LymphoSign Journal

The journal of inherited immune disorders

Volume 8, Number 1, 2021 EISSN 2292-5945

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LymphoSign Journal (ISSN electronic 2292-5945) is published quarterly in March, June, September, and December by LymphoSign Journal Limited Partnership, Toronto, Ontario, Canada; Tel.: 416-986-3508; Fax: 416-964-6594.

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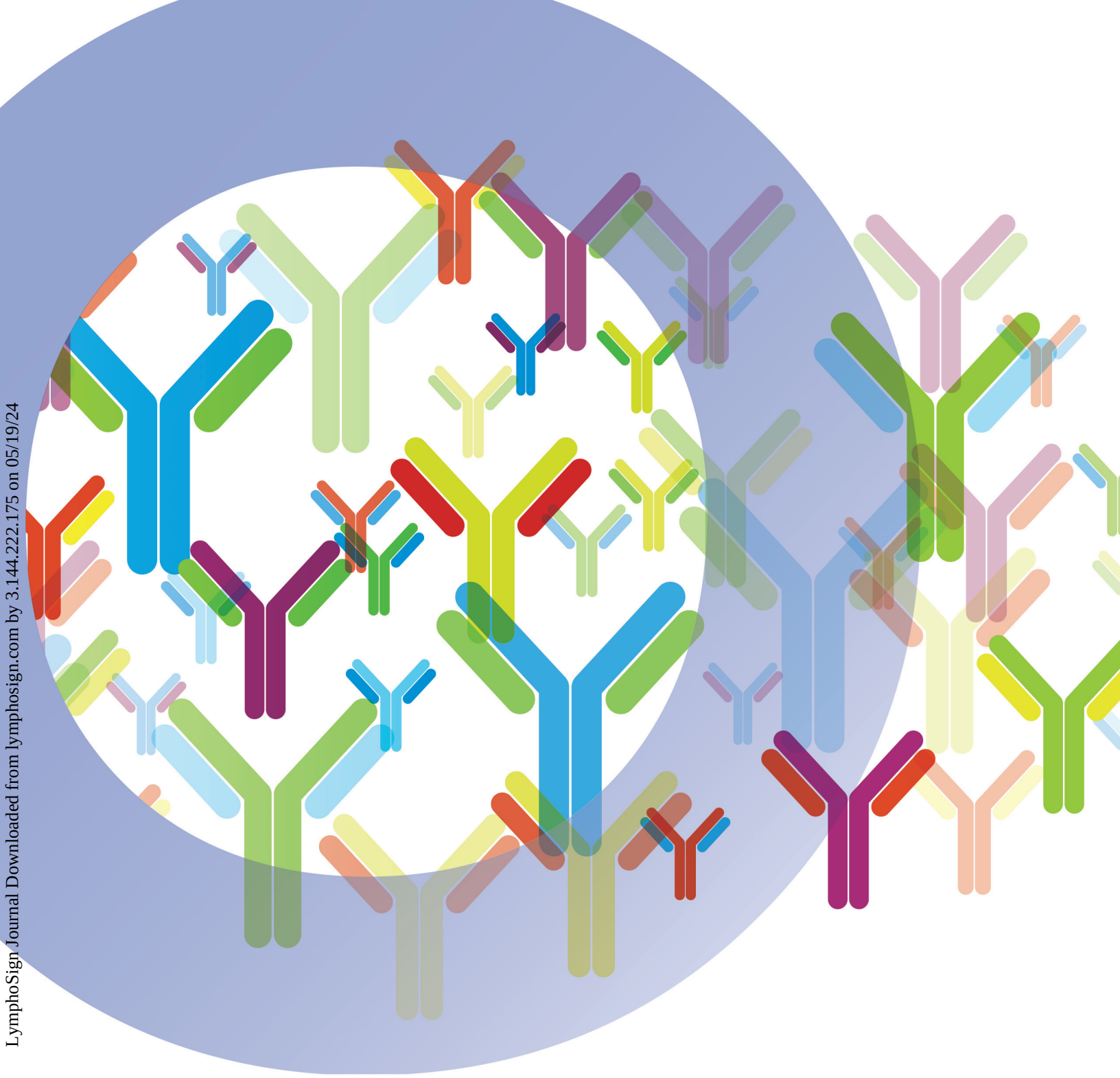

LymphoSign Journal

Volume 8, Number 1, 2021 EISSN 2292-5945

A novel splice site variant in *FOXN1* in a patient with abnormal newborn screening for severe combined immunodeficiency and congenital lymphopenia

Ori Scott[a*], Jenny Garkaby[a], Jessica Willett-Pachul[a], Amarilla B. Mandola[b], and Yehonatan Pasternak[a]

ABSTRACT

Background: The Forkhead box protein N1 (FOXN1) is a key regulator of thymic epithelial development, and its complete deficiency leads to a nude-severe combined immunodeficiency (SCID) phenotype. More recently, heterozygous mutations in *FOXN1* have been linked with a syndrome of congenital lymphopenia and a wide clinical spectrum, with most cases being caused by missense mutations.

Aim: To broaden the genotypic and phenotypic spectrum of heterozygous *FOXN1* deficiency.

Methods: Case report of a patient with *FOXN1* haploinsufficiency due to a novel splice-site mutation.

Results: Our patient was identified at 3 weeks of life given an abnormal newborn screen (NBS) for SCID, and was found to have congenital lymphopenia preferentially affecting $CD8^+$ T-cells. Her cellular and humoral function were both excellent, and she has remained entirely asymptomatic and thriving for the first 3 years of her life. The patient was found on whole exome sequencing to carry a heterozygous splice-site mutation in the *FOXN1* gene, affecting the Forkhead domain. The mutation was also identified in her asymptomatic mother.

Conclusion: Heterozygous *FOXN1* mutations are an increasingly-recognized cause of congenital lymphopenia. Our experience suggests most patients remain clinically well, with main manifestation including T-lymphopenia, mostly affecting $CD8^+$ cells. Identification of the same variant in an asymptomatic parent suggests age-dependent improvement in T-cell counts and an overall benign course, while provides impetus for diligent conservative management with regular follow-up.

Statement of novelty: Heterozygous *FOXN1* deficiency is a relatively new entity, attributed in most cases to missense mutations in *FOXN1*. To further expand the knowledge basis regarding this emerging disorder, as well as its genotypic repertoire, we herein report a case of heterozygous *FOXN1* deficiency caused by a splice site mutation.

