# IL-2-inducible T-cell kinase deficiency: clinical presentation and therapeutic approach

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## ABSTRACT

Mutations in the IL-2-inducible T-cell kinase gene have recently been shown to cause an autosomal recessive fatal Epstein Barr virus (EBV) associated lymphoproliferation. We report 3 cases from a single family who presented with EBV-positive B-cell proliferation diagnosed as Hodgkin's lymphoma. Single nucleotide polymorphism array-based genome-wide linkage analysis revealed IL-2-inducible T-cell kinase as a candidate gene for this disorder. All 3 patients harbored the same novel homozygous nonsense mutation C1764G which causes a premature stop-codon in the kinase domain. All cases were initially treated with chemotherapy. One patient remains in durable remission, the second patient subsequently developed severe hemophagocytic lymphohistiocytosis with multi-organ failure and died, and the third patient underwent a successful allogeneic bone marrow transplantation. IL-2-inducible T-cell kinase deficiency underlies a new primary immune deficiency which may account for part of the spectrum of Epstein Barr virus related lymphoproliferative disorders which can be successfully corrected by bone marrow transplantation.

Key words: IL-2-inducible T-cell kinase (ITK) deficiency, hereditary childhood EBV-positive B-cell lymphoma, bone marrow transplantation.

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## Introduction

The association between primary immune deficiency and malignant lymphoma of childhood is well recognized. Several primary immunodeficiency diseases (PID) are associated with malignant lymphoproliferative disorders, including Wiskott Aldrich syndrome, hyper-IgM syndrome, common variable immunodeficiency, Nijmegen syndrome and ataxia telangiectasia.[1-6] X-linked lymphoproliferative disease (XLP) is a genetic disorder with a variable clinical presentation that causes severe immune dysregulation following a primary Epstein Barr virus infection and presents as fatal mononucleosis, hemophagocytosis, hypogammaglobulinemia and lymphoproliferation.[7-9] Mutations in two genes on chromosome X have been identified in XLP: SAP (SLAM-associated protein, encoded by SH2D1A) is mutated in XLP1, whereas mutations in XIAP (X-linked inhibitor of apoptosis, encoded by BIRC4) underlie the rare form XLP2.[10,11] Recently, Huck *et al.* have shown that a homozygous mutation in the SH2 domain of the IL-2-inducible T-cell kinase (ITK) gene is associated with fatal Epstein Barr virus associated lymphoproliferation in girls as well as in boys, with a clinical picture similar to that seen in XLP.[12] Both SAP and ITK are intracellular enzymes found primarily in T cells, and both have been shown to be required for the development of NK-T cells which probably play a critical role in the response to Epstein Barr virus infection.[13,14]

We report an immunodeficiency syndrome in a family of Arab origin caused by a biallelic mutation in the *ITK* gene.

## Design and Methods

### Generation of DNA

Genomic DNA was extracted from blood samples of affected children, their parents and one healthy brother (subjects IV-5, IV 3, IV-4, III-16, III-17, III-3, III-4, IV-7, respectively, Figure 1). All experiments involving DNA were performed after obtaining written informed consent and were approved by both the Hadassah and the Israeli Ministry of Health Ethical Review Boards.

**PS and MW contributed equally to this work.*

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### Homozygocity mapping

We searched for homozygous regions in the DNA samples of subjects IV-4 and IV-3 using GeneChip Human Mapping 250K NspI Array of Affymetrix. The chip allows genotyping of SNPs with an average distance of approximately 50 kb between the markers. Digestion with NspI, ligation of the adaptors, and amplification with generic primers that recognize the adaptor sequence were followed by fragmentation, end labeling, and hybridization to the chip in accordance with the manufacturer's instructions. Homozygous regions greater than 5.0 Mb were manually detected.[15]

### Mutation analysis

Mutation analysis was performed by direct sequencing of PCR fragments obtained after nested amplification of the exonic and flanking intronic region coding sequences of *ITK* 17 exons. Primers to amplify the genomic DNA samples were designed according to GenBank sequences. Direct cycle sequencing of all PCR fragments was performed with BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems) and analyzed by capillary electrophoresis on an ABI Prism 3130 Genetic Analyzer (Applied Biosystems). Analyzed sequences were compared with the cDNA and genomic DNA sequences in GenBank accession numbers NM_005546 (human *ITK* mRNA).

