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# Treatment-related toxicities in children with acute lymphoblastic leukaemia predisposition syndromes

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ABSTRACT

Although most children with acute lymphoblastic leukaemia (ALL) do not harbor germline mutations that strongly predispose them to development of this malignancy, large syndrome registries and detailed mapping of exomes or whole genomes of familial leukaemia kindreds have revealed that 3–5% of all childhood ALL cases are due to such germline mutations, but the figure may be higher. Most of these syndromes are primarily characterized by their non-malignant phenotype, whereas ALL may be the dominating or even only striking manifestation of the syndrome in some families. Identification of such ALL patients is important in order to adjust therapy and offer genetic counseling and cancer surveillance to mutation carriers in the family. In the coming years large genomic screening projects are expected to reveal further hitherto unrecognised familial ALL syndromes. The treatment of ALL cases harboring cancer predisposing mutations can be challenging for both the physician and the patient due to their preexisting symptoms, their reduced tolerance to radio- and/or chemotherapy with enhanced risk of life-threatening organ toxicities, and the paucity of data from ALL patients with the same or similar syndromes being treated by contemporary protocols. Recent studies clearly indicate that many of these patients stand a good chance of cure, and that they should be offered chemotherapy with the intention to cure. Some of these syndromes are characterized by reduced tolerance to radiotherapy and/or specific anticancer agents, while others are not. This review summarises our current knowledge on the risk of acute toxicities for these ALL patients and provides guidance for treatment adjustments.



## 1. Introduction

Treating a malignancy in a child with a cancer predisposition syndrome can be a very delicate balance between efficacy and toxicity, since many of these patients are burdened by their medical condition and may in addition be at increased risk for chemo- and radiotherapy-induced toxicities. It adds to the problem that such patients are generally excluded from collaborative clinical trials, their outcome is rarely reported, and accordingly little is currently known with respect to the treatment intensity needed to provide a reasonable balance between efficacy and toxicity.

Childhood acute lymphoblastic leukaemia (ALL) in patients with predisposing germline mutations provides an excellent example of these treatment challenges, but the questions that arise are equally relevant for many other childhood malignancies, where the relative frequencies of predisposition syndromes are much higher, such as myeloid neoplasias or brain tumors (Locatelli and Niemeyer, 2015; Hasle et al., 2000; Malkin et al., 2014).

Acute lymphoblastic leukaemia (ALL), the most common childhood cancer, was universally fatal just two generations ago, but now yields five years overall survival rates of ninety percent with the best contemporary treatment (Pui et al., 2012). As a consequence, the risk of death due to leukaemia currently equals the risk of treatment-related mortality, primarily due to infections (Lund et al., 2011) or second cancer (Schmiegelow et al., 2013), and a considerable proportion of survivors, even from standard risk ALL, are burdened by life-long sequelae (Winther and Schmiegelow, 2014). Accordingly, collaborative clinical trials have in recent years focused not only on preventing leukaemic relapse, but also on

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identifying patients who can be cured by less intensive therapy to minimise toxicity, and international groups have been established to reach consensus on definitions and reporting of several toxicities (e.g. the Ponte di Legno toxicity working group (Hunger et al., 2013)). Unfortunately, patients with predisposing syndromes have also in these efforts been excluded, emphasising the need to specifically address this subset of children with ALL. This review summarises our current knowledge on the risk of acute toxicities for these ALL patients and provides guidance for treatment adjustments.

## 2. Childhood ALL predisposing syndromes

Most syndromes associated with an increased risk of childhood ALL (Table 1) are primarily characterised by their non-malignant phenotype. However, genome-wide and targeted germline DNA sequence analyses have in recent years identified several syndromes associated with development of ALL as their primary, or even only phenotype (Zhang et al., 2015a; Shah et al., 2013a; Holmfeldt et al., 2013), and it is expected that this list will grow in parallel with whole exome (WES) or whole genome sequencing (WGS) of increasing patient numbers.

The critical pathway(s) responsible for the strong association between childhood ALL and Down syndrome still remain to be revealed (Hasle et al., 2000). In contrast, the rarer ALL predisposing syndromes can be classified according to their affected cellular pathways, which involve tumor suppressor genes, DNA repair and RAS-MAPK pathway genes, and more rarely immune deficiencies and bone marrow failure syndromes. To this adds the heterogenous group of familial ALL syndromes where childhood ALL is a dominating phenotype (Schmiegelow et al., 2012), and where the driving mutations are just beginning to be revealed (e.g. *ETV6* and *PAX5* mutations) (Zhang et al., 2015a; Shah et al., 2013a).

