Updates of cancer hallmarks in patients with inborn errors of immunity

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Purpose of review
The development of cancer in patients with genetically determined inborn errors of immunity (IEI) is much higher than in the general population. The hallmarks of cancer are a conceptualization tool that can refine the complexities of cancer development and pathophysiology. Each genetic defect may impose a different pathological tumor predisposition, which needs to be identified and linked with known hallmarks of cancer.

Recent findings
Four new hallmarks of cancer have been suggested, recently, including unlocking phenotypic plasticity, senescent cells, nonmutational epigenetic reprogramming, and polymorphic microbiomes. Moreover, more than 50 new IEI genes have been discovered during the last 2 years from which 15 monogenic defects perturb tumor immune surveillance in patients.

Summary
This review provides a more comprehensive and updated overview of all 14 cancer hallmarks in IEI patients and covers aspects of cancer predisposition in novel genes in the ever-increasing field of IEI.

Keywords
epigenetic, hallmarks of cancer, inborn errors of immunity, microbiome, primary immunodeficiency, senescence

INTRODUCTION
Inborn errors of immunity (IEI, previously labeled as primary immunodeficiency) are a group of diseases constituted approximately 500 known monogenic defects. One-third of identified genes have a direct role in tumorigenesis and the development of different types of cancer hallmarks.

Hallmarks of cancer were proposed with the rationale of better understanding human cancer etiological multistep processes. These hallmarks have also been further developed based on the cornerstone mechanisms discovered in different human malignancies. Currently, the last update of these hallmarks of cancer contains 14 major entities. There were 10 hallmarks proposed until 2011, which are 8 hallmark capabilities: sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, resisting cell death [1], and 2 enabling characteristics: reprogramming cellular metabolism and avoiding immune destruction. Lately, additional two emerging hallmarks ‘Unlocking phenotypic plasticity’ and ‘Senescent cells’ and two enabling characteristics ‘Nonmutational epigenetic reprogramming’ and ‘Polymorphic microbiomes’ have been proposed (Fig. 1) [2**].

Previously, we mapped functional capabilities among 450 IEI germline mutations in 10 cancer-hallmarks to the distinguishable steps of malignancy pathogenesis [3**]. In this review, the integrative concept of new dimensions of four oncologic hallmarks associated with IEI is presented. Moreover, 55 novel genes with enigmatic pathogenic roles in different immune cell subsets have been discovered recently and updated in the International Union of Immunological (IUIS) classification [4**]. Therefore, we introduce and link these new genes with all the

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KEY POINTS

- Among four new emerging cancer hallmarks patients with monogenic inborn errors of immunity are more predisposed to nonmutational epigenetic reprogramming and polymorphic microbiomes.
- Epigenetic alteration is the most diverse and complicated cancer hallmark, which can be because of varied mutations affecting DNA methylation, histone modification, telomerase regulation, and transcription factor accessibility.
- Novel genes in inborn errors of immunity (updated since January 2020) found in malignant patients expands four main cancer hallmarks; mainly in avoiding immune destruction and tumor-promoting inflammation are predisposing patients to lymphoproliferation and lymphoma.

UNLOCKING PHENOTYPIC PLASTICITY

One of the main emerging hallmarks of cancer is unlocking phenotypic plasticity. Cellular differentiation is considered as a clear blockade for neoplasia. The majority of neoplastic cells escape the terminal differentiation through three main mechanisms including blocked differentiation, de-differentiation or trans-differentiation.

Blocked differentiation

Of note, many known IEI genes have a significant role in both adaptive and innate immune cell differentiation. Well described genes have been reported to be associated with terminal lymphocyte differentiation, including regulators of phosphoinositide 3-kinases.