Introduction

The Forkhead box (FOX) superfamily comprises of transcription factors with key roles in tissue development and homeostasis (Lam et al. 2013). Within the FOX family, FOX protein N1 (FOXN1) is a key regulator of thymic epithelium and skin development. FOXN1 dictates gene expression involved in thymic epithelial cell (TEC) differentiation, lymphoid progenitor migration from the bone marrow, antigen processing and thymocyte selection (Nowell et al. 2011; Romano et al. 2013; Žuklys et al. 2016). Complete *FOXN1* deficiency was first identified in mice displaying the nude/severe combined immunodeficiency (SCID) phenotype, consisting of

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Submitted 4 February 2021
Accepted 25 February 2021
Available online 26 February 2021

LymphoSign Journal 8:1–4 (2021)
dx.doi.org/10.14785/lymphosign-2021-0013

congenital alopecia totalis, nail dystrophy and thymic aplasia (Flanagan 1966). An equivalent phenotype was later described in humans harbouring biallelic loss-of-function (LOF) mutations in the *FOXN1* gene (Pignata et al. 1996; Frank et al. 1999). In contrast to the well-established phenotype seen with complete *FOXN1* LOF, the role of heterozygous *FOXN1* mutations in human immunity has been slower to emerge. In a recent case-series, Bosticardo et al. (2019) described for the first time a cohort of children with heterozygous *FOXN1* mutations, who were found to have low T-cell receptor excision circles (TREC) levels and (or) lymphopenia.

Functional and clinical presentation

Clinical case

An asymptomatic female newborn was referred to our Immunology clinic at the age of 3 weeks by the Ontario newborn screening (NBS) program. The reason for referral was a finding of low T-cell receptor excision circles (TREC) levels from a dried blood spot, representing an abnormal screening test for severe combined immunodeficiency (SCID). On review of history, the girl was the product of spontaneous pregnancy with adequate prenatal follow-up and no known pregnancy complications. She was born at 39 + 2 weeks via spontaneous vaginal delivery with no resuscitation required, and had an uneventful neonatal course. Family history identified non-consanguineous parents of mixed English, Dutch, and African-American ancestry. Father had required a tonsillectomy and adenoidectomy as a child for recurrent tonsillitis, and had a number of acute otitis media infections until the age of 4 years, for which he did not require any surgical intervention. Mother was healthy with no history of recurrent infections. Two maternal half siblings were healthy as well. There was no extended family history of immunodeficiency, autoimmunity, inflammation, or early-onset malignancy. When seen at our clinic at the age of 3 weeks, the girl had been growing and feeding well and had no notable concerns for infection, autoimmunity, or inflammation. Her physical exam was within normal limits, including normal growth parameters, presence of normal lymph nodes and tonsillar tissue, no adenopathy, hepatosplenomegaly, or skin rashes; in particular, she has not demonstrated any alopecia or dermatitis.

Investigations

TREC levels were low, both on initial testing (48 copies/3 μL; cutoff: ≥75), and on repeat testing 1 month later (41.3 copies/3 μL). TREC measurement has not been repeated since. Adenosine deaminase and purine nucleoside phosphorylase metabolite profiles were normal. Complete blood count and differential were normal, including a normal absolute lymphocyte count of 2.55×10^9/L (normal: 2–17×10^9/L). Lymphocyte immunophenotyping, however was abnormal, with low $CD3^+CD4^+$ (837 cells/μL; normal: 1700–5300 cells/μL) and $CD3^+CD8^+$ (178 cells/μL; normal: 400–1700 cells/μL) counts. $CD19^+$ cells were normal (903 cells/μL; normal: 600–1900 cells/μL), as were $CD16^+CD56^+$ cells (438 cells/μL; normal: 186–724 cells/μL). Total immunoglobulin levels, PHA stimulation index, T-cell receptor Vβ repertoire, and analysis of naïve/memory T-cells (CD45RA/RO) were all within normal limits. On subsequent evaluations over the following 3 years, the she continued to have evidence of T-cell lymphopenia preferentially affecting $CD3^+CD8^+$, though this has remained in the moderate range. Her B and NK cells remain unaffected, and her functional assessment continues to be excellent for both the humoral and cellular arms. Following administration of killed immunizations, normal specific antibody titres were noted to both diphtheria and tetanus toxoid.

Genetic analysis began with normal karyotype and fluorescent in-situ hybridization for 22q11.2. Further analysis involved a primary immunodeficiency panel, which did not reveal the cause of the patient's presentation. Whole exome sequencing was finally performed, revealing a novel heterozygous intronic variant of unknown significance in the *FOXN1* gene: NM_003593 c.927+1G>C. The variant has not been reported in large population databases, and is predicted to eliminate an obligatory donor splice site in the Forkhead domain resulting in a deleterious effect. The variant was also detected in the girl's mother, and not in her father (Figure 1). On further testing, mother demonstrated a normal complete blood count and differential.

Outcome

Over the following 3 years, the patient has continued to be well with no recurrent or unusual infections, growth retardation, or immune dysregulation. She continues to have T-lymphopenia preferentially affecting CD8+ T-cells, although this has remained in the moderate range, with excellent T-cell stimulation responses. She is soon due to begin her live viral immunization series.

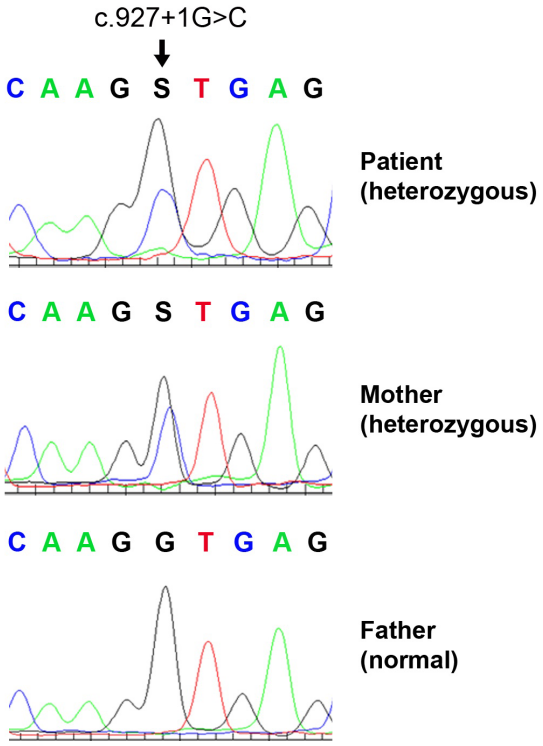

Figure 1: Electropherogram demonstrating the *FOXN1* heterozygous mutation NM_003593 c.927 +1G>C, identified in our patient and her mother, but not in the girl's father.

