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# A pilot genome-wide association study meta-analysis of gastroparesis

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## Abstract

**Background:** Gastroparesis (GP) is characterized by delayed gastric emptying in the absence of mechanical obstruction.

**Objective:** Genetic predisposition may play a role; however, investigation at the genome-wide level has not been performed.

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**Methods:** We carried out a genome-wide association study (GWAS) meta-analysis on (i) 478 GP patients from the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium (GpCRC) compared to 9931 population-based controls from the University of Michigan Health and Retirement Study; and (ii) 402 GP cases compared to 48,340 non-gastroparesis controls from the Michigan Genomics Initiative. Associations for 5,811,784 high-quality SNPs were tested on a total of 880 GP patients and 58,271 controls, using logistic mixed models adjusted for age, sex, and principal components. Gene mapping was obtained based on genomic position and expression quantitative trait loci, and a gene-set network enrichment analysis was performed. Genetic associations with clinical data were tested in GpCRC patients. Protein expression of selected candidate genes was determined in full thickness gastric biopsies from GpCRC patients and controls.

**Results:** While no SNP associations were detected at strict significance ($p \leq 5 \times 10^{-8}$), nine independent genomic loci were associated at suggestive significance ($p \leq 1 \times 10^{-5}$), with the strongest signal (rs9273363, odds ratio = 1.4, $p = 1 \times 10^{-7}$) mapped to the human leukocyte antigen region. Computational annotation of suggestive risk loci identified 14 protein-coding candidate genes. Gene-set network enrichment analysis revealed pathways potentially involved in immune and motor dysregulation ($p_{FDR} \leq 0.05$). The GP risk allele rs6984536A (Peroxidasin-Like; *PXDNL*) was associated with increased abdominal pain severity scores (Beta = 0.13, $p = 0.03$). Gastric muscularis expression of PXDNL also positively correlated with abdominal pain in GP patients ($r = 0.8$, $p = 0.02$). Dickkopf WNT Signaling Pathway Inhibitor 1 showed decreased expression in diabetic GP patients ($p = 0.005$ vs. controls).

**Conclusion:** We report preliminary GWAS findings for GP, which highlight candidate genes and pathways related to immune and sensory-motor dysregulation. Larger studies are needed to validate and expand these findings in independent datasets.

**KEYWORDS**
abdominal pain, delayed gastric emptying, diabetes, enteric nervous system, gastroparesis, genetics, immune dysregulation, inflammation, motor function, *PXDNL*

## INTRODUCTION

Gastroparesis (GP) is a gastric sensory-motor disorder characterized by delayed gastric emptying and symptoms of post-prandial fullness/early satiety, nausea/vomiting, and bloating.[1,2] The most recent European consensus (ESNM/UEG) suggests that post-prandial fullness/early satiety are likely cardinal symptoms of functional dyspepsia, a related upper GI neurogastrointestinal disorder.[3] Diagnosing GP relies on demonstration of delayed gastric emptying on a solid meal-based scintigraphy or $^{13}$C-octanoic acid breath test.[1] GP affects patients' quality of life and is associated with greater comorbidities.[4,5] Diabetic and idiopathic cases comprise the vast majority of GP patients, and clinical presentation may vary by etiology.[1] Despite the prevalence of a definite GP diagnosis being reported to be low (0.02%), recent epidemiological surveys suggest that GP may affect many more individuals (0.2%–2%).[6,7]

Studies carried out over the last decade have led to significant progress in the clinical and molecular understanding of GP and related upper GI disorders.[1] In addition to abnormal gastric motility, GP pathogenesis may involve sensory neuropathy, duodenal inflammation, and immune dysregulation. Analyses of full-thickness gastric biopsies from GP patients have identified loss or injury of interstitial cells of Cajal (ICC), the essential pacemakers that transmit contractile stimuli to the smooth muscle cells.[8] Additionally, a subset of GP patients demonstrates loss or damage to the enteric neurons in the gastric muscularis, which may also result in the impairment of gastric motility. More recently, animal studies have demonstrated macrophage-based immune dysregulation resulting in injury to ICC.[9]

In addition, transcriptomic and proteomic assessments of human biopsies have revealed increased expression of genes and proteins associated with pro-inflammatory macrophages in GP, highlighting the potential role of the innate immune system in GP pathogenesis.[10,11]

As observed in other GI motility disorders, underlying genetic factors may play a predisposing role in GP through mechanisms that lead to immune dysregulation, dysmotility, and abnormal gut-brain crosstalk.[12,13] Despite this, genetic studies of GP have been scarce, mostly limited to candidate genes, and the heritability of GP remains unknown.[14,15] To gain initial insights into the genetic predisposition and pathophysiology of GP, we conducted a pilot genome-wide association study (GWAS) meta-analysis in a total of 880 well-characterized GP cases and 58,271 controls of European ancestry from two independent GP case-control cohorts.

**Key summary**

**1. Summarize the established knowledge on this subject**

- Gastroparesis (GP) is a gastric sensory-motor disorder characterized by delayed gastric emptying.
- Studies over the last decade suggest macrophage-driven immune dysregulation and associated loss or injury of pacemaker cells and enteric neurons as drivers of GP pathophysiology.
- Genetic risk factors may play a role in GP; however, there is a lack of investigations at the genome-wide level.

**2. What are the significant and/or new findings of this study?**

- We carried out a pilot genome-wide association study (GWAS) meta-analysis testing 5,811,784 high-quality SNPs on a total of 880 GP patients and 58,271 controls
- Nine independent genomic loci were mapped at suggestive significance ($p \leq 1 \times 10^{-5}$), revealing candidate genes (such as *PXDNL* - Peroxidasin-Like and *Dickkopf WNT Signaling Pathway Inhibitor 1 (DKK1))* and pathways potentially involved in immune and motor function.
- A *PXDNL* variant as well as its gastric muscle protein expression correlated with the severity of abdominal pain.

## MATERIALS AND METHODS

### Study cohorts and Gastroparesis cases and controls definitions

#### Gastroparesis Clinical Research Consortium cohort

The Gastroparesis Clinical Research Consortium (GpCRC) is a network of GI tertiary centers in the United States sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) that aims to advance knowledge and treatments for GP.[16] A total of 478 GpCRC patients were included as GP cases in the GWAS, based on following inclusion criteria: delayed gastric emptying on scintigraphy (gastric retention (GR) of >60% at 2 h and/or >10% at 4 h); no clinical diagnosis for functional dyspepsia or chronic unexplained nausea and vomiting; no evidence of gastric obstruction; symptoms lasting at least 12-weeks; European ancestry determined by Principal Component Analysis (PCA); and high genotyping quality metrics (see Supplementary Methods). Genotyping was performed with Illumina GSA arrays at the Australian Genome Reference Facility (https://www.agrf.org.au/). Informed consent was obtained from all participants, and the global study protocol was approved by the Monash University Institutional Review Board (IRB) (approval number: 19564).

