# VEOIBD immunológiai kivizsgálása

*“A csiribí- csiribá hadművelet”*

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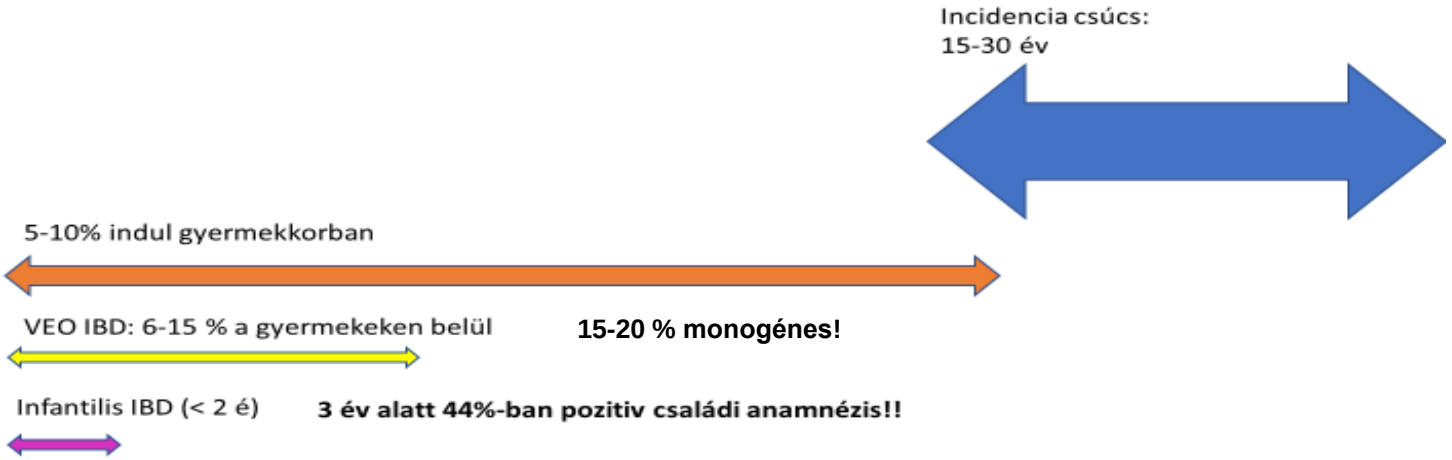
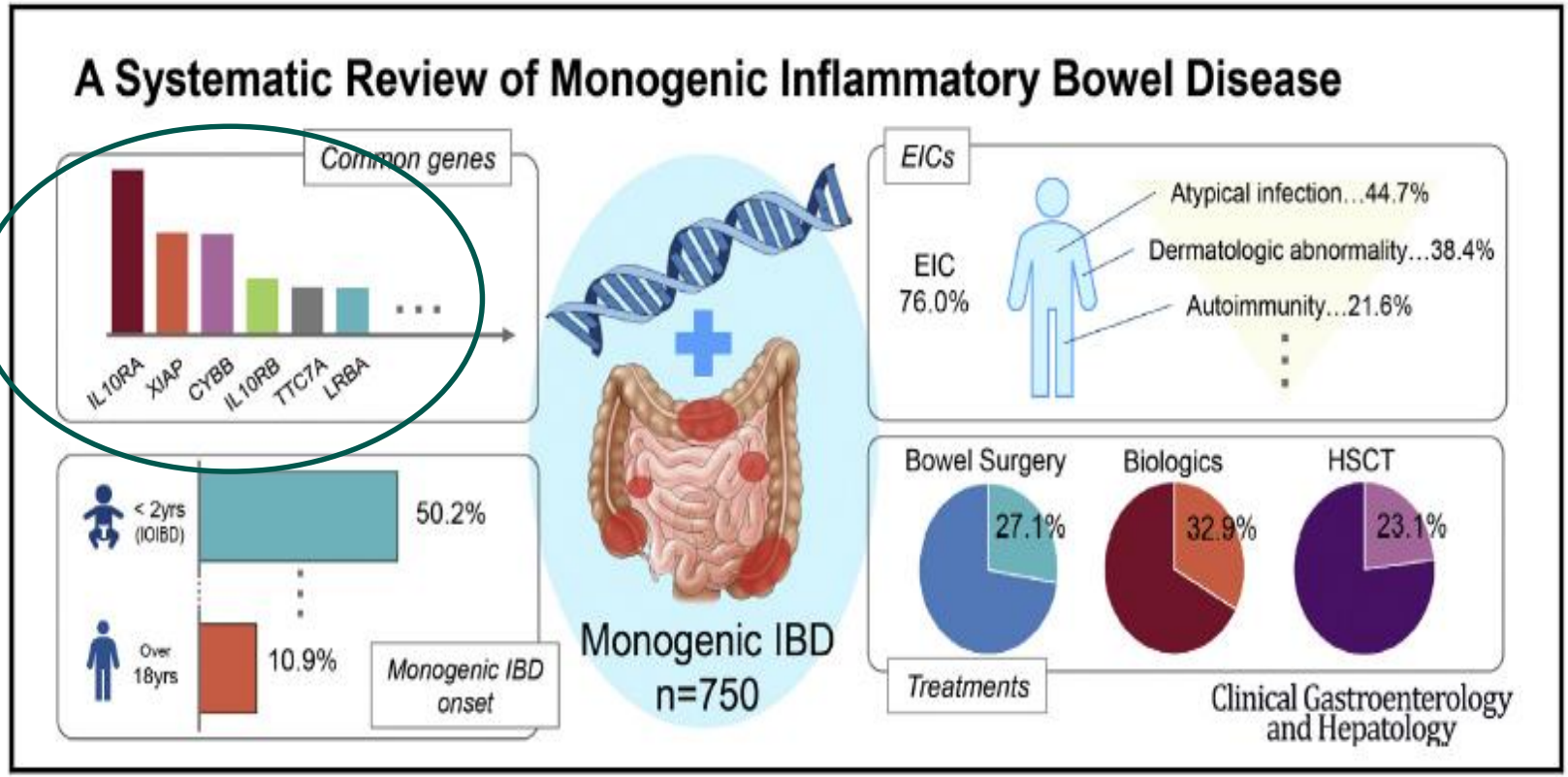
# Epidemiológia