Discussion

The implementation of NBS in Ontario, as well as in various provinces across Canada, has led to an increased detection rate of patients with non-SCID lymphopenia who display low TREC levels shortly after birth. In this regard, heterozygous *FOXN1* mutations have been recently identified as a genetic etiology in a subset of children with abnormal NBS and (or) lymphopenia. The current report contributes to the expanding spectrum of heterozygous *FOXN1* deficiency, both genotypically and phenotypically. Clinically, our patient has always been well, and would likely have not presented to Immunology had it not been for her abnormal NBS result. She has had persistent moderate $CD8^+$ lymphopenia and mild and improving $CD4^+$ lymphopenia, with normal T-cell function and no humoral abnormalities. The patient was found to carry a heterozygous splice-site mutation in *FOXN1*, likely resulting in a loss of function. Interestingly, her mother who is clinically well and had a normal absolute lymphocyte count as an adult, was found to carry the same mutation. This may be attributed to the age-dependent function of *FOXN1*, which undergoes extensive methylation changes over time and its contribution to T-cell development likely wanes.

A recent case series has outlined a multi-centre experience caring for 25 children and 22 adults with heterozygous *FOXN1* mutations (Bosticardo et al. 2019). Of the children, 21 were identified following an abnormal NBS result, while 4 others were investigated for persistent severe lymphopenia and (or) recurrent infections. Most were clinically well except for viral respiratory infections, and were managed conservatively. Common non-infectious manifestations included eczema and nail dystrophy (not seen in our patient). Five patients displayed evidence of more profound lymphopenia and (or) severe infections, and 3 received a hematopoietic stem cell transplant for a clinical diagnosis of SCID, before their *FOXN1* mutations had been identified. Unfortunately, transplant outcome has included persistent lymphopenia despite engraftment in 2 children, and mortality of infection in the third patient. With respect to adults included in the report, the majority did not report on any substantial recurrent infectious history; however, it is possible that individuals impacted by severe infections would not have survived into adulthood, thus *de-facto* excluding persons with more profound disease manifestations from the adult cohort. In terms of laboratory evaluation, the most common and consistent manifestation in infants and children was T-lymphopenia impacting both $CD4^+$ and $CD8^+$ populations, with improvement in $CD4^+$ noted toward the second year of life. Among adult participants, $CD8^+$ lymphopenia was the only persistent disease abnormality identified in some.

The spectrum of clinical manifestations and severity hitherto reported among children with heterozygous *FOXN1* mutations has been broad, with no clear genotype-phenotype correlation with respect to location and nature of the mutations. Indeed, mutations reported by Bosticardo et al. (2019) spanned all gene domains, and included substitutions, insertions and deletions, in both exonic and intronic regions. However, the majority of cases involved missense mutations, while a splice site mutation was only reported in 1 child. It therefore remains to be determined whether splice-site variants result in a unique phenotype compared with other *FOXN1* mutations. Importantly, while splice site mutations may be identified on whole exome sequencing given their proximity to exonic regions, deep intronic mutations would not be identified using

this method, and would require either targeted sequencing of the *FOXN1* gene in its entirety, or whole genome sequencing. Of note, deep intronic mutations have never been identified as causing heterozygous *FOXN1* deficiency, but as whole genome sequencing becomes more prominently embedded in clinical practice, this observation may very well change.

In regards to management of children with heterozygous *FOXN1* mutations, our centre has practiced conservative, yet diligent follow-up of any patient with abnormal lymphocyte counts and (or) function. In regards to live vaccines, our experience suggests that in children with *FOXN1* mutations and normal T-cell function, whose T-lymphopenia is mild and improving or fully resolved, live viral vaccinations may be administered safely. However, a case-by-case discussion should be held with families, identified the potential risks and benefits of such an approach. Finally, genetic testing and counselling may be considered for asymptomatic first-degree family members as well.

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Identification of a novel RAG1 hypomorphic mutation in a child presenting with disseminated vaccine-strain varicella

Mei Xu[a], Brenda Reid[a], and Chaim M. Roifman[a,b]*

ABSTRACT

Background: Recombination-activating gene 1 (RAG1) and recombination-activating gene 2 (RAG2) encode unique lymphocyte endonuclease proteins that are crucial in T and B cell development through V(D)J recombination. RAG1 gene defects lead to variable phenotypes, ranging from immunocompetent to severe combined immunodeficiency (SCID). Curative therapy for severe manifestations can be achieved through hematopoietic stem cell transplantation (HSCT). Advances in genomic sequencing have led to the discovery of new variants and it is recognized that the level of recombinase activity correlates with disease severity.

Aim: To report the clinical presentation, immunological work-up, decision process to undergo HSCT, and confirmatory genetic diagnosis in a patient who was well until her initial presentation with disseminated vaccine-strain varicella.

Methods: Clinical data was gathered through retrospective chart review. Immunological investigations, targeted gene sequencing, and thymic biopsy results were reviewed. Further genetic analysis, including whole exome and whole genome sequencing was performed.

Results: Whole exome sequencing identified a single missense mutation in RAG1, R474C (c.1420C>T), which would not account for the clinical presentation. Healthy individuals with only 1 mutation have been reported. Subsequently, whole genome sequencing revealed a novel second heterozygous missense variant, H945D (c.2833G>T) in the RAG1 gene.

Conclusion: Hypomorphic RAG1 mutations with residual activity have a diverse phenotypic expression. Identifying and understanding the implications of these mutations is crucial for disease prognostication and tailoring management.

Statement of novelty: We present a novel RAG1 missense variant, with likely complete or partial loss of function, in a patient with significant impairment in cellular immunity.

Introduction

Recombination-activating gene 1 (RAG1) and recombination-activating gene 2 (RAG2) encode unique lymphocyte endonuclease proteins that form the complex required for somatic V(D)J gene recombination (Fugmann 2001). This process generates receptor diversity—equipping T and B cells with a broad repertoire for antigen recognition. DNA is cleaved at recombination signal sequences, resulting in hairpin-capped double-strand breaks that are opened and processed by Artemis (Sadofsky 2001). The ends are eventually

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Submitted 6 February 2021
Accepted 19 February 2021
Available online 21 February 2021

LymphoSign Journal 8:5–10 (2021)
dx.doi.org/10.14785/lymphosign-2021-0014

joined by non-homologous end joining with DNA ligase (Notarangelo et al. 2016). RAG1 may also facilitate the subsequent joining of the coding ends (Notarangelo et al. 2016; Delmonte et al. 2018). T and B cell development is dependent on this process and cannot progress beyond the DN3 and pre-B-1 stage without RAG1 or RAG2 (Gennery 2019). The discarded DNA from thymic T-cell rearrangement forms a loop known as a T-cell receptor excision circle (TREC), which is now used in newborn screening (NBS) for severe combined immunodeficiency (SCID) (Chitty-Lopez et al. 2020).

