

1 **Systems Biology Framework Unravels Molecular Substrates Underlying
2 Comorbidity Between Parkinson's and Crohn's Disease**

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34

35 **Abstract**

36

37 In an era of global aging, the escalating burden of chronic disease comorbidity presents a
38 major clinical challenge, making it imperative to decipher the molecular underpinnings of
39 such links to advance diagnostics and therapies. The mechanistic basis for the comorbidity
40 between Parkinson's and Crohn's disease, in particular, remains obscure. Systems biology
41 framework in the current study deciphers this enigmatic nexus by integrating genetic
42 architecture with tissue-specific functional genomics and pathway network. A significant
43 shared genetic landscape is established, converging on host-pathogen interactions and barrier
44 integrity. Translating this to a functional context reveals profound transcriptional synergy,
45 wherein the blood milieu in Crohn's disease is highly aligned with the substantia nigra
46 pathological state of Parkinson's disease. The physical conduit for this aberrant crosstalk is
47 identified as a sequential breach of the gut epithelial, gut-vascular, and blood-brain barriers.
48 These findings culminate in a cohesive "gut-blood-brain axis" model, positing a directional
49 cascade where peripheral inflammation in Crohn's disease directly facilitates central nervous
50 system degeneration. This work reframes the etiology of Parkinson's disease, positioning
51 peripheral inflammatory triggers as direct contributors to neurodegeneration and offering a
52 new paradigm for therapeutic intervention.

53

54 **1. Introduction**

55 As one of the devastating neurodegenerative diseases, Parkinson's disease is characterized by
56 both progressive motor and non-motor symptoms which affect daily life, and is reported by
57 The Global Burden of Disease study to have the fastest increase in global prevalence and
58 mortality among neurological diseases.^[1] In 2016, there are about 6.1 million Parkinson's
59 patients in aged populations worldwide^[2] and the number is anticipated to be double by
60 2040,^[3] which exerts a critical mental and financial burden on caregivers and societies.
61 Parkinson's disease results in more than 340,000 deaths per year around the globe and the
62 mortality has been ever soaring with 38.3% increase during ten years from 2007 to 2017.^[4]
63 Though how Parkinson's disease occurs and evolves remains elusive, mounting evidence
64 indicates vital roles of genetics in its sporadic form.^[5-6] Despite substantial paradigm shift^[7]
65 and ever-lasting translational and clinical efforts, to date there are still no efficacious disease-
66 attenuating drugs and therapies for patients with Parkinson's disease.^[8] Thus, decoding
67 underlying mechanisms driving Parkinson's disease is an urgent unmet need for
68 pharmaceutical development and disease curation.

69

70 Crohn's disease, a chronic type of inflammatory bowel disease (IBD), often occurring in the
71 ileocolic and/or colonic part(s) of the intestine,^[9] accompanied by a morbidity about 30 cases
72 out of 100,000 people one year.^[10] For the United States only, there are more than 700,000
73 Crohn's patients.^[11] It is widely accepted that the pathogenesis of Crohn's disease is
74 comprised of genetic, microbiomic, and other environmental elements.^[9, 12] Genome-wide
75 association studies (GWAS) have contributed to the identification of more than 200 markedly
76 predispositional Crohn's disease genetic sites.^[13] However, these well-established loci could
77 only account for approximately 13% of Crohn's morbidity,^[12] which indicates a wide gap
78 between current state of the art and definitive underpinnings of Crohn's disease.

79

80 It has been acknowledged early Parkinson's patients are at increasing risk to have bowel
81 symptoms, e.g., constipation.^[14] Growing knowledge has led to the hypothesis that chronic
82 intestinal inflammation or IBD might elicit Parkinson's disease etiology.^[15-16] While
83 controversies on the impact of Crohn's disease on Parkinson's disease exist,^[17-19] more and
84 more genetic,^[20-23] epidemiological, and biochemical studies^[24] have strengthened the
85 connections between Parkinson's and Crohn's disease in various populations, incl.
86 Taiwanese,^[25] Swedes,^[26] Danes,^[27] Americans,^[28] and South Koreans.^[29] As a result, IBD
87 treatment might be able to ameliorate the susceptibility or postpone the onset of Parkinson's

88 disease.^[28, 30] Although multiple efforts have been made, insights into the systemic pairwise
89 relation between Parkinson's and Crohn's disease are still lacking,^[31] and investigations on
90 elucidating causal relationship between Parkinson's and Crohn's disease from a holistic
91 perspective, may pave a brand-new way for mechanistic decryption.

92

93 This enigmatic comorbidity is deciphered herein through a systems biology framework that
94 bridges the genetic landscape with tissue-specific functional genomics and pathway network.
95 We begin by curating and dissecting the shared genetic architecture of Parkinson's and
96 Crohn's disease, revealing a profound, non-random overlap that converges on host-pathogen
97 interactions and barrier integrity. We then systematically interrogate the transcriptional
98 activity of these genetic pathways across five disease-relevant tissues—the ileal and colonic
99 mucosa, blood, and substantia nigra—uncovering remarkable intra- and cross-tissue synergy
100 and a strong transcriptional alignment between the systemic milieu of Crohn's disease and the
101 substantia nigra pathology of Parkinson's disease. Building on this, we provide a tangible
102 physical basis for this crosstalk by demonstrating a sequential breach of the gut epithelial, gut-
103 vascular, and blood-brain barriers. Our findings culminate in a cohesive gut-blood-brain axis
104 model for Parkinson's and Crohn's disease comorbidity, which posits a directional pathogenic
105 cascade initiated by intestinal pathology in Crohn's disease that directly promotes
106 neurodegeneration in Parkinson's disease. This work not only provides a comprehensive,
107 data-driven framework for the comorbidity but also reframes the etiology of Parkinson's
108 disease, positioning peripheral inflammatory triggers as direct contributors to central nervous
109 system pathology.

110

111 **2. Results**

112 **2.1. A shared genetic landscape underpins Parkinson's and Crohn's disease**

113 Following a stringent processing strategy (**Figure 1a** and “*Genetic association data curation*”
114 in Experimental Section), our keyword-based search on PubMed initially yielded 4,411 and
115 3,137 publications for Parkinson's and Crohn's disease, respectively. A meticulous literature
116 filtration process subsequently narrowed this corpus to 677 and 318 publications with genuine
117 relevance to genetic variants in Parkinson's and Crohn's disease. Finally, a comprehensive
118 full-text review allowed us to curate a high-confidence dataset comprising 747 genetic
119 variants in 313 genes for Parkinson's disease, and 623 variants in 319 genes for Crohn's
120 disease (Figure 1b; Table S1 and S2, Supporting Information).

121

122 A comparative analysis of these datasets revealed a significant genetic intersection, with 26
123 variants and 31 genes shared between Parkinson's and Crohn's disease (Figure 1c).
124 Intriguingly, 16 of these 31 shared genes were exclusively linked to disease-specific variants.
125 This finding points toward a compelling comorbid mechanism wherein distinct genetic
126 perturbations converge upon a common set of genes, thereby orchestrating shared
127 downstream pathological events. Among these shared genes, MMP9^[32] and ABCB1^[33] are
128 known to modulate blood-brain barrier permeability, providing a potential conduit for
129 Crohn's peripheral pathologies to influence central nervous system processes in Parkinson's
130 disease. The presence of PGLYRP4, a peptidoglycan recognition protein,^[34] hints at a shared
131 role for bacterial sensing and immune response in both disorders. Angiotensin-converting
132 enzyme (ACE) links the shared genetic risk to dysregulated blood pressure, a non-motor
133 feature associated with Parkinson's pathology.^[35] The inflammasome component NLRP3,<sup>[36-
134 37]</sup> along with downstream NF-κB signaling cascade,^[38-39] points to a shared inflammatory
135 axis, which is pathologically active in Parkinson's and Crohn's disease. Mutations of
136 LRRK2—a multi-domain protein—confer significant risk for both conditions.^[40-41]
137 Collectively, these findings establish a substantive genetic nexus between Parkinson's and
138 Crohn's disease.

139
140 To ascertain that the observed genetic overlap was statistically significant and not a product of
141 random chance, we employed a Monte Carlo simulation approach with 100,000 iterations to
142 calculate empirical *P*-values. The simulation robustly confirmed the profound statistical
143 significance of the overlap for both the genetic variants and their associated genes ($P < 10^{-5}$
144 for both), underscoring the authenticity of this shared genetic architecture (Figure 1d, e).

145
146 We further delved into the genomic distribution and functional annotation of the variant
147 datasets, which revealed strikingly similar patterns between the two diseases (Figure S1a, b,
148 Supporting Information). Variants for both were distributed across the autosomes. However,
149 several key distinctions emerged. Notably, Crohn's variants were identified on the Y
150 chromosome while Parkinson's variants were not, an observation that aligns perfectly with
151 recent reports negating a strong link between Parkinson's disease and the Y chromosome.^[42]
152 Conversely, mitochondrial variants were unique to Parkinson's disease (Figure S1c,
153 Supporting Information), suggesting that mitochondrial dysfunction, while a hallmark of
154 Parkinson's disease, may not be a primary genetic driver in Crohn's disease. The pathogenic
155 contribution of mitochondrial variants in Parkinson's disease does not appear to be dominated

156 by any single functional class. Instead, synonymous, missense and unannotated variants are
157 present in commensurate frequencies and uniformly scattered across the mitochondrial
158 genome, raising the possibility that all three types contribute significantly to the disease's
159 genetic risk. A comparison of variant functional annotations further solidified this disease
160 similarity, with variants predominantly located in intronic regions, followed by missense and
161 unannotated variants (Figure 1f). This highlights that the functional consequences of many
162 variants implicated in Parkinson's and Crohn's comorbidity remain to be elucidated.
163

164 Expanding our analysis to the gene level, we observed a continued trend of functional
165 similarity. In both diseases, over 90% of the genetically-implicated genes were protein-coding
166 (Figure 1g). This starkly contrasts with the vastness of the non-coding genome, highlighting a
167 significant knowledge gap and potential bias in current genetic studies. To address this deficit,
168 we leveraged variant annotations from the dbSNP database to predict novel disease-related
169 genes, successfully identifying 110 and 50 potential candidates for Parkinson's and Crohn's
170 disease, respectively (Table S3 and S4, Supporting Information). The credibility of these
171 predictions was substantiated through both extensive literature mining and quantitative
172 evidence from our recently proposed transcriptomic meta-analysis method, AWmeta^[43]
173 (“Transcriptomic meta-analysis of Parkinson's and Crohn's disease” in Experimental
174 Section). An examination of these expanded gene sets revealed a dramatic shift: non-coding
175 genes now constitute over 50% of the total in both diseases (Figure 1h). This effort effectively
176 supplements the initial protein-coding-centric view, providing a more comprehensive and
177 balanced genetic landscape for exploring the comorbidity between Parkinson's and Crohn's
178 disease.
179

180 **2.2. Variant-enriched disease pathways implicate Parkinson's and Crohn's disease 181 comorbidity**

182 Given that the Kyoto Encyclopedia of Genes and Genomes (KEGG)^[44] provides a well-
183 curated repository of biological pathways linked to human diseases, it serves as a powerful
184 platform for investigating inter-disease connections at a functional enrichment level. We
185 therefore performed a disease pathway enrichment analysis on the Parkinson's and Crohn's
186 genetic variants (“Bio-functional aggregation of genetic association data” in Experimental
187 Section). Our objective was to map the broader disease landscape associated with each
188 disorder, thereby gaining novel perspectives on the mechanistic underpinnings of their
189 comorbidity.