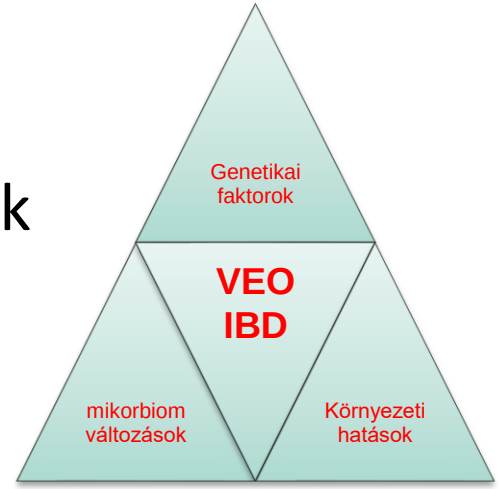


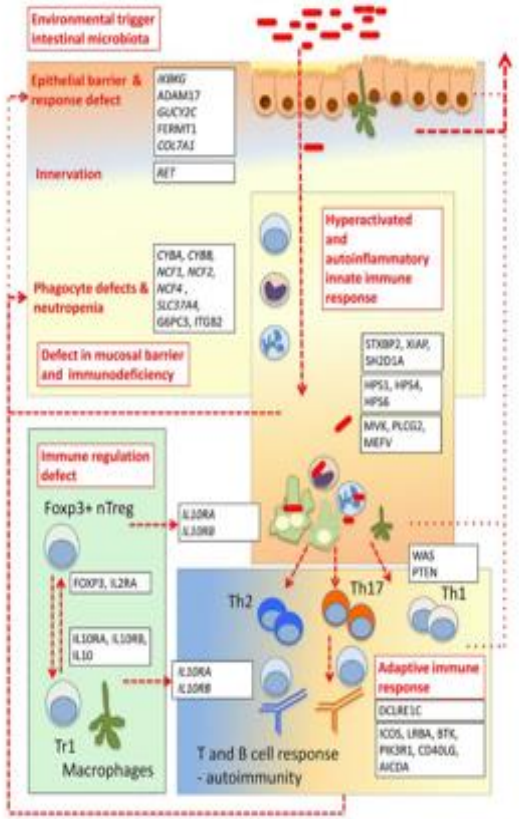

*Adatok az alábbi cikkekből kiemelve:*
*What is the peak age of onset for IBD?JOhnston RD et al:Inflamm Bowel Dis 2008*
*Childrens with early-onset IBD : Analysis of a pediatric IBD consortiumregistry Heiman MN et al:Pediatr 2005*