FIGURE 1. Updates on recently discovered monogenic defects and newly described cancer hallmarks in different types of monogenic inborn errors of immunity according to the International Union of Immunological Societies classification. IUIS – Table1: immunodeficiencies affecting cellular and humoral immunity; IUIS – Table 2: combined immunodeficiencies with associated or syndromic features; IUIS – Table 3: predominant antibody deficiencies; IUIS – Table 4: diseases of immune dysregulation; IUIS – Table 6: defects in intrinsic and innate immunity; IUIS – Table 7: autoinflamatory disorders; IUIS – Table 9: bone marrow failure. IUIS, International Union of Immunological Societies.
(PI3Ks) pathway (PIK3CD and PIK3R1 required for CD4+ T-cell differentiation through AKT and mTOR pathway [5] and B-cell differentiation via FOXO activation [6–8]), the regulator of nuclear factor kappa B (NF-kB) pathway (NFKB1 and NFKB2 are required for plasmablast cell differentiation through the NF-kB signaling pathway [9,10]), MCM4 and MCM10 (required for natural killer (NK) cell differentiation) [11–13]. Moreover, X-linked IPEX syndrome (FOXp3 deficiency) and CD25 deficiency (IL2RA) affect T-cell differentiation into regulatory T cells and then result in lymphoproliferation and, subsequently, lymphoma [14,15]. Therefore, monogenic mutations in the genes, which can block the differentiation but not proliferation might be a tumor-predisposing factor because cancer cells enable to escape cell terminal development and resume proliferative expansion [16].

De-differentiation and trans-differentiation

Microphthalmia-associated transcription factor (MITF) acts as a master of melanocyte differentiation [17], and it has been clearly shown that low MITF levels are related to malignancy [18]. Malignancies in patients with PTEN deficiency might also be associated with MITF degradation and destabilization through deregulating humoral immune response via increasing the PI3K/AKT activity [19–21]. Trans-differentiation (or metaplasia) can also be identified in many IEI monogenic defects as a predisposing stage to the development of neoplasia, mainly in nonhematologic cancers [22]. IEI patients with chronic tissue damage and the subsequent unregulated inflammatory response can often lead to the formation of fibrotic tissue that prevents effective regeneration mainly in the lung (e.g. interstitial lung disease in common variable immunodeficiency) and liver (Tricho-Hepato-Enteric syndrome in TTC37 and SKIV2L deficiencies). The proposed pathology for this phenomenon linked the oxidative stress and cytokines released from innate immune cells inducing transdifferentiation of fibrogenic myofibroblasts, thereby contributing to fibrosis in the perportal parenchyma [23]. Other changes in unlocking phenotypic plasticity and differentiation can also induce IEI patients to develop malignancy via modification of epigenetic alteration of hematopoietic stem cells, which are separated in a distinct cancer hallmark.

NONMUTATIONAL EPIGENETIC REPROGRAMMING

The aberration of epigenetic regulation (DNA methylation, chromatin remodeling and histone modifications) on tumorigenesis is crucial and now is well described with hallmark abilities [24,25]. Fine-tuning of epigenetic processes in the immune system is required for punctual gene transcription during differentiation of the hematopoietic stem cell (HSC) and lymphoid and myeloid lineage commitment. Genetic defects in some IEI genes potentially can affect the DNA methylation signatures and histone modification patterns and contribute to the pathogenesis of clinical manifestations, including malignancy phenotype [26]. Moreover, this mechanism has been proposed as the main cause of some unknown IEI disorders without monogenic mutation but with high susceptibility to cancers including common variable immunodeficiency or IgA deficiency [27–29]. For instance, alteration in DNA methyltransferase associated with some transcription factors (namely PAX5, E2F and EBF1) have been shown to lead to the blockade of the early stages of B-cell development (from pro-B to pre-B cells) in selected patients with common variable immunodeficiency [30,31]. Moreover, studies on the DNA methylome of these patients highlighted the gross demethylation during the late stage of B-cell development mainly in the memory B-cell stage [32]. Some other IEI genetic defects are because of well known mutations in epigenetic factors including DNA methyltransferase 3 beta (DNMT3B) and its associated molecules ZBTB24, CDC7 and HELLs [33]. These defects are classified as immunodeficiency with centromeric instability and facial anomalies (ICF) syndrome. Genomic instability of pericentromeric and telomeric regions, and more generalized whole-genome hypomethylation have been observed. Although they are extremely rare syndromes with few patients followed until adulthood, cancers and mainly lymphoma because of abnormal early maturation of lymphocytes have been reported in some ICF patients [34]. The other two main IEI genes, which are controlling lymphocyte development and lineage commitment are activation-induced cytidine deaminase (AID) and Tet methylcytosine dioxygenase 2 (TET2). AID is not only responsible for converting cytosines in DNA to uracil during class-switch recombination and somatic hypermutation, but is also implicated in the demethylation of 5-methylcytosines (5mC) to thymine, particularly during early embryogenesis [35]. Similarly, TET2 in HSCs can oxidize 5mC to 5-hydroxymethylcytosine (5hmC) essential for the development of B and T cells [36]. Defects in both genes also have been reported to predispose IEI patients to hematological neoplasia [37].

