

Yao syndrome (NOD2-associated autoinflammatory disease) and the gastrointestinal tract: Future perspectives and research priorities

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Received date: August 12, 2025
Accepted date: October 10, 2025

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Abstract

Yao syndrome (YAOS) is a *NOD2*-associated autoinflammatory disease marked by periodic fevers, dermatitis, polyarthritis, distal extremity swelling, and nearly universal gastrointestinal symptoms. A recent study was the first to comprehensively assess the gastrointestinal symptoms and manifestations of YAOS, finding that most testing is normal, without gastrointestinal mucosal inflammation, and many patients have constipation and rectal evacuation disorders. Building on this foundation, this paper highlights future directions and research priorities in furthering the understanding of YAOS. These draw heavily from the literature on Crohn disease, which is also associated with *NOD2* variants. These future research priorities include detailed genotype-phenotype correlation focusing on specific *NOD2* variants, prospective, comprehensive gastrointestinal phenotyping, and multi-omics approaches to investigate genetic, microbiome, epigenetic, and environmental interactions underlying YAOS pathogenesis. Insights gained from such investigation may guide improved diagnostic criteria and targeted, personalized therapeutic development for patients with YAOS.

Keywords: Yao syndrome, Autoinflammatory disease, *NOD2*, Microbiome, Crohn disease, Inflammatory bowel disease

Background

Yao syndrome (YAOS) is a nucleotide-binding oligomerization domain 2 (*NOD2*)-associated autoinflammatory disease characterized by periodic fevers, dermatitis, polyarthritis, swelling of distal extremities, and gastrointestinal symptoms in patients with specific *NOD2* variants [1]. Gastrointestinal symptoms are a near universal feature of the disease, and abdominal pain and/or diarrhea are included as one of the minor clinical criteria to diagnose YAOS [2]. My colleagues and I recently published the first comprehensive analysis of the gastrointestinal manifestations of YAOS, drawing on both patient-reported symptoms from 14 patients *via* a validated gastrointestinal symptom survey and an extensive retrospective analysis of gastrointestinal and hepatobiliary testing from 24 patients including blood testing, stool testing, imaging studies, endoscopic evaluations, histopathology from gastrointestinal mucosa, motility testing, and any others [3].

In this study, fourteen patients completed the validated Gastrointestinal Symptoms Rating Survey, revealing 100% prevalence of gastrointestinal symptoms, and symptoms were most commonly severe. Bloating had the highest symptoms scores. Unexpectedly, the majority of the gastrointestinal specific testing including blood and stool tests, imaging studies, and endoscopies with biopsies were normal, specifically showing no mucosal inflammation. Most motility testing was also normal, excluding significant gastrointestinal dysmotility. However, the most common abnormality identified was a

heightened stool burden indicative of constipation, which was seen in 86% of abdominal radiographs and very commonly in cross-sectional imaging as well. While most transit studies were normal, 100% of patients who had undergone anorectal physiology testing had abnormal results indicative of a rectal evacuation disorder. There was a minority of patients who had comorbid inflammatory disorders affecting various parts of the gastrointestinal tract, including one with eosinophilic esophagitis, one with lymphocytic esophagitis, one with collagenous gastritis, one with celiac disease, one with an autoimmune-like enteritis, and one with collagenous colitis [3]. This study was limited by a small sample size of 24 patients, with 14 filling out the symptom survey. Furthermore, this was a retrospective study, and the patients were asked to recall symptoms at the time of symptom onset, introducing the possibility of both selection and recall biases. Nonetheless, this was the largest and most comprehensive analysis of the gastrointestinal manifestations of YAOS to date, and should help guide future investigations and research efforts to better understand why gastrointestinal symptoms and dysfunction arise. In this vein, future directions and research priorities are highlighted subsequently.

