR, Andicoechea A, Saro C, Rodrigo L, Vizoso FJ. Comparative analysis of the expression of metalloproteases and their inhibitors in resected crohn's disease and complicated diverticular disease. *Inflamm Bowel Dis* 2012;18:120–130.
  35. Bode MK, Karttunen TJ, Mäkelä J, Risteli L, Risteli J. Type I and III collagens in human colon cancer and diverticulosis. *Scand J Gastroenterol* 2000;35:747–752.
  36. Peery AF, Keil A, Jicha K, Galanko JA, Sandler RS. Association of obesity with colonic diverticulosis in women. *Clin Gastroenterol Hepatol* 2019 May 8 [E-pub ahead of print].
  37. Kanda N, Watanabe S. Regulatory roles of sex hormones in cutaneous biology and immunology. *J Dermatol Sci* 2005;38:1–7.
  38. Leblanc DR, Schneider M, Angele P, Vollmer G, Docheva D. The effect of estrogen on tendon and ligament metabolism and function. *J Steroid Biochem Mol Biol* 2017;172:106–116.
  39. Tworoger SS, Eliassen AH, Missmer SA, Baer H, Rich-Edwards J, Michels KB, Barbieri RL, Dowsett M, Hankinson SE. Birthweight and body size throughout life in relation to sex hormones and prolactin concentrations in premenopausal women. *Cancer Epidemiol Biomarkers Prev* 2006;15:2494–2501.
  40. Jones RB, Fodor AA, Peery AF, Tsilimigras MCB, Wingler K, McCoy A, Sioda M, Sandler RS, Keku TO. An aberrant microbiota is not strongly associated with incidental colonic diverticulosis. *Sci Rep* 2018;8:4951.
  41. Gallego D, Espín F, Mikulka J, Šmirg O, Gil V, Faundez-Zanuy M, Jiménez M, Clavé P. In vitro motor patterns and electrophysiological changes in patients with colonic diverticular disease. *Int J Colorectal Dis* 2013;28:1413–1422.
  42. Mattii L, Ippolito C, Segnani C, Battolla B, Colucci R, Dolfi A, Bassotti G, Blandizzi C, Bernardini N. Altered expression pattern of molecular factors involved in colonic smooth muscle functions: an immunohistochemical study in patients with diverticular disease. *PLoS One* 2013;8:e57023.
  43. Böttner M, Barrenschee M, Hellwig I, Harde J, Egberts JH, Becker T, Zorenkov D, Wedel T. The enteric serotonergic system is altered in patients with diverticular disease. *Gut* 2013;62:1753–1762.
  44. Bassotti G, Battaglia E, De Roberto G, Morelli A, Tonini M, Villanacci V. Alterations in colonic motility and relationship to pain in colonic diverticulosis. *Clin Gastroenterol Hepatol* 2005;3:248–253.
  45. Liu PH, Cao Y, Keeley BR, Tam I, Wu K, Strate LL, Giovannucci EL, Chan AT. Adherence to a healthy lifestyle is associated with a lower risk of diverticulitis among men. *Am J Gastroenterol* 2017;112:1868–1876.
  46. Bharucha AE, Parthasarathy G, Ditah I, Fletcher JG, Ewelukwa O, Pendlimari R, Yawn BP, Melton LJ, Schleck C, Zinsmeister AR. Temporal trends in the incidence and natural history of diverticulitis: a population-based study. *Am J Gastroenterol* 2015;110:1589–1596.
  47. Jovani M, Ma W, Joshi AD, Liu PH, Nguyen LH, Cao Y, Tam I, Wu K, Giovannucci EL, Chan AT, Strate LL. Menopausal hormone therapy and risk of diverticulitis. *Am J Gastroenterol* 2019;114:315–321.
  48. Ma W, Jovani M, Liu PH, Nguyen LH, Cao Y, Tam I, Wu K, Giovannucci EL, Strate LL, Chan AT. Association between obesity and weight change and risk of diverticulitis in women. *Gastroenterology* 2018;155:58–66.e4.
  49. Cao Y, Strate LL, Keeley BR, Tam I, Wu K, Giovannucci EL, Chan AT. Meat intake and risk of diverticulitis among men. *Gut* 2018;67:466–472.