Another level of epigenetic control at the DNA level, which has been connected to IEI genetic defects occurs at telomeric sequences. It is well known that the double-stranded repeat structure of telomeres protects genome stability together with
heterochromatin domains of subtelomeric regions during rapid-cell replications as one of the main characteristics of highly proliferative immune cells. Recombination between telomeric sequences or activity of telomerase as reverse transcriptase protects telomeric repeats [37]. Some IEI monogenic defects can lead to telomere decreasing to a critically short length and result in epigenetic defects at subtelomeres mainly at histone and DNA modifications. These patients (with mutations in DKC1, TERC, TERT, NOP10, NHP2 and TINF2 genes) are known as dyskeratosis congenita or Hoyeraal Hreidarson syndrome with the main feature of bone marrow failure and hematopoietic malignancies. All these proteins participate in the ribonucleoprotein complex of telomerase including the catalytic subunit (TERT), its RNA component (TERC), and the four major associated dyskerin proteins [38].

More recently, proteins that control the process of histone modifications have been identified as the main cause of syndromic IEI known as Kabuki syndrome. The main two proteins associated with this syndrome are histone KMT2D methyltransferase (on H3K4 position) and histone demethylase KDM6A (on H3K27 position) whose expression regulates embryogenesis, particularly the development of lymphocytes [39,40]. On the other hand, the predominant gene deletion associated with IEI in DiGeorge syndrome (22q11.2 microdeletion) is TBX1 (T-box 1), which is also a methyltransferase (on H3K4 position similar to KMT2D), and can lead to multiorgan defects and immunodeficiency mainly because of absence of thymus and thymic development of T cells [41]. Both patients with Kabuki syndrome and DiGeorge syndrome were reported to suffer from malignancies mainly lymphoma [3**].

Moreover, several transcription factors (TFs) that control the histone expression profile after specific immune activation or synapses perform epigenetic regulation on the promoters of targeted genes via their motif. Mutation in these transcription factors can be detected in certain types of IEIs [4**]. These monogenic defects will influence the epigenetic process, such as chromatin accessibility [42–44] and posttranscriptional modification [45,46]. One of the main TFs is IKAROS, encoded by the _IKZF1_ gene, which is considered a critical factor for early B-cell development through the energy–stress sensor AMPK pathway [47]. Mutations of _IKZF1_ are associated with defective development of T cells, B cells and NK cells [48,49]. _IKZF1_ monogenic mutations are considered the main predisposing reason for B-cell acute lymphoblastic leukemia (B-ALL) transformation in these patients [50] and are classified as ‘sustaining proliferative signaling’ hallmarks [3**]. As one of the proteins in the IKZF family, AIOLOS, which is encoded by _IKZF3_, the AIOLOS-G159R variant can cause defective IKAROS binding site activity by forming IKAROS-AIOLOS-G159R heterodimers, which are considered to cause heterodimeric transcription interference [51]. With higher susceptibility to Epstein–Barr virus (EBV) infection, patients with AIOLOS-G159R autosomal dominant variant developed B-cell lymphoma.

**SENEGENT CELLS**

Cellular senescence leads to ‘senescence-associated secretory phenotype (SASP)’, including over-production of chemokines, cytokines, chronic inflammation and processes alteration of nonsenescent neighboring cells, which has been verified to promote tumor development and malignant progression [52–55]. SASP is typically associated with the DNA damage response (DDR). Persistent DDR can promote SASP by increasing cytosolic chromatin fragments (CCFs) [56]. Thus, monogenic diseases of DNA repair may affect the induction of senescence markers [57]. For example, _ATM_ mutation is associated with mitochondrial dysfunction-induced SASP by triggering the STING-dependent pathway [58]. NBS1 mutation modulates SASP in stress-induced signaling activation of the P38/MK2 pathway [59]. Similarly, HSCs from IEI patients with telomeric dysfunction as mentioned above with dyskeratosis congenita or Hoyeraal Hreidarson syndromes can show high DNA damage levels and become senescent [60].