Deeper Disease Phenotyping Leading to Mechanistically Targeted Treatments

Clearly, YAOS is a heterogenous condition [4]. It is plausible that some of the heterogeneity of the disease derives from specific *NOD2* variants. This is a well described phenomenon in Crohn disease (CD), an inflammatory bowel disease also associated with *NOD2* variants. Indeed in CD, specific *NOD2* variants hold prognostic implications. For example, the presence of variants R702W, G908R, and 1007fs is associated with more complicated disease phenotypes, specifically featuring earlier onset, stricturing and penetrating behavior, and a higher likelihood of requiring surgeries [5,6]. Similarly, the rs72796353 (IVS4+10 A>C) variant has been identified as a predictor for the development of perianal disease [7]. Accordingly, the presence of two *NOD2* variants has 98% specificity for complicated CD [8]. In YAOS, the most common *NOD2* variants are IVS8⁺¹⁵⁸ (c.2798 + 158C>T) and R702W (c.2104C>T, p.Arg702Trp) [2,4,9], but novel variants continue to be reported, including a patient in our study with a previously unreported c.902C>T (p.Ala301Val) variant [3]. While there has not been a consistent signal linking specific genotypes to disease activity or severity to date [4], specific genotypes have been associated with different cytokine profiles. For example, the Q902K variant is associated with activation of the NOD2-RIP2-MAPK pathway [10]. Moreover, in the setting of IVS8⁺¹⁵⁸ heterozygosity, there is elevated basal IL-6 expression, which may explain the benefit of IL-6 receptor antagonism (tocilizumab) in these patients [11]. Conversely, compound heterozygotes (IVS8⁺¹⁵⁸ plus R702W) have suppressed NF- κ B and TNF- α activity [11]. A deeper understanding of the functional consequences of specific genotypes may help better risk stratify patients and target treatments, as is being actively and enthusiastically pursued in CD [12,13].

Prospective Comprehensive Gastrointestinal Investigation

The principal limitation of our gastrointestinal manifestations study was its retrospective nature. There was heterogeneity for when in the disease course patients underwent testing, and many were already on some sort of treatment, which certainly could confound the results. Similarly, the symptom survey required patients to think back before their diagnosis (which in many cases was several years prior), introducing recall bias. And since not all patients in our

YAOS cohort responded to the survey, there could also be selection bias. A more definitive approach to characterizing the gastrointestinal manifestations of YAOS is a comprehensive prospective analysis. This should include symptoms (measured from validated gastrointestinal symptom surveys) as well as objective testing such as blood and stool tests, cross-sectional imaging, endoscopy with gastrointestinal mucosal histopathology, and motility studies. This would allow for refinement of the diagnostic criteria for YAOS and earlier identification of patients.

Characterizing the symptoms is of particular importance. Currently, there is discrepancy between the diagnostic criteria and the findings from our analysis, specifically as they relate to diarrhea (one of the minor clinical criteria) [2]. Diarrhea was reported in only two out of the initial seven patients first described to have YAOS [1]. In the largest case series to date of 52 patients with YAOS, 65.4% had abdominal pain or diarrhea, so it is uncertain how frequently just diarrhea was [2]. A previous analysis of our same cohort found diarrhea reported by a striking 90.1% [4]. However, our more comprehensive investigation which identified a high prevalence of constipation and rectal evacuation disorders as well as dolichocolon actually argues for constipation over diarrhea, and that the purported diarrhea reported by patients may actually represent the overflow phenomenon [3]. An alternative explanation is that the constipation and rectal evacuation disorders develop as a compensatory response to chronic diarrhea, as has been demonstrated in other diarrheal disorders such as functional diarrhea and inflammatory bowel disease [14,15]. A prospective evaluation of patient symptoms in conjunction with objective diagnostics including imaging and anorectal physiology testing will help clarify the underlying abnormality, and potentially refine the diagnostic criteria. Related, further anatomical and motility investigations such as transit scintigraphy and imaging evaluation for dolichocolon should be undertaken to identify how and why constipation and rectal evacuation disorders arise.

Since we did not find mucosal inflammation using standard methodology, perhaps more specialized investigations are warranted, such as immunohistochemical investigation of NOD2 expression and evaluation for specific protein and/or cytokine profiles. This approach in one study identified increased small intestinal mucosal NOD2 expression in both YAOS and CD compared with healthy controls, as well as increased phosphorylated RIP2, phosphorylated NF- κ B p65, and phosphorylated p38 MAPK, the latter being even greater in YAOS than in CD [10].

Similarly, symptoms potentially suggestive of mast cell activation have been described in YAOS [4]. Additionally, IL-1 β receptor antagonism with canakinumab is one of the agents commonly used to treat YAOS, and is particularly efficacious for the management of gastrointestinal symptoms [2,4,10,16,17]. The clinical benefit of canakinumab may relate in part to mast cell physiology, since IL-1 directly activates mast cells and promotes an inflammatory response [18]. An increase in mucosal mast cells has been identified in several gastrointestinal disease states including CD [19] and disorders of gut-brain interaction [20]. Indeed, in CD, there is an expansion of NOD2+ mast cells, which may promote the recruitment of inflammatory cells through CXCL10 and urokinase-type plasminogen activator [21]. Mast cells are not readily visualized with routine hematoxylin and eosin staining, and require immunohistochemical assessment such as with CD117 (c-KIT), tryptase, CD25, and CD2 [22]. Notably, in one of our YAOS patients in whom we specifically requested mucosal

mast cell evaluation, there was no increased mast cell density or abnormal morphology. Specific prospective evaluation of mast cells on mucosal biopsies should be considered.