## 3. Germline polymorphisms

Several single nucleotide polymorphisms (SNPs) such as *ARID5B*, *CDKN2A*, *IKFZ1*, *and GATA3*, have been associated with the risk of developing childhood ALL in general or of specific subsets (Xu et al., 2015; Trevino et al., 2009), including high-hyperdiploidy (Trevino et al., 2009), Ph+ ALL (Perez-Andreu et al., 2013), and older age at diagnosis (Perez-Andreu et al., 2015), and several of these genes are frequently also affected by somatic mutations (e.g. *IKFZ1*, *CDKN2A*, *GATA3*), emphasising the continuum between germline variants and somatic mutations for leukaemogenesis. Compatible with the relatively low ALL odds ratios for carriers of these risk alleles most are non-coding variants, but even coding variants have been detected (Xu et al., 2015). So far none of the genes affected by these ALL predisposing variants in otherwise healthy individuals have so far not been reported to be germline mutated in familial ALL kindreds or been associated with specific toxicities. However, *CDKN2A* is the most commonly mutated gene in familial melanoma (Meyle and Guldberg, 2009), and Ikaros, which plays a critical role in normal hemato- and lymphopoiesis, have been reported germline mutated in congential pancytopenia (Goldman et al., 2012). In addition, other single nucleotide polymorphisms (SNPs) may

**Table 1**
Familial acute lymphoblastic syndromes. AD = autosomal dominant; AR = autosomal recessive; GI = gastrointestinal; HD-MTX = high-dose methotrexate; XL = X-linked.* For most of the syndromes the risk figures are very uncertain due to low numbers of leukaemia cases and/or lack of cohort-based registries.

| | Gen | Locus | Inheritance | All subtype association | Risk of all* | Enhanced toxicities | Treatment adaptation or enhanced surveillance |
|---|---|---|---|---|---|---|---|
| **Down syndrome (trisomi 21)** | No specific candidate genes | | >95% sporadic | B-cell precursor | 1–2% | Infections, GI toxicity | Reduction/avoidance of anthracyclines; reduced, individualised HD-MTX doses, immunoglobulin substitution |
| **Tumor suppressor gene syndromes** | | | | | | | |
| Li-Fraumeni syndrome | *TP53*, *CHEK2* | 17p13.1, 22q12.1 | AD | Hypodiploid | ~5% | SMN | Avoid prophylactic CNS irradiation |
| **DNA repair gene syndromes** | | | | | | | |
| Mismatch repair cancer syndrome | *MLH1*, *MSH2*, *MSH6*, *PMS2*, | 3p22.2, 2p21, 2p16, 7p22.2 | AD[1] | T-cell | 5–10% | Unknown | Potentially reduced sensitivity to DNA damaging drugs, including thiopurines |
| Fanconi anemia | *FANC A-E*, *BRCA* | 16q24.3, 9q22 | AR | ? | Very low | Radiosensitivity | Avoid irradiation and DNA damaging drugs |
| Ataxia telangiectasis | *ATM* | 11q22.3 | AR | T-lineage | ~5% | Radiosensitivity | Consider reduction of anthracyclines and alkylating agents |
| Nijmegen breakage syndrome | *NBS1* | 8q21.3 | AR | T-lineage | 50% | Radiosensitivity | Consider reduction of anthracyclines and alkylating agents |
| Bloom syndrome | *BLM* | 15q26.1 | AR | ? | 5–10% | Radiosensitivity, diabetes? | Potential increased risk of hyperglycemia with steroids |
| **RAS pathway mutations, incl NF1** | | | AD | ? | <1% | | No treatment adaptation |
| **Bone marrow failure syndromes** | | | | | | | |
| Diamond-Blackfan anemia | *RPS19*, *RPL5*, *RPL11* | 19q13.2, 1p22.1, 1p35 | AD, AR, S | ? | Increased? | | No data supporting treatment adaptation |
| Dyskeratosis congenita | | | AD, AR, S, XL | ? | Increased? | | Avoid/reduce alkylating agents and radiation |
| TAR syndrome | *RBM8A* | 1q21.1 | AR, S | ? | Increased? | | No data supporting treatment adaptation |
| **Immunodeficiency syndromes** | | | | | | | |
| Wiskott-Aldrich syndrome | *WASP* | Xp11.23 | XL | ? | Increased? | | Immunoglobulin substitution |
| Brutons agammaglobulinemia | *BTK* | Xq22.1 | XL | ? | Increased? | | Immunoglobulin substitution |
| **Pure familial ALL** | | | | | | | |
| PAX5 syndrome | *PAX5* | 9p13.1 | AD | BCP | Very high | | No data supporting treatment adaptation |
| ETV6 syndrome | *ETV6* | 12p13 | AD | BCP | Very high | Myelosuppression | Dose reduction may be warranted in case of severe myelosuppression |
| RUNX1 syndrome | *RUNX1* | 7p/q | AD | T-ALL | Unknown | | No data supporting treatment adaptation |

