LymphoSign Journal

The journal of inherited immune disorders

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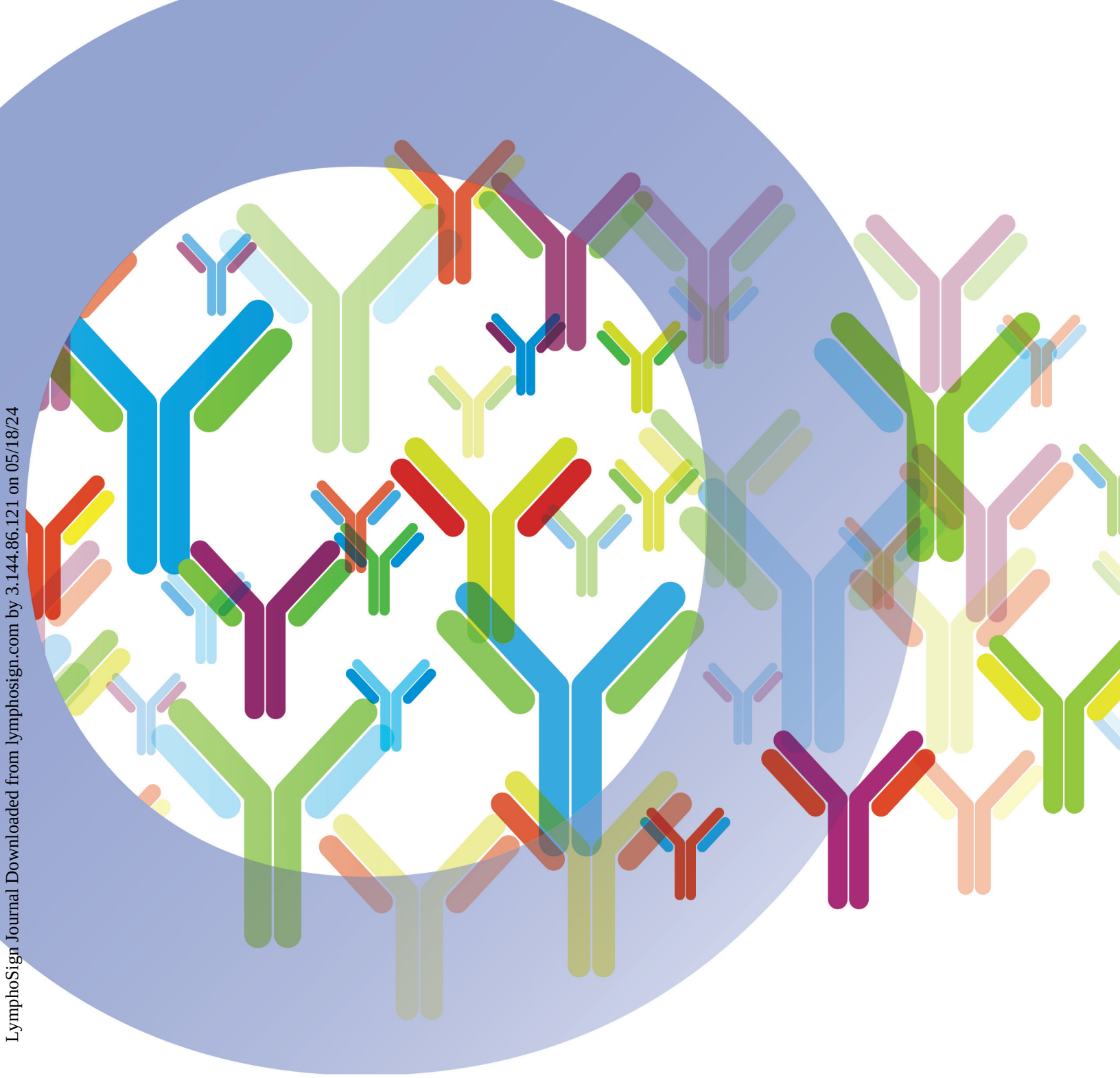

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Case report of a novel mutation in Bruton's tyrosine kinase gene with confirmed agammaglobulinemia and absent B lymphocytes

Nouf Bedaiwy[a,b†], Shatha Alhamdi[b,c†], Wafaa Al Suwairi[b,d,e], and Mohammad Alsalamah[b,c*]

ABSTRACT

Background: X-linked agammaglobulinemia type 1 (XLA) is one of the most common pediatric inborn errors of immunity affecting the humoral immune system. The condition is caused by a mutation in the Bruton's tyrosine kinase gene (*BTK*), located in the long arm of the X-chromosome. BTK is crucial for B lymphocyte differentiation and activation. Therefore, a defect in BTK results in B lymphocyte maturation arrest, absence of plasma cells, and failure of immunoglobulin production. XLA affected individuals present with a history of frequent severe pyogenic infections such as pneumonia, conjunctivitis, otitis media, and bacteremia. Laboratory evaluation classically reveals undetectable immunoglobulins and the absence of B cells. The mainstay treatment is immunoglobulin replacement which can be administered intravenously (IVIG) or subcutaneously (SCIG). Aggressive antimicrobial treatment is also administered to reduce complications such as bronchiectasis or invasive bacterial infections during active infections.

Aim: To report the clinical presentation, immune features, and genetic mutation in a case of a four-year-old boy with a novel mutation in the *BTK* gene leading to XLA.

Results: The patient's chart was reviewed. We describe the phenotypical and diagnostic characteristics of an established case in a four-year-old boy who suffered from recurrent infections. Genetic analysis revealed a pathogenic novel mutation in the *BTK* gene (c.1953C>A; p.Tyr651*), while flow cytometry found 0% CD19+ (B cells), and low serum Ig levels.

Discussion: We report the clinical presentation, immune features, and genetic mutation in a patient with a novel mutation in the *BTK* gene causing XLA. Genetic analysis along with patient history, physical examination, and laboratory results are necessary to identify and diagnose XLA associated with pathogenic mutations in the *BTK* gene.

Statement of novelty: We present an established case of a novel mutation in the *BTK* gene (c.1953C>A; p.Tyr651*), based on genetic analysis, absent CD19+cells (B cells), and low Ig serum levels.

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Introduction

X-linked agammaglobulinemia type 1 (XLA) is one of the most common pediatric inborn errors of immunity affecting the humoral immune system. It is inherited in an X-linked recessive manner, thus, only males are affected and females are asymptomatic carriers. The estimated prevalence of agammaglobulinemia in Saudi Arabia is 250 cases per 100 000 males. In the United States, the prevalence is 1 case per 190 000 males (Al-Attas et al.1998; Taneja et al. 2020).

The condition is caused by a mutation in the Bruton's tyrosine kinase gene (*BTK*), located in the long arm of the X-chromosome (Xq21.3 – Xq22). Bruton's tyrosine kinase (BTK) is crucial for B lymphocyte differentiation and activation. Therefore, a defect in BTK results in B lymphocyte maturation arrest, absence of plasma cells, and failure of immunoglobulin (Ig) production (Lackey and Ahmad 2021).

XLA affected individuals are at risk of serious infections. The most common responsible pathogens are encapsulated bacteria, and patients may present with frequent severe pyogenic infections such as pneumonia, otitis media, and bacteremia. In the first year of life, enteroviruses cause serious and sometimes life-threatening infections such as meningoencephalitis, hepatitis, or dermatomyositis (Person and Chin 2019). Diagnosis can be established by quantitative Ig assessment and B cell enumeration. Genetic testing may reveal mutations in the *BTK* gene. The mainstay treatment is Ig replacement which can be administered intravenously (IVIG) or subcutaneously (SCIG). Aggressive antimicrobial treatment is needed to reduce complications such as bronchiectasis or invasive bacterial infections during active infections.

There are more than 600 different pathogenic variants reported in the *BTK* gene, and no single pathogenic variant accounts for more than 3% of individuals (Holinski-Feder et al. 1998; Conley et al. 2005; Lindvall et al. 2005; Väliaho et al. 2006). A study conducted in Turkey found 544 mutations were linked with the disorder. The variants were missense, nonsense, splice-site mutations, deletions, and insertions. Among these mutations, a missense mutation was the single most frequent genetic occurrence. Spontaneous mutations occurred in 60% of people while only 40% had a positive family history (Doğruel et al. 2019; Taneja et al. 2020; Justiz Vaillant and Ramphul 2021).

In this case report, we present an established case of a novel mutation in the *BTK* gene (c.1953C>A; p.Tyr651*). The patient had 0% CD19+ cells (B cells) and low Ig serum levels.

Functional and clinical presentation

We present a case of a four-year-old boy with a family history of a brother who died of sepsis at infancy. Initially, he presented at the age of 18 months with knee arthritis that progressed over the next year to involve all large joints including, knees, ankles, elbows, and wrists. He was diagnosed at the age of 3 years with undifferentiated juvenile idiopathic arthritis (JIA). Investigations revealed negative anti-nuclear antibody (ANA), Cyclic Citrullinated Peptide (anti-CCP), and significant elevation of Erythrocyte sedimentation rate (ESR) and C-Reactive protein (CRP). Since his arthritis failed to be controlled completely by JIA standard therapy, including weekly methotrexate and adalimumab, the possibility of *LACC1* gene-associated JIA was considered. However, direct Sanger sequencing of the *LACC1* gene was negative. Interestingly, a 2-year trial of arthritis treatment saw an increase in frequency of chest infections requiring hospital admission (four to five times per year), raising the possibility of primary immunodeficiency. He was then referred to the immunology clinic. Initial blood workup revealed a low white blood cell count of 3.31×10^9/L and a normal lymphocyte count of 2.09×10^9/L. Flow cytometry showed a total lymphocyte count of 2350 cells/μL, CD3 (T cells) count of 2126.8 cells/μL, CD4 (T-helper cells) count of 1222 cells/μL, CD8 (T-cytotoxic cells) count of 904.8 cells/μL, Natural Killer T (NK cells) count of 176.3 cells/μL, CD3+ CD45RA (naïve T cells) count of 1339.5 cells/μL, CD3+ CD45RO (memory T cells) count of 881.3 cells/μL, Human Leukocyte Antigen–DR isotype (HLA-DR) count of 611 cells/μL that represents Major Histocompatibility Complex Class II (MHC-II), and CD19+ (B cells) count of 0 cells/μL. Ig levels testing showed reduced IgG < 0.33 g/L, IgA < 0.07 g/L, IgM < 0.05 g/L. Based on these results, molecular genetic analysis was performed and a heterozygous pathogenic variant was identified in the *BTK* gene (c.1953C>A; p.Tyr651*). According to these findings and the immunological workup, he was

diagnosed with XLA in Dec 2020. Currently, the patient is on Amoxicillin prophylaxis and IVIG replacement every 28 days. Adalimumab and MTX were discontinued. Since then, he has been clinically well with no episodes of infections.

Discussion

XLA is the culprit defect in 85% of patients with agammaglobulinemia (El-Sayed et al. 2019). This disorder results from mutations in a crucial B cell development protein, BTK, encoded by the *BTK* gene. BTK is a cytoplasmic tyrosine kinase expressed mainly in hematopoietic cells. As a member of the Tec kinase family, BTK is activated by an Src kinase. Activated BTK then activates PLCγ2 via phosphorylation resulting in calcium influx and downstream signaling. A defect in BTK leads to absent or very low numbers of peripheral B cells and agammaglobulinemia, a crucial arm of the adaptive immune system in fighting infections. Indeed, patients with XLA suffer from serious recurrent infections. A large cohort of 226 patients with XLA showed that more than 70% had upper and lowered respiratory tract infections, one-third suffered from skin infections, and 12% had CNS infections (Groth et al. 2020).

Other clinical manifestations of XLA include arthritis, neutropenia, thrombocytopenia, and inflammatory bowel disease. Hernandez-Trujillo et al. (2014) reported 128 patients with XLA collected from the United States Immune Deficiency Network (USIDNET) registry; 69% reported having at least one inflammatory symptom, 20% had joint pain, and 11% noted joint swelling. Although several subjects reported symptoms compatible with joint disease, only 7% had been formally diagnosed with arthritis. Specifically, 2% reported being diagnosed with rheumatoid arthritis, and 5% having "other" arthritis (Hernandez-Trujillo et al. 2014. El-Sayed et al. (2019) described 783 patients from 40 centers around the world with XLA; 62 patients (7.9%) were reported to have arthritis (El-Sayed et al. 2019).

