Natural Killer Cell Deficiency: Clinical and Genetic Characterisitics

(NKD)

Manar Abdalgani, MBBS
Columbia University Irving Medical Center
09/04/2025. Bastad, Sweden

COLUMBIA | VAGELOS COLLEGE OF PHYSICIANS AND SURGEONS

Disclose

- Nothing to disclose

Goals

- Understand NK cell biology

- Define NK cell deficiency (NKD)

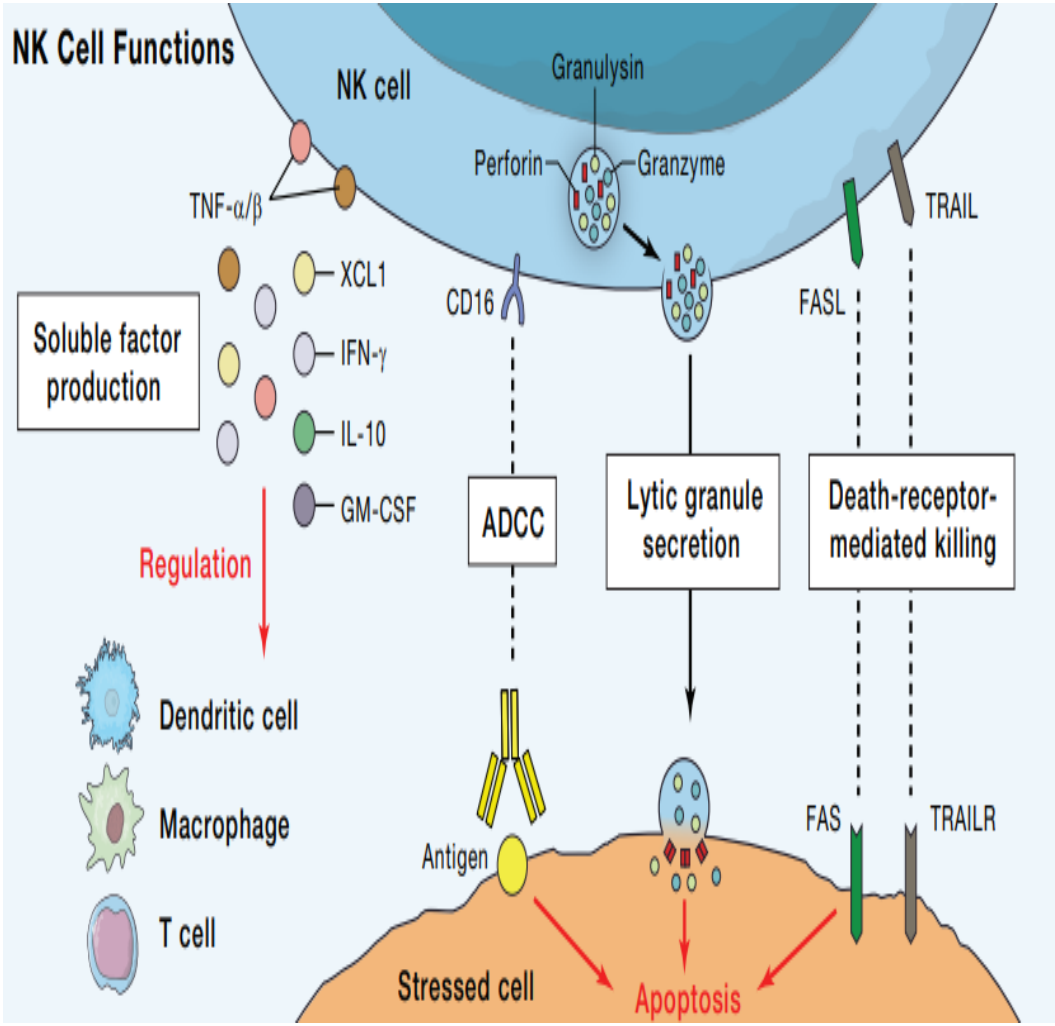
-- Explore clinical and genetic characteristics of 148 patients of Professor Jordan Orange's NEAR project.

- Diagnosis and management

- Future directions

Introduction to NK Cells

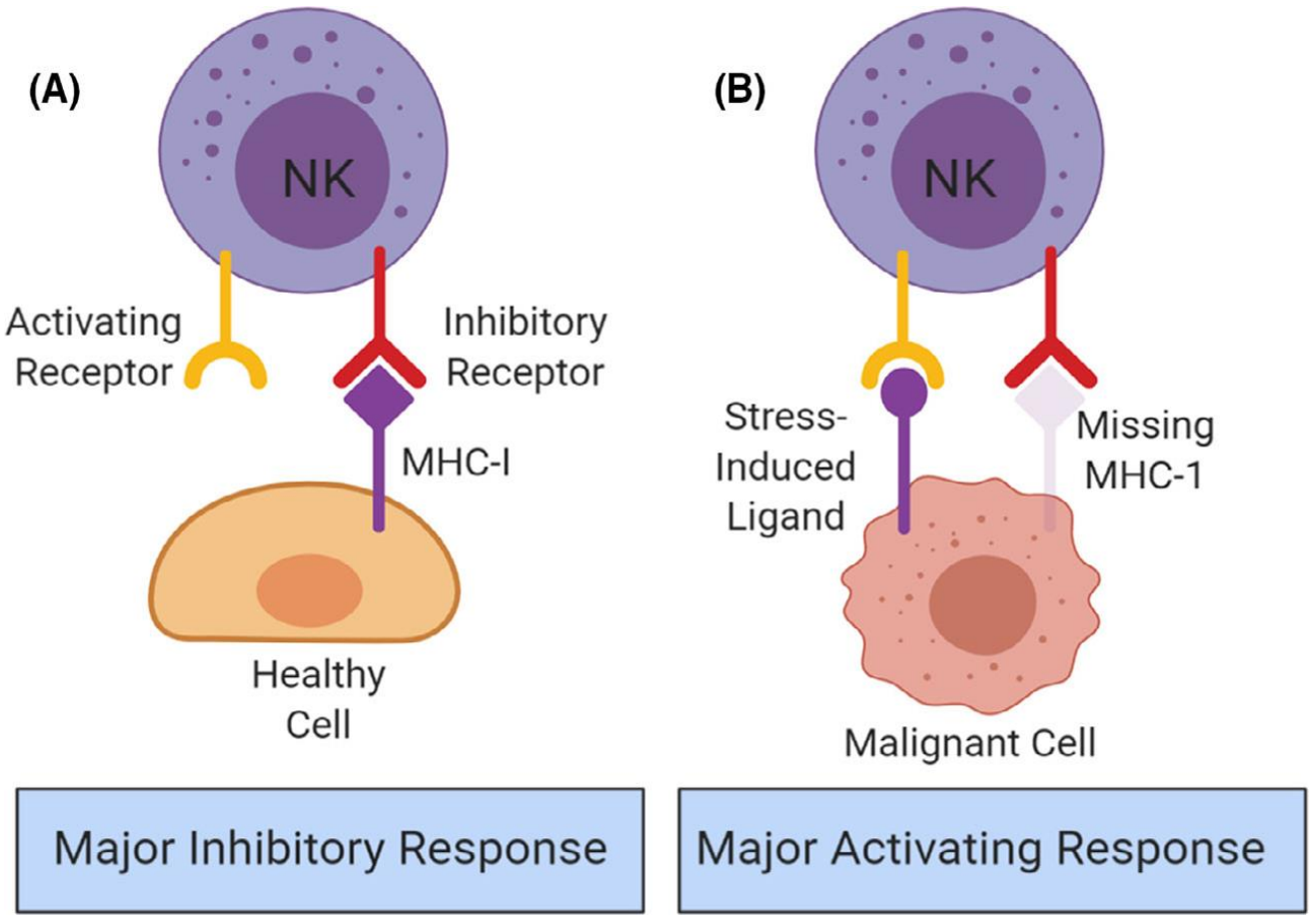
- NK cells represents 10% of the circulating lymphocytes and play a crucial role in antiviral immunity and tumor surveillance.
- NK cell role in immune surveillance
  - **Cytotoxicity**
    - Lytic granules secretions
    - ADCC
    - Death receptor mediated killing (FASL-TRAIL)
  - **Cytokine production**
    - Immune defense against intracellular pathogens
    - Pro-inflammatory and autoimmune
  - **Co-stimulation**
    - Contact dependent stimulation.



Rafei H, Daher M, Rezvani K. Br J Haematol. 2021 Apr;193(2):216-230. dPMID: 33216984

Mechanisms of NK Cell Activation

- NK cells are activated by a complex interaction between the inhibitory and activating receptors that recognize ligands on target cells.
- When activating signals dominate, NK cells trigger cytotoxicity and cytokine release against target cells.



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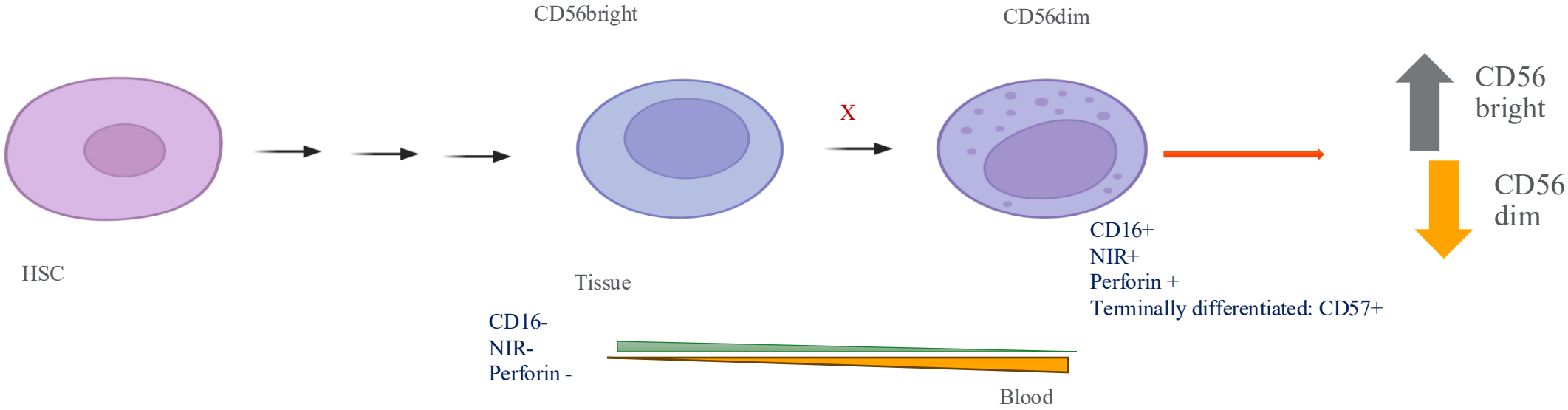
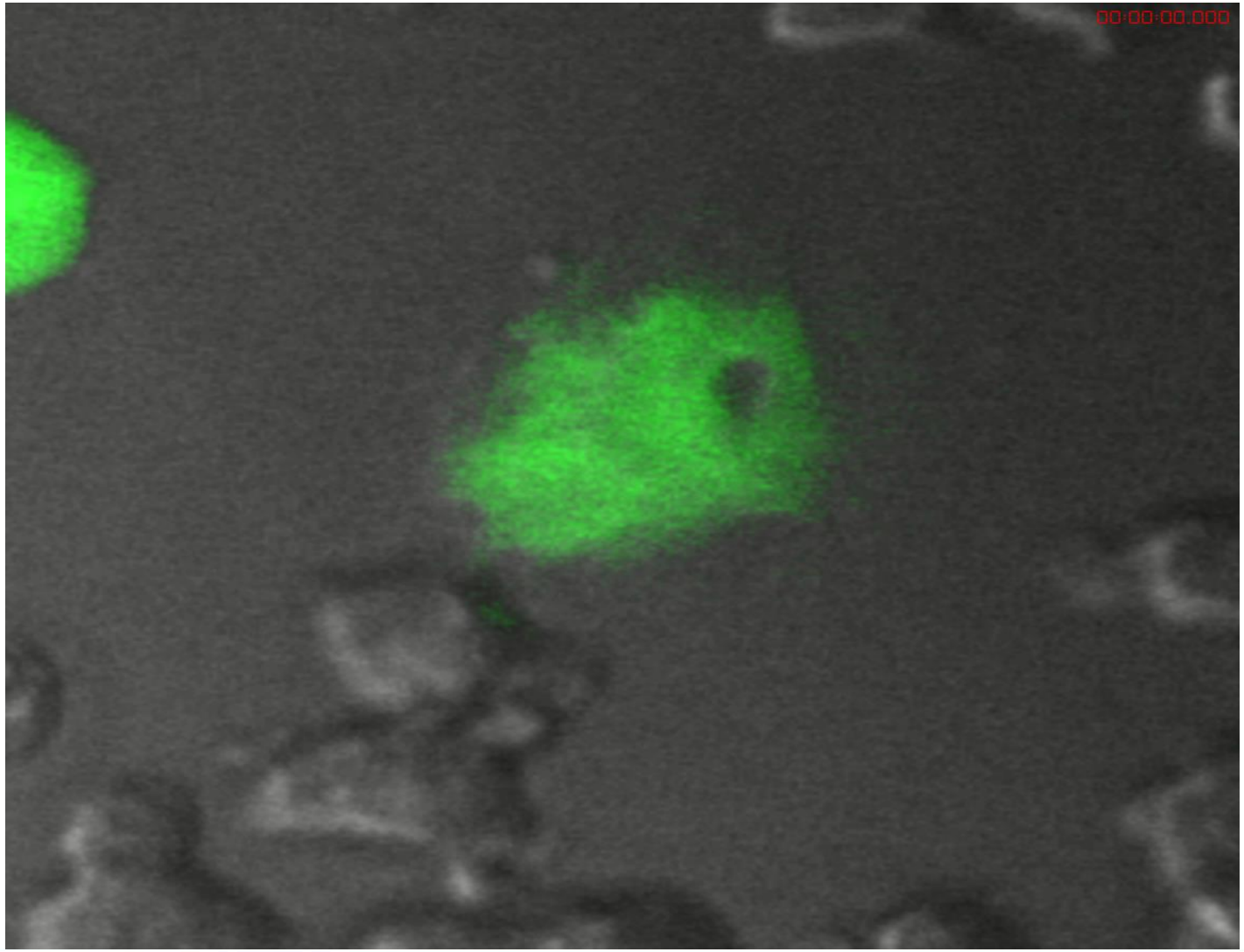
NK Cell Development – CD56bright and CD56dim