  50. Strate LL, Keeley BR, Cao Y, Wu K, Giovannucci EL, Chan AT. Western dietary pattern increases, and prudent dietary pattern decreases, risk of incident diverticulitis in a prospective cohort study. *Gastroenterology* 2017;152:1023–1030.e2.
  51. Strate LL, Liu YL, Aldoori WH, Giovannucci EL. Physical activity decreases diverticular complications. *Am J Gastroenterol* 2009;104:1221–1230.
  52. Strate LL, Liu YL, Aldoori WH, Syngal S, Giovannucci EL. Obesity increases the risks of diverticulitis and diverticular bleeding. *Gastroenterology* 2009;136:115–122.e1.
  53. Strate LL, Liu YL, Huang ES, Giovannucci EL, Chan AT. Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding. *Gastroenterology* 2011;140:1427–1433.
  54. Sachar DB; NDSG. Diverticulitis in immunosuppressed patients. *J Clin Gastroenterol* 2008;42:1154–1155.
  55. Young-Fadok TM. Diverticulitis. *N Engl J Med* 2019;380:500–501.
  56. Jovani M, Ma W, Staller K, Joshi AD, Cao Y, Nguyen LH, Liu P-H, Tam I, Wu K, Chan AT, Strate LL. Association between bowel movements and diverticulitis in women. *Gastroenterology* 2019;156(Suppl 1):S1069.
  57. Wedel T, Büsing V, Heinrichs G, Nohroudi K, Bruch HP, Roblick UJ, Böttner M. Diverticular disease is associated with an enteric neuropathy as revealed by morphometric analysis. *Neurogastroenterol Motil* 2010;22:407–414.e93–94.
  58. Barrenschee M, Wedel T, Lange C, Hohmeier I, Cossais F, Ebsen M, Vogel I, Böttner M. No neuronal loss, but alterations of the GDNF system in asymptomatic diverticulosis. *PLoS One* 2017;12:e0171416.

59. Golder M, Burleigh DE, Ghali L, Feakins RM, Lunniss PJ, Williams NS, Navsaria HA. Longitudinal muscle shows abnormal relaxation responses to nitric oxide and contains altered levels of NOS1 and elastin in uncomplicated diverticular disease. *Colorectal Dis* 2007;9:218–228.
60. Coble JL, Sheldon KE, Yue F, Salameh TJ, Harris LR III, Deiling S, Ruggiero FM, Eshelman MA, Yochum GS, Koltun WA, Gerhard GS, Broach JR. Identification of a rare LAMB4 variant associated with familial diverticulitis through exome sequencing. *Hum Mol Genet* 2017;26:3212–3220.
61. Rosemar A, Ivarsson ML, Börjesson L, Holmdahl L. Increased concentration of tissue-degrading matrix metalloproteinases and their inhibitor in complicated diverticular disease. *Scand J Gastroenterol* 2007;42:215–220.
62. Whiteway J, Morson BC. Elastosis in diverticular disease of the sigmoid colon. *Gut* 1985;26:258–266.
63. Daniels L, Philipszoon LE, Boermeester MA. A hypothesis: important role for gut microbiota in the etiopathogenesis of diverticular disease. *Dis Colon Rectum* 2014;57:539–543.
64. Nguyen LH, Cao Y, Ma W, Jovani M, Liu P-H, Huttenhower C, Ludvigsson JF, Wu K, Giovannucci E, Strate LL, Chan AT. Chronic antibiotic use and subsequent development of diverticulitis. *Gastroenterology* 2019;156(Suppl 1):S1155.
65. Gueimonde M, Ouwehand A, Huhtinen H, Salminen E, Salminen S. Qualitative and quantitative analyses of the bifidobacterial microbiota in the colonic mucosa of patients with colorectal cancer, diverticulitis and inflammatory bowel disease. *World J Gastroenterol* 2007;13:3985–3989.
66. Daniels L, Budding AE, de Korte N, Eck A, Bogaards JA, Stockmann HB, Consten EC, Savelkoul PH, Boermeester MA. Fecal microbiome analysis as a diagnostic test for diverticulitis. *Eur J Clin Microbiol Infect Dis* 2014;33:1927–1936.
67. Hullar MA, Sandstrom R, Stamatoyannopoulos JA, Lampe JW, Strate LL. The fecal microbiome in diverticulitis and uncomplicated diverticulosis. *Gastroenterology* 2014;146(Suppl 1):S45.