Clinical Gastroenterology and Hepatology 2022;20:e653–e663

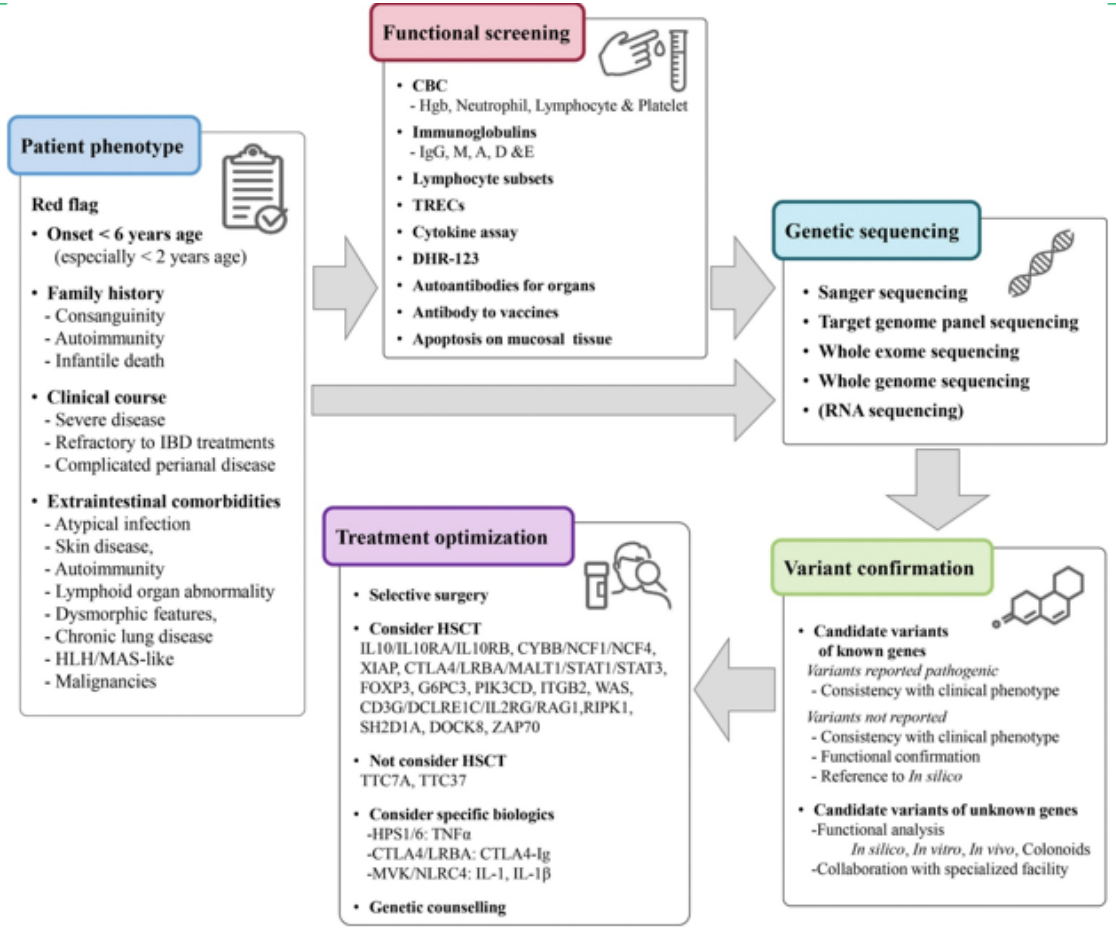
# Patomechanizmusok




1. Epithel barrier funkció defektusa ( pl TTC7a)
2. Hyperinflammációval járó betegség ( T-sejtes citotoxicitás, inflammoszóma betegség)
3. Neutrofil diszfunkció (pl. CGD)
4. T sejtes tolerancia csökkenése ( pl IPEX, IPEX-like, CTLA4 haplo)
5. IL-10 jelátivteli zavar ( IL-10, Treg defektus)
6. Primer antitest hiány T sejt defektussal ( BTK, TACI)

*( Uhig et al 2014)*




Nambu R, Warner N, Mulder DJ, et al. A systematic review of monogenic inflammatory bowel disease. Clin Gastroenterol Hepatol. 2022;20(4):e653-e663.

# VEO-IBD kivizsgálási algoritmus

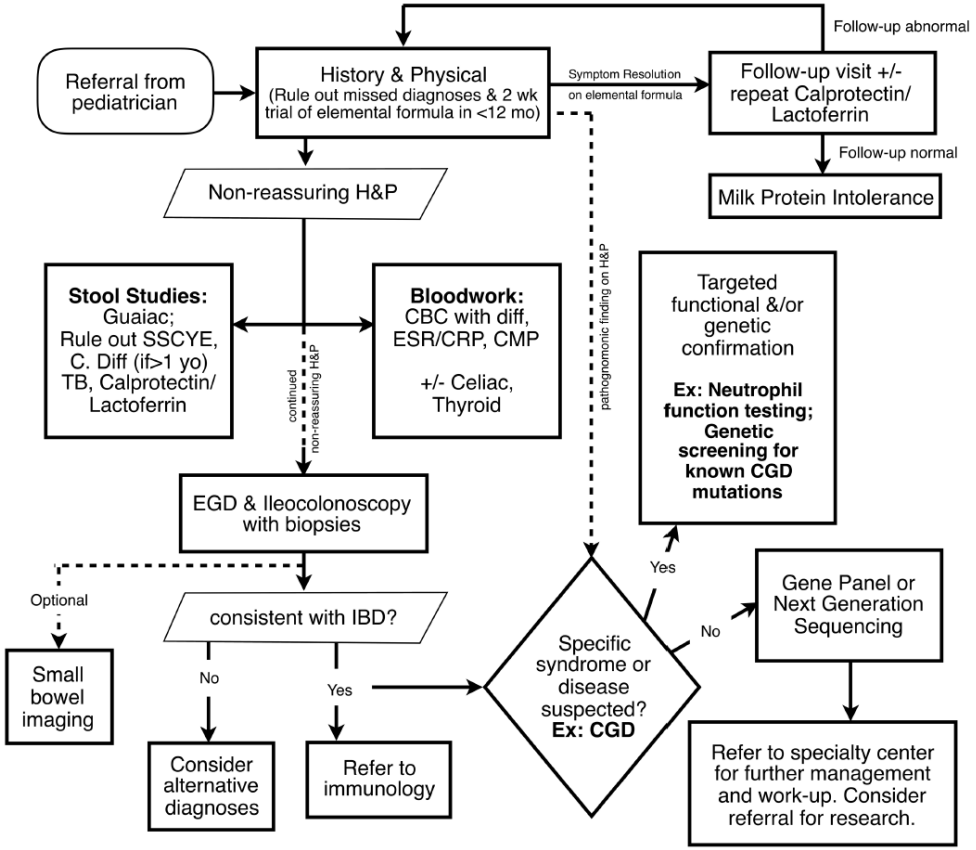
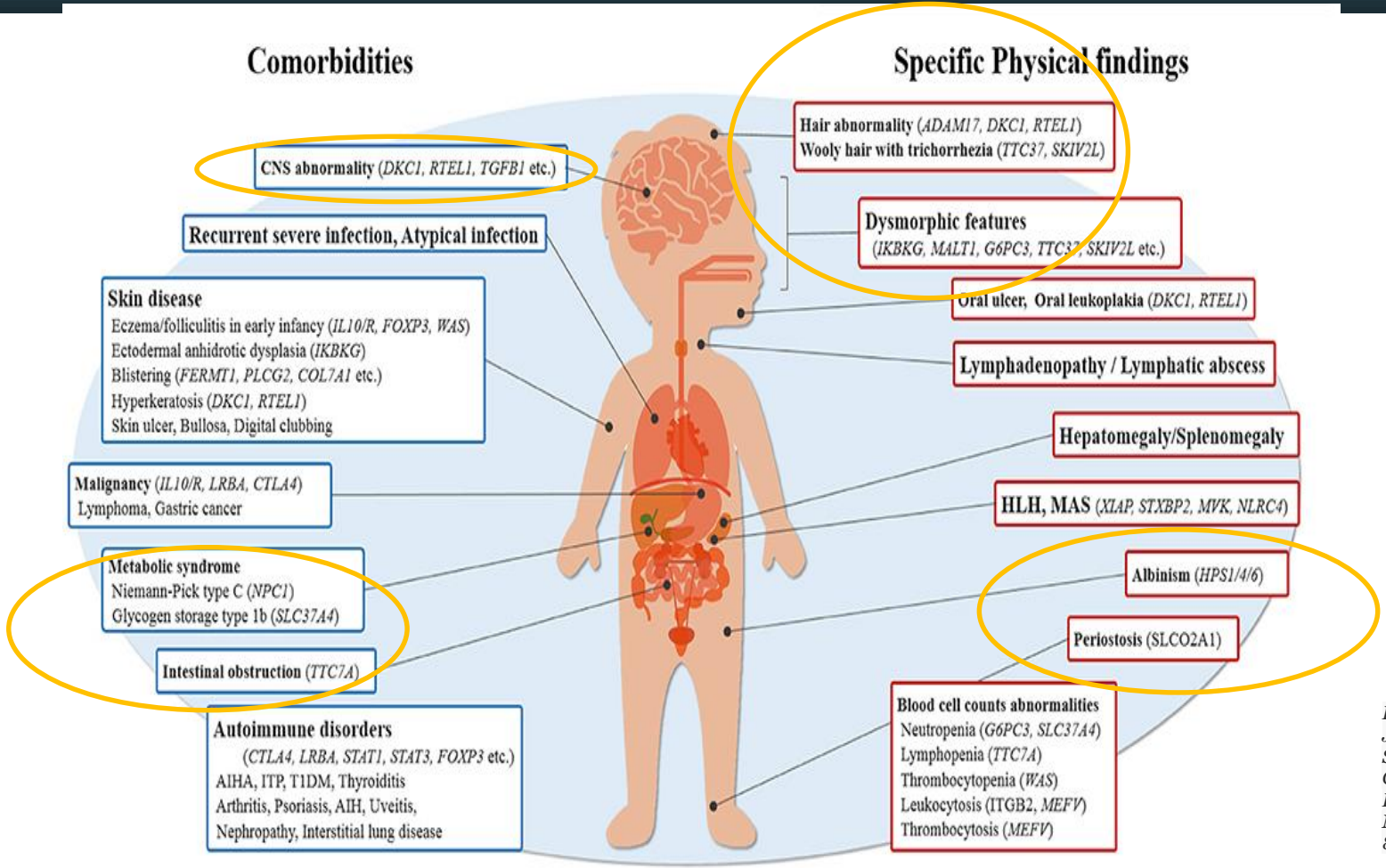