Feature	CD56^bright NK cells	CD56^dim NK cells
Receptors	Low CD16, higher adhesion molecules	High CD16, strong killer function
Function	High cytokine production (IFN-γ, TNF)	High cytotoxicity (perforin, granzymes)
Location	Lymphoid tissues, inflammation sites	Peripheral blood, spleen, bone marrow
Frequency	~10% of blood NK cells	~90% of blood NK cells

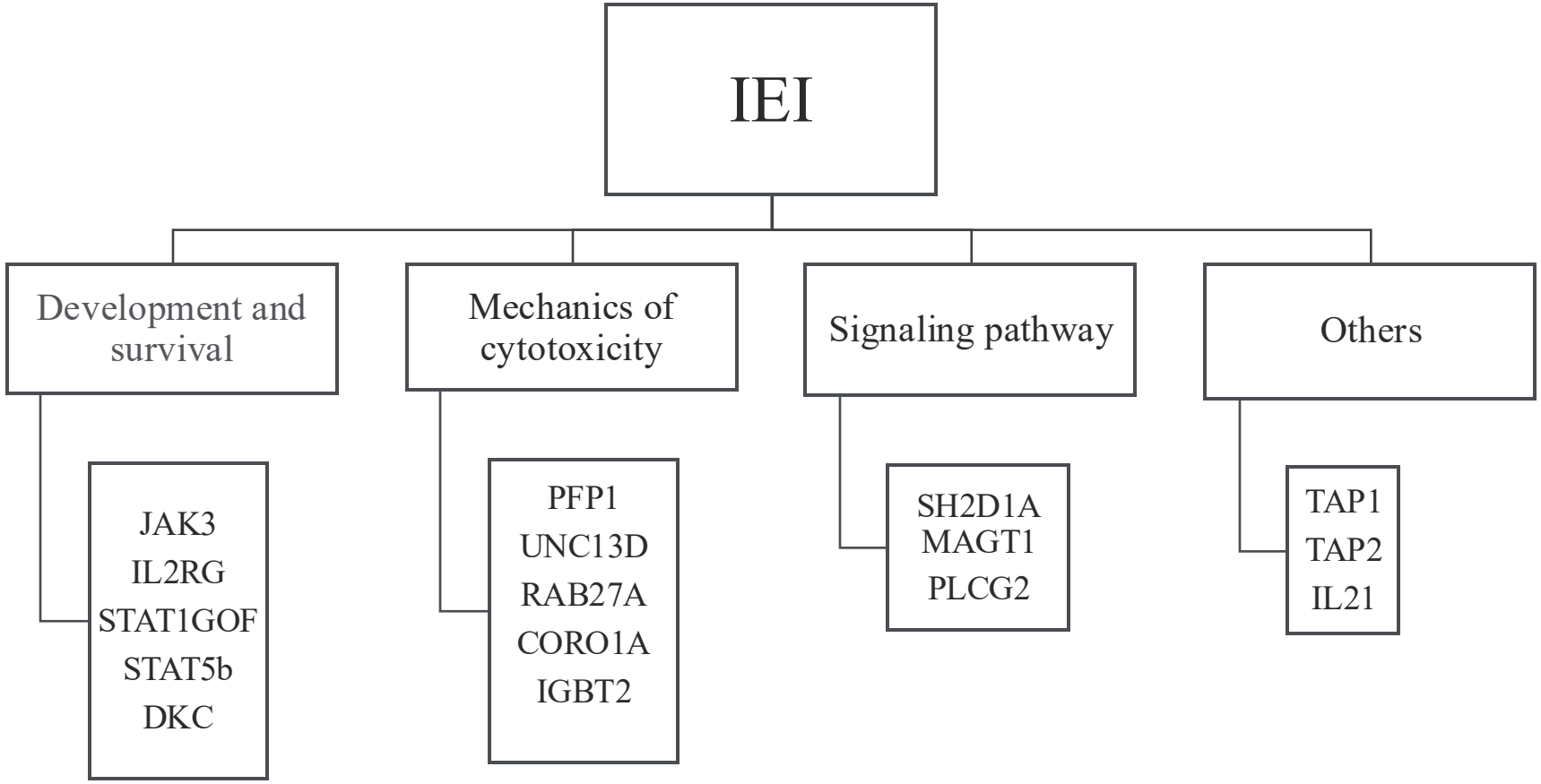
Mace EM, Gunesch JT, Dixon A, Orange JS. *Nat Commun*. 2016;7:12171. 2016 Jul 20. doi:10.1038

NK Cell Antiviral Killing



Green = Vital dye
Red = death marker

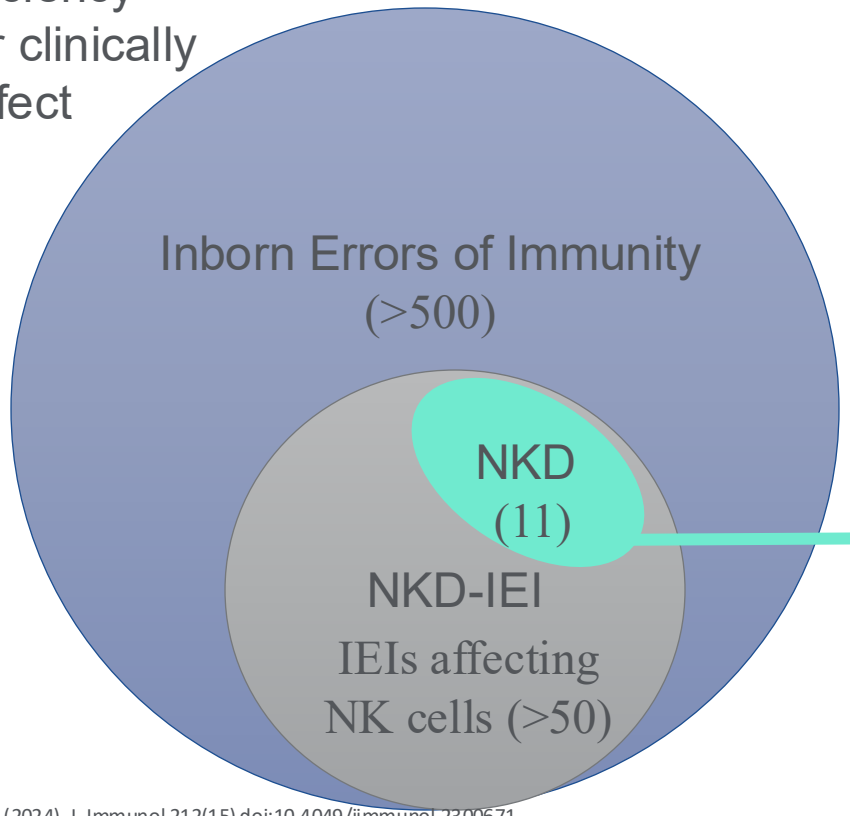
NK Cell Implication in Human Disease- NKD in IEI

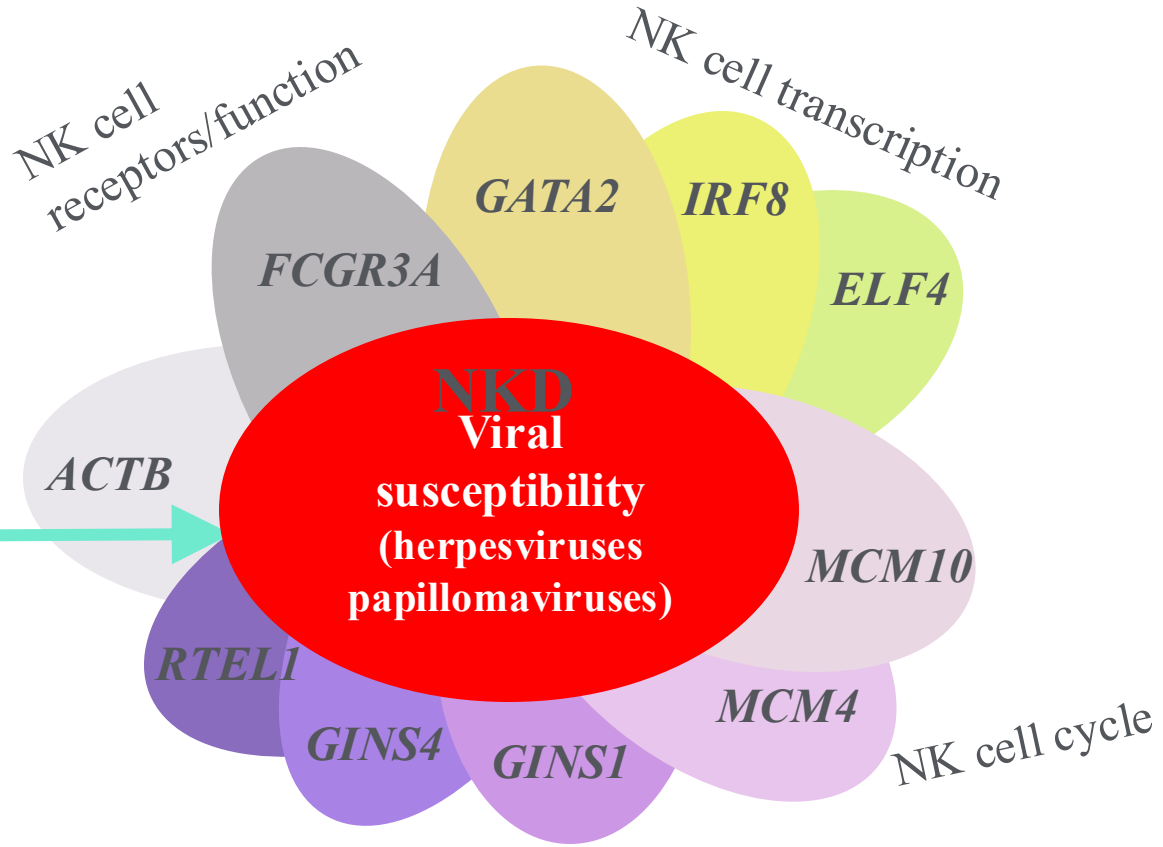


NK-IEI: NK cell defect **is part of a broader immune defect** and is **NOT** the main clinically relevant

IEI that Affect NK cells and NKD

NKD:
NK cell deficiency is the major clinically relevant defect





ACTB: Reed, A.... Orange, J.S. (2024). J. Immunol 212(15) doi:10.4049/jimmunol.2300671
ELF4: Salinas, S., . . . Orange, J. S. (2022). *JCI Insight, 7*(21). doi:10.1172/jci.insight.
FCGR3A: Grier, J. T.,. . . Orange, J. S. (2012). *J Clin Invest,* doi:10.1172/JCI64837
GATA2: Mace, E. M., . . . Orange, J. S. (2013). *Blood,* doi:10.1182/blood-2012-09-453969
GINS4: Conte, M. I., . . . Orange, J. S. (2022). *JCI Insight, 7*(21). doi:10.1172/jci.insight.154948
GINS1: Cottineau, J., . . . Jouanguy, E. (2017). *J Clin Invest,* doi:10.1172/JCI90727
IRF8: Mace, E. M.,. . . Orange, J. S. (2017). *J Clin Invest, 127*(1), doi:10.1172/JCI86276
MCM10: Mace, E. M., . . . Orange, J. S. (2020). *J Clin Invest, 130*(10), doi:10.1172/JCI134966
PLCG2: Alinger, JB... Orange, JS, French, AR (2024). J. Allergy Clin Immunol doi:10.1016/j.jaci.2023.09.002
RTEL1: Hanna, S., ... Casanova, J. L., Etzioni, A. (2015). *J Allergy Clin Immunol,* doi:10.1016/j.jaci.2015.04.021