68. Hullar MA, Sandstrom R, Lampe JW, Strate LL. The fecal microbiome differentiates patients with a history of diverticulitis v. those with uncomplicated diverticulosis. *Gastroenterology* 2017;152(Suppl 1):S624.
69. Humes DJ, Fleming KM, Spiller RC, West J. Concurrent drug use and the risk of perforated colonic diverticular disease: a population-based case-control study. *Gut* 2011;60:219–224.
70. Ma W, Jovani M, Nguyen LH, Song M, Liu P-H, Cao Y, Tam I, Wu K, Giovannucci E, Strate LL, Chan AT. Inflammatory potential of diet, circulating inflammatory markers, and risk of diverticulitis. *Gastroenterology* 2019;156(Suppl 1):S1056.
71. Strate LL, Erichsen R, Horváth-Puhó E, Pedersen L, Baron JA, Sørensen HT. Diverticular disease is associated with increased risk of subsequent arterial and venous thromboembolic events. *Clin Gastroenterol Hepatol* 2014;12:1695–1701.e1.
72. Strate LL, Gralnek IM. ACG clinical guideline: Management of patients with acute lower gastrointestinal bleeding. *Am J Gastroenterol* 2016;111:755.
73. Wheat CL, Strate LL. Trends in hospitalization for diverticulitis and diverticular bleeding in the United States from 2000 to 2010. *Clin Gastroenterol Hepatol* 2016;14:96–103.e1.
74. Okamoto T, Watabe H, Yamada A, Hirata Y, Yoshida H, Koike K. The association between arteriosclerosis related diseases and diverticular bleeding. *Int J Colorectal Dis* 2012;27:1161–1166.
75. Yuhara H, Corley DA, Nakahara F, Nakajima T, Koike J, Igarashi M, Suauki T, Mine T. Aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. *J Gastroenterol* 2014;49:992–1000.
76. Vajravelu RK, Mamtani R, Scott FI, Waxman A, Lewis JD. Incidence, risk factors, and clinical effects of recurrent diverticular hemorrhage: a large cohort study. *Gastroenterology* 2018;155:1416–1427.
77. Edwards RA, Lutz PL, Baden DG. Relationship between energy expenditure and ion channel density in the turtle and rat brain. *Am J Physiol* 1989;257:R1354–R1358.
78. Connelly TM, Choi CS, Berg AS, Harris L 3rd, Coble J, Koltun WA. Diverticulitis and Crohn's disease have distinct but overlapping tumor necrosis superfamily 15 haplotypes. *J Surg Res* 2017;214:262–269.
79. Lee JC, Biaseci D, Roberts R, Geary RB, Mansfield JC, Ahmad T, Prescott NJ, Satsangi J, Wilson DC, Jostins L, Anderson CA, UK IBD Genetics Consortium, Traherne JA, Lyons PA, Parkes M, Smith KG. Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn's disease. *Nat Genet* 2017;49:262–268.
80. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Dayani NE, Franke L, Fuyuno Y, Hart A, Juyal RC, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JY, Malekzadeh R, Westra HJ, Yamazaki K, Yang SK, International Multiple Sclerosis Genetics Consortium; , International IBD Genetics Consortium, Barrett JC, Alizadeh BZ, Parkes M, Bk T, Daly MJ, Kubo M, Anderson. CA, Weersma RK. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015;47:979–986.
81. Franchini M, Lippi G. Relative risks of thrombosis and bleeding in different ABO blood groups. *Semin Thromb Hemost* 2016;42:112–117.
82. Huang ES, Khalili H, Strate LL, Chan AT. ABO blood group and the risk of gastrointestinal bleeding. *Gastroenterology* 2012;142(Suppl 1):S503.
83. Krämer A, Green J, Pollard J Jr, Tugendreich S. Causal analysis approaches in Ingenuity Pathway Analysis. *Bioinformatics* 2014;30:523–530.

84. Yu J, Gu X, Yi S. Ingenuity Pathway Analysis of gene expression profiles in distal nerve stump following nerve injury: Insights into Wallerian Degeneration. *Front Cell Neurosci* 2016;10:274.