FIGURE 1. Algorithm for work-up of VEO-IBD. Abs, antibodies; CBC with diff, complete blood count with differential; CGD, chronic granulomatous disease; CMP, comprehensive metabolic panel; CRP, C reactive protein; EGD, esophogastroduodenoscopy; ESR, erythrocyte sedimentation rate; H&P, history and physical; mo, month; NOBA, neutrophil oxidative burst assay; TB, tuberculosis; SSCYE, Salmonella, Shigella, Campylobacter jejuni, Yersinia enterocolitica, and E coli; C. Diff, C. Difficile; Wk, week.

*Ouahed et al Inflamm Bowel Dis 2019*




*Front. Pediatr., 22 January 2021, Sec. Pediatr, c Gastroenterology, Hepatology and Nutrition, Volume 8 - 2020*

# “A CSIRIBIS beteg”: immunhiány kivizsgálás felmerül

**A**típusos jelek:dysmorfiás jelek, bőr/nyh tünetek, endokrinopathiák

**C**s**aládi anamnézis pozitivitás:** IBD-re v PID-re

**I**gen korai kezdet

**R**ezisztens a kezelésre: sebészi/ biol terápiák/HSCT igény

**I**mmundiszreguláció jelei: autoimmun társbetegségek

**B**esorolási nehézségek: IBD -U akár 30%-ban, később csak 4-10%

**I**nfekciók, tisztázatlan lázas állapotok, szokatlan kórokozók

**S**úlyos lefolyás : pancolitis 40%!, súlyos perianális érintettség

# Gastroenterológiai kivizsgálás fontos részei

- Beteg kórelőzménye, családi anamnézis
- IBD  igazolása
- Infekciók kizárása: SSCYE +/- Giardia, Cryptococcus, CMV, Clostridium ( 12 hó felett), Tbc, HIV, egyéb opprtunista kórokozó igazolása)
- Egyéb gyulladásos bélbetegség igazolása /kizárása ( coeliakia, allergiás colitis, ritka ionvesztő enteropátiák..stb.)
- Súlyfejlődés dokumentálása ( stagnálás, AS alapú tápszer mellett is)
- Széklet vizsgálatok: vér, calprotectin stb.
- We, CRP, Vérkép, máj/vesefunkciók, ionok, összfehérje, albumin,
- Ig szintek?