Our patient shared the previously reported clinical manifestations of XLA, such as recurrent respiratory infections and arthritis and the classical immunological findings of absent B cells and agammaglobulinemia. Our case revealed a novel pathogenic mutation in the *BTK* gene (c.1953C>A; p.Tyr651*). This nonsense mutation introduces a stop codon to the gene sequence by replacing the nucleotide cytosine with adenosine. Therefore, the amino acid tyrosine changes to a stop codon at the 651 position, resulting in premature chain cessation. Over 900 variants have already been described in this gene; however, new pathogenic variants remain to be identified (Kraft et al. 2021). In this article, we report a new novel variant of the *BTK* gene.

Conflict of interest

The authors declare that they have no conflict of interest.

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A novel mutation in *TRAC* in a patient with abnormal newborn screening for severe combined immunodeficiency

Jenny Garkaby[a*], Laura Edith Abrego Fuentes[a], Jessica Willett Pachul[a], Abby Watts-Dickens[b], and Meghan Fraser[b]

ABSTRACT

Background: The T cell receptor (TCR)-α chain plays a key role in TCR structure and function. Biallelic mutations in *TRAC*, encoding the constant region of the TCR-α chain, obliterates TCR expression and results in immunodeficiency. TCR-α chain deficiency presents at infancy or childhood with repeated viral and bacterial infections, enlarged liver, spleen, and lymph nodes as well as autoimmune features and lymphoma (OMIM #615387).

Aim: To broaden the genotypic and phenotypic spectrum of TCR-α chain deficiency.

Methods: We present a case report of a patient with severe combined immunodeficiency (SCID) due to a novel autosomal recessive mutation in *TRAC*.

Results: Our patient was identified at 13 days of life due to abnormal T cell receptor excision circle levels detected by newborn screening (NBS). Immune evaluation revealed profound lymphopenia, depressed responses to the mitogen PHA and a skewed T cell repertoire, all consistent with SCID. The patient was found to carry a novel homozygous mutation in the *TRAC* gene.

Conclusion: A novel homozygous mutation in the *TRAC* gene caused profound T cell lymphopenia and aberrant in vitro mitogenic response, the hallmarks of SCID.

Statement of Novelty: TCR-α chain deficiency is a rare and relatively new condition and not very well defined. We herein report a novel mutation in *TRAC* resulting in SCID.

Introduction

Several genetic defects lead to the clinical syndrome of severe combined immunodeficiency (SCID), characterized by profound susceptibility to bacterial, viral, and opportunistic infections, failure to thrive, and death in infancy in the absence of appropriate treatment. SCID is caused by genetic defects that affect the T cell receptor (TCR), T cell differentiation, maturation, survival, or function (Roifman 2019). The TCR is composed of two subunits with discrete functions: (1) an antigen-recognizing heterodimer consisting either α and β chains or γ and δ chains (each with a variable region and constant region), and (2) a signal transduction unit composed of three invariant CD3 dimers (Gouaillard et al. 2001). The *TRAC* gene encodes for the constant region of the TCR-α chain. The first cases of TCR-α chain deficiency were reported by Morgan et al. (2011) in 2 unrelated children from consanguineous families of Pakistani descent. They presented in

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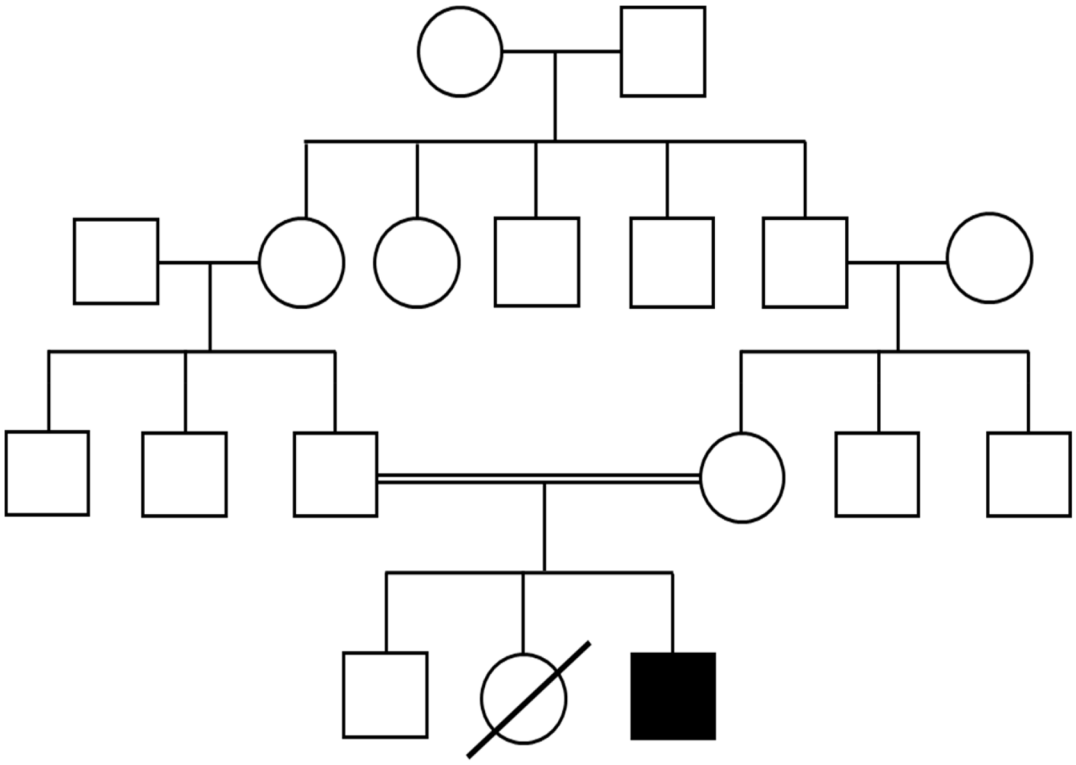

Figure 1: Family pedigree.

infancy with recurrent respiratory infections, otitis media, candidiasis, diarrhea, and failure to thrive. Both patients also had features of immune dysregulation and were treated with hematopoietic stem cell transplantation (HSCT) (Morgan et al. 2011). In a recent case series, Rawat et al. (2021) reported a nonconsanguineous East Indian family in which 3 siblings had an immunodeficiency disorder resulting in death in all patients aged between 12 months and 11 years. Five patients have been so far identified with TCR-α chain deficiency. All carry an identical homozygous G to A transition in exon 3, located in the consensus 5' splice site, predicting aberrant transcription, skipping of exon 3, and a protein that is lacking significant portions of the transmembrane and cytoplasmic domains of the TCR-α chain.

TCR-α chain deficiency is a rare and relatively new condition that remains ill-defined, and is attributed to mutations in the *TRAC* gene. We herein report a novel mutation in *TRAC* resulting in SCID.

Case presentation

Clinical case

An asymptomatic newborn male was found to have low T cell receptor excision circles (TREC) by the Ontario newborn screening (NBS) program for SCID.

The infant was the product of consanguineous parents of East Indian descent. He was born at 35 + 6 weeks after induced vaginal delivery due to concern for intrauterine growth restriction and had an uneventful postnatal course. His birth weight was 2060 gr (<3rd WHO percentile). The family history was remarkable for a female sibling who died in India at 8 months of age with a history of recurrent bacterial infections, oral thrush, diarrhea, and failure to thrive. His parents were healthy (Figure 1). On physical exam the patient had no palpable lymph nodes and lacked dysmorphic features. His growth and development appeared normal.

Investigations

TREC levels were undetectable (0 copies; cut-off >75). Further analysis of adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) metabolite profiles were normal, and targeted testing for mutations in IKBKB and Zap70 were negative. Complete blood count and differential were normal apart from mildly low lymphocytes count of 1.79×10^9/L (normal: 1.96–8.94×10^9/L). Lymphocyte immunophenotyping was

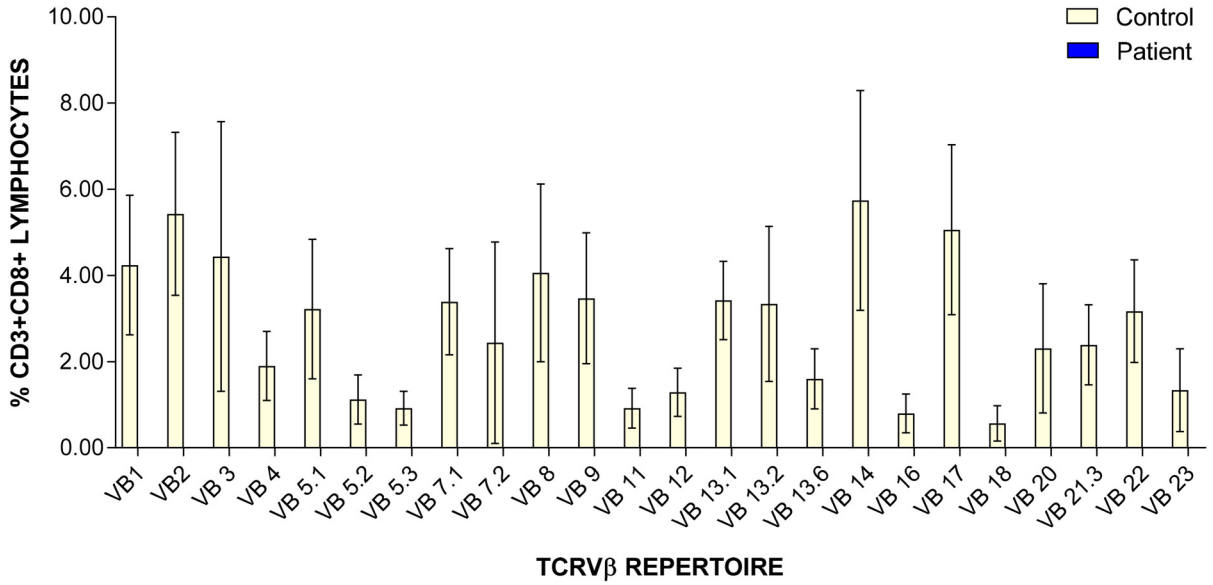

Figure 2: CD8+ TCRVβ repertoire.

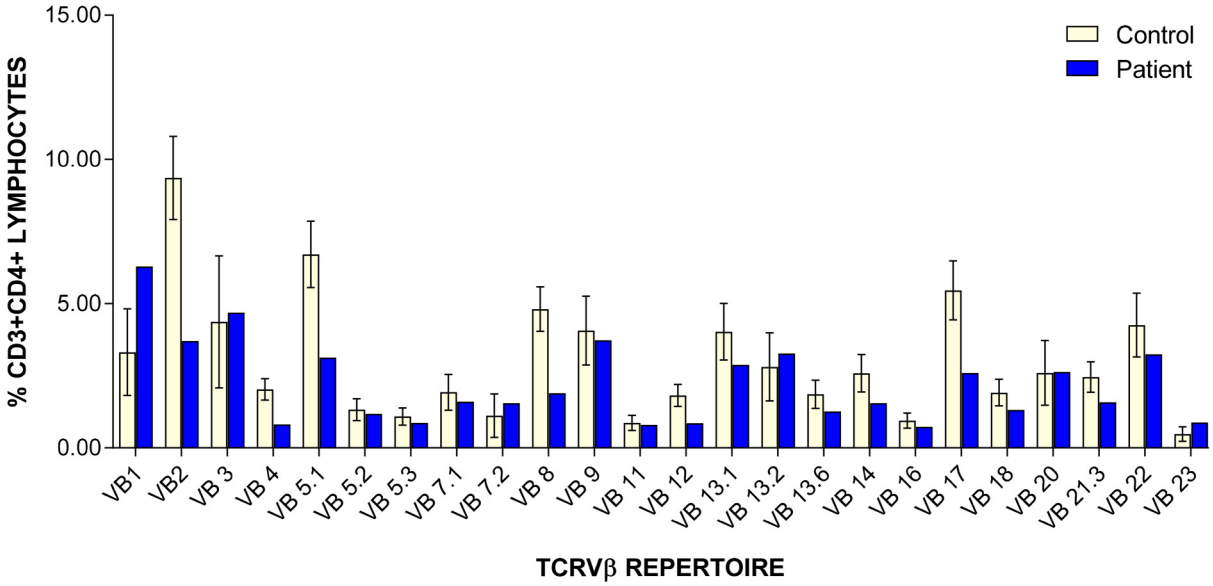

Figure 3: CD4+ TCRVβ repertoire.

abnormal, with extremely low CD3+CD4+ (113 cells/μL; normal: 1700–5300 cells/μL) and CD3+CD8+ (76 cells/μL; normal: 400–1700 cells/μL) counts. CD19+ cells were normal (638 cells/μL; normal: 600–1900 cells/μL), as were CD16+CD56+ cells (710 cells/μL; normal: 186–724 cells/μL). PHA stimulation index was severely depressed at 33 (control: 2010), T cell receptor Vβ (TCRVβ) repertoire showed under representation of most CD4+ Vβ families and absent representation of all the CD8+ Vβ families (Figures 2 and 3). Analysis of naïve/memory T cells (CD45RA/RO) was abnormal with predominance of memory cells and low percentage of naïve cells. Karyotyping was negative for maternal engraftment.