There is a recognized spectrum of phenotypes which correlates with the level of recombinase activity (Delmonte et al. 2018; Gennery 2019). Null mutations give rise to a T-B-NK+ SCID phenotype, whereas hypomorphic missense mutations with residual RAG activity can be found in Omenn syndrome (Gennery 2019). RAG mutations have also been implicated in cases of combined immunodeficiencies, common variable immunodeficiency (CVID), antibody deficiencies, granulomatous disease, and autoimmunity (Delmonte et al. 2018). We report a unique case of a patient with compound heterozygous RAG1 variants, who was well until her initial presentation with vaccine-strain varicella.

Methods

Chart review

Patient data was gathered by retrospective chart review. This included immunological investigations pre- and post-transplant, targeted gene sequencing results, thymic biopsy findings, and clinical documentation. Informed consent was obtained from the family in accordance with the SickKids Research Ethics Board (Protocol No. 1000005598).

Genetic analysis

DNA from blood was submitted for analysis at the TCAG, Hospital for Sick Children, Toronto, Ontario. For whole exome sequencing (WES), 100 ng of input DNA was utilized for library preparation (Ion AmpliSeq Exome Kit; Life Technologies). The exome library was subsequently immobilized on Ion PI™ Ion Sphere particles (Ion PI Template OT2 200 Kit v3; Life Technologies) and sequenced on the Ion PI™ Sequencing 200 Kit v3 and Ion PITM Chip v2 in the Ion Proton semiconductor sequencing system (Life Technologies). Alignment and variant calling were performed with 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 35 (based on Annovar), 36 and RefSeq gene models (downloaded from UCSC). For whole genome sequencing (WGS), the library was prepared using 700 ng of genomic DNA and sequenced on 1 lane (average depth of 37X) of the Illumina HiSeq X platform. Reads were aligned using BWA mem v0.7.12 to GRCh37; single nucleotide variants (SNVs) and insertions/deletions (INDELs) were called using GATK 3.7 haplotype caller. Copy number variants (CNV), comprising losses and gains with size ≥1 kb, were called using a pipeline based on the read depth callers ERDS and CNVnator. Variants were prioritized based on variant quality, allele frequency, molecular effect, gene function, and phenotype. Genomic coordinates are based on hg19/build37. Gene product effects were reported, unless otherwise indicated, in relation to the RefSeq transcript predicted as principal by APPRIS4. Only SNVs and INDELs with GATK VQSR filter PASS were considered for further analysis. Allele frequencies of SNVs and INDELs were obtained from gnomAD and ExAC. Missense impact predictions were obtained from dbNSFP for SIFT, PolyPhen2, Mutation Assessor and CADD. Splicing impact predictions were obtained from SPIDEX and dbscSNV.

Results

Clinical features

The patient was born at term following an uneventful pregnancy. She was infection-free with no concerns for growth, development, autoimmunity, or atopy until she received her live vaccines. These consisted of measles, mumps, rubella, and varicella at the age of 1. Within 2 weeks she developed fever and a vesicular rash, suspected to be varicella, which progressed to purpura of the limbs. Given the similarities between her and a sibling who had passed away, she was admitted to the intensive care unit and treated aggressively with immunosuppressants, steroids, and antivirals. Renal biopsy was normal, with no markers of collagen vascular disease. Skin biopsy was consistent with small vessel vasculopathy and microthrombosis. Her bone marrow had decreased lymphocytes but no malignant cells. Vaccine-strain varicella was isolated from skin lesions and cerebral spinal fluid, although there was no evidence of central nervous system or internal organ involvement. Treatment was advanced to include

infliximab and rituximab, in conjunction with steroids and cyclosporin, with good clinical response. She was discharged home to continue intravenous immunoglobulin (IVIG), immunosuppressants, prophylactic antibiotics, and antivirals. Physical examination did not reveal any dysmorphisms, organomegaly, or erythroderma. Small lymph nodes were palpable; she had a normal cardiorespiratory and musculoskeletal exam.

Following discharge, she developed diarrhea and failure to thrive (FTT), necessitating nasogastric tube feeding. She was given a provisional diagnosis of celiac disease. The patient was also found to be positive for norovirus and *C. difficile*, which was treated. There was mild eczema that was well controlled with topical hydrocortisone and moisturizers. She experienced 1 episode of pneumonia around the age of 2, which responded to oral antibiotics. Her immune work-up was initially complicated due to her intercurrent illness, immunosuppressants, and IVIG. Following discontinuation of her medications, she continued to demonstrate impaired T-cell functioning with poor phytohemagglutinin (PHA) response, undetectable TRECs, abnormal expansion of TCR-Vbeta repertoire, and an abnormal thymic biopsy. There were also impaired antibody responses.

Family history

Parents were non-consanguineous and healthy. Three years prior to our patient's presentation, they had given birth to fraternal twins. The boy was healthy. The girl developed a severe vasculitic rash prior to the age of 1 and was hospitalized. Biopsy of the rash was concerning for infantile polyarthritis nodosa. She had decreased C3 and C4 with hypergammaglobulinemia. She developed several line-related infections during her hospitalization. Despite treatment with IVIG, steroids, and cyclophosphamide, she passed away at the age of 2 from gastrointestinal and pulmonary vasculitis, as well as renal failure. Autopsy revealed minimal germinal follicles in her lymph nodes. The germinal centres and paracortex lacked well-formed secondary follicles and were mainly composed of primary lymphoid follicles. However, it was difficult to discern if this was a primary finding or secondary to her illness and immunosuppression.

Immunological investigations pre-transplant

The patient was initially seen by Immunology as an inpatient. However, at that time immune work-up could have been complicated by her acute illness and multiple therapies. After cessation of IVIG and immunosuppressants, initial immunological work-up revealed reduced WBC of 2.8×10^9/L and lymphocytes of 1.12×10^9/L. Immunoglobulins were normal (IgG 8.9, IgA 0.9, IgM 0.6). Isohemagglutinin anti-B was negative. Lymphocyte immunophenotyping revealed CD4+364 (normal 1573–2949), CD8+ 76 (normal 472–1107), CD16+56+ 412 (normal 155–565), and CD19+ 178 (normal 434–1274). Lymphocyte proliferation test was significantly decreased at 8% of control (stimulation index 40/455). TRECs were undetectable. TCR-Vbeta repertoire was abnormal, with expansion in Vbeta7, Vbeta24, Vbeta3, and Vbeta14 clones, accompanied by underrepresentation of other TCR clones. There was lack of a CD45RA naïve population. Targeted gene sequencing did not reveal a genetic diagnosis. A thymic biopsy showed absence of Hassall's corpuscles and no clear corticomedullary distinction.

