

1 Mapping the comorbid landscape of Parkinson's disease and 2 Crohn's disease along the gut-blood-brain axis

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7 Abstract

8 Parkinson's disease (PD) and Crohn's disease (CD) are primarily localized to the brain and gut, respectively. Never-
9 theless, epidemiological evidence increasingly links these two seemingly unrelated disorders. Although genomic or
10 transcriptomic efforts have been dedicated to understanding this phenomenon, the precise landscape underlying this
11 comorbidity remains elusive. Here, a systematic multi-omics approach is employed to panoramically map this patho-
12 genic nexus for the first time. By curating a comprehensive genetic corpus related to PD and CD from extensive pub-
13 lications, we uncovered a shared genetic architecture converging on biological functions governing host-pathogen
14 interactions and barrier integrity maintenance. Further, multi-tissue transcriptomic datasets were meta-analyzed to
15 validate genomic insights in transcriptional circumstances, which identified pervasive transcriptional synergies of PD
16 and CD pathways within the blood context, indicating in blood CD pathological milieu could create a permissive en-
17 vironment for PD pathogenesis. Finally, delineating the aberrant gut-blood-brain axis through the sequential com-
18 promise of gut epithelial barrier, gut-vascular barrier and blood-brain barrier, we revealed a directional cascade where
19 CD intestinal pathology facilitates PD substantia nigra degeneration via blood circulation, establishing a theoretical
20 foundation for preventive and therapeutic interventions for PD and CD comorbidity. Crucially, this study provides a
21 blueprint for dissecting the molecular etiology of comorbidities in other complex diseases affecting disparate anatom-
22 ical sites.

23 **Keywords:** Parkinson's disease; Crohn's disease; gut-blood-brain axis; multi-omics; transcriptomic meta-analysis; bar-
24 rier integrity; host-pathogen interactions

25 1. Introduction

26 As one of the devastating neurodegenerative diseases, Parkinson's disease (PD) is characterized by both progres-
27 sive motor and non-motor symptoms which affect daily life, and is reported by The Global Burden of Disease study to
28 have the fastest increase in global prevalence and mortality among neurological diseases [1]. Though how PD occurs
29 and evolves remains elusive, mounting evidence indicates vital roles of genetics in its sporadic form [2,3]. Crohn's
30 disease (CD), a chronic and recurrent type of inflammatory bowel disease (IBD), often occurs in the ileocolic and co-
31 lonic parts of the intestine [4,5]. For the United States only, there are more than 700,000 CD patients [6]. It is widely
32 accepted that CD pathogenesis is comprised of genetic, microbiomic and other environmental elements [4,7]. Growing
33 knowledge has led to the hypothesis that chronic intestinal inflammation or IBD might elicit PD [8,9]. While contro-
34 versies on the impact of CD on PD exist [10-12], more and more epidemiological [13-17], genomic [18-21],
35 transcriptomic [22,23], and biochemical studies [24] have strengthened the connections between these two diseases.

36 Numerous investigations have endeavored to dissect the shared molecular mechanisms driving PD and CD
37 comorbidity through diverse perspectives. Kang *et al.* [20] unraveled the intricate genetic interplay between PD and
38 IBD by identifying novel pleiotropic loci that exhibit a mixture of synergistic and antagonistic effects, thereby high-
39 lighting the pivotal role of immune-mediated mechanisms and post-translational modifications in their shared etiol-
40 ogy. By leveraging whole-genome data from cohorts with comorbid IBD and PD, Kars *et al.* [21] characterizes the
41 landscape of shared high-impact rare variants, confirming *LRRK2* pleiotropy while identifying novel candidate genes
42 involved in inflammation and autophagy, such as *IL10RA*, through network-based heterogeneity clustering and
43 genome-wide association studies. However, these two studies are restricted to the genomic level, which lacks sub-
44 sequent functional validation (e.g., transcriptional activity) of these genetic findings. Zheng *et al.* [22] and Sun *et al.* [23]

45 separately sought to uncover pathogenic pathways enriched in common differentially expressed genes (DEGs) from
46 transcriptomes in the same tissue, i.e., peripheral blood of PD and CD patients, and from those in the different tissues,
47 i.e., PD substantia nigra and IBD colonic mucosa. Reliance on single transcriptomic dataset is frequently plagued by
48 small-sample bias, potentially compromising the robustness and reproducibility of study conclusions [25]. Further-
49 more, juxtaposing transcriptomic alterations across spatially distinct tissues—such as the substantia nigra in PD ver-
50 sus the colon in CD—offers limited insight into the intrinsic etiology of this comorbidity. Given that both pathologies
51 possess substantial heritable components [2,7], exclusive reliance on transcriptomic profiling may prove insufficient to
52 pinpoint the definitive drivers governing their co-occurrence. Given systemic insights into the pairwise relation be-
53 tween PD and CD are still lacking [26], proposing a multi-omics framework, which synergizes genomics and
54 transcriptomics in a systems biology architecture to identify bona fide pathogenic drivers for PD-CD comorbidity in a
55 holistic resolution, is imperative.

56 In the current study, a systematic approach is employed to panoramically decipher the molecular mechanisms
57 underpinning the comorbidity of PD and CD for the first time. We initiated our investigation by compiling a compre-
58 hensive catalog of genetic variants and genes relevant to PD and CD from extensive literature and databases, unveil-
59 ing a shared genetic architecture that converges on biological functions governing host-pathogen interactions and
60 barrier integrity maintenance. To ensure robustness and refine these genomic insights in transcriptional contexts,
61 transcriptomic datasets in various tissues were integrated through meta-analysis technique, which identified critical
62 driver factors and uncovered profound transcriptional synergies of PD and CD within the blood compartment. Nota-
63 bly, this analysis revealed a suggestive transcriptional resemblance between the CD blood milieu and the substantia
64 nigra pathology of PD. We further substantiated a physical basis for this connection by delineating a sequential breach
65 of the gut epithelial barrier, gut-vascular barrier and blood-brain barrier. These findings culminate in a cohesive
66 gut-blood-brain axis model, positing a directional pathogenic cascade where intestinal pathology in CD promotes PD
67 neurodegeneration via blood circulation, thereby establishing a theoretical foundation for future preventive and
68 therapeutic interventions for PD and CD comorbidity.

69 2. Materials and Methods

70 2.1. Genetic association data curation

71 We utilized a tailored pipeline (Figure 1a) to retrieve, aggregate and normalize genetic association data for PD
72 and CD. Specifically, in the light of the unbiased nature of genome-wide association study (GWAS) to unearth genetic
73 variants across whole genome [27], PheGenI [28] was leveraged to obtain GWAS data of PD and CD. Only variants
74 which surpass genome-wide significant threshold were kept. Considering complex disorder phenotypes, such as PD
75 and CD, are typically featured by synergistic variants with very small or mild individual effects [29], genetic factors not
76 satisfying stringent cutoff but with suggestive or nominal associations might virtually matter. So, candidate
77 gene-based genetic association studies as complements were also taken into consideration. This kind of studies has
78 two- (or three-) fold evidence: pre-study biological hints, within-study conclusions (and post-study validations).

79 Due to the fact that MeSH term labelling is time-consuming and lagging [30,31], PubMed search using MeSH
80 terms would undoubtedly omit quite a lot of related literature. Thus, in order to fetch as many relevant publications
81 indexed in PubMed as possible, we revised our previous literature retrieval terms [32] as “Parkinson* AND (Poly-
82 morphism OR Genotype OR Alleles) NOT Neoplasms” and “Crohn* AND (Polymorphism OR Genotype OR Alleles)
83 NOT Neoplasms” for PD and CD, respectively. All abstracts were scanned and only genetic association studies re-
84 porting significant associations with PD and CD from retrieved publication corpus were included for in-detailed se-
85 lection. Further, full contents of all qualified papers were reviewed to ensure the consistency of those drawn conclu-
86 sions. To converge irregular variants into a uniform corpus, several tools were adopted for final variant standardiza-
87 tion. UCSC liftOver [33] was utilized to calibrate PD and CD-related variants from various genome coordinate versions
88 to GRCh38 assembly. SNPedia [34], LitVar [35] and ClinVar [36] were used to normalize polymorphic sites into
89 standard formats.

90 Monte Carlo experiment was implemented to testify if variant- and gene-level commonalities between PD and CD
91 are biologically meaningful. Specifically, let G designate whole human variants (667,501,404 live Ref SNPs in NCBI
92 dbSNP database) / genes (61,197 in NCBI Entrez Gene database). Let P and C denote the variant/gene sizes related to
93 PD and CD separately. We randomly chose variants with the same number as PD and CD ones from G 100,000 times

94 distinctively, and the empirical P -value was calculated as the number of scenarios with no fewer than the observed N
95 shared variants / genes divided by 100,000. The final P -value is given by the following formula:

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

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

96 where T is constant 100,000, S_i is a Boolean variable indicating the status in the i -th experiment, in which P_i and C_i are
97 variant / gene sets of PD and CD correspondingly.

98 2.2. Bio-functional aggregation of genetic association data

99 Capitalizing on latest Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG),
100 clusterProfiler [37] was leveraged to detect biological meanings hidden behind PD and CD genetic association genes
101 with over-representation analysis (ORA) method. GO provides the world's largest information multiplicity source on
102 gene function, saturated with Biological Process (BP), Cellular Component (CC) and Molecular Function (MF) facets.
103 Described as a directed acyclic graph, GO possesses loose hierarchies in which child (leaf) items are more specialized
104 and concrete than corresponding parent (root) terms. With the notion that leaf GO terms are more informative than
105 root terms, a customized strategy was used in the current study: leaf enriched GO terms were picked as agents for
106 biology-level interpretations. All overrepresented GO / pathway terms were further refined by multiple testing cor-
107 rection with false discovery rate (FDR) value 0.05 as significance threshold.