Multi-omics Investigation

Little is known at present about the pathogenesis of YAOS. It is considered a genetically transitional disease, where *NOD2* variants are necessary but not sufficient for disease development. Drawing on evidence from other autoinflammatory diseases, potential triggers include infections, toxins and pollutants, physical and psychosocial stress, and lifestyle habits [23]. Accordingly, infections and vaccination have been reported as triggers of YAOS flares [4]. Further investigation into the exposome should be undertaken to understand risk factors, exposures, and epigenetic contributors to the development of YAOS. Anecdotally, many YAOS patients report infections preceding the onset of their symptoms. In CD, there has been increasing appreciation that infections may trigger the disease in a subset of patients, most notably with Epstein-Barr virus [24,25], a pathogen associated with the subsequent development of numerous autoimmune and immune-mediated inflammatory conditions including multiple sclerosis, systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, and others [26,27]. Preliminary findings from a phenome-wide association study at our institution have identified that *NOD2* variants are associated with an increased risk of inflammatory disorders, gastroenteritis and colitis, infections, and requiring long-term antibiotics [28].

Future research should also seek to better characterize the role of the gut microbiota and microbial metabolites in YAOS. Mechanistically, the *NOD2* protein functions primarily as a pattern recognition receptor expressed principally within monocytes, macrophages, dendritic cells, and the intestinal endothelium. It contributes to immune surveillance, specifically to recognize and bind muramyl dipeptide from bacterial peptidoglycan through leucine-rich repeats (LRR) [29]. *NOD2* variants, especially those which affect the LRR region, can impair pathogen recognition. YAOS-associated variants have demonstrated decreased signaling in response to muramyl dipeptide, as well as an amplified and aberrant cytokine response such as increased IL-6 elaboration [11]. Dysfunction of *NOD2* is strongly linked to dysbiosis, or unfavorable shifts in the structure, function, and composition of the gut microbiota, best described in CD. *NOD2* has been described as the “Intestinal Gatekeeper,” [30] given its central role in regulation of the intestinal microbiota [31,32]. Dysbiosis and epithelial barrier dysfunction are hallmarks of CD, mediated in large part by *NOD2* [33,34]. Taken together, dysfunctional *NOD2* impairs host ability to sense and respond to pathogenic microbes. This leads to reduced microbial killing and impaired production of antimicrobial compounds, allowing for overgrowth and colonization of pathobionts and pathogens. Ultimately this creates a shift in the microbiota toward a pro-inflammatory milieu characterized by destabilization of the gut epithelial barrier, metabolic endotoxemia, and incitement of an inflammatory cascade. A previous study found an association between YAOS and Whipple disease (a rare multi-system, though primarily gastrointestinal infectious disease due to infection by the Gram positive actinobacterium *Tropheryma whippelii* featuring intestinal malabsorption, chronic diarrhea, weight loss, abdominal pain, and extraintestinal symptoms such as fever, lymphadenopathy, endocarditis, pleuritis, and neurologic symptoms) [35]; however, our cohort did not identify any patients with Whipple disease. In light of

the crucial role of *NOD2* in regulation of the intestinal microbiota and the fact that many of the *NOD2* variants in YAOS are also seen in CD, future research should leverage microbiome sequencing techniques to elucidate the role of the microbiota in the pathogenesis of YAOS.

Conclusions

YAOS is a *NOD2*-associated autoinflammatory disease which almost universally features gastrointestinal symptoms. There is still much unknown about the disease, but building on the knowledge of other *NOD2*-associated diseases, particularly CD, should help inform future research efforts. A clearer understanding of YAOS pathogenesis may be achieved with better characterization of the functional consequences of specific *NOD2* variants, a prospective investigation of gastrointestinal symptoms and manifestations, and a comprehensive multi-omics evaluation to determine the role and interaction of genetics, epigenetics, intestinal microbiota, and environmental factors such as infections.

Funding

None.

Disclosures

Dr. Damianos has received clinical trial research funding from ExeGi Pharma as well as consulting fees, and speakers bureau fees from i-Health.