Genetic analysis began with normal karyotype and normal *in-situ* hybridization for 22q11.2. Further analysis involved a primary immunodeficiency panel, which revealed a nonsense homozygous variant in exon 3 of the *TRAC* gene, c.C347G; p.Ser116Ter (Figure 4).

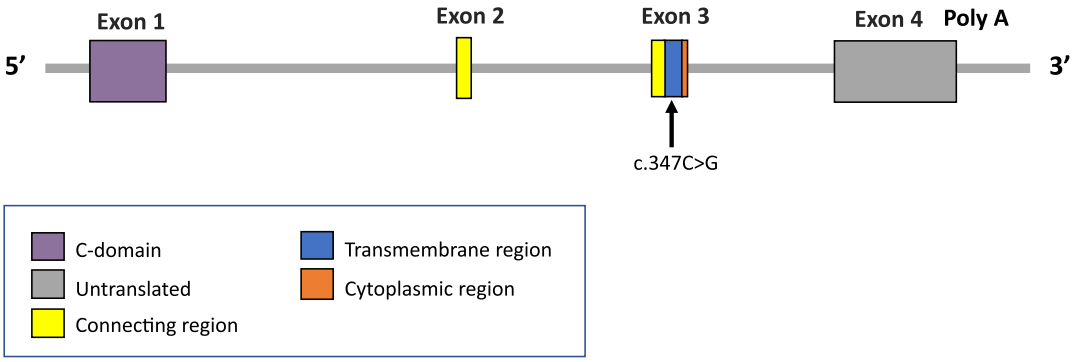

Figure 4: Schematic representation of the *TRAC* gene.

This variant was identified in 2 of 234 700 alleles from presumed healthy individuals in large population databases (GnomAD allele frequency 0.00085%) and has not been reported in the literature or in ClinVar. The variant results in the introduction of a premature termination codon, predicted to cause a truncation of the encoded protein or absence of the protein due to nonsense-mediated decay which are known mechanisms of disease (Shelton et al. 2001).

An additional finding on the panel was a missense variant detected in the *RAC2* gene, c.C545T; p.Thr182Met. This variant has not been reported in affected individuals in the literature. In ClinVar, one laboratory considers this a variant of unknown significance (VUS) and another classifies it as likely benign. This variant was identified in 32 of 281 160 alleles from presumed healthy controls in large population databases (GnomAD allele frequency 0.011%). Mutations in this gene are associated with neutrophil immunodeficiency syndrome (OMIM# 608203, 618987, 618986), which clearly does not match the features observed in this patient, and was therefore considered irrelevant.

Outcome

IVIG replacement therapy and PJP prophylaxis were commenced, and HSCT offered.

Discussion

The development and implementation of NBS have led to increased early detection of patients with SCID, allowing affected infants to be treated appropriately with HSCT before the onset of complications. As reported previously, X-linked IL2RG SCID is most frequently observed, while other causes of SCID include JAK3 mutations, ADA deficiency, deficiency of RAG1 or RAG2, IL7R deficiency, TCR CD3 δ, ε, and ξ chains deficiencies, Artemis mutations, and syndromic SCID such as Cartilage hair hypoplasia. Despite advanced genetic testing of known SCID genes, up to 10% of infants with SCID remain without a proven genotype. In this regard, homozygous mutations in *TRAC* resulting in TCR-α chain constant deficiency were not previously reported in the context of positive NBS (Kwan et al. 2014; Dinur et al. 2019; Mandola et al. 2019; Giżewska et al. 2020; Kumrah et al. 2020; Scott et al. 2021).

The first report of mutations in *TRAC* to cause immunodeficiency was by Morgan et al. in 2011 describing 2 patients. Both patients displayed features of combined immunodeficiency with recurrent bacterial infections, candidiasis, diarrhea, and failure to thrive. One patient also displayed chronic EBV, varicella, and human herpesvirus 6 (HHV6) viremia while the other patient was able to clear varicella at the age of 6 years uneventfully. In addition to immunodeficiency, both patients had evidence of immune dysregulation with hypereosinophilia, low-titer antinuclear antibodies (ANA), vitiligo, and alopecia areata in one patient and hypereosinophilia, eczema, autoimmune hemolytic anemia, anti-TTG antibodies, low-titer ANA in the other patient. Interestingly, humoral immunity against vaccine antigens appeared normal despite T cells abnormalities of abnormal CD3+ cells which expressed TCRαβ at extremely low levels and low PHA stimulation index (<50% of the control). When assessed by flow cytometry, surface staining for TCR-αβ was strongly reduced in patient cells. Functional studies showed that the *TRAC* mutation resulted in mislocalization of the TCR-α and -β chains. Furthermore, patient cells showed undetectably low expression of

both TCR-α or TCR-β polypeptides, suggesting that the *TRAC* mutation not only resulted in TCR-α deficiency but also reduced TCR-β expression.

An additional recent case series of 3 patients was reported by Rawat et al. in 2021. The patients were 3 siblings born to a non-consanguineous family from Northwest India who all succumbed due to complications of immunodeficiency. All three had similar clinical and immunological features, manifesting as recurrent ear and chest infections, deep seated abscesses, cutaneous warts and lymphadenopathy, however, the youngest child also developed non-Hodgkin's lymphoma in infancy. Genetic analysis revealed a previously reported variant in the *TRAC* gene (Rawat et al. 2021).

Clinically, our patient displayed lymphopenia and PHA < 10% of the control, in complete agreement with a diagnosis of T-B+NK+ SCID (Shearer et al. 2015), and has been well for the first months of life with supportive care until he received a HSCT. This patient would likely have presented with recurrent life-threatening infections as described thus far in the literature with low overall survival rate had it not been for the early detection through NBS.

The β chain gene is rearranged before the α chain, and, if productive, the TCR-β chain is initially expressed with pre-T-α, the invariant chain. Functional signaling through this complex must occur for progression of α chain rearrangement to take place (Anderson et al. 1996). Furthermore, defective expression of TCR-α would be expected to impair αβ T cell development beyond β selection because of a failure to deliver positively selecting signals as was shown by Morgan et al. (2011).

Our patient's variant, a nonsense homozygous variant in exon 3 of the *TRAC* gene, c.C347G; p.Ser116Ter, results in a premature termination codon in exon 3, predicted to cause truncation of the encoded protein or complete absence. As the *TRAC* gene encodes for the constant region of the TCR-α chain and is essential for membrane expression of the TCR-αβ heterodimer, we presume that in our patient this probably resulted in a non-functional TCR-α chain, which is essential for T cell development, explaining the T-B+NK+ phenotype as well as the near complete lack of representation of CD4+ and CD8+ Vβ families, respectively.

The current report contributes to the spectrum of mutations in *TRAC*, both genotypically and phenotypically. Furthermore, to our knowledge, this is the first of case of a mutation in *TRAC* reported in regard to positive NBS for SCID.

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Novel mutation in *PIK3CD* affecting the Ras-binding domain

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ABSTRACT

Introduction: The phosphoinositide 3-kinase (PI3K) pathway plays critical roles in diverse cellular processes, including differentiation, proliferation, motility, survival, and growth. PI3Kδ, comprised of the catalytic subunit p110δ and regulatory subunit p85α, is essential for normal lymphocyte and myeloid development and function. Gain-of-function mutations in *PIK3CD* (encoding p110δ) cause a combined immunodeficiency known as activated PI3Kδ syndrome (APDS), in which patients frequently present with recurrent respiratory infections, severe recurrent (or persistent) infections with herpes family viruses, and lymphadenopathy.

Aim: To describe the clinical presentation, immune evaluation, and genetic work-up of 2 patients (daughter and mother) with recurrent sinopulmonary, soft tissue, and skin infections.

Results: Both daughter and mother presented with recurrent sinopulmonary and soft tissue infections. Immune evaluation of the daughter revealed intermittent hypogammaglobulinemia and abnormal specific vaccine responses, while immune parameters of her mother were normal. Whole exome sequencing identified a novel mutation in *PIK3CD* (NM_005026), c.C719T, resulting in p.T240M. Western blot analysis of downstream AKT levels revealed increased basal phosphorylation, in line with gain-of-function mutations of *PIK3CD*.

Conclusion: The novel missense mutation in *PIK3CD* occurs in the region encoding the Ras-binding domain (RBD) of p110δ, and likely alters the structural configuration of the domain. To date, pathogenic mutations targeting the RBD of p110δ have not yet been described. Our results expand on the genotypic spectrum of APDS.

Statement of Novelty: We describe a novel mutation in the Ras-binding domain of *PIK3CD* leading to a presentation of recurrent sinopulmonary and soft tissue infections in the context of APDS.

Introduction

Phosphoinositide 3-kinase (PI3K) activity is required for normal immune cell development and function, and plays essential roles in diverse cellular processes such as differentiation, proliferation, motility, growth, and survival (Okkenhaug and Vanhaesebroeck 2003; Fruman et al. 2017). The class I PI3K lipid kinases are heterodimers comprising a catalytic subunit (p110α, p110β, or p110δ) and a regulatory subunit (p85α, p55α, p50α, or p55γ), and with the exception of p110δ, are distributed broadly throughout tissues. Under resting conditions, the regulatory subunit stabilizes the catalytic subunit to inhibit downstream signaling activity.

The p110δ subunit, encoded by *PIK3CD*, is expressed by majority in lymphocytes and myeloid cells (Okkenhaug and Vanhaesebroeck 2003; Fruman et al. 2017). Together

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with p85α, this heterodimer (termed PI3Kδ) is critical f or immune function, including B cell receptor (BCR) and T cell receptor (TCR) signaling (Okkenhaug 2013). Within immune cells, antigen-, cytokine-, costimulatory-, and growth factor receptor-dependent engagement and activation of tyrosine kinases recruits the p85α subunit of PI3Kδ to the cell membrane, thus releasing the inhibitory interaction with p110δ to form active PI3Kδ. PI3Kδ catalyzes the phosphorylation of phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphoinositide-3,4,5-trisphosphate (PIP3), which acts as a membrane tether for signaling proteins with pleckstrin homology (PH) domains. Downstream PI3Kδ signaling targets include BTK (which promotes phospholipase C-dependent responses), PDK1, and AKT (which activates mTOR complex 1 to promote protein synthesis, T cell activation, and differentiation of T cell effector phenotypes, as well as regulating FOXO1-dependent migration of T cells from lymph nodes to the circulation). Dephosphorylation of PIP3 by phosphatase and tensin homolog (PTEN) or inositol 5′-phosphatase terminates the PI3Kδ signal.