190
191 This enrichment analysis revealed that Parkinson's and Crohn's disease share 38 human
192 disease pathways (Figure S2; Table S5 and S6, Supporting Information). Notably, these
193 commonly enriched pathways consistently demonstrated greater statistical significance than
194 the disease-specific pathways for either condition, suggesting they represent core pathological
195 processes of central importance to both Parkinson's and Crohn's disease. As a critical internal
196 validation of our gene sets, the top-enriched pathway for Parkinson's disease was "Parkinson
197 disease" itself, with the three most significant hits all being neurodegenerative disorders;
198 similarly, the premier hit for Crohn's disease was "Inflammatory bowel disease".
199
200 A striking asymmetry emerged from this analysis. While "Inflammatory bowel disease"
201 ranked as the eighth most significant pathway for the Parkinson's genes, the reciprocal was
202 not true: "Parkinson disease", or indeed any neuro-related pathway, was conspicuously absent
203 from the Crohn's enrichment results. This non-reciprocal relationship strongly suggests a
204 directional influence, where the genetic architecture of Parkinson's disease encompasses
205 susceptibility to Inflammatory bowel disease-like processes, whereas the genetic basis of
206 Crohn's disease does not inherently predispose to parkinsonism. This finding lends a strong
207 genetic support to the clinical hypothesis that inflammatory processes originating in
208 conditions like Crohn's disease can act as a catalyst for the initiation or progression of
209 Parkinson's disease, while the reverse is not established.^[45-46]
210
211 Further exploration of the shared pathways provided deeper mechanistic insights. The
212 enrichment of "Lipid and atherosclerosis" and "Fluid shear stress and atherosclerosis"
213 implicates dysregulated lipid metabolism as a common pathological feature.^[47-48] Similarly,
214 the shared enrichment of "Type I diabetes mellitus" and "Insulin resistance" points toward
215 aberrant insulin signaling as a convergent metabolic vulnerability in both diseases.^[49-50]
216
217 Intriguingly, an examination of the disease-specific pathways unveiled a potential etiological
218 link. Pathways for "Hepatitis B" and "Hepatitis C" were uniquely enriched in the Crohn's
219 gene set; concurrently, "Hepatocellular carcinoma" was a specific enrichment item for
220 Parkinson's disease. Given that chronic viral hepatitis is a primary driver of hepatocellular
221 carcinoma,^[51] this constellation of findings hints at a possible pathogenic trajectory where
222 systemic inflammation and hepatic stress associated with Crohn's genetic background may
223 contribute to a cellular environment conducive to pathologies seen in Parkinson's disease.

224

225 **2.3. Parkinson's and Crohn's genetic variants converge on host-pathogen interactions**
226 **and barrier integrity**

227 To obtain a panoramic view of the biological functions encoded by the shared genetic
228 architecture of Parkinson's and Crohn's disease, we first conducted a broad-stroke Gene
229 Ontology (GO) enrichment analysis using WebGestalt.^[52] This revealed a remarkably
230 congruent functional landscape for both diseases at a high level (**Figure 2a**). Within the
231 Biological Process (GO-BP) category, terms such as "biological regulation", "response to
232 stimulus", and "metabolic process" were top hits for both, implicating shared roles for
233 regulatory homeostasis, environmental stress responses, and metabolism. Similarly, in the
234 Molecular Function (GO-MF) and Cellular Component (GO-CC) domains, terms like "protein
235 binding", "ion binding", and "membrane" were commonly enriched, highlighting the
236 importance of molecular interactions at cellular membranes in the etiology of both disorders.

237

238 To achieve greater functional resolution, we performed a more detailed GO enrichment
239 analysis ("Bio-functional aggregation of genetic association data" in Experimental Section).
240 Examination of the top 40 shared significantly-enriched GO-BP terms unveiled a striking
241 thematic convergence on pathogen recognition and host defense (Figure 2b; Table S7,
242 Supporting Information). A substantial proportion of these terms, including "response to
243 peptidoglycan", "lipopolysaccharide-mediated signaling pathway", and "detection of
244 molecule of bacterial origin", strongly implicated host-pathogen interactions as a central
245 element of the shared genetic risk. Two particularly compelling findings emerged from this
246 analysis. First, the enrichment of "positive regulation of nitric-oxide biosynthetic process"
247 was surprising, as nitric oxide is a potent modulator of blood-brain barrier integrity.^[53] This
248 finding provides a direct genetic link to potential blood-brain barrier dysfunction as a
249 component of the comorbidity. Second, the enrichment of "maintenance of gastrointestinal
250 epithelium" pointed directly to the intestinal epithelium's homeostasis as a shared biological
251 vulnerability. The GO-MF and GO-CC results further substantiated the pathogen response
252 theme (Figure 2c; Table S8–S11, Supporting Information), solidifying the hypothesis that
253 processes governing the recognition of and resistance to pathogens and their derivatives play a
254 pivotal role in the shared Parkinson's and Crohn's mechanism. We designated these
255 potentially functional terms as "GO hotspots" (indicated by red asterisks in Figure 2).

256

257 To further determine if these genetically-defined GO hotspots were functionally active in
258 disease-relevant tissues, we analyzed their transcriptional status across our five tissue datasets,
259 i.e., the substantia nigra and blood in Parkinson's disease, and the ileal and colonic mucosa
260 and blood in Crohn's disease (**Figure 3**; “*Transcriptomic GO and pathway enrichment of*
261 *Parkinson's and Crohn's disease*” in Experimental Section). Remarkably, the pathogen
262 recognition and resistance processes were significantly and broadly activated (Normalized
263 Enrichment Score, NES > 0) across all five contexts. This system-wide activation signature
264 strongly suggests a persistent state of heightened immune surveillance, likely driven by an
265 elevated presence of pathogens or their molecular patterns in these tissues compared to
266 healthy controls.

267
268 As expected, processes related to neuronal activity were globally downregulated (NES < 0) in
269 the Parkinson's substantia nigra, reflecting its characteristic neurodegenerative pathology.
270 These same processes showed no consistent dysregulation in the other four tissues,
271 underscoring their tissue-specific nature. Notably, however, “positive regulation of neuron
272 apoptotic process” was significantly upregulated across all three Crohn's tissues, revealing a
273 potential, previously underappreciated pro-apoptotic systemic environment in Crohn's disease
274 that could impact neuronal health. Furthermore, we observed a significant activation of the
275 “positive regulation of Wnt signaling pathway” in both the ileal and colonic mucosa of
276 Crohn's patients. Given that aberrant Wnt activation is a recognized hallmark of compromised
277 intestinal barrier integrity and increased permeability,^[54-55] this result provides direct
278 transcriptomic evidence of a defective gut barrier in Crohn's disease, lending mechanistic
279 support to the gut-origin hypothesis of the comorbidity.

280
281 Finally, to assess the relative importance of different biological processes at the genetic level,
282 we compared the top 40 enriched GO-BP terms for each disease (Figure S3; Table S12 and
283 S13, Supporting Information). This revealed that the shared functional space was almost
284 exclusively dominated by immune-related processes, cementing the immune system's role as
285 the central arena for the Parkinson's and Crohn's disease interaction. Moreover, for Crohn's
286 disease, nearly all of its top 40 enriched terms were immune-related, confirming that immune
287 dysregulation is the preeminent feature of its genetic etiology.

288
289 **2.4. Genetically-informed genes and biological pathways exhibit coordinated**
290 **transcriptional activities within and across tissues in Parkinson's and Crohn's disease**

291 To translate the genetic findings into a functional context, we next determined the biological
292 pathways enriched within the Parkinson's and Crohn's variants ("Bio-functional aggregation
293 of genetic association data" in Experimental Section). This investigation uncovered 18 shared
294 pathways whose enrichment consistently reached a higher statistical significance than
295 pathways specific to either disease alone, underscoring their central importance to the shared
296 pathophysiology (**Figure 4a**; Table S14 and S15, Supporting Information). Among these, the
297 co-enrichments of the "IL-17 signaling pathway" and "Th17 cell differentiation" resonate
298 with our GO findings, as hyperactive Th17 cells are potent producers of the cytokine IL-17, a
299 key mediator of antimicrobial peptide production,^[56] thus reinforcing the theme of host-
300 pathogen interactions. Intriguingly, the "Intestinal immune network for IgA production" was
301 also a shared pathway, implying that immune processes within the gut may be a common
302 feature and thus pointing to a potential nexus between the two diseases. The "Hematopoietic
303 cell lineage" pathway emerged as one of the most statistically significant shared pathways.
304 This observation aligns with clinical evidence where hematopoietic stem cell transplantation
305 has proven effective in ameliorating symptoms of both Parkinson's and Crohn's disease,^[57-58]
306 highlighting the critical role of hematopoietic differentiation in their common mechanisms.
307 Furthermore, the presence of the "TNF signaling pathway" is particularly salient, given that
308 anti-TNF therapies for Crohn's disease are associated with a substantially reduced risk of
309 developing Parkinson's disease.^[59] The enrichment of the "Adipocytokine signaling pathway"
310 lends further support to the role of aberrant lipid metabolism as a convergent process in both
311 disorders, while the most statistically significant shared pathway, "HIF-1 signaling pathway",
312 implicates hypoxia—a condition known to be pivotal in both Parkinson's^[60] and Crohn's
313 disease^[61-63]—as a critical nexus linking mitochondrial dysfunction, oxidative stress, and
314 impaired protein degradation.^[64]

315

316 An exploration of the disease-specific pathways also yielded profound insights into both
317 distinct and convergent mechanisms. For Parkinson's disease, the unique enrichment of
318 "Ferroptosis" aligns with its known role in dopaminergic neuron death and glial activation,^[65]
319 while "Thermogenesis" provides a molecular correlate for the clinical observation of
320 temperature sensitivity in patients with Parkinson's disease.^[66-68] Intriguingly, longevity-
321 regulating pathways were enriched in both diseases—"Longevity regulating pathway" and
322 "mTOR signaling pathway" for Parkinson's disease, and "FoxO signaling pathway" for
323 Crohn's disease—suggesting a deeper, shared connection to cellular aging processes that
324 warrants further investigation. The Parkinson's specific enrichment of "Circadian rhythm"

325 supports the widespread prevalence of sleep and circadian disruptions in these patients.^[69-70]
326 Crucially, several pathways converged on the theme of cell adhesion. The Parkinson's
327 specific "Rap1 signaling pathway", which governs cell-cell junction formation via integrin
328 regulation, alongside the Crohn's specific "Cell adhesion molecules" and "Adherens junction"
329 pathways, collectively point to compromised barrier function as a fundamental, albeit
330 genetically distinct, feature. This is further reinforced by the Parkinson's specific "VEGF
331 signaling pathway", a known mediator of blood-brain barrier damage.^[53] Together, these
332 results illustrate a complex etiological landscape where both shared and disease-specific
333 pathways ultimately converge upon common pathological themes, suggesting a multifaceted
334 basis for the comorbidity.

335
336 To elucidate if these genetically-implicated pathways were functionally active *in vivo*, we
337 assessed their transcriptional activities across five disease-relevant tissues ("Transcriptomic
338 GO and pathway enrichment of Parkinson's and Crohn's disease" in Experimental Section).
339 A striking pattern emerged where Parkinson's and Crohn's genetic pathways were
340 significantly engaged in the pathological processes of all five tissues (Figure 4b). Parkinson's
341 specific pathways were pervasively downregulated in both substantia nigra and blood,
342 indicative of a systemic degenerative state in Parkinson's disease. Notably, "Dopaminergic
343 synapse" and "Serotonergic synapse" were suppressed not only in the Parkinson's substantia
344 nigra but also in the Crohn's ileal and colonic mucosa. Given the direct communication
345 between the brain and gut via the vagus nerve,^[71] this concurrent downregulation suggests a
346 potential trans-synaptic or neuro-inflammatory link between these distant tissues. Parkinson's
347 specific "VEGF signaling pathway" was significantly upregulated in the Crohn's ileal and
348 colonic mucosa. As a non-pathogenic pathway in these contexts, its activation may represent a
349 compensatory response to repair the compromised mucosal barrier.^[72-73] Crohn's specific
350 pathways were generally upregulated in the Crohn's intestinal mucosa but displayed divergent
351 activity patterns in Crohn's blood, suggesting distinct functional roles in systemic versus local
352 compartments. Interestingly, Crohn's specific "Cell adhesion molecules" and "Adherens
353 junction" pathways were significantly activated in the Parkinson's substantia nigra and blood.
354 Since their activation can be a reparative response,^[74] this signature hints at a pre-existing or
355 ongoing compromise of the blood-brain barrier in Parkinson's disease. Finally, the shared
356 genetic pathways were consistently activated across all five tissues, strongly suggesting a
357 synergistic interplay that underpins the comorbidity.