85. Schafmayer C, Harrison JW, Buch S, Lange C, Reichert MC, Hofer P, Cossais F, Kupcinkas J, von Schönfels W, Schniewind B, Kruis W, Tepel J, Zobel M, Rosendahl J, Jacobi T, Walther-Berends A, Schroeder M, Vogel I, Sergeev P, Boedeker H, Hinrichsen H, Volk A, Erk JU, Burmeister G, Hendricks A, Hinz S, Wolff S, Böttner M, Wood AR, Tyrrell J, Beaumont RN, Langheinrich M, Kucharzik T, Brezina S, Huber-Schönauer U, Pietsch L, Noack LS, Brosch M, Herrmann A, Thangapandi RV, Schimming HW, Zeissig S, Palm S, Focke G, Andreasson A, Schmidt PT, Weitz J, Krawczak M, Völzke H, Leeb G, Michl P, Lieb W, Grützmann R, Franke A, Lammert F, Becker T, Kupcinkas L, D'Amato M, Wedel T, Datz C, Gsur A, Weedon MN, Hampe J. Genome-wide association analysis of diverticular disease points towards neuromuscular, connective tissue and epithelial pathomechanisms. *Gut* 2019;68:854–865.
86. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES, Mesirov JP. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A* 2005;102:15545–15550.
87. Mishra A, MacGregor S. A novel approach for pathway analysis of GWAS data highlights role of BMP signaling and muscle cell differentiation in colorectal cancer susceptibility. *Twin Res Hum Genet* 2017;20:1–9.
88. Sigurdsson S, Alexandersson KF, Sulem P, Feenstra B, Gudmundsdottir S, Halldorsson GH, Olafsson S, Sigurdsson A, Rafnar T, Thorgeirsson T, Sørensen E, Nordholm-Carstensen A, Burcharth J, Andersen J, Jørgensen HS, Posselt-Møller E, Ullum H, Thorleifsson G, Masson G, Thorsteinsdottir U, Melbye M, Gudbjartsson DF, Stefansson T, Jonsdottir I, Stefansson K. Sequence variants in ARHGAP15, COLQ and FAM155A associate with diverticular disease and diverticulitis. *Nat Commun* 2017;8:15789.
89. Maguire LH, Handelman SK, Du X, Chen Y, Pers TH, Speliotes EK. Genome-wide association analyses identify 39 new susceptibility loci for diverticular disease. *Nat Genet* 2018;50:1359–1365.
90. Coyle D, Kelly DA, O'Donnell AM, Gillick J, Puri P. Use of anoctamin 1 (ANO1) to evaluate interstitial cells of Cajal in Hirschsprung's disease. *Pediatr Surg Int* 2016;32:125–133.
91. Tang T, Chen Q, Ma C, Ni L, Jiang J, Li N. Expression of TMEM16A in the colon of intractable functional constipation patients and its clinical implications. *Zhonghua Wei Chang Wai Ke Za Zhi* 2015;18:713–717.
92. Gomez-Pinilla PJ, Gibbons SJ, Bardsley MR, Lorincz A, Pozo MJ, Pasricha PJ, Van de Rijn M, West RB, Sarr MG, Kendrick ML, Cima RR, Dozois EJ, Larson DW, Ordog T, Farrugia G. Ano1 is a selective marker of interstitial cells of Cajal in the human and mouse gastrointestinal tract. *Am J Physiol Gastrointest Liver Physiol* 2009;296:G1370–G1381.
93. Smigiel R, Szafranska A, Czyzewska M, Rauch A, Zweier Ch, Patkowski D. Severe clinical course of Hirschsprung disease in a Mowat-Wilson syndrome patient. *J Appl Genet* 2010;51:111–113.
94. Costa C, Germena G, Martin-Conte EL, Molineris I, Bosco E, Marengo S, Azzolino O, Altruda F, Ranieri VM, Hirsch E. The RacGAP ArhGAP15 is a master negative regulator of neutrophil functions. *Blood* 2011;118:1099–1108.
95. Zamboni V, Armentano M, Sarò G, Ciralo E, Ghigo A, Germena G, Umbach A, Valnegri P, Passafaro M, Carabelli V, Gavello D, Bianchi V, D'Adamo P, de Curtis I, El-Assawi N, Mauro A, Priano L, Ferri N, Hirsch E, Merlo GR. Disruption of ArhGAP15 results in hyperactive Rac1, affects the architecture and function of hippocampal inhibitory neurons and causes cognitive deficits. *Sci Rep* 2016;6:34877.