The University of Michigan Health and Retirement Study (HRS) is a longitudinal and representative panel of individuals from the US population aged 50 and above, designed to investigate aspects related to work, aging, and retirement (https://hrsonline.isr.umich.edu/).[17] Genotype data (Illumina HumanOmni 2.5) of HRS participants was obtained from the database of Genotypes and Phenotypes (dbGap:phs000428.v2.p2) and served as a control group to derive allele frequencies for reference alleles. A total of 9931 HRS participants with PCA-derived European ancestry, high-quality genetic parameters and available demographic (age and sex) data were included in the GWAS. No other exclusion criteria were applied in the absence of available clinical information for HRS participants. The HRS data was accessed under the application number 22399.

#### Michigan Genomics Initiative cohort

The Michigan Genomics Initiative (MGI) is a longitudinal cohort comprising patients recruited primarily during inpatient surgical procedures at the Michigan Medicine healthcare system. Patients provided consent for linkage of their blood sample and genotyping data (Illumina HumanCoreExome v12.1 arrays) to their existing and future electronic medical records (EMR).[18] We used data from MGI freeze-3 participants of PCA-derived European ancestry. Michigan Genomics Initiative GP cases and controls were defined based on the presence or absence of International Classification of Disease 10$^{th}$ Revision (ICD10) diagnosis for GP (code K31.84) in their EMR. Individuals with potentially confounding ICD10 diagnoses, such as functional dyspepsia (K30), duodenal obstruction (K31.5), and intestinal obstruction (K56.1–6), were excluded. The GWAS included 402 MGI GP cases and 48,340 non-GP controls. Broad research usage of MGI data was reviewed and approved by the University of Michigan IRB.[18]

## Gastroparesis genome-wide association study meta-analysis

A common quality control and imputation pipeline was applied to two independent GP GWAS analyses on GpCRC/HRS and MGI case-control cohorts. Association analyses were based on logistic mixed models (SAIGE v0.42.1[19]) adjusted for age (at DNA collection), sex, and the first 4–10 top PCs. In total, 5,811,784 high-quality SNPs were tested in the meta-analysis based on a fixed-effect inverse-variance model (METAL v2011-03-25[20]). Annotation of suggestive ($p \leq 1 \times 10^{-5}$) risk loci was performed with Functional Annotation of GWAS (Functional Mapping and Annotation of Genome-Wide Association Studies) v1.3.5 (https://fuma.ctglab.nl/tutorial) and a gene-set co-expression network enrichment analysis was performed using GeneNetwork v2.0 (https://genenetwork.nl/). Genetic association tests stratified by diabetic status and with clinical data are described in the Supplementary Methods.

## Gastric full-thickness biopsy immunohistochemistry for candidate genes

To assess whether some of the genes highlighted via GWAS were differentially expressed between GP patients and healthy controls, we performed immunohistochemistry (IHC) staining in human gastric muscle biopsies from 10 GP patients (5 diabetic and 5 idiopathic) and 10 sex- and age-matched controls (5 diabetic and 5 non-diabetic).

Additional details of methods and bioinformatics are provided in the online Supplementary Material.

# RESULTS

## Demographic and clinical characteristics of study cohorts

The demographic characteristics of cases and controls in the two cohorts (GpCRC/HRS and MGI) are summarized in Table 1. In both cohorts, GP cases were predominantly female (85% in GpCRC and 67% in MGI were female), while the sex ratio among controls was balanced (58% and 52% were female in respective GpCRC/HRS and MGI controls). Among MGI GP cases, 62% had a diagnosis of diabetes mellitus (DM) either before or after GP diagnosis, identified through E10 or E11 ICD10 codes for type 1 and 2 DM, respectively. For GpCRC GP cases, 26% were diagnosed with DM based on detailed clinical information available in the GpCRC database (Table 1).

Further clinical characteristics were available specifically for GpCRC patients, including body mass index (BMI), scintigraphy-based GR measured at 2 and 4 h after a solid meal, and scores from the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM)[21] questionnaire, which assessed GP symptom severity (see Supplementary Material). On average, GpCRC patients were slightly overweight (mean BMI [SD] = 26.8 [7.2]) and had moderate delayed gastric emptying (mean GR of 65% at 2h and 31% at 4h) (Table S1). Regarding symptom profile, post-prandial fullness/early satiety was reported as the most severe on average (mean [SD] = 3.4 [1.1]), followed by upper abdominal pain and bloating (mean [SD] = 3.1 [1.5 and 1.6, respectively]), on a 0–5 scale indicating increasing symptom severity (Table S1).

**TABLE 1** Sample size and demographics of Gastroparesis Clinical Research Consortium (GpCRC)/Health and Retirement Study (HRS) and Michigan Genomics Initiative (MGI) case-control cohorts included in the genome-wide association study (GWAS) meta-analysis.

| Cohort | GpCRC/HRS | MGI |
|---|---|---|
| *N* | | |
| Cases | 478 | 402 |
| Controls | 9931 | 48,340 |
| Female (%) | | |
| Cases | 84.7% | 66.9% |
| Controls | 57.6% | 52.0% |
| Age (SD) | | |
| Cases | 42.7 (13.8) | 54.2 (14.3) |
| Controls | 67.0 (8.9) | 57.2 (16.4) |
| Diabetic (%) | | |
| Cases | 25.9% | 62.4% |

*Note*: Individuals with PCA-derived European ancestry from the Health and Retirement Study served as population-matched controls for GpCRC GP cases. See Material and Methods for detailed definition criteria of GpCRC and MGI cases and controls.