Apart from the DNA repair syndrome, SASP is a very common phenomenon in the disease of immune dysregulation due to uncontrolled chronic inflammatory reactions. These continued activations and inflammation lead to reduced expression of co-stimulatory CD28 or CD27 molecule on CD45RA+ CD4+ T cells and present a reduced antigen-dependent proliferation but increased inflammatory cytokine production. On the other hand, CD8+ T cells switch from the typical T-cell receptor (TCR)-mediated activity to an NK-like activity by expressing protein complexes typical of NK cells [61,62]. A typical known mutation associated with premature immunosenescence and accelerated inflammation is Tripeptidyl peptidase II (TPP2) deficiency. The homeostatic function of TPP2 is downstream of proteasomes in cytosolic proteolysis and contributes to antiapoptotic phenotype, particularly in CD8+ T cells. Although the majority of TPP2 cases are pediatric patients, lymphoproliferative diseases are one of the main manifestations of the disease [63,64].

**POLYMORPHIC MICROBIOMES**

Microbiomes, including commensal bacteria and fungi, are recently expansively identified for their
diverse impacts on the mucosal area of the gastrointestinal tract and respiratory system, and are considered to have an association with cancer phenotypes [2]. Over 50% of IEI patients present with gastrointestinal diseases, among which, CVID is associated with higher susceptibility to diverse complications, including chronic diarrhea, nodular lymphoid hyperplasia, liver and biliary tract diseases [65] and 10-fold increase in risk of gastrointestinal cancer compared with immune-competent individuals [66]. NFKB1 expression is necessary for epithelial cells to regulate the bacterial barrier [67]. Virulence factors produced by Helicobacter pylori have been proposed as one of the driving reasons leading to gastric cancer through aberrant Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling and inflammatory mediators by loss of NF-κB1[68]. Therefore, monogenic diseases will influence the susceptibility to develop malignancy, such as NFKB1 and NFKB2 deficiencies [66,69–71]. Microbiomes maintain homeostasis and avoid microbial translocation in the gastrointestinal system through the production of antimicrobial peptides (AMP) by a downstream MyD88-dependent pathway [72,73]. Of note, IEI genetic defects related to the MyD88 pathway (such as TLR3, TLR7, TLR8, IRAK4 and IKBA) may increase microbial translocation by dysregulating the immune system [74,75]. Microbiome-related metabolites influence the innate immunity of homeostatic interaction in the gastrointestinal system [76–79]. IEI monogenetic diseases have effects on the cellular pathways among innate cells in the gastrointestinal system, including monocytes, macrophages, innate lymphoid cells, γδT cells, and mucosal-associated invariant T (MAIT) cells and NK cells. Interferon-gamma (IFN-γ) is critical for gastrointestinal innate immunity against intracellular bacterial infections and drives immunostimulatory impact. In the microbiome of mucosal area, macrophages are stimulated and produce IL-1 and IL-23. γδT cells are activated by the IL-2 and IL-23, then produce IL-17 for further adaptive immunity [80]. MAIT cells particularly respond to a wide range of microorganisms and produce IL-17 and IFN-γ to perform immune stimulation [81]. Of note, IFN-γ receptor 1 (IFNγR1) deficiency and IFN-γ receptor 2 (IFNγR2) deficiency are linked to EBV-associated lymphoma and intestinal pseudotuberculosis by impairing the downstream immune cells binding and stimulating by IFN-γ [65].

Adaptive immunity against the mucosal microbiome can be affected by the mutations associated with Th17 cells, FOXP3 regulatory T cells, B cells, CD4+ T cells, CD8+ T cells, and follicular helper T (Tfh) cells. Therefore, the monogenic diseases that affect V(D)J recombination and class-switch recombination and reduce the diversity of the secretory IgA repertoire (eg. RAG1, RAG2, ATM, BLM and MSH6 deficiencies) and thus predispose towards microbiota dysbiosis and gastrointestinal tumorigenesis [65,79,82] Moreover, the function of controlling intestinal inflammation by IL-10 (IL10, IL10RA and IL10RB deficiencies) is of importance for promoting gut homeostasis [83–85]. Moreover, hypomorphic defects of cellular immunity by dysfunction of T cells can present long-term chronic diarrhea and gastrointestinal cancer development consequently due to dysbiosis.

**NOVEL INBORN ERRORS OF IMMUNITY GENES ASSOCIATED WITH HALLMARKS OF CANCER**

We reported that more than one-third of IEI monogenic defects have been linked with cancer hallmarks according to the IUIS classification of 2020 [3]. Among 55 novel IEI genes discovered during the last 2 years [4], although the number of patients is still very limited for each disease to guarantee the association or dissociation from malignancy, we have reported here 15 genes in which cancer is a component of the main clinical phenotype observed among these rare case reports and tried to classify them mechanistically based on the known cancer hallmarks (Table 1).

