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REVIEW

# Primary immunodeficiencies and their associated risk of malignancies in children: an overview

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## Abstract

Primary immunodeficiency disorders represent a heterogeneous spectrum of diseases, predisposing to recurrent infections, allergy, and autoimmunity. While an association between primary immunodeficiency disorders and increased risk of cancer has been suggested since the 1970s, renewed attention has been given to this topic in the last decade, largely in light of the availability of large registries as well as advances in next generation sequencing. In this narrative review, we will give an insight of the primary immunodeficiencies that are commonly responsible for the greater number of cancers in the primary immunodeficiency disorders population. We will describe clinical presentations, underlying genetic lesions (if known), molecular mechanisms for carcinogenesis, as well as some management considerations. We will also comment on the future directions and challenges related to this topic.

*Conclusion*: The awareness of the association between several primary immunodeficiencies and cancer is crucial to provide the best care for these patients.

**What is Known:**

- *Patients with primary immunodeficiency have an increased risk of malignancy. The type of malignancy is highly dependent on the specific primary immunodeficiency disorder.*

**What is New:**

- *Survival in patients with primary immunodeficiency disorders has been improving, and conversely also their lifetime risk of malignancy.*
- *International collaboration and multinational registries are needed to improve our knowledge and therapeutic strategies.*

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**Keywords** Pediatrics · Primary immunodeficiencies · Cancer · Lymphoma · Surveillance

**Abbreviations**

| | |
|---|---|
| PID | Primary immunodeficiency disorders |
| AT | Ataxia telangiectasia |
| UV | Ultraviolet |
| NHL | Non-Hodgkin lymphoma |
| BS | Bloom syndrome |
| AML | Acute myeloid leukemia |
| ALL | Acute lymphoblastic leukemia |
| NBS | Nijmegen breakage syndrome |
| CVID | Common variable immunodeficiency |
| ALPS | Autoimmune lymphoproliferative syndrome |
| MDS | Myelodysplastic syndrome |
| WAS | Wiskott–Aldrich syndrome |
| HSCT | Hematopoietic stem cell transplantation |

## Introduction

Primary immunodeficiency disorders (PID) represent a heterogeneous spectrum of diseases, predisposing to recurrent infections, allergy, and autoimmunity. A significant proportion of patients have an increased risk of malignancy [1]. Advances in diagnostics, treatment, and supportive care have improved survival which conversely increases lifetime risk of malignancy.

The incidence of PID in international registries is 11.2 per 100,000 births [2], of which 71% are diagnosed < 18 years of age [3]. The lifetime risk for children with PID to develop cancer is estimated at 5–25% [4, 5]. The type of malignancy is highly dependent on the PID and although many causative genes have been identified, the underlying mechanisms for malignancies are largely unknown [6–8] (Fig. 1).

In this review, we discuss some representative PIDs commonly associated with cancer [9] (Table 1). We will group these into DNA breakage diseases, predominantly antibody disorders, and immune dysregulation.

## DNA breakage disorders

### Ataxia telangiectasia

Ataxia telangiectasia (AT) is a DNA repair disorder with multisystem involvement, caused by bi-allelic mutations in *ATM* on chromosome 11q22-q23 (OMIM #208900) [10]. *ATM* encodes phosphatidylinositol 3-kinase protein, which has a key role in coordinating the cellular response to double-strand breaks in DNA.

Presentation is classically in preschool years with progressive ataxia, dysarthria, abnormal eye movements, and cerebellar atrophy on imaging. Telangiectasias are usually apparent later and prominent in conjunctivae. Other manifestations include abnormal growth, feeding difficulties, sinopulmonary infections, chronic lung disease, pubertal delay, and premature aging [11]. Immune deficiency is present in two-thirds of individuals and includes reduced levels of immunoglobulins, poor vaccine responses, and reduced B or T lymphocyte counts [12].

AT has a very high lifetime risks of malignancy of up to 40% with a median age of 10–14 years at diagnosis [13]. Non-Hodgkin lymphomas (NHL) and leukemias predominate, though other solid tumors are reported. Notably, heterozygous carriers of the *ATM* gene also have an increased risk of malignancies, mostly female breast cancer. The pathogenesis is connected to genetic instability and accumulation of genetic aberrations which are caused by inappropriate repair response to DNA breaks. Consequently, there is profound sensitivity to the genotoxic effect of ionizing radiation [14].