Classical (cNKD) — Abnormal development of NK cells +/- low peripheral numbers

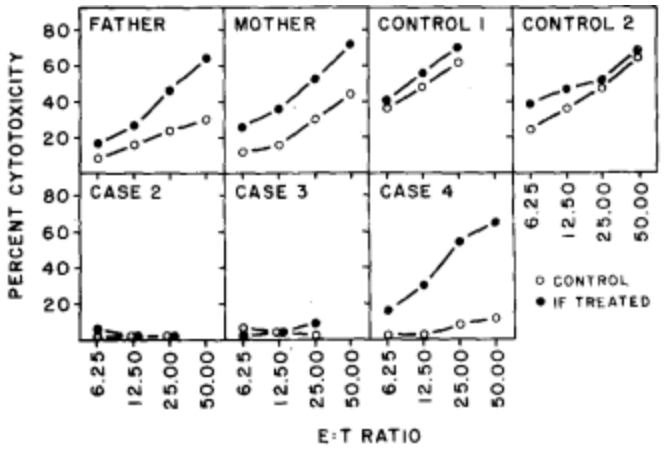
Functional (fNKD) — **Persistently abnormal cytotoxicity with normal NK cell numbers and development**

NK Cell Implication in Human Disease- Isolated NKD

A non–X-linked syndrome with susceptibility to severe Epstein-Barr virus infections

Three siblings developed severe (two) or fatal (one) infectious mononucleosis. This family differed from previously described kindreds with a susceptibility to overwhelming Epstein-Barr virus infections in that: (1) both males and females were affected; (2) they had a history of recurrent bacterial infections; (3) they produced the full spectrum of antibodies to EBV in the expected range of titers; and (4) survivors recovered completely. Two of these youths, but not their parents or an unaffected sibling with mild IM, had a deficiency of natural killer activity that did not respond to preincubation of their peripheral blood mononuclear cells with interferon. NK activity may have an important role in controlling infections with EBV.

Gary Fleisher, M.D.,*· ** Stuart Starr, M.D.,
Norman Koven, M.D., *Philadelphia, Pa.,*
Hitoshi Kamiya, M.D., *Tokyo, Japan,* **Steven D. Douglas, M.D.,*****
and Werner Henle, M.D.,**** *Philadelphia, Pa.*



SEVERE HERPESVIRUS INFECTIONS IN AN ADOLESCENT WITHOUT NATURAL KILLER CELLS

CHRISTINE A. BIRON, PH.D., KEVIN S. BYRON, AND JOHN L. SULLIVAN, M.D.

NATURAL killer cells are a population of T-cell-receptor–negative (CD3−) lymphocytes that spontaneously mediate the lysis of sensitive target cells. Natural killer cells are similar morphologically to large granular lymphocytes.[1] They have the CD16 receptor for Fc portions of immunoglobulin molecules,[2] and they express a member of the complement receptor–lymphocyte adhesion family of molecules, CD11b,[3] on their cell surfaces, as well as the determinant NKH-1, which is specific to large granular lymphocytes.[4] Although endogenous killer cells isolated from normal persons lyse only a limited range of highly sensitive target cells, both interferon and interleukin-2 can activate killer cells to lyse a broad range of target cells, including those infected with certain viruses.[5-7]

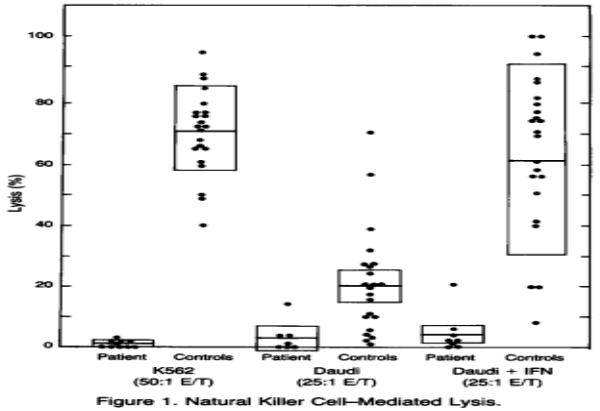


Figure 1. Natural Killer Cell–Mediated Lysis.

Fleisher G, …Henle W. *J Pediatr*. 1982;100(5):727-730
Biron CA, Byron KS, Sullivan JL. *N Engl J Med*. 1989;320(26):1731-1735

NEAR (NK Cell Evaluation And Research)

NEAR program

- Started in 2006
- First program to study the phenotypes of

of NKD established by Professor Jordan Orange

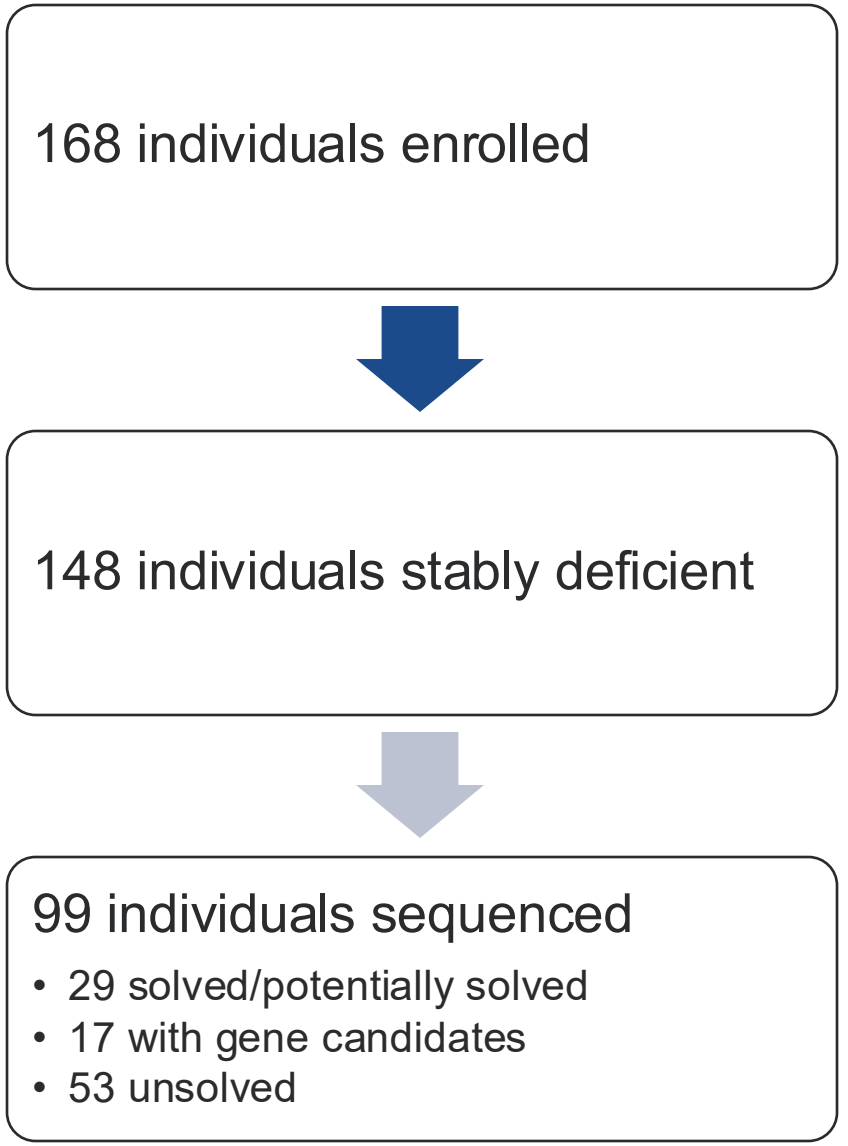
Inclusion criteria

- Severe or recurrent herpesviral infection
- And/or stably abnormal NK cell laboratory value
- Lack of other well characterized genetic or phenotypic IEI

Data analysis

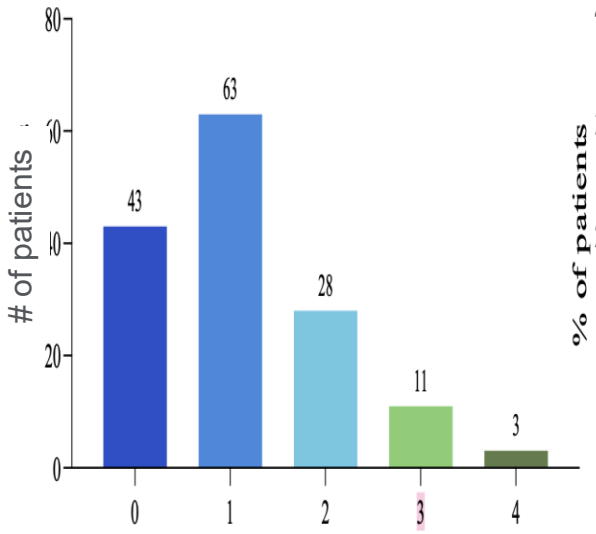
Started in 3/2023

The Clinical, Immunologic, and Genetic Characteristics of 148 Patients with Natural Killer Cell Deficiency

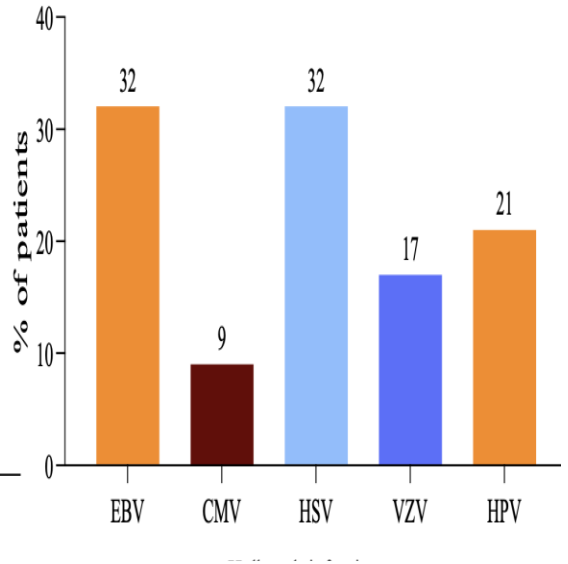


Abdalgani M,…Orange JS, et al.. *J Allergy Clin Immunol*. 2025;155(5):1623-1634.

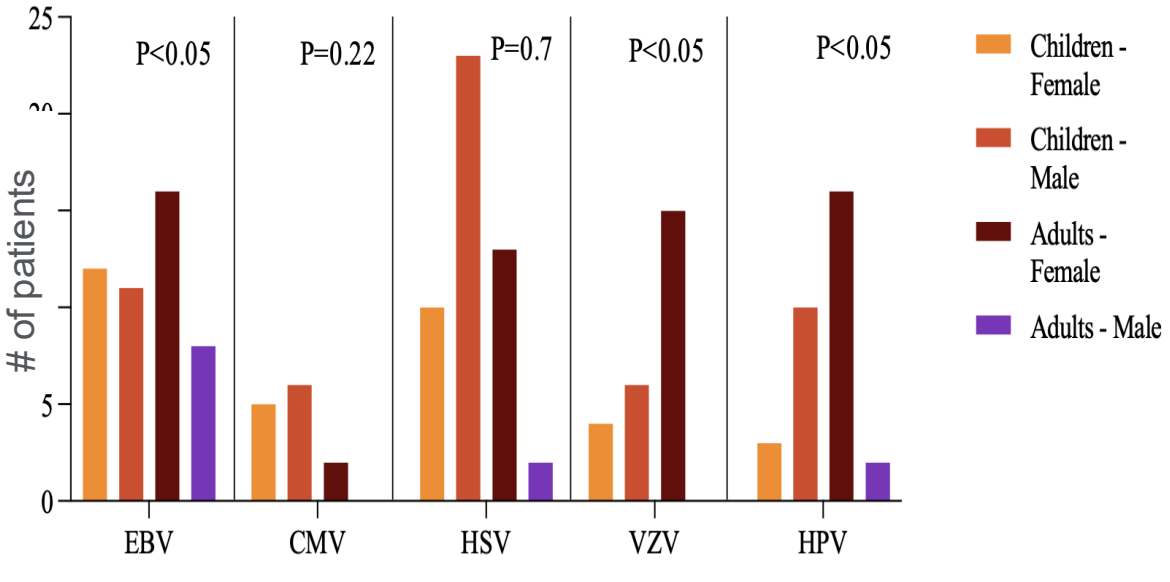
Increased Herpetic and Papilloma Infections/Diseases Among Patients with NKD (n=148)