**Avoiding immune destruction**

Patients with DIAPH1 deficiency are predisposed to EBV infection, which may progress to the subsequent development of diffuse large B-cell lymphoma (DLBCL). Mutations in genes that coordinate CD8+ T-cell activation increase the susceptibility to herpes virus family infections. Also, DIAPH1 has been suggested as a necessary genetic factor of T-cell activation and formation, which probably modulates T-cell cytokoskeletal regulation [87,88]. TET2 coordinates B-cell transition activity to germinal centers via DNA methylation by oxidizing 5mC and epigenetic controls as mentioned in the above section [89]. However, loss of function of TET2 is associated with defective B-cell class-switch recombination and autoimmune lymphoproliferation, which is considered as the predisposition to B-lymphoma because of these abnormalities in the function of immune cells [90]. SYK (the spleen tyrosine kinase) plays a critical and complex role in several immune cellular processes. Classical immunoreceptors (BCRs, TCRs and FcRs) need SYK to regulate downstream through ITAMs-based (cytosolic immunoreceptor tyrosine-based activation motifs) signaling pathway, SYK is also involved in B-cell development, innate pathogen recognition and inflammasome activation [91]. SYK deficiency increases the risk of developing DLBCLs [92].
### Table 1. Demographic and clinical presentation of patients with novel inborn errors of immunity monogenic defects and predisposition to lymphoproliferation and malignancies

| IUIS | Gene | Protein | Pathway                     | Patient ID index of paper | Gender | Mutation   | Malignancies                          | Predisposition to lymphoproliferation | Hallmarks                  | PMID          | Year |
|------|------|---------|-----------------------------|---------------------------|--------|------------|---------------------------------------|---------------------------------------|-------------------------------|----------------|------|
|      | IKZF1 | IKAROS: zinc finger transcription factor | AMPK pathway              | PALL 1-3                  | UN     | R347C      | B-ALL                                 | Autoimmune disease, immune dysregulations, recurrent/severe bacterial infections | Sustaining proliferative signaling | PMID: 33392855 | 2021 |
|      | SASH3 | SLY, SH3-containing lymphocyte protein | TCR-signaling pathway     | P1                        | M      | R347C      | LGL proliferation                      | Recurrent pulmonary infections, skin/salt tissue infections, warts | Avoiding immune destruction | PMID: 33876203 | 2021 |
|      | IKZF2 | HELIOS: zinc finger transcription factor | IFN-γ and IL-2-signaling pathways | P2                        | M      | Y200X      | HL                                   | Chronic lymphadenopathy              | Tumor-promoting inflammation | PMID: 34826260 | 2021 |
|      | PC1   | MCM10: minichromosomal maintenance complex member 10 | DNA repair pathway        | P1                        | M      | R426C and R582X | HLH                               | Lymphadenopathy, CMV infection, NK Deficiency | Genome instability and mutation | PMID: 32865517 | 2020 |
|      | DIAPH1 | DIAPH1/mDIA1: evolutionarily conserved formin diaphanous homolog 1 | Rho-mDia1 pathway | P1                        | M      | c. 684+1G>A | DLBCL                               | Bacterial otitis media, candida, mycobacteria, VZV, HSV, EBV, Molluscus contagiosum | Avoiding immune destruction | PMID: 33662367 | 2021 |
|      | P2    | M      | c. 684+1G>A | HL-like                  | P6    | F         | F9235X                  | Respiratory infections             |                               |                             |                             |
|      |      |         |                      |                          |       | F         | G159R                  | EBV infection, recurrent sinopulmonary infections | Nonmutational epigenetic reprogramming, avoiding immune destruction, activating invasion and metastasis | PMID: 34155405 | 2021 |
|      |      |         |                      |                          |       | F         | G159R                  | B-cell lymphoma                   | EBV infection, recurrent sinopulmonary infections | Nonmutational epigenetic reprogramming, avoiding immune destruction, activating invasion and metastasis | PMID: 34155405 | 2021 |
|      |      |         |                      |                          |       | F         | G159R                  | B-cell lymphoma                   | EBV infection, recurrent sinopulmonary infections | Nonmutational epigenetic reprogramming, avoiding immune destruction, activating invasion and metastasis | PMID: 34155405 | 2021 |
|      |      |         |                      |                          |       | F         | G18R                   | Benign epithelial tumor            | Recurrent sinopulmonary infections; Severe hypogammaglobulinemia | PMID: 34694366 | 2021 |
|      |      |         |                      |                          |       | F         | G18R                   | Severe HPV infection, CMV, EBV high, parainfluenza positive | Severe HPV infection, CMV, EBV high, heavy warts | Avoiding immune destruction | PMID: 34214472 | 2021 |
|      |      |         |                      |                          |       | F         | G18R                   | Severe HPV infection; EBV high, heavy warts | Severe HPV infection, CMV, EBV high, heavy warts | Avoiding immune destruction | PMID: 34214472 | 2021 |
Table 1 (Continued)