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influence the risk of cancer for patients with a specific cancer predisposing syndrome (Id Said and Malkin, 2015), and many SNPs modify the efficacy and toxicity of childhood ALL therapy (Moriyama et al., 2015). However, for patients with familial ALL syndromes extensive international collaboration is needed to determine, if the impact of these response modifying SNPs is enhanced in familial ALL syndrome patients.

## 4. ALL non-predisposing syndromes

Due to the very high number of childhood ALL cases diagnosed globally each year, occasional cases will present with both ALL and a non-associated syndrome, which in addition may be detected only due to the routine cytogenetic work-up, e.g. Klinefelter syndrome or Turner syndrome (Hasle et al., 1996; Bache et al., 2006). Although, these syndromes are not associated with leukaemogenesis, they may influence drug disposition or toxicity profiles with anticancer therapy. Accordingly there is also a need for collaborative, prospective, systematic and standardised registration of such co-morbidities in childhood ALL, but they will not be addressed further in this review.

## 5. Treatment-related toxicities

The excellent overall survival rates for childhood ALL has been achieved by extensive exploration of the biology of the malignant clone and the pharmacology of the antileukaemic agents, by detailed monitoring of treatment response, and by numerous, well-designed, randomized clinical trials (Pui et al., 2012). However, it is incompletely determined, which of the multiple targets of the broadly acting and routinely applied 10–15 antileukaemic drugs that are responsible for the cell kill, and which are superfluous for the individual patient.

The antileukaemic drugs routinely used in front-line therapy can roughly be divided into three groups: A) antimetabolites (i.e. methotrexate, thiopurines, cytarabine) that are affecting the reduced folate pool, nucleotide metabolism, or act as nucleotide analogues and are incorporated into DNA, B) the directly DNA-damaging drugs (anthracyclines and alkylating agents), and C) post-transcriptionally acting drugs (vincristine, glucocorticosteroids and asparaginase). Due to their profound myelo- and immunosuppressive and DNA-damaging effects it is primarily the use of group B agents that in recent years have been reduced or even avoided for standard risk ALL, but both group A and group C drugs have been associated with significant or even life-threatening toxicities, including ileus (vincristine), pancreatitis (asparaginase), osteonecrosis (glucocorticosteroids), leukoencephalopathy (methotrexate), and second cancers (asparaginase and thiopurines). No drugs are “safe”, and which drugs that are most critical for cure of the individual patient, or strongest associated with toxicity cannot yet be determined. Since cancer is driven by mutations, and these in general occur more frequently in the patients with an ALL predisposition syndrome, it is specifically the use of group B agents that have been reduced or avoided in patients with known predisposition syndromes. However, the scientific support hereof is generally weak, and in many cases an individualised trial and error approach is warranted.