Defects in components of the PI3Kδ signaling pathway cause significant functional deficits leading to immunodeficiency and immune dysregulation (Angulo et al. 2013; Lucas et al. 2014). Gain-of-function mutations in *PIK3CD* and *PIK3R1* (encoding the p85α subunit) that were first identified by next generation sequencing techniques cause a combined immunodeficiency known as activated PI3Kδ syndrome (APDS, class 1 or class 2, respectively; OMIM #615513) (Angulo et al. 2013; Lucas et al. 2014, 2016; Crank et al 2014; Takeda et al. 2017; Heurtier et al. 2017; Rae et al. 2017; Wentink 2017; Dulau Florea et al. 2017). APDS is characterized by a wide spectrum of clinical manifestations, although most affected patients present with recurrent respiratory infections and associated lung damage, severe recurrent (or persistent) infections with herpes family viruses, and lymphadenopathy (Elgizouli et al. 2016; Elkaim et al. 2016; Coulter et al. 2017). Individuals with APDS frequently exhibit B and T cell dysfunction, autoimmunity, and are at increased risk of B cell lymphoma (Coulter et al. 2017; Kracker et al. 2014); however, the outcome for these patients vary widely from early death during childhood to adults who remain asymptomatic. Interestingly, rare loss-of-function mutations also present with immunodeficiency (Conley et al. 2012; Zhang et al. 2013).

Here, we describe 2 patients (a daughter and mother) with recurrent sinopulmonary and soft tissue infections in whom a novel missense mutation in the Ras-binding domain (RBD) of *PIK3CD* was identified.

Methods

Patients

Patient data were compiled prospectively and retrospectively from medical records and entered into the Canadian Centre for Primary Immunodeficiency Registry and Tissue Bank, which has been approved by the SickKids Research Ethics board (protocol No. 1000005598). Consent and assent from each patient and parents were obtained for testing.

Lymphocyte proliferation

Lymphocyte proliferative responses to phytohemagglutinin (PHA) were evaluated. All assays were performed in triplicate and were compared with simultaneously stimulated normal controls, as previously described Sharfe et al. (2014).

Western blotting

Studies were performed on Ficoll-separated peripheral blood lymphocytes. Both patient and control cells were obtained, and either left unstimulated or were stimulated with anti-CD3 antibody (5 μg for 4×10^6 cells) for 10 minutes at 37 °C. Cells were subsequently lysed in 1% Triton X-100 vanadate lysis buffer and protein expression assessed by Western blotting. All blots were repeated at least twice. The primary antibodies used for Western blotting were: Anti-pAKT Ser473 (Invitrogen) and anti-GAPDH (Cell Signaling), followed by appropriate horseradish peroxidase-conjugated secondary antibody. Immunoreactive proteins were visualized by enhanced chemiluminescence.

Whole exome sequencing and variant calling

DNA from blood was submitted to The Centre for Applied Genomics (TCAG), Toronto, Canada, for exome library preparation and sequencing. DNA was quantified by Qubit DNA HS assay (Life Technologies, Carlsbad, CA) and 100 ng of input DNA was used for library preparation using the Ion AmpliSeq Exome Kit (Life Technologies) according to the manufacturer's recommendations. The Ampliseq Exome library was immobilized on Ion PI™ Ion Sphere™ particles using

the Ion PI Template OT2 200 Kit v3. Sequencing was performed with the Ion PI Sequencing 200 Kit v3 and Ion PI Chip v2 in the Ion Proton™ semiconductor sequencing system following the manufacturer's recommendation.

Alignment and variant calling were performed using Torrent Suite (v4.0) on the Ion Proton Server, using the Ion Proton ampliseq germline low stringency setting and the hg19 reference genome. The variants were annotated using an in-house annotation pipeline based on Annovar (November 2014 version) (Wang et al. 2010) and RefSeq gene models (downloaded from UCSC 01 August 2015).

Sanger sequencing

Patient genomic DNA was extracted from peripheral blood lymphocytes using the Geneaid Genomic DNA Mini Kit. Genomic DNA was amplified by PCR with specific primers designed upstream and downstream of the *PI3KCD* gene. Sequencing was done using GenomeLab Dye Terminator Cycle Sequencing (DTCS) Quick Start Kit (Beckman Coulter) and analyzed on CEQ 8000 Genetic Analysis System (Beckman Coulter).

Results

Patient 1

The proband presented to medical attention at the age of 4 years. At the time, she presented with recurrent sinopulmonary infections (most notably acute otitis media and sinusitis), and 3 episodes of dental abscesses secondary to caries. She later developed a peri-orbital abscess following traumatic injury, as well as skin infections caused by atypical bacteria (*Vagococcus fluvialis* and *Acinebacter lwoffii*). Additionally, she suffered from *Haemophilus Influenzae* vulvovaginitis requiring treatment with IV antibiotics. Past medical history for this patient included an unremarkable pregnancy with normal prenatal follow-up, term vaginal delivery, a normal neonatal course, and no other medical history. She had been on no medications. Her family history was notable for a mother with recurrent infections (see "Patient 2" below), and a healthy father and brother. There is a history of maternal grandfather with Crohn's disease, and a paternal grandfather passed away from gastric cancer. There is no history of any other immune disorders in the family.

Physical examination demonstrated a well-grown and developing child, with no dysmorphic features, hair, nail or skin abnormalities beyond the reported skin infections, normal tonsillar tissues and lymph nodes, a normal cardiorespiratory exam and no organomegaly. Immune evaluation (Table 1) revealed intermittent hypogammaglobulinemia and abnormal specific vaccine responses, although she has not required immunoglobulin supplementation given spontaneous resolution of sinopulmonary infections with age.

Patient 2

Patient 2, the proband's mother, is a 42-year-old female with a long-standing history of sinopulmonary infections starting in her early 20s. She suffered frequent sinus and ear infections requiring multiple courses of antibiotics, an episode of facial abscess/cellulitis which progressed to bacteremia, and an episode of dental abscess. She had not suffered from any skin infections as identified in her daughter. She had no other infectious, autoimmune or inflammatory history. As noted above, she had a father with Crohn's disease but no other notable family history. Her immune evaluation has been unremarkable (Table 1), with normal immunoglobulin levels and vaccine responses.

Genetics

Genetic testing was done via a Primary Immunodeficiency Panel Plus (Blueprint Genetics), followed by research whole exome sequencing. Testing of the proband identified a heterozygous missense variant in *PIK3CD* (NM_005026), c.C719T, resulting in p.T240M. The substitution of amino acid residue threonine (T) to methionine (M) at position 240 is predicted *in-silico* to be deleterious or borderline deleterious, resulting in loss of polarity and a longer side chain, and likely altering the structural configuration of the RBD. Targeted sequencing of *PIK3CD* revealed the identical missense variant in her mother but not her father or brother.

Cell signaling

Peripheral blood lymphocytes (PBL) from patient 2 and a healthy control were stimulated with anti-CD3 antibodies. Western blot analysis showed an increase in basal phosphorylated AKT (pAKT) levels in the patient, consistent with APDS (Figure 1). Levels of pAKT following cell stimulation did not increase

Table 1: **Immune evaluation of patients 1 and 2.**

Lab parameters	Patient 1	Reference range	Patient 2	Reference range
WBC	5.73	4.23–9.99 (10^9 cells/L)	6.55	4.37–9.6 (10^9 cells/L)
Neutrophils	2.84	1.45–6.75 (10^9 cells/L)	3.9	1.45–6.75 (10^9 cells/L)
Lymphocytes	2.34	1.34–4.12 (10^9 cells/L)	2.01	1.16–3.18 (10^9 cells/L)
Eosinophils	0.06	0.06–0.97 (10^9 cells/L)	0.11	0.03–0.27 (10^9 cells/L)
Platelets	309	203–431 (10^9 cells/L)	300	186–353 (10^9 cells/L)
Hemoglobin	130	106–132 g/L	145	106–135 g/L
CD3+	1582	1239–2611 (10^9 cells/L)	1613	700–2100 (10^9 cells/L)
CD19+	24.7	12–24 (10^9 cells/L)	154	100–500 (10^9 cells/L)
CD3+/CD4+	1006	646–1515 (10^9 cells/L)	1136	300–1400 (10^9 cells/L)
CD3+/CD8+	473	365–945 (10^9 cells/L)	441	200–900 (10^9 cells/L)
NK	136	120–483 (10^9 cells/L)	316	90–600 (10^9 cells/L)
IgG	**5.8**	6.6–15.3 (g/L)	10.8	5.5–16.3 (g/L)
IgA	**0.2**	0.5–2.2 (g/L)	1.2	0.7–4.2 (g/L)
IgM	1.4	0.5–1.9 (g/L)	0.9	0.3–2.9 (g/L)
PHA stimulation index (SI)	2306	>400 (>50% of ctrl)	1848	>400 (>50% of ctrl)
Anti-tetanus serology	0.29	>0.1 IU/mL	2.84	>0.1 IU/mL
Diphtheria serology	0.08	>0.1 IU/mL	0.05	>0.1 IU/mL
Measles, mumps, rubella serologies	Non-reactive to all		Protective to all	

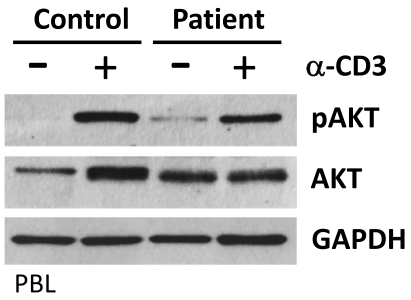

Figure 1: Western blot analysis of downstream AKT phosphorylation in patient carrying a gain-of-function *PIK3CD* missense variant. Peripheral blood lymphocytes from Patient 2 and a healthy control were stimulated with anti-CD3 for 10 minutes. Western blot analysis was performed to determine levels of phosphorylated AKT (pAKT), a downstream binding partner activated by PI3Kδ signaling. Levels of pAKT expression were higher at baseline in the patient compared to control.

further following stimulation, compared with a typical increase in the control sample (Figure 1).

Discussion

We describe here a mother and daughter with a novel mutation in the RBD of *PIK3CD*. Their clinical manifestations were typical of APDS, including recurrent sinopulmonary infections, soft tissue and dental abscesses, cellulitis, and humoral deficiency (in the proband) (Coulter et al. 2017).

APDS is caused by gain-of-function mutations in *PIK3CD,* coding for the p110δ subunit, which is comprised of an adaptor-binding domain (ABD) responsible for binding p85α, a Ras-binding domain (RBD), a C2 domain, a helical domain, and a lipid kinase domain (N-lobe and C-lobe) (Figure 2). Previously reported mutations affected the C2, helical and lipid kinase domains of p110δ, which are the inhibitory contact points for the p85α regulatory subunit (Lucas et al. 2016; Coulter et al. 2017), as well as the ABD and ABD-RBD linker region, responsible for proper ABD orientation (Takeda et al. 2017). These variants lead to overactivation of PI3Kδ, by preventing binding of p110δ with p85α or enhancing the mobilization of p110δ to the cell membrane and increasing the catalytic activity.

To our knowledge, this is the first variant in the RBD leading to APDS. Our functional assessment has determined this variant to result in a gain-of-function phenotype, as basal AKT phosphorylation was elevated Mandola et al. (2020), with essentially no further phosphorylation noted following stimulation, as frequently seen in gain-of-function mutations affecting other signaling molecules (Sharfe et al. 2015). It is possible that the mutated protein results in enhanced or prolonged binding of Ras-superfamily

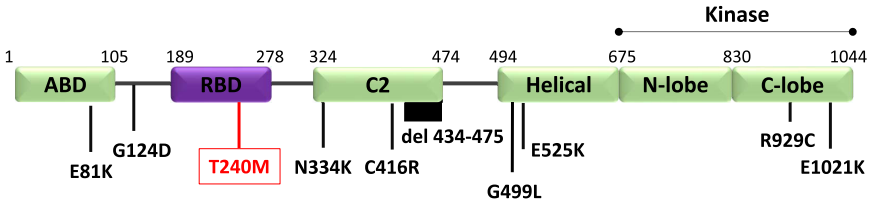

Figure 2: Schematic diagram of structural domains of p110δ encoded by *PIK3CD*. The p110δ subunit is comprised of an adaptor-binding domain (ABD) responsible for binding p85α, a Ras-binding domain (RBD), a C2 domain, a helical domain, and a lipid kinase domain (N-lobe and C-lobe). Previously reported mutations are noted in black. The mutation reported in this study, affecting the RBD, is highlighted in red.