96. Radu M, Rawat SJ, Beeser A, Iliuk A, Tao WA, Chernoff J. ArhGAP15, a Rac-specific GTPase-activating protein, plays a dual role in inhibiting small GTPase signaling. *J Biol Chem* 2013;288:21117–21125.
97. Seoh ML, Ng CH, Yong J, Lim L, Leung T. ArhGAP15, a novel human RacGAP protein with GTPase binding property. *FEBS Lett* 2003;539:131–137.
98. Sigoillot SM, Bourgeois F, Lambergeon M, Strohlic L, Legay C. ColQ controls postsynaptic differentiation at the neuromuscular junction. *J Neurosci* 2010;30:13–23.
99. GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* 2015;348:648–660.
100. Engel AG, Shen XM, Selcen D, Sine SM. Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. *Lancet Neurol* 2015;14:420–434.
101. Ohno K, Brengman J, Tsujino A, Engel AG. Human endplate acetylcholinesterase deficiency caused by mutations in the collagen-like tail subunit (ColQ) of the asymmetric enzyme. *Proc Natl Acad Sci U S A* 1998;95:9654–9659.
102. Mori D, Hori M, Murata T, Ohama T, Kishi H, Kobayashi S, Ozaki H. Synchronous phosphorylation of CPI-17 and MYPT1 is essential for inducing Ca(2+) sensitization in intestinal smooth muscle. *Neurogastroenterol Motil* 2011;23:1111–1122.
103. Hu W, Mahavadi S, Li F, Murthy KS. Upregulation of RGS4 and downregulation of CPI-17 mediate inhibition of colonic muscle contraction by interleukin-1beta. *Am J Physiol Cell Physiol* 2007;293:C1991–C2000.
104. Somara S, Gilmont RR, Martens JR, Bitar KN. Ectopic expression of caveolin-1 restores physiological contractile response of aged colonic smooth muscle. *Am J Physiol Gastrointest Liver Physiol* 2007;293:G240–G249.

105. Li JL, Fu Y, Qin SB, Liang GK, Liu J, Nie XY, Chen J, Shi LW, Shao H, Lu Y. Association between P2RY12 gene polymorphisms and adverse clinical events in coronary artery disease patients treated with clopidogrel: a systematic review and meta-analysis. *Gene* 2018;657:69–80.
106. von Kügelgen I. Structure, pharmacology and roles in physiology of the P2Y<sub>12</sub> receptor. *Adv Exp Med Biol* 2017;1051:123–138.
107. Chauhan M, Yallampalli U, Banadakappa M, Yallampalli C. Involvement of receptor activity-modifying protein 3 (RAMP3) in the vascular actions of adreno-medullin in rat mesenteric artery smooth muscle cells. *Biol Reprod* 2015;93:116.
108. Wang P, Liu X, Zhu B, Ma Y, Yong L, Teng Z, Liang C, He G, Liu X. Association of IL17RC and COL6A1 genetic polymorphisms with susceptibility to ossification of the thoracic posterior longitudinal ligament in Chinese patients. *J Orthop Surg Res* 2018; 13:109.
109. Butterfield RJ, Dunn DM, Hu Y, Johnson K, Bönnemann CG, Weiss RB. Transcriptome profiling identifies regulators of pathogenesis in collagen VI related muscular dystrophy. *PLoS One* 2017;12: e0189664.
110. Cescon M, Chen P, Castagnaro S, Gregorio I, Bonaldo P. Lack of collagen VI promotes neurodegeneration by impairing autophagy and inducing apoptosis during aging. *Aging (Albany NY)* 2016; 8:1083–1101.
111. Chen P, Cescon M, Megighian A, Bonaldo P. Collagen VI regulates peripheral nerve myelination and function. *FASEB J* 2014;28:1145–1156.
112. Soret R, Mennetrey M, Bergeron KF, Dariel A, Neunlist M, Grunder F, Faure C, Silversides DW, Pilon N; Ente-Hirsch Study Group. A collagen VI-dependent pathogenic mechanism for Hirschsprung's disease. *J Clin Invest* 2015;125:4483–4496.
113. Bönnemann CG. The collagen VI-related myopathies: muscle meets its matrix. *Nat Rev Neurol* 2011; 7:379–390.
114. Cescon M, Gregorio I, Eiber N, Borgia D, Fusto A, Sabatelli P, Scorzeto M, Megighian A, Pegoraro E, Hashemolhosseini S, Bonaldo P. Collagen VI is required for the structural and functional integrity of the neuromuscular junction. *Acta Neuropathol* 2018; 136:483–499.