## 6. Down syndrome

Children with Down syndrome (DS) are at high risk of developing B-cell precursor ALL (DS-ALL), and they account for 2–3% of all childhood ALL cases (Hasle et al., 2000). Their inferior outcome reflects both an increased risk of relapse and of infection-associated mortality, especially during induction but notably throughout all treatment phases (Buitenkamp et al., 2014), whereas their risk of second cancer seems reduced (Schmiegelow et al., 2013). Patients with DS-ALL encounter more gastrointestinal toxicity, which may be related to a gene dose effect of the reduced folate carrier (*SLC19A1*) encoded on chromosome 21 (Buitenkamp et al., 2010; Garre et al., 1987). Although some treatment guidelines have been provided to avoid toxicity (Izraeli et al., 2014), these are not evidence-based. The well-documented excessive risk of infections and treatment-related mortality (Buitenkamp et al., 2014) in DS-ALL patients reflect severe quantitative and qualitative developmental and functional immune deficiencies being most pronounced for the B-cell compartment (Cetiner et al., 2010; Ram and Chinen, 2011), and even in non-leukemic children with DS, the immunodeficiencies are reflected in increased susceptibility to severe respiratory infections and bacteremias (Ram and Chinen, 2011). It is uncertain how the trisomic gene-dose effect determines the immunodeficiency, and the aberrant gene expressions profile of DS-ALL extents beyond the chromosome 21 genes (Letourneau et al., 2014). For the 10–15% of DS-ALL patients, who harbor an *ETV6-RUNX1* translocation or a high-hyperdiploid clone, the risk of relapse is significantly reduced (overall event hazard ratios 0.14 and 0.68, respectively), and for these subsets deescalation of chemotherapy may be indicated to avoid life-threatening toxicity (Buitenkamp et al., 2014). Accordingly, many collaborative groups now restrict the use of anthracyclines in induction therapy to those patients who responded poorly on day 15, and offer reduction in high-dose methotrexate (HD-MTX) due to its association with enhanced risk of toxicity with subsequent toxicity-guided dose escalation (Izraeli et al., 2014). For non-DS ALL patients, post-HD-MTX myelosuppression can be reduced or avoided by lowering the dose of concurrently administered 6-mercaptopurine (Vang et al., 2015), but the benefit of this approach has not been explored in DS-ALL. Since methotrexate/mercaptopurine-based maintenance therapy even in non-DS patients induce significant immune deficiency, not least in the B-cell compartment (Caver et al., 1998; Luczynski et al., 2004), DS-ALL patients should be monitored closely and offered preventive immunoglobulin substitution, if hypogammaglobulinemia is encountered. Importantly, the tendency to unnecessarily reduce the treatment intensity for these patients has in a recent study been shown to significantly increase the risk of relapse (Bohnstedt et al., 2013).

## 7. Li-Fraumeni syndrome

Li-Fraumeni syndrome is an autosomal dominant disorder characterized by a dramatically increased lifetime risk of developing cancer (specifically breast cancer, sarcomas, brain tumors (especially glioblastoma), adrenocortical carcinoma, and more rarely leukaemias and lymphomas), and the cumulative risk for cancer is virtually 100% (Bougeard et al., 2015). Most patients harbor a germline mutation in *TP53* encoding p53, which is involved in DNA-damage response and cell cycle control. Some Li-Fraumeni-like families carry mutations in p53 regulating genes (e.g. *CHEK2*), while for other Li-Fraumeni-like families no mutations have been identified (Bougeard et al., 2015). p53's critical role in cancer is emphasized by it being somatically mutated in >50% of all human cancers.

Patients with *TP53* and mutation are expected may be more sensitive to the DNA-damaging effect of chemotherapy and not least irradiation, but currently there is little data to adjust treatment modification in ALL patients with germline *TP53* or *CHEK2* mutated patients (Wong and Han, 2014; Kappel et al., 2015). The risk of second cancers in patients with Li-Fraumeni syndrome is clearly increased, but this may primarily reflect the predisposition syndrome, although radiotherapy and to a lesser extent

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chemotherapy also seem to play a role (Talwalkar et al., 2010; Schulz et al., 2012; Felix et al., 1996; Cohen et al., 2005). Prophylactic cranial irradiation should be avoided, not least since the necessity of this treatment component is generally questioned as part of front-line ALL therapy (Richards et al., 2013). For children with central nervous system relapse, the cure of the patient is the primary goal and cranial irradiation should be given according to normal standards of care.