Management

The patient had evidence of severe cellular impairment on immunological work-up. Given these findings, in conjunction with her FTT, thymic dysplasia, infection history, and sibling's course, the decision was made to proceed with bone marrow transplant (BMT). This was reached after careful deliberation in consultation with other experts and the family, as she did not yet have a genetic diagnosis at that time. She underwent a matched sibling donor BMT at the age of 2. Mild skin graft-versus-host disease occurred during her cyclosporin wean but she otherwise tolerated the procedure well. She was slowly weaned off her immunosuppressants; her IVIG and antibiotic prophylaxis were subsequently stopped. She had full engraftment with good evidence of immune reconstitution. Two years post-transplant the patient received her killed vaccines. The following year, she tolerated her live-viral vaccines. She developed 1 episode of *Streptococcus pneumoniae* bacteremia and a few episodes of pneumonia between the ages of 6–9, which resolved after initiation of chest physiotherapy and a steroid inhaler.

Immunological investigations post-transplant

Post-transplant, full engraftment with 100% donor chimerism was achieved. Her most recent evaluation reveals a normal complete blood count with WBC of 4.37×10^9/L and lymphocytes of 2.0×10^9/L. Normal immunoglobulins (IgG 10, IgA 1.3 and IgM 0.9). Isohemagglutinin anti-B was 1:8. Vaccine titres were

protective, including varicella. Lymphocyte immunophenotyping was all within normal range (CD4+ 916, CD8+ 443, CD16+56+ 279, CD19 314). Lymphocyte proliferation was robust with a stimulation index of 605. TCR-Vbeta revealed slight expansion of Vbeta5 and borderline low representation of Vbeta9—there was good representation of all other families. Furthermore, she had appropriate numbers of both naïve and memory T-cells.

Genetic work-up

Around the time of her initial presentation, targeted sequencing of CD3delta, AIRE, and ReIB were negative. Whole exome sequencing in 2014 identified a single mutation in RAG1; however, this was deemed insufficient to explain the phenotypic presentation.

Subsequently, in 2020 WGS revealed 2 separate heterozygous missense variants in the RAG1 gene (NM_000448): R474C (c.1420C>T) and H945D (c.2833 G>T) (Table 1). Sanger sequencing of parental DNA revealed the mother to be heterozygous for the R474C variant and the father was heterozygous for the H945D variant.

Discussion and conclusions

We present a case of a child with a concerning family history who presented after her first live-viral vaccinations and was found to have severe T-cell dysfunction. Live-viral vaccines are contraindicated in individuals with severe impairment of cellular immunity. Several cases of vaccine-strain illnesses, including varicella, have been reported in immunodeficient patients (Bayer et al. 2014; Leung et al. 2014). With the available testing at the time, our patient presented a diagnostic and therapeutic dilemma as there was no genetic diagnosis. However, her family history pressed upon the gravity of a timely decision, which was made following deliberation and an abnormal thymic biopsy. Successful immune reconstitution was achieved through BMT. Diagnostic confirmation of 2 RAG1 variants was found several years later, with advancements in genomic testing through WGS.

RAG1 gene defects lead to variable phenotypes, some of which are yet to be discovered or described. SCID is characterized by life-threatening infections in early infancy due to absent or minimal T-cell numbers and functioning; mutations in RAG1 account for approximately 4% of cases (Delmonte et al. 2018). Omenn syndrome is the result of hypomorphic mutations that allow for occasional recombination events (Shearer et al. 2014). Individuals present in early infancy with erythroderma, lymphadenopathy, and eosinophilia due to autoreactive oligoclonal T-cell expansion that infiltrates the skin, gut, liver, and other organs (Delmonte et al. 2018). Atypical SCID presents with a severe rash but lacks the organomegaly from lymphoproliferation (Delmonte et al. 2018). Our patient presented later in life and did not display erythroderma, lymphadenopathy, or organomegaly. She did have manifestations of autoimmunity and responded to immunosuppression and immunomodulation. In 2008, a report of 3 unrelated females who presented later in life with granulomas, severe viral infections, and B-cell lymphoma highlighted RAG variants who present later with autoimmunity and inflammation (Schuetz et al. 2008). The frequency of RAG1/2 hypomorphic mutations in the general population is higher than previously thought. Kumánovics et al. (2017) estimated a population frequency of up to 1:181 000 and suggested mutations likely contribute to undiagnosed cases of combined immunodeficiencies.

The RAG1 gene is located on chromosome 11p12; it has 1 protein-coding exon and is composed of 1043 amino acids (Notarangelo et al. 2016). Two missense RAG1 variants were identified in our patient, R474C and H945D, and are likely causal given her phenotypic presentation (Figure 1). Furthermore, both mutations occur in the catalytic core of human RAG1, which is comprised of amino acids 387–1011 (Notarangelo et al. 2016).

The R474C mutation has previously been reported in cases of SCID, Omenn syndrome, and CD4+ T-cell lymphopenia (Chen et al. 2014). Schönberger et al. (2009) published a case of a 3-month-old girl with

Table 1: **Missense RAG1 variants.**

Variants	chr11:36596274:C>T	chr11:36597687:C>G
Change details	NM_000448:exon2:c.C1420T:p.R474C	NM_000448:exon2:c.C2833G:p.H945D

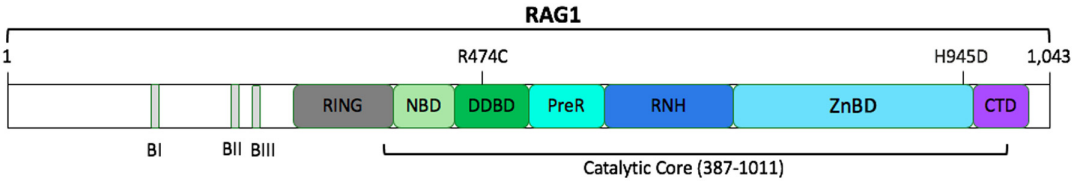

Figure 1: Mutations in relation to the RAG1 protein domains. The R474C and H945D mutations are both found within the catalytic core. Numbers correspond with amino acid locations. BI-BIII, basic I-III domain; RING, ring finger domain; NBD, nonamer-binding domain; DDBD, dimerization and DNA-binding domain; PreR, pre-RNase H; RNH, catalytic RNase H; ZnBD, zinc-binding domain; CTD, carboxy-terminal domain.