## Genome-wide association study meta-analysis of Gastroparesis

We conducted independent GWAS of GP in GpCRC/HRS and MGI case-control cohorts using a common methodological pipeline for quality control, imputation, and association tests (Supplementary Methods). Individual GWAS results were included in a meta-analysis, which in total comprised association data for 5,811,784 high-quality SNP markers on a total of 880 GP cases and 58,271 controls. While no associations were detected at genome-wide significance ($p \leq 5 \times 10^{-8}$) in the meta-analysis, associations reaching suggestive significance ($p \leq 1 \times 10^{-5}$) were mapped to nine independent genomic loci, with lead SNP association *p*-values ranging from $1 \times 10^{-7}$ to $7 \times 10^{-6}$ (Table 2 and Figure 1). The strongest association *p*-value signals (rs9273363: $p = 1 \times 10^{-7}$ and rs9277545: $p = 4 \times 10^{-7}$; odds ratio (OR) = 1.4 for both) were mapped to the human leukocyte antigen (HLA) class II region on chromosome 6 near the *HLA-DQB1* (rs9273363) and *HLA-DPB1* (rs9277545) loci. No significant heterogeneity was observed across the two studies (Cochran's $p > 0.05$), and all lead SNPs showed concordant risk effects (same direction of association) in individual GpCRC/HRS and

**TABLE 2** Gastroparesis (GP) genome-wide association study (GWAS) meta-analysis association results and mapped genes.

| Lead SNP | CHR | POS | EA | OA | EAF | *p*-value | OR (95% CI) | Nearest gene | Mapped genes |
|---|---|---|---|---|---|---|---|---|---|
| rs6550256 | 3 | 34,210,894 | A | G | 0.09 | 1.1E−06 | 1.7 (1.4–2.1) | | |
| rs275478 | 5 | 6,835,073 | A | G | 0.40 | 3.6E−06 | 1.3 (1.2–1.5) | | |
| rs9273363 | 6 | 32,626,272 | A | C | 0.28 | 1.2E−07 | 1.4 (1.2–1.6) | *HLA-DQB1* | |
| rs9277545 | 6 | 33,055,323 | T | C | 0.26 | 4.4E−07 | 1.4 (1.2–1.6) | *HLA-DPB1* | |
| rs10224770 | 7 | 156,797,411 | A | G | 0.09 | 2.9E−06 | 1.7 (1.4–2.1) | *MNX1* | *MNX1* [p,e] |
| | | | | | | | | | *NOM1* [e] |
| rs6984536 | 8 | 52,230,988 | A | G | 0.27 | 3.9E−06 | 1.4 (1.2–1.5) | *PXDNL* | *PXDNL* [p,e] |
| | | | | | | | | | *SNTG1* [e] |
| rs17823772 | 10 | 105,928,767 | T | C | 0.12 | 5.9E−06 | 1.6 (1.3–1.9) | *CFAP43* | *CFAP43* [p] |
| | | | | | | | | | *SFR1* [p] |
| | | | | | | | | | *GSTO2* [e] |
| rs58826461 | 10 | 53,980,627 | T | G | 0.10 | 7.2E−06 | 0.6 (0.5–0.8) | *PRKG1* | *PRKG1* [p] |
| | | | | | | | | | *DKK1* [e] |
| rs61655672 | 15 | 90,313,476 | T | C | 0.97 | 1.8E−06 | 0.4 (0.3–0.6) | *MESP2* | *MESP2* [p] |
| | | | | | | | | | *MESP1* [e] |
| | | | | | | | | | *PLIN1* [e] |
| | | | | | | | | | *ANPEP* [p] |
| | | | | | | | | | *GDPGP1* [e] |

*Note*: Associations tests for 5,811,784 high-quality SNPs were based on logistic mixed regressions adjusted for age, sex, and principal components, on a total of 880 GP cases and 58,271 controls in the meta-analysis. Nearest gene: the nearest protein-coding gene within 100kb from lead SNP (if any); Mapped genes: *p* genes physically mapped; *e* genes mapped by cis-eQTL.

Abbreviations: CHR, chromosome; EA, effect allele; EAF, effect allele frequency; OA, other allele; OR (95%CI), odds ratio and 95% confidence interval (CI); POS, base-pair position based on the Genome Reference Consortium Human Build 37; *p*-value, GWAS *p*-value.

MGI cohorts (Figure 2 and Table S2). Risk loci regional association plots are shown in Figure S1.

Lead SNP associations were individually tested in diabetic (251 cases and 9940 controls) and non-diabetic (151 cases and 38,400 controls) patients (only feasible in the MGI cohort; see Supplementary Methods). The full results are shown in Table S3. HLA lead SNPs were associated with GP risk at nominal statistical significance ($p \leq 0.05$) only in the MGI diabetic cohort (rs9273363: OR = 1.5, $p = 2 \times 10^{-5}$ and rs9277545: OR = 1.5, $p = 3 \times 10^{-4}$) (Figure 2). Similarly, rs10224770 (*MNX1*) and rs17823772 (*CF4P43*) associations were only present in the diabetic cohort (Figure 2 and Table S3). On the contrary, the signal led by rs6984536 (*PXDNL*) was associated only in the non-diabetic (OR = 1.7, $p = 2 \times 10^{-4}$) but not in the diabetic cohort (OR = 1.1, $p = 0.26$) (Figure 2 and Table S3). No differences between diabetic and non-diabetic association results were observed for the other lead SNPs.

## Functional annotation of risk loci

While GWAS statistical power was limited, as an attempt to highlight potential candidate genes, we focused on association signals reaching suggestive threshold of significance ($p \leq 1 \times 10^{-5}$). Based on positional and expression quantitative trait loci (eQTL) mapping (Supplementary Methods), computational annotation of suggestive GP risk loci resulted in the identification of 14 protein-coding genes, namely *NOM1*, *MNX1*, *SNTG1*, *PXDNL*, *PRKG1*, *DKK1*, *SFR1*, *WDR96*, *GSTO2*, *PLIN1*, *MESP1*, *MESP2*, *ANPEP*, *GDPGP1* (Table 2). Some of these play a role in relevant biological mechanisms, such as metabolic and oxidative stress cytoprotection (*PXDNL*), regulation of muscle activity (*MESP1*, *MESP2*, *PRKG1*, and *GSTO2*), and neurogenesis (*MNX1*, *DKK1*). Notably, two candidate genes were associated with expression quantitative trait loci (eQTLs) in GI tissues from multiple variants (lead SNP or LD proxies $r^2 > 0.8$), including *MNX1* in esophagus mucosa ($p = 1.4 \times 10^{-5}$), and *DKK1* in gastroesophageal junction ($p = 1.4 \times 10^{-6}$) and sigmoid colon ($p = 1.4 \times 10^{-5}$) from the Genotype-Tissue Expression (GTEx, https://gtexportal.org) database (Figure S2).