Currently, there is no evidence-based support for reduction of chemotherapy for Li-Fraumeni children with ALL. Published data on patients with hypodiploid ALL offer some indication of the risk of chemotherapy-induced toxicity in childhood ALL. Forty-three percent of patients with low-hypodiploid ALL harbor germline *TP53* mutations (Holmfeldt et al., 2013). Although the toxicity burden for this subset of hypodiploid patients has not been explored in depth, two somewhat overlapping cohort studies from the Ponte di Legno group (Nachman et al., 2007) and the US Childrens Oncology Group (Heerema et al., 1999) indicate an overall increased risk of death during induction or in first in remission for patients with hypodiploid ALL being 7–8% compared to only 2–3% in non-Li Fraumeni patients (Lund et al., 2011; Prucker et al., 2009). Due to the generally poor outcome for patients with hypodiploid ALL (Nachman et al., 2007), these data do not by themselves indicate reduction of treatment intensity for ALL patients with Li-Fraumeni syndrome, but they do indicate intensified surveillance and supportive measures.

## 8. DNA repair gene syndromes

DNA damage surveillance and repair mechanisms are critical cellular survival processes that are constantly active as a response to random or induced (e.g. by irradiation or chemotherapy) changes in nucleotide sequence or spatial DNA structure. When they fail, mutations can accumulate, and if they do not lead to senescence or programmed cell death, ultimately uncontrolled cell proliferation occurs i.e. cancer. Not surprisingly, patients with DNA repair gene syndromes have an extreme risk of adverse reactions to radiation therapy (Pollard and Gatti, 2009).

### 8.1. Constitutional mismatch repair deficiency syndrome

Monoallelic mutations in the mismatch repair genes mostly cause colorectal cancers, typically in the 4th or 5th decade of life, and childhood cancer in this context is a rare phenotype. However, patients with biallelic mutations of mismatch repair genes, i.e. *MLH1*, *MSH2*, *MSH6 or PMS2*, (constitutional mismatch repair deficiency) have an excessive risk of childhood cancers (primarily brain, gastrointestinal and hematological malignancies) (Wimmer et al., 2014; Bakry et al., 2014a), including increased risk of childhood ALL (Wimmer and Kratz, 2010). Although these patients' mismatch repair markedly enhance their risk of developing malignancies, it may also reduce their response to DNA damaging chemotherapy, including to the accumulation of thioguanine nucleotides in DNA during thiopurine-based maintenance therapy, since the cytotoxicity of thiopurines specifically depend on interaction with an intact mismatch repair system (Bodo et al., 2015; Hedeland et al., 2010; Waters and Swann, 1997; Swann et al., 1996; Durno et al., 2015; Bakry et al., 2014b). However, their mismatch repair deficiency may open up for novel treatment approaches (Le et al., 2015).

### 8.2. Fanconi anemia

This recessive disorder involves mutations in a cluster of genes involved in the Fanconia anemia (FA) core complex (Kim et al., 2012). In addition to their non-malignant phenotype, including short stature and bone-marrow failure, FA patients have a propensity for development of myeloid neoplasias, although cases of ALL have also been described (Spinella et al., 2015; Shah et al., 2013b). They are excessively sensitive to DNA cross-linking anticancer agents and radiotherapy, and both conventional antileukaemia therapy chemotherapy and conditioning regimens for hematopoietic stem cell transplantation (hSCT) should be modified accordingly to avoid (or markedly reduce) such exposures (Goldsby et al., 1999). Case reports indicate that antimetabolite-based chemotherapy is well tolerated (Mehta et al., 2007), and post-transcriptional antileukemic agents should in case of ALL be given at full doses (see above).

### 8.3. Ataxia telangiectasia (AT) and Nijmegen breakage syndrome (NBS)

Whereas the phenotypes of these DNA repair deficiency syndromes are quite different, they share excessive risk of cancer (especially lymphoid malignancies), enhanced radiosensitivity (Pollard and Gatti, 2009), and immune deficiency. Importantly, these syndromes have not always been recognized at the time of malignancy development (Bienemann et al., 2011; Hersby et al., 2015). Although, the cure rate for such patients previously was reported to be quite dismal (Sandoval and Swift, 1998), a recent large German cohort encompassing 38 children with AT or NBS showed acceptable overall survival rates (>50%), even among patients who received reduced chemotherapy doses (Bienemann et al., 2011). They may have an increased risk for cyclophosphamide-induced cystitis, which supports dose reductions of this agent (Sandoval and Swift, 1998). Their reported 10–20% increased risk of toxic death (Bienemann et al., 2011) probably reflect both their immune deficiency and increased chemosensitivity. Thus, the balance between pursual of cure and avoidance of toxicities should reflect the preexisting burden of symptoms for the individual patient. Initial treatment adaptation may be warranted. Anthracyclines and alkylating agents should probably be given during induction therapy, with subsequent full drug dosage as by protocol therapy depending on the tolerance to chemotherapy. Central nervous system (CNS) irradiation should always be avoided.

