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# It's ALL in the Family: *IKZF1* and Hereditary Leukemia

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## Abstract

*IKZF1* plays an essential role in lymphopoiesis, and somatic *IKZF1* variants in acute lymphoblastic leukemia (ALL) are associated with poor prognosis. In this issue of *Cancer Cell*, Churchman et al. add to the list of leukemia predisposition genes with the identification and characterization of germline *IKZF1* variants in childhood ALL.

Acute lymphoblastic leukemia (ALL), the most common childhood malignancy, has traditionally been regarded as a non-hereditary disease. With the exception of rare familial cases, initial genetic studies in ALL, as in other cancers, have largely focused on somatically acquired mutations in malignant cells. However, given that pediatric cancers occur early in life, it is perhaps not surprising that germline mutations predisposing to childhood cancers have increasingly been described, even among cases initially presumed to be sporadic (Kratz et al., 2016). Germline mutations inform medical management and advance our understanding of the role of these genes in development and tumorigenesis.

Germline *TP53* mutations, for example, cause Li-Fraumeni syndrome, with increased risks of a variety of cancers, including ALL. Genomic profiling has identified somatic mutations in approximately 90% of low-hypodiploid ALL, with about 40% concurrently present in nontumor cells, suggesting likely germline origin (Holmfeldt et al., 2013). Another growing category of genes implicated in predisposition to lymphoid malignancy are those encoding transcription factors that orchestrate lymphoid development. Somatic variants of *PAX5*, critical for the maturation of B cells from pro/pre-B cells, are seen in about 30% of B-ALL, and germline variants have also been described in familial cases (Auer et al., 2014; Shah et al., 2013). Germline alterations in *ETV6*, encoding an ETS family transcriptional repressor important in the maintenance and differentiation of hematopoietic stem cells and megakaryopoiesis, lead to thrombocytopenia, ALL, and myeloid malignancies (Hock and Shimamura, 2017).

In this issue of *Cancer Cell*, Churchman, Mullighan, and colleagues add *IKZF1* to the growing number of genes involved in lymphoid leukemia predisposition (Churchman et al., 2018). *IKZF1* encodes IKAROS, a member of a zinc-finger transcription factor family. IKAROS has an N-terminal DNA binding domain composed of four zinc fingers and a C-terminal dimerization domain with two zinc fingers required for homo- or

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heterodimerization (Churchman and Mullighan, 2017; Marke et al., 2018) (Figure 1A). Dominant-negative isoforms result when DNA binding (N-terminal) is disrupted but dimerization (C-terminal) remains intact. The multifaceted role of IKAROS in cancer is also driven by interactions with an array of epigenetic regulator complexes. IKAROS interacts with the SWItch/Sucrose Non-Fermentable (SWI/SNF) related complex, the nucleosome remodeling and deacetylase (NuRD) complex, and the polycomb repressive complex 2 (PRC2) that regulates both transcriptional repression and activation across a large set of genes. These global epigenetic interactions and the role of IKAROS in transcriptional regulation are context-dependent on cell type and developmental timing. Murine models demonstrate an essential role for *Ikzf1* in lymphopoiesis of all lymphoid lineages, as well as a role in hematopoietic differentiation. Mice with mutant *Ikzf1* also develop lymphoid malignancies, either spontaneously or in combination with oncogenic transgenes (Marke et al., 2018).

In human leukemia, somatic alterations in *IKZF1* are seen in about 15% of B-ALL overall. *IKZF1* mutations are found in over 70% of BCR-ABL1 ($Ph^+$) ALL and in Ph-like ALL and are associated with adverse outcomes. Poor outcomes are also associated with alterations of *IKZF1* in standard-risk B-ALL subtypes, including those with high hyperdiploidy. Somatic deletions or sequence alterations in *IKZF1* lead to loss of function or dominant-negative isoforms, resulting in acquisition of a hematopoietic stem-cell-like phenotype with impaired leukemia cell maturation and dysregulated cell adhesion (Churchman and Mullighan, 2017; Marke et al., 2018).