## Gene-set network enrichment analysis

In order to gain biological insight, a gene-set co-expression network enrichment analysis focused on the 14 GP-associated genes was

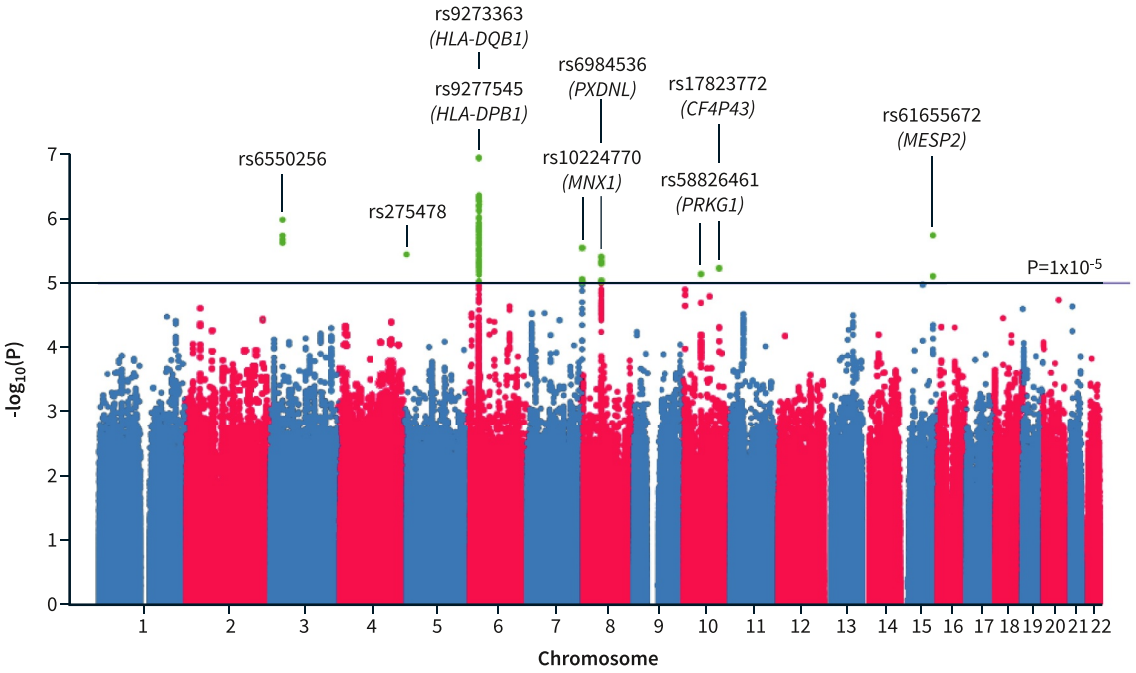


**FIGURE 1** Manhattan plot of the Gastroparesis (GP) genome-wide association study (GWAS) meta-analysis association results. Each circle denotes a marker with regard to its physical location (based on the Genome Reference Consortium Human Build 37) and associated $-\log_{10}$ *p*-value. SNPs reaching a suggestive significance threshold ($p \leq 1 \times 10^{-5}$, indicated with a vertical blue line) are colored in green. The lead SNP rsID associated with the strongest association signal from each locus and the nearest protein-coding gene (if available) are annotated.

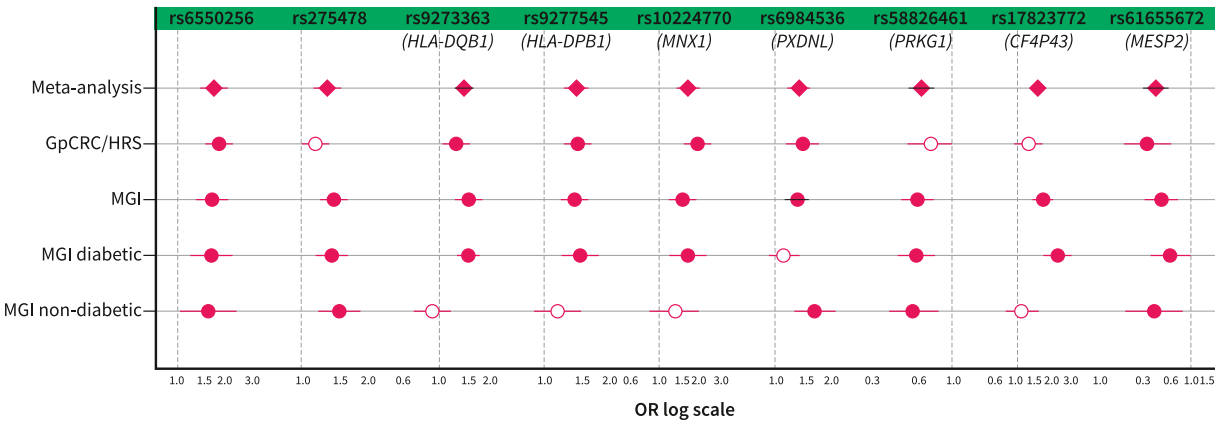


**FIGURE 2** Forest plots showing the odds ratio (OR) and 95% confidence intervals (on a $\log_{10}$ scale) for the nine Gastroparesis (GP) meta-analysis lead SNPs in the meta-analysis, individual genome-wide association study (GWAS) (Gastroparesis Clinical Research Consortium (GpCRC)/Health and Retirement Study (HRS) and Michigan Genomics Initiative (MGI)), and MGI analyses stratified by diabetic status (MGI diabetic and MGI non-diabetic). Circles filled in black are nominally significant associations ($p \leq 0.05$). Nearest protein-coding genes (if available) are annotated below lead SNP rsIDs. GpCRC/HRS GWAS included 478 cases and 9931 controls, and MGI GWAS included 402 cases and 48,340 controls. The diabetic MGI cohort included 251 cases and 9940 controls, while the non-diabetic MGI cohort included 151 cases and 38,400 controls. Full lead SNP association results for each cohort are shown in Tables S2 and S3.

performed to predict pathway membership and human phenotype associations (Supplementary. Methods). After false discovery rate correction for multiple tests, this analysis revealed significant ($p_{FDR} \leq 0.05$) enrichment for 636 gene-set terms (Table S4), highlighting the Notch signaling pathway among the top enriched ('*Signaling by NOTCH*', $p = 8 \times 10^{-3}$), as well as the pentose-phosphate pathway, and biological processes related to immune response (including glycosaminoglycan degradation) and nicotinic acetylcholine (nACh) receptors (Figure 3a). Nervous system and muscular defects from the Human Phenotype ontology were also associated, such as poor motor