358

359 To move beyond isolated analyses and investigate the coordinated behavior of the genetic
360 association genes (313 genes for Parkinson's disease, 319 for Crohn's disease, and 31 for
361 common), we calculated the transcriptional correlation of four gene sets, i.e., shared genes,
362 Parkinson's specific genes, Crohn's specific genes, and all combined genes, within and across
363 tissues using the SMIC algorithm ("Transcriptomic gene and pathway correlation calculation
364 of Parkinson's and Crohn's disease using signed maximal information coefficient" in
365 Experimental Section). Within the blood, a shared tissue, all four gene sets displayed positive
366 correlation, with the shared gene set reaching statistical significance ($\text{SMIC} = 0.33, P < 0.05$),
367 indicating a functional mechanistic link within the circulatory system (Figure S4, Supporting
368 Information). As expected, correlations between the Crohn's ileal and colonic mucosa were
369 exceptionally high across all gene sets ($\text{SMIC} > 0.3, P < 0.001$), confirming their profound
370 molecular similarity. A striking and unexpected finding emerged from the cross-disease
371 analysis: a consistent, positive correlation was observed between the Crohn's blood and the
372 Parkinson's substantia nigra for all four gene sets, reaching statistical significance for the
373 Crohn's specific and combined gene sets ($P < 0.05$ and $P < 0.01$). In contrast, the correlation
374 between Parkinson's blood and substantia nigra was inconsistent. This critical asymmetry
375 suggests that the pathological state of the blood in Crohn's disease, more so than in
376 Parkinson's disease itself, is transcriptionally aligned with the pathological processes
377 occurring in the Parkinsonian brain.

378
379 We then extended this correlational analysis to the pathway level, applying SMIC to the
380 transcriptional activities of four corresponding sets of genetic pathways. While this again
381 confirmed the strong positive correlation between the Crohn's ileal and colonic mucosa, other
382 intra- and inter-tissue comparisons failed to yield consistent or significant results (Figure S5,
383 Supporting Information), suggesting that simple correlation may be insufficient to capture the
384 complexity of disease linkage. We therefore deployed the ACS method to quantify synergy, a
385 more nuanced measure of synergistic activity ("Transcriptomic pathway synergy measure of
386 Parkinson's and Crohn's disease based on acting-in-concert score" in Experimental Section).

387 The ACS results revealed widespread synergistic relationships among the five disease tissues
388 (Figure S6, Supporting Information), implying a high degree of functional influence.

389
390 Recognizing that pathway-level activity scores (e.g., NES) can obscure the individual
391 contributions of member genes, we performed a more granular analysis by calculating both
392 SMIC-based correlation and ACS-based synergy for each genetic pathway based on the

393 differential expression of its constituent genes. The correlation analysis again highlighted the
394 strong, consistent relationship between the Crohn's ileum and colon but yielded few other
395 significant findings (Figure S7a, Supporting Information). However, the synergy analysis
396 produced several compelling insights (Figure S7b, Supporting Information). Beyond the
397 robust synergy between the Crohn's ileal and colonic mucosa, we observed significant
398 synergy for shared genetic pathways between Parkinson's and Crohn's blood, indicating a
399 direct cooperative interaction within the circulation. More critically, a high degree of synergy
400 for shared pathways was detected between Parkinson's substantia nigra and Crohn's blood,
401 reinforcing the hypothesis that Crohn's systemic factors directly and synergistically impact
402 central nervous system pathology in Parkinson's disease. Finally, we observed heightened
403 synergistic scores for Crohn's specific pathways between Parkinson's substantia nigra and
404 Crohn's colonic mucosa, providing further evidence for a direct gut-brain axis of interaction
405 that contributes to the shared disease landscape.

406

407 **2.5. Increased gut epithelial permeability facilitates ileal and colonic mucosal pathologies
408 in Crohn's disease**

409 Building upon the above discovery of intricate multi-tissue functional associations between
410 Parkinson's and Crohn's disease, we next sought to establish a plausible physical basis for
411 this pathological crosstalk. Given that Parkinson's and Crohn's disease are canonically
412 defined by pathology primarily localized to the brain and intestine, respectively,^[75-76] any
413 molecular dialogue between them must navigate the gut-brain axis. This axis is anatomically
414 fortified by a series of three sequential biological barriers: the gut epithelial barrier (GEB), the
415 gut-vascular barrier (GVB), and the blood-brain barrier (BBB). We therefore posited a
416 "sequential-breach" hypothesis, wherein molecular pathology originating in the Crohn's gut
417 must progressively traverse these three checkpoints to exert a tangible influence on
418 neuropathogenesis in the Parkinson's brain. The compromise of these barriers would thus
419 represent the fundamental physical conduit for the observed comorbidity. Accordingly, our
420 investigation first focused on interrogating the integrity of the initial line of defense—the
421 GEB—within the context of active Crohn's pathology.

422

423 To empirically test this, we interrogated the transcriptomic profiles of the ileal and colonic
424 mucosa from Crohn's patients, focusing on our curated panel of GEB permeability
425 biomarkers. Our analysis revealed that a striking majority of these markers exhibited
426 expression changes that were not only statistically significant but also directionally consistent

427 with the states indicative of impaired barrier function (**Figure 5a**; Table S16, Supporting
428 Information). This provides compelling molecular evidence for the structural disruption of
429 intercellular tight and adherens junctions in the Crohn's gut, leading to heightened epithelial
430 permeability. This breach effectively dismantles the first physical safeguard, permitting the
431 translocation of luminal contents into the lamina propria (Figure 5b). While the expression of
432 most markers aligned with this conclusion, three biomarkers—claudin 1, claudin 2, and
433 JAM3—displayed a consistent and significant transcriptional upregulation, a finding
434 seemingly at odds with their protein-level functions in maintaining barrier integrity. As these
435 are not Crohn's disease susceptibility genes, we propose this transcriptional induction may
436 represent a compensatory, albeit insufficient, response to protein-level degradation or
437 mislocalization, a complex regulatory feedback loop that warrants further mechanistic
438 elucidation.

439
440 The consequence of this compromised GEB is an influx of microbial products and other
441 luminal antigens into the intestinal wall, a perturbation expected to profoundly remodel the
442 local biological network. To visualize these downstream effects, we integrated our
443 transcriptomic activity data (pathway NES and *P*-values) with the foundational biological
444 pathway network (“*Human biological pathway network construction*” in Experimental
445 Section). By filtering for significantly perturbed pathways while preserving network
446 connectivity, we constructed context-specific pathway networks for both the Crohn's ileum
447 and colon (Figure 5c, d). The resultant networks were remarkably congruent, corroborating
448 our prior correlational analyses and underscoring the profound mechanistic similarity between
449 the two intestinal sites. Intriguingly, these networks retained several pathways without direct
450 genetic links to Crohn's disease, including some with Parkinson's specific genetic
451 underpinnings. Their topological persistence reveals their critical role as indispensable
452 functional bridges that connect otherwise disconnected hubs of significantly altered Crohn's
453 pathways. The specific inclusion of Parkinson's genetic pathways as such conduits within the
454 Crohn's intestinal milieu provides compelling evidence for a latent molecular comorbidity at
455 the gut level. While direct investigation of Parkinson's disease-related pathology in the ileum
456 and colon remains a nascent field, our findings lay a novel conceptual groundwork and
457 provide a strong impetus for future research into this unexplored facet of the gut-brain axis.

458
459 **2.6. Gut-vascular barrier dysfunction underlies the blood-borne intersection of**
460 **Parkinson's and Crohn's disease**

461 We next assessed the integrity of the GVB, the second critical checkpoint in the gut-brain axis.
462 To this end, we analyzed blood transcriptomes from both Parkinson's and Crohn's cohorts for
463 permeability biomarker signatures. This analysis revealed a compelling transcriptomic profile
464 of GVB impairment in Crohn's disease, with most biomarkers showing statistically robust
465 expression changes indicative of increased permeability; conversely, these changes were
466 largely non-significant in Parkinson's disease, suggesting the GVB remains substantially
467 intact in this condition (**Figure 6a**; Table S17, Supporting Information). The paradoxical
468 upregulation of claudin 5 in Crohn's blood, a potential compensatory response, was a notable
469 exception. These transcriptomic signatures strongly suggest a compromised GVB in Crohn's
470 disease, characterized by the disruption of its intercellular junctions, which facilitates the
471 infiltration of gut-derived molecules into the bloodstream (Figure 6b).

472
473 To model the systemic consequences of this GVB breach in Crohn's disease, we constructed
474 the blood-specific biological landscape for both Parkinson's and Crohn's disease (Figure 6c)
475 by integrating transcriptomic activity onto the foundational pathway network ("Human
476 *biological pathway network construction*" in Experimental Section). We then classified
477 interaction for any same pathway in Parkinson's and Crohn's disease as either synergistic
478 (both up- or down-regulated) or antagonistic (divergently regulated). The synergistic mode
479 would theoretically promote comorbidity, while the antagonistic mode would counteract it.
480 The landscape was overwhelmingly dominated by synergistic effects, revealing a powerful
481 systemic synergy. Antagonistic interactions were rare and confined to the network's periphery,
482 exerting negligible global influence. This systemic synergy provides a molecular basis for
483 how the pathological milieu in Crohn's blood could create a permissive environment for
484 Parkinson's pathogenesis. Notably, the network's structural integrity relied on several non-
485 genetically associated "bridge" pathways, highlighting their critical role in mediating this
486 pathological crosstalk and marking them as targets for future investigation.

487
488 **2.7. Crohn's blood signature promotes substantia nigra degeneration in Parkinson's**
489 **disease through blood-brain barrier disruption**

490 Our investigation culminated at the final and most critical gatekeeper of the gut-brain axis,
491 BBB. We sought to determine if this terminal interface is breached under the pathological
492 conditions of Crohn's or Parkinson's disease, thereby permitting the influx of peripheral
493 molecules into the brain parenchyma.

494

495 A transcriptomic interrogation of permeability biomarkers yielded unambiguous evidence
496 (**Figure 7a**; Table S18, Supporting Information). In the blood of patients with Crohn's disease,
497 the entire panel of BBB markers exhibited expression changes that were both statistically
498 robust and directionally consistent with compromised barrier integrity. In contrast, these
499 markers remained largely quiescent in Parkinson's blood, suggesting that the systemic milieu
500 in Parkinson's disease does not induce a BBB breach. However, a direct analysis of the
501 Parkinson's substantia nigra painted a different picture, revealing a significant local disruption
502 of the BBB. This dual-front assault on the BBB—a systemic challenge from the Crohn's
503 periphery and a localized compromise from intrinsic Parkinson's pathology—creates a
504 permissive gateway for pathological crosstalk (Figure 7b). Notably, the paradoxical
505 transcriptional upregulation of claudin 5 and JAM3 within the Parkinson's substantia nigra
506 suggests a putative, albeit insufficient, compensatory response to protein-level junctional
507 instability.

508
509 To delineate the functional architecture of the diseased brain following this BBB breach, we
510 constructed a substantia nigra-specific pathological network (Figure 7c) by integrating
511 transcriptomic activity data onto the foundational pathway landscape ("Human biological
512 pathway network construction" in Experimental Section). The resulting network was
513 dominated by pervasive pathway downregulations, a molecular portrait of the degenerative
514 state characteristic of the Parkinson's brain. Critically, the network's structural integrity was
515 maintained by several topological keystones, including pathways with specific genetic links to
516 Crohn's disease. These pathways, though not directly implicated in Parkinson's genetics,
517 serve as indispensable functional conduits connecting significantly altered Parkinson's
518 disease-centric hubs. The presence of these Crohn's specific pathways within the brain
519 pathological network in Parkinson's disease provides a tantalizing glimpse into a latent
520 molecular comorbidity within the brain itself. This finding posits a novel mechanism for the
521 comorbidity, suggesting that systemic factors in Crohn's disease may directly engage and
522 exacerbate the intrinsic pathological cascades of Parkinson's disease, a hypothesis that opens a
523 new frontier for research into the gut-brain connection in neurodegeneration.