108 2.3. Human biological pathway network construction

109 Distinctive biological pathways act in a concerted manner to organize micro- and macro-phenotypes. However,
110 current biological pathways are largely discrete and need to be weaved together. Our previous work attempted solving
111 this problem using network separation distance metric [38]. In present study, this framework was implemented in the
112 context of a high-quality human protein interactome [39]. Albeit lots of pathway resources have been available, such as
113 KEGG and reactome [40], pathway definitions and criteria of these databases differ from each other, and merging or
114 comparing various pathway resources is a pretty arduous task. As a widely used pathway source, only KEGG pathway
115 system was used to construct human biological pathway network. KEGG pathways belonging to the category "Human
116 Diseases" were filtered out for further analysis, because these specific ones are meta-pathways, i.e., merged version of
117 many involved pathways, not reflecting the original physiological profiles inside human cells. Members of a pathway
118 tend to converge into one or more module(s) in the context of human interactome. Pathways with significant network
119 modularity were deemed real biological pathways and retained. As indicated by our previous work [38], network
120 distance between two pathways should be negative if this pathway pair has connections, thus pathways with network
121 separation distance less than zero were kept.

122 2.4. Transcriptomic meta-analysis of PD and CD

123 Transcriptome is able to figure out how the genetic factors virtually function. PD and CD transcriptomic data
124 were fetched from GEO, SRA, and ArrayExpress. As the most affected sites, substantia nigra transcriptome data were
125 used for PD, and colonic and ileal mucosa ones for CD. Owing to currently no public transcriptomic dataset(s) of in-
126 dividual patients with both PD and CD and the fact that blood transcriptomic profiling has proved to be unbiased and
127 shown efficacy in idiopathic PD and CD diagnosis [41-44], as a compromise, peripheral blood datasets in either PD or
128 CD were used for preliminary dissection of etiological linkages between these two disorders. The detailed information
129 of transcriptomic data collection and processing used in this study can be found in our recent work [45], where a novel
130 transcriptomic meta-analysis method, AWmeta, was proposed to aggregate multiple PD or CD transcriptomic data in
131 these five tissues for robust DEGs with reliable fold change (FC) and corrected P -value, respectively.

132 2.5. Transcriptomic GO and pathway enrichment of PD and CD

133 To elucidate the functional manifestation of the genetic architecture in relevant tissues, we performed a mul-
134 ti-level transcriptomic analysis. First, we identified DEGs from the transcriptomic meta-analyses across five dis-
135 ease-relevant contexts: the substantia nigra and blood in PD, and the ileal and colonic mucosa and blood in CD (see

136 “*Transcriptomic meta-analysis of PD and CD*” section for details). A stringent statistical threshold of $|log_2FC| > log_21.5$
137 and $P < 0.05$ was applied to define the DEG sets. Subsequently, to comprehensively map the functional landscape, we
138 conducted enrichment analyses for both GO terms and biological pathways using two complementary algorithms:
139 ORA on the DEG sets and gene set enrichment analysis (GSEA) on the complete ranked gene lists [46]. To leverage the
140 unique strengths of both methods, we adopted a consolidated approach, assigning the minimum P -value obtained
141 from either ORA or GSEA as the definitive significance score for each item. Finally, to quantify the functional activity of
142 key biological processes identified at the genetic level, we focused on the previously identified GO hotspots and the
143 genetically-implicated biological pathways. We utilized normalized enrichment score (NES) derived from GSEA as a
144 robust metric to represent the activation or suppression status of these specific pathways and GO terms within each of
145 the five disease-tissue profiles.

146 **2.6. Transcriptomic genes and pathway correlation calculation of PD and CD using signed maximal information
147 coefficient**

148 To interrogate the associative relationships between transcriptional signatures in PD and CD at both the gene and
149 pathway levels, we sought a metric capable of transcending the limitations of conventional linear correlation measures.
150 Recognizing that biological systems are governed by complex and often non-linear dynamics, we employed a robust
151 approach based on the maximal information coefficient (MIC), a novel measure of dependence that excels at detecting
152 a wide spectrum of both linear and non-linear associations with high statistical power [47]. However, as an unsigned
153 metric, MIC quantifies the strength but not the directionality of an association. To preserve this critical information, we
154 implemented a signed version, the signed maximal information coefficient (SMIC), by integrating the MIC value with
155 the directionality provided by the Spearman’s rank correlation coefficient (ρ). The SMIC between two variables, X and
156 Y, is formally defined as:

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

where $\text{sign}_\rho(X, Y)$ denotes the sign (+1 or -1) of the Spearman correlation. MIC values were computed using the minerva R package [48]. This hybrid approach allows us to capture the full complexity of transcriptional relationships while retaining an intuitive understanding of the crucial directional context.

157 **2.7. Transcriptomic pathway synergy measure of PD and CD based on acting-in-concert score**

158 Recognizing that simple correlation metrics are often insufficient to capture the intricate interplay between complex diseases, we moved beyond simple pairwise associations to quantify functional cooperativity at the pathway level. The overall activity of a shared biological pathway can be misleading, as it may obscure critical synergistic or antagonistic behaviors among its constituent members. To dissect these sub-pathway dynamics, we conceptualized and implemented a novel metric, the acting-in-concert score (ACS), designed to quantify the degree of concordant regulation within a given pathway across two disease states. A gene is defined as “acting in concert” if it is directionally consistent in its dysregulation, i.e., up- or down-regulated in both diseases. The ACS for a given pathway is calculated as:

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

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

166 **2.8. Intestinal and brain barrier permeability biomarker collection**

167 To evaluate the integrity of key biological interfaces implicated in the gut-brain axis, we curated comprehensive
168 panels of molecular biomarkers based on an extensive literature review. Recognizing that compromised barrier function
169 is a pivotal event in initiating and perpetuating pathological inflammatory and neurodegenerative cascades, we
170 focused on three critical barriers. First, for gut epithelial barrier (GEB), which delineates the intestinal lumen from the
171 lamina propria and serves as the primary sentinel against the translocation of luminal pathogens and antigens [49], we
172 compiled a list of established permeability markers (Table S1). Subsequently, we collated a set of indicators reflective of

173 the integrity of gut-vascular barrier (GVB) (Table S2), a crucial checkpoint that restricts the passage of microbial de-
174 rivatives from the intestinal interstitium into systemic circulation, thereby preventing systemic dissemination and
175 end-organ damage [50]. Finally, to probe the status of the central nervous system interface, we assembled a panel of
176 well-characterized biomarkers for blood-brain barrier (BBB) (Table S3), a highly selective physiological boundary that
177 meticulously regulates molecular traffic between the periphery and the brain parenchyma to safeguard neural home-
178 ostasis against blood-borne insults [51].

179 3. Results

180 3.1. Variant-centric dissection reveals a shared genetic architecture of PD and CD

181 Following a stringent processing strategy (Figure 1a and “Genetic association data curation” in Materials and
182 Methods), our keyword-based search on PubMed initially yielded 4,411 and 3,137 publications for PD and CD, re-
183 spectively. A meticulous literature filtration process subsequently narrowed this corpus to 677 and 318 publications
184 with genuine relevance to genetic variants in PD and CD. Finally, a comprehensive full-text review allowed us to cu-
185 rate a high-confidence dataset comprising 747 genetic variants in 313 genes for PD, and 623 variants in 319 genes for
186 CD (Figure 1b; Table S4 and S5).

187 A comparative analysis of these datasets revealed a significant genetic intersection, with 26 variants and 31 genes
188 shared between PD and CD (Figure 1c). Intriguingly, 16 of these 31 shared genes were exclusively linked to dis-
189 ease-specific variants. This finding points toward a compelling comorbid mechanism wherein distinct genetic pertur-
190 bations converge upon a common set of genes, thereby orchestrating shared downstream pathological events. Among
191 these shared genes, *MMP9* [52] and *ABCB1* [53] are known to modulate blood-brain barrier permeability, providing a
192 potential conduit for CD peripheral pathologies to influence central nervous system processes in PD. The presence of
193 *PGLYRP4*, a peptidoglycan recognition protein [54], hints at a shared role for bacterial sensing and immune response in
194 both disorders. *ACE* links the shared genetic risk to dysregulated blood pressure, a non-motor feature associated with
195 PD pathology [55]. The inflammasome component *NLRP3* [56,57], along with downstream NF- κ B signaling cascade
196 [58,59], points to a shared inflammatory axis, which is pathologically active in PD and CD. Mutations of *LRRK2*—a
197 multi-domain protein—confer significant risk for both conditions [60,61]. Collectively, these findings establish a sub-
198 stantive genetic nexus between PD and CD.

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

203 We further delved into the genomic distribution and functional annotation of the variant datasets, which revealed
204 strikingly similar patterns between the two diseases (Figure S1a, b). Variants for both were distributed across the au-
205 tosomes. However, several key distinctions emerged. Notably, CD variants were identified on the Y chromosome
206 while PD variants were not, an observation that aligns perfectly with recent reports negating a strong link between PD
207 and the Y chromosome [62]. Conversely, mitochondrial variants were unique to PD (Figure S1c), suggesting that mi-
208tochondrial dysfunction, while a hallmark of PD, may not be a primary genetic driver in CD. The pathogenic contri-
209 bution of mitochondrial variants in PD does not appear to be dominated by any single functional class. Instead, syn-
210 onymous, missense and unannotated variants are present in commensurate frequencies and uniformly scattered
211 across the mitochondrial genome, raising the possibility that all three types contribute significantly to the disease ge-
212 netic risk. A comparison of variant functional annotations further solidified this disease similarity, with variants pre-
213 dominantly located in intronic regions, followed by missense and unannotated variants (Figure 1f). This highlights that
214 the functional consequences of many variants implicated in PD and CD comorbidity remain to be elucidated.

215 Expanding our analysis to the gene level, we observed a continued trend of functional similarity. In both diseases,
216 over 90% of the genetically-implicated genes were protein-coding (Figure 1g). This starkly contrasts with the vastness
217 of the non-coding genome, highlighting a significant knowledge gap and potential bias in current genetic studies. To
218 address this deficit, we leveraged variant annotations from the dbSNP database to predict novel disease-related genes,
219 identifying 110 and 50 potential candidates for PD and CD, respectively (Table S6 and S7). The credibility of these
220 predictions was substantiated through both extensive literature mining and quantitative evidence from AWmeta [45].
221 An examination of these expanded gene sets revealed a dramatic shift: non-coding genes now constitute over 50% of

222 the total in both diseases (Figure 1h). This effort effectively supplements the initial protein-coding-centric view,
223 providing a more comprehensive and balanced genetic landscape for exploring the comorbidity between PD and CD.