115. Oltedal S, Skaland I, Maple-Grødem J, Tjensvoll K, Janssen EAM, Gilje B, Smaaland R, Heikkilä R, Nordgård O. Expression profiling and intracellular localization studies of the novel proline-, histidine-, and glycine-rich protein 1 suggest an essential role in gastrointestinal epithelium and a potential clinical application in colorectal cancer diagnostics. *BMC Gastroenterol* 2018; 18:26.
116. Yamamoto F. Review: ABO blood group system—ABH oligosaccharide antigens, anti-A and anti-B, A and B glycosyltransferases, and ABO genes. *Immunohematology* 2004;20:3–22.
117. Madureira PA, O'Connell PA, Surette AP, Miller VA, Waisman DM. The biochemistry and regulation of S100A10: a multifunctional plasminogen receptor involved in oncogenesis. *J Biomed Biotechnol* 2012; 2012:353687.
118. Zhao Y, Zhang M, Liu H, Wang J. Signaling by growth/differentiation factor 5 through the bone morphogenetic protein receptor type IB protects neurons against kainic acid-induced neurodegeneration. *Neurosci Lett* 2017; 651:36–42.
119. Racacho L, Byrnes AM, MacDonald H, Dranse HJ, Nikkel SM, Allanson J, Rosser E, Underhill TM, Bulman DE. Two novel disease-causing variants in BMPR1B are associated with brachydactyly type A1. *Eur J Hum Genet* 2015;23:1640–1645.
120. Wiberg A, Ng M, Schmid AB, Smillie RW, Baskozos G, Holmes MV, Künnapuu K, Mägi R, Bennett DL, Furniss D. A genome-wide association analysis identifies 16 novel susceptibility loci for carpal tunnel syndrome. *Nat Commun* 2019;10:1030.
121. Zhang K, Huentelman MJ, Rao F, Sun EI, Corneveaux JJ, Schork AJ, Wei Z, Waalen J, Miramontes-Gonzalez JP, Hightower CM, Maihofer AX, Mahata M, Pastinen T, Ehret GB, International Consortium for Blood Pressure Genome-Wide Association Studies, Schork NJ, Eskin E, Nievergelt CM, Saier MH Jr, O'Connor DT. Genetic implication of a novel thiamine transporter in human hypertension. *J Am Coll Cardiol* 2014;63:1542–1555.
122. Khiriani L, Obri A, Ramos-Brossier M, Rousseaud A, Moriceau S, Nicot AS, Mera P, Kosmidis S, Karnavas T, Saudou F, Gao XB, Oury F, Kandel E, Karsenty G. Gpr158 mediates osteocalcin's regulation of cognition. *J Exp Med* 2017;214:2859–2873.
123. Piaggi P, Masindova I, Muller YL, Mercader J, Wiessner GB, Chen P, SIGMA Type 2 Diabetes Consortium, Kobes S, Hsueh WC, Mongalo M, Knowler WC, Krakoff J, Hanson RL, Bogardus C, Baier LJ. A genome-wide association study using a custom genotyping array identifies variants in *GPR158* associated with reduced energy expenditure in American Indians. *Diabetes* 2017; 66:2284–2295.
124. Ge X, Yamamoto S, Tsutsumi S, Midorikawa Y, Ihara S, Wang SM, Aburatani H. Interpreting expression profiles of cancers by genome-wide survey of breadth of expression in normal tissues. *Genomics* 2005; 86:127–141.
125. Su AI, Wiltshire T, Batalov S, Lapp H, Ching KA, Block D, Zhang J, Soden R, Hayakawa M, Kreiman G, Cooke MP, Walker JR, Hogenesch JB. A gene atlas of the mouse and human protein-encoding transcriptomes. *Proc Natl Acad Sci U S A* 2004;101:6062–6067.
126. Boraxbekk CJ, Ames D, Kochan NA, Lee T, Thalamuthu A, Wen W, Armstrong NJ, Kwok JB, Schofield PR, Reppermund S, Wright MJ, Trollor JN, Brodaty H, Sachdev P, Mather KA. Investigating the influence of KIBRA and CLSTN2 genetic polymorphisms on cross-sectional and longitudinal measures of memory performance and hippocampal volume in older individuals. *Neuropsychologia* 2015;78:10–17.