# of Hallmark infections



Hallmark infection



Hallmark infection

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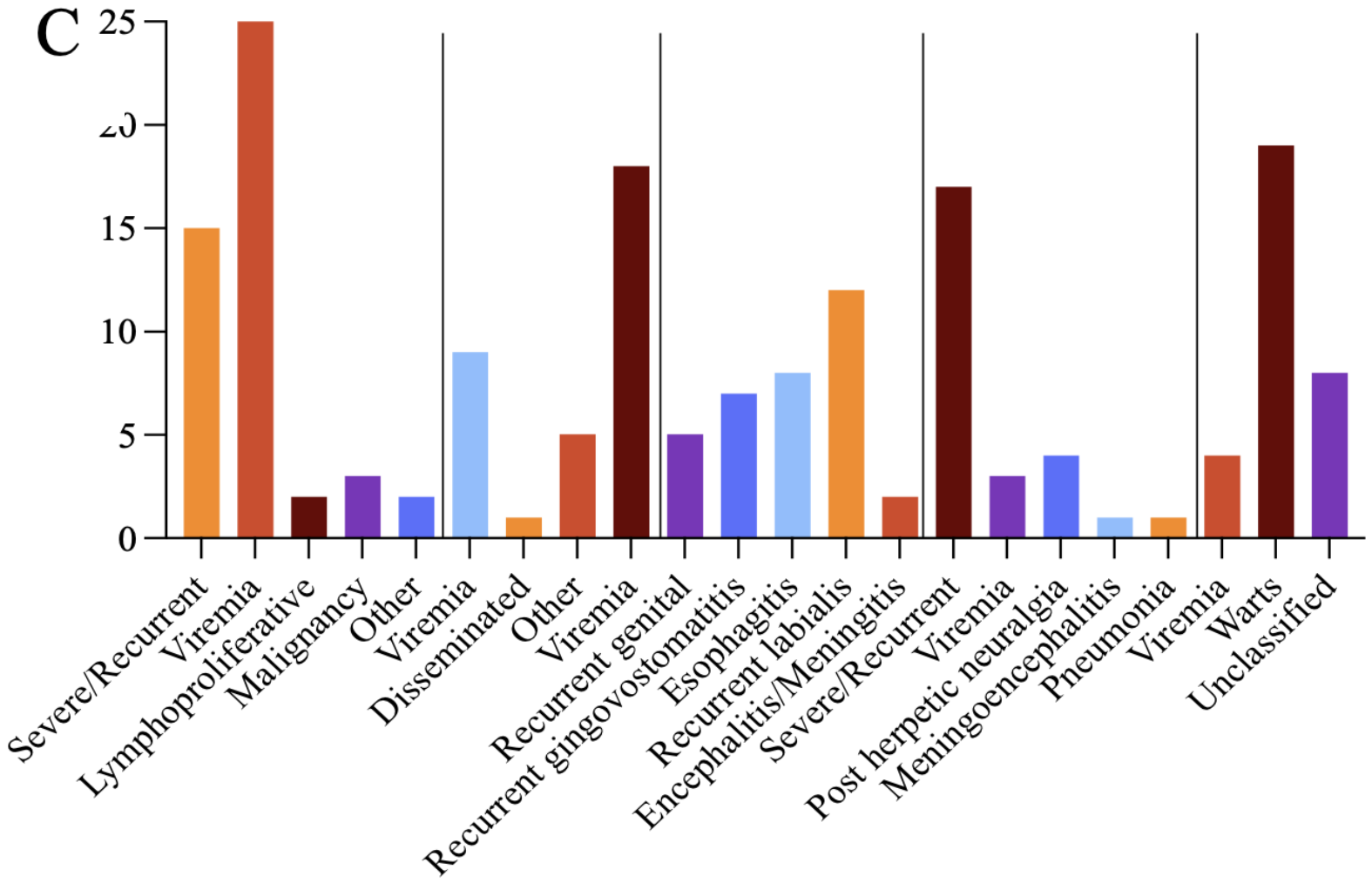
Type of Herpetic infections Among Patient Cohort

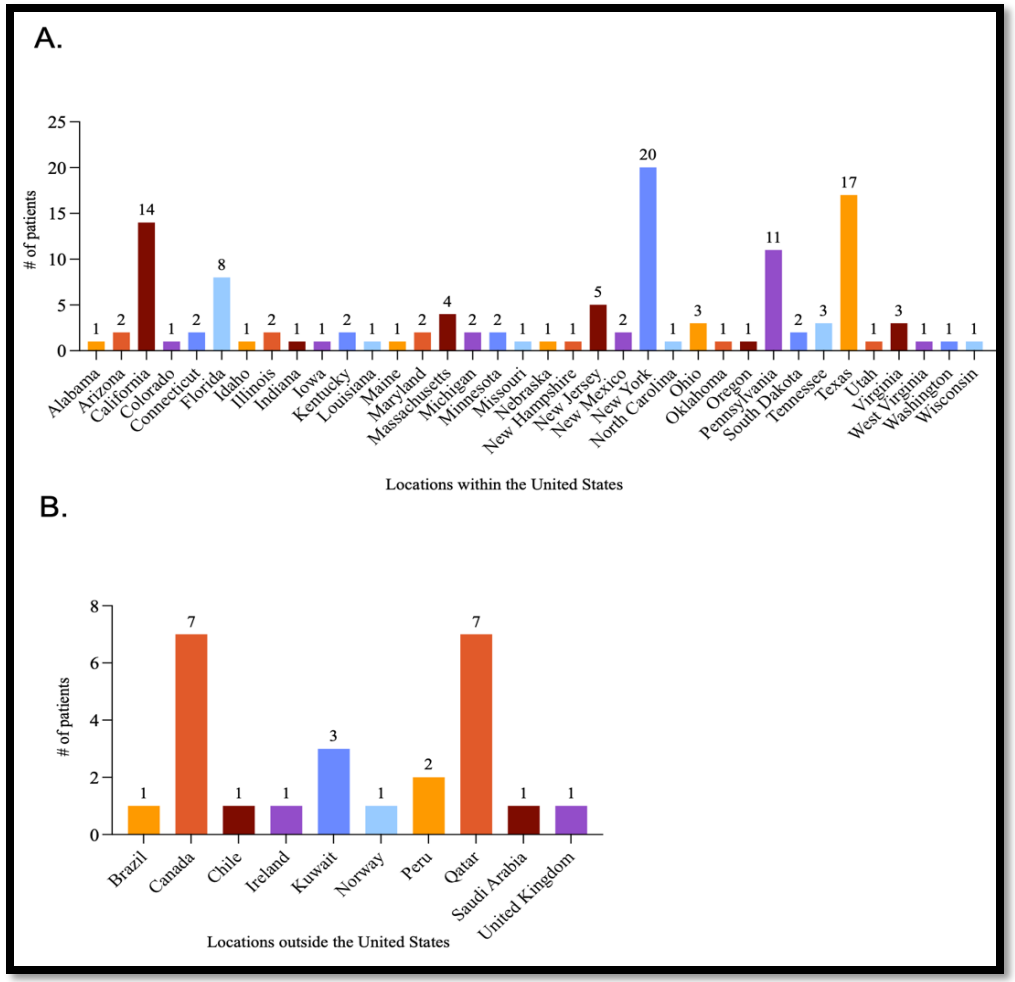


Abdalgani M,…Orange JS, et al.. *J Allergy Clin Immunol*. 2025;155(5):1623-1634

Patient's Demographics, Characteristics and Locations at Time of Enrollment

Table I: Patient demographics and characteristics at enrollment

	N (%) of total patients n=148 (%)	Female children n=38 (%)	Male children n=59 (%)	Female adults n=41 (%)	Male adults n=10 (%)
Age, median (range), y	13 (0-76)	9 (0 -17)	8 (0 -17)	36 (18-76)	33 (18-76)
0-3	28 (19)	9 (24)	18 (31)	0	0
4-17	69 (47)	29 (76)	41 (69)	0	0
18-49	41 (28)	0	0	34 (83)	7 (70)
>50	10 (7)	0	0	7 (17)	3 (30)
Race/Ethnicity					
Non-Hispanic White	79 (53)	19 (50)	30 (51)	21 (52)	8 (80)
Non-Hispanic Black	1 (1)	0	1 (2)	0	0
Non-Hispanic Asian	3 (2)	3 (8)	0	0	0
Non-Hispanic Other	14 (9)	1 (3)	6 (10)	5 (12)	0
Hispanic	11 (7)	3 (8)	5 (8)	1 (2)	0
Patient locations					
USA	123 (83)	27 (71)	45 (76)	41	10
Outside USA	25 (17)	11 (29)	14 (24)	0	0
Referral status					
Self-referred	9 (6)	1 (2)	1 (2)	5 (12)	2 (20)
Health care provider	139 (94)	37 (98)	58 (98)	36 (87)	8 (80)
Family history					
Consanguinity	8 (5)	4 (11)	3 (5)	1 (2)	0
Adopted	2 (1)	1 (3)	1 (2)	0	0
Immunodeficiency	8 (5)	2 (5)	6 (10)	0	0
Early Malignancy	24 (16)	3 (8)	5 (8)	13 (32)	3 (30)
Autoimmune disease	22 (15)	6 (16)	7 (12)	8 (19)	1 (11)
Hallmark infection	16 (11)	2 (5)	9 (15)	4 (10)	1 (11)
Outcome					
Alive	142 (96)	35 (92)	58 (98)	41	8 (80)
Deceased	6 (4)	3 (8)	1 (2)	0	2 (20)



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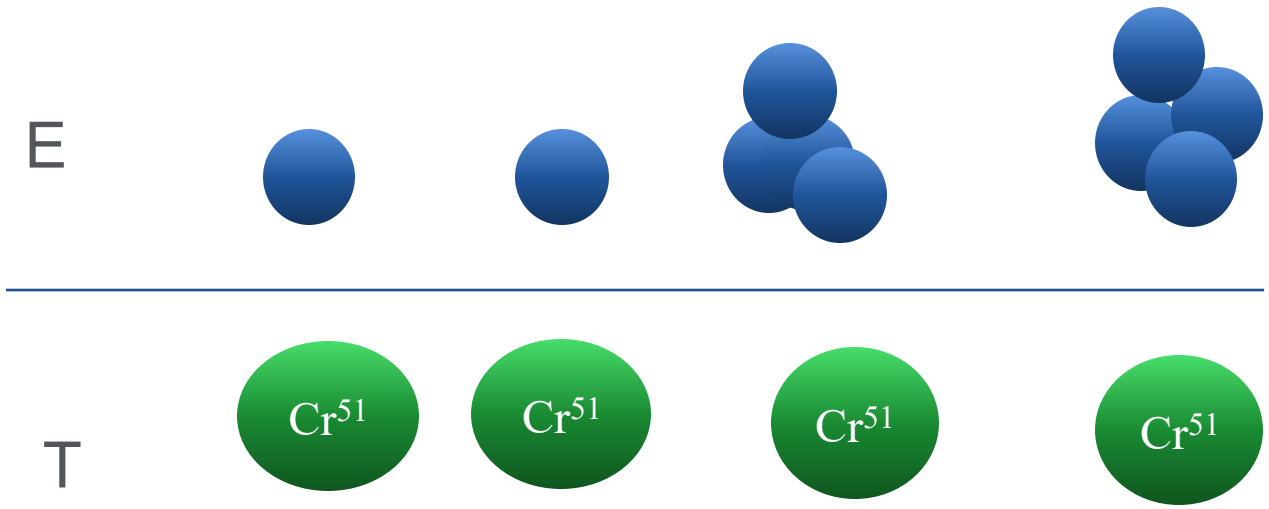
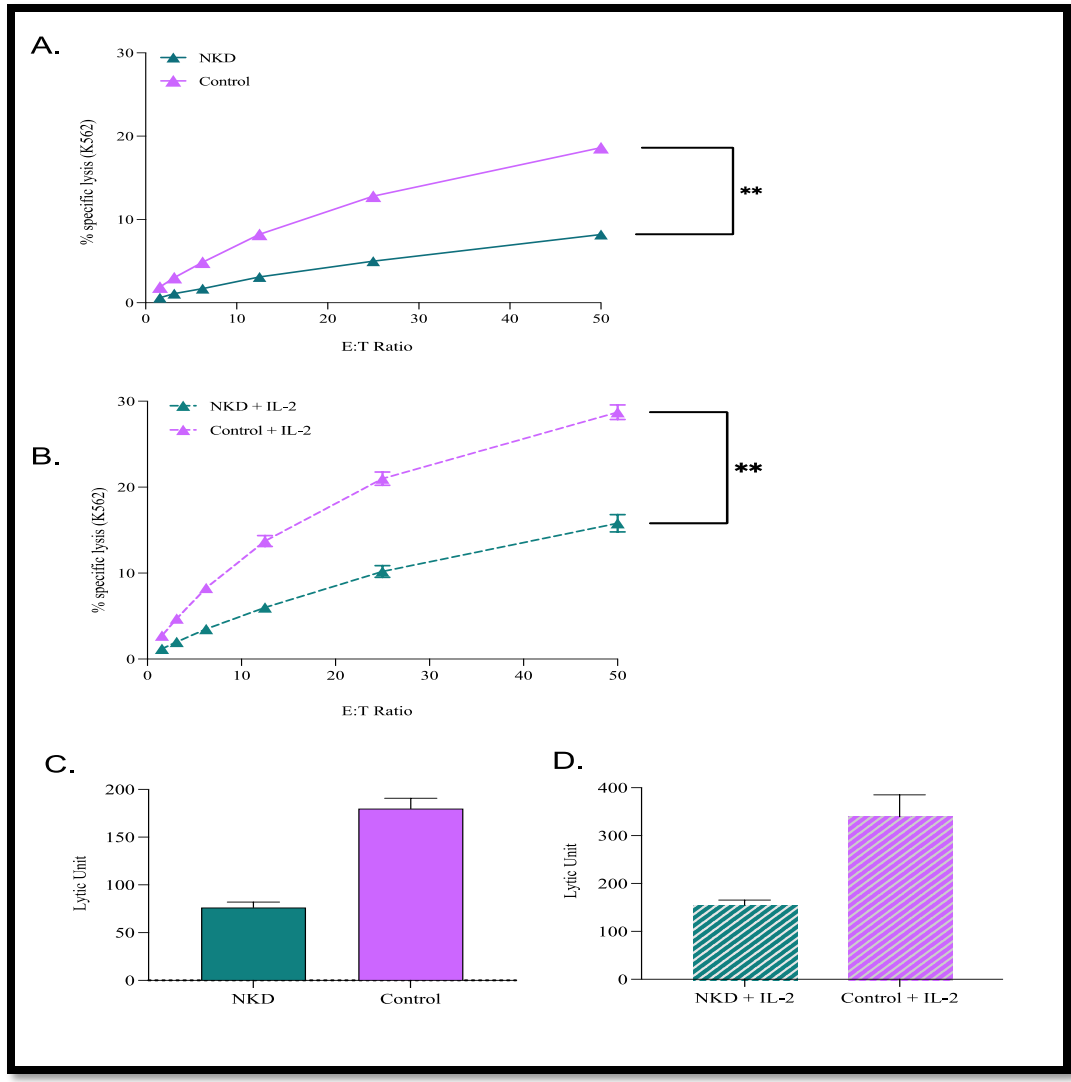
Decreased Cytotoxicty Not Rescued by IL-2 Stimulation in NKD Patients Compared to Controls