224 **3.2. Variant-enriched disease pathways implicate PD and CD comorbidity**

225 Given that KEGG provides a well-curated repository of biological pathways linked to human diseases [63], it
226 serves as a powerful platform for investigating inter-disease connections at a functional enrichment level. We therefore
227 performed a disease pathway enrichment analysis on the PD and CD genetic variants (see “*Bio-functional aggregation of*
228 *genetic association data*” in Materials and Methods). Our objective was to map the broader disease landscape associated
229 with each disorder, thereby gaining novel perspectives on the mechanistic underpinnings of their comorbidity.

230 This enrichment analysis revealed that PD and CD share 38 human disease pathways (Figure S2; Table S8 and S9).
231 Notably, these commonly enriched pathways consistently demonstrated greater statistical significance than the dis-
232 ease-specific pathways for either condition, suggesting they represent core pathological processes of central im-
233 portance to both PD and CD. As a critical internal validation of our gene sets, the top-enriched pathway for PD was
234 “Parkinson disease” itself, with the three most significant hits all being neurodegenerative disorders; similarly, the
235 premier hit for CD was “Inflammatory bowel disease”.

236 A striking asymmetry emerged from this analysis. While “Inflammatory bowel disease” ranked as the eighth most
237 significant pathway for the PD genes, the reciprocal was not true: “Parkinson disease”, or indeed any neuro-related
238 pathway, was conspicuously absent from the CD enrichment results. This non-reciprocal relationship suggests a di-
239 rectional influence, where the genetic architecture of PD encompasses susceptibility to Inflammatory bowel dis-
240 ease-like processes, whereas the genetic basis of CD does not inherently predispose to parkinsonism. This finding lends
241 a genetic support to the clinical hypothesis that inflammatory processes originating in conditions like CD can act as a
242 catalyst for PD initiation or progression, while the reverse is not established [64,65].

243 Further exploration of the shared pathways provided deeper mechanistic insights. The enrichment of “Lipid and
244 atherosclerosis” and “Fluid shear stress and atherosclerosis” implicates dysregulated lipid metabolism as a common
245 pathological feature [66,67]. Similarly, the shared enrichment of “Type I diabetes mellitus” and “Insulin resistance”
246 points toward aberrant insulin signaling as a convergent metabolic vulnerability in both diseases [68,69].

247 Intriguingly, an examination of the disease-specific pathways unveiled a potential etiological link. Pathways for
248 “Hepatitis B” and “Hepatitis C” were uniquely enriched in the CD gene set; concurrently, “Hepatocellular carcinoma”
249 was a specific enrichment item for PD. Given that chronic viral hepatitis is a primary driver of hepatocellular carci-
250 noma [70], this constellation of findings hints at a possible pathogenic trajectory where systemic inflammation and
251 hepatic stress associated with CD genetic background may contribute to a cellular environment conducive to patholo-
252 gies seen in PD.

253 **3.3. PD and CD genetic variants converge on biological functions involving host-pathogen interactions and barrier**
254 **integrity maintenance**

255 To obtain a panoramic view of the biological functions encoded by the shared genetic architecture of PD and CD,
256 we first conducted a broad-stroke GO enrichment analysis using WebGestalt [71]. This revealed a remarkably con-
257 gruent functional landscape for both diseases at a high level (Figure 2a). Within GO-BP category, terms such as “bio-
258 logical regulation”, “response to stimulus”, and “metabolic process” were top hits for both, implicating shared roles for
259 regulatory homeostasis, environmental stress responses, and metabolism. Similarly, in GO-MF and GO-CC domains,
260 terms like “protein binding”, “ion binding”, and “membrane” were commonly enriched, highlighting the importance
261 of molecular interactions at cellular membranes in the etiology of both disorders.

262 To achieve greater functional resolution, we performed a more detailed GO enrichment analysis. Examination of
263 the top 40 shared significantly-enriched GO-BP terms unveiled a striking thematic convergence on pathogen recogni-
264 tion and host defense (Figure 2b; Table S10). A substantial proportion of these terms, including “response to pepti-
265 doglycan”, “lipopolysaccharide-mediated signaling pathway”, and “detection of molecule of bacterial origin”,
266 strongly implicated host-pathogen interactions as a central element of the shared genetic risk. Two particularly com-
267 pelling findings emerged from this analysis. First, the enrichment of “positive regulation of nitric-oxide biosynthetic
268 process” was surprising, as nitric oxide is a potent modulator of blood-brain barrier integrity [72]. This finding pro-
269 vides a direct genetic link to potential blood-brain barrier dysfunction as a component of the comorbidity. Second, the
270 enrichment of “maintenance of gastrointestinal epithelium” pointed directly to the intestinal epithelium’s homeostasis

271 as a shared biological vulnerability. The GO-MF and GO-CC results further substantiated the pathogen response theme
272 (Figure 2c; Table S11–S14), solidifying the hypothesis that processes governing the recognition of and resistance to
273 pathogens and their derivatives play a pivotal role in the shared PD and CD mechanism. We designated these potentially
274 functional terms as “GO hotspots” (indicated by red asterisks in Figure 2).

275 To further determine if these genetically-defined GO hotspots were functionally active in disease-relevant tissues,
276 we analyzed their transcriptional status across the five tissue datasets, i.e., the substantia nigra and blood in PD, and
277 the ileal and colonic mucosa and blood in CD (Figure 3). Remarkably, the pathogen recognition and resistance pro-
278 cesses were significantly and broadly activated ($\text{NES} > 0$) across all five contexts. This system-wide activation signature
279 strongly suggests a persistent state of heightened immune surveillance, likely driven by an elevated presence of
280 pathogens or their molecular patterns in these tissues compared to healthy controls.

281 As expected, processes related to neuronal activity were globally downregulated ($\text{NES} < 0$) in PD substantia nigra,
282 reflecting its neurodegenerative pathology. These same processes showed no consistent dysregulation in the other four
283 tissues, highlighting their tissue-specific nature. Notably, “positive regulation of neuron apoptotic process” was sig-
284 nificantly upregulated across all CD tissues, revealing a previously underappreciated pro-apoptotic process in CD that
285 could impact neuronal health. Furthermore, we observed a significant activation of the “positive regulation of Wnt
286 signaling pathway” in both the ileal and colonic mucosa of CD patients. Given that aberrant Wnt activation is a rec-
287 ognized hallmark of compromised intestinal barrier integrity and increased permeability [73,74], this result provides
288 direct transcriptomic evidence of a defective gut barrier in CD, lending mechanistic support to the gut-origin hypoth-
289 esis of the comorbidity.

290 Finally, to assess the relative importance of different biological processes at the genetic level, we compared the top
291 40 enriched GO-BP terms for each disease (Figure S3; Table S15 and S16). This revealed that the shared functional space
292 was almost exclusively dominated by immune-related processes, cementing the immune system’s role as the central
293 arena for the PD-CD interaction. Moreover, for CD, nearly all of its top 40 enriched terms were immune-related, con-
294 firming that immune dysregulation is the preeminent feature of its genetic etiology.

295 ***3.4. Genetically-informed genes and pathways exhibit coordinated transcriptional activities within and across tissues 296 in PD and CD***

297 To translate the genetic findings into functional contexts, we next determined the biological pathways enriched
298 within the PD and CD variants. This investigation uncovered 18 shared pathways whose enrichment consistently
299 reached a higher statistical significance than pathways specific to either disease alone, underscoring their central im-
300 portance to the shared pathophysiology (Figure 4a; Table S17 and S18). Among these, the co-enrichments of the “IL-17
301 signaling pathway” and “Th17 cell differentiation” resonate with our GO findings, as hyperactive Th17 cells are po-
302 tent producers of the cytokine IL-17, a key mediator of antimicrobial peptide production [75], thus reinforcing the
303 theme of host-pathogen interactions. Intriguingly, the “Intestinal immune network for IgA production” was also a
304 shared pathway, implying that immune processes within the gut may be a common feature and thus pointing to a
305 potential nexus between the two diseases. The “Hematopoietic cell lineage” pathway emerged as one of the most sta-
306 tistically significant shared pathways. This observation aligns with clinical evidence where hematopoietic stem cell
307 transplantation has proven effective in ameliorating symptoms of both PD and CD [76,77], highlighting the critical
308 role of hematopoietic differentiation in their common mechanisms. Furthermore, the presence of the “TNF signaling
309 pathway” is particularly salient, given that anti-TNF therapies for CD are associated with a substantially reduced risk
310 of developing PD [78]. The enrichment of the “Adipocytokine signaling pathway” lends further support to the role of
311 aberrant lipid metabolism as a convergent process in both disorders, while the most statistically significant shared
312 pathway, “HIF-1 signaling pathway”, implicates hypoxia—a condition known to be pivotal in both PD [79] and CD
313 [80-82]—as a critical nexus linking mitochondrial dysfunction, oxidative stress, and impaired protein degradation
314 [83].

315 An exploration of the disease-specific pathways also yielded profound insights into both distinct and convergent
316 mechanisms. For PD, the unique enrichment of “Ferroptosis” aligns with its known role in dopaminergic neuron
317 death and glial activation [84], while “Thermogenesis” provides a molecular correlate for the clinical observation of
318 temperature sensitivity in PD patients [85-87]. Intriguingly, longevity-regulating pathways were enriched in both
319 diseases, incl. “Longevity regulating pathway” and “mTOR signaling pathway” for PD, and “FoxO signaling pathway”
320 for CD, which suggests a deeper shared connection to cellular aging processes that warrants further investigation. The

321 PD specific enrichment of “Circadian rhythm” supports the widespread prevalence of sleep and circadian disruptions
322 in these patients [88,89]. Crucially, several pathways converged on the theme of cell adhesion. The PD specific “Rap1
323 signaling pathway”, which governs cell-cell junction formation via integrin regulation, alongside the CD specific “Cell
324 adhesion molecules” and “Adherens junction” pathways, collectively point to compromised barrier function as a
325 fundamental, albeit genetically distinct feature. This is further reinforced by the PD specific “VEGF signaling path-
326 way”, a known mediator of blood-brain barrier damage [72]. Together, these results illustrate a complex etiological
327 landscape where both shared and disease-specific pathways ultimately converge upon common pathological themes,
328 suggesting a multifaceted basis for the comorbidity.