Previously reported germline mutations in *IKZF1* have been studied in the context of inherited immunodeficiency, with mutations in the DNA-binding zinc finger domain leading to common variable immunodeficiency (CVID) and reduced numbers of B cells. Interestingly, 2 of 29 such individuals in one series were noted to also develop B-ALL (Kuehn et al., 2016), suggesting a role for *IKZF1* in human leukemia.

Churchman and colleagues now identify *IKZF1* as a new leukemia predisposition gene (Churchman et al., 2018). They investigated an index family, with B-ALL arising in two members who were found to share a heterozygous germline deletion in *IKZF1*, c.del556 (D186fs), leading to a protein truncated at residue 192. Other carriers of the truncating *IKZF1* mutation in the pedigree were found to be lymphopenic without frank clinical immunodeficiency. The authors investigate the prevalence of *IKZF1* mutations with targeted sequencing of remission samples from an impressive 4,963 cases of childhood leukemia. They identified 43 cases from these cohorts, with a total of 28 unique *IKZF1* variants, the majority from patients with B-ALL. To confirm the germline origin of a subset of these variants, the authors analyzed bone marrow-derived mesenchymal stromal cells from four patients and identified the same *IKZF1* genetic aberrations. No deletions were identified with germline single-nucleotide polymorphism array or with whole-genome sequencing on a subset of 697 cases.

Churchman and colleagues next assessed the functional consequences of each of the 28 *IKZF1* variants, testing their ability to repress transcription of a known IKAROS target, DNA binding, dimerization, subcellular localization, and effects on cell adhesion. They also

assessed sensitivity to antineoplastic drugs, including the tyrosine kinase inhibitor dasatinib and dexamethasone. The authors observed functional consequences for 22 of the 28 *IKZF1* variants. The authors note only a 65% concordance of pathogenicity between *in silico* prediction algorithms and the outcome of these functional assays. The observation that different assays identified different patterns of functional impairments across the spectrum of *IKZF1* variants highlights the complexity of assessing variant pathogenicity. The current work uses both genomics and functional studies to define the relevance of identified germline variants as a benchmark for future studies.

Taken together, Churchman and colleagues identify a new leukemia predisposition gene, *IKZF1*, first shown within a family and then expanded to include almost 1% of B-ALL cases otherwise presumed to be sporadic. The identification of a germline cancer risk carries profound clinical impact (Godley and Shimamura, 2017). For patients requiring a bone marrow transplant, germline genetic diagnosis allows the screening of familial transplant donors to avoid choosing an affected but clinically silent donor. Some germline cancer predisposition disorders require tailored therapies to avoid excessive treatment-related toxicities or to minimize relapse risk. Diagnosis of genetic cancer predisposition may also inform surveillance strategies for cancer and other associated medical co-morbidities. It is of critical importance, therefore, to distinguish germline from somatic mutations.

This study highlights the insights gained from studying rare families with cancer predisposition to advance our overall understanding of these genes in cancer biology and in normal development (Figure 1B). Although each cancer predisposition gene individually accounts for a relatively small number of patients, taken together as a group, germline cancer predisposition constitutes an increasingly significant subset of malignancies previously believed to be sporadic. As we continue to characterize the genomic landscape of leukemias, the list of cancer predisposition genes is likely to expand.