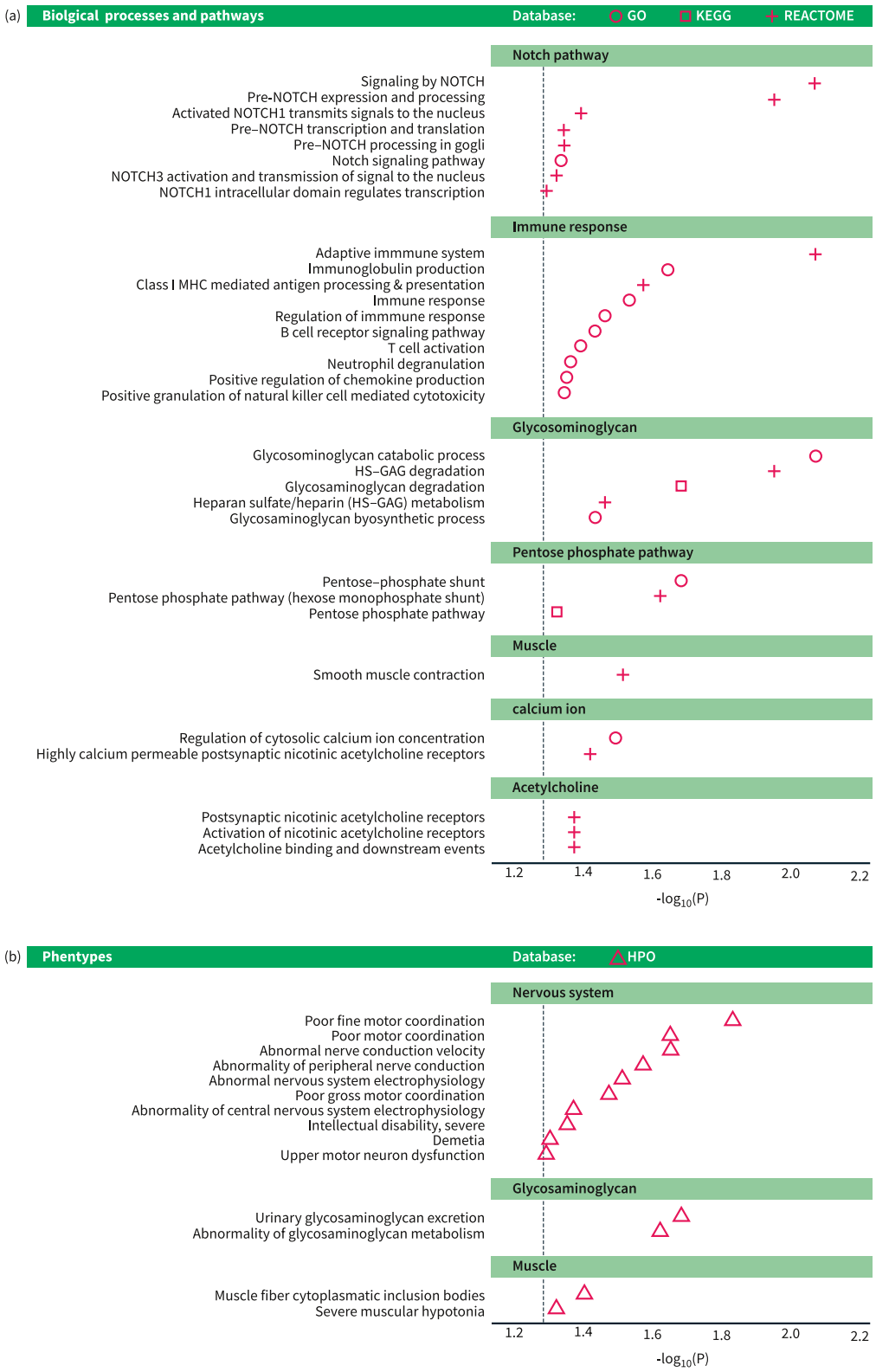


**FIGURE 3** Selected results of the gene-set network enrichment analysis (GSEA) performed with GeneNetwork. Selected ontology terms for (a) Biological processes/pathways from the gene-set libraries Gene Ontology (GO), REACTOME, and Kyoto Encyclopedia of Genes and Genomes (KEGG) and (b) Phenotypes from the Human Phenotype Ontology (HPO). The dashed gray line indicates the significative *p*-value threshold ($p_{FDR} \leq 0.05$). MHC: major histocompatibility complex; HS: heparan sulfate; GAG: glycosaminoglycan. Full GeneNetwork results are shown in Table S4.

coordination, abnormality of peripheral nerve conduction, and severe muscular hypotonia (Figure 3b).

## Genetic associations with clinical data

Using GpCRC patients' clinical data, we tested lead SNP associations with GR data and PAGI-SYM symptom scores (Supplementary Methods). Gastroparesis risk alleles from two loci were associated: rs6550256A with lower 4h-gastric retention (beta [SE] = −0.18 [0.09], $p$ = 0.04) and rs6984536A (*PXDNL*) with increased upper abdominal pain severity scores (beta [SE] = 0.13 [0.06], $p$ = 0.03). See Table S5 for all lead SNP association results with clinical variables.

## Gastric muscularis protein expression profile for selected candidate genes

To gain further insights into candidate genes with biological plausibility to cause dysmotility or enteric nervous system (ENS) injuries, IHC was performed for specific markers (DKK1, GSTO2, PRKG1, and PXDNL) (Supplementary Methods). Compared to corresponding controls, we found that DKK1 expression was reduced in diabetic GP patients ($p$ = 0.005), while unchanged in idiopathic GP (Figure 4). No differences in expression (vs. controls) were observed for the other tested markers. No-primary and no-secondary antibody controls are provided in Figure S3. When computing the correlation between expression levels and PAGI-SYM symptom scores in GP patients, we found that PXDNL expression was positively correlated with abdominal pain ($r$ = 0.8, $p$ = 0.02) and tended to have a positive correlation with the clinical variable 'stomach visibly larger', which captures the clinical phenotype of bloating ($r$ = 0.6, $p$ = 0.06). No associations were noted between the expression of remaining genes and the PAGI-SYM subscores.

## DISCUSSION

We report here a first pilot GWAS meta-analysis of GP performed exploiting genotype, demographical and clinical data from independent sources (NIDDK GpCRC/HRS, and MGI). Although almost 60,000 individuals were studied, only 880 GP cases were included in the meta-analysis. Hence, while statistical power was limited, we focused on a suggestive threshold of significance (association signals with $p \leq 1 \times 10^{-5}$, as adopted in other GWAS[22,23]) to generate initial hypotheses and highlight potential candidate genes and mechanisms for follow-up investigations. We identified suggestive GP-risk associated signals at nine independent loci (lead SNPs $p$-values $<7 \times 10^{-6}$) mapping plausible candidate genes and biological pathways, thus providing initial insight into the genetic predisposition to GP.