329 To elucidate if these genetically-implicated pathways were functionally active *in vivo*, we assessed their tran-
330 scriptional activities across five disease-relevant tissues. A striking pattern emerged where PD and CD genetic path-
331 ways were significantly engaged in the pathological processes of all five tissues (Figure 4b). PD specific pathways
332 were pervasively downregulated in both substantia nigra and blood, indicative of a systemic degenerative state in PD.
333 Notably, “Dopaminergic synapse” and “Serotonergic synapse” were suppressed not only in the PD substantia nigra
334 but also in the CD ileal and colonic mucosa. Given the direct communication between the brain and gut via the vagus
335 nerve [90], this concurrent downregulation suggests a potential trans-synaptic or neuro-inflammatory link between
336 these distant tissues. PD specific “VEGF signaling pathway” was significantly upregulated in the CD ileal and colonic
337 mucosa. As a non-pathogenic pathway in these contexts, its activation may represent a compensatory response to re-
338 pair the compromised mucosal barrier [91,92]. CD specific pathways were generally upregulated in the CD intestinal
339 mucosa but displayed divergent activity patterns in CD blood, suggesting distinct functional roles in systemic versus
340 local compartments. Interestingly, CD specific “Cell adhesion molecules” and “Adherens junction” pathways were
341 significantly activated in the PD substantia nigra and blood. Since their activation can be a reparative response [93],
342 this signature hints at a pre-existing or ongoing compromise of the blood-brain barrier in PD. Finally, the shared ge-
343 netic pathways were consistently activated across all five tissues, strongly suggesting a synergistic interplay that un-
344 derpins the comorbidity.

345 To move beyond isolated analyses and investigate the coordinated behavior of the genetic association genes (313
346 genes for PD, 319 for CD, and 31 for common), we calculated the transcriptional correlation of four gene sets, i.e.,
347 shared genes, PD specific genes, CD specific genes, and all combined genes, within and across tissues using the SMIC
348 algorithm. Within the blood, a shared tissue, all four gene sets displayed positive correlation, with the shared gene set
349 reaching statistical significance ($SMIC = 0.33, P < 0.05$), indicating a functional mechanistic link within the circulatory
350 system (Figure S4). As expected, correlations between the CD ileal and colonic mucosa were exceptionally high across
351 all gene sets ($SMIC > 0.3, P < 0.001$), confirming their profound molecular similarity. An unexpected finding emerged
352 from the cross-disease analysis: a consistent, positive correlation was observed between the CD blood and the PD
353 substantia nigra for all four gene sets, reaching statistical significance for the CD specific and combined gene sets ($P <$
354 0.05 and $P < 0.01$). In contrast, the correlation between PD blood and substantia nigra was inconsistent. This critical
355 asymmetry suggests that the pathological state of the blood in CD, more so than in PD itself, is transcriptionally
356 aligned with the pathological processes occurring in the Parkinsonian brain.

357 We then extended this correlational analysis to the pathway level, applying SMIC to the transcriptional activities
358 of four corresponding sets of genetic pathways. While this again confirmed the strong positive correlation between
359 the CD ileal and colonic mucosa, other intra- and inter-tissue comparisons failed to yield consistent or significant re-
360 sults (Figure S5), suggesting that simple correlation may be insufficient to capture the complexity of disease linkage.
361 We therefore deployed the ACS method to quantify synergy, a more nuanced measure of synergistic activity. The
362 ACS results revealed widespread synergistic relationships among all five disease tissues (Figure S6), implying a high
363 degree of functional influence.

364 Recognizing that pathway-level activity scores (i.e., NES in this study) can obscure the individual contributions
365 of member genes, we performed a more granular analysis by calculating both SMIC-based correlation and ACS-based
366 synergy for each genetic pathway based on the differential expression of its constituent genes. The correlation analysis
367 again highlighted the strong, consistent relationship between the CD ileum and colon but yielded few other signifi-
368 cant findings (Figure S7a). However, the synergy analysis produced several compelling insights (Figure S7b). Beyond
369 the robust synergy between the CD ileal and colonic mucosa, we observed significant synergy for shared genetic
370 pathways between PD and CD blood, indicating a direct cooperative interaction within the circulation. More critically,
371 a high degree of synergy for shared pathways was detected between PD substantia nigra and CD blood, reinforcing

372 the hypothesis that CD systemic factors directly and synergistically impact central nervous system pathology in PD.
373 Finally, we observed heightened synergistic scores for CD specific pathways between PD substantia nigra and CD
374 colonic mucosa, providing further evidence for a direct gut-brain axis of interaction that contributes to the shared
375 disease landscape.

376 **3.5. Increased GEB permeability facilitates ileal and colonic mucosal pathologies in CD**

377 Building upon the above discovery of intricate multi-tissue functional associations between PD and CD, we next
378 sought to establish a plausible physical basis for this pathological crosstalk. Given that PD and CD are canonically
379 defined by pathology primarily localized to the brain and intestine, respectively [94,95], any molecular dialogue be-
380 tween them must navigate the gut-brain axis. This axis is anatomically fortified by a series of three sequential biological
381 barriers: GEB, GVB, and BBB. We therefore posited a sequential-breach hypothesis, wherein molecular pathology
382 originating in the CD gut must progressively traverse these three checkpoints to exert a tangible influence on
383 neuropathogenesis in the PD brain. The compromise of these barriers would thus represent the fundamental physical
384 conduit for the observed comorbidity. Accordingly, our investigation first focused on interrogating the integrity of the
385 initial line of defense, GEB, within the context of active CD pathology.

386 To empirically test this, we explored the transcriptomic profiles of the ileal and colonic mucosa from CD patients,
387 focusing on the curated GEB permeability biomarker panel. Our analysis revealed that a striking majority of these
388 markers exhibited expression changes that were not only statistically significant but also directionally consistent with
389 the states indicative of impaired barrier function (Figure 5a). This provides compelling molecular evidence for the
390 structural disruption of intercellular tight and adherens junctions in the CD gut, leading to heightened epithelial per-
391 meability. This breach effectively dismantles the first physical safeguard, permitting the translocation of luminal con-
392 tents into the lamina propria (Figure 5b). While the expression of most markers aligned with this conclusion, three
393 biomarkers—claudin 1, claudin 2, and JAM3—displayed a consistent and significant transcriptional upregulation, a
394 finding seemingly at odds with their protein-level functions in maintaining barrier integrity. As these are not CD sus-
395 ceptibility genes, we propose this transcriptional induction may represent a compensatory, albeit insufficient, response
396 to protein-level degradation or mislocalization, a complex regulatory feedback loop that warrants further mechanistic
397 elucidation.

398 The consequence of this compromised GEB is an influx of microbial products and other luminal antigens into the
399 intestinal wall, a perturbation expected to profoundly remodel the local biological network. To visualize these down-
400 stream effects, we integrated our transcriptomic activity data (pathway NES and P-values) with the foundational bio-
401 logical pathway network (“Human biological pathway network construction” in Materials and Methods). By filtering for
402 significantly perturbed pathways while preserving network connectivity, we constructed context-specific pathway
403 networks for both the CD ileum and colon (Figure 5c, d). The resultant networks were remarkably congruent, corrob-
404 orating our prior correlational analyses and underscoring the profound mechanistic similarity between the two intesti-
405 nal sites. Intriguingly, these networks retained several pathways without direct genetic links to CD, including some
406 with PD specific genetic underpinnings. Their topological persistence reveals their critical role as indispensable func-
407 tional bridges that connect otherwise disconnected hubs of significantly altered CD pathways. The specific inclusion of
408 PD genetic pathways as such conduits within the CD intestinal milieu provides compelling evidence for a latent mo-
409 lecular comorbidity at the gut level. While direct investigation of PD-related pathology in the ileum and colon remains
410 a nascent field, our findings lay a novel conceptual groundwork and provide a strong impetus for future research into
411 this unexplored facet of the gut-brain axis.

412 **3.6. GVB dysfunction underlies the blood-borne comorbidity of PD and CD**

413 We next assessed the integrity of GVB, the second critical checkpoint in the gut-brain axis. To this end, we ana-
414 lyzed blood transcriptomes from both PD and CD cohorts for permeability biomarker signatures. This analysis re-
415 vealed a compelling transcriptomic profile of GVB impairment in CD, with most biomarkers showing statistically ro-
416 bust expression changes indicative of increased permeability; conversely, these changes were largely non-significant in
417 PD, suggesting the GVB remains substantially intact in this condition (Figure 6a). The paradoxical upregulation of
418 claudin 5 in CD blood, a potential compensatory response, was a notable exception. These transcriptomic signatures
419 strongly suggest a compromised GVB in CD, characterized by the disruption of its intercellular junctions, which facil-
420 itates the infiltration of gut-derived molecules into the bloodstream (Figure 6b).

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

3.7. CD blood signature promotes substantia nigra degeneration in PD through BBB disruption

Our investigation culminated at the final and most critical gatekeeper of the gut-brain axis, BBB. We sought to determine if this terminal interface is breached under the pathological conditions of CD or PD, thereby permitting the influx of peripheral molecules into the brain parenchyma.

A transcriptomic interrogation of permeability biomarkers yielded unambiguous evidence (Figure 7a). In the blood of patients with CD, the entire panel of BBB markers exhibited expression changes that were both statistically robust and directionally consistent with compromised barrier integrity. In contrast, these markers remained largely quiescent in PD blood, suggesting that the systemic milieu in PD does not induce a BBB breach. However, a direct analysis of the PD substantia nigra painted a different picture, revealing a significant local disruption of BBB. This dual-front assault on BBB—a systemic challenge from the CD periphery and a localized compromise from intrinsic PD pathology—creates a permissive gateway for pathological crosstalk (Figure 7b). Notably, the paradoxical transcriptional upregulation of claudin 5 and JAM3 within the PD substantia nigra suggests a compensatory response to protein-level junctional instability.