GTPases to the RBD; however, the precise mechanism leading to this gain-of-function remains to be elucidated. Overall, this report enhances the genotypic spectrum of APDS and proposes a broader range of gain-of-function mutations in *PIK3CD* underlying this disease.

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2022 Canadian resource guides for individuals and families affected by primary immunodeficiency

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ABSTRACT

A diagnosis of immunodeficiency can be challenging for families as they navigate the emotional impact of this diagnosis, as well the potential financial burden of treatment. As is the case with many rare diseases, there existed a paucity of information for families looking for appropriate resources related to their diagnosis. The Primary Immunodeficiency Social Work Network was established in 2011 by Immunodeficiency Canada to develop a network of social workers across Canada who work with patients diagnosed with primary immunodeficiency. This network has had a focus on support programs, education, and research. Resource guides were created by the network with the goal of providing comprehensive support and information on resources available for families and individuals affected by primary immunodeficiency in each province as well as those available nationally.

Statement of Novelty: National and provincial resources guides, reviewed and updated yearly, have been created for families and individuals affected by primary immunodeficiency.

Background

A diagnosis of immunodeficiency can be challenging for families as they navigate the emotional impact of this diagnosis, as well as the potential financial burden of treatment. For rare diseases such as primary immunodeficiency (PI), patients are often required to take a proactive role in managing their own care and may be engaged with healthcare providers who have minimal experience with PI disease. These providers may also have limited access to information on the resources available for this population. A review of the information available showed that a paucity of information existed for these families who were looking for appropriate resources related to their diagnosis. The PI Social Work Network was established in 2011 by Immunodeficiency Canada to develop a network of social workers across Canada who work with patients diagnosed with PI. This network has had a focus on support programs, education, and research. Resource guides were created by the network to support families by providing information on both provincial as well as national resources available. While these lists are not exhaustive, there is an attempt to keep them as up to date as possible. The current guide was updated in February 2022. If additional psychosocial support would be beneficial or a family requires support accessing resources, they should be directed to their local hospital social worker, or they may contact Wendy Shama, MSW, RSW, at Immunodeficiency Canada.

National resources

Financial resources

Canada Child Benefit (CCB)

This is a tax-free monthly payment made to eligible families to help them with the cost of raising children

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under 18 years of age. The CCB might include the child disability benefit and any related provincial and territorial programs. The Canada Revenue Agency uses information from your income tax and benefit return to calculate how much your CCB payments will be. To get the CCB, you have to file your return every year, even if you did not have income in the year. If you have a spouse or common-law partner, they also have to file a return every year.

https://www.canada.ca/en/revenue-agency/services/child-family-benefits/canada-child-benefit-overview.html

Child Disability Benefit

If approved for the Disability Tax Credit, you are automatically assessed for this benefit. You do not need to apply. This benefit is based on family income, is tax-free, and paid monthly for low to moderate income families caring for a child under the age of 18 with a severe and prolonged impairment in mental or physical functions.

https://www.canada.ca/en/revenue-agency/services/child-family-benefits/child-disability-benefit.html

Disability Tax Credit

The Disability Tax Credit (DTC) is known as the "disability amount" on your income tax return. The DTC is a non-refundable credit that reduces the amount of income tax that a person with a disability, or their supporting person, might otherwise have to pay. The DTC is also used to determine eligibility for the Child Disability Benefit, an amount available under the Canada Child Tax Benefit for a child under 18 with a disability. In order to claim the DTC, a person must file a completed Form T2201, Disability Tax Credit Certificate, signed by a qualified person. Forms are available at CRA offices, or by calling 1-800-959-2221; the form can also be downloaded from the CRA Website.

https://www.canada.ca/en/revenue-agency/services/tax/individuals/segments/tax-credits-deductions-persons-disabilities/disability-tax-credit.html

EI Caregiving Benefits & Leave

Through Employment Insurance, you could receive financial assistance of up to 55% of your earnings, to a maximum of $562 a week to provide care or support to a critically ill or injured person or someone needing end-of-life care. As a caregiver, you don't have to be related to or live with the person you care for or support, but they must consider you to be like family.

There are two different types of Benefits:

- Family Caregiver Benefits for Children

  Time off is needed to care for an ill child. Maximum weeks payable up to 35 weeks.

- Compassionate Care Benefits

  End-of-life care is defined as providing care or support to a person who has a serious medical condition with a significant risk of death within 26 weeks. Maximum weeks payable up to 26 weeks.

Prerequisites:

- Your regular weekly earnings from work have decreased by more than 40% for at least one week because you need to take time away from work to provide care or support to the person. You accumulated 600 insured hours of work in the 52 weeks before the start of your claim, or since the start of your last claim, whichever is shorter.
- Medical Certificate from Physician is needed.

https://www.canada.ca/en/services/benefits/ei/caregiving.html

Canada Caregiver Credit

This is a tax credit that can be applied for when filing your current year tax return. The child must have a medical or physical infirmity and as a result of that infirmity is, and is likely to be for a long continued period of indefinite duration, dependent on others for significantly more assistance in attending to the child's personal needs and care when compared to children of the same age.

https://www.canada.ca/en/revenue-agency/services/tax/individuals/topics/about-your-tax-return/tax-return/completing-a-tax-return/deductions-credits-expenses/canada-caregiver-amount.html

Medical Expenses Tax Credit

This applies to individuals who have significant medical expenses for themselves or their dependents. This is an income tax credit which is claimed when filing your current year tax return.

https://www.canada.ca/en/revenue-agency/services/tax/individuals/topics/about-your-tax-return/tax-return/completing-a-tax-return/deductions-credits-expenses/lines-33099-33199-eligible-medical-expenses-you-claim-on-your-tax-return.html

Programs and services

Big Brothers and Big Sisters of Canada

Each Big Brother/Big Sister agency provides direct service to children by matching adults and children in quality mentoring relationships. Agency staff members are experts at screening volunteers and matching them with a child having similar interests.

www.bigbrothersbigsisters.ca

Easter Seals Canada

Since 1922, Easter Seals has been leading the way to opportunities for Canadians with disabilities. Easter Seals operates as a network of provincially licensed members that deliver programs and services to Canadians with physical disabilities in their community.

https://easterseals.ca/english/

Immune Deficiency Foundation

This is a national non-profit health organization dedicated to improving the diagnosis and treatment of primary immune deficiency diseases through research and education. IDF is governed by a Board of Trustees, has an active Medical Advisory Committee comprised of prominent clinical immunologists, a nationwide volunteer support network, and a dedicated professional staff.

https://primaryimmune.org/

Jordan's Principle

Jordan's Principle helps First Nations children living in Canada to access products, services, and supports that they need. Funding can help with a wide range of health, social, and educational needs.

https://www.sac-isc.gc.ca/eng/1568396042341/1568396159824#chp02

Make-A-Wish Canada

Children's Wish/Make A Wish have merged as Make-A-Wish Canada. Their mission is to grant the wishes of children with life-threatening medical conditions. Their goal is to ensure that all experiences create lifelong memories for the wish child and believe that each wish experience should be as unique and special as the child who wished for it.

Children may only have ONE wish either through Make-A-Wish or Starlight Foundation.

https://makeawish.ca/

MedicAlert Foundation of Canada

Canada MedicAlert Foundation offers free medic alert bracelets to children across Canada. *No Child Without* includes a free medical identification bracelet and electronic health record with 24/7 access so that critical health information is quickly available during a medical emergency. MedicAlert memberships are for students (from age 4 to their 14th birthday) in select schools (www.nochildwithout.ca). The *Membership Assistance Program* ensures that any person with potentially life-threatening medical conditions can have access to services offered by MedicAlert, regardless of his/her ability to pay.

http://www.medicalert.ca/education/en/programs/assistance.asp

National Organization for Rare Disorders

This is a federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

www.rarediseases.org

Primary Immunodeficiency Resource Center

This website is designed to be a central resource on Primary Immunodeficiency. Its goal is to allow researchers, scientists, physicians, government, industry, patients and their families to be able to access this information quickly, efficiently, and seamlessly.

http://www.info4pi.org/

Shine Through the Rain Foundation

This foundation helps families who have a child with a life-threatening illness.

The Rainy Day Fund provides emergency payments directly to the utility companies and landlords, as well as grocery gift cards & hospital transportation and parking costs. Shine Through The Rain also reviews special requests for consideration above and beyond the scope of services already covered.

https://shinethroughtherain.ca/

Songs of Love

Songs of Love is a non-profit organization that provides personalized songs for children and young adults with a life-threatening or chronic illness.

www.songsoflove.org

Starlight Children's Foundation Canada

Starlight Children's Foundation is a non-profit organization dedicated to making a world of difference for seriously ill children and their families. Starlight offers an array of in-hospital, out-patient, school, and home-based programs and services that help to brighten the lives of children and families facing serious illnesses. *Child may only have ONE wish either through Make-A-Wish, or Starlight Foundation*.

www.starlightcanada.org

Transportation

Air Canada Kids Horizon Program

This program provides free flights for children and a caregiver traveling anywhere in Canada for clinic appointments. Please contact your local children's hospital for availability. Families are responsible for taxes and fees.

http://www.aircanada.com/en/about/community/kids.html

Hope Air

Hope Air (formerly Mission Air) is a national Canadian charity that arranges free air transportation for Canadians that need to travel to non-emergency medical care outside of their home communities and cannot afford the flight costs. To make a flight request or for more information call the bilingual staff Monday through Friday, 9:00 AM – 4:30 PM EST or visit them at their website.

https://hopeair.ca/

Wigs

A Child's Voice–Angel Hair for Kids

Angel Hair for Kids provides wigs for eligible children who have hair loss due to chemotherapy, radiation, burns, or alopecia. This is a program through A Child's Voice Foundation.

https://www.acvf.ca/angel-hair-for-kids

Wigs for Kids

This is a non-profit organization that provides hair replacement systems for eligible children 18 years or younger who have hair loss as a result of chemotherapy, alopecia, radiation treatments, burns, or other medical circumstances.

www.wigsforkids.org

Immunodeficiency Canada

Emergency financial assistance

The Alastair Fund provides funding to families dealing with financial strain due to illness from a primary immunodeficiency. It is available to families with a child registered as a patient at: Alberta's Children's Hospital, British Columbia's Children's Hospital, Montreal's Children's Hospital, and Toronto Hospital for Sick Children. Families can access financial assistance for transportation, overnight stays, food, parking, and other critical needs. Families should talk to the Hospital Social Work Department to access this fund.

Publications

Immunodeficiency Canada strives to provide information that is relevant and up to date. Some materials are available in both English and French. Many materials are downloadable or print copies may be requested. Resources Guide for individuals and families affected by Primary Immunodeficiency include:

- What is Primary Immunodeficiency pamphlet
- 10 Warning Signs
- Newsletters (current and past issues)

www.immunodeficiency.ca

Social media

Individuals are invited to join others affected by Primary Immunodeficiency and stay up to date through social media. Look for Immunodeficiency Canada on Facebook, LinkedIn, and the YouTube Channel.

Social events

Immunodeficiency Canada sponsors and hosts events for families, adults, teens, and children to help break the isolation many individuals and families feel and build networks of mutual support. Kids' picnics have been held in Montreal, Toronto, and Calgary organized in partnership through local health care facilities. In the Greater Toronto Area, meet and greet evenings for

adults and fun-filled events for teens are organized each year.

Provincial resources—Alberta

Accomodation

Ronald McDonald House of Southern Alberta

111 West Campus Place NW
Calgary, Alberta T3B 2R6
Tel: 403-240-3000

https://rmhcalberta.org/

Dental

Recipients of Income Supports, Alberta Child Health Benefit or the Alberta Adult Health Benefit may receive coverage for extraordinary dental work. Their dentist needs to provide information to the applicable program which will then send a claim through the ADSC via a Health Benefits Exception request.