| IUIS | Gene     | Protein | Pathway                                      | Patient ID | Gender | Mutation | Malignancies                       | Predisposition to lymphoproliferation                             | Hallmarks                              | PMID          | Year |
|------|----------|---------|----------------------------------------------|------------|--------|----------|------------------------------------|------------------------------------------------------------------|----------------------------------------|---------------|------|
|      | PIK3CG   |         | PI3K-akt1-mTOR pathway                        | P1         | F      | R982fsX and R2021P                  | -                                                                 | Antibody defects; lymphadenopathy/splenomegaly                     | Tumor-promoting inflammation            | 31955793      | 2019 |
|      |          |         |                                              | P1         | F      | R495 and N1085S                      | HU-like                                                          | Systemic inflammation                                              | PMID: 33054089  | 2020 |
| CTNNB1| CTNNB1   |        | AID-associated pathway                        | P1         | F      | M466V                                | -                                                                 | Progressive hypogammaglobulinemia; autoimmune cytopenias; recurrent infections | Genomic instability and mutation          | 32484799      | 2020 |

Table 4

| RHOG | Rho G: Ras homolog gene G | Cytotoxic lymphocytes transduction pathway | P1 | M | E171K | HUH | Avoiding immune destruction | PMID: 33513601 | 2021 |

| SOCS1| SOCS1: suppressor of cytokine signaling 1 | Type I and type II IFN signaling pathway | P1 | M | A378fsX48 | - | Anemic and neutropenic; multisystem inflammatory syndrome; Evans syndrome; immune thrombocytopenia | Tumor-promoting inflammation | PMID: 32853638 | 2020 |

| TET2 | TET2: ten-eleven translocation methylcytosine dioxygenase 2 | Hematopoiesis cell differentiation and development | P4 | M | A999fsX76 | HL | Coeliac disease panniculitis | PMID: 32518946 | 2020 |

| TET2 | TET2: ten-eleven translocation methylcytosine dioxygenase 2 | Hematopoiesis cell differentiation and development | P2 | M | H1382X | Lymphoma | Recurrent respiratory tract infections; bronchectasis; herpes viral infection; lymphadenopathy; hepato-splenomegaly; auto immune cytopenias; auto antibodies | Non-mutational epigenetic reprogramming | PMID: 32518946 | 2020 |

| TET2 | TET2: ten-eleven translocation methylcytosine dioxygenase 2 | Hematopoiesis cell differentiation and development | P3 | F | Q1632X | Lymphoma | Recurrent respiratory tract infections; bronchectasis; herpes viral infection; lymphadenopathy; hepato-splenomegaly | - | PMID: 32518946 | 2020 |

Table 6

| NOS2 | NOS2: nitric oxide synthase 2 | dT3-dependent pathway | P1 | F | I391fsX26 | - | EBV infection; Fatal CMV infection | Activating invasion and metastasis | PMID: 33872655 | 2021 |

| ZNF1 | ZNF1: zinc finger nrf1-type domain containing protein 1 | dT3-dependent pathway | P1 | F | I391fsX26 | - | EBV infection; Fatal CMV infection | Activating invasion and metastasis | PMID: 33872655 | 2021 |
### Table 1 (Continued)

| Patient ID of paper | Gender | Mutation | Malignancies | Predisposition to lymphoproliferation | Hallmarks | PMID | Year |
|---------------------|--------|----------|--------------|--------------------------------------|-----------|------|------|
| P1                  | M      | P432L    | -            | Lymphadenopathy, infection: Clostridium septicum bacteremia | Tumor-promoting inflammation | 33512449 | 2021 |
| P2                  | M      | P432L    | -            | Lymphadenopathy, infection: Pneumonia and otitis media | -         | -    | -    |
| P3                  | M      | F494L    | -            | Lymphadenopathy, infection: lymphadenitis | -         | -    | -    |
| P4                  | M      | P432L    | -            | Lymphadenopathy, infection: Nocardia | -         | -    | -    |
| P5                  | M      | P432L    | -            | Lymphadenopathy, idiopathic thrombocytopenia; lymphadenopathy; recurrent GI inflammation/infection | -         | -    | -    |
| P6                  | M      | G527D    | -            | Lymphadenopathy, infection: otitis media, fungal infections | -         | -    | -    |