K652
erythroleukemic cells



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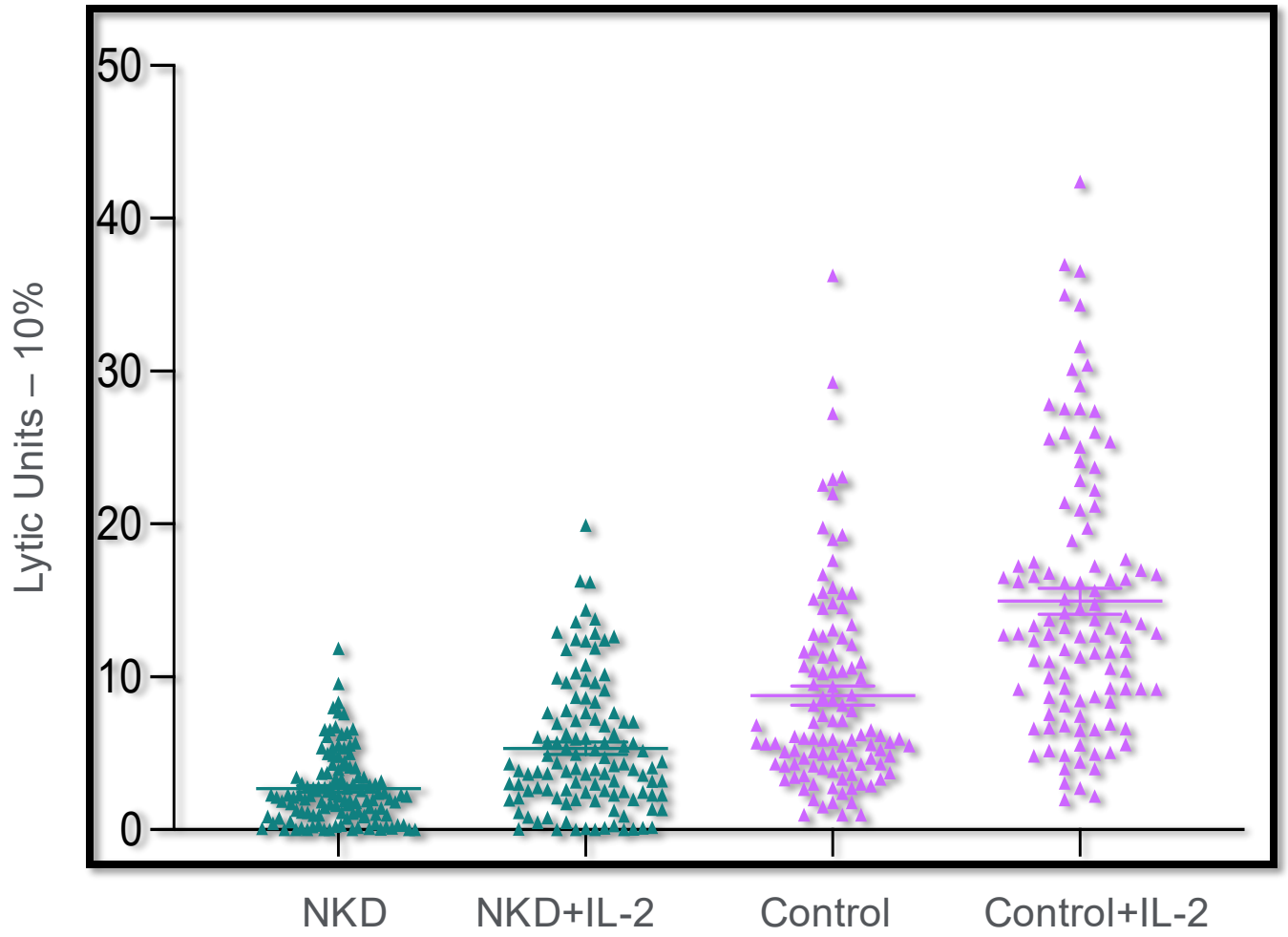
Decreased Cytotoxicty Not Rescued by IL-2 Stimulation in NKD Patients Compared to Controls.

Lytic unit (LU) refers to the number of natural killer cells required to lyse or kill 10% of target cells in a cytotoxicity assay, typically 10%



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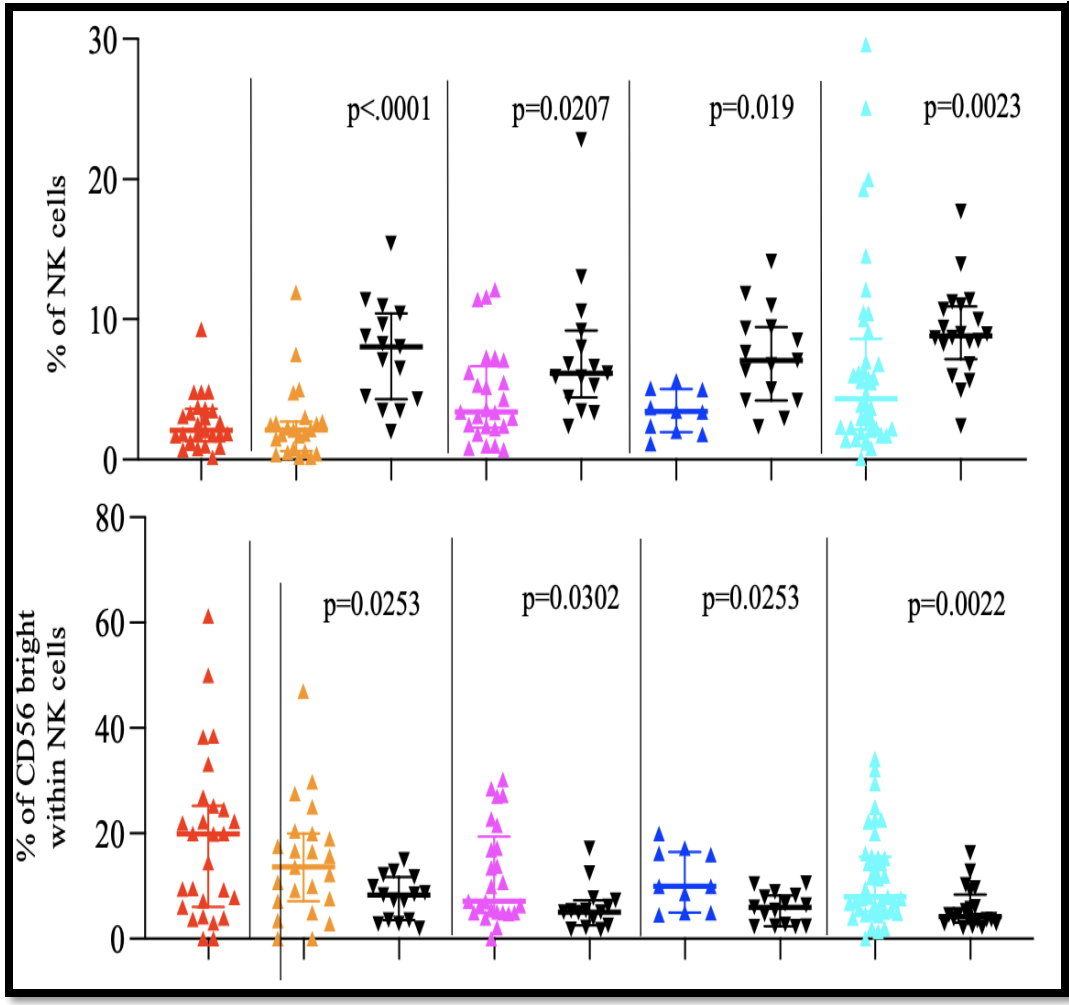
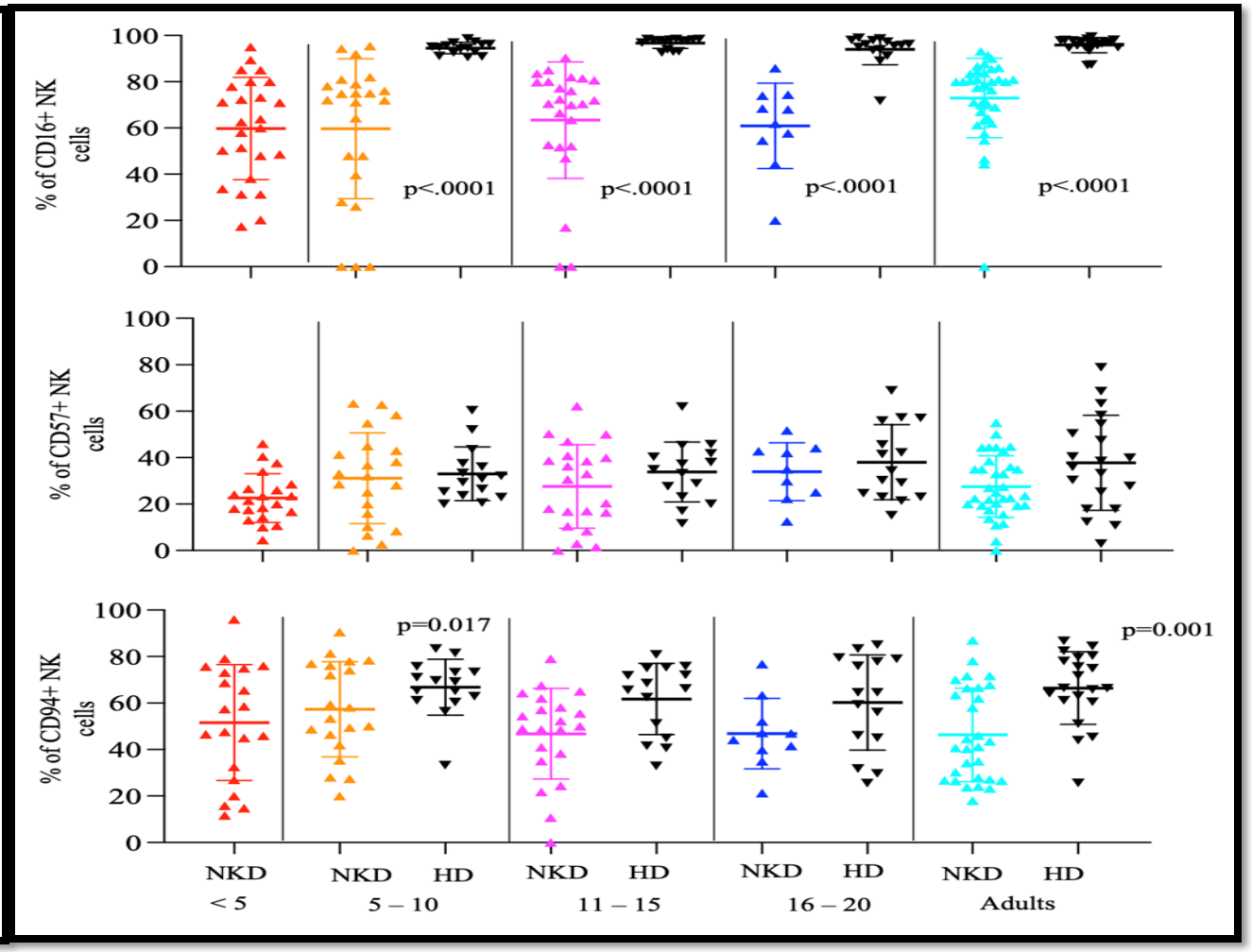
Decreased Percentages and Abnormal Development of NK Cells in NKD Patients Compared to Controls (n=125)





cNKD: 30% with NK%<2%, +15% CD56bright >20%= 45%

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Infectious, Inflammatory and Autoimmune Complications Among Patients (n=148)