Some individual genes mapped in our GWAS meta-analysis represent plausible candidates to be involved in GP pathophysiology. For example, the gene *PXDNL* (Peroxidasin-Like), mapped to the rs6984536 locus, encodes a peroxidasin protein secreted in the extracellular matrix that plays a role in heme oxygenase 1 (HO-1) dependent cell adhesion, promoting cytoprotection against metabolic and oxidative stress.[24] This may be important to GP in view of recent studies that reported increased levels of pro-inflammatory M1 macrophages linked to oxidative stress and inflammation in gastric biopsies of GP patients.[10,25] Particularly, prevention of disease in mouse models of GP has been demonstrated in previous studies upon cytoprotection of pacemaker cells (like ICCs) promoted by anti-inflammatory M2 macrophages expressing elevated levels of HO-1 against oxidative injury.[9] Moreover, a link between peroxidasin deficiency, increased reactive oxygen species, and pro-inflammatory M1 macrophage recruitment has been recently demonstrated.[24] We previously reported genetic variations (short tandem repeats specifically) in the *HO-1* gene to be associated with GP risk and worst nausea symptoms in African Americans.[15] In this study, the *PXDNL* rs6984536 A allele was associated with risk of GP (OR = 1.4) and higher upper abdominal pain scores in GpCRC patients. Although no eQTLs in GI tissues are linked to this gene, our IHC staining revealed higher PXDNL expression in gastric biopsies of GP patients with increased abdominal pain severity scores. The specific triggers and mechanisms are unclear, and it is tempting to speculate that the *PXDNL* locus might be involved in the pathobiology of abdominal pain in GP through a stress-response defensive mechanism. In addition, the rs6984536 association was observed only at statistical significance in non-diabetic MGI analysis, suggesting this is a diabetes-independent GP risk locus.

Another potentially relevant candidate gene is *DKK1*, which was mapped to the rs58826461 risk locus via eQTLs in GI tissues from GTEx. In particular, the DKK1 rs58826461 T allele was linked to eQTLs that led to higher *DKK1* expression in colonic and esophageal tissues. Also, this allele was associated with protective effects on GP (OR = 0.6) in our GWAS analysis. Therefore, lower expression of DKK1 would be expected to be in the direction of GP risk. In consistency with this, our IHC analysis revealed reduced DKK1 expression in gastric biopsies of diabetic GP patients compared with diabetic controls. Notably, *DKK1* (mapped via rs58826461) encodes an inhibitor of the Wnt signaling pathway involved in the regulation of intestinal epithelial homeostasis and motor coordination.[26,27] Reduced DKK1 expression (leading to enhanced $\beta$-catenin signaling) in a mouse model of intestinal inflammation was associated with intestinal epithelial morphology irregularities, such as crypt distortion that is a hallmark of inflammatory bowel disease.[26,28] Notably, histologic abnormalities have also been reported in GP patients.[8] The functional relevance of DKK1 to GP pathophysiology, however, needs to be elucidated. Positionally mapped to the same rs58826461 risk locus as *DKK1*, *PRKG1* (Protein Kinase cGMP-Dependent 1) also appeared a possible candidate gene for GP risk, as it plays a role in GI motility through regulation of contractile proteins expression and modulation of intracellular $Ca^{2+}$ levels via the nitric oxide -cyclic guanosine monophosphate signaling.[29] Nevertheless, IHC staining did not reveal PRKG1 differential expression between GP cases and controls, possibly suggesting *DKK1* as a better candidate gene in this