### Constructs and immunoblot analyses

Transient expression of HA-tagged ITK (NM 005546) and HA-ITK$^{\Delta 588\text{-}620}$ in HEK 293 cells, as well as cell lysis and immunoblotting were carried out as described before,[16] using similar expression vectors. Blood leukocytes were separated by Ficoll gradient and CD3 positive selected (Miltenyi Biotech) before cell lysis: $5{\cdot}10^5$ cells per lane or $2{\cdot}10^5$ HEK 293 cells per lane (48 h after transfection) were subjected to SDS PAGE (8% gels) and Western blotting. Blots were probed with monoclonal antibodies to the N-terminus of ITK (ab32039, Abcam).

## Results and Discussion

### Clinical phenotype

The family tree and a clinical summary of the affected family are presented in Figure 1A and Table 1. Subject IV-5 presented at the age of 4.5 years with fever, lymphadenopathy and splenomegaly. Her past history was significant for recurrent febrile episodes which had started at four years of age. Lymph node biopsy revealed Hodgkin's lymphoma, CD30$^+$ and EBV-LMP$^+$ and CD20-. She was treated with a regimen for advanced stage Hodgkin's disease with a good response. Four months off

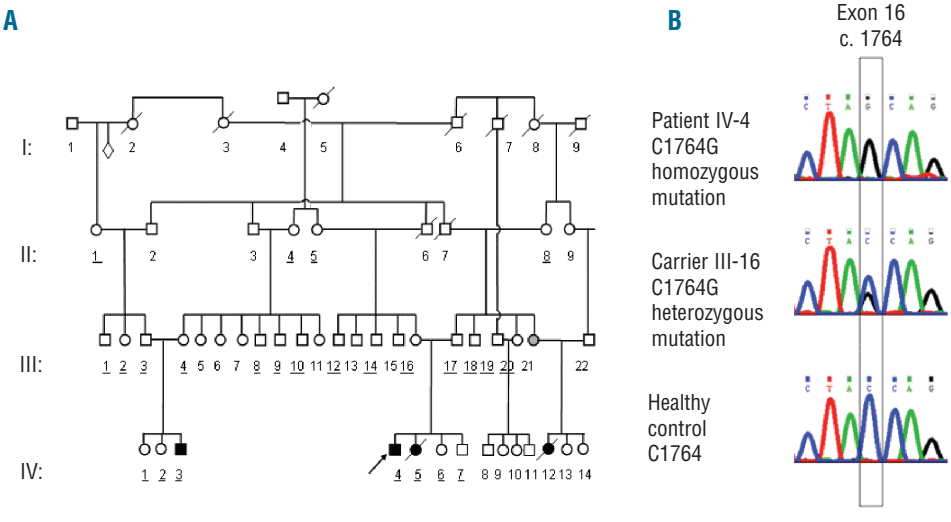


**Figure 1.** (A) The pedigree of affected family. Subject IV -12 died before the index case (subject IV-5) presented to our institute and therefore her DNA was not analyzed. (B) Relevant section of 3→5 ITK sequencing for Patients IV 3, IV-4 and IV-5. All 3 affected children shared a single homozygous mutation c. 1764 C->G in exon 16. The parents and sibling IV-7 were heterozygous for the mutation.