Table II: Infectious, autoimmune, and inflammatory complications

	Adults n=51(%)	Children n=97(%)	Relative risk	P-value
Recurrent URTI	12 (24)	31 (32)	0.736	0.38
Recurrent pneumonia	17 (33)	27 (28)	1.13	0.61
Recurrent sinusitis	22 (43)	26 (27)	1.61	0.067
Recurrent otitis media	3 (6)	19 (20)	0.3	0.029*
Bronchiectasis	0	3 (3)	0	N/A
Skin infections/soft tissue abscesses	16 (31)	36 (37)	0.845	0.61
Recurrent candidiasis	6 (12)	12 (12)	0.951	1
Gastrointestinal infections	15 (29)	34 (35)	0.839	0.61
Hepatitis	1 (2)	4 (4)	0.26	0.35
Molluscum	1 (2)	7 (7)	0.272	0.26
HHV-6	1 (2)	1 (1)	1.9	1
Myocarditis	1 (2)	2 (2)	0.521	1
Cytopenia	10 (20)	27 (28)	0.704	0.37
Thyroid disease	10 (20)	2 (2)	9.51	0.0004*
Inflammatory bowel disease	1 (2)	4 (4)	0.26	0.35
HLH	0	5 (5)	N/A	N/A
Malignancy	4 (8)	5 (5)	1.52	0.5
Neurologic disease	12 (24)	13 (13)	1.76	0.18
Hepatosplenomegaly	0	15 (15)	N/A	N/A

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Prevalence of Malignancy Among Patients with NKD (n=148)

Age at diagnosis (yrs)	Biological sex	Malignancy	Genetic diagnosis	Outcome
2	M	Neuroblastoma	N/A	Remission
6	F	Non-Hodgkin's lymphoma (EBV+)	Yes	Deceased
29	M	Hodgkin's lymphoma (EBV+)	Yes	Deceased
48	F	Hürthle cell carcinoma	N/A	Remission
13	M	Non-Hodgkin's lymphoma	N/A	Remission
18	F	Lymphoma	N/A	Resmission
12	F	Small muscle tumor (EBV+)	N/A	Resmission
15	F	B cell and Burkitt's lymphoma	N/A	Remission
31	F	Vaginal squamosa cell sarcoma	N/A	Remission

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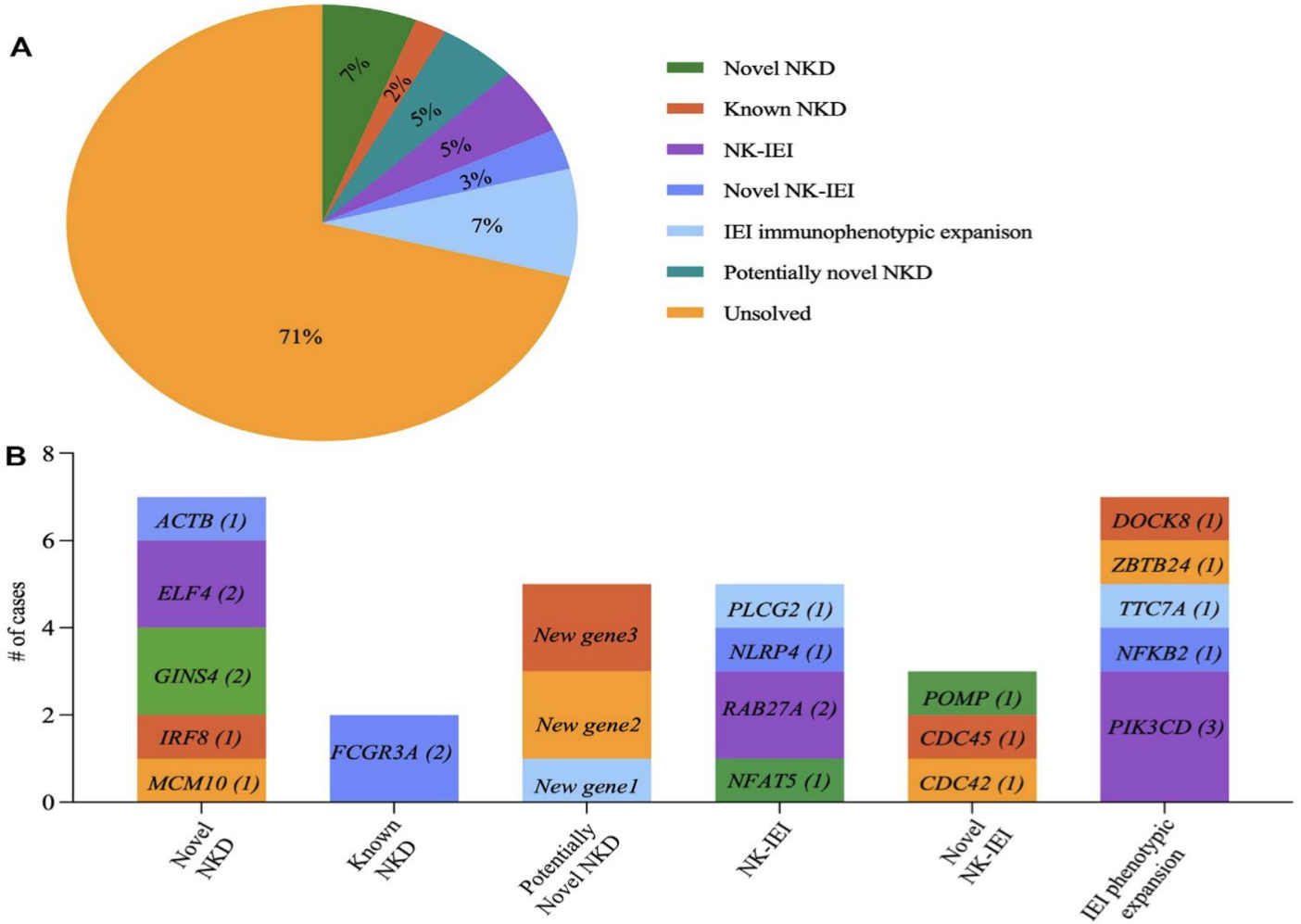
Genetic Diagnostic Yield Among 99 patients with NKD



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Prevalence of Death Among Patients with NKD (n=148)

Table E7: Death prevalence amongst 148 patients with NKD

Age at death (yr)	Biological sex	Genetic diagnosis	Cause of death
2	Male	*MCM10*	Disseminated CMV disease
30	Male	*ACTB*	EBV+ Hodgkin lymphoma
1	Female	*CDC42*	Secondary HLH after transplant
7	Female	*NLRP4*	B-large cell non-Hodgkin lymphoma
9	Female	N/A	Sepsis
13	Female	*NFKB2*	Disseminated CMV disease
74	Male	*ELF4*	Angioimmunoblastic T cell lymphoma

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Low NK <1%, Genetic Diagnosis, CMV Viremia and Autoimmune/Inflammatory Complications Are Associated with Severe Outcome

	Severe outcome risk with categorical factor present (n = 19)	Severe outcome risk with categorical factor absent (n = 129)	RR with factor present	*P* value
Age at enrollment, median (IQR)	12 (7.5-17)	13 (5-30)	—	ns
Biological sex, female, n/N (%)	12/80 (15)	7/68 (10.3)	1.46	ns
Biological sex, male, n/N (%)	7/80 (8.8)	12/68 (17.6)	0.5	ns
History of EBV, n/N (%)	8/47 (17)	11/101 (10.9)	1.56	ns
History of HSV, n/N (%)	5/48 (10.4)	14/100 (14)	0.74	ns
History of CMV, n/N (%)	6/13 (46.2)	13/135 (9.6)	4.79	.002
History of VZV, n/N (%)	1/25 (4)	18/123 (14.6)	0.27	ns
History of HPV, n/N (%)	5/31 (16.1)	14/117 (12)	1.35	ns
fNKD, n/N (%)	8/91 (8.8)	11/57 (19.3)	0.46	.110
cNKD, n/N (%)	11/57 (19.3)	8/91 (8.8)	2.2	.110
<4% NK cells, n/N (%)	13/78 (16.7)	6/70 (8.6)	1.94	ns
<2% NK cells, n/N (%)	8/37 (21.6)	11/111 (9.9)	2.18	.087
<1% NK cells, n/N (%)	7/17 (41.2)	12/131 (9.2)	4.5	.002
>20% CD56 bright cells, n/N (%)	5/34 (14.7)	14/114 (12.3)	1.2	ns
Solved, n/N (%)	10/29 (34.5)	9/119 (7.6)	4.56	.0005
Unsolved, n/N (%)	6/70 (8.6)	13/78 (16.7)	0.51	ns
Chronic EBV viremia, n/N (%)	3/25 (12)	16/123 (13)	0.92	ns
EBV lymphoproliferative, n/N (%)	1/2 (50)	18/146 (12.3)	4.06	ns
EBV malignancy, n/N (%)	3/3 (100)	16/145 (11)	9.06	ns
EBV HLH, n/N (%)	1/1 (100)	18/147 (12.2)	8.17	ns
EBV dacryoadenitis, n/N (%)	0/1 (0)	19/147 (12.9)	0	ns
HSV viremia, n/N (%)	3/18 (16.7)	16/130 (12.3)	1.35	ns
Recurrent herpetic gingivostomatitis, n/N (%)	0/7 (0)	19/141 (13.5)	0	ns
HSV esophagitis and other disseminated infection, n/N (%)	1/8 (12.5)	18/140 (12.9)	0.97	ns
HSV encephalitis and meningitis, n/N (%)	0/2 (0)	19/146 (13)	0	ns
CMV viremia, n/N (%)	5/9 (55.6)	14/139 (10.1)	5.52	.0019
Congenital CMV, n/N (%)	0/2 (0)	19/146 (13)	0	ns
Disseminated CMV disease, n/N (%)	0/1 (0)	19/147 (12.9)	0	ns
VZV viremia, n/N (%)	0/3 (0)	19/145 (13.1)	0	ns
Varicella pneumonia, n/N (%)	0/1 (0)	19/147 (12.9)	0	ns
Varicella meningoencephalitis, n/N (%)	0/1 (0)	19/147 (12.9)	0	ns
Post herpetic neuralgia, n/N (%)	0/1 (0)	19/147 (12.9)	0	ns
HPV viremia, n/N (%)	2/4 (50)	17/144 (11.8)	4.24	ns
Autoimmune and autoinflammatory, n/N (%)	13/49 (26.5)	6/99 (6.1)	4.38	.0012

History of CMV

NK cell count <1%

Solved

CMV viremia

Autoimmune and autoinflammatory

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Clinical Vignette- The expanding phenotypic spectrum of NKD genes

History:

A male patient with **childhood-onset common variable immunodeficiency (CVID)** presented with recurrent pneumonia, bronchiectasis, and **hypogammaglobulinemia**. He was initiated on **intravenous immunoglobulin (IVIG)** replacement therapy. Despite this, he developed **refractory thrombocytopenia**, which required **splenectomy** and subsequent **sirolimus** therapy.

During follow-up, he experienced **high-grade Epstein–Barr virus (EBV) viremia and lymphoproliferative disease**, necessitating **monthly rituximab infusions**. Three years later, the patient developed **fulminant hepatic failure**. A **liver biopsy** demonstrated **sclerosing cholangitis with biliopathy**. Testing confirmed **cryptosporidium infection**, which required nearly one year of **nitazoxanide** therapy for clearance.

The etiology remained uncertain; immune dysregulation, post-splenectomy complication, and cryptosporidium infection.

Family History:

Non-contributory.

Cont'ed

- Persistent absence of B cells Post Rituximab
- $CD3^+$ T cells elevated, with marked $CD4^+$ T cell predominance.
- $CD8^+$ T cells persistently low, resulting in a chronically elevated CD4/CD8 ratio (6–9).
- NK cells fluctuating, with intermittent relative expansion (up to 408/μL) but often low-normal. NK function was abnormal
- Immunoglobulins: IgA low (80 IU/mL), IgM undetectable (<5), IgG maintained on IVIG (~1684).