There are expert opinion–based cancer surveillance guidelines [15, 16]. Exposure to ionizing radiation should be avoided unless essential for diagnostic or therapeutic reasons. Interestingly, despite the cutaneous manifestations, individuals with AT do not have an increased risk of malignancy from ultraviolet (UV) exposure of sunlight as opposed to other syndromes such as Bloom syndrome (BS).

### Bloom syndrome

BS was originally described as a combination of severe pre- and postnatal growth deficiency with short final stature, and sun-sensitive skin lesions predominantly on the face. Affected individuals with BS exhibit telangiectasias, hypo- or hyperpigmented skin lesions, and decreased subcutaneous fat. Classical facial appearance is bird-like and voice is high-pitched. Feeding difficulties in infancy, insulin resistance, and diabetes mellitus are associated problems. Gastroesophageal reflux with respiratory tract infections is

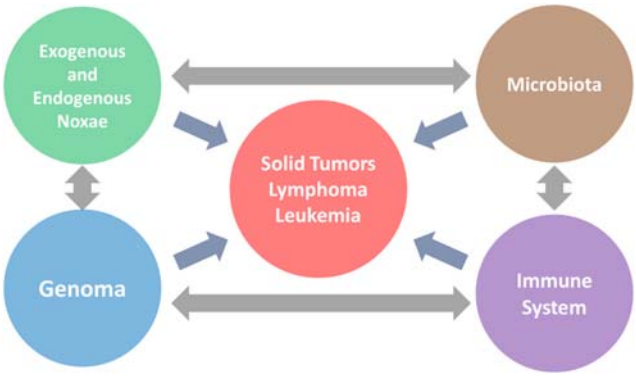


**Fig. 1** Factors possibly involved in carcinogenesis in subjects affected by primary immunodeficiency disorders

**Table 1** Primary immune deficiencies and associated malignancies in children

| PID | Main gene identified | Inheritance pattern(s) | Incidence in the general population | Immune deficiency | Specific findings that might hint towards this particular PID | Mechanism of developing malignancy | Main types of associated malignancy | Lifetime risk of malignancy (%) | Age at first malignancy (median in years) |
|---|---|---|---|---|---|---|---|---|---|
| DNA breakage disorders | | | | | | | | | |
| Ataxia telangiectasia | *ATM* | AR | 1:40,000–1:100,000 | Low immunoglobulins and decreased cellular immunity | Cerebellar atrophy, ataxia, ocular telangiectasia | DNA repair deficiency | Lymphomas and leukemias | 20–40 | 12.5 years |
| Bloom's syndrome | *RECQL3* | AR | Unknown | Hypogammaglobulinemia, reduced lymphocyte proliferation | growth deficiency; sun-sensitive, telangiectatic, hypo- and hyperpigmented skin | DNA repair deficiency | Lymphomas, acute leukemias, carcinomas | 20 | 25 years |
| Nijmegen breakage syndrome | *NBN* | AR | Unknown | Defects of both the humoral and cellular components of the immune system | Microcephaly with bird-like facial aspect, growth deficiency, progressive intellectual disability | DNA repair deficiency | Lymphomas, leukemias, some brain tumors | > 40 | Usually < 15 years |
| Predominantly antibody disorders | | | | | | | | | |
| Common variable immunodeficiency | heterogeneous | AR, AD | 1:1200 | Defective immunoglobulin production; abnormal T cell numbers or function | Recurrent sinopulmonal infections; granulomas; autoimmunity | impaired immunity to herpes viruses, chronic inflammation, and DNA repair defects | Non-Hodgkin lymphoma, gastric, thyroid and skin cancer | Up to 20 | 30 years |
| Immune dysregulation | | | | | | | | | |
| Autoimmune lymphoproliferative syndrome | *FAS* | AD (> 65%), AR | Unknown | Immune dysregulation; neutropenia | Chronic non-malignant lymphoproliferation, autoimmune blood cytopenias | Dysregulation of the FAS pathway with defective lymphocyte apoptosis | Lymphoma (NHL and HL) | 10–15 | 25 years |
| GATA2 deficiency | *GATA2* | AD | Unknown | (Congenital) cytopenias, viral and fungal infection, pulmonary alveolar proteinosis, dendritic, B and T cell deficiency | Primary lymphedema, deafness, dysmorphic features | Nuclear regulatory protein involved in early hematopoiesis | MDS/AML; EBV and HPV-driven tumors | 75 | 20 years |
| Other | | | | | | | | | |
| Wiskott-Aldrich syndrome | *WAS* | X-linked | 1,4: 1,000,000 | T cell and NK deficiency | Recurrent infections, microthrombocytopenia, eczema | Impaired dendritic cells, T lymphocytes and NK cell immune surveillance | Lymphoma, MDS, ALL | Severe forms: 13–22, mild forms: 5 | Severe forms: 9.5 years |