**Table 1.** Summary of clinical manifestations and laboratory tests for the 3 patients.

| IV-4 | IV-3 | IV-5 | |
|---|---|---|---|
| | | | On presentation |
| EBV-VCA IgG-negative, EBV-VCA IgM-negative, EBNA1-IgG-positive | EBV-VCA IgG-positive, EBV-VCA IgM-negative, EBNA1-IgG-negative | Not determined | EBV serology |
| 93,000 copies | Not determined | Not determined | EBV PCR in blood |
| Low(291 mg/dL) | Low(291 mg/dL) | Normal(963 mg/dL) | IgG levels |
| Hodgkin's disease (CD30$^+$,CD20$^+$) | Hodgkin's disease (CD30$^+$,CD20$^-$) | Hodgkin's disease (CD30$^+$,CD20$^-$) | Clinical manifestation |
| | | | After remission |
| After BMT | Not determined | EBNA1-IgG-positive | EBV serology |
| Negative | 225-7700 copies, negative after antiviral treatment | 6,100-125,850 copies | EBV PCR in blood |
| Normal (post-BMT) | Normal (751mg/dL) | Low(463mg/dL) | IgG |
| Normal (post-BMT) | Lymphadenopathy, splenomegaly, renal disease | Fulminant hemophagocytosis | Clinical manifestation |

therapy she presented with fever, skin rash, lung disease, splenomegaly, trilineage cytopenia, hypertriglyceridemia, hypofibrinogenemia and hyperferritinemia. Bone marrow evaluation showed hemophagocytosis with Hodgkin cells positive for CD20, CD30 and EBV-LMP. Serum EBV PCR showed 125,850 copies/mL and positive EBNA IgG. Immunoglobulins were low (IgG 463 mg/dL, undetectable IgA and IgM). She was diagnosed with relapsed Hodgkin's lymphoma and hemophagocytic lymphohistiocytosis. Therapy with steroids, rituximab and chemotherapy (VP-16, vinorelbine and gemcitabine) was started but she developed further disease progression with respiratory failure and died.

Subject IV-3 presented at five years of age with fever and lymphadenopathy. His past history included a profound sensorineural hearing defect, mild mental retardation and recurrent infections. Laboratory tests showed hypogammaglobulinemia (IgG 291 mg/dL, IgA and IgM below 42 and 32, respectively), positive anti-EBV VCA IgG, and negative anti-EBNA. EBV PCR was not carried out. A lymph node biopsy showed mixed cellularity Hodgkin's lymphoma with numerous Hodgkin's cells and few CD30 positive and CD20 negative Reed-Sternberg cells. He was treated with chemotherapy with a good initial response. One month off therapy he developed mild renal failure and proteinuria. Renal biopsy demonstrated diffuse mesangial and focal segmental proliferative glomerulonephritis. He was followed without further treatment. Six months later, he developed splenomegaly. Epstein Barr virus PCR in his blood showed 7,770 copies/mL. Immunoglobulin levels were normal. A splenic biopsy demonstrated significant engorgement of red pulp with follicular hyperplasia of white pulp with no evidence for relapsed Hodgkin's disease. Anti-viral therapy with valacyclovir was started with a good clinical and laboratory response. He remains in remission thirty-six months off therapy, with normal renal function and without proteinuria. Epstein Barr virus PCR remained negative. At that time point, immunophenotyping showed a very low number of NKT (0.03%) and naïve CD45RA$^+$ T cells (17% of CD4$^+$) although some residual NKT cells could be detected (Figure 2A). He has two siblings who are HLA incompatible.

Subject IV-4, the sibling of our index case, presented at the age of three years with fever and lymphadenopathy. His past history was unremarkable apart for recurrent viral infections. On presentation he had low levels of IgG (291 mg/dL) with normal levels of IgM (208 mg/dL) and undetectable levels of IgA. Anti-EBV VCA IgG was positive and anti-EBNA was negative. Serum EBV PCR showed 93,000 copies/mL. PET-CT showed involvement of lungs and kidneys, and a renal biopsy was carried out. Pathology showed large atypical lymphatic cells, partially resembling Hodgkin's cells and partially resembling Reed-Sternberg cells, CD20 and CD30 positive and CD3 and CD15 negative. These cells were also positive for EBV-LMP. Classic Hodgkin's lymphoma was diagnosed. Treatment was started with the advanced stage Hodgkin's disease regimen. EBV PCR decreased and became negative. Due to a high index of suspicion for a primary familial immune deficiency, he underwent bone marrow transplantation (BMT) from a matched sibling donor (subject IV-7). The donor was EBV positive with normal immunoglobulins and we used these parameters as surrogate markers for the absence of the presumed familial primary immune deficiency. Pre-transplant conditioning consisted of fludarabine 180 mg/kg, melphalan 140 mg/kg, ATG (Thymoglobulin) 10 mg/kg, and one dose of rituximab (Mabthera 375 mg/m$^2$). He was transplanted with untreated bone marrow and received 34×10$^6$/kg CD34$^+$ and 12.3×10$^7$/kg CD3$^+$ cells. Cyclosporine A was used as graft *versus* host disease prophylaxis. His post-transplant course was uneventful except for one episode of adenoviral gastroenteritis. Now thirty months after transplantation he is clinically well with 100% donor chimerism and without evidence of primary immunodeficiency.