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

4. Discussion and Conclusions

In this study, the multi-omics systems biology investigation, spanning from genetic variants to tissue-specific transcriptional networks, converges on a cohesive and compelling mechanistic interpretation for the comorbidity between PD and CD. Based on our findings, a gut-blood-brain axis model is proposed to elucidate a plausible, directional cascade through which peripheral intestinal pathology in CD may promote PD neurodegeneration (Figure 8). This model posits a sequential breach of three critical biological barriers. The process is initiated by a compromised GEB in CD ileum and colon (Figure 8a), which permits the translocation of luminal antigens and microbial products, thereby remodeling the local mucosal pathobiology (Figure 8b, c). This is followed by the permeabilization of GVB, leading to the systemic dissemination of these pro-inflammatory molecules into the bloodstream (Figure 8d). Our analysis reveals that this creates a systemic milieu in CD blood that not only acts synergistically with that in PD blood (Figure 8e) but also is transcriptionally aligned with the pathological state of PD substantia nigra. The cascade culminates in the compromise of BBB, a dual-front assault driven by both systemic factors from CD periphery and intrinsic pathology within the PD substantia nigra (Figure 8f), ultimately allowing peripheral insults to engage and exacerbate central nervous system degeneration (Figure 8g). This model provides, for the first time, a tangible physical and molecular basis for the well-documented epidemiological link between these two seemingly disparate disorders.

470 A key strength of our study lies in its integrative, systems-level design, which bridges the gap between static ge-
471 netic risk and dynamic, tissue-specific functional consequences. By employing novel computational approaches such
472 as SMIC and newly proposed ACS, we were able to move beyond simple correlation to uncover complex, non-linear
473 relationships and synergistic interplay between pathways and tissues. This methodology provides a powerful blue-
474 print for investigating other complex comorbidities, particularly those spanning the gut-brain axis. Our findings rede-
475 fine the etiological landscape of PD-CD comorbidity by positioning peripheral inflammatory conditions not merely as
476 risk factors, but as active participants in neuropathogenesis, offering a paradigm shift that could inform new diagnostic
477 and therapeutic strategies focused on maintaining gut barrier integrity and mitigating systemic inflammation to pre-
478 serve neurological health.

479 While our data-driven discoveries provide valuable insights, we acknowledge several limitations that chart a clear course for future research. Foremost, our findings are computationally derived and constitute a rich portfolio of
480 data-driven hypotheses that await rigorous experimental validation. Methodologically, our ACS metric represents a
481 prototype approach; future iterations could incorporate the magnitude of gene expression changes, not just the direc-
482 tion, to achieve a more quantitative measure of synergy. Furthermore, validation across multi-omics lay-
483 ers—including proteomics and metabolomics—is imperative to capture post-transcriptional nuances and confirm that
484 the observed transcriptional synergies translate to the functional protein and metabolite levels. The current analysis is
485 also constrained by the availability of matched tissue datasets. Acquiring transcriptomic data from the substantia
486 nigra in CD and the PD intestinal mucosa represents a critical next step to complete the mechanistic puzzle. Finally,
487 leveraging the power of single-cell and spatial transcriptomics and proteomics will be crucial for dissecting the cell
488 type- and niche-specific contributions to barrier dysfunction, and intra- and inter-tissue crosstalk, elevating the reso-
489 lution of our proposed comorbidity model from the tissue to the cellular level.

490 In conclusion, this study transitions the understanding of PD and CD comorbidity from epidemiological correlation
491 to a mechanistically defined gut-blood-brain axis. By delineating the trajectory from shared genetic defects in
492 barrier maintenance to a sequential collapse of physiological boundaries, we demonstrate how peripheral intestinal
493 pathology can transcriptionally imprint upon the central nervous system in the context of PD and CD comorbidity.
494 Ultimately, beyond deciphering this specific pathogenic nexus, the analytical framework established herein stands as
495 a scalable paradigm for unraveling the molecular routes bridging anatomically distinct diseases.

497 **Figure Lengends**

498 **Figure 1.** Variant-centric dissection reveals a shared genetic architecture of PD and CD. (a) Retrieval, integration, and standardiza-
499 tion process of PD and CD genetic variants. (b) Statistics of initial PubMed retrieval, filtration, and final genetic variants and genes
500 relevant to PD and CD. (c) Literature-derived variant-to-gene mapping showcases the gene intersection between PD and CD can be
501 derived from common variants (Parkinson's & Crohn's common-to-common mapping) or disease-specific variants (Parkinson's or
502 Crohn's specific-to-common mapping). (d, e) The gene and variant intersections between PD and CD are statistically significant,
503 with empirical P-value determined by 100,000 Monte Carlo experiments. (f) Functional consequences of PD and CD genetic variants.
504 (g) Functional consequences of PD and CD genetic association genes. (h) Functional consequences of PD and CD dbSNP-predicted
505 genes.

506 **Figure 2.** PD and CD genetic variants converge on biological functions involving pathogen- and derivative-induced infection,
507 recognition and resistance and barrier integrity maintenance. (a) Broad GO terms enriched by genetic association genes in PD and
508 CD. The x-axis represents the number of genes included in the enriched GO terms (y-axis). Red, purple, and green indicate GO-BP,
509 GO-MF, and GO-CC, respectively. (b) The same significantly enriched GO-BP terms (top 40) for genetic association genes in both PD
510 and CD. (c) Significantly enriched GO-MF and GO-CC terms for genetic association genes in PD and CD. The x-axis represents the
511 enrichment ratio of the enriched GO terms (y-axis). The sphere size indicates the number of genes enriched in each GO term, and the
512 sphere color the enrichment significance. GO term name in red denotes the same GO terms enriched by genetic association genes in
513 both PD and CD within the GO-MF and GO-CC categories. GO terms marked with red asterisks are GO hotspots, whose transcrip-
514 tional activities in multiple disease tissues were quantified in Figure 3.

515 **Figure 3.** Tissue-wise transcriptional activities of GO hotspots in PD and CD. Pink shading indicates GO hotspots related to the
516 recognition and resistance of pathogens and their relevant derivatives, and gray shading those related to neural activity. NES is used
517 to quantify transcriptional activities of GO hotspots in PD and CD, with red shading representing activation and blue shading re-
518 pression. FDR with green shading indicates corresponding activity quantification is statistically significant.

519 **Figure 4.** Genetic variant-enriched pathways are transcriptionally active across tissues in PD and CD. (a) Enriched non-disease
520 pathways for genetic variants in PD and CD. This pathway enrichment was done against biological pathways within KEGG
521 non-disease categories by ORA approach, with FDR, enrichment ratio and gene counts shown in PD and CD specific and common
522 pathway classes. (b) Tissue-wise transcriptional activities of genetic variant-enriched pathways in PD and CD. NES is used to
523 quantify transcriptional activities of genetic pathways in PD and CD tissues, with red shading representing activation and blue
524 shading repression. FDR with green shading indicates corresponding activity quantification is statistically significant.

525 **Figure 5.** Increased GEB permeability facilitates ileal and colonic mucosal pathologies in CD. (a) Transcriptional change profile of
526 gut epithelial barrier permeability biomarkers in ileal and colonic mucosa of CD. (b) Schematic diagram of the mechanism under-
527 lying increased gut epithelial barrier permeability in the ileum and colon of CD. (c) Biological pathway network in ileal mucosa of
528 CD. (d) Biological pathway network in colonic mucosa of CD. The thickness of the edges between pathway nodes represents the
529 pathway crosstalk intensity: the thicker the edge, the greater the crosstalk intensity. The pathway node size denotes the network
530 node degree: the larger the node, the higher the node degree. IM, ileal mucosa. CM, colonic mucosa. TJ, tight junction. AJ, adherens
531 junction.

532 **Figure 6.** GVB dysfunction underlies the blood-borne comorbidity of PD and CD. (a) Transcriptional change profile of gut-vascular
533 barrier permeability biomarkers in blood of PD and CD. (b) Schematic diagram of the mechanism underlying increased gut-vascular
534 barrier permeability in PD and CD. (c) Biological pathway network in blood of PD and CD. The thickness of the edges between
535 pathway nodes represents the pathway crosstalk intensity: the thicker the edge, the greater the crosstalk intensity. The pathway
536 node size denotes the network node degree: the larger the node, the higher the node degree. WB, whole blood. TJ, tight junction. AJ,
537 adherens junction.

538 **Figure 7.** CD blood signature promotes substantia nigra degeneration in PD through BBB disruption. (a) Transcriptional change
539 profile of blood-brain barrier permeability biomarkers in blood of PD and CD, and PD substantia nigra. (b) Schematic diagram of
540 the mechanism underlying increased blood-brain barrier permeability in PD and CD. (c) Biological pathway network in PD
541 substantia nigra. The thickness of the edges between pathway nodes represents the pathway crosstalk intensity: the thicker the edge,
542 the greater the crosstalk intensity. The pathway node size denotes the network node degree: the larger the node, the higher the node
543 degree. WB, whole blood. SN, substantia nigra. TJ, tight junction.

544 **Figure 8.** Gut-blood-brain axis model for the comorbidity between PD and CD. (a) GEBs of the ileal and colonic mucosa are im-
545 paired in the molecular pathological context of CD. (b, c) The biological pathway networks in CD ileal and colonic mucosa are es-
546 tablished following GEB breakdown. (d) GVB disruption causes microorganisms and their derivatives to cross the barrier and enter
547 the blood circulation. (e) Blood pathway network synergy of PD and CD after GVB disruption. (f) BBB impairment against the
548 background of CD related blood pathology, enables blood contents to cross the blockade and enter the brain parenchyma. (g) The
549 biological pathway network in PD substantia nigra is influenced following BBB impairment. TJ, tight junction. AJ, adherens junc-
550 tion.