common, leading to chronic lung disease and bronchiectasis. BS is associated with B and T lymphocyte deficiencies. Women are prone to infertility and early menopause, while males are infertile. Although most affected individuals have normal intellectual ability, some exhibit learning difficulties. The prevalence of BS is unknown. In total, a few hundred individuals are described in the literature, one-third of those in the Ashkenazi Jewish population, where a founder mutation is known with a carrier frequency of approximately 1% [17]. The frequency of affected individuals among the Ashkenazi Jewish population was estimated at 1:46,000 to 1:58,000. [17, 18].

Homozygous or compound heterozygous variations in the gene encoding DNA helicase RecQ protein-like-3 (*RECQL3*; OMIM #604610) were identified as the causal underlying genetic mechanism. The product of the *RECQL3* gene is the BLM protein, which acts as a helicase and is involved in all activities that need the opening of the duplex DNA strand, such as DNA replication, RNA transcription, homologous recombination, and other forms of DNA repair. High sister chromatid exchange rates and increased chromosomal breakage due to this defect lead to a high mutational load.

The mean age at cancer diagnosis is 25 years (range 2–49 years). Of 212 malignancies reported in 136 affected individuals, 17% were NHL (mean age 22 years), 13% acute myeloid leukemia (AML; mean age 18 years), 6% acute lymphoblastic leukemia (ALL; mean age 20 years), and carcinomas (intestinal, 15%, 35 years; skin, 13%, 32 years; upper gastrointestinal and respiratory, 10%, 38 years; genitourinary, 9%, 17 years; and breast, 8%, 35 years). Overall, 20% of individuals with BS develop some form of cancer over their lifetime. Screening recommendations include colonoscopy starting at 15 years of age [16].

### Nijmegen breakage syndrome

Nijmegen breakage syndrome (NBS) is an autosomal recessive disease with characteristic features of microcephaly, "bird-like" facies, delayed growth, and progressive intellectual disability. NBS is associated with defects of both the humoral and cellular components of the immune system, as well as a significantly increased risk of developing particularly lymphoid malignancies [19].

NBS was first described in 1981 and the *NBN* gene was identified in 1998 (OMIM #251260). The prevalence is unknown, but seems higher in Eastern European populations [20]. The great majority of NBS patients have a specific *NBN* mutation (NM_002485.4:c.657_661delACAAA, rs587776650). *NBN* encodes for Nibrin, a protein that forms the trimeric MRN complex with MRE11 and RAD50, which plays an essential role in the correct functioning of the *ATM* protein, which is a major player in the cellular response to double-strand DNA breaks [21]. Over 40% of patients with NBS will develop a malignancy by the age of 20, and approximately 25% of all patients will develop a second malignancy [21]. There is a 50-fold risk compared with the general population of developing any cancer, and up to 250-fold risk of lymphomas, predominantly NHL, with diffuse large B cell lymphoma and T cell lymphoblastic lymphoma most commonly reported [19]. Other associated malignancies include acute leukemias, especially T cell ALL and AML, as well as brain tumors, such as medulloblastoma, glioma, and meningioma [22]. Rarely, extracranial solid tumors have been reported, particularly rhabdomyosarcoma.