Genetics:

- IRF8 c.1279dupT (p.Ter427Leuext*42), heterozygous, de novo, located in exon 9/9.
- Variant causes a frameshift stop-loss
- Absent from population databases, supporting pathogenicity.
- IRF8 is critical for monocyte/dendritic cell development and B-cell support. This variant expands the phenotypic spectrum of heterozygous IRF8 deficiency beyond classical mycobacterial susceptibility to include combined immunodeficiency, autoimmunity, viral susceptibility, and hepatobiliary disease.

Question to Immunology?

- Is IRF8 a disease-causing variant?
- Should we proceed with liver transplant, BMT or both?
- If both, which one should be done first?

Phenotypic Diversity in IRF8 Deficiency

IRF8 AR (homozygous K108E)

- Severe phenotype with disseminated BCG, cachexia, candidiasis; absent monocytes/DCs, preserved B/NK counts.
- Profound functional defect: no IL-12, poor IFN-γ/TNF-α/IL-10/IL-6 → defective myeloid/DC response.
- Pathology shows myeloid hyperplasia, granulomata with AFB; AR inheritance.

IRF8 AD (heterozygous)

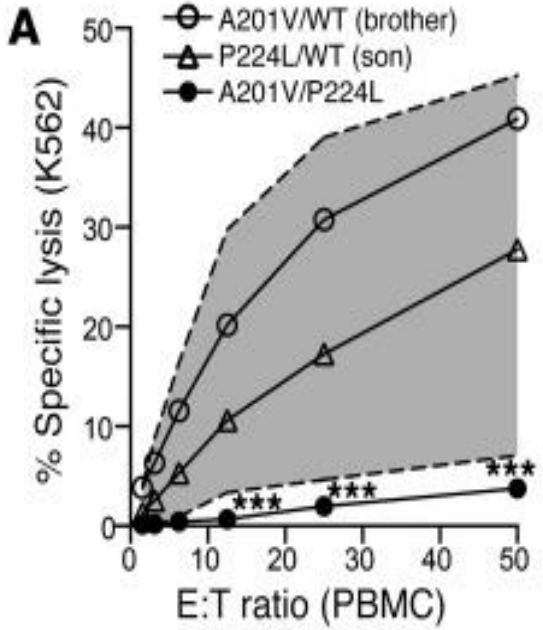
- AD form is milder, with selective $CD1c^+$ DC loss, intact NK compartment, and limited mycobacterial susceptibility, not the broad, profound DC/myeloid dysfunction seen in AR disease.

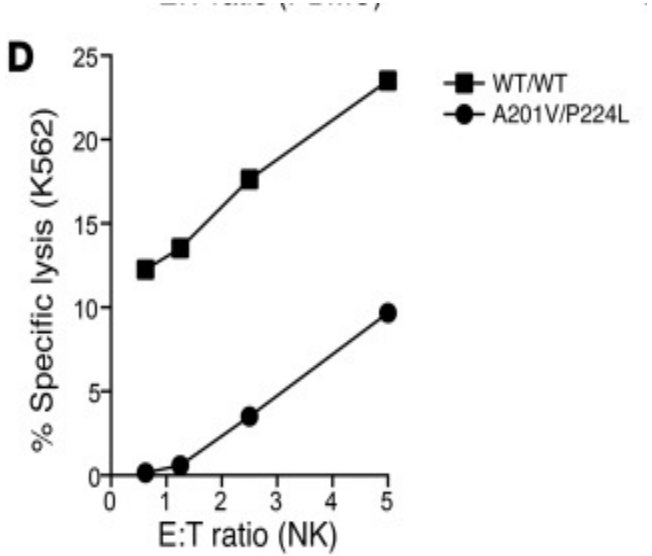
AR IRF8 associated with classic NKD

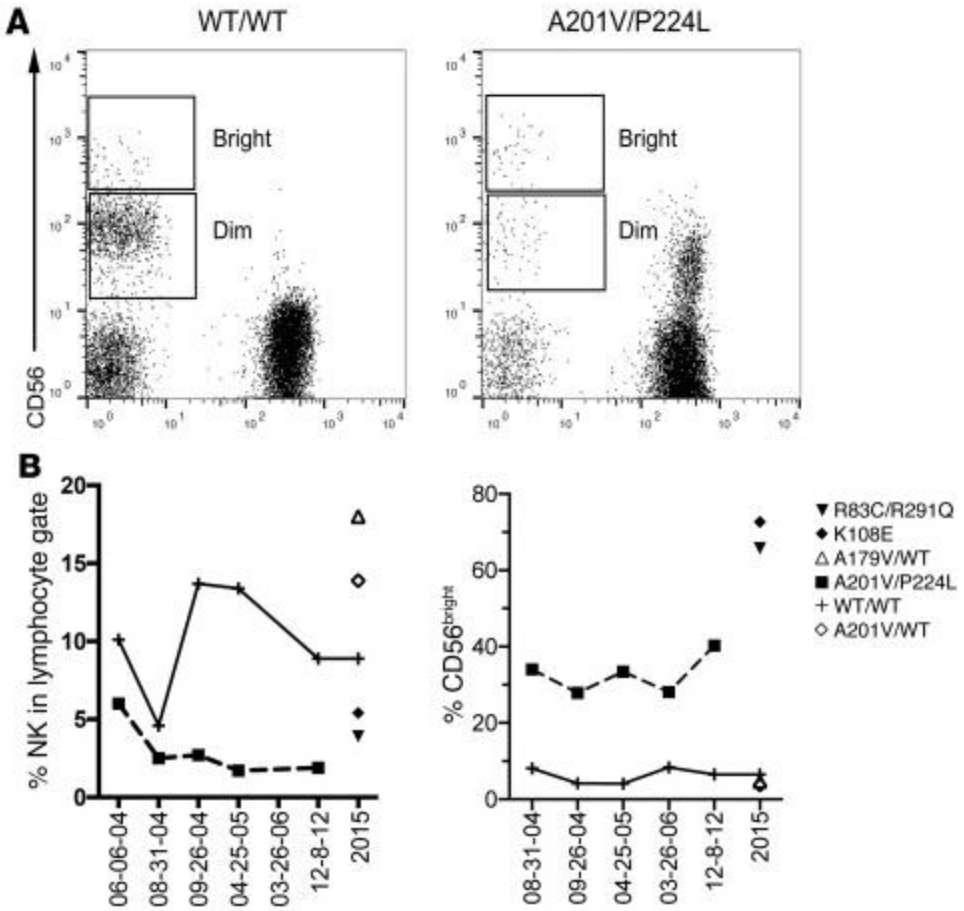
- **Clinical features**
  - Recurrent sinusitis, chronic mucosal disease, viral respiratory infections
  - EBV illness in affected siblings occurred in different calendar years
  - Lymphadenopathy & bronchiectasis in some siblings
  - Proband: no bronchiectasis or lymphadenopathy
- **Family history**
  - Proband:
    - Childhood sinopulmonary infections
    - Severe EBV mononucleosis at 22 yrs → prolonged hospitalization
  - Brother: died age 16 yrs → multiorgan failure from severe EBV mononucleosis
  - Sister: died age 38 yrs → progressive pulmonary disease; severe EBV at 17 yrs
  - Brother: EBV mononucleosis at 21 yrs, typical course, no complications
  - Parents non-consanguineous
- **Immunologic findings**
  - Normal T- and B-cell counts
  - Normal immunoglobulin levels and function

Mace et al, J Clin Invest. 2017 Jan 3; 127(1): 306–320

Decreased NK cell counts and Terminal Differentiation







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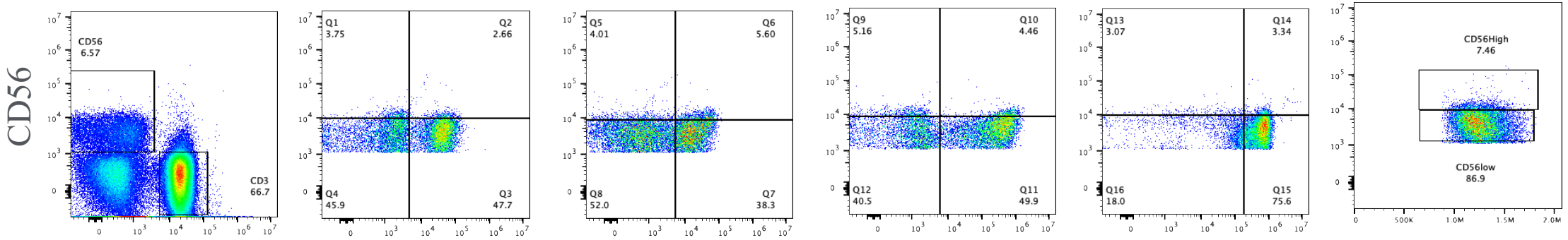
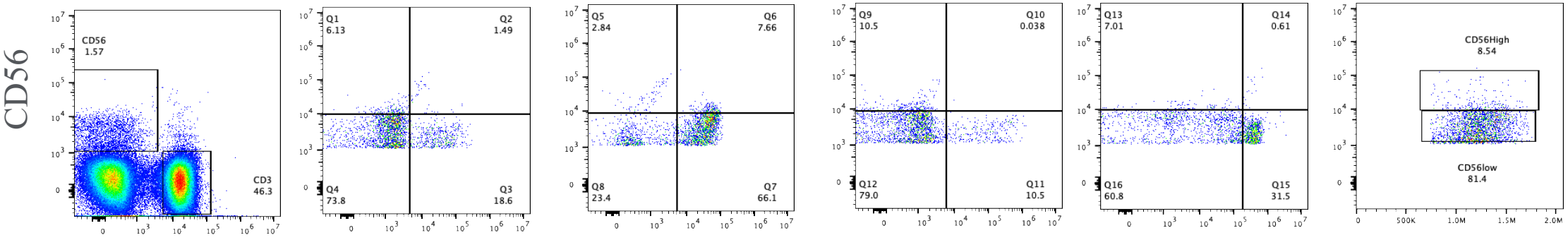
Our patient- Decreased CD56 bright and expression of activating receptors

Lab Control

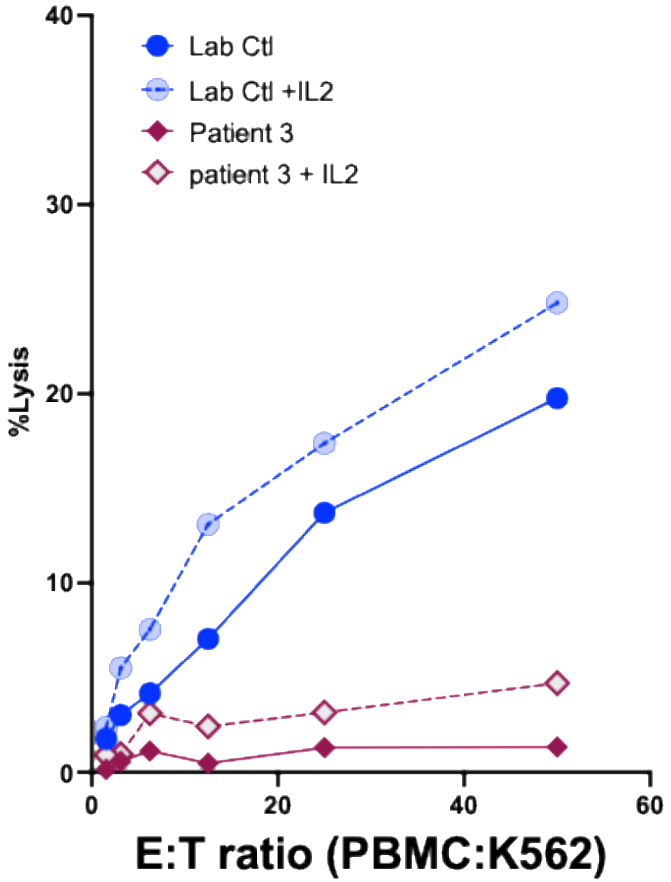


Patient



CD3 KIR CD94 CD57 CD16 FSC

Decreased NK Cell Cytotoxicity Not Rescued by IL-2



The effect of the variant is ongoing.
Increased expression of protein signifying a
Gain of function effect yet abnormal function
Is currently being investigated.