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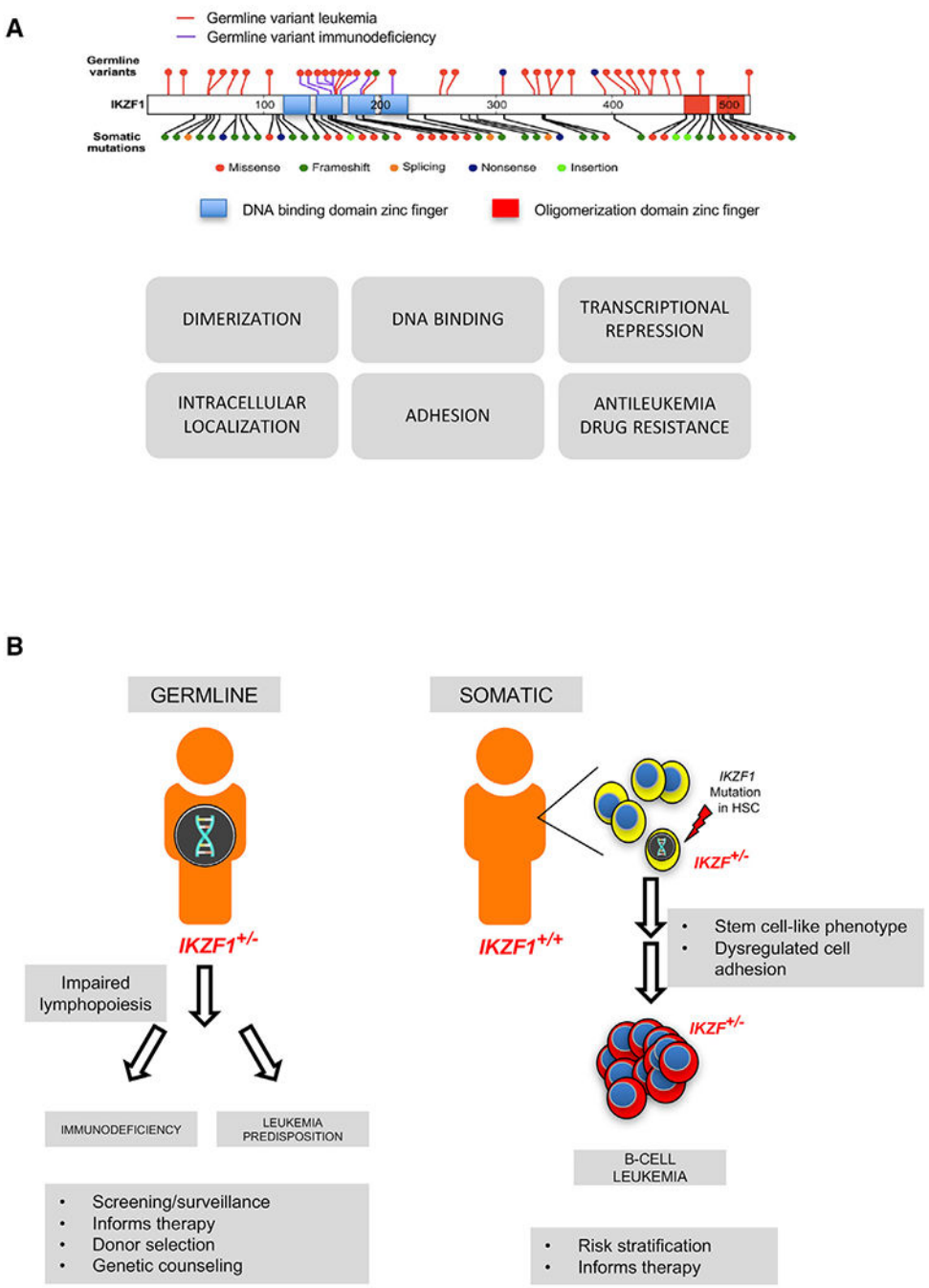


**Figure 1. *IKZF1* Germline and Somatic Mutations**

(A) *IKZF1* structural domains and mutations (top), modified from Churchman et al. (2018), and functional assays used by Churchman et al. to assess pathogenicity of identified *IKZF1* variants (bottom). (B) Germline *IKZF1* mutations are associated with immunodeficiency and predisposition to B cell leukemia. Acquisition of somatic mutations in *IZKF1* also promote the development of B cell leukemia. HSC, hematopoietic stem cell. Figure 1B modified from https://pixabay.com/en/man-user-profile-person-icon-42934/.