As seen in other DNA breakage disorders, there is an extreme hypersensitivity to ionizing radiation. It remains controversial whether the common approach of decreasing treatment intensity in this patient cohort in order to minimize toxicity is justified considering the aggressive course of malignancies in NBS [20, 21].

### Artemis syndrome

Artemis syndrome is a T and B cell–negative, natural killer cell–positive severe combined immunodeficiency characterized by extreme sensitivity to ionizing radiation (RS-SCID; OMIM 602450). This is an autosomal recessive disease caused by a mutation on chromosome 10p13 in the gene encoding Artemis (DCLRE1C) [23]. Artemis is a multifunctional protein which plays an important role in maintaining genome stability by intervening in the repair process after DNA double-strain damage [24]. It is also an essential cofactor of V(D)J recombination process in lymphocyte development [25].

The clinical phenotype of this syndrome is broad but usually resembles classical SCID. However, less severe clinical courses have been reported [26].

Different types of malignancies are described, predominantly (EBV-related) lymphomas and carcinomas [27]. Hematopoietic stem cell transplant (HSCT) is the main curative approach, as for other types of SCID [28, 29].

## Predominantly antibody disorders

### Common variable immunodeficiency

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders caused by impairment in B cell differentiation, resulting in defective immunoglobulin production with reduced or absent specific antibody production [30, 31]. CVID is the most common symptomatic PID [5] and is characterized by recurrent bacterial sinopulmonary infections, autoimmune manifestations, gastrointestinal complications, granulomatous disease, and increased susceptibility to malignancies. Clinically, five distinct phenotypes have been

described, i.e., no complications, autoimmunity, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancy. Eighty-three percent of patients have only one of these phenotypes [3, 32, 33]. Laboratory hallmarks include hypogammaglobulinemia, a marked decrease in at least one of the isotypes IgM or IgA, absent isohemagglutinins and/or poor response to vaccines [30, 31]. Approximately, 20% of the patients are diagnosed before 20 years of age, but typically CVID is not diagnosed until 20–40 years of age.

Although several genetic mutations have been reported in subsets of CVID patients, the molecular basis of this disorder remains unclear for the majority of patients [34].

The incidence of malignancy among CVID patients is approximately 10% (range 1.5 to 20.7%) [2]. Knowledge about the process of malignant transformation is limited [35]. However, impaired immunity to herpes viruses, chronic inflammation, and DNA repair defects are known predisposing factors in this group of patients [7, 36].

In a study by the United States Immunodeficiency Network, over 9% of 1285 patients were diagnosed with cancer, 70% of those were CVID patients. They developed most commonly lymphomas ($n = 37$), skin cancer ($n = 23$), and breast cancer ($n = 8$). Twenty percent of malignancies ($n = 24$) were diagnosed in patients < 20 years of age [2].

In a cohort of 233 patients in the Netherlands with CVID, 12.5% developed a malignancy. The malignancies were mostly lymphomas (31%), and the risk of childhood malignancy was significantly increased compared with the general population [3] (Fig. 2).

There are no specific surveillance or treatment protocols for malignancies in CVID patients. Whole genome studies in combination with profiling of patient-derived tumor tissue might elucidate mechanisms of increased susceptibility to malignancies in the future [35].

## Autoimmune lymphoproliferative syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is a genetic disease characterized by a defect in lymphocyte apoptosis, which leads to immune dysregulation. The exact incidence and prevalence of this syndrome is unknown, as a significant proportion of patients remain undiagnosed [37]. Over 500 patients with hereditary ALPS have been reported from over 300 families [38]. In up to two-thirds of ALPS patients, the pathogenesis results from defective lymphocyte apoptosis through dysregulation of the FAS pathway, with a heterozygous germline mutation in the FAS gene (*TNFRSF6*; CD95; OMIM #134637) [37]. A smaller proportion of patients has mutations in other genes within the same pathway such as Caspase 10 and Fas-Ligand [39]. In some, a causative genetic alteration cannot be found despite the increased use of novel sequencing methods [40].