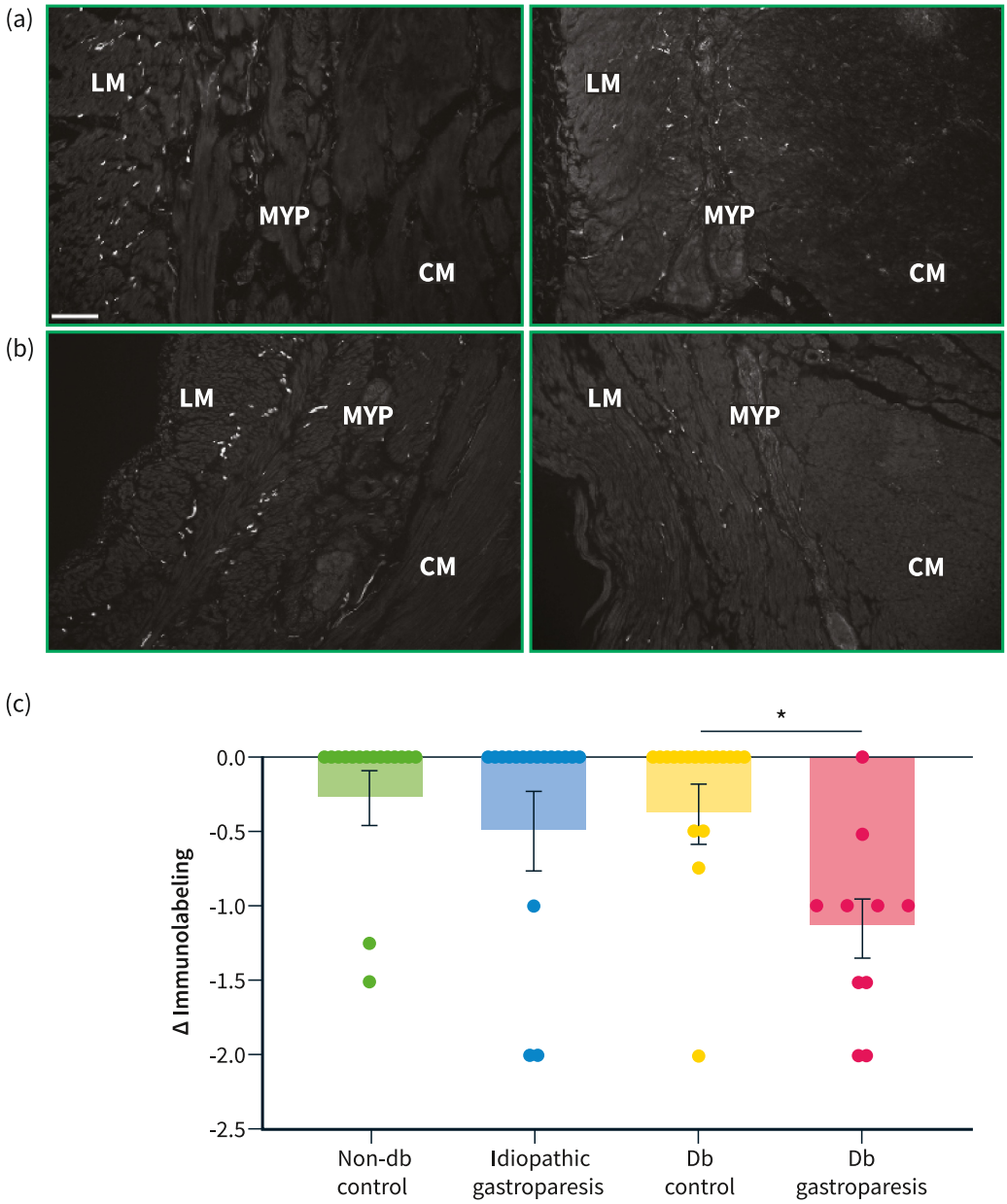


**FIGURE 4** Dickkopf WNT Signaling Pathway Inhibitor 1 (DKK1) immunoreactivity in gastric muscularis propria of controls and Gastroparesis (GP) patients and quantification of changes. Representative images from (a) Non-diabetic control (on the left) and Idiopathic GP (on the right), showing no appreciable changes; (b) Diabetic control (on the left) and Diabetic GP (on the right), showing significantly decreased DKK1-IR in the longitudinal muscle (LM) and myenteric plexus (MYP) regions in the diabetic GP sample; (c) Quantification of the relative change in DKK1 expression, showing a significant decrease in DKK1-IR in Diabetic GP. Data are mean ± SEM; *, $P < 0.05$; Two-tailed Mann-Whitney test (e and f). Scale bar = 50 μm.

locus. Likewise, *GSTO2* (Glutathione S-transferase), which was mapped to an independent locus on chromosome 10 (lead SNP rs17823772), also regulates GI motility via modulation of intestinal $Ca^{2+}$ absorption,[30] but it did not show differential expression in our gastric expression studies.

Our gene-set network enrichment analysis (GSEA) signaling found statistically significant ($p_{FDR} \leq 0.05$) associations with biological processes that may be relevant to GP pathogenesis. This includes the Notch pathway, which plays a role in immunomodulation by promoting M1 macrophage polarization[31] and is regulated by the candidate genes Mesoderm Posterior BHLH Transcription Factors (*MESP*) *1* & *2* mapped at the rs61655672 locus. Signaling pathways downstream of Notch activation tightly regulate enteric neural crest cells progenitor's maintenance, proliferation and differentiation, which are essential for a functional ENS development.[32] In line with this, we found significant GSEA associations with the pentose

phosphate pathway, which leads to the production of ROS and NO upon pro-inflammatory M1 macrophage activation.[33] Also of importance, GSEA revealed enrichment of biological processes associated with nACh receptors, which via acetylcholine neurotransmission in the ENS are key for controlling gastric motility[34] and inflammatory responses.[35] Altogether, these data shed light on the possible roles of the Notch, pentose phosphate, and nACh receptor pathways in the progression of GP, warranting further investigation in future mechanistic studies.

The most significant (best *p*-values) GWAS signals for GP risk were observed in the HLA class II region, close to the *HLA-DQB1* (rs9273363) and *HLA-DPB1* (rs9277545) loci. HLA genes play essential roles in immune responses, including antigen processing and presentation, and are greatly expressed on monocytes-derived cells.[36] Of note, HLA genetic variations are widely recognized as the strongest genetic risk factors for DM, accounting for 40%–50% of type 1 DM genetic susceptibility,[13] which is an autoimmune disease strongly linked to GP etiology. In type 1 DM, HLA variants can disrupt antigen presentation, triggering autoreactive T-cell responses and ultimately leading to the destruction of insulin-producing pancreatic $\beta$ cells.[37] In our analysis stratified by diabetes status, HLA associations with GP were absent when diabetic patients were excluded from the MGI cohort. This suggests that the observed effects of HLA on GP risk may be specific to GP patients with concomitant diabetes, for which HLA is a strong genetic risk factor. This may implicate different genetic etiologies for diabetic and non-diabetic forms of GP. It is important to highlight that no fine-mapping analysis aiming at identifying causal SNPs and genes was performed, as for this purpose more robust signals at genome-wide significance would be required.

Despite rs6550256A being associated with lower GR, this is an intronic variant without nearby protein-coding genes. Moreover, neither this nor other SNPs in high linkage disequilibrium ($r^2 > 0.8$) have been linked to other traits or diseases in previous GWASs. Therefore, it is currently difficult to draw biological plausibility behind this association. If validated in further studies, it will be of interest to dissect the role of this locus.

This study has limitations beyond the limited GWAS statistical power. It focused on individuals of European ancestry, which limits generalizability. The diagnosis of GP in the MGI cohort relied on ICD10 codes, which may not align with delayed gastric emptying on scintigraphy. The GpCRC cohort consists of tertiary care patients who have often added psychosocial comorbidities, limiting the generalization to the broader spectrum of GP patients. However, it was reassuring to note the concordant associations between the two cohorts. While no exclusion criteria were applied for the HRS control group (in the absence of clinical data), this is a common practice in GWAS studies where control data are derived from the general population.[38,39] Similarly, detailed clinical and physiological data were exclusively available to the GpCRC cohort, limiting the strength and validation of genetic associations with clinical parameters. The signaling pathway analysis is exploratory and does not necessarily imply effects on GP-related targets. Lastly, immunohistochemical analysis was performed on a small cohort and for selected markers.

In summary, our study provides preliminary insight into genetic predisposition to GP. These data point toward plausible candidate genes that map to biological processes/pathways that may be involved in sensory-motor and immune dysregulation observed in GP. Future studies are needed to validate these findings in much larger cohorts. Additionally, mechanistic studies will be needed to determine the role of these proteins in the end-organ pathophysiology of GP.

