# RESEARCH LETTER

## Histopathological Features of Monogenic Inflammatory Bowel Disease: Subanalysis of Systematic Review

Recent advances in genomic technology, such as next-generation sequencing, have made it possible to diagnose patients with a monogenic form of inflammatory bowel disease (IBD) where rare genetic variants appear to be driving the disease process. IBD because of variants transmitted by Mendelian inheritance patterns is described as "monogenic" IBD, as opposed to classical IBD.[1]

We have previously reported our findings of a systematic review of monogenic IBD cases, demonstrating that monogenic IBD diagnosis and management is a challenging but important clinical problem across many age groups.[2] Several studies have shown that the histopathological features of monogenic IBD in very early onset are different from those of classical IBD.[3,4] In this study, we comprehensively reviewed histopathological features of monogenic IBD as a subanalysis of our systematic review and specifically investigated the relationship between the characteristic histopathological findings and the respective monogenic disorders that cause IBD.

From 750 cases in a systematic review, we extracted only those cases in which pathologic findings were mentioned in detail (Supplementary Methods). The 315 included cases with monogenic IBD came from a total of 180 articles (Figure A1A). The cohort included 202 males, 99 females, and 14 with gender not reported. Infantile onset IBD (with disease onset less than 2 years of age) was the most common group (n = 144, 45.7%). On the other hand, 9.5% of patients (n = 30) developed IBD after 18 years of age (Figure A1B). This group covered 54 of the 75 genes known to be associated with monogenic IBD. The most reported gene was *CYBB*, followed by *XIAP*, *TTC7A*, *IL10RA*, and *HPS1* (Figure A1C). The characteristic histopathological findings reported in each case of monogenic IBD are as follows (Figure and Table A1).

Characteristic granuloma was reported in 100 cases with a high frequency in chronic granulomatous disease (CGD; n = 40, 72.7%; *CYBB*, *NCF1*, *NCF4*), followed by XIAP deficiency (n = 16, 47.1%; *XIAP*), Hermansky-Pudlak syndrome (HPS; n = 14, 73.7%; *HPS1*, *HPS4*), and Niemann-Pick disease type C (NP-C; n = 7, 87.5%; *NPC1*). Eosinophilic infiltration was shown in 61 cases and was more frequent in Loeys-Dietz syndrome (n = 4, 80%; *TGFBR1*, *TGFBR2*) and TTC7A deficiency (n = 17, 54.8%). In CGD, eosinophilic infiltration was reported in large numbers of cases but not at a high rate (n = 10, 18.1%; *CYBB*, *NCF4*).

Epithelial cell apoptosis was seen in 55 patients with the highest frequency in TTC7A deficiency (n = 30, 96.7%; *TTC7A*). In trichohepatoenteric syndrome (n = 5, 60%; *SKIV2L*, *TTC37*), Hoyeraal-Hreidarsson syndrome (n = 8, 50%; *DKC1*, *RTEL1*), and RIPK1 deficiency (n = 3, 50%; *RIPK1*), epithelial cell apoptosis was reported at a high rate, whereas in XIAP deficiency (n = 6, 17.6%; *XIAP*) and IPEX-like syndrome (n = 5, 23.8%; *LRBA*, *IL21*, *CTLA4*) epithelial cell apoptosis was reported in large numbers but not at a high rate. Villous blunting was described in 30 cases with IPEX being the most frequent (n = 4, 50%; *FOXP3*), followed by IPEX-like syndrome (n = 10, 47.6%; *LRBA*, *CTLA4*, *MALT1*, *STAT3 GOF*). Pigmented macrophages were reported in 37 cases with CGD (n = 30, 54.5%; *CYBB*, *NCF1*) and HPS (n = 7, 36.8%; *HPS1*, *HPS4*).

In this study, we define the characteristic histopathological findings that have been reported for each case of monogenic IBD by gene. Specific pathological findings may be useful in predicting the existence of monogenic disorder causing IBD when combined with clinical course and the result of molecular tests. Although some review articles have summarized the pathologic features of monogenic IBD, this is the first study to comprehensively analyze all previous reports and to clarify the gene-by-gene distribution of each monogenic IBD gene.

Characteristic granuloma can be seen in the classical IBD, as Rubio et al[5] showed that 53.8% of the pediatric patients with CD had granulomas. Conrad et al[4] reported that granulomas are not seen more frequently in very early onset IBD compared with older-onset pediatric IBD. In considering that monogenic IBD is more prevalent under the age of 6 years, when granuloma is seen in younger-onset IBD, molecular diagnostic tests that can differentiate CGD and XIAP deficiency, may be considered. The presence of pigmented macrophages along with granuloma further might help identify CGD (or HPS). Eosinophil infiltration is a common finding in classical IBD but appears to be more related to disease activity than IBD subtype.[6]

Epithelial cell apoptosis and villous blunting are generally not seen in classical IBD, but now we can say this is also a finding that can increase suspicion of monogenic IBD.[7,8] Villous blunting is rarely seen in Crohn's disease but is more commonly related to celiac disease or congenital diarrhea and enteropathy.[9] The mechanism of villous blunting seen among monogenic IBDs is unclear, although it was frequently found in IPEX or IPEX-like syndrome, implying a potential role for regulatory T lymphocytes.