Uhlig HH, Schwerd T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014;147(5):990-1007.e3.

# Immunológiai kivizsgálás fontos részei VEOIBD-ben

- Vérkép,IgGAM
- IgE, IgG alosztályok
- FACS: T/B/NK/Treg
- Specifikus antitest titerek
- DHR
- Systemás autoimmun jelenség, AI serol. panel kieg.
- Cytopenia dg. (Coombs, anti neutrofil at, sz. e. csv.)
- WES PID/VEOIBD panel, ritkán célzottan Sanger szekvenálás

- NK sejt aktivitás
- Mevalonsav ürítés, IgD
- TNF-alfa, IFN-gamma szintek
- WASP expresszió ( UK)
- Oszt. váltott mem B arány
- Follicularis helper T arány
- CTLA4 expresszió
- Sol CD25 expresszió
- CD55
- SCID panel
- IL-10 indukálta STAT-3 foszforiláció
- TCR repertoár

# A fejleszések következő lépcsőfoka

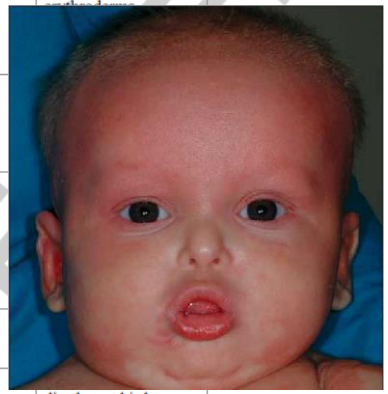
**Targeted functional analysis (*recommended*)**

| *Gene* | *Functional analysis* |
|---|---|
| *IL10RA*<br>*IL10RB* | IL10-induced STAT3 phosphorylation by flow cytometry or immunoblotting |
| *NCF1*<br>*NCF2*<br>*CYBA*<br>*CYBB* | Neutrophil oxidative burst study, DHR-123 test |
| *NCF4**<br>*CYBC1* | Neutrophil oxidative burst study |
| *TTC7A* | Immunohistochemistry-TTC7A, apoptosis |
| *WAS* | WASP expression by flow cytometry |
| *XIAP* | XIAP expression by flow cytometry TNF, IL-8, and MCP-1 expression in response to MDP stimulation |
| *SLCO2A1* | Immunohistochemistry-SLCO2A1 |
| *NPC1* | Filipin staining of cultured skin fibroblasts |
| *SLC37A4* | G6Pase enzyme activity in Liver tissue (non-frozen) |
| *MVK* | Increased urine mevalonic acid when fever |
| *TNFAIP3* | A20 expression by immunoblotting RT-PCR using total RNA |
| *CTLA4* | CTLA-4 expression within stimulated Treg cells by flow cytometry |
| *LRBA* | LRBA expression in response to PHA stimulation by flow cytometry |
| *FOXP3* | FOXP3 expression by flow cytometry |
| *STAT1*(GOF) | CD25 expression by flow cytometry |
| *STAT3*(GOF) | STAT3 reporter luciferase assay under basal or stimulated condition (IL-6/growth hormone) in cell lines<br>SOCS3 expression levels under basal or stimulated condition |

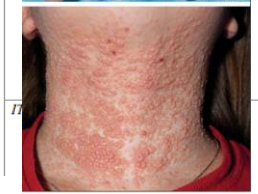
# ESPHGAN position paper:
# Key evaulation features of the common monogenic forms

***Defects in adaptive immunity***

| | | | | |
|---|---|---|---|---|
| ***Defects in Epithelial Barrier Function*** | | | | |
| *ADAM17* [33,115,116] | | AR | Staphylococcal infections Psoriasiform | Slightly low TNF response to LPS in PBMCs and T cells. |
| *IKBKG* [73,117] | NEMO | XL | | |
| *GUCY2C* [89] | Familial Diarrhea | AD GOF | | |
| *TTC7A* [4,118, 119] | Hereditary multiple intestinal atresia | AR | | |
| *SLC26A3* [108,120,121] | Congenital Chloride diarrhea | AR | diarrhea at birth, inflammation occurs later in life | |
| ***COL7A1*** [122] | Epidermolysis Bullosa | AR | Recurrent blistering or erosions, esophageal stricture, anal fissures and stenosis, enteropathy, hair and nail abnormalities | |
| ***FERMT1*** [36] | Klinder Syndrome | AR | Recurrent skin blisters, esophageal strictures, colonic involvement | |



| | | | | |
|---|---|---|---|---|
| *IL10* [55,123] | IL-10 deficiency | AR | IBD onset near birth, Folliculitis, perianal disease, arthritis, increased risk of lymphoma, particularly large B cell lymphoma | Defective IL10 signaling, dysfunctional Tregs |
| *IL10RA, IL10RB* [1,123 1,55,123] | IL-10RA/RB deficiency | AR | IBD onset near birth Folliculitis, perianal disease, arthritis, increased risk of lymphoma, particularly large B cell lymphoma | Dysfunctional Tregs, Reduced frequency of $T_{FH}$ Lack of IL-10 suppression of LPS response |
| *BTK* [124] | X-linked agammaglobulinemia, Bruton's agammaglobulinemia | XL | Infections, small tonsils, diarrhea | Very low B cells and immunoglobulins |
| *DKC1* [125] | Dyskeratosis congentia | XL | Microcephalic, cerebellar hypoplasia, IUGR, Small, nail dystrophy, aplastic anemia and bone marrow failure | Progressive decrease in B and T cells, Low NK cells |
| *DOCK8* [126,1 27] | Hyper-IgE Syndrome | AR | Presents in infancy, cutaneous viral, fungus, staphylococcus infections, eosinophilia, eczema, poor growth, diarrhea with or without blood | Low T cells and poor proliferation, poorly function Tregs, very low memory B cells, poor peripheral B cell tolerance, low NK cells |
| *IC* | | | Infectious enteritis, founder effect along the Danube river, small bowel disease prominent and nodular lymphoid hyperplasia of GI tract Splenomegaly | Absent class switched memory B cells, low TFH, poor germinal centers in lymph nodes, low IgG |
| *IT* | | | Severe infections, delayed separation of umbilical cord Gingivitis, scarring | High WBC/ANC, low CD18 expression, reduction of factor XIIIa+ DC in lymph |