524

525 **3. Discussion**

526 In this study, the multi-scale systems biology investigation, spanning from genetic variants to
527 tissue-specific transcriptional networks, converges on a cohesive and compelling mechanistic
528 framework for the comorbidity between Parkinson's and Crohn's disease. A "gut-blood-brain

529 axis” model is proposed to elucidate a plausible, directional cascade through which peripheral
530 intestinal pathology in Crohn’s disease may directly promote neurodegeneration in
531 Parkinson’s disease (**Figure 8**). This model posits a sequential breach of three critical
532 biological barriers. The process is initiated by a compromised gut epithelial barrier in the
533 Crohn’s ileum and colon (Figure 8a), which permits the translocation of luminal antigens and
534 microbial products, thereby remodeling the local mucosal pathobiology (Figure 8b, c). This is
535 followed by the permeabilization of the gut-vascular barrier, leading to the systemic
536 dissemination of these pro-inflammatory molecules into the bloodstream (Figure 8d). Our
537 analysis reveals that this creates a systemic milieu in Crohn’s blood that not only acts
538 synergistically with that in Parkinson’s blood (Figure 8e) but also is transcriptionally aligned
539 with the pathological state of the Parkinson’s substantia nigra. The cascade culminates in the
540 compromise of the blood-brain barrier, a dual-front assault driven by both systemic factors
541 from the Crohn’s periphery and intrinsic pathology within the Parkinson’s substantia nigra
542 (Figure 8f), ultimately allowing peripheral insults to engage and exacerbate central nervous
543 system degeneration (Figure 8g). This model provides, for the first time, a tangible physical
544 and molecular basis for the well-documented epidemiological link between these two
545 seemingly disparate disorders.

546
547 A key strength of our study lies in its integrative, systems-level design, which bridges the gap
548 between static genetic risk and dynamic, tissue-specific functional consequences. By
549 employing novel computational approaches such as SMIC and our newly proposed ACS, we
550 were able to move beyond simple correlation to uncover complex, non-linear relationships
551 and synergistic interplay between pathways and tissues. This methodology provides a
552 powerful blueprint for investigating other complex comorbidities, particularly those spanning
553 the gut-brain axis. Our findings redefine the etiological landscape of Parkinson’s disease by
554 positioning peripheral inflammatory conditions not merely as risk factors, but as active
555 participants in neuropathogenesis, offering a paradigm shift that could inform new diagnostic
556 and therapeutic strategies focused on maintaining gut barrier integrity and mitigating systemic
557 inflammation to preserve neurological health.

558
559 While our data-driven discoveries provide a robust framework, we acknowledge several
560 limitations that chart a clear course for future research. Foremost, our findings are
561 computationally derived and constitute a rich portfolio of data-driven hypotheses that await
562 rigorous experimental validation. Methodologically, our ACS metric represents a prototype

563 approach; future iterations could incorporate the magnitude of gene expression changes, not
564 just the direction, to achieve a more quantitative measure of synergy. Furthermore, validation
565 across multi-omic layers—including proteomics and metabolomics—is imperative to capture
566 post-transcriptional nuances and confirm that the observed transcriptional synergies translate
567 to the functional protein and metabolite levels. The current analysis is also constrained by the
568 availability of matched tissue datasets. Acquiring transcriptomic data from the substantia
569 nigra in Crohn’s disease and the Parkinson’s intestinal mucosa represents a critical next step
570 to complete the mechanistic puzzle. Finally, leveraging the power of single-cell and spatial
571 transcriptomics will be crucial for dissecting the cell-type-specific contributions to barrier
572 dysfunction, and intra- and inter-tissue crosstalk, elevating the resolution of our proposed
573 comorbidity model from the tissue to the cellular level.

574

575 **4. Experimental Section**

576 *Genetic association data curation:* We utilized a tailored pipeline (Figure 1a) to retrieve,
577 aggregate and normalize genetic association data for Parkinson’s and Crohn’s disease.
578 Specifically, in the light of the unbiased nature of GWAS to unearth genetic variants across
579 whole genome,^[77] PheGenI^[78] was leveraged to obtain GWAS data of Parkinson’s and
580 Crohn’s disease. Only variants which surpass genome-wide significant threshold were kept.
581 Considering complex disorder phenotypes, such as Parkinson’s and Crohn’s disease, are
582 typically featured by synergistic variants with very small or mild individual effects,^[79] genetic
583 factors not satisfying stringent cutoff but with suggestive or nominal associations might
584 virtually matter. So, candidate gene-based genetic association studies as complements were
585 also taken into consideration. This kind of studies has two- (or three-) fold evidence: pre-
586 study biological hints, within-study conclusions (and post-study validations). The original
587 publications were gained from PubMed.

588

589 Due to the fact that MeSH term labelling is time-consuming and lagging,^[80-81] PubMed search
590 using MeSH terms would undoubtedly omit quite a lot of related literature. Thus, in order to
591 fetch most relevant publications indexed in PubMed, we revised our previous literature
592 retrieval terms^[82] as “Parkinson* AND (Polymorphism OR Genotype OR Alleles) NOT
593 Neoplasms” and “Crohn* AND (Polymorphism OR Genotype OR Alleles) NOT Neoplasms”
594 for Parkinson’s and Crohn’s disease, respectively. Non-English-written papers were removed.
595 All abstracts were scanned and only genetic association studies reporting significant genetic
596 associations with Parkinson’s and Crohn’s disease from retrieved publication corpus were

597 included for in-detailed selection. Further, full contents of all qualified papers were reviewed
598 to ensure the consistency of those drawn conclusions.

599

600 To converge irregular variants into a uniform corpus, several tools were adopted for final
601 variant standardization. UCSC liftOver^[83] was utilized to calibrate Parkinson's and Crohn's
602 disease related variants from various genome coordinate versions to GRCh38 assembly.
603 SNPedia,^[84] LitVar,^[85] and ClinVar^[86] were used to normalize polymorphic sites into standard
604 formats.

605

606 Monte Carlo experiment was implemented to testify if variant- and gene-level commonalities
607 between Parkinson's and Crohn's disease are biologically meaningful or statistically random.
608 Specifically, let G designate whole number of human variants (667,501,404 live Ref SNPs in
609 NCBI dbSNP Database) / genes (61,197 in NCBI Entrez Gene Database). Let P and C denote
610 the variant/gene sizes related to Parkinson's and Crohn's disease separately. We randomly
611 chose variants with the same number as Parkinson's and Crohn's ones from the
612 aforementioned live Ref SNPs and genes 100,000 times distinctively, and the empirical P -
613 value was calculated as the number of sets of overlapping variants/genes no less than the real
614 observed common size N divided by 100,000. The final P -value could be given by the
615 following formula:

$$616 \quad P_1(X \geq N|G, P, C) = \frac{1}{T} \sum_{i=1}^T S_i \quad (1)$$

$$617 \quad S_i = \begin{cases} 0, & \text{if } |P_i \cap C_i| < N \\ 1, & \text{if } |P_i \cap C_i| \geq N \end{cases} \quad (2)$$

618 where T is constant 100,000, S_i is a Boolean variable indicating the status in the i -th
619 experiment, P_i and C_i are variant / gene sets of Parkinson's and Crohn's disease
620 correspondingly.

621

622 *Bio-functional aggregation of genetic association data:* Capitalizing on latest GO and
623 pathway knowledgebase—KEGG, clusterProfiler^[87] was leveraged to detect biological
624 meanings hidden behind Parkinson's and Crohn's genetic association genes. GO provides the
625 world's largest information multiplicity source on gene function, saturated with BP, CC, and
626 MF facets. Described as a directed acyclic graph, GO possesses loose hierarchies in which
627 child (leaf) items are more specialized and concrete than corresponding parent (root) terms.
628 With the notion that leaf GO terms are more informative than root terms, a customized
629 strategy was used in the current study: leaf enriched GO terms were picked as potent agents

630 for biology-level interpretations. All overrepresented GO / pathway terms were further refined
631 by multiple testing correction with false positive rate (FDR) value 0.05 as significance
632 threshold.

633

634 *Human biological pathway network construction:* Distinctive biological pathways act in a
635 concerted manner to organize micro- and macro-phenotypes. However, current biological
636 pathways are largely discrete and need to be weaved together. Our previous work attempted
637 solving this problem using network separation distance metric.^[88] In present study, this
638 framework was implemented in the context of a high-quality human protein interactome^[89].
639 Albeit lots of pathway resources have been available, such as KEGG^[44], reactome,^[90] pathway
640 definitions and criteria of these databases differ from each other, and merging or comparing
641 various pathway resources is a pretty arduous task. As a widely used pathway source, only
642 KEGG pathway system was used to construct human biological pathway network. KEGG
643 pathways belonging to the category “Human Diseases” were filtered out for further analysis,
644 because pathways of this category are meta-pathways, i.e., merged version of many involved
645 pathways, not reflecting the original physiological profiles inside human cells. Members of a
646 pathway tend to converge into one or more module(s) in the context of human interactome.
647 Pathways with significant network modularity were deemed real biological pathways and
648 retained. As indicated by our previous work,^[88] network distance between two pathways
649 should be negative if this pathway pair has connections, thus pathways with network
650 separation distance less than zero were kept.

651

652 *Transcriptomic meta-analysis of Parkinson’s and Crohn’s disease:* Transcriptome is able to
653 figure out how the genetic factors virtually function. Parkinson’s and Crohn’s transcriptomic
654 data were fetched from GEO, SRA, and ArrayExpress. As the most affected sites, substantia
655 nigra transcriptome data were used for Parkinson’s disease, and colonic and ileal mucosa ones
656 for Crohn’s disease. Owing to currently no transcriptomic dataset(s) of individual patients
657 with both Parkinson’s and Crohn’s disease and the fact that blood transcriptomic profiling has
658 proved to be unbiased and shown efficacy in idiopathic Parkinson’s and Crohn’s patients
659 diagnosis,^[91-94] as a compromise, peripheral blood datasets in either Parkinson’s or Crohn’s
660 disease were used for preliminary dissection of etiological linkages between these two
661 disorders. The detailed information of transcriptomic data collection and processing used in
662 this study can be found in our recent work,^[43] where a new transcriptomic *meta-analysis*
663 method, AWmeta, was proposed to aggregate multiple Parkinson’s or Crohn’s transcriptomic

664 data in these five tissues for robust differentially expressed genes (DEGs) with reliable fold
665 change (FC) and corrected *P*-value, respectively.

666

667 *Transcriptomic GO and pathway enrichment of Parkinson's and Crohn's disease:* To
668 elucidate the functional manifestation of the genetic architecture in relevant tissues, we
669 performed a multi-level transcriptomic analysis. First, we identified DEGs from our
670 transcriptomic meta-analyses across five disease-relevant contexts: the substantia nigra and
671 blood in Parkinson's disease, and the ileal and colonic mucosa and blood in Crohn's disease
672 (see "*Transcriptomic meta-analysis of Parkinson's and Crohn's disease*" section for details).
673 A stringent statistical threshold of $|\log_2\text{FC}| > \log_2 1.5$ and $P < 0.05$ was applied to define the
674 DEG sets. Subsequently, to comprehensively map the functional landscape, we conducted
675 enrichment analyses for both GO terms and biological pathways using two complementary
676 algorithms: Over-Representation Analysis (ORA) on the DEG sets and Gene Set Enrichment
677 Analysis (GSEA) on the complete ranked gene lists.^[95] To leverage the unique strengths of
678 both methods, we adopted a consolidated approach, assigning the minimum *P*-value obtained
679 from either ORA or GSEA as the definitive significance score for each item.

680

681 Finally, to quantify the functional activity of key biological processes identified at the genetic
682 level, we focused on the previously identified GO hotspots and the genetically-implicated
683 biological pathways. We utilized NES derived from GSEA as a robust metric to represent the
684 activation or suppression status of these specific pathways and GO terms within each of the
685 five disease-tissue profiles.

686

687 *Transcriptomic genes and pathway correlation calculation of Parkinson's and Crohn's
688 disease using signed maximal information coefficient:* To interrogate the associative
689 relationships between transcriptional signatures in Parkinson's and Crohn's disease at both the
690 gene and pathway levels, we sought a metric capable of transcending the limitations of
691 conventional linear correlation measures. Recognizing that biological systems are governed
692 by complex and often non-linear dynamics, we employed a robust approach based on the
693 maximal information coefficient (MIC), a novel measure of dependence that excels at
694 detecting a wide spectrum of both linear and non-linear associations with high statistical
695 power.^[96] However, as an unsigned metric, MIC quantifies the strength but not the
696 directionality of an association. To preserve this critical information, we implemented a
697 signed version, the signed maximal information coefficient (SMIC), by integrating the MIC

698 value with the directionality provided by the Spearman's rank correlation coefficient (ρ). The
699 SMIC between two variables, X and Y, is formally defined as:

700
$$\text{SMIC}_{X,Y} = \text{sign}_\rho(X, Y) \times \text{MIC} \quad (3)$$

701 where $\text{sign}_\rho(X, Y)$ denotes the sign (+1 or -1) of the Spearman correlation. MIC values were
702 computed using the minerva R package.^[97] This hybrid approach allows us to capture the full
703 complexity of transcriptional relationships while retaining an intuitive understanding of the
704 crucial directional context.