Interleukin (IL) 10 and IL-10-receptor-associated colitis, which has the largest number of reports in monogenic IBD, had no characteristic pathologic findings.[2,10] In addition, pathologic findings in many monogenic IBDs have simply not been reported or

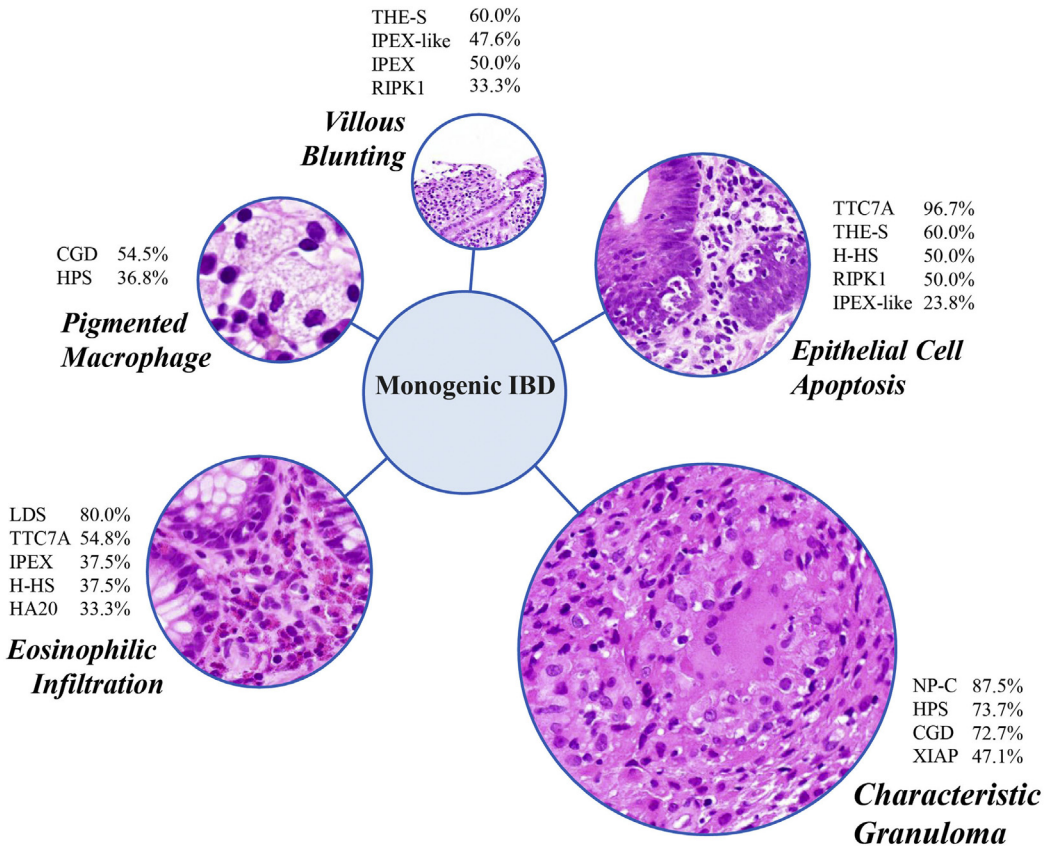


**Figure.** Most commonly reported histopathologic features of monogenic IBDs. Only diseases with more than 5 cases and findings that were found in more than 20% of cases are listed. CGD, chronic granulomatous disease; HA20, haploinsufficiency of A20; H-HS, Hoyeraal-Hreidarsson Syndrome; HPS, Hermansky-Pudlak syndrome; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; IPEX-like, immunodysregulation polyendocrinopathy enteropathy X-linked -like syndrome; LDS, Loeys-Dietz syndrome; NP-C, Niemann-Pick disease type C; RIPK1, RIPK1 deficiency; THE-S, tricho-hepatoenteric syndrome; TTC7A, TTC7A deficiency; XIAP, XIAP deficiency.

have been reported in very small numbers. Although the characteristic pathologic findings increase the suspicion of a specific monogenic IBD, they cannot be used to rule out the presence of a single genetic abnormality in the case.

This study is limited mostly by the nature of systematic reviews. In most reports, negative findings are not described, and histopathology reporting is a non-standardized part of disease evaluation. This can lead to reporting bias. We excluded cases in which the pathologic findings were absent or vaguely described, again leading to potential bias for reporting of highly abnormal, rare findings. If a case was described ambiguously as IBD-like or acute chronic inflammation, the rates of characteristic findings reported in this study might have been overestimated. However, we have shown that certain histopathological findings are associated with some monogenic IBD diseases and can be used to support a suspicion of genetic abnormalities. However, there does not appear to be any pathognomonic or even highly specific histopathologic features that identify specific monogenic IBD diseases. For example, infants with typical pathologic features of CD should alert the clinician to IL-10R deficiency, and infants with atresia or stricturing disease and apoptosis should be screened for TTC7A deficiency. Further case reports and prospective observational studies are still required, but this study supports the need for early next-generation sequencing in patients where monogenic IBD and characteristic pathologic features.

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## Supplementary Materials

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***Abbreviations used in this paper:*** **CGD, chronic granulomatous disease; HPS, Hermansky-Pudlak syndrome; IBD, inflammatory bowel disease; IL, Interleukin; NP-C, Niemann-Pick disease type C**

**Most current article**



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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

**Data Transparency Statement:**
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.