Omenn syndrome who successfully underwent a matched cord transplant. She had a compound heterozygous defect within the RAG1 gene, R474C and R975W. A 2-year-old girl with recurrent, severe cavitating pneumonias and herpes zoster infections was found to have CD4 T-cell lymphopenia (Avila et al. 2010). Mutational analysis of RAG1 showed compound heterozygosity with R474C (c.1420C>T) and K86fs (c.256-7 DelAA) (Avila et al. 2010). Engraftment was achieved following a matched unrelated BMT. Kuijpers et al. (2011) identified 2 missense mutations in RAG1, R474C) and L506F. The child presented with hemorrhagic cutaneous skin lesions and varicella-associated pneumonia, bronchiectasis, reduced naïve lymphocytes and low TRECs (Kuijpers et al. 2011). Interestingly, proliferation capacity was intact and antibody titres to vaccines were protective (Kuijpers et al. 2011). The R474C recombinant protein was found to have 25% recombinase activity compared to wild type, while the L506F had no activity (Kuijpers et al. 2011). Chen et al. (2014) described a family with 2 phenotypically affected children, each with the compound heterozygous mutations c.1420C>T and c.2949delA. Both developed vaccine-strain varicella from a vaccinated family contact, autoimmune cytopenias, and reduced naïve CD4+ T-cell numbers (Chen et al. 2014). Sanger sequencing revealed that the parents were each a carrier of 1 mutation and there were 2 unaffected siblings with the R474C (c.1420C>T) mutation (Chen et al. 2014).

The H945D (c.2833G>T) variant in our patient is a novel mutation that has not been previously described in the literature. Individuals carrying a single R474C (c.1420C>T) mutation have been found to be healthy; only when a second mutation with similar or further reduced recombinase activity is present, does it lead to clinical sequalae (Chen et al. 2014). Thus, the H945D mutation results in either complete or partial loss of function and it is the combination of both mutations that is responsible for our patient's presentation. This is further evident as her clinically healthy parents carry one of each mutation—with the mother being a carrier for the R474C variant and the father for the H945D variant. Consequently, it is pertinent to consider compound heterozygous RAG1 mutations in individuals with impaired cellular immunity, autoimmunity, and lymphopenia.

With the introduction of TREC quantification on the NBS, this may lead to earlier detection of individuals with RAG1 hypomorphic mutations. For our patient, SCID NBS had not yet been implemented. However, TREC levels measured after her acute presentation were undetectable. Although we are unable to definitively conclude if she would have been picked up on NBS, it can be postulated that she could have had abnormal TREC levels from birth given her impaired T-cell function. As the second H945D mutation was only identified after improved detection capabilities onWGS, it would be important to consider employing such methods of work-up when conventional genetic panels do not yield findings. Early HSCT following detection of pathogenic variants is postulated to circumvent autoimmune complications and the development of significant infections (Chen et al. 2014). However, given the diversity of disease severity, ongoing efforts to correlate genotype with phenotype will help with understanding the implication of novel variants. In the absence of genetic confirmation, consideration of clinical progression, immunologic work-up, and family history is warranted. Diagnostic tests and management strategies should be selected accordingly.

Disclosures

There are no conflicts or funding sources to declare.

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Homozygous NF-kB1 mutation causing combined immunodeficiency: a histopathological analysis

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ABSTRACT

Introduction: The nuclear factor-kB (NF-kB) signaling pathway plays a major role in mediating multiple cellular processes, including immune and inflammatory responses.

Aims: We describe the histopathological findings of lymph nodes from a patient with a homozygous NF-kB subunit 1 (NF-kB1) mutation causing a combined immunodeficiency phenotype.

Results: A nodal biopsy was performed for lymphadenopathy evaluation, in the context of development of persistent EBV infection. Our findings show that this patient has normal lymph node tissue present, however, abnormal histopathology features were observed, including atrophic germinal centers. B cell subset components within the B cell domain were also analyzed. The development of the B cell response during EBV infection was found to be significantly impaired.

Conclusion: Aberrant signaling due to NF-kB1 deficiency has a significant impact on the development of B cell immunoproliferative responses.

Statement of novelty: We report on the abnormal histopathology findings of lymph node biopsy from a patient with homozygous NF-kB1 mutation.

Background

The nuclear factor-kB (NF-kB) signaling pathway plays a major role in mediating multiple cellular processes, including immune and inflammatory responses, lymphocyte development, ectodermal development, cell growth, and programmed death (Zhang et al. 2017). The NF-kB transcription factor family consists of 5 Rel proteins, p50/p105, p52/p100, RelA, RelB, and c-Rel, which dimerize with each other and drive or inhibit gene expression in the nucleus. There are 2 well characterized NF-κB signaling pathways, the canonical and non-canonical pathways (Gilmore 2006).

Recently, a novel homozygous mutation in the NF-κB subunit 1 (NF-kB1) gene, encoding p50/p105, was described as causing a profound disruption of the classical NF-kB pathway resulting in combined immunodeficiency (CID). The mutation in *NFKB1* predicted a glycine to arginine substitution at position 960 (p.Gly960Arg). G960R is located in the C-terminal of p105, distal to the death domain. This position is highly conserved across vertebrates and thus a change is expected to have significant pathogenicity which manifests with abnormal differentiation of T and B cells, aberrant specific antibody formation, cytokine secretion, and cell proliferation (Mandola et al. 2021).

In addition to immunological investigation and genetic analysis, histopathological examination of tissue may have an important role in supporting the diagnosis of immunodeficiency or to be perused if malignancy is

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Submitted 28 January 2021
Accepted 23 February 2021
Available online 26 February 2021

LymphoSign Journal 8:11–18 (2021)
dx.doi.org/10.14785/lymphosign-2021-0012

suspected as a complication. As a consequence of inborn errors in immunity, variable defects of lymphocyte development and morphology of lymph organs may occur. The lack of NF-κB1 appears to also markedly disrupt the architecture of lymphoid tissues as was shown in NF-κB1-/- mice (Weih et al. 2001; Lo et al. 2006).

There are several known findings on lymph node histopathology in SCID that vary according to underlying pathophysiology. It has been reported that lymph nodes from T-B+ SCID patients regularly contain B cells, either as scattered cells or remnants of follicles without formation of germinal centers. T-B- SCID patients have severe depletion of B and T cells, and resulting "stromal" nodes contain fibroblasts, flat endothelial cells, and macrophages. In SCID due to JAK3 deficiency the lymphoid tissue is completely absent (Ratech et al. 1989; Facchetti et al. 1998).