### Molecular studies

The search for common homozygous regions using DNA SNP array, disclosed a single homozygous region which was shared by Patients IV 3, IV-4 and IV-5. Within this approximately 8.73 Mb on chromosome 5 at 150.4-159.2 Mb, the haplotype of 925 consecutive SNPs was identical in the 3 patients. Forty-five genes are encoded within this region, including *ITK*, which appeared the most likely candidate for harboring a mutation. Sequencing of the 17 coding exons of this gene disclosed a single homozygous mutation c. 1764 C->G which causes a premature stop-codon Y588X. This is likely to result in a truncated translation product with the consequent disruption of the ITK kinase domain, which spans amino-acids 326–619. The parents and sibling IV-7 were heterozygous for the mutation (Figure 1B).

Western blot analyses revealed, that the truncated

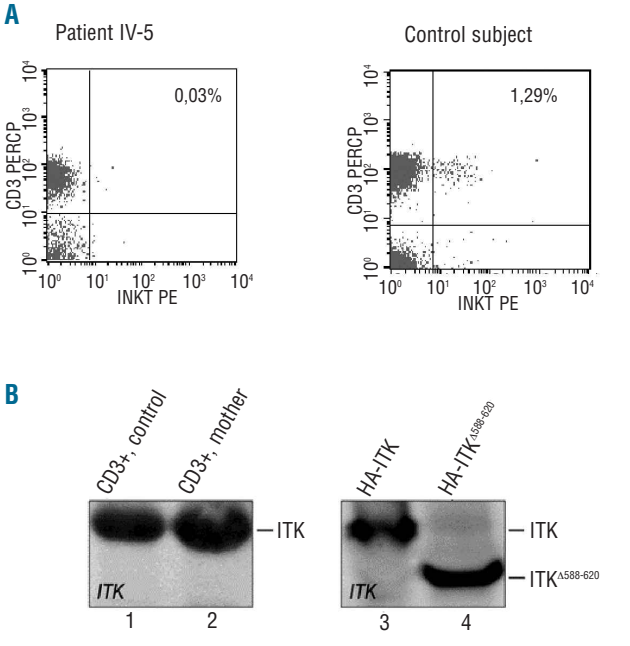


**Figure 2.** (A) Measurement of NKT cells by FACS. After gating of CD3+ cells, NKT cells were determined by TCR Vβ11 and TCR Vα24 double positive cells. In patient IV-5 NKT cells were low (0.03%), whereas in a healthy control subject NKT cells were 1.29%. (B) Immunoblot analysis of ITK. Unstimulated CD3+ cells from an ITK wild-type control subject (lane 1) and a heterozygous ITK$^{\Delta 588-620}$ carrier (lane 2, mother) as well as HEK 293 cells, transiently expressing HA-ITK (lane 3) or HA-ITK$_{\Delta 588-620}$ constructs (lane 4) were subjected to immunoblot analyses. Blots were probed with antibodies against the N-terminus of ITK.

enzyme is not detectable in T cells of the heterozygous mother (Figure 2B, left) whereas corresponding constructs transiently expressed in HEK 293 cells do not show a significantly diminished expression level (Figure 2b, right).