127. de Ramon Francàs G, Alther T, Stoeckli ET. Calsyntenins are expressed in a dynamic and partially overlapping



- manner during neural development. *Front Neuroanat* 2017;11:76.
128. Rasmussen MB, Kreiborg S, Jensen P, Bak M, Mang Y, Lodahl M, Budtz-Jørgensen E, Tommerup N, Tranebjærg L, Rendtorff ND. Phenotypic subregions within the split-hand/foot malformation 1 locus. *Hum Genet* 2016;135:345–357.
  129. Usener D, Schadendorf D, Koch J, Dübel S, Eichmüller S. cTAGE: a cutaneous T cell lymphoma associated antigen family with tumor-specific splicing. *J Invest Dermatol* 2003;121:198–206.
  130. Schellhaus AK, Moreno-Andrés D, Chugh M, Yokoyama H, Moschopoulou A, De S, Bono F, Hipp K, Schäffer E, Antonin W. Developmentally regulated GTP binding protein 1 (DRG1) controls microtubule dynamics. *Sci Rep* 2017;7:9996.
  131. Lee H, Kim M, Kim N, Macfarlan T, Pfaff SL, Mastick GS, Song MR. Slit and Semaphorin signaling governed by islet transcription factors positions motor neuron somata within the neural tube. *Exp Neurol* 2015;269:17–27.
  132. Wang N, Deng Z, Wang M, Li R, Xu G, Bao G. Additional evidence supports association of common genetic variants in VT11A and ETFA with increased risk of glioma susceptibility. *J Neurol Sci* 2017;375:282–288.
  133. Edwards TL, Hartmann KE, Velez Edwards DR. Variants in BET1L and TNRC6B associate with increasing fibroid volume and fibroid type among European Americans. *Hum Genet* 2013;132:1361–1369.
  134. Lin YJ, Chang JS, Liu X, Lin TH, Huang SM, Liao CC, Lin CW, Chien WK, Chen JH, Wu JY, Chen CH, Chang LC, Tsang H, Jeang KT, Chen CY, Tsai FJ. Sorting nexin 24 genetic variation associates with coronary artery aneurysm severity in Kawasaki disease patients. *Cell Biosci* 2013;3:44.
  135. Rohrbach S, Aurich AC, Li L, Niemann B. Age-associated loss in adiponectin-activation by caloric restriction: lack of compensation by enhanced inducibility of adiponectin paralogs CTRP2 and CTRP7. *Mol Cell Endocrinol* 2007;277:26–34.
  136. Dick DM, Aliev F, Krueger RF, Edwards A, Agrawal A, Lynskey M, Lin P, Schuckit M, Hesselbrock V, Nurnberger J Jr, Almasy L, Porjesz B, Edenberg HJ, Bucholz K, Kramer J, Kuperman S, Bierut L. Genome-wide association study of conduct disorder symptomatology. *Mol Psychiatry* 2011;16:800–808.
  137. Ochaba J, Monteys AM, O'Rourke JG, Reidling JC, Steffan JS, Davidson BL, Thompson LM. PIAS1 regulates mutant huntingtin accumulation and Huntington's disease-associated phenotypes in vivo. *Neuron* 2016;90:507–520.
  138. Farrell SA, Sodhi S, Marshall CR, Guerin A, Slavotinek A, Paton T, Chong K, Sirkin WL, Scherer SW, Bérubé-Simard FA, Pilon N. HLX is a candidate gene for a pattern of anomalies associated with congenital diaphragmatic hernia, short bowel, and asplenia. *Am J Med Genet A* 2017;173:3070–3074.
  139. Rajaraman G, Murthi P, Pathirage N, Brennecke SP, Kalionis B. Downstream targets of homeobox gene HLX show altered expression in human idiopathic fetal growth restriction. *Am J Pathol* 2010;176:278–287.
  140. Suttner K, Ruoss I, Rosenstiel P, Depner M, Pinto LA, Schedel M, Adamski J, Illig T, Schreiber S, von Mutius E, Kabesch M. HLX1 gene variants influence the development of childhood asthma. *J Allergy Clin Immunol* 2009;123:82–88.e6.
  141. Rose JE, Behm FM, Drgon T, Johnson C, Uhl GR. Personalized smoking cessation: interactions between nicotine dose, dependence and quit-success genotype score. *Mol Med* 2010;16:247–253.