In this study, we describe the histopathological features within the lymph node of a patient with loss of a major B cell activation pathway initiator, due to the presence of a homozygous mutation in NF-kB1. The lymph node was biopsied and examined when the patient developed persistent lymphadenopathy due to EBV infection. Our findings demonstrate that the loss of NF-kB1 did not affect the development or histogenesis of B or T cells, however, there was a major impact on the development of B cell immuno proliferative responses within the germinal centers.

Case presentation

Our patient, a 7 year old male born to consanguineous parents of Pakistani-descent, was recently diagnosed with a novel homozygous G to A transition (c.2878G>A) in the *NFKB1* gene (Mandola et al. 2021).

His clinical history was significant for severe, flaky, and difficult to manage atopic dermatitis, repeated episodes of otitis media by the age of 3 months, chronic diarrhea at 5 months, failure to thrive, and lymphadenopathy. At the age of 7 months, he was hospitalized for respiratory distress syndrome, requiring assisted ventilation secondary to *Pneumocystis jirovecii*. On that hospital admission he also developed candidial urinary tract infection (UTI). At age 9 months, he was admitted for prolonged fever lasting 2 weeks, diarrhea, generalized lymphadenopathy, hepatosplenomegaly, and increased liver enzymes in association with very high copy numbers of EBV (10^4 to 10^6 copies) detected in the blood and on bronchoalveolar lavage (BAL). On that admission he was also treated for enterococcal UTI. Despite regular intravenous immunoglobulin replacement and periodic treatment with ganciclovir, he continued to experience repeated episodes of microbial infections as well as periodic increase in EBV viremia associated with generalized lymphadenopathy.

Laboratory workup revealed elevated IgE and eosinophil levels. His further work-up showed normal IgG, elevated IgA and low IgM levels. He was also found to have an abnormal humoral immune response to vaccinations. Total lymphocyte and T cell counts were normal, but over time, a gradual reduction in CD4+ cells were observed and the number of circulating CD8+ T cells increased over time. T cell depressed responsiveness to mitogen stimulation was noted and T cell receptor repertoire analysis appeared skewed. Analysis of CD4+ cells demonstrated under representation of several Vβ families, including Vβ11, Vβ13.6, and Vβ20, and overrepresentation of Vβ4, Vβ7.2, Vβ13.1, and Vβ18. CD8+ T cells showed under representation of Vβ5.3 and Vβ7.1, however, overrepresentation of Vβ2, Vβ3, Vβ5.2, Vβ7.2, Vβ14, and Vβ16 was prominent, suggesting peripheral T-cell expansion, and in complete agreement with the marked shift to differentiated cells observed in flow cytometry studies.

Outcome and follow up

Our patient has been relatively well and is currently on *Pneumocystis jirovecii* prophylaxis and intravenous immunoglobulin replacement therapy. Human leukocyte antigen evaluation has not been suggestive of a compatible match in the family for hematopoietic stem cell transplantation, and given his age and infectious complications in the past, his course of transplant may be complicated. Given that his past few years have been uneventful together with the considerations mentioned, hematopoietic stem cell transplantation has not become a part of his treatment.

Methods

Patient

Patient informed consent was obtained, and clinical information was collected from medical records in

accordance with approved protocols from the Research Ethics Board at the Hospital for Sick Children.

Lymph node histopathology

The nodal biopsy was performed during the initial clinical evaluation of this patient, in the context of development of persistent EBV infection and was obtained from the left inguinal region.

Lymph node was received fresh, fixed in buffered formalin for 24 hours and subsequently embedded in paraffin. Control lymph nodes were selected from the tissue archive from patients diagnosed with non-specific reactive lymphadenopathies. Histologic sections of the patient's lymph node were stained with hematoxylin eosin (H&E) or for immunohistological studies, unstained sections were stained with the following commercially available antibodies supplied by DAKO/Agilent (Santa Clara, California, US) : pan-T cell receptor CD3 (rabbit polyclonal GA503), germinal B cell marker Bcl-6 (monoclonal Clone BG-B6P), activated post germinal center B cell/plasma cell marker Mum-1 (**MU**ltiple **M**yeloma **1**), and anti-apoptosis protein Bcl-2 (monoclonal Clone 124). Antibodies were supplied pre-diluted and the de-paraffinized slides were incubated with each of the antibodies according to the staining procedures supplied by the supplier.

The post-antibody binding detection was amplified using the polymer amplification and visualized by using Di-azo-benzidine (DAB) as a chromogen. All of these were suppled as Envision Flex High pH kit) Stains were performed using an automated staining system by DAKO Omnis.

Bcl-6 and Mum-1 immunostaining were used as germinal center markers for histological characterization and malignancy detection.

Results

Lymph node pathology

Abnormal histopathology features in the lymph node of this patient were observed. H&E stained sections showed atrophic/underdeveloped germinal centers throughout the lymph node cortex (Figures 1A and 1B) compared to control (Figure 1C). Many had the appearance of primary germinal centers (Figure 1A), surrounded by a thick cuff of mantle cells. Nonreactive marginal zones were noted. There was a lack of reactive features within the germinal center domain (Figure 1B), including no tingible body macrophages and only small numbers of centroblasts present. There is no segregation of the centroblasts and centrocytes into pale and dense zones.

Using a combination of immunostains (including the pan B cell marker CD20, follicular dendritic cell marker CD21, and T cell receptor complex antigen CD3), the immune-anatomical locations and development of B cell, T cell, and follicular dendritic cell domains within the patient's lymph node were found to be normal (not shown). The B cell subset components within the B cell domain were analyzed further with a panel of antibodies to detect proteins that relate to B cell maturation and function.

Bcl-2 protein, which blocks apoptosis, is normally absent within the reactive centrocytes and centroblasts within the germinal center and is expressed on the mantle B lymphocytes and adjacent T cells. In normal lymph nodes, immunostaining for Bcl-2 revealed germinal centers that were significantly diminished in size (Figures 2A and 2B) compared to control (Figure 2C).

Bcl-6 is a transcriptional repressor required in mature B cells during the germinal center reaction, through DNA binding and recruitment of co-repressor complexes on the promoter of its targets. Its expression is tightly regulated during mature B cell differentiation, with Bcl-6 protein expression restricted to the germinal center stage of differentiation (Basso and Dalla-Favera 2012). Bcl-6 is critical for the development of a diverse primary B cell repertoire and protects germinal center B cells against DNA damage-induced apoptosis during somatic hypermutation and class switch recombination (Duy et al. 2010). Histologically, Bcl-6 is expressed by B cells that migrate into germinal centers and is thus a useful marker for germinal center B cells. In our patient, immunostaining for Bcl-6 (Figure 3A) demonstrated almost complete loss of Bcl-6 positive cells in the germinal centers while some positively stained cells could be detected in the peripheral areas. This is in contrast to the normal control (Figure 3B), where the majority of Bcl-6 cells are present in the germinal center. Together, this suggests that without proper NF-κB1 signaling, these cells fail to migrate to the germinal centers, or alternatively, they fail to transform into activated B cells and continue to emigrate bearing the Bcl-6 marker.