705

706 *Transcriptomic pathway synergy measure of Parkinson's and Crohn's disease based on*
707 *acting-in-concert score*: Recognizing that simple correlation metrics are often insufficient to
708 capture the intricate interplay between complex diseases, we moved beyond simple pairwise
709 associations to quantify functional cooperativity at the pathway level. The overall activity of a
710 shared biological pathway can be misleading, as it may obscure critical synergistic or
711 antagonistic behaviors among its constituent members. To dissect these sub-pathway
712 dynamics, we conceptualized and implemented a novel metric, the acting-in-concert score
713 (ACS), designed to quantify the degree of concordant regulation within a given pathway
714 across two disease states.

715

716 We define a gene as "acting in concert" if it is directionally consistent in its dysregulation, i.e.,
717 up- or down-regulated in both diseases. The ACS for a given pathway is then formally
718 calculated as:

719
$$\text{ACS} = \frac{N_{AC}}{N} - 0.5 \quad (4)$$

720 where N_{AC} is the number of constituent genes acting in concert, and N is the total number of
721 genes in the pathway. A positive ACS signifies a net synergistic propensity within the
722 pathway, suggesting that the pathological states of the two diseases reinforce each other,
723 while a negative ACS indicates a predominantly antagonistic relationship.

724

725 *Intestinal and brain barrier permeability biomarker collection*: To evaluate the integrity of
726 key biological interfaces implicated in the gut-brain axis, we curated comprehensive panels of
727 molecular biomarkers based on an extensive literature review. Recognizing that compromised
728 barrier function is a pivotal event in initiating and perpetuating pathological inflammatory and
729 neurodegenerative cascades, we focused on three critical barriers. First, for GEB, which
730 delineates the intestinal lumen from the lamina propria and serves as the primary sentinel

731 against the translocation of luminal pathogens and antigens,^[98] we compiled a list of
732 established permeability markers (Table S16, Supporting Information). Subsequently, we
733 collated a set of indicators reflective of the integrity of GVB, a crucial checkpoint that
734 restricts the passage of microbial derivatives from the intestinal interstitium into systemic
735 circulation, thereby preventing systemic dissemination and end-organ damage (Table S17,
736 Supporting Information).^[99] Finally, to probe the status of the central nervous system interface,
737 we assembled a panel of well-characterized biomarkers for BBB, a highly selective
738 physiological boundary that meticulously regulates molecular traffic between the periphery
739 and the brain parenchyma to safeguard neural homeostasis against blood-borne insults (Table
740 S18, Supporting Information).^[100]

741

742

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750

751

752 **Data Availability Statement**

753 The data that support the findings of this study are available in the supplementary material of
754 this article.

755

756

757 **Figure Legends**

758 **Figure 1.** Variant-centric dissection reveals a shared genetic architecture of Parkinson's and Crohn's
759 disease. **a**, Retrieval, integration, and standardization process of Parkinson's and Crohn's genetic
760 variants. **b**, Statistics of initial PubMed retrieval, filtration, and final genetic variants and genes
761 relevant to Parkinson's and Crohn's disease. **c–e**, Literature-derived variant-to-gene mapping
762 showcases significant variant and gene intersections between Parkinson's and Crohn's disease. The
763 gene intersection can be derived from common variants (Parkinson's & Crohn's common-to-common
764 mapping) or disease-specific variants (Parkinson's or Crohn's specific-to-common mapping) (**c**), and
765 these variant (**d**) and gene (**e**) intersections are statistically significant, with empirical *P*-value

766 determined by 100,000 Monte Carlo experiments. **f**, Functional consequences of Parkinson's and
767 Crohn's genetic variants. **g**, Functional consequences of Parkinson's and Crohn's genetic genes. **h**,
768 Functional consequences of Parkinson's and Crohn's predicted genes. PD, Parkinson's disease; CD,
769 Crohn's disease.

770

771 **Figure 2.** Genetic variants of Parkinson's and Crohn's disease converge on pathogen- and derivative-
772 induced infection, recognition and resistance and barrier integrity. **a**, Broad GO terms enriched by
773 genetic association genes in Parkinson's and Crohn's disease. The x-axis represents the number of
774 genes included in the enriched GO terms (y-axis). Red, purple, and green indicate GO-BP, GO-MF,
775 and GO-CC, respectively. **b**, The same significantly enriched GO-BP terms (top 40) for genetic
776 association genes in both Parkinson's and Crohn's disease. **c**, Significantly enriched GO-MF and GO-
777 CC terms for genetic association genes in Parkinson's and Crohn's disease. The x-axis represents the
778 enrichment ratio of the enriched GO terms (y-axis). The sphere size indicates the number of genes
779 enriched in each GO term, and the sphere color the enrichment significance. GO term name in red
780 denotes the same GO terms enriched by genetic association genes in both Parkinson's and Crohn's
781 disease within the GO-MF and GO-CC categories. GO terms marked with red asterisks are GO
782 hotspots, whose transcriptional activities in multiple disease tissues were quantified in Figure 3.

783

784 **Figure 3.** Tissue-wise transcriptional activities of GO hotspots in Parkinson's and Crohn's disease.
785 Pink shading indicates GO hotspots related to the recognition and resistance of pathogens and their
786 relevant derivatives, and green shading those related to neural activity. NES is used to quantify
787 transcriptional activities of GO hotspots in Parkinson's and Crohn's tissues, with red shading
788 representing activation and blue shading repression. FDR with green shading indicates corresponding
789 activity quantification is statistically significant.

790

791 **Figure 4.** Genetic variant-enriched pathways are functionally active across tissues in Parkinson's and
792 Crohn's disease. **a**, Enriched non-disease pathways for genetic variants in Parkinson's and Crohn's
793 disease. This pathway enrichment was done against biological pathways within KEGG non-disease
794 categories by ORA approach, with FDR, enrichment ratio and gene counts shown in Parkinson's and
795 Crohn's specific and common pathway classes. **b**, Tissue-wise transcriptional activities of genetic
796 variant-enriched pathways in Parkinson's and Crohn's disease. NES is used to quantify transcriptional
797 activities of genetic pathways in Parkinson's and Crohn's tissues, with red shading representing
798 activation and blue shading repression. FDR with green shading indicates corresponding activity
799 quantification is statistically significant.

800

801 **Figure 5.** Increased intestinal epithelial permeability facilitates ileal and colonic mucosal pathologies
802 in Crohn's disease. **a**, Transcriptional change profile of gut epithelial barrier permeability biomarkers

803 in ileal and colonic mucosa of Crohn's disease. **b**, Schematic diagram of the mechanism underlying
804 increased gut epithelial barrier permeability in the ileum and colon of Crohn's disease. **c**, Biological
805 pathway network in ileal mucosa of Crohn's disease. **d**, Biological pathway network in colonic
806 mucosa of Crohn's disease. The thickness of the edges between pathway nodes represents the pathway
807 crosstalk intensity: the thicker the edge, the greater the crosstalk intensity. The pathway node size
808 denotes the network node degree: the larger the node, the higher the node degree. IM, ileal mucosa.
809 CM, colonic mucosa. FC, fold change. NES, normalized enrichment score. FDR, false discovery rate.
810 GEB, gut epithelial barrier. TJ, tight junction. AJ, adherens junction.

811

812 **Figure 6.** Gut-vascular barrier dysfunction underlies the blood-borne intersection of Parkinson's and
813 Crohn's disease. **a**, Transcriptional change profile of gut-vascular barrier permeability biomarkers in
814 blood of Parkinson's and Crohn's disease. **b**, Schematic diagram of the mechanism underlying
815 increased gut-vascular barrier permeability in Parkinson's and Crohn's disease. **c**, Biological pathway
816 network in blood of Parkinson's and Crohn's disease. The thickness of the edges between pathway
817 nodes represents the pathway crosstalk intensity: the thicker the edge, the greater the crosstalk
818 intensity. The pathway node size denotes the network node degree: the larger the node, the higher the
819 node degree. WB, whole blood. FC, fold change. NES, normalized enrichment score. FDR, false
820 discovery rate. GVB, gut-vascular barrier. TJ, tight junction. AJ, adherens junction.

821

822 **Figure 7.** Crohn's blood signature promotes substantia nigra degeneration in Parkinson's disease
823 through blood-brain barrier disruption. **a**, Transcriptional change profile of blood-brain barrier
824 permeability biomarkers in blood of Parkinson's and Crohn's disease, and substantia nigra of
825 Parkinson's disease. **b**, Schematic diagram of the mechanism underlying increased blood-brain barrier
826 permeability in Parkinson's and Crohn's disease. **c**, Biological pathway network in substantia nigra of
827 Parkinson's disease. The thickness of the edges between pathway nodes represents the pathway
828 crosstalk intensity: the thicker the edge, the greater the crosstalk intensity. The pathway node size
829 denotes the network node degree: the larger the node, the higher the node degree. WB, whole blood.
830 SN, substantia nigra. FC, fold change. FDR, false discovery rate. BBB, blood-brain barrier. TJ, tight
831 junction.

832

833 **Figure 8.** Gut-blood-brain axis model for the comorbidity between Parkinson's and Crohn's disease.
834 In the molecular pathological process of Crohn's disease, the gut epithelial barriers of the ileal and
835 colonic mucosa are impaired (**a**), allowing the contents of the intestinal lumen to cross the barrier and
836 enter the inner wall of the intestine. This further affects the biological pathway networks in the ileal (**b**)
837 and colonic (**c**) mucosa of Crohn's disease. Subsequently, the gut-vascular barrier is damaged (**d**),
838 causing microorganisms and their derivatives to cross the barrier and enter the blood circulation,
839 which in turn impacts the blood biological pathway networks of Parkinson's and Crohn's disease (**e**).

840 Finally, against the background of Crohn's disease related blood pathology, the blood-brain barrier is
841 impaired (**f**), enabling blood contents to cross the blockade and enter the brain parenchyma, thereby
842 influencing the biological pathway network in the substantia nigra of the Parkinson's brain (**g**). GEB,
843 gut epithelial barrier. GVB, gut-vascular barrier. BBB, blood-brain barrier. TJ, tight junction. AJ,
844 adherens junction.