  142. Szafranski P, Gambin T, Dharmadhikari AV, Akdemir KC, Jhangiani SN, Schuette J, Godiwala N, Yatsenko SA, Sebastian J, Madan-Khetarpal S, Surti U, Abellar RG, Bateman DA, Wilson AL, Markham MH, Slamon J, Santos-Simarro F, Palomares M, Nevado J, Lapunzina P, Chung BH, Wong WL, Chu YW, Mok GT, Kerem E, Reiter J, Ambalavanan N, Anderson SA, Kelly DR, Shieh J, Rosenthal TC, Scheible K, Steiner L, Iqbal MA, McKinnon ML, Hamilton SJ, Schlade-Bartusiak K, English D, Henderson G, Roeder ER, DeNapoli TS, Littlejohn RO, Wolff DJ, Wagner CL, Yeung A, Francis D, Fiorino EK, Edelman M, Fox J, Hayes DA, Janssens S, De Baere E, Menten B, Loccufier A, Vanwalleghem L, Moerman P, Sznajder Y, Lay AS, Kussmann JL, Chawla J, Payton DJ, Phillips GE, Brosens E, Tibboel D, de Klein A, Maystadt I, Fisher R, Sebire N, Male A, Chopra M, Pinner J, Malcolm G, Peters G, Arbuckle S, Lees M, Mead Z, Quarrell O, Sayers R, Owens M, Shaw-Smith C, Liou J, McKay E, de Leeuw N, Feenstra I, Spruijt L, Elmslie F, Thiruchelvam T, Bacino CA, Langston C, Lupski JR, Sen P, Popek E, Stankiewicz P. Pathogenetics of alveolar capillary dysplasia with misalignment of pulmonary veins. *Hum Genet* 2016;135:569–586.
  143. Katoh Y, Katoh M. Hedgehog signaling pathway and gastric cancer. *Cancer Biol Ther* 2005;4:1050–1054.
  144. Soldatov NM. CACNB2: An emerging pharmacological target for hypertension, heart failure, arrhythmia and mental disorders. *Curr Mol Pharmacol* 2015;8:32–42.
  145. Papaioannou A, Higa A, Jégou G, Jouan F, Pineau R, Saas L, Avril T, Pluquet O, Chevet E. Alterations of EDEM1 functions enhance ATF6 pro-survival signaling. *FEBS J* 2018;285:4146–4164.
  146. Palmieri F. The mitochondrial transporter family SLC25: identification, properties and physiopathology. *Mol Aspects Med* 2013;34:465–484.
  147. Cordat E, Reithmeier RA. Structure, function, and trafficking of SLC4 and SLC26 anion transporters. *Curr Top Membr* 2014;73:1–67.
  148. Xu M, Xie YA, Abouzeid H, Gordon CT, Fiorentino A, Sun Z, Lehman A, Osman IS, Dharmat R, Riveiro-Alvarez R, Bapst-Wicht L, Babino D, Arno G, Busetto V, Zhao L, Li H, Lopez-Martinez MA, Azevedo LF, Hubert L, Pontikos N, Eblimit A, Lorda-Sanchez I, Kheir V, Plagnol V, Oufadem M, Soens ZT, Yang L, Bole-Feysot C, Pfundt R, Allaman-Pillet N, Nitschké P, Cheetham ME, Lyonnet S, Agrawal SA, Li H, Pinton G, Michaelides M, Besmond C, Li Y, Yuan Z, von Lintig J, Webster AR, Le Hir H, Stoilov P, UK Inherited Retinal Dystrophy Consortium, Amiel J, Hardcastle AJ, Ayuso C, Sui R, Chen R, Allikmets R,

Schorderet DF. Mutations in the spliceosome component CWC27 cause retinal degeneration with or without additional developmental anomalies. *Am J Hum Genet* 2017;100:592–604.

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**Acknowledgments**

The authors thank Mrs Cindy Stanislav for excellent secretarial support.

**Conflicts of interest**

The authors disclose no conflicts.

**Funding**

This work was supported by National Institutes of Health grants R01DK115950 (to Michael Camilleri), P30-DK034987 (Robert S. Sandler), R01DK09473 (to Robert S. Sandler), and K23DK113225 (to Anne F. Peery).

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Received April 25, 2019. Accepted July 18, 2019.

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