References

1. Yao Q, Zhou L, Cusumano P, Bose N, Piliang M, Jayakar B, et al. A new category of autoinflammatory disease associated with *NOD2* gene mutations. *Arthritis Res Ther.* 2011;13(5):R148.
2. Yao Q, Shen B. A Systematic Analysis of Treatment and Outcomes of *NOD2*-Associated Autoinflammatory Disease. *Am J Med.* 2017 Mar;130(3):365.e13–365.e18.
3. Damianos JA, Nehra AK, Murray JA, Loftus EV Jr, Davis JM 3rd, Nehra V. Gastrointestinal Manifestations of Yao Syndrome (*NOD2*-Associated Autoinflammatory Disease). *Dig Dis Sci.* 2025 Jul 25.
4. Williamson KA, Samec MJ, Patel JA, Orandi AB, Wang B, Crowson CS, et al. Clinical phenotype, *NOD2* genotypes, and treatment observations in Yao syndrome: a retrospective case series. *Front Immunol.* 2024 Oct 4;15:1304792.
5. Cleynen I, González JR, Figueroa C, Franke A, McGovern D, Bortlik M, et al. Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: results from the IBDchip European Project. *Gut.* 2013 Nov;62(11):1556–65.
6. Ashton JJ, Seaby EG, Beattie RM, Ennis S. *NOD2* in Crohn's Disease-Unfinished Business. *J Crohns Colitis.* 2023 Apr 3;17(3):450–8.
7. Schnitzler F, Friedrich M, Wolf C, Stallhofer J, Angelberger M, Diegelmann J, et al. The *NOD2* Single Nucleotide Polymorphism rs72796353 (IVS4+10 A>C) Is a Predictor for Perianal Fistulas in Patients with Crohn's Disease in the Absence of Other *NOD2* Mutations. *PLoS One.* 2015 Jul 6;10(7):e0116044.
8. Adler J, Rangwalla SC, Dwamena BA, Higgins PD. The prognostic power of the *NOD2* genotype for complicated Crohn's disease: a meta-analysis. *Am J Gastroenterol.* 2011 Apr;106(4):699–712.
9. Nomani H, Wu S, Saif A, Hwang F, Metzger J, Navetta-Modrov B, et al. Comprehensive clinical phenotype, genotype and therapy in Yao syndrome. *Front Immunol.* 2024 Sep 20;15:1458118.