ACCEPTED

***Defects in adaptive immunity cont.***

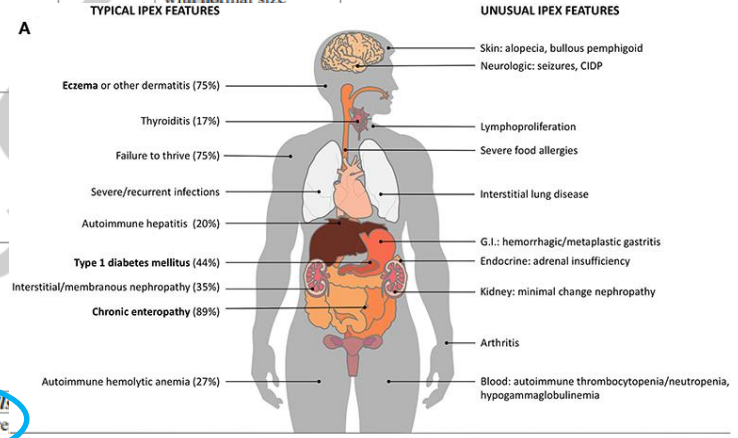
| | | | | |
|---|---|---|---|---|
| | | | poor growth, diarrhea | |
| | | | | |
| *ZBTB24*[5] | Immunodeficiency with centromeric instability and facial anomalies, ICF2 | AR | Diarrhea, facial dysmorphic features, developmental delay, bacterial/opportunistic infections, cytopenias, malignancies, multiradial configurations of chromosomes 1, 9, 16 | Decreased B cells, T cells can be decreased or normal |
| *PIK3CD* P100 [130] | | AD GOF | Infections, PSC, herpes, lymphoma | High IgM, low IgG, low CD4/CD45RA, |
| *PIK3R1* P85[131] | | | resistance, short stature, nodular lymphoid hyperplasia | l, low IgG, CD45RA, |
| PTEN [132] | | AD | Autoimmunity: thyroiditis, autoimmune hemolytic anemia; hamartomas, lymphoproliferation, adenopathy, large tonsils, macrocephaly, developmental | low IgG |
| **ITCH**[133] | | AR | Autoimmune inflammatory cell infiltration of lungs, liver, gut, growth | T cell abnormalities, increased Th2, decreased switched memory B cells |
| **RAG1** | Omenn | A[R] | | |

Nincs hasmenés, de jelentős súlyállás Listeria agytályog után. Sirolimus mellett egyensúlyban

Véres hasmenés heteken át adenovirus infekcióban, később ITPben véres széklet

| | | | | |
|---|---|---|---|---|
| **RAG2**[68,69,134] | Syndrome/SCID | | infections, chronic diarrhea, failure to thrive, variable intestinal involvement | cells |
| **ZAP70**[135] | Omenn Syndrome/SCID | AR | Recurrent severe infections, chronic diarrhea, failure to thrive, variable intestinal involvement | Low CD8+ T cells, normal CD4, but poor function |
| **IL7R**[72] | Omenn Syndrome/SCID | AR | Skin inflammation, variable intestinal involvement | Very low T cells |
| *WASP* [86,136] | Wiskott-Aldrich Syndrome | XL AR LOF | Thrombocytopenia with small platelets, recurrent viral infections, eczema, diarrhea, autoimmune disease | |
| *ARPC1B*[137] | | AR LOF | Thrombocytopenia with normal size | Poor T/B/NK function |
| *TGFBR1*[138] | | | | |
| *TGFBR2*[138] | | | | |
| ***Impaired Regulatory T cell:*** | | | | |
| *FOXP3* [139-142] | Immunodysregulation polyendocrinopathy x linked (IPEX) | | diarrhea, with or without blood, Autoimmunity: | cells, elevated IgE, IgA |

“Ekcémás fiúcsecsemő intesztinális vérzése”: lehet részleges tünettan!