845

846

847 **References**

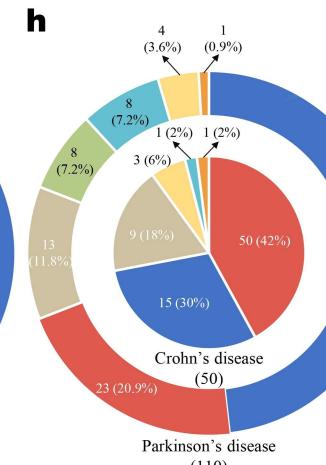
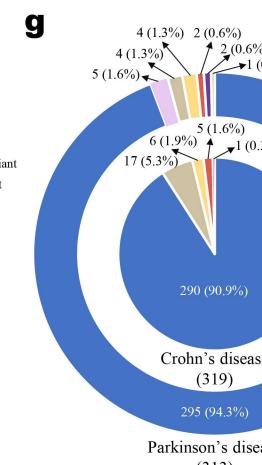
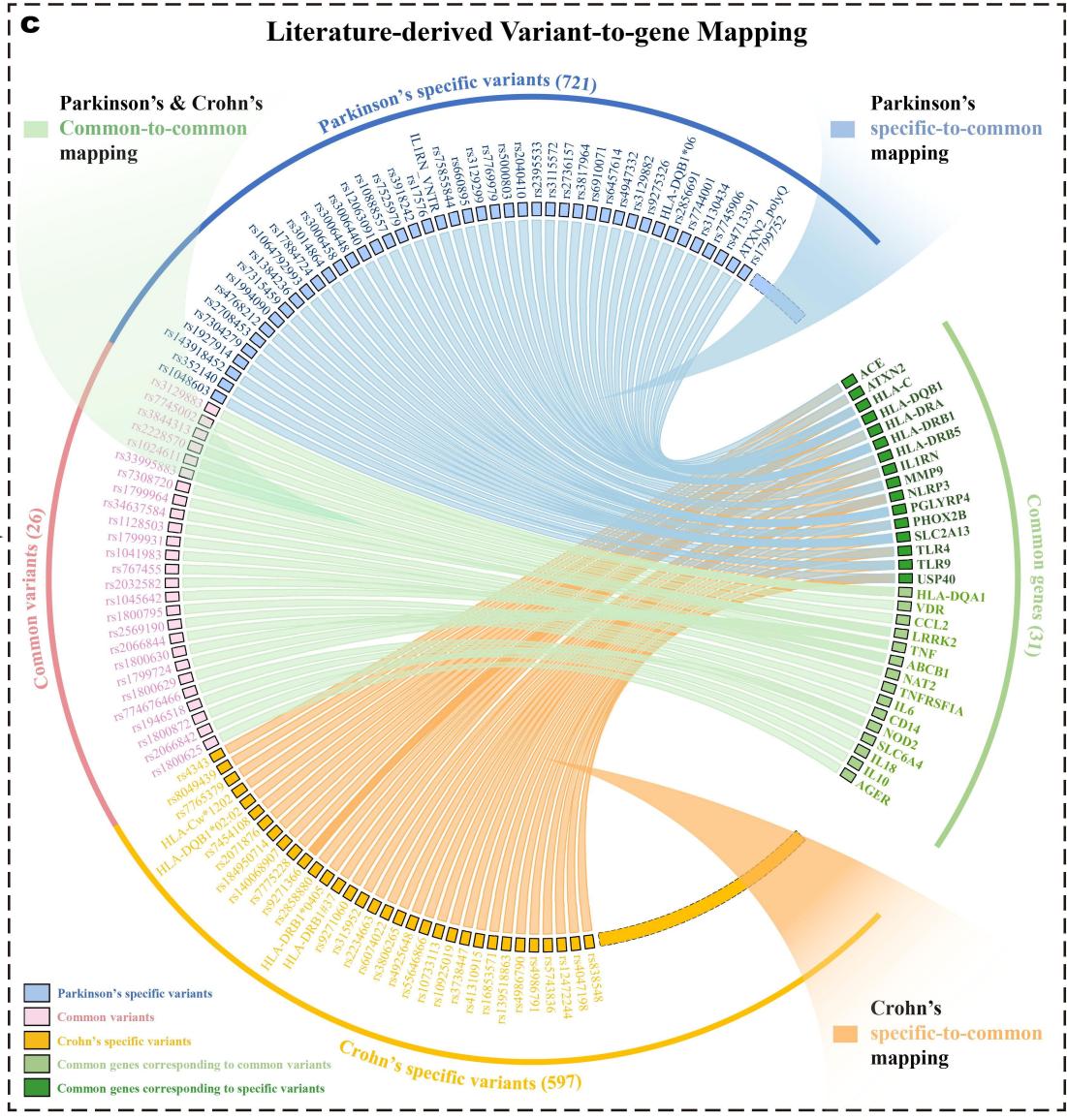
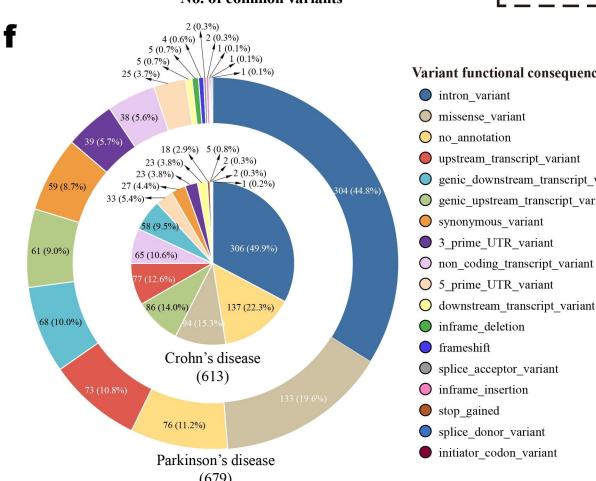
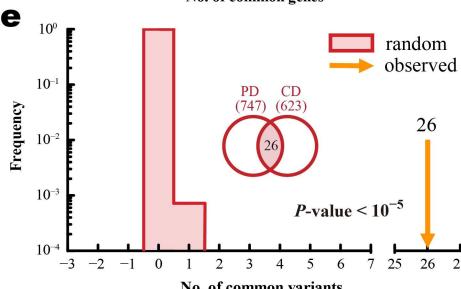
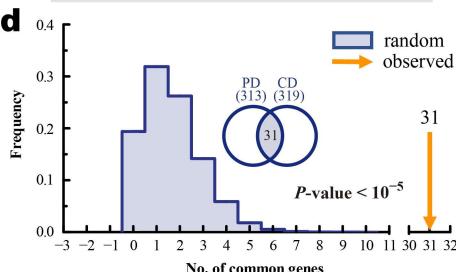
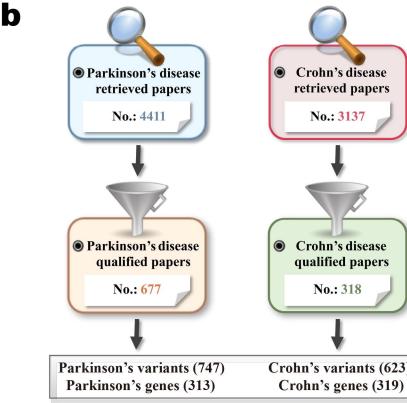
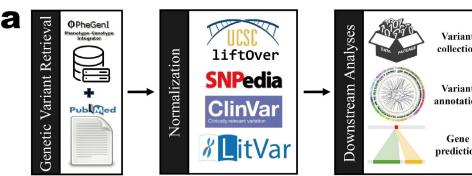
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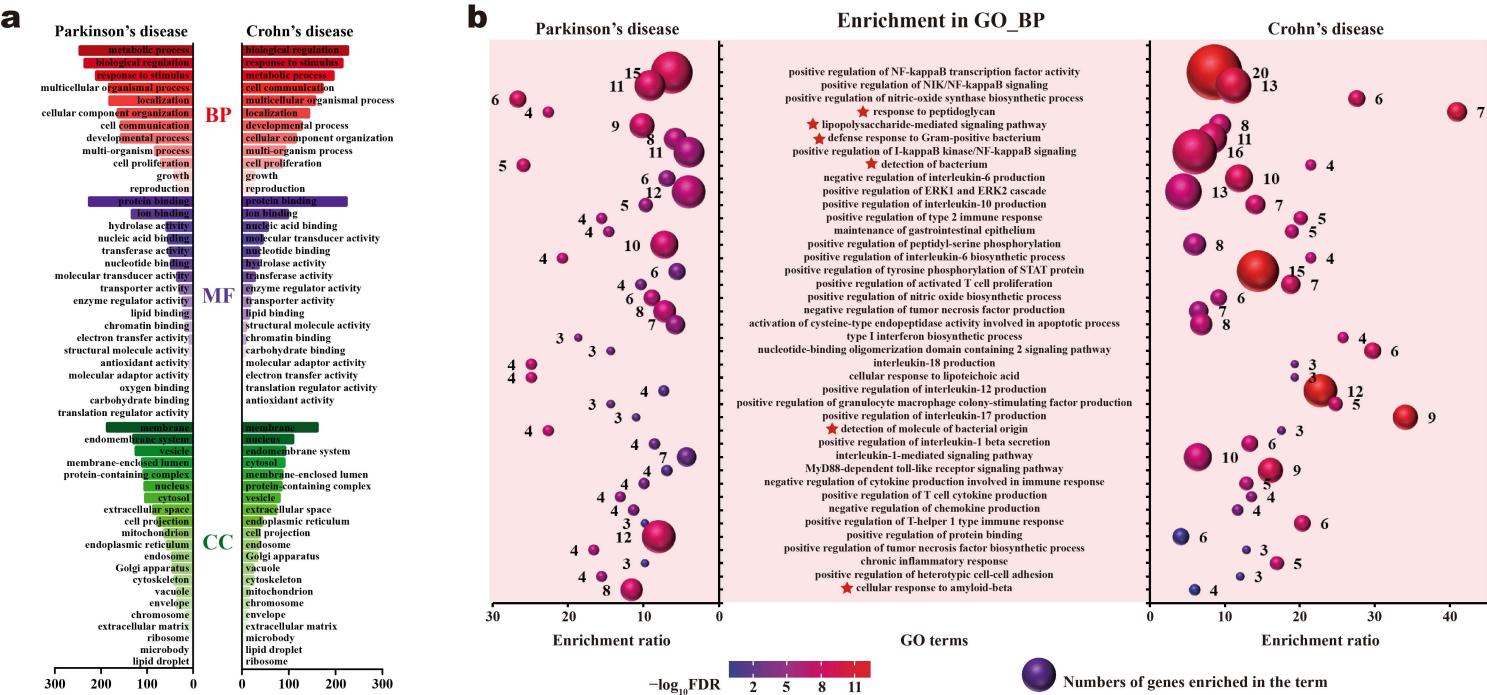
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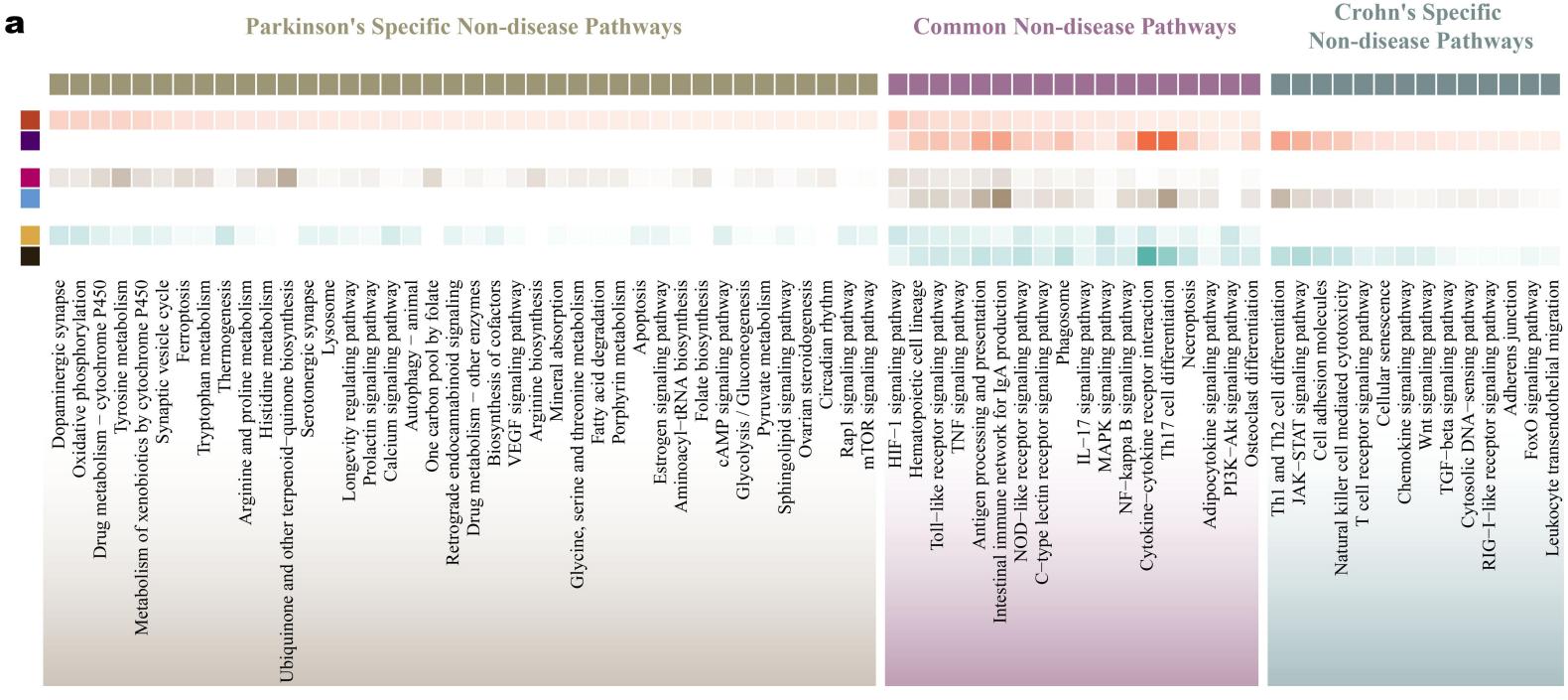
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GO Term	Parkinson's Substantia Nigra			Parkinson's Whole Blood			Crohn's Whole Blood			Crohn's Ileal Mucosa			Crohn's Colonic Mucosa		
	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio
response to peptidoglycan	1.09	3.54E-01	1.42	1.08	3.69E-01	2.21	1.34	1.13E-01	1.72	1.61	2.02E-02	1.89	1.67	1.32E-02	2.30
	0.72	9.73E-01	0.31	1.20	5.10E-01	1.43	1.55	8.77E-03	1.11	1.96	1.89E-04	1.33	1.88	9.49E-04	1.49
	1.09	2.08E-01	1.26	1.15	1.12E-04	4.20	1.72	2.35E-04	1.49	2.18	3.23E-06	1.40	2.12	4.20E-06	1.70
	0.87	8.27E-01	0.75	1.19	5.39E-02	2.78	1.28	1.21E-01	1.23	1.91	1.83E-04	1.13	1.47	2.90E-02	1.09
	1.53	8.47E-03	0.98	1.59	4.83E-03	1.45	1.63	7.01E-04	0.96	1.70	7.29E-04	0.93	2.32	2.12E-06	1.28
	1.04	3.91E-02	1.09	1.65	5.73E-03	2.03	1.65	4.13E-04	1.80	1.59	2.49E-02	1.41	1.90	5.76E-04	1.48
	1.12	1.71E-03	1.61	1.38	2.17E-02	1.41	1.68	2.89E-05	1.96	1.89	4.81E-04	1.54	1.57	3.22E-02	1.61
	0.89	1.06E-01	1.46	1.40	8.35E-01	0.57	1.12	4.12E-02	1.38	1.73	2.57E-03	1.05	1.37	2.17E-02	1.41
	0.99	3.78E-04	1.87	0.86	1.01E-01	1.87	1.33	4.81E-02	0.93	1.44	2.22E-02	1.40	1.25	1.76E-03	1.43
	-0.93	2.52E-05	2.44	-1.19	5.56E-01	1.08	-0.90	5.32E-04	1.68	-0.67	9.80E-01	1.17	0.75	6.45E-01	0.96
virus receptor activity	1.26	9.45E-03	1.62	-0.74	1.87E-01	1.65	1.25	4.33E-03	1.42	1.71	7.23E-04	1.30	1.71	5.36E-04	1.44
positive regulation of neuron apoptotic process	1.44	6.58E-02	1.47	0.83	8.40E-02	2.14	1.29	2.59E-03	1.51	1.52	1.50E-02	1.32	1.39	3.39E-02	1.16
	-1.24	4.71E-04	1.55	0.79	6.06E-01	0.95	1.11	1.01E-03	1.31	1.50	2.29E-03	1.22	1.69	8.62E-06	1.46
	-1.31	4.05E-02	0.98	1.11	9.56E-01	0.42	1.15	1.88E-01	0.25	-1.47	7.09E-03	0.97	-0.96	5.46E-01	0.39
	1.10	2.13E-01	1.54	1.59	2.00E-02	1.43	-0.70	9.05E-01	0.63	1.37	9.77E-02	1.22	0.83	7.23E-01	1.19
	-0.89	3.84E-04	2.61	1.52	8.24E-01	0.77	1.24	1.82E-01	0.83	-1.43	5.36E-02	0.94	1.05	3.66E-01	1.07
	1.04	1.39E-01	1.65	1.10	1.82E-01	2.56	-0.91	1.23E-01	1.42	1.21	2.17E-01	1.29	1.20	2.13E-01	1.07
	-1.65	1.79E-02	1.61	-0.87	6.40E-01	0.96	0.99	4.88E-01	0.62	1.05	3.71E-01	1.16	1.19	2.24E-01	0.59
	-1.82	7.24E-17	1.99	1.15	2.68E-01	1.19	0.84	9.65E-01	1.04	1.09	5.53E-03	1.13	1.09	3.21E-02	1.13
	-1.27	1.03E-04	2.00	0.95	8.07E-01	0.67	-1.21	1.15E-01	0.74	-1.24	5.21E-01	1.01	1.04	3.62E-01	0.76
	-1.56	1.71E-03	1.61	1.23	9.56E-01	0.42	0.83	8.57E-01	0.60	0.70	4.68E-01	1.02	0.87	8.17E-01	0.69
integral component of presynaptic membrane	-1.51	2.43E-12	1.85	0.87	2.59E-01	1.20	0.83	9.68E-01	1.02	-0.89	3.91E-02	1.09	-1.11	1.48E-01	1.03
	-1.50	1.12E-01	1.87	1.33	4.01E-01	1.09	-0.75	8.26E-01	0.96	1.03	4.70E-02	1.48	1.17	2.52E-01	1.09
	-1.38	2.04E-04	2.46	0.98	7.60E-01	0.72	1.08	3.31E-01	1.35	0.69	8.88E-01	0.83	1.12	2.63E-01	1.04
	-1.20	2.69E-04	3.36	0.76	7.92E-01	0.93	0.83	7.15E-01	0.77	1.18	4.70E-02	1.48	0.63	1.40E-01	1.45
	-1.55	7.46E-03	2.00	1.24	7.60E-01	0.72	1.04	3.99E-01	0.87	0.62	6.10E-02	1.28	-1.14	2.32E-01	0.67
	-1.09	4.11E-01	1.31	1.30	4.52E-01	1.11	-0.73	8.38E-01	1.12	0.99	3.14E-02	1.57	-1.24	5.28E-02	1.69
	-2.11	5.55E-07	2.35	1.19	4.92E-01	1.07	0.68	9.88E-01	0.49	-0.76	7.74E-01	0.93	0.88	7.40E-01	0.86