551 Data Availability Statement

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

553 Author Contributions

554 **Yanshi Hu:** Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - re-
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556 & editing. **Xinjian Yu:** Data curation, Writing - review & editing. **Wenqi Wu:** Data curation, Writing - review & editing. **Ming
557 Chen:** Conceptualization, Supervision, Funding acquisition, Project administration, Writing - review & editing.

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565 Conflicts of Interest

566 The authors declare no conflicts of interest.

567 Abbreviations

568 The following abbreviations are used in this manuscript:

PD	Parkinson's disease
CD	Crohn's disease
IBD	Inflammatory bowel disease
DEG	Differentially expressed gene
GWAS	Genome-wide association study
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
ORA	Over-representation analysis
BP	Biological Process
CC	Cellular Component
MF	Molecular Function
FDR	False discovery rate
FC	Fold change
GSEA	Gene set enrichment analysis
NES	Normalized enrichment score
MIC	Maximal information coefficient
SMIC	Signed maximal information coefficient
ACS	Acting-in-concert score
GEB	Gut epithelial barrier
GVB	Gut-vascular barrier
BBB	Blood-brain barrier
IM	Ileal mucosa
CM	Colonic mucosa
TJ	Tight junction
AJ	Adherens junction
WB	Whole blood
SN	Substantia nigra

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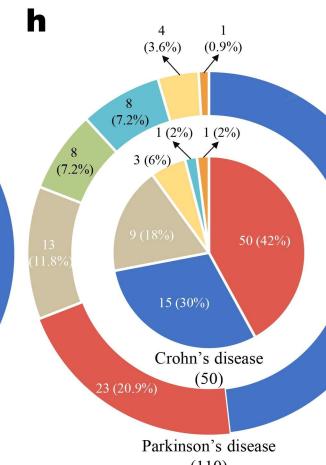
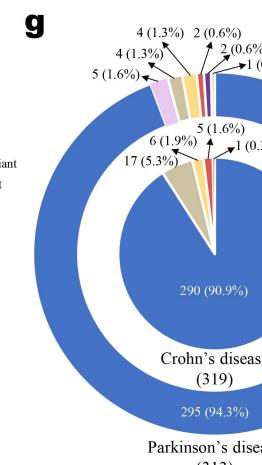
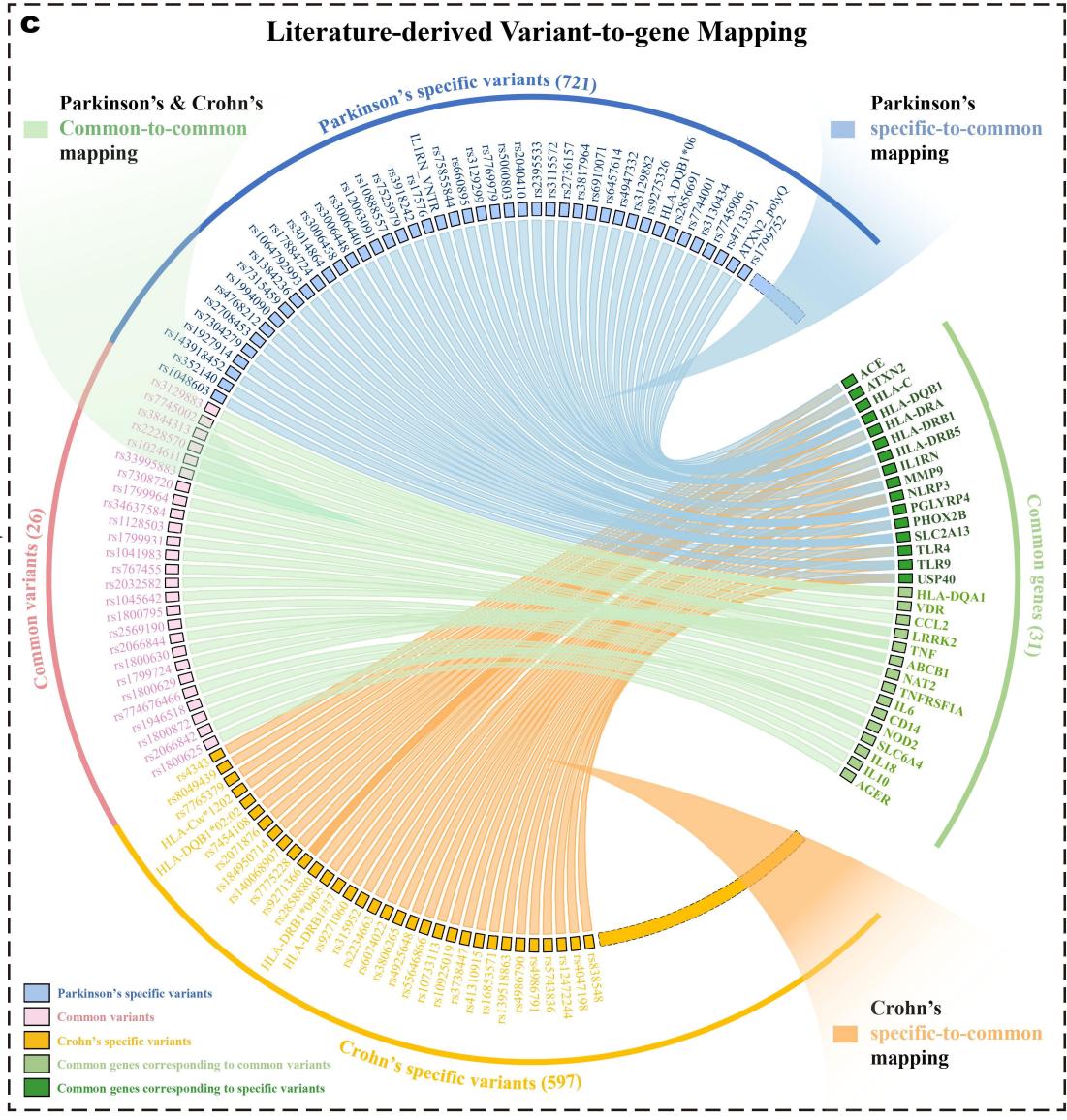
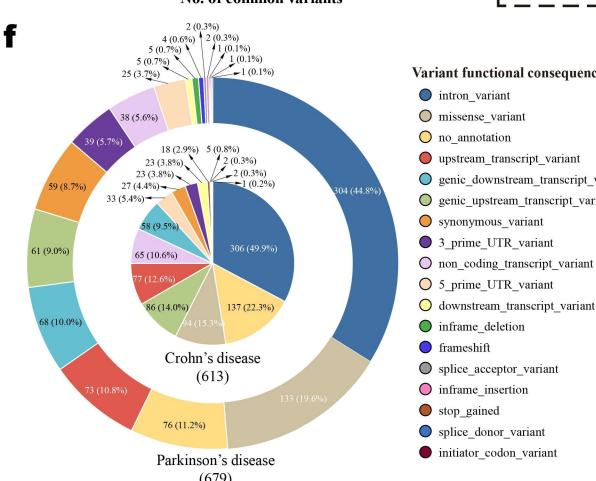
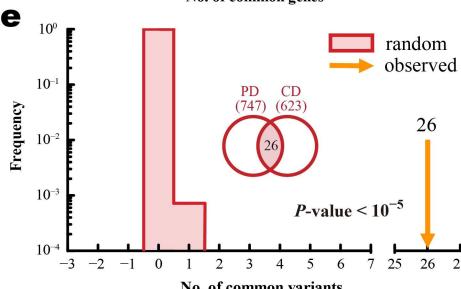
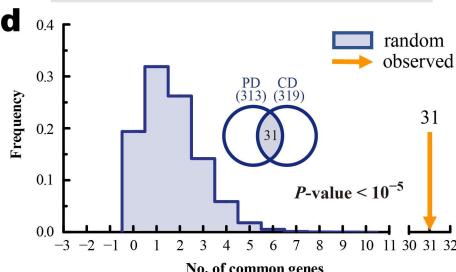
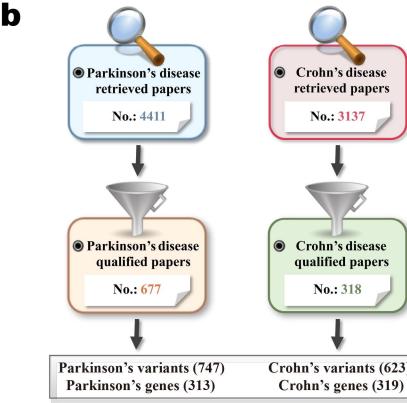
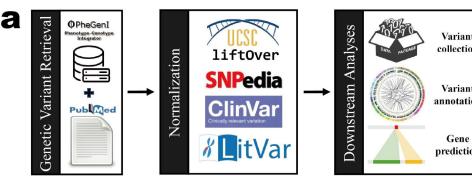
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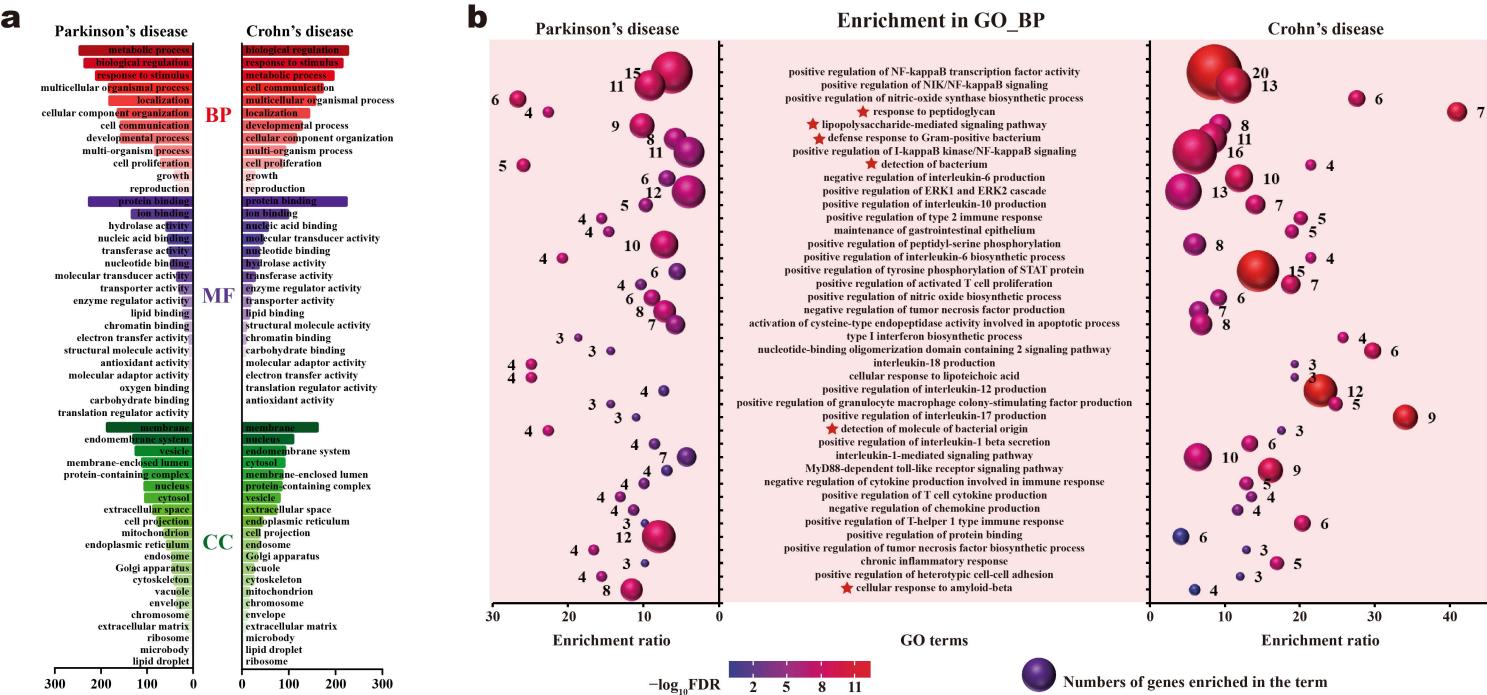
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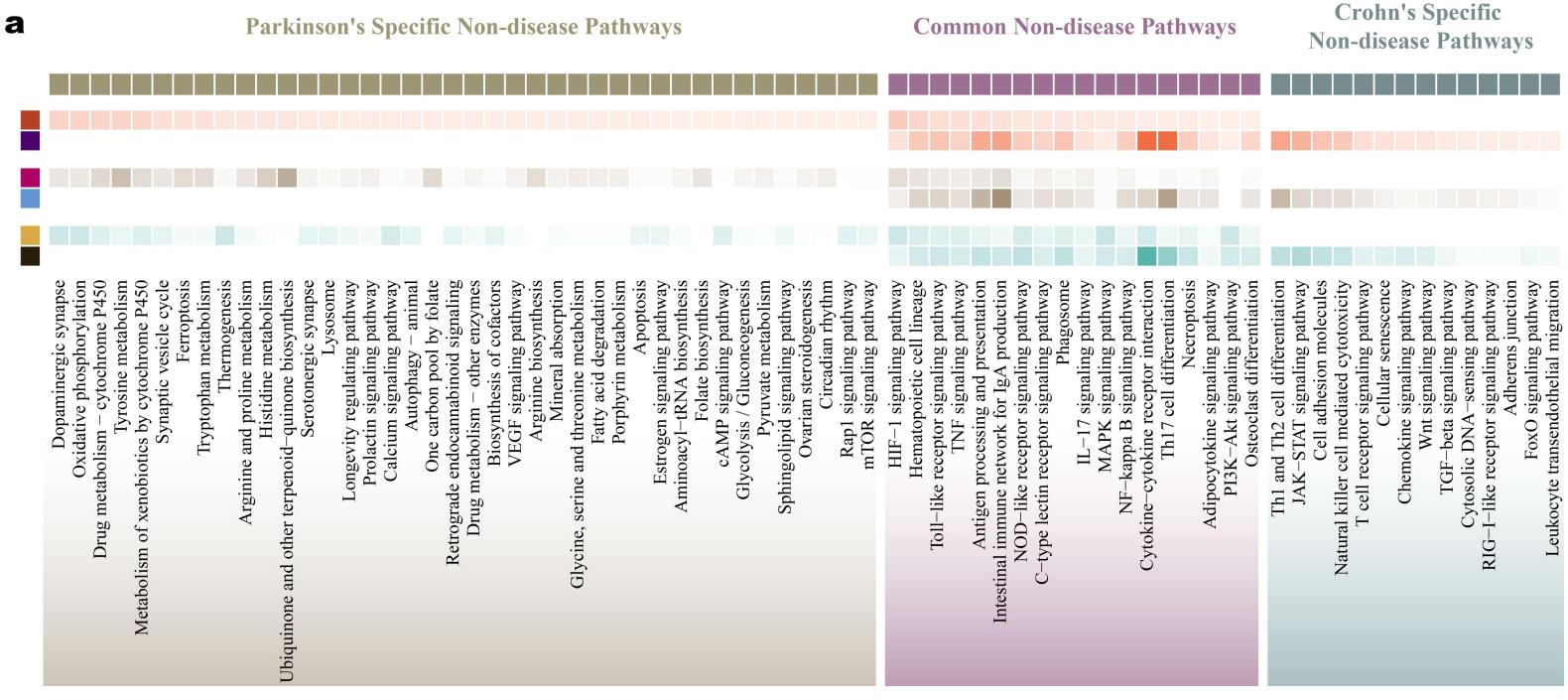
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GO Term	Parkinson's Substantia Nigra			Parkinson's Whole Blood			Crohn's Whole Blood			Crohn's Ileal Mucosa			Crohn's Colonic Mucosa		
	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment Ratio	NES	FDR	Enrichment 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