Clinical Vignette- IRF8

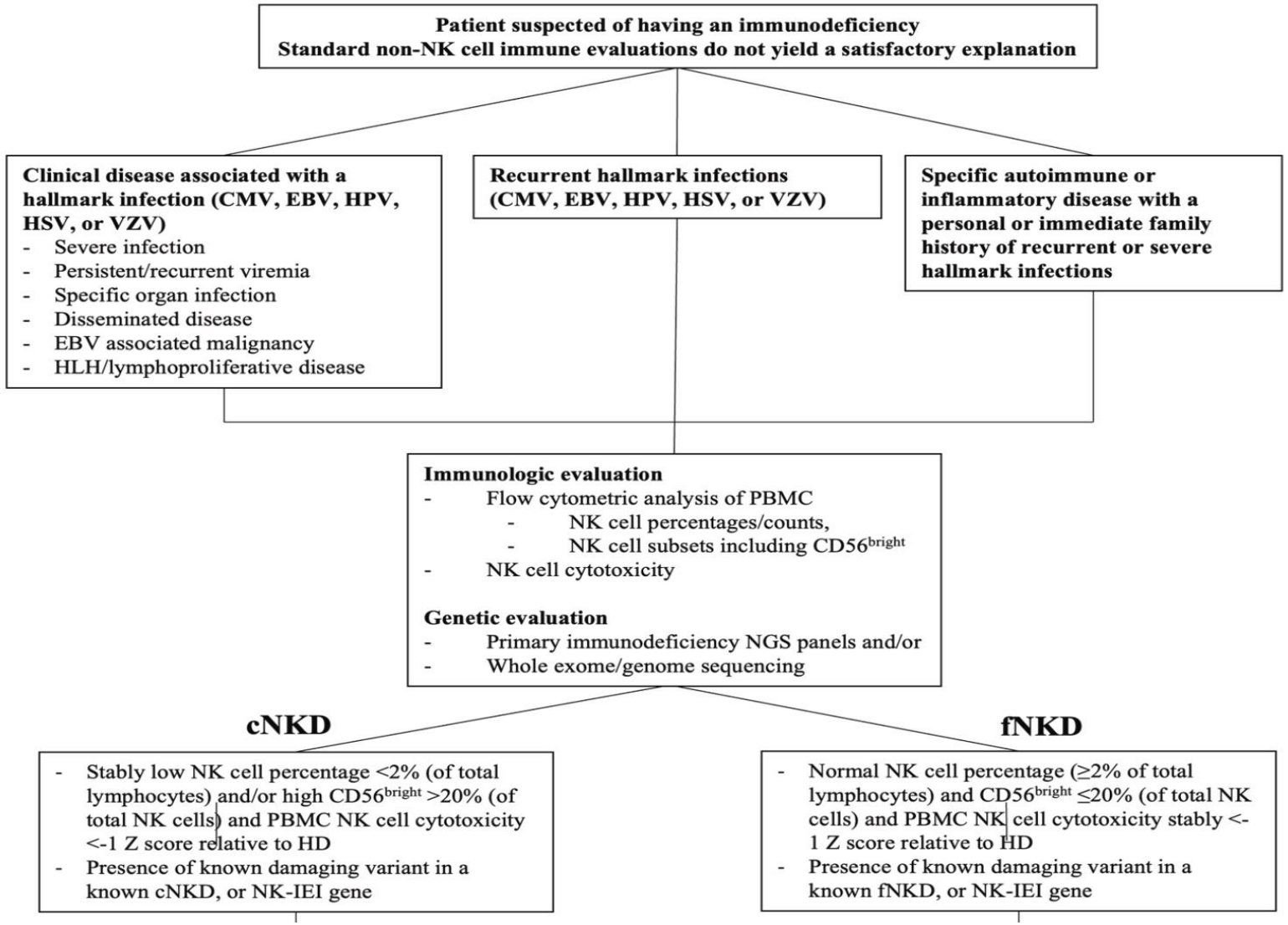
- Given the immune defect and liver condition, both liver and HSCT were thought to be needed
- Liver was determined to be first given the liver condition
- First liver transplant – cadaveric donor on 6/28/2024. Complicated by multiple infections and loss of graft-recurrence of fulminant liver failure
- Second liver transplant- Never regained hepatic function and died of hepatic failure and infectious complications

- Heterozygous IRF8 c.1279dupT is associated with distinctive phenotype of NK cell dysfunction+ autoimmunity and CVID pic. Two other patients in the NIH have been diagnosed with severe outcome (one death, the other had graft failure and was re-transplanted again)

Genetic causes of NKD

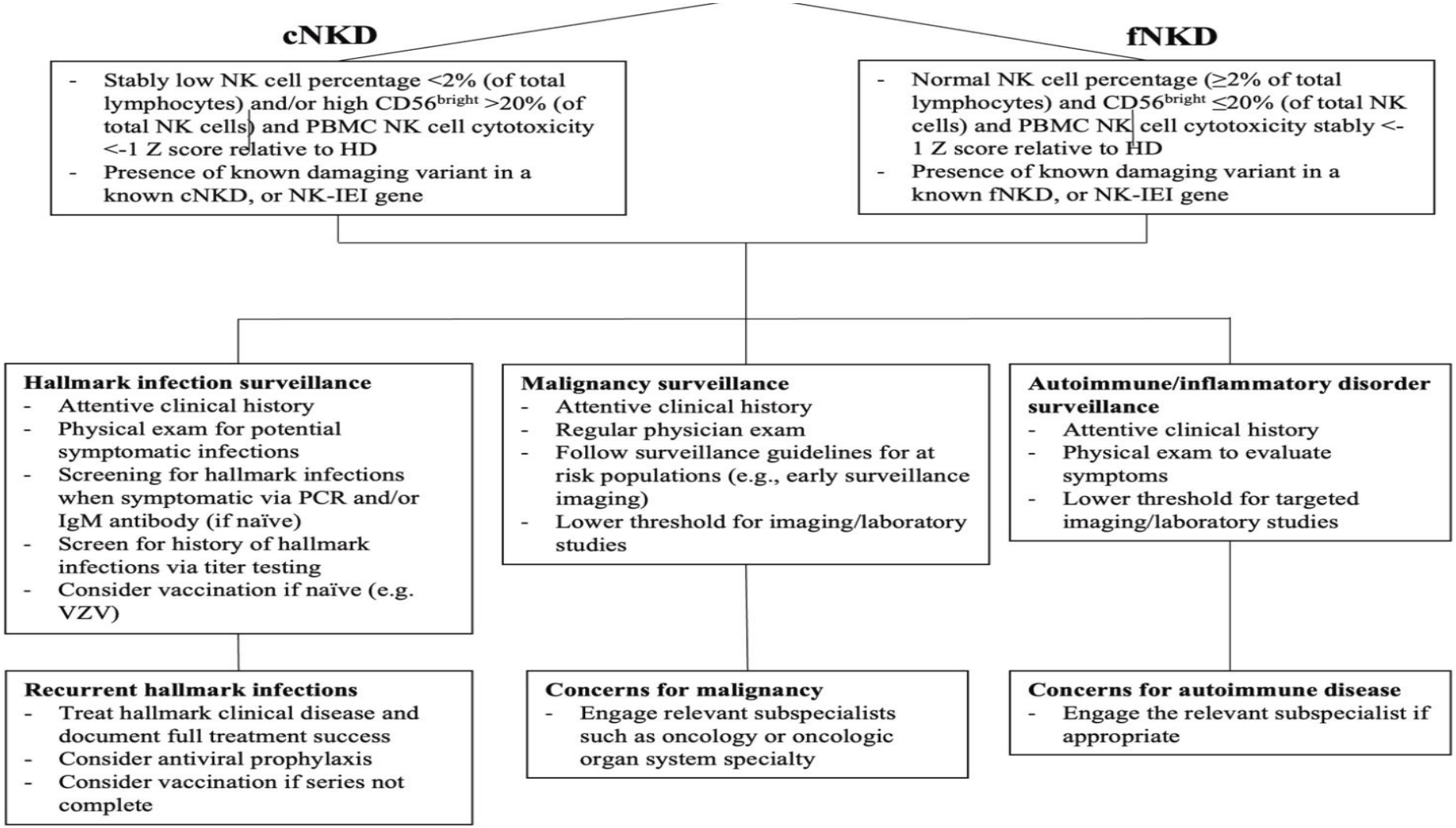
Gene`	Inheritance	NK effect	Extra features
GATA2	AD	↓ NK count	Cytopenias, MDS
IRF8	AR-AD	↓ NK count	DC defect
ELF4	AR	↓ count + function	
MCM4	AR	↓ count + function	Adrenal issues
MCM10	AR	↓ count + function	
RTEL1	AR	↓ count + function	Telomere defect
GINS1	AR	↓ count + function	
GINS4	AR	↓ count + function	
FCGR3A	AR	Normal count, ↓ function	Functional NKD
ACTB	AR	↓ count	Functional NKD
GCC2	AR	Normal count, ↓ function	Functional NKD

Management and screening- flow chart



Abdalgani M,…Orange JS, et al.. *J Allergy Clin Immunol*. 2025;155(5):1623-1634

Management and screening- flow chart



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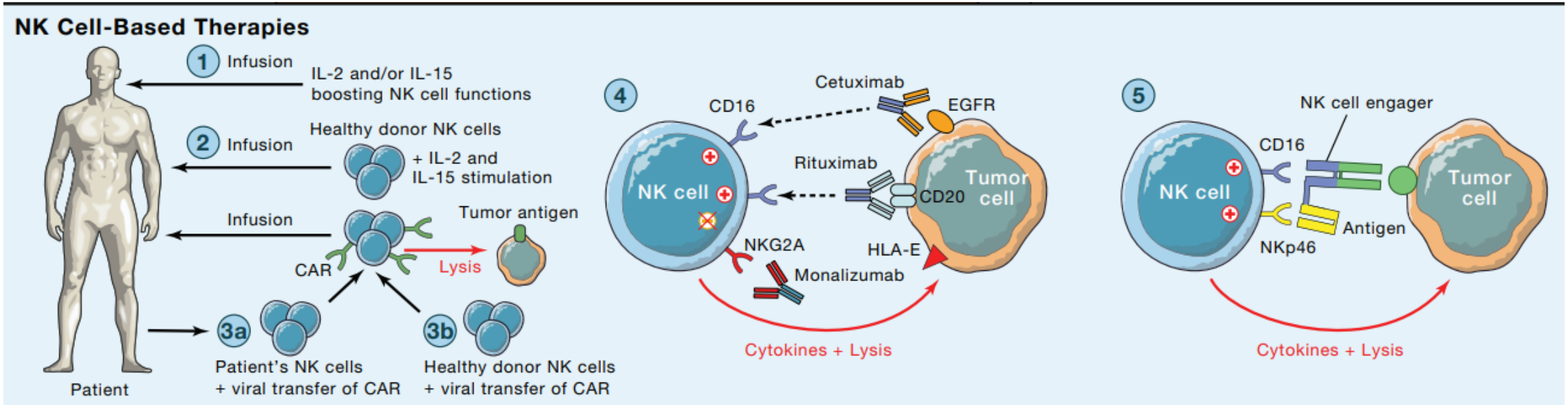
Future Directions

Content:

Gene discovery

NK biology insights

Toward targeted therapy



Gauthier L, Morel A, Anceriz N, et al.. *Cell*. 2019;177(7):1701-1713.

Conclusion and Future Prospects

- This study stresses the unique role of NK cells in the immune defense against Herpes infections and calls for evaluation for NKD in patients with severe and recurrent herpes or papilloma viral infections
- The increased risk of malignancy, although potentially underestimated due to the young age of the cohort, highlights the important role of NK cells in tumor immunity.
- Functional NKD, is likely significantly underdiagnosed, emphasizing the need for integrated functional studies in the evaluation of patients with suggestive phenotypes of NKD.
- Understanding the genetic underpinnings of NKD provides valuable insight into the disease's mechanisms and guide more precise targeted therapies in the future.
- The NEAR program encourages patient enrollment from around the world to better understand the characteristics and genetics of NKD, ultimately leading to improved early recognition and monitoring of these potentially life-threatening diseases.

THE END

Functional NKD (fNKD)- FCGR3A (CD16)

Normal NK maturation and phenotype

Impaired natural cytotoxicity but intact ADCC

Recurrent HSV, HPV, EBV-driven Castleman's disease

Diagnostic: loss of CD16 detection by B73.1 clone

fNKD- ACTB

ACTB (β-actin), critical cytoskeletal component

Developmental delay, immunodeficiency, recurrent infections

Defective cytoskeletal dynamics → impaired immune synapse formation

Reduced NK cell cytotoxicity despite normal counts

NKD due to **signaling/cytoskeletal defect**

Classical NKD (cNKD)

Impaired NK cell development

Ranges from absent NK cells to subset imbalance

Low CD56dim with skewed CD56bright

Five genetic causes identified

GATA2 Deficiency

Heterozygous mutations

Severe herpesvirus infections (CMV, HSV, VZV)

NK cells absent or <1%

Reduced CD56bright subset

Clinical heterogeneity (isolated NKD to Emberger's syndrome)

CMG Helicase Mutations (MCM4,GINS1)

Mutations in DNA helicase complex

Susceptibility to EBV, CMV, HSV, VZV

Extra-immune features: short stature, adrenal insufficiency

Low NK cell numbers, skewed CD56bright subset

Impaired proliferation, increased apoptosis

RTEL1 Deficiency

Regulator of telomerase elongation gene

Typically causes Hoyeraal-Hreidersson syndrome

Unique case: isolated NKD (fatal varicella)

Low NK numbers, impaired cytotoxicity

Suggests NK cells are sensitive to telomere/replication defects

Summary

fNKD: impaired function, normal counts (FCGR3A/CD16), ACTB

cNKD: impaired development/low counts

Key causes: GATA2, MCM4, GINS1, IRF8, RTEL1

Clinical hallmark: severe/recurrent viral infections

Need for better diagnostics and molecular insights