**TLR8, GOF**

TLR8: toll-like receptor 8 TLR pathway

| Patient ID of paper | Gender | Mutation | Malignancies | Predisposition to lymphoproliferation | Hallmarks | PMID | Year |
|---------------------|--------|----------|--------------|--------------------------------------|-----------|------|------|
| P1                  | F      | S550Y    | -            | Lymphadenopathy, hypogammaglobulinemia; recurrent infections; intestinal inflammation | Avoiding immune destruction | 33782605 | 2021 |
| P2                  | F      | S550F    | -            | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |
| P3                  | M      | S550F    | -            | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |
| P4                  | UN     | P342T    | -            | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |
| P5                  | UN     | A450I    | DLBCL        | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |
| P6                  | UN     | A353T    | DLBCL        | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |

**SYK, GOF**

SYK: spleen tyrosine kinase ITAM-based signaling pathway

| Patient ID of paper | Gender | Mutation | Malignancies | Predisposition to lymphoproliferation | Hallmarks | PMID | Year |
|---------------------|--------|----------|--------------|--------------------------------------|-----------|------|------|
| P1                  | F      | S550Y    | -            | Lymphadenopathy, hypogammaglobulinemia; recurrent infections; intestinal inflammation | Avoiding immune destruction | 33782605 | 2021 |
| P2                  | F      | S550F    | -            | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |
| P3                  | M      | S550F    | -            | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |
| P4                  | UN     | P342T    | -            | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |
| P5                  | UN     | A450I    | DLBCL        | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |
| P6                  | UN     | A353T    | DLBCL        | Hypogammaglobulinemia; recurrent infections; intestinal inflammation | -         | -    | -    |

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**Table 7**

**AID, activation-induced cytidine deaminase; B-ALL, B-cell acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; F, female; GI, gastrointestinal tract; GOF, gain-of-function; AMPK, AMP-activated protein kinase; HL, Hodgkin’s lymphoma; HLH, hemophagocytic lymphohistiocytosis; HPV, human papillomavirus; HSV, herpes simplex virus type 1; IFN-R, interferon-gamma; IL-2, interleukin 2; ITAM, immunoreceptor tyrosine-based activation motif; LGI, large granular lymphocytic; M, male; NK, natural killer cells; TCR, T-cell receptor; TLR, toll-like receptor; UN, unknown; VZV, varicella-zoster virus.**
SLY, encoded by sterile alpha motif (SAM) and Src homology-3 (SH3) domain-containing 3 (SASH3), is a scaffolding protein with critical function in T-cell proliferation, TCR signaling activation and T-cell survival [93]. Patients with genetic defects in SASH3 present with immune dysfunction alongside tumor-predisposition clinical phenotypes, including large granular lymphocyte (LGL) proliferation and CD4+ T-cell lymphopenia. Another novel IEI with impairment in cytotoxic defects is because of the variants in AIOLOS, encoded by IKZF3. This protein is mainly expressed in B and T lymphocytes based on several animal models, especially in immature and recirculating B cells [94,95]. Patients with AIOLOS deficiency have abnormal T-cell subsets, combined immunodeficiency and high susceptibility to EBV infection, increasing the possibility of developing EBV-driven malignancy [51]. CD28 is an important co-stimulatory signal for CD4+ T-cell proliferation (via CD28/CD8 crosstalk) [96] and T-helper type-2 (Th2) development [97]. CD28 deficiency leads to the impairment of T-cell response and reduced ability to combat EBV, cytomegalovirus (CMV) and human papillomavirus (HPV). Multifocal, benign epithelial tumor at a late stage has been observed in patients with underlying CD28 deficiency [98]. Ras homology (RHO) GTPases can be triggered by antigen receptor activation in lymphocytes via ERM (ezrin–radixin–moesin) kinases, which are essential for normal hematopoietic cell development, including lymphocyte migration, morphological polarization and adhesion [99–101]. It has been shown that lack of nonredundant exocytosis function in cytotoxic T cells and NK cells in patients with RHOG deficiency, may result in the subsequent development of lymphoproliferation and hemophagocytic lymphohistiocytosis (HLH) [102].