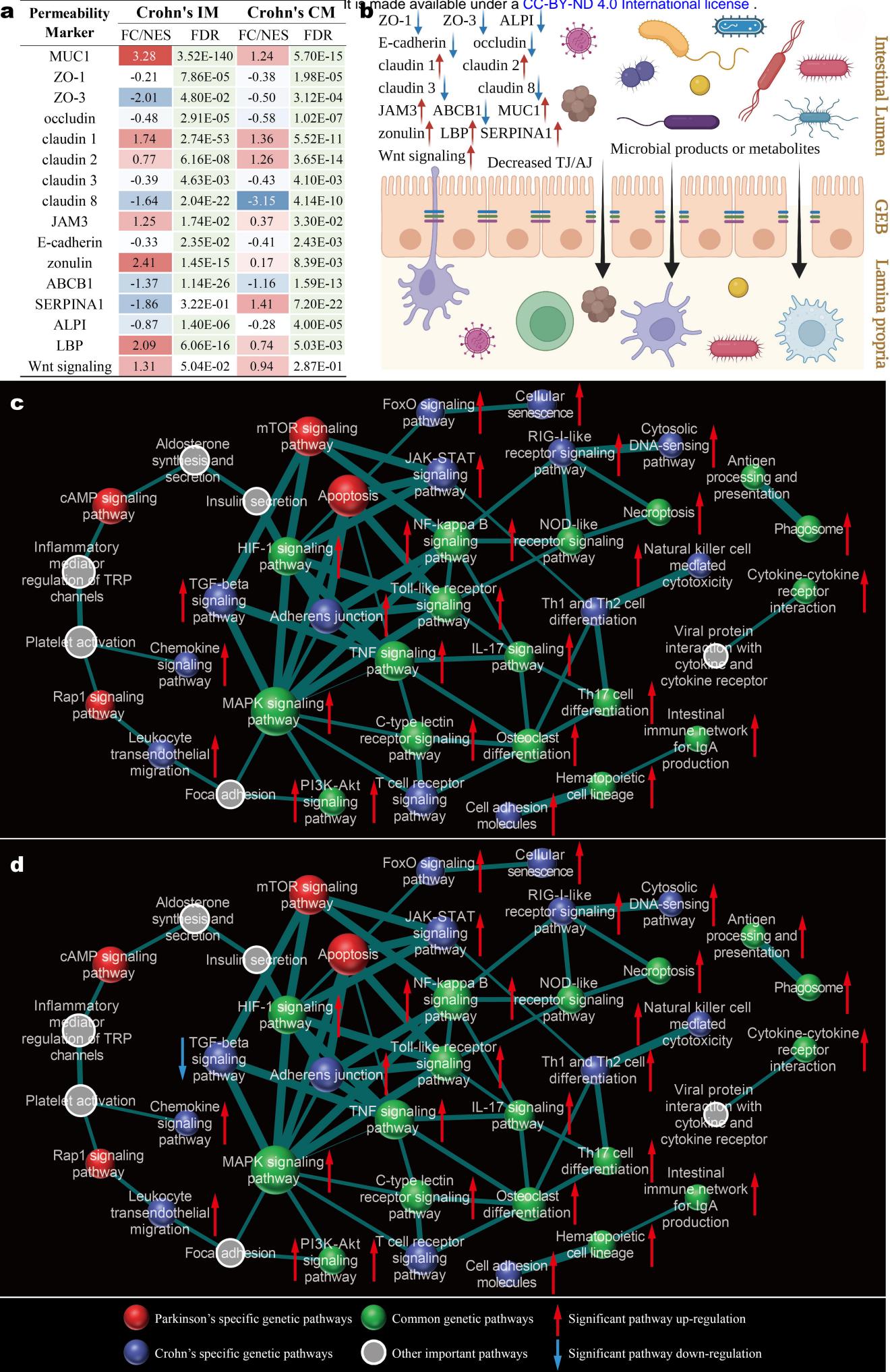
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Parkinson's Specific Genetic Pathways