Financial resources

Alberta Aids to Daily Living Program (A.A.D.L.)

This provides funding for some medical supplies and equipment and is available to all residents of Alberta. The cost share is A.A.D.L. 75% and the family 25%.

Edmonton: 780-427-0731, or toll free in Alberta: 310-0000, then 780-427-0731.

https://www.alberta.ca/aadl-eligibility-and-application-for-benefits.aspx

Alberta Adult Health Benefit/ Alberta Child Health Benefit programs

Alberta Adult Health Benefit/ Alberta Child Health Benefit programs are designed to assist families meet daily needs. Qualifying families may receive support for items such as prescription drugs, eye glasses, and diabetic supplies.

Edmonton 780-427-6848 or 1-877-469-5437 (toll free province wide).

http://humanservices.alberta.ca/financial-support/2076.html

Alberta Works Housing and Utility support

Alberta Works Housing and Utility support offers Albertans access to emergency accommodation, transportation, and meals when criteria are met.

Edmonton 780-644-5135 (24 hour/day, 7 days/week). Across Alberta 1-866-644-5135

www.humanservices.alberta.ca/financial-support/3171.html

Community Key

Community Key helps families with children that are seriously-ill or critically-injured that spend a lot of time in hospital. They help with up to 2 months of mortgage support (or up to $2000).

https://www.keyed.ca/

Eye See… Eye Learn Program

This program was initiated by the Alberta Association of Optometrists. Children in Kindergarten are eligible to receive free glasses and frames.

Tel: 1-855-424-ESEL (3735)

www.eyeseeeyelearn.ca

Family Support for Children with Disabilities (FSCD)

The FSCD program uses a family-centered approach to provide parents with funding to access a range of supports and services that strengthen their ability to promote their child's healthy growth and development. In addition, FSCD assists with some of the extraordinary costs of raising a child with a disability. Services are available to eligible children with disabilities and their families until the child turns 18 years old.

https://www.alberta.ca/fscd.aspx

Hope for Kids (Mountain View country)

Hope 4 MVC Kids is a charity that provides families with children with a medical diagnosis who live in Mountain View County assistance with expenses including meals, transportation, medical equipment, accommodation, and various bills.

https://hope4mvckids.org/

Request for a Health Benefit Exception

Parents/guardians, who receive the Alberta Adult or Child Health Benefit and have a child that has been prescribed a medication that is not listed on the Health and Wellness Drug Benefit List, should refer to instructions pertaining to submitting a "Request for Drugs and Nutritional Products" form. Parents/guardians and the prescribing physician are required to complete forms

that are sent for review by the Health Benefit Review Committee. Requests for Prescribed infant formula and special diet items may also be considered for funding using these forms.

Programs and services

Calgary Immigrant Aid Society

The Calgary Immigrant Aid Society was established in 1977 and has, over the past 30 years, helped over 250 000 immigrants settle into their new life and home in Calgary, Alberta. The organization's focus is on individuals and families first, providing a sense of community and connection.

9107 Ave SW
Calgary, Alberta T2P 3N8
Tel: 403-265-1120

www.immigrantservicescalgary.ca

Children's Link Society

Children's Link Society is a family-centered, community-based, central access point of information for families of children with special needs in Calgary and Area. The Children's Link Society provides drop-in and phone support in walking through steps of transition.

Suite 245, 720 - 28th Street N.E
Calgary, Alberta T2A 6R3
Tel: 403-230-9158

www.childrenslink.ca

Jamie's Preschool

Jamie's Preschool provides a safer haven for immune-compromised children and their siblings. The program aims at keeping children who are immune-compromised, healthy, active, and engaged.

Unit 1, 3303 Capitol Hill Cres. NW
Calgary, Alberta T2M 2R2
Tel: 403-808-2296

www.jamiespreschool.ca

Pace Kids

Pace Kids is a family-focused program and strives to offer excellence in the treatment of children with special needs, emphasizing an intra-disciplinary direct treatment approach. This program is funded by Family Support for Children with Disability (FSCD).

#112 5211 MacLeod Trail S
Calgary, Alberta T2H 0J3
Tel: 403-234-7876

www.pacekids.ca

Provincial resources—British Columbia

Accomodation

Ronald McDonald House British Columbia

4567 Heather St
Vancouver, British Columbia V5Z 0C9
Tel: 604-736-2957
Fax: 604-736-5974

http://www.rmhbc.ca/

Easter Seals House

Easter Seals House in Vancouver provides a low-cost place to stay for more than 100 parents and children every night. For more information:

3981 Oak St
Vancouver, British Columbia V6H 4H5
Tel: 604-736-3475
Reservations only: 1-800-818-3666

https://www.eastersealsbcy.ca/how-we-help/easter-seals-house/

Financial resources

BC Family Residence Program

This is a program through The Ministry of Health providing accommodation assistance to enable families to stay together when their child requires medical care at BC Children's Hospital or Sunny Hill Health Centre for Children. Enhanced travel assistance is also provided through improved ground transportation for children and air transportation for patients of all ages.

http://www.bcfamilyresidence.gov.bc.ca/

BC PharmaCare

BC PharmaCare helps B.C. residents with the cost of eligible prescription drugs and certain medical supplies. It provides access to drug therapy through several drug plans. The largest is the income based Fair PharmaCare plan which is passed on your family's net income. It is available to single people or to families.

Your coverage is updated on January 1 of every year based on your current income information.

https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents

Friends of Children

Friends of Children is a registered charity providing free and confidential service to Northern BC and East Kootenay families travelling to access medical treatments for their children. Their goal is to relieve emotional and financial strain by assisting with the fuel, accommodation, and meal costs associated with these appointments, surgeries, and consultations. They may also be able to assist with therapies and specialized equipment related to a child's medical condition.

https://www.friendsofchildren.ca/

Variety, Children's Charity

This provides grants for equipment, medical/therapeutic supplies, specialized therapy, dental/orthodontic treatment, and bursaries for tuition/tutoring/summer camp. They also provide emergency grants to assist with funding to access medical care, supplies, accommodation, transportation, prescriptions, ambulance bills, formula, and breast pumps. The child must be under 19 years, be a BC resident for a minimum of 3 months, have a qualified special need (medical, physical, developmental, cognitive, social, psychiatric, emotional), and be in financial need.

www.variety.bc.ca

Provincial resources—Manitoba

Accomodation

Ronald McDonald House Manitoba

566 Bannatyne Avenue
Winnipeg, Manitoba R3A 0G7
Tel: 204-774-4777

http://www.rmh.mb.ca

Will's Place

Will's Place are maintained 2 bedroom fully furnished apartments for families with children undergoing Bone Marrow Transplant (BMT). Referral needed by the BMT team.

Financial resources

Children's Hospital Research Foundation

Children's Hospital Research Foundation is a registered charity that helps with the purchase of equipment, support programs and fund medical research.

http://goodbear.mb.ca

Daniel Lee Dorward Compassionate Fund for SickKids

This is a charity of last resort, designed to help families cope with the day-to-day and extraordinary costs of having a child who has a chronic and/or life-threatening illness. Social Workers at Winnipeg Children's Hospital refer families after all other resources have been exhausted. Assistance from this fund reduces some of the financial stress associate with having a seriously ill child.

https://secure.goodbear.ca/site/TR/Events/ThirdParty-Fundraisers?px=1048242&pg=personal&fr_id=1100#.XgOP_fxybb0

Employment and Income Assistance

Employment and Income Assistance (EIA) provides financial help to Manitobans who have no other way to support themselves or their families. For people who are able to work, EIA will help them go back to work by providing supports to employment.

https://www.gov.mb.ca/fs/eia/index.html

Lions Foundation of Manitoba and North Western Ontario

Lions Foundation of Manitoba and North Western Ontario supports, promotes and fosters programs for the benefit of both children and adults that are in need of assistance that live in the communities throughout Manitoba and Northwestern Ontario. They assist with three areas: (1) non-medical costs as set forth by Foundation guidelines which would include modest accommodations, meal allowance, and necessary ground transportation and for medication cost over and above those not covered by the present health care system; (2) non-medical costs for treatment not available in the province; and (3) costs to purchase specialized equipment for the physically challenged.

http://lionsfoundation.org/

Pharmacare

Pharmacare is a drug benefit program for eligible Manitobans, regardless of disease or age, whose income is seriously affected by high prescription drug costs. Pharmacare coverage is based on both your total family income and the amount you pay for eligible prescription drugs. The total family income is adjusted to include a spouse and the number of dependents, if applicable. Each year you are required to pay a portion of the cost of your eligible prescription drugs. This amount is your annual Pharmacare deductible. Pharmacare sets your deductible based on your adjusted family income.

http://www.gov.mb.ca/health/pharmacare/

Variety Manitoba

Variety Manitoba provides special needs program funding for children from newborn to their 18th birthday who are residents of Manitoba. The Special Need qualifies in the category of medical, physical, developmental, cognitive, social, and emotional as recognized by a designated professional and/or where the family is unable to financially afford the item, service, or therapy required.

http://varietymanitoba.com/

Westman Dreams for Kids

Westman Dreams for Kids is a non-profit, local registered organization dedicated to helping kids in the Westman area who are affected by a serious illness.

http://www.westmandreamsforkids.ca/

Provincial resources—New Brunswick

Financial resources

East Coast Fund

East Coast Fund is accessed by a social worker at SickKids Hospital for families from the East Coast undergoing bone marrow transplant in Toronto. It can assist with expenses related to travel and stay in Toronto. Connect with a SickKids social worker for application to this fund.

Family Supports for Children with Disabilities

Family Supports for Children with Disabilities provides social work support and financial resources to families to assist with the care and support required to meet the special developmental needs of their child with disability.

http://www2.gnb.ca/content/gnb/en/services/services_renderer.10195.Family_Supports_for_Children_with_Disabilities_.html

Fuel the Care

Fuel the Care provides fuel gift cards to parents who must frequently travel to provide their children with urgent medical care. This program is for families in Atlantic Canada and New England.

https://www.irvingoil.com/en-CA/discover-irving/fuel-the-care

The New Brunswick Drug Plan

The New Brunswick Drug Plan is a prescription drug plan that provides drug coverage for uninsured New Brunswick residents who have an active Medicare card. Any New Brunswick resident who has questions about the New Brunswick Drug Plan may call the information line toll free at 1-855-540-7325, email info@nbdrugs-medicamentsnb.ca, and may view the list of eligible drugs covered by the New Brunswick Drug Plan by visiting the New Brunswick Drug Plans Formulary.

https://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/NBDrugPlan.html

The New Brunswick Prescription Drug Program

The New Brunswick Prescription Drug Program (NBPDP) provides prescription drug benefits to eligible residents of New Brunswick. Information on the eligible beneficiary groups is outlined at https://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/TheNewBrunswickPrescriptionDrugProgram/BeneficiaryGroups.html

https://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/TheNewBrunswickPrescriptionDrugProgram.html

Moncton Lion's Sick Kids Fund

Moncton Lion's Sick Kids Fund can provide assistance with travel (for medically referred travel out of town), prescription drug assistance, medical equipment and other support. Children qualify for assistance up until their 19th birthday.

https://lionssickkids.ca/

Provincial resources—Newfoundland and Labrador

Accomodation

Ronald McDonald House Newfoundland & Labrador

P.O. Box 28091
St. John's, Newfoundland A1B 1X0
Tel: 709-738-0000

www.OurHouseNL.ca

Financial resources

East Coast Fund

East Coast Fund is accessed by a social worker at SickKids Hospital for families from the East Coast undergoing bone marrow transplant in Toronto. It can assist with expenses related to travel and stay in Toronto. Connect with a SickKids social worker for application to this fund.