### 8.4. Bloom syndrome

These patients harbor biallelic mutations in the *BLM* gene characterized by genomic instability and phenotypically by short stature, a facial rash in early life after sunlight exposure, and high cancer predisposition. These patients also have an increased risk for development of diabetes, and is may be relevant to monitor hyperglycemia during glucocorticosteroid and asparaginase containing antileukemic therapy, although this has not been explored in Bloom syndrome patients. Little is known of their tolerance to anticancer therapy, but the guidelines listed for AT and NBS are likely to be applicable.

## 9. RAS signalling pathway mutations

Somatic mutations in the RAS signaling pathway are common in ALL, and childhood ALL has occasionally been reported in patients with germline mutations in this pathway. Such patients include neurofibromatosis type 1, Noonan syndrome and Noonan syndrome with multiple lentigines, and cardiofaciocutaneous syndrome (Wimmer et al., 2014; Kratz et al., 2011). Patients with the most common RASopathies, neurofibromatosis type 1 and Noonan syndrome, primarily develop juvenile myelomonocytic leukaemia, however, childhood ALL has also been reported to occur in these

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patients. However, the risk of ALL in patients with RASopathies is only very moderately increased (Kratz et al., 2015). Currently, there is no data supporting ALL treatment adaptation for these patients.

## 10. Other bone-marrow failure syndromes

Cancer is five-fold increased among patients with Diamond-Blackfan anaemia (Vlachos et al., 2012; Alter, 2007), but almost no ALL cases have been reported (Willig et al., 2000), either because this is not an ALL prone syndrome, or hypothetically due to the common treatment of Blackfan-Diamond anemia with glucocorticosteroids that could eliminate preleukemic cells at an early stage of leukemogenesis (Schmiegelow et al., 2008). If ALL is diagnosed in such patients, there is no indication for treatment adaptation, although ALL development in spite of glucocorticosteroids therapy indicates stratification to higher risk therapy. Patients with other bone-marrow failure syndromes may develop myeloid neoplasias, but only very few cases of ALL have been reported in patients with dyskeratosis congenita (Kalasekhar et al., 2015) or thrombocytopenia with absent radii syndrome (Alter, 2007; Camitta and Rock, 1993). Treatment modifications and intensified surveillance may be indicated depending on specific preexisting organ deficiencies. Furthermore, many patients with bone-marrow failure syndromes, including dyskeratosis congenital, are highly sensitive to radiation and alkylating agents (Chirnomas and Kupfer, 2013).

## 11. Immune deficiency syndromes

These syndromes, including Wiskott-Aldrich syndrome and Brutons X-linked agammaglobulinemia, are know to be associated with an increased risk of lymphoma, whereas almost no cases of childhood ALL has been reported (Hoshino et al., 2015; Albert et al., 2011). Except for substitution of immunoglobulins, no adaptation of therapy is indicated.

## 12. Pure familial ALL

The very high ALL subtype concordance rate for familial cases of ALL indicates that germline mutations, even among sporadic cases, may be more common than generally anticipated, since ALL may be the only or at least dominant phenotype in these, sometime called “pure”, familial ALL syndromes (Schmiegelow et al., 2012; Winther et al., 2001; Hemminki and Chen, 2004). Recent studies have supported this by identifying germline mutations in genes that not only plays a key role in B-lympocyte development and differentiation, but which frequently are somatically mutated in childhood ALL, i.e. *PAX5*, *ETV6*, and *RUNX1*. Importantly, the clinical presentation and cure rate for so-called pure familial ALL seem similar to that of sporadic ALL (Schmiegelow et al., 2012), indicating that their risk of toxic death in general is not markedly increased, although some of the syndromes may be associated with significant toxicity (Zhang et al., 2015a; Topka et al., 2015).

*PAX5*: Heterozygous germline variant in *PAX5* has recently been found in two unrelated kindreds with B-lineage ALL, where all patients had deletion of the normal allele at 9p13 (Shah et al., 2013a; Miething et al., 2013; Auer et al., 2014a, 2014b). Importantly, neither the obligate carriers nor the patients with ALL had any other clinical manifestations. In total 10 individuals had been diagnosed with ALL in these two kindreds. No data on their response to chemotherapy were reported, but seven of nine cases diagnosed with ALL in the two youngest generations were alive at the time of publication.