Common Genetic Pathways

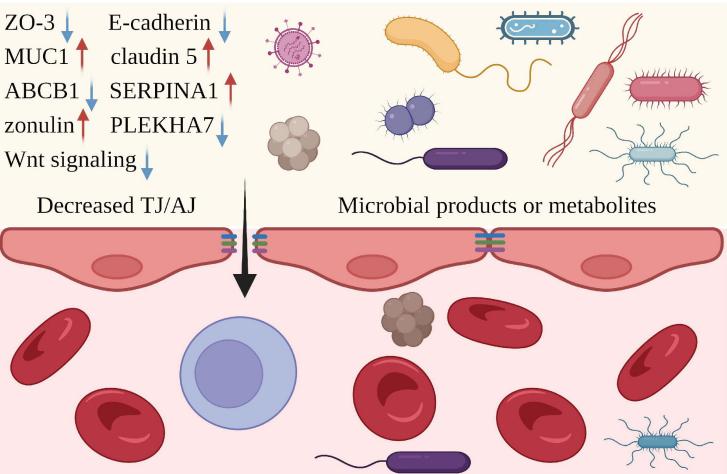
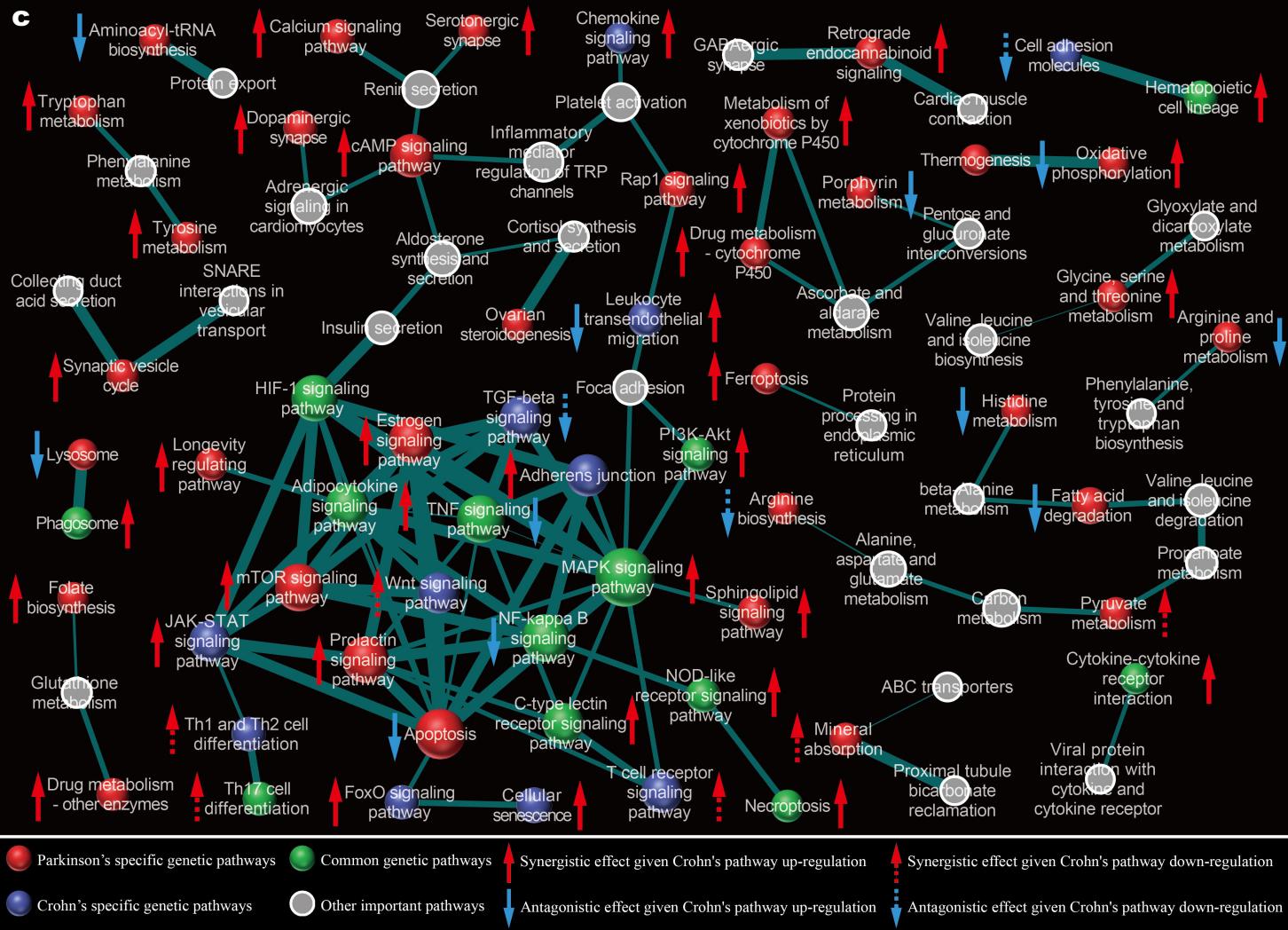
Crohn's Specific Genetic Pathways

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
Thermogenesis	-1.43	3.70E-07	2.13	-0.72	9.69E-07	2.06	0.45	5.00E-07	2.11	-1.46	4.61E-02	1.83	-1.68	4.45E-06	2.06
Arginine and proline metabolism	-1.00	7.39E-04	2.68	-1.22	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	6.90E-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



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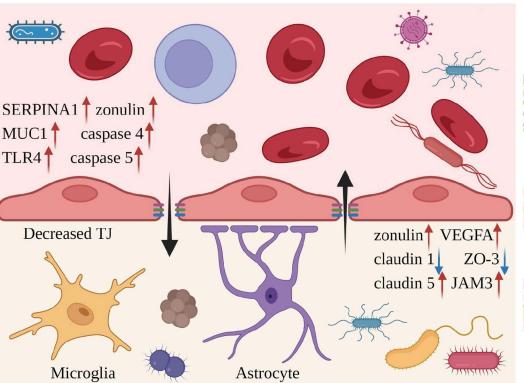
Permeability Marker	Crohn's WB		Parkinson's WB	
	FC/NES	FDR	FC/NES	FDR
ZO-3	-0.58	2.71E-02	-0.12	4.37E-02
E-cadherin	-0.42	1.02E-05	-0.22	5.92E-02
MUC1	0.25	1.70E-03	0.04	4.63E-01
claudin 5	0.88	3.11E-02	-0.12	4.93E-01
ABCB1	-0.65	1.48E-06	0.03	5.39E-01
SERPINA1	0.18	1.32E-04	0.23	3.94E-02
zonulin	1.44	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**

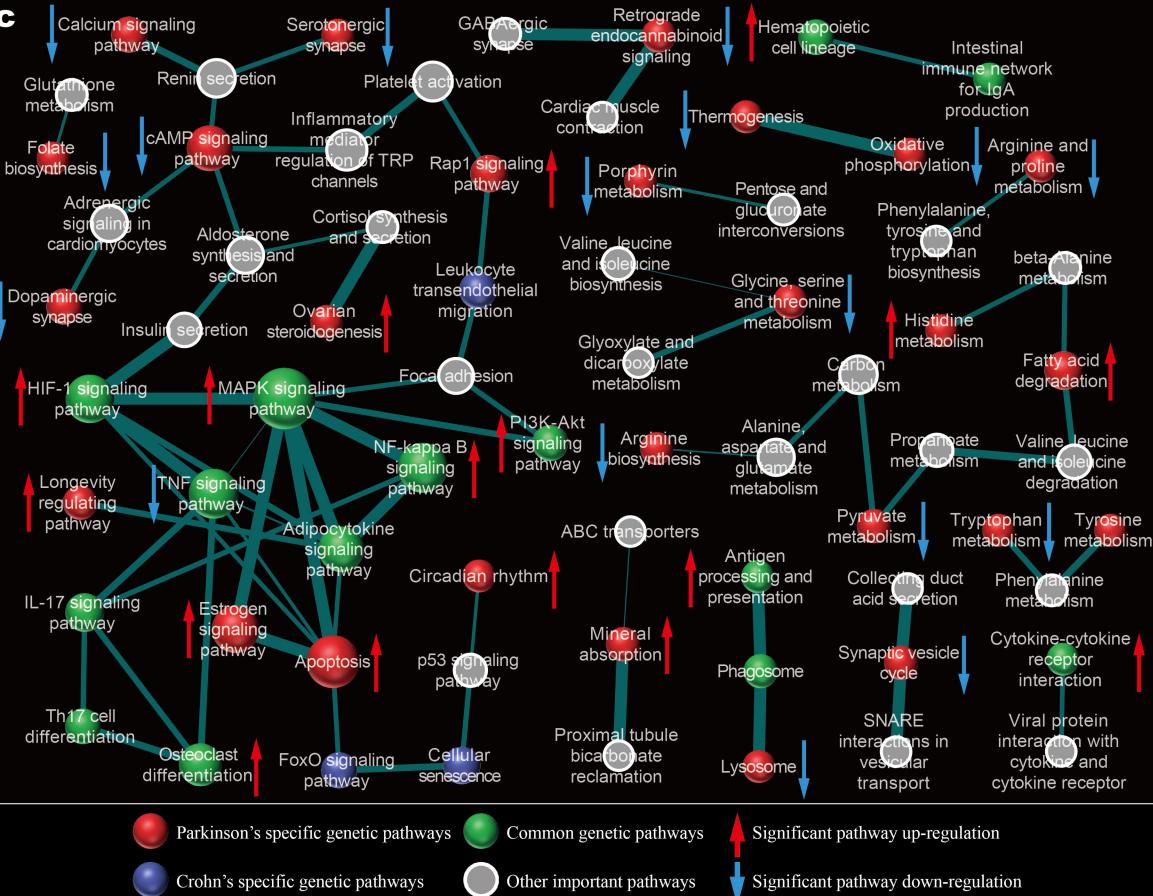
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Permeability Marker	Crohn's WB		Parkinson's WB		Parkinson's SN	
	FC	FDR	FC	FDR	FC	FDR
SERPINA1	0.18	1.32E-04	0.23	3.94E-02	-	-
MUC1	0.25	1.70E-03	0.04	7.03E-01	-	-
TLR4	0.63	1.25E-05	-0.02	9.52E-02	-	-
caspase 4	0.31	1.54E-06	0.14	3.17E-01	-	-
caspase 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