## *Impaired Regulatory T-cells folyt.*

| | | | | |
|---|---|---|---|---|
| | | | psoriaform dermatitis, alopecia, endocrinopathies: type 1 diabetes | |
| *CTLA4* [82-84] | | AD | Autoimmunity, autoimmune | Low immunoglobulins, low |
| *LRBA* [81] | LRBA deficiency | AR | Infections, interstitial pneumonitis, autoimmunity (idiopathic thrombocytopenia, autoimmune hemolytic anemia, type 1 diabetes etc) and IBD | Low immunoglobulins, low switched memory B cells, low CD4 T cells |
| STAT1 [143] | STAT1 Deficiency | AD GOF | Pleomorphic autoimmunity, candida, other infections Poor growth | Low NK cells, low IgA |
| STAT3 [144-146] | | AD GOF | Lymphoproliferation, recurrent infections, pleomorphic autoimmunity: diabetes, thyroid, Poor growth, eczema | Decreased B and T cells, low regulatory T cells, low IgG |
| STAT5b[147] | | AR | Growth failure, IGF-I deficiency, Chronic pulmonary disease, dysmorphic features, autoimmunity | Modestly decreased T cells |
| ***IL-2RB***[148] | | XL | Enteropathy, eczema, autoinflammatory disease, lymphoproliferation | Normal to decreased T cells, impaired T cell profileration |
| IL21R [149,150] | | AR | Recurrent infection, Pneumocystitis jiroveci, Cryptosporidia | Low cytokine production, low switched memory B cells |
| | | | cholangitis | |
| IL21 [149,150] | | AR | Severe early onset colonic disease, recurrent sinopulmonary infections | T cells poor function, low B cells, low switched memory B cells, low IgG |
| ***Autoinflammatory and Hyperinflammatory defects*** | | | | |
| *SKIV2L* [151,152] | | AR | IUGR, FTT, Trichorrhexis nodosa, frontal bossing, villous atrophy | low immunoglobulins, low T cells |
| *TTC37* [153] | | AR | IUGR, FTT, Trichorrhexis nodosa, frontal bossing, villous atrophy | low immunoglobulins, low T cells |
| *RTEL* [154] | regulator of telomere elongation (RTEL1) deficiency | AR or AD | IUGR, FTT, microcephaly, fine hair, hyperpigmentation of skin, palmar hyperkeratosis, premalignant oral leukoplakia, pancytopenia, myelodysplasia, +/-, apoptosis in biopsy | Low NK cells |
| *STXBP2* [155] | | AR | Fever, hepatosplenomegaly, cytopenias, HLH | Poor NK function, low IgG |
| *XIAP* [3,156 2] | XIAP deficiency (XLP2) | XL | Infantile onset IBD, EBV infection, hepatitis, HLH, Splenomegaly | normal or increased activated T cells, low/normal iNK T cells, normal or reduced memory B |
| | autoinflammatory syndrome 4 | | | |

Súlyos cytopeniák, lymphoprolifertív betegség (CML!), súlyos atopia, alopecia

Hónapokon át tartó, kora csecsemőkortól induló véres-nyálkás székletek, Súlyállás. Szteroid dependencia (biol terápia nem indult), colonoscopia Th: infliximab bridging, allo HSCT (abszolút indikáció alapján). Kimenetel: exit TRM miatt (systemás gomba infekció)

ACCEPTED

| | | | | |
|---|---|---|---|---|
| *MEFV*[90,91] | Familial Mediterranean fever | AR | Periodic fever, founder effect in Mediterranean Oral ulcers, arthritis, serositis, rash, enteropathy | |
| *MVK*[157,158] | Mevalonate kinase deficiency (Hyper IgD syndrome) | AR | Nausea, fever episodically, | Elevated IgD, increased urine ic acid |
| *HPS1*[159-161] | Hermansky-Pudlak syndrome Type 1 | AR | order, recurrent infections, oculocutaneous albinism, pulmonary fibrosis, colitis, can develop HLH | |
| *HPS4*[162] | Hermansky-Pudlak syndrome Type 4 | AR | Bleeding disorder, recurrent infections, oculocutaneous albinism, pulmonary fibrosis, colitis, can develop HLH | |
| *TRIM22*[100] | | AR | Granulomatous colitis severe perianal disease | |
| *CASP8*[163] | | AR | recurrent bacterial and viral infections, especially sinopulmonary infections, hypogammaglobuilnemia, enteropathy Lymphadenopathy, splenomegaly | Slightly increased T cells |
| *PLCG2* [164,165] | PLAID, PLAID (PLCg2 associated antibody deficiency and immune dysregulation) or familial cold autoinflammatory syndrome 3 or | AD | Pleomorphic inflammation, cold urticaria, dermatitis | Low immunoglobulins, low switched memory B cells |

Krónikus hasi fájdalom, hasmenés, súlyfejlődés zavara, periodikus láz

| | | | | |
|---|---|---|---|---|
| | APLAID (c2120A>C) | | | |
| ***Phagocytic and NADPH oxidase complex defects*** | | | | |
| *CYBA* P22phox[101] | Chronic granulomatous disease | AR | Infections, autoinflammatory phenotype | Low DHR, reduced switched memory B cells, low T cells |
| *CYBB* Gp91phox [101] | Chronic granulomatous disease | XL | Infections, autoimmunity, maternal discoid lupus | Low DHR, reduced switched memory B cells, low T cells |
| *NCF1* P47phox [46,47] | Chronic granulomatous disease | AR | Infections, | Low DHR, reduced B |
| *NCF2* [46,47] P67phox[166] | Chronic granulomatous disease | AR | Infections phenotype | Low DHR, reduced memory B cells, low T cells |
| *NCF4* P40phox[43] | Chronic granulomatous disease | AR | Infections, autoinflammatory phenotype | DHR slightly low only |
| *G6PC3* [30] | Congenital neutropenia | AR | Cardiac anomalies, urogenital defects, IUGR Superficial vessels enlarged | Neutropenia, intermittent thrombocytopenia, lymphopenia in severe forms |
| *SLC37A4* [167] | | AR | Hypoglycemic episodes Hepatomegaly | Neutropenia |