Fuel the Care

Fuel the Care provides a fuel gift cards to parents who must frequently travel to provide their children with urgent medical care. This program is for families in Atlantic Canada and New England.

https://www.irvingoil.com/en-CA/discover-irving/fuel-the-care

Newfoundland and Labrador Prescription Drug Program

Newfoundland and Labrador Prescription Drug Program provides assistance in the purchase of pharmaceuticals, and some related medical supplies to residents who qualify for benefit coverage. The focus of the program is that residents of the province should not be denied access to health care because of financial need.

https://www.gov.nl.ca/hcs/prescription/

Special Assistance Program

Special Assistance Program — Medical equipment and supplies provides basic medical supplies and equipment to assist with activities of daily living for individuals living in the community who meet the eligibility criteria for the program. Benefits of the program include: medical supplies (such as dressings, catheters and incontinent supplies), oxygen and related equipment and supplies, Orthotics such as braces and burn garments, and Equipment such as wheelchairs, commodes, or walkers.

https://www.gov.nl.ca/hcs/personsdisabilities/fundingprograms-hcs/#scwap

Special Child Welfare Allowance Program

Special Child Welfare Allowance Program provides assistance with the cost of services/supports to families with a child (under the age of eighteen years) who has a physical or intellectual disability living at home. The assistance is designed to enable families to purchase items and/or services which are necessary due to the child's disability. The amount of monthly assistance for each family is determined through financial need.

https://www.gov.nl.ca/hcs/personsdisabilities/fundingprograms-hcs/#scwap

Transportation

The Medical Transportation Assistance Program (MTAP)

The Medical Transportation Assistance Program provides financial assistance to beneficiaries of the Medical Care Plan (MCP) who incur substantial out-of-pocket travel costs to access specialized insured medical services which are not available in their immediate area of residence and/or within the Province. Claimable expenses include airfare, accommodations purchased from a registered accommodations provider, such as a hostel, hotel, motel and/or registered apartment, scheduled busing services, and taxis when used in conjunction with commercial air travel.

https://www.gov.nl.ca/hcs/mcp/travelassistance/

Provincial resources—Nova Scotia

Accomodation

Ronald McDonald House Atlantic Canada

1133 Tower Road
Halifax, Nova Scotia B3H 2Y7
Tel: 902-429-4044

www.rmhatlantic.ca

Halifax Haven

A non-profit organization through the Mennonite Church that provides accommodation for patients while they undergo treatment in Halifax. Shared guest home. Donation of $40 per day, if possible. A continental breakfast is provided on-site. Military Families may be

able to access emergency accommodation support through the Military Family Resource Centre.

5897 Inglis Street
Halifax, Nova Scotia B3H 1K7 Canada
Tel: 902-421-1650

Financial resources

Fuel the Care

Fuel the Care provides a fuel gift card to assist with a portion of fuel cost to eligible family members who must frequently travel more than 100 km from home to provide their child with urgent medical care and who are not receiving other funding for transportation. This program is for families in Atlantic Canada. It can be accessed through the IWK Health Centre Social Work Department; however, it is subject to availability.

https://www.irvingoil.com/en-CA/discover-irving/fuel-the-care

Local Service Clubs

Local Service Clubs also provide support including local chapters of Lion's, Elk's and Kinsmen Clubs. Contact your local service club through websites, telephone book, or personal contacts.

Out-of-Province Travel & Accommodation Assistance

Out-of-Province Travel & Accommodation Assistance provides funds to individuals who are approved to travel out of province for insured medical care that is not available in Nova Scotia. The policy provides a maximum of $1,000 in travel assistance (round trip) and $125 per night up to $1,500 per month in accommodation assistance. This provides assistance for short-term stays. If a longer term stay is anticipated, patients are encouraged to seek longer term accommodations, such as apartment rental.

https://novascotia.ca/dhw/Travel-and-Accommodation-Assistance/

Pharmacare options for Nova Scotia

Income Assistance

For families that collect income assistance (IA), the cost of approved medications is a $5 'co-pay'. If there are more than 3 medications per child, the co-pay can be waived by IA. Over-the-counter medications (like Tylenol or Advil) may be covered with a letter from your doctor (submitted to Income Assistance) stating the reason this medication is needed, dosage required, how long it is needed, and the monthly cost.

Family Pharmacare

All Nova Scotia families are eligible for this program as well as single adults over age 18. The Nova Scotia Family Pharmacare Program is a provincial drug insurance plan designed to help Nova Scotians with the cost of their prescription drugs. The Program offers protection against drug costs for families who have no drug coverage or if the cost of the prescription drugs becomes a financial burden to them.

This coverage can be paired with private health insurance (e.g., Blue Cross, Great West Life) when co-payment amounts are high or when pre-existing conditions aren't covered.

Low income Pharmacare for children and youth

Children under 18 whose parents collect the NS portion of the Child Tax Benefit (usually requires income less than $25,000 year) are eligible for this program.

All approved medications cost $5. For more information, call 1-866-424-1269

Direct family support for children

This program is for children with severe intellectual or physical disabilities.

All medications and over-the-counter drugs can be covered for children in the program with a letter from your doctor.

Condition-specific & palliative care/end of life coverage

Certain health conditions have specific coverage available to families. Coverage may be available for palliative care and end-of-life symptom management or for patients with unique health conditions.

http://novascotia.ca/dhw/pharmacare/

Provincial resources—Ontario

Accomodation

Ronald McDonald House Toronto

240 McCaul St.
Toronto, Ontario M5T 1L1
Tel: 416-977-0458

www.rmhtoronto.org

Dental services

Children in Need of Dental Program (CINOT)

CINOT is a program through the Ontario Ministry of Health and Long-Term Care and provides dental coverage for children from birth to Grade 8 or their 14th birthday.

For more information call the INFO line:
Tel: 1-866-532-3161
TTY: 1-800-387-5559
Hours of Operation: 8:30 AM – 5:00 PM

https://www.toronto.ca/311/knowledgebase/kb/docs/articles/public-health/dental-and-oral-health-services/dental-and-oral-health-services/children-in-need-of-dental-treatment-cinot.html

Healthy Smiles Ontario

This is a government-funded dental program that provides free preventive, routine, and emergency dental services for children and youth 17 years old and under from low-income households.

The program includes regular visits to a licensed dental provider and covers the costs of treatment including:

- check-ups
- cleaning
- fillings (for a cavity)
- X-rays
- scaling
- tooth extraction
- urgent or emergency dental care (including treatment of a child's toothache or tooth pain)

Children are automatically eligible for Healthy Smiles Ontario if they or their family receive:

- Ontario Works
- Temporary Care Assistance
- Ontario Disability Support Program
- Assistance for Children with Severe Disabilities

Children are eligible for the program if they:

- Are 17 years of age and under live in Ontario are from low-income families

https://www.ontario.ca/page/services-covered-by-healthy-smiles-ontario

Financial resources

Assistance for Children with Severe Disabilities (ACSD)

The ACSD program provides financial assistance to parents to help with the extraordinary cost related to their child's severe disability. This program is for low to moderate income families. A qualifying family will receive no less than $25 per month to no more than $500 per month to assist with expenses related to illness. In addition, the child will receive drug and dental coverage.

Ministry of Children and Youth Services Client Services Unit
900 Bay Street, M1-57 Macdonald Block, Toronto, Ontario M7A 1R3
Toll Free: 1-866-821-7770
TTY: 1-800-387-5559

http://www.children.gov.on.ca/htdocs/English/specialneeds/disabilities.aspx

Assistive Devices Program (ADP)

This program provides funding assistance towards equipment and supplies for people with long-term physical disabilities who need personalized assistive devices. The majority of receipts will receive 75% coverage, and those on Ontario Works or receiving Assistance for Children with Severe Disabilities receive 100% coverage. Examples are medical supplies, mobility devices, prosthetics, orthotics, sensory devices, and diabetes supplies.

http://www.health.gov.on.ca/en/public/programs/adp/default.aspx

Jennifer Ashleigh Foundation

The Jennifer Ashleigh Foundation assists children who are seriously ill, are 21 years of age or under, and whose permanent residence is in Ontario. Family income impacts on assistance decisions. The Foundation will consider requests for assistance in the following areas as they are related to the child's illness:

- Emergency financial relief
- Respite for a pre-determined period of time
- Developmental therapies (excluding Hyperbaric Oxygen Treatment) Educational programs, materials, instruction

- Specially adapted computer equipment and software
- Medical treatments not covered by government health plans or insurance Recreation that promotes a child's involvement in the community.

10800 Concession 5
Uxbridge, Ontario L9P 1R1
Tel: 905-852-1799

Easter Seals Incontinence Supplies Grant

The program is for children and youth between the ages of 3 to 18 years of age with a chronic disability resulting in irreversible incontinence lasting longer than 6 months. Some children under the age of 3 may be eligible for funding depending on their diagnosis. The application must be completed and signed by a medical physician licensed to practice in Ontario. The child must be a resident of Ontario and hold a valid Ontario health card.

For more information on the incontinence supplies grant contact:

Julianna Phen
Easter Seals Ontario
One Concorde Gate, Suite 700
Toronto, Ontario M3C 3N6
Tel: 1-800-668-6252 ext. 314

https://services.easterseals.org/incontinence-supplies-grant/

Special Services at Home (SSAH)

This program helps families who are caring for a child with a developmental or physical disability, as well as adults with a developmental disability. It helps families pay for special services in the home or outside the family home as long as the child is not receiving support from a residential program.

http://www.children.gov.on.ca/htdocs/English/specialneeds/specialservices.aspx

Ministry of Children and Youth Services Client Services Unit

900 Bay Street, M1-57 Macdonald Block
Toronto, Ontario M7A 1R3
Toll Free: 1-866-821-7770
TTY: 1-800-387-5559

www.gov.on.ca/mcys

Trillium drug program (TDP)

The Trillium Drug Program (TDP) is for people who spend approximately 3 to 4 per cent or more of their after-tax household income on prescription-drug costs. The incomes of TDP household members under age 25 would still be factored into the household deductible calculation. However, any medications funded through OHIP+ (for children and youth that do not have coverage through a private plan) do not contribute towards the household's TDP deductible, as they are not considered out-of-pocket expenses.

For more information:
P.O. Box 337, Station D
Etobicoke, Ontario M9A 4X3
Tel: 416-642-3038
Fax: 416-642-3034
Toll-Free: 1-800-575-5386
Email: trillium@resolve.com

https://www.ontario.ca/page/get-help-high-prescription-drug-costs.

Programs and services

Child Development Institute

Child Development Institute offers a wide range of programs and services for children aged 0-12 and their families. In some programs they are able to remain connected with children up to age 18. In all programs the commitment is to strengthen families and promote healthy child development.

For all general inquiries, please contact the main office at:

Child Development Institute
197 Euclid Ave.
Toronto, Ontario M6J 2J8
Tel: 416-603-1827
Fax: 416-603-6655
Email: mail@childdevelop.ca

www.childdevelop.ca

Ontario Early Years Centres

Ontario Early Years Centres are places where parents and caregivers can take part with their children in a range of programs and activities, get answers to questions, get information about programs and services that are available for young children, talk to early years professionals, as well as other parents and caregivers in

the community. If you have a question about your child's development, or want to know how to get information or services for children up to the age of six, please call or visit your Ontario Early Years Centre in your community.

For a complete list of locations:

Call the INFO line:
Toll-free: 1-866-821-7770
TTY: 1-800-387-5559

https://www.ontario.ca/page/find-earlyon-child-and-family-centre

Respite services

Enhanced Respite Care

This is a grant to help families caring for a medically fragile child who depends on a technological device, and/or requires care all day and night, including frequent or time-consuming caregiver intervention and monitoring on a 24 hour basis. Eligibility is determined by the local Community Care Access Center (CCAC).

http://www.children.gov.on.ca/htdocs/English/specialneeds/respite.aspx

Transportation

Accessible Parking Permit

This permit entitles a vehicle to be parked in a designated 'accessible parking' space.

An accessible parking permit will be issued to an individual if one of the following eligibility criteria apply:

- Cannot walk without assistance of another person or a brace, cane, crutch, a limb prosthetic device or similar assistive device or who requires the assistance of a wheelchair.
- Suffers from lung disease to such an extent that forced expiratory volume in one second is less than one litre.
- Portable oxygen is a medical necessity.
- Cardiovascular disease impairment classified as Class III or Class IV to standards accepted by the American Heart Association or Class III or IV according to the Canadian Cardiovascular Standard.
- Severely limited in the ability to walk due to an arthritic, neurological, musculoskeletal, or orthopaedic condition.
- Visual acuity is 20/200 or poorer in the better eye with or without corrective lenses or whose greatest diameter of the field of vision in both eyes is 20 degrees or less.
- Condition(s) or functional impairment that severely limits his or her mobility.

https://www.ontario.ca/page/get-accessible-parking-permit

OHIP+

OHIP+ makes more than 4,400 drug products free for anyone age 24 years or younger who is not covered by a private plan. Anyone 24 years and under who has OHIP coverage and is not covered by a private plan is covered by OHIP+. You do not have to enroll or register to access OHIP+ coverage.