*ETV6*: Several independent studies have recently identified families with germline mutations in ETV6 and high propensity for mild to moderate thrombocytopenia, red cell macrocytosis and ALL (Zhang et al., 2015a; Topka et al., 2015; Noetzli et al., 2015). One carrier clearly had dysmorphic features (Topka et al., 2015), but it remains to be reported how many additional patients have dysmorphic traits. Noteworthy, the risk of other cancers, including myeloid neoplasia and carcinomas, seemed to very high in the reported families. Although based on few cases, some were reported to have an increased risk of severe chemotherapy-induced myelosuppression (Zhang et al., 2015a; Topka et al., 2015).

*RUNX1*: Germline mutations in *RUNX1* are known to cause familial platelet disorder and an increased risk of myeloid malignancies. However, some mutation carriers lack a bleeding and/or thrombocytopenia history and a few cases of T-cell ALL have been reported (Liew and Owen, 2011). The tolerance to chemotherapy in these T-ALL patients have not been reported, and although these patients may more frequent require thrombocyte transfusions, general adjustments of chemotherapy doses is not warranted.

## 13. Discussion

Although most of the ALL predisposing syndromes affect DNA integrity or haematopoiesis, the risk of cancer development, and specifically ALL, vary widely as do their tolerance to chemotherapy, and no general dose adjustments guidelines can be given. Due to the rarity of these patients, there is an unmet need for an international registry of case reports of treatment-related toxicities in children with ALL predisposition syndromes. Although potential platforms for such case reporting already exist (e.g. www.casereports.bmj.com), the cases are unsystematically reported.

Recent whole genome or whole exome sequencing have demonstrated that almost 10% of all childhood cancer patients harbour germline mutations likely to have contributed to their cancer development (Zhang et al., 2015b). However, even within each cancer predisposition syndrome significant genotype-phenotype diversity exists. This has most extensively been explored for patients with Li-Fraumeni syndrome, where germline mutations in the DNA binding portion of *TP53* cause higher cancer risks in Li-Fraumeni families than mutations outside this region (Sorrell et al., 2013). Furthermore, common SNPs in *TP53* may also modify cancer risks and/or prognosis (Horgan et al., 2011).

The most important task for the paediatric oncologist is the recognition of these syndromes, not least since ALL may be their first manifestation. Siblings and parents may be undiagnosed germline mutation carriers, which can be critical for decisions on therapy, including in determining if the child with ALL are to benefit from any of these close relatives as donors for allogeneic hSCT. To this adds indications for genetic counselling, obtaining a pedigree and future surveillance of both the patient and affected familiar members (Villani et al., 2011).

Due to the relatively high frequency of DS among childhood ALL patients, several large multinational cohort studies have in recent years explored the risk of life-threatening toxicities for these patients, and some guidelines on how to counteract them has emerged. For the remaining syndromes very little is known in this respect. This emphasizes the need for establishment of an international register for rare familial ALL syndromes (as well as for other syndromes with increased childhood cancer susceptibility) with detailed registration of exposures to chemotherapeutic agents, radiotherapy and hSCT, as well as occurrence of toxicities. Once established such a registration must be user-friendly and simple, yet covering a broad spectrum of toxicities, which has been shown feasible for childhood ALL in general (Frandsen et al., 2014). A European Working group with this target has recently been established (see introductory commentary).

Future large scale studies of the genomic landscape of both pediatric tumors as well as the patients' germline DNA, such as the

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Paediatric Cancer Genome Project (http://explore.pediatriccancergenomeproject.org/) will provide not only an unprecedented platform for understanding cancer development, but also the impact of germline mutations and modifiers of their penetrance, as well as associations with the risk of side effects. As humans we all both benefit from and are burdened by our unique and private genome, which are excessively tested when we expose patients to the shotgun effects of conventional anticancer therapy. The large and costly genome mapping projects will yield huge amounts of data, but their ultimate clinical value for the individual patient will be strongly dependent on the efforts and resources put into deep phenotyping, which includes detailed registration of treatment responses for cancer occurring in patients both without and with cancer-promoting germline mutations.

## Conflicts of interest

Nothing to declare.

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