Hemicolectomia, szteroid dependencia

Szteroid rezisztens IBD-U

ACCEPTED

# Allogén HSCT  eredményessége VEO-IBD-ben
# Autológ HSCT= reset, TCR újragenerálása

**TABLE 3.** Efficacy of Healing Intestinal Disease With Stem Cell Transplantation in Some Cases of VEO-IBD

| Condition | HSCT May Be Efficacious for Intestinal Disease | HSCT Not Efficacious for Intestinal Disease |
|---|---|---|
| | IL-10RA, IL-10RB, IL-10 deficiency | TTC7A |
| | IPEX | STXBP2 |
| | WAS | IKBKG (NEMO) |
| | Many forms of SCID | |
| | CD40L | |
| | XIAP | |
| | CGD | |
| | LRBA | |
| | CTLA4 | |
| | DOCK8 | |

*Ouahed et al Very-early onset IBD: Role of genetics and Underlying Immune deficiencies Inflamm Bowel Dis 2019*

# Expect the unexpected!

**Köszönöm a figyelmet!**

Berg Judit: Panka és Csiribí

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| GROUP | GENE DEFECT | CLINICAL PHENOTYPE | SPECIFIC TREATMENT |
|---|---|---|---|
| **Epithelial Barrier Dysfunction** | | | |
| NEMO deficiency | *IKBKG* | Ectodermal dysplasia, antibody deficiency, enterocolitis | |
| ADAM17 deficiency | *ADAM17* | Erythematous psoriasiform rash, dermatitis, enteropathy | |
| TTC7A deficiency | *TTC7A* | Intestinal atresia, enterocolitis, SCID | |
| Dystrophic epidermolysis bulls | *COL7A1* | Dystrophic epidermolysis bulbosa, esophageal strictures, Crohn's disease | |
| Kindler syndrome | *FERMT1* | Skin blistering, atrophy, cancer, ulcerative colitis | |
| Loeys-Dietz syndrome | *TGFBR1 and 2* | Skeletal abnormalities, craniofacial abnormalities, vascular injury, enterocolitis | |
| Congenital chloride diarrhea | *SLC9A3* | Infantile diarrhea, enteropathy with electrolyte abnormalities | |
| Familial diarrhea | *GUCY2* | Secretory diarrhea, enteropathy with electrolyte abnormalities | |
| **Phagocytic Defects** | | | |
| Chronic Granulomatous Disease (CGD) | *CYBB, CYBA, NCF1, NCF2, NCF4* | Severe bacterial and fungal infections throughout the body, fistulizing Crohn's Disease with granulomas, intestinal obstruction, perianal abscesses | Anti-microbial prophylaxis, Anti-IL1 blockade, HCT |
| Leukocyte Adhesion deficiency (LAD1) | *ITGB2* | Delayed separation of umbilical cord, infection, leukocytosis, enteropathy | Anti-microbial prophylaxis, HCT |
| **T and B Defects** | | | |
| Severe Combined Immunodeficiency (SCID) | *ARTEMIS, ZAP70,RAG1/2, IL2RG, ILRA7, LIG4, JACK3, ADA* | Recurrent infections, variable enteropathy and enterocolitis | HCT |
| Omenn syndrome | *IL7R* | Diffuse erythroderma, lymphadenopathy, eosinophilia, cartilage and hair hypoplasia, hepatomegaly intestinal inflammation | HCT |
| CTLA-4 deficiency | *CTLA4* | Type 1 diabetes, cytopenias, respiratory infections, enteropathy | Gammaglobulin, Abatacept, Sirolimus |
| ICOS deficiency | *ICOS* | CVID with recurrent viral and bacterial infections, splenomegaly, colitis | Gammaglobulin |
| Bruton's or X-linked agammaglobulinemia | *BTK* | Sinusitis, acute otitis media, colitis | Gammaglobulin |
| Wiskott-Aldrich syndrome | *WAS* | Thrombocytopenia, eczema, eosinophilia, colitis | HCT |

| GROUP | GENE DEFECT | CLINICAL PHENOTYPE | SPECIFIC TREATMENT |
|---|---|---|---|
| **T regulatory cells and regulatory pathway defects** | | | |
| IPEX syndrome | *FoxP3* | Type 1 diabetes, dermatitis, skin and respiratory infections, enteropathy, | Cyclosporin, Tacrolimus, Sirolimus, anti-TNF, HCT |
| IPEX-like syndrome | *STAT1, STAT3, LRBA, IL2RA,* | STAT1 and STAT3: enteropathy, severe viral and bacterial infections, and endocrinopathy.<br>LRBA: enteropathy, cytopenias, lymphadenopathy, and hepatosplenomegaly.<br>IL2RA: enteropathy, eczema, recurrent viral infections, and autoimmune anemia | JAK inhibitors, Sirolimus, HCT |
| IL-10 signaling defects | *IL-10RA, IL-10RB* | Colitis, folliculitis, perianal fistulas, B cell lymphoma, occasional arthritis | HCT |
| **Hyperinflammatory and auto inflammatory defects** | | | |
| X-linked lymphoproliferative syndrome 2 | *XIAP* | Splenomegaly, hemophagocytic lymphohistiocytosis (HLH), fistulizing enteropathy | HCT |
| NLRC4 | *NLRC4* | Infantile enterocolitis, autoinflammation | Anti-IL18 blockade |
| Mevalonate kinase deficiency | *MVK* | Episodic fevers, peritonitis, arthritis, bloody enterocolitis | Anti-IL1 blockade |
| NOD2 signaling defect | *TRIM22* | Perianal fistulizing disease, enterocolitis | |