Clinically, the hallmark of this disease is non-malignant lymphoproliferation (lymphadenopathy and hepatosplenomegaly with or without hypersplenism), usually found incidentally in an otherwise healthy-looking child [38, 41]. Patients can also present with autoimmune disease. Eighty percent present with pallor, fatigue, and jaundice due to hemolytic anemia, while the rest result in thrombocytopenia-related bleeding and bacterial infections due to neutropenia. The pathognomonic laboratory finding is increased CD4-CD8-TCR alpha/beta+ (double negative) T cells double negative T cells [38].

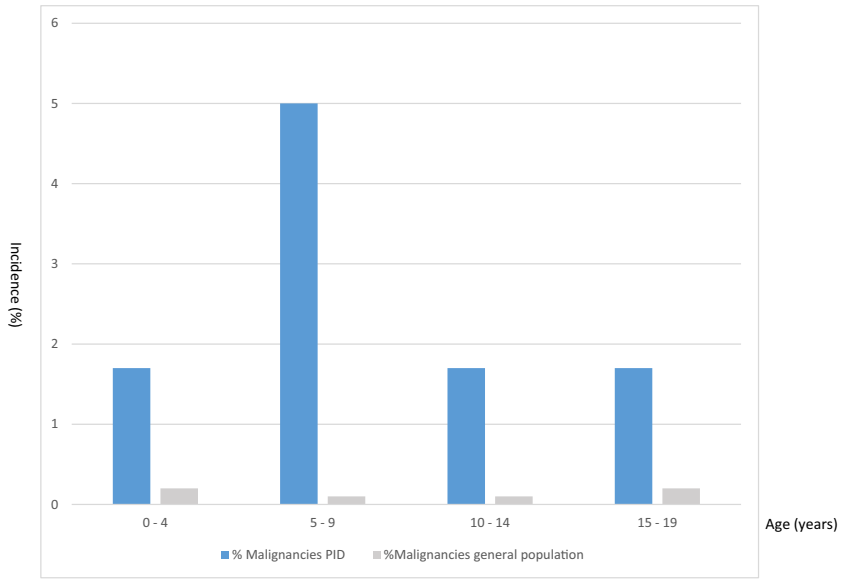


**Fig. 2** Age distribution of malignancies in children with CVID vs general population[3]

*FAS* is thought to be a tumor suppressor gene silenced in several different types of tumors. ALPS has been mainly associated with a 50-fold increased risk of developing Hodgkin lymphoma (HL), and a 14 times increase in occurrence of NHL compared with the general population [38]. Researchers from the National Institute of Health reported a total of 26 malignancies from 346 ALPS patients. While 21 patients had lymphomas, other tumors included testicular cancer, squamous cell carcinoma of the tongue, parotid gland acinic tumor, chronic myeloid leukemia, and Philadelphia positive ALL [42].

### GATA2 deficiency

A spectrum of disorders is associated with GATA2 deficiency. Emberger syndrome is characterized by primary lymphedema, lymphocyte subset changes with a low CD4/CD8 ratio, severe and widespread cutaneous warts, and sensorineural deafness [43]. MonoMAC syndrome was termed in 2011 based on the features of severely low or absent monocytes and disseminated non-tuberculous mycobacterial infections, classically *Mycobacterium avium* complex [44]. B lymphocytes, natural killer cells, and dendritic cells are also often low. Human papilloma virus (HPV) infections, opportunistic fungal infections, and pulmonary disorders with alveolar proteinosis are reported [45]. Hypocellular bone marrow with dysplasia of all lineages is often present. Patients have a high risk for developing myelodysplastic syndrome (MDS) and AML.

*GATA2* (OMIM #3137295) was initially associated with myeloid malignancies in 2011 and later identified as the most common germline predisposition gene in pediatric MDS, with 7% of all primary MDS and 15% of advanced MDS patients harboring a *GATA2* germline mutation [46]. Bone marrow cytogenetic changes of monosomy 7 and trisomy 8 are seen in 37% and 16% of patients with *GATA2* germline mutations, respectively. Adolescents with MDS are at increased risk of having a germline *GATA2* germline mutation without impact on prognosis compared with MDS without underlying germline changes [47].