## AUTHOR CONTRIBUTIONS:

**Leticia Camargo Tavares:** Analysis of data (lead); statistical analysis (lead); interpretation of data (lead); writing-original draft (lead); writing-review & editing (lead); visualization (lead); technical or material support (supporting). **Tenghao Zheng:** Analysis of data (supporting); statistical analysis (supporting); writing-review & editing (supporting). **Madeline Kwicklis:** Analysis of data (supporting); statistical analysis (supporting); writing-review & editing (supporting). **Emily Mitchell:** Technical or material support (supporting). **Anita Pandit:** Writing-review & editing (supporting); Technical or material support (supporting). **Suraj Pullapantula**: Analysis of data (supporting); statistical analysis (supporting); writing-review & editing: (supporting). **Cheryl Bernard:** Writing-review & editing (supporting); technical or material support (supporting). **Maris Teder-Laving:** Writing-review & editing (supporting); technical or material support (supporting). **Francine Z. Marques:** Writing-review & editing (supporting). **Tonu Esko:** Writing-review & editing (supporting); technical or material support (supporting). **Braden Kuo:** Writing-review & editing (supporting); technical or material support (supporting). **Robert J. Shulman** Writing-review & editing: (supporting) Technical or material support (supporting). **Bruno P. Chumpitazi:** Writing-review & editing (supporting); technical or material support (supporting). **Kenneth L. Koch:** Writing-review & editing (supporting); technical or material support (supporting). **Irene Sarosiek:** Writing-review & editing (supporting); technical or material support (supporting). **Thomas L. Abell:** Writing-review & editing (supporting); technical or material support (supporting). **Richard W. McCallum:** Writing-review & editing (supporting); technical or material support: (supporting). **Henry P. Parkman:** Writing-review & editing (supporting); Technical or material support (supporting). **Pankaj J. Pasricha:** Writing-review & editing (supporting); technical or material support (supporting). **Frank A. Hamilton:** Writing-review & editing (supporting); technical or material support (supporting). **James Tonascia:** Writing-review & editing (supporting); technical or material support (supporting). **Matthew Zawistowski:** Acquisition of data (lead); interpretation of data (supporting); writing-review & editing (supporting); technical or material support (supporting). **Gianrico Farrugia:** Study concept and design (supporting); acquisition of data (supporting); interpretation of data (supporting); writing-review & editing (supporting); funding acquisition (lead); technical or material support (supporting). **Madhusudan Grover:** Study concept and design (lead); acquisition of data (lead); interpretation of data (lead); writing-original draft (supporting); writing-

review & editing (lead); visualization (supporting); funding acquisition (lead); technical or material support (lead); study supervision (lead). **Mauro D'Amato:** Study concept and design (lead); acquisition of data (lead); interpretation of data (lead); writing-original draft (supporting); writing-review & editing (lead); visualization (supporting); funding acquisition (lead); technical or material support (lead); study supervision (lead).

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## CONFLICT OF INTEREST STATEMENT

Dr. Grover receives research support from Takeda, Donga, Alfasigma and Alexza pharmaceuticals. None for other authors.

## DATA AVAILABILITY STATEMENT

Genome-wide association study summary statistics will be made publicly available in the GWAS catalog.

## ETHICS APPROVAL

The study was approved by the Monash University Ethics Review Board (protocol Nr: 19564).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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## APPENDIX A

### GpCRC Credit roster

**Members of the Gastroparesis Clinical Research Consortium as of June 2020:**

**Adult Clinical Centers:**

**Mayo Clinic, Phoenix, AZ**: Pankaj Jay Pasricha, MD (Principal Investigator).

**Johns Hopkins University, Baltimore, MD:** Robert Bulat, MD (Co-Investigator); Robert Burns; Guillermo Barahona Hernandez; Megan McKnight.

**Massachusetts General Hospital, Boston, MA:** Braden Kuo, MD, MSc (Principal Investigator); April Mendez, Kyle Staller, MD; Andrea Thurler, NP; Christopher Velez, MD; Casey Silvernale.

**Temple University, Philadelphia, PA:** Henry P. Parkman, MD (Principal Investigator); Zubair Malik, MD; Alan Maurer, MD; Amiya Palit, MD.

**Texas Tech University Health Sciences Center, El Paso, TX:** Richard W. McCallum, MD (Principal Investigator); Irene Sarosiek, MD (Principal Investigator); Natalia Vega, CCRC; Denise Vasquez; Sean Connery, Karina Espino, Marvin Friedman, PhD (Mount Sinai).

**University of Louisville, Louisville, KY:** T Thomas Abell, MD (Principal Investigator); Abigail Stocker, MD (Co-Investigator); Bridget Cannon, RN; Lindsay McElmurray, PA-C; Kelly Cooper, NP; Catherine McBride.

**Wake Forest University, Winston-Salem, NC:** Kenneth Koch, MD (Principal Investigator); Lynn Baxter; Anya Brown; Paula Stuart, PA; Amirah Abdullah.

**Pediatric Clinical Centers:**

**Baylor College of Medicine, Houston, TX:** Robert Shulman, MD (Principal Investigator); Bruno Chumpitazi, MD (Co-Investigator); Liz

Febo-Rodriguez, MD; John Hollier, MD; Cynthia Bouette; Heather Charron.

**Boston Children's Hospital, Boston, MA:** Samuel Nurko, MD (Site Principal Investigator); Stephanie Wall, Madeline Kane.

**Nationwide Children's Hospital, Columbus, OH:** Kent Williams, MD (Site Principal Investigator); Lina Yossef-Salameh; Frederick Woodley.

**Resource Centers:**

**Pathology Resource Center:**

**Mayo Clinic College of Medicine, Rochester, MN:** Gianrico Farrugia, MD (Principal Investigator); Madhusudan Grover, MD (Co-Principal Investigator); Cheryl Bernard; Margaret Breen-Lyles, CRC.

**National Institute of Diabetes, Digestive and Kidney Diseases, Bethesda, MD:** Jose Serrano, MD, PhD (Program Official); Frank Hamilton, MD, MPH (Project Scientist); Sherry Hall, MS; Stephen James, MD; Rebecca Torrance, RN, MSN.

**Scientific Data Research Center:**

**Johns Hopkins University, Bloomberg School of Public Health), Baltimore, MD:** James Tonascia, PhD (Principal Investigator); Margaret Adamo, BS; Patricia Belt, BS; John Dodge (2006–2018); Michele Donithan, MHS (2006–2017), MHS; Milana Isaacson, BS (2006–2018); Linda Lee, MD; Jill Meinert; Laura Miriel, BS; Emily Sharkey, BSN, MPH, MBA; Jacqueline Smith, AA; Michael Smith, BS; Alice Sternberg, ScM; Mark Van Natta, MHS; Annette Wagoner; Laura A Wilson, ScM; Goro Yamada PhD, MHS, MHS, MMS (2016–2019); Katherine P Yates, ScM.

**Legacy Clinical Centers**.

**California Pacific Medical Center, San Francisco, CA (2008–2017)**: William Snape, MD (Principal Investigator); Nata DeVole, RN; Karen Earle, MD; Kjersti Kirkeby, MD; Candice Lee; Mimi Lin, MD; Doug Troyer, Anna von Bakonyi.

**MetroHealth Medical Center, Cleveland, OH (2013–2016)**: Jorge Calles-Escandon, MD (Principal Investigator).

**Stanford University, Stanford, CA (2008–2017):** Linda Nguyen, MD (Principal Investigator); Emerald Adler, MD; Chiara Orlando.

**University of Michigan, Ann Arbor, MI (2006–2017):** William Hasler, MD (Principal Investigator); William Herman, MD; Andrew Kraftson, MD; Amy E. Rothberg, MD; Sophanara Wootten.