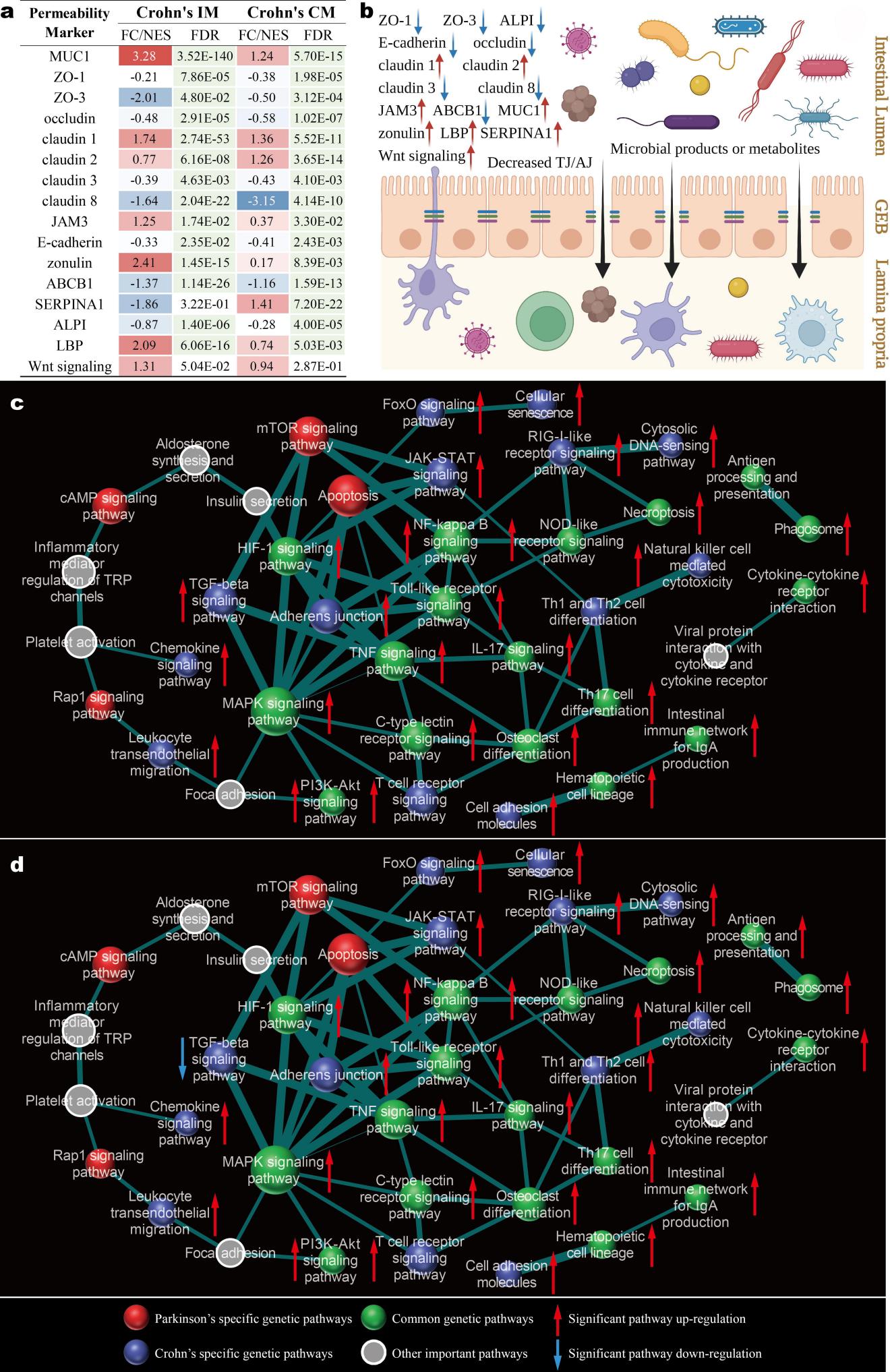
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Parkinson's Specific Genetic Pathways

Common Genetic Pathways

Crohn's Specific Genetic Pathways

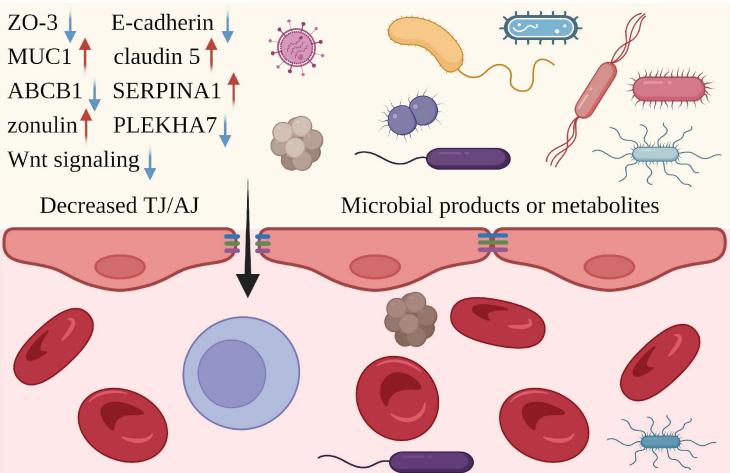
Pathway	Parkinson's Substantia Nigra			Parkinson's Whole Blood			Crohn's Whole Blood			Crohn's Ileal Mucosa			Crohn's Colonic Mucosa		
	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio
Dopaminergic synapse	-2.15	2.83E-08	1.91	1.20	2.15E-03	1.85	0.64	1.58E-03	1.89	-1.32	1.37E-02	1.68	-1.00	2.19E-03	1.85
Oxidative phosphorylation	-2.11	4.79E-08	3.06	0.78	2.25E-10	2.96	0.46	1.13E-10	3.03	-1.52	9.77E-04	2.64	-1.66	2.40E-04	2.95
Tyrosine metabolism	0.82	8.24E-01	1.61	0.66	9.24E-02	1.55	1.00	8.15E-02	1.59	-2.72	2.85E-12	2.83	-2.18	3.69E-07	1.55
Drug metabolism - cytochrome P450	-1.33	1.38E-05	3.79	0.64	1.97E-05	3.67	1.15	1.54E-05	3.76	0.91	5.02E-07	3.94	-1.40	4.51E-02	3.67
Histidine metabolism	-0.95	8.87E-05	3.25	0.67	1.25E-04	3.15	0.88	9.86E-05	3.22	1.02	2.96E-08	4.01	-1.68	4.45E-06	2.06
Synaptic vesicle cycle	-2.61	3.87E-11	2.56	0.54	1.46E-04	2.48	0.71	1.08E-04	2.53	0.84	8.48E-04	2.16	0.74	1.48E-04	2.47
Ferroptosis	1.37	7.30E-02	0.51	1.12	9.22E-01	0.50	0.83	9.16E-01	0.51	0.98	4.93E-01	0.65	0.94	5.63E-03	0.50
Tryptophan metabolism	-0.95	8.87E-05	3.25	0.67	1.25E-04	3.15	0.88	9.86E-05	3.22	1.02	2.96E-08	4.01	-1.68	4.45E-06	2.06
Arginine and proline metabolism	-1.00	7.39E-04	2.68	-0.72	1.01E-03	2.59	0.79	8.15E-04	2.65	1.02	1.16E-03	2.43	0.96	1.02E-03	2.59
Histidine metabolism	0.79	1.28E-05	4.78	-0.72	1.73E-05	4.62	0.87	1.41E-05	4.73	-1.34	5.80E-05	4.03	-1.02	1.74E-05	4.61
Ubiquinone and other terpenoid-quinone biosynthesis	0.63	9.00E-01	0.80	-0.70	7.19E-01	1.20	0.79	3.34E-01	0.89	-1.10	3.34E-01	0.81	-0.87	6.52E-01	0.63
Serotonergic synapse	-1.54	5.78E-03	1.46	0.73	9.73E-02	1.41	0.86	8.34E-02	1.45	-1.35	1.77E-02	1.85	-0.85	9.81E-02	1.41
Lysosome	-0.80	5.92E-04	1.99	-0.82	2.44E-05	2.23	1.27	6.90E-04	1.97	0.97	7.74E-03	2.62	1.20	8.97E-06	2.31
Longevity regulating pathway	1.15	3.89E-03	2.01	0.91	5.44E-03	1.94	0.97	1.17E-03	1.99	-1.10	2.01E-02	1.69	-1.04	5.51E-03	1.94
Prolactin signaling pathway	-1.02	3.48E-01	1.20	0.92	3.83E-01	1.16	1.09	3.59E-01	1.19	1.30	3.93E-01	1.14	1.31	3.84E-01	1.16
Calcium signaling pathway	-1.46	1.09E-10	2.45	0.80	3.94E-10	2.37	0.54	1.63E-10	2.43	1.28	6.10E-08	2.07	-1.05	4.13E-02	2.37
Autophagy - animal	-0.84	8.50E-01	0.45	-0.58	7.93E-01	0.58	1.02	9.95E-01	0.44	-0.74	9.83E-01	0.69	0.72	9.78E-01	0.58
One carbon pool by folate	0.85	7.12E-01	1.05	-0.74	5.99E-01	1.02	1.03	5.86E-01	1.04	0.94	5.40E-01	1.03	1.26	1.75E-01	1.02
Retrograde endocannabinoid signaling	-1.76	7.59E-05	1.21	1.06	2.86E-01	1.17	0.67	2.55E-01	1.19	-1.35	1.17E-02	1.02	-1.13	1.59E-01	1.17
Drug metabolism - other enzymes	-0.79	8.74E-01	0.53	0.92	9.62E-01	0.51	1.00	9.56E-01	0.52	-2.18	4.54E-07	0.89	-1.85	8.52E-05	0