GATA2 is a nuclear regulatory protein and highly expressed in immature hematopoietic cells. Disruption of its activity is believed to contribute to leukemogenesis. Myeloid neoplasia presents at an average age of 20 years with a wide range in the literature. Some cohorts reported up to 90% of affected individuals with a myeloid malignancy. There are reports of squamous cell carcinomas of the genital tract, and head and neck solid tumors, which are associated with viral infections (EBV, HPV). Solid tumors are seen in 14% of affected individuals and include breast cancer, adenocarcinoma of the pancreas, renal cell carcinoma, and locally invasive desmoid tumors of the chest wall. Skin cancers (basal cell carcinoma, squamous cell carcinoma, and malignant melanoma) were found in 6/57 patients in one report (11%) [43]. The high risk of malignancies favors close follow-up of patients tailored to their respective presentation and timely consideration of HSCT for MDS and AML [47].

## Combined immunodeficiency

### Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency disorder known by the classic triad of immunodeficiency, microthrombocytopenia, and eczema [48]. The incidence is approximately one to four cases per million live male births, with an average age at diagnosis of 24 months in classic cases. The *WAS* gene is located at Xp11.22–p11.23.1 (OMIM #300392) and encodes the WAS protein (WASp), which is expressed in non-erythroid hematopoietic cells [48].

Clinically, most patients with WAS suffer from recurrent infections and bleeding due to thrombocytopenia. Other manifestations may include eczema, autoimmune phenomena, and malignancy. The development of malignancies in WAS is frequent, and affected individuals have a poor prognosis. In children with a severe phenotype, prevalence of malignancy ranges from 13 to 22% with an average age of onset of 9.5 years. This risk is 5% in milder forms of the disease with an average age of onset of 34 years [49]. Lymphomas, predominantly NHL, are often EBV-associated and the most frequent form of neoplasm, presenting mostly in extranodal sites. Other hematopoietic malignancies include myeloproliferative diseases and myelodysplasia. Solid malignancies include testicular seminoma and carcinoma, glioma, and Kaposi sarcoma [50].

The increased risk of developing malignancies may be explained by abnormal WASp function leading to impaired dendritic cell function, T lymphocytes, and NK cell cytotoxicity. This results in defective elimination of virally infected and/or malignant cells. Currently, HSCT is the only curative treatment option for patients with WAS [51]. Gene therapy however is a promising potentially curative treatment [52].

## Discussion

PID are relatively rare and large-scale statistics on pediatric patients with malignancies, and their entire spectrum of preexisting conditions, clinical characteristics, and outcome are scarce. The majority of data originates from retrospective analyses for individual subtypes of PID or specific malignancies such as NHL. Children and adolescents with PID tend to be younger at presentation with their malignancy, and there is a male predominance [53]. NHL, predominantly B cell type,

higher histological grade, extranodal involvement, such as gastrointestinal and central nervous system, as well as EBV-related lymphoproliferative disease are more common in patients with PID [1, 53, 54]. Multiple factors might be involved in developing malignancies in the different PIDs, such as failure in surveillance, infection susceptibility, and DNA breakage. Collaboration between immunologists and hematologist/oncologists in a multinational registry for children and adolescents with PIDs and malignancies is required to better understand the full spectrum of malignancies and associated complications. This would capture detailed information on chemotherapy regimens, specific adjustments, treatment-related toxicity, and outcome data including event-free and overall survival, and second malignancies. Sequencing of germline and somatic tissues would allow identification of high-risk patients and to potentially perform targeted trials [55].

Specific recommendations for cancer surveillance are limited, but for several syndromes, recommendations for surveillance have been published, though these guidelines are based on expert panel opinion due to limited data [15]. In general, once PID is diagnosed, physical exams as surveillance, with or without laboratory testing and imaging evaluations, is encouraged. Most importantly, patients should be taught to have a high index of suspicion for malignancies and report changes in their health. Education of physicians about the risk of malignancies during childhood in PID and the awareness of considering underlying PID in children who present with a malignancy will accelerate diagnosis, personalize treatment, and ultimately improve outcome in the future.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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