**Tumor-promoting inflammation**

As a transcriptional repressor in lymphocytes, Helios, encoded by IKZF2, has a significant role in regulating effector T-cell activity, similar to the previous function described for IKZF1 [103,104]. Patients with IKZF2 deficiency present with chronic overactivation of proinflammatory cytokine production with this being the most likely driver of tumor predisposition [103] [mainly because of the up-regulation in both interferon-gamma (IFN-γ) and interleukin-2 (IL-2) downstream signaling pathways] [103]. In this group of patients, a variable clinical phenotype can be observed in different mutation sites [103,105], and lymphoma has been reported in patients with both underlying autosomal dominant and recessive forms of IKZF2 deficiency [103]. Suppressor Of Cytokine Signaling 1 (SOCS1) mutations lead to autoimmune diseases by increasing the JAK-STAT pathway activation with the production of IFN-γ, IL-2 and IL-4. A patient with heterozygous SOCS1 mutation has been reported with Hodgkin lymphoma [106]. Toll-like receptor 8 (TLR8), acts as an endosomal-sensing receptor mainly expressed in neutrophils and monocytes. Gain-of-function of TLR8 results in increases in the proinflammatory cytokines (IL-18, TNF-α and IFN-γ) through NF-kB pathway activation. Patients with TLR8 gain-of-function mutation developed T-LGL leukemia possibly through proinflammatory cytokines affecting the development of neutrophil differentiation and B-cell maturation [107]. PI3Kγ, encoded by PIK3CG, is mainly expressed in leukocytes. PI3Kγ deficiency results in immunoglobulin production impairment, inflammatory diseases and HLH-like diseases, considered related to dysfunction of the PI3K–AKT–mTOR pathway with abnormal cytokine and chemokine production and antigen receptor stimulation [108,109].

**Genome instability and mutation**

Monichromosome maintenance complex component 10 (MCM10) is involved in DNA replication and cell-cycle progression, which functionally stabilizes the replisome and maintains genome stability. Loss of function of MCM10 results in increasing chronic replication stress and decreasing cell viability [108,109], and overexpressed MCM10 has been described in a variety of cancer types [111]. Furthermore, MCM10’s additional role in NK-cell terminal differentiation, maturation, and function has been also verified [13]. The patients with MCM10 monogenic loss-of-function germline mutation result in decreased numbers of NK cells with NK-cell dysfunction, severe CMV infections and developed an HLH-like phenotype predisposing to malignancy development [13]. The recently discovered AID-interacting protein, CTNNBL1 plays an important interaction in assisting intracellular trafficking of AID and delivering AID to the appropriate Ig locus, enabling class-switch recombination and somatic hypermutation [112,113]. Biallelic defects of CTNNBL1 may result in increased off-target effects of AID, which may contribute to genome instability and increase the possibility of malignant transformation by the activation of oncogenes and chromosome translocations [114,115].

**Activating invasion and metastasis**

Monogenic IEI diseases underlying the susceptibility of various oncogenic viral infections have high
relevance to human malignancy. Among 55 novel IEI genes, patients underlying IKZF3 deficiency have a high susceptibility to EBV infections, which could lead to B-lymphocyte immortalization and further polyclonal proliferation through latent membrane protein 1 (LMP1) activation [51,116]. Similarly, NO52 (encoding NO synthase) deficiency has attenuated responses to herpes viruses including EBV, which can directly induce metastasis in cancer cells, and also result in a predisposition to severe CMV viral infection [117]. CD28 deficiency is associated with severe HPV infections, which can regulate the PS3 pathway through HPV E6 oncogene production and regulate cell mobility and invasion [118]. Genetic defects on ZNF71, which encode a double-stranded RNA (dsRNA) sensor, will increase the susceptibility to both RNA/DNA virus infections and directly trigger HLH-like diseases [118].

CONCLUSION
The concept of cancer hallmark assignments in patients with inborn errors of immunity is rapidly growing during recent years, and it is required that the causes of cancer predisposition in these monogenic diseases will be investigated using patient-oriented experimental studies and multiomics technologies to prove these hallmarks. Basic findings and confirmatory functional assays will pave the way for the acceleration of accurate prognosis estimation and targeted treatment.

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Conflicts of interest
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