10. Zhang J, Luo Y, Wu B, Huang X, Zhao M, Wu N, et al. Identifying functional dysregulation of NOD2 variant Q902K in patients with Yao syndrome. *Arthritis Res Ther.* 2024 Feb 23;26(1):58.
11. McDonald C, Shen M, Johnson EE, Kabi A, Yao Q. Alterations in nucleotide-binding oligomerization domain-2 expression, pathway activation, and cytokine production in Yao syndrome. *Autoimmunity.* 2018 Mar;51(2):53–61.
12. Hoffmann P, Lamerz D, Hill P, Kirchner M, Gauss A. Gene Polymorphisms of NOD2, IL23R, PTPN2 and ATG16L1 in Patients with Crohn's Disease: On the Way to Personalized Medicine? *Genes (Basel).* 2021 Jun 5;12(6):866.
13. Plaza J, Mínguez A, Bastida G, Marqués R, Nos P, Poveda JL, et al. Genetic Variants Associated with Biological Treatment Response in Inflammatory Bowel Disease: A Systematic Review. *Int J Mol Sci.* 2024 Mar 27;25(7):3717.
14. Sannaa W, BouSaba J, Magnus Y, Vijayvargiya P, Camilleri M. Rectal Evacuation Disorders in Patients Presenting With Chronic Functional Diarrhea. *Gastro Hep Adv.* 2022 May 2;1(4):549–52.
15. Perera LP, Ananthkrishnan AN, Guilday C, Remshak K, Zadornova Y, Naik AS, et al. Dyssynergic defecation: a treatable cause of persistent symptoms when inflammatory bowel disease is in remission. *Dig Dis Sci.* 2013 Dec;58(12):3600–5.
16. Brailsford CJ, Khamdan F, Elston DM. Treatment of refractory Yao syndrome with canakinumab. *JAAD Case Rep.* 2022 Aug 28;29:37–40.
17. Yao Q. Effectiveness of canakinumab for the treatment of patients with Yao syndrome. *J Am Acad Dermatol.* 2023 Mar;88(3):653–4.
18. Gallenga CE, Pandolfi F, Caraffa AI, Kritas SK, Ronconi G, Toniato E, et al. Interleukin-1 family cytokines and mast cells: activation and inhibition. *J Biol Regul Homeost Agents.* 2019 Jan-Feb;33(1):1–6.
19. Xu X, Rivkind A, Pikarsky A, Pappo O, Bischoff SC, Levi-Schaffer F. Mast cells and eosinophils have a potential profibrogenic role in Crohn disease. *Scand J Gastroenterol.* 2004 May;39(5):440–7.
20. Vanuytsel T, Bercik P, Boeckxstaens G. Understanding neuroimmune interactions in disorders of gut-brain interaction: from functional to immune-mediated disorders. *Gut.* 2023 Apr;72(4):787–98.
21. Okumura S, Yuki K, Kobayashi R, Okamura S, Ohmori K, Saito H, et al. Hyperexpression of NOD2 in intestinal mast cells of Crohn's disease patients: preferential expression of inflammatory cell-recruiting molecules via NOD2 in mast cells. *Clin Immunol.* 2009 Feb;130(2):175–85.
22. Zimmermann N, Abonia JP, Dreskin SC, Akin C, Bolton S, Happel CS, et al. Developing a standardized approach for assessing mast cells and eosinophils on tissue biopsies: A Work Group Report of the AAAAI Allergic Skin Diseases Committee. *J Allergy Clin Immunol.* 2021 Oct;148(4):964–83.
23. Miller FW. Environment, Lifestyles, and Climate Change: The Many Nongenetic Contributors to The Long and Winding Road to Autoimmune Diseases. *Arthritis Care Res (Hoboken).* 2025 Jan;77(1):3–11.
24. Wagner J, Sim WH, Lee KJ, Kirkwood CD. Current knowledge and systematic review of viruses associated with Crohn's disease. *Rev Med Virol.* 2013 May;23(3):145–71.
25. Nandy A, Petralia F, Porter CK, Elledge S; Viruses and IBD Study Group; Colombel JF, Snapper SB. Epstein-Barr Virus Exposure Precedes Crohn's Disease Development. *Gastroenterology.* 2025 Jul;169(1):150–3.
26. Draborg A, Izarzugaza JM, Houen G. How compelling are the data for Epstein-Barr virus being a trigger for systemic lupus and other autoimmune diseases? *Curr Opin Rheumatol.* 2016 Jul;28(4):398–404.
27. Houen G, Trier NH. Epstein-Barr Virus and Systemic Autoimmune Diseases. *Front Immunol.* 2021 Jan 7;11:587380.
28. Davis J, Atkinson E, Kronzer V, Crowson C, Alavi A, Damianos J, et al. Immune-related Diagnoses Associated with NOD2 Variants in Human Subjects: A Phenome-wide Association Study. *ACR Convergence;* 10/26/2025, 2025; Chicago, IL.
29. Yao Q. Nucleotide-binding oligomerization domain containing 2: structure, function, and diseases. *Semin Arthritis Rheum.* 2013 Aug;43(1):125–30.
30. Al Nabhani Z, Dietrich G, Hugot JP, Barreau F. Nod2: The intestinal gate keeper. *PLoS Pathog.* 2017 Mar 2;13(3):e1006177
31. Petnicki-Ocwieja T, Hrnčir T, Liu YJ, Biswas A, Hudcovic T, Tlaskalova-Hogenova H, et al. Nod2 is required for the regulation of commensal microbiota in the intestine. *Proc Natl Acad Sci U S A.* 2009 Sep 15;106(37):15813–8.
32. Rehman A, Sina C, Gavrilova O, Häslér R, Ott S, Baines JF, et al. Nod2 is essential for temporal development of intestinal microbial communities. *Gut.* 2011 Oct;60(10):1354–62.
33. Lauro ML, Burch JM, Grimes CL. The effect of NOD2 on the microbiota in Crohn's disease. *Curr Opin Biotechnol.* 2016 Aug;40:97–102.
34. Li E, Zhang Y, Tian X, Wang X, Gathungu G, Wolber A, et al. Influence of Crohn's disease related polymorphisms in innate immune function on ileal microbiome. *PLoS One.* 2019 Feb 28;14(2):e0213108.
35. Williamson KA, Yun M, Koster MJ, Arment C, Patnaik A, Chang TW, et al. Susceptibility of nucleotide-binding oligomerization domain 2 mutations to Whipple's disease. *Rheumatology (Oxford).* 2024 May 2;63(5):1291–96.