## Discussion

We report a second family with 3 cases of primary immunodeficiency diseases associated with a homozygous nonsense mutation in the *ITK* gene and presenting with a similar but not identical phenotype to that described for XLP. The first patient with ITK deficiency reported by Huck *et al.* presented with a fatal course of Epstein Barr virus related lymphoproliferative disease and a homozygous missense mutation C1085T which caused substitution of an arginine by tryptophan residue at position 335 of SH2 domain of ITK protein. This was not found as an SNP in 100 healthy controls. While mutated and wild-type mRNA expression was equal, R335W mutant protein showed pronounced instability and was nearly undetectable by Western blot analysis.[12]

We found a novel homozygous mutation C1764G causing a premature stop-codon Y588X predicted to cause truncation of translated product (mRNA/protein). Interestingly, heterozygous individuals do not show a detectable expression of the truncated protein in T cells (Figure 2A, left), suggesting an enhanced degradation of the enzyme. This degradation does not seem to be due to a generally increased instability of the protein, since corresponding constructs show a comparable expression to wild-type ITK in HEK 293 cells (Figure 2B, right). This suggests a cell type dependent mechanism, regulating the degradation of the truncated enzyme.

ITK is a member of the Tec Kinase family. These proteins are important mediators of antigen receptor signaling in lymphocytes, and ITK is believed to be the predominant TEC kinase in T cells and one of the key molecules involved in NKT cell maturation and survival.[17-21]

Our report, and the previous report of ITK deficiency, reveals a different clinical spectrum from that of classical XLP. First, while in XLP the predominant lymphoproliferation is Burkitt's lymphoma, 4 out of 5 published patients with ITK deficiency had Hodgkin's disease.[7] Second, there are reports of patients with XLP who present with lymphoproliferation with no evidence of infection with Epstein Barr virus.[22] We show that in ITK-mutated lymphoproliferation, infection with Epstein Barr virus is a universal component of the phenotype. Lastly, as in XLP, not all 3 classic clinical manifestations may develop and patients with ITK deficiency can develop different immune mediated syndromes including fatal hemophagocytosis, hypogammaglobulinemia and autoimmune phenomena presenting as renal disease.

With only two types of molecular defects reported, genotype-phenotype associations are difficult to ascertain. Both ITK mutations described lead either to protein absence on Western blot analysis or at least the loss of kinase activity due to stop-codon mutations upstream to the kinase domain (even if there is residual non-functional protein). At the same time, the clinical presentation is variable and together with a very severe phenotype associated with tryptophan to arginine substitution in position 335 of SH2 domain we found cases with different phenotypes in our patients. The first presentation was that of Hodgkin's lymphoma, while hemophagocytosis and severe mononucleosis appeared after remission of lymphoma, indicating, perhaps, a more rapid progression and a stronger tendency to malignant transformation of the disease after primary Epstein Barr virus infection. Interestingly, the cousin of the above-mentioned patient, sharing the same mutation, is alive and well five years after a similar presentation without evidence of active Epstein Barr virus infection. Notably, he has a trace number (approximately 10-fold less compared to controls, 0.03%) of NKT cells in contrast to a reported ITK deficient patient with a more severe phenotype[12] which may be sufficient to control reactivation of Epstein Barr virus infection. All our ITK-deficient patients with lymphoma had a favorable response to initial chemotherapy without T-cell dependent infections.

We report the first successful bone marrow transplantation in this new disorder. The indications for transplantation in this case were the family history of fatal Epstein Barr virus associated Hodgkin's disease and the availability of a matched family donor. Attainment of remission and control of the Epstein Barr virus infection may have contributed to the successful transplantation. We also found that heterozygous carriers had no clinical disease and it appears that bone marrow transplantation performed from an HLA identical, ITK-mutated heterozygous sibling, can correct the primary immune defect.

Finally, many lymphoproliferative disorders have familial clustering with an undefined genetic basis.[23-25] In the light of our report and that of Huck *et al.* we propose that ITK deficiency is an autosomal recessive inherited lymphoproliferative disorder. Many males considered to have XLP on clinical grounds do not have mutations in the genes known to cause XLP, as do females with familial lymphoproliferation. ITK deficiency is a molecular defect which may explain part of the Epstein Barr virus related lymphoproliferation spectrum. We also show that homozygosity mapping followed by sequence determination of candidate genes is an efficient approach for the evaluation of undiagnosed familial disorders.

## Authorship and Disclosures

*The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.*

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