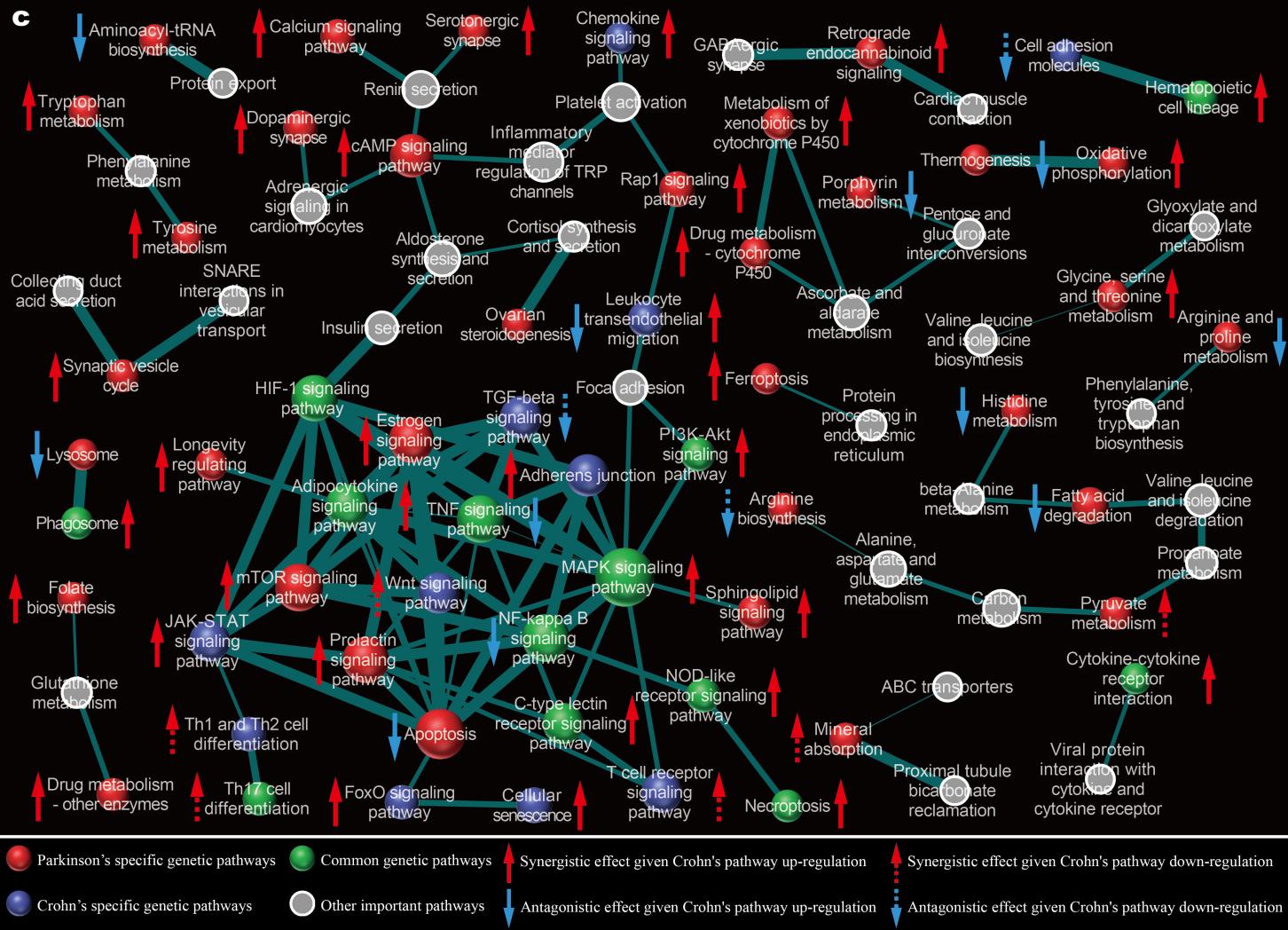
a

Permeability Marker	Crohn's WB		Parkinson's WB	
	FC/NES	FDR	FC/NES	FDR
ZO-3	-0.58	2.71E-02	-0.12	4.37E-02
E-cadherin	-0.42	1.02E-05	-0.22	5.92E-02
MUC1	0.25	1.70E-03	0.04	4.63E-01
claudin 5	0.88	3.11E-02	-0.12	4.93E-01
ABCB1	-0.65	1.48E-06	0.03	5.39E-01
SERPINA1	0.18	1.32E-04	0.23	3.94E-02
zonulin	1.44	5.78E-07	1.01	6.03E-02
PLEKHA7	-0.44	1.07E-03	0.13	8.78E-01
Wnt signaling	-0.65	2.85E-01	-0.93	6.49E-01

b

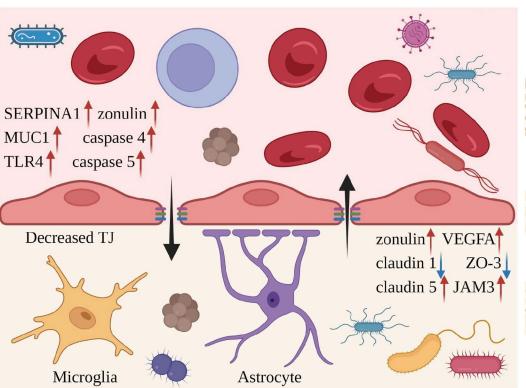
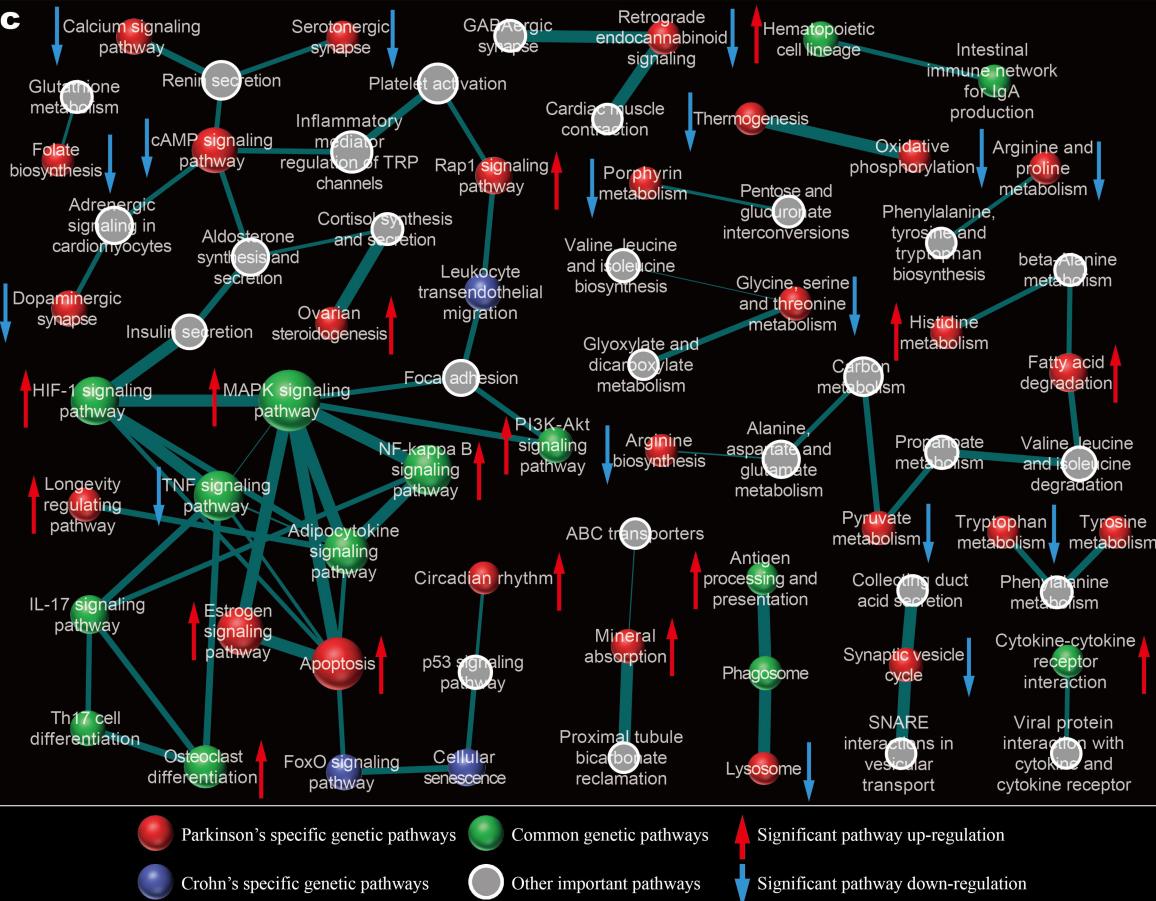


C



a

Permeability Marker	Crohn's WB		Parkinson's WB		Parkinson's SN	
	FC	FDR	FC	FDR	FC	FDR
SERPINA1	0.18	1.32E-04	0.23	3.94E-02	-	-
MUC1	0.25	1.70E-03	0.04	7.03E-01	-	-
TLR4	0.63	1.25E-05	-0.02	9.52E-02	-	-
caspase 4	0.31	1.54E-06	0.14	3.17E-01	-	-
caspase 5	0.28	2.91E-07	0.01	6.39E-01	-	-
zonulin	1.44	5.78E-07	1.01	6.03E-02	0.51	2.63E-02
VEGFA	-	-	-	-	0.84	1.50E-02
claudin 1	-	-	-	-	-0.75	7.46E-04
claudin 5	-	-	-	-	0.54	1.73E-02
ZO-3	-	-	-	-	-0.30	1.12E-01
JAM3	-	-	-	-	0.38	4.01E-04

b**c**

Gut-blood-brain axis for Parkinson's and Crohn's disease comorbidity