OHIP+ coverage will stop on your 25th birthday or if you become covered by a private plan, but you may qualify for other financial help with prescription drug costs.

If you have coverage through a private plan, but your household still has significant out-of-pocket costs, you can apply for additional financial support through the Trillium Drug Program. The Trillium Drug Program is available to all OHIP-insured Ontarians who have high prescription drug costs compared to their household income.

http://www.health.gov.on.ca/en/pro/programs/drugs/ohipplus/

Exceptional Access Program

The Exceptional Access Program (EAP) provides patients access to drugs not listed on the ODB Formulary, or where no listed alternative is available. In this case, you can get help paying for it when you qualify for the Exceptional Access Program. Children and youth with no private plan and an approved EAP request are fully covered for the cost of their medications under OHIP+.

https://www.ontario.ca/page/applying-exceptional-access-program#section-0

If you have immediate questions or concerns regarding the EAP, please contact OHIPplus@ontario.ca.

Northern Travel Grant

Travel grants are funded by the Ministry of Health and Long-Term Care to help defray the transportation

costs for eligible residents of Northern Ontario who must travel long distances within Ontario or to Manitoba to receive medically needed insured specialty services that are not available locally.

For more information:

Ministry INFO line:
1-866-532-3161 (Toll-free in Ontario only)
TTY: 1-800-387-5559

To download a copy of the application visit:

http://www.health.gov.on.ca/english/public/pub/ohip/northern.html

Provincial resources—Prince Edward Island

Financial resources

East Coast Fund

East Coast Fund is accessed by a social worker at SickKids Hospital for families from the East Coast undergoing bone marrow transplant in Toronto. It can assist with expenses related to travel and stay in Toronto. Connect with a SickKids social worker for application to this fund.

The Catastrophic Drug Program

The Catastrophic Drug Program provides assistance to Islanders whose eligible prescription drug costs are affecting their household's ability to maintain life essentials. Through this new program Islanders will have their annual out-of-pocket drug costs for eligible prescription medications capped at an amount not exceeding a set percentage of their household income, referred to as 'household cap'.

https://www.princeedwardisland.ca/en/information/health-pei/catastrophic-drug-program

Family Health Benefit Drug Program

Family Health Benefit Drug Program covers approved prescription medications for children under 18 and dependent students who are still registered as a full-time student and under the age of 25. Coverage is dependent on income level and number of dependents.

https://www.princeedwardisland.ca/en/information/health-pei/family-health-benefit-drug-program

High Cost Drug Program

High Cost Drug Program provides assistance to Islanders for the purchase of approved high cost drugs. All medications have specific medical criteria that must be met before coverage will be approved.

https://www.princeedwardisland.ca/en/information/health-pei/high-cost-drug-program

AccessAbility Supports

The Disability Support Program has expanded and is now called **AccessAbility Supports.** New supports offer more and better assistance to Islanders living with disabilities. Support is provided in the following five areas: Personal Support, Housing Support, Community Support, Caregiver Support, and Financial Support.

https://www.princeedwardisland.ca/en/information/social-development-and-housing/accessability-supports

Transportation

The Medical Transportation Assistance Program (MTAP)

The Medical Transportation Assistance Program provides financial assistance to beneficiaries of the Medical Care Plan (MCP) who incur substantial out-of-pocket travel costs to access specialized insured medical services which are not available in their immediate area of residence and/or within the Province. Claimable expenses include airfare, accommodations purchased from a registered accommodations provider, such as a hostel, hotel, motel and/or registered apartment, scheduled busing services, and taxis when used in conjunction with commercial air travel.

http://www.health.gov.nl.ca/health/mcp/travelassistance.html

Provincial resources—Quebec

Accomodation

Ronald McDonald House Montreal

5800 Hudson Road
Montreal, Quebec H3S 2G5
Tel: 514-731-2871

www.manoirmontreal.qc.ca

Financial resources

Medication Plan

For families that do not have private drug coverage, this public provides free medication for children under the age of 18 years.

http://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/Pages/prescription-drug-insurance.aspx

Sun Youth/Jeunesse au Soleil

Sun Youth is an organization that provides financial assistance with medication, heating, food, school supplies and recreation programs including providing bicycles, camp and sports programs.

4251 Saint-Urbain, Montreal
Quebec, Canada H2W 1V6

www.sunyouthorg.com

Supplement of the Handicapped Child

This provides financial assistance for families to help with the care and education of a handicapped child. The handicap must significantly limit the child in carrying out daily activities for a period expected to last for at least 1 year. It provides non-taxable $185 a month, for all children who meet the eligibility criteria.

http://www.rrq.gouv.qc.ca/en/programmes/soutien_enfants/supplement/Pages/supplement.aspx

APIQ - Association des Patients Immunodéficients du Québec

The Association of Quebec immunocompromised patients (APIQ) is a non-profit organization comprised of patients with immunodeficiencies and patients with hereditary angioedema (HAE), their families and health professionals concerned with these diseases. Their mission is to contribute to improving the health and quality of life for people with immune deficiencies Association immunocompromised patients Québec aims.

http://www.cipo-apiq.ca/fr/index.php

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Content statement

The descriptions of the programs and resources within this document are provided directly from the websites/links cited.

Disclaimer

Information in the pages of the *Canadian Resources for individuals and families affected by Primary Immunodeficiency* are of a general nature, are subject to change without notice and are not intended to be relied on by readers as advice in any particular matter. The information is believed to be accurate and complete, but the Immunodeficiency Canada cannot guarantee that it will remain accurate or complete or that it will be current at all times. Immunodeficiency Canada is not responsible for direct, indirect, special or consequential damages, howsoever caused, arising out of the use of this Resource for individuals and families affected by primary immunodeficiency.

Primary Immunodeficiency

There are more than 400 genetic defects and disorders of the immune system that are recognized as Primary Immunodeficiency. Approximately 29,000 Canadians suffer from forms ranging widely in severity and symptoms. Over 70% are undiagnosed.

Red Flags for **Primary Immunodeficiency**

- Repeated invasive infection (two or more pneumonias, recurrent septicemia, abscesses, meningitis).[1]
- Infections with unusual or opportunistic pathogens (PJP).[1]
- Poor response to prolonged or multiple antibiotic therapies.[1]
- Chronic diarrhea with or without evidence of colitis.[1]
- Chronic failure to gain weight and grow.[2]
- Persistent (or recurrent) unusual (atypical) or resistant to treatment oral lesions (thrush) or skin rash (erythroderma, telangiectasias, recurrent pustules/nodules/plaques).[1]
- Structurally abnormal hair (kinky, silvery) nails (dystrophic) or teeth (pointy).[2]
- Low serum IgG, chronic lymphopenia, neutropenia or thrombocytopenia.[1]
- Absent lymph nodes and tonsils or chronic enlargement of lymphoid tissues.[1]
- A family history of Primary Immunodeficiency, autoimmunity or leukemia/lymphoma. [1]

References:
[1] All age groups
[2] Infancy and childhood

Early diagnosis and treatment are vital in saving lives. Treatment can improve or prevent long term organ damage. Each Red Flag alone should alert healthcare providers to the possibility of Primary Immunodeficiency and require further testing and investigation. Two or more Red Flags should trigger an urgent referral to an Immunologist.

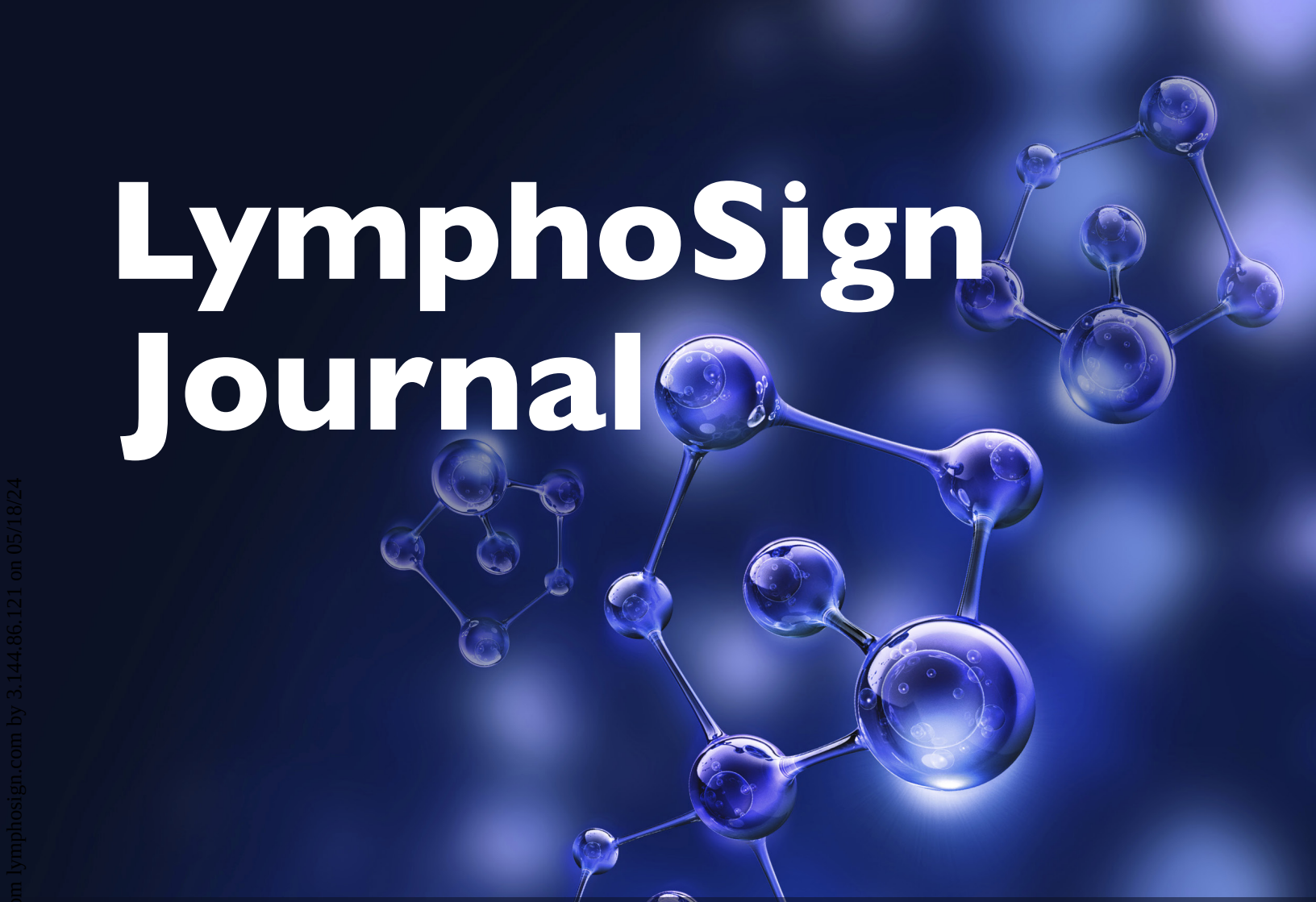
Immunodeficiency Canada
Immunodéficience Canada

Providing patient support, education and research to cure Primary Immunodeficiency

Suite 848, 439 University Ave., Toronto, Ontario M5G 1Y8
Tel 416-964-3434 **Fax** 416-964-6594
contactus@immunodeficiency.ca
charitable # 87276 0897 RR0001

www.immunodeficiency.ca

LymphoSign Journal



Working together for patients with PI

Immunodeficiency Canada
Immunodéficience Canada

jmcn Jeffrey Modell Centers Network

Canadian Science Publishing