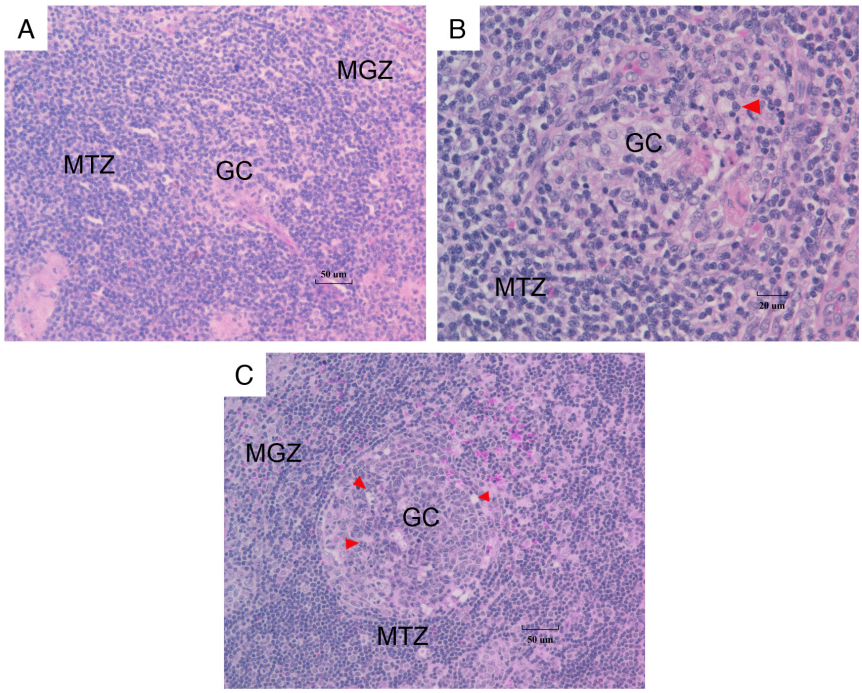

Figure 1: H&E stain of lymph node biopsy. (A) Atrophic germinal centers (GC), thick concentric mantle zones (MTZ) and nonreactive marginal zones (MGZ) were noted. (B) Higher magnification of another atrophic/underdeveloped germinal center shows lack of reactive features within the germinal center domain. There are no tingible body macrophages and only small numbers of centroblasts are present. There is no segregation of the centroblasts and centrocytes into pale and dense zones. (C) A normal reactive germinal center containing numerous tingible body macrophages mixed with reactive centrocytes and centroblasts. Note that they segregate into a pale zone (in the 9 o'clock region) and a dense zone (in the 3 o'clock region) of the germinal center shown. The germinal center is sharply demarcated by a thin concentric array of small dark blue lymphocytes which are the inhabitants of the mantle zone. The parafollicular region has numerous reactive paracortical macrophages. Red arrowheads indicate tingible body macrophages.

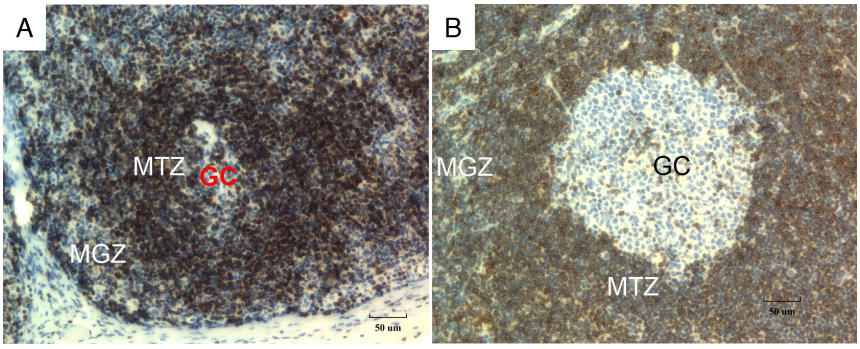

Figure 2: Bcl-2 immunostaining of B cells in the germinal center and mantle zone. (A) The size of the germinal center domain that normally contains Bcl-2 negative germinal center B cells was markedly diminished in our patient. In contrast, in the normal control (B) immunostain for Bcl-2 showed negative staining for germinal center B cells and positive staining for interfollicular lymphocytes.

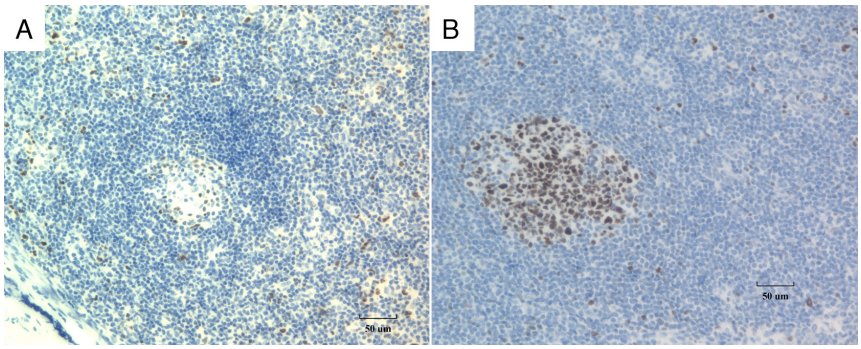

Figure 3: Detection of Bcl-6, a marker of B cell maturation. (A) Bcl-6 immunostaining shows a few Bcl-6-positive germinal center B cells within the germinal center. Some of the Bcl-6-positive cells do not enter the germinal center and remain in the interfollicular zones. (B) In the normal control, immunostain for Bcl-6 shows numerous positively stained cells with the germinal centers and only a few in the interfollicular zone.

Mum-1 is a transcriptional factor which is expressed in the final step of intra-germinal center B cell differentiation and in post-germinal center (late centrocyte) or activated B cells (Gualco et al. 2010). It is normally expressed in the nuclei and cytoplasm of plasma cells and a small percentage of germinal center B cells mainly located in the "light zone". Polymerase chain reaction (PCR) analysis of Mum-1 positive cells isolated from germinal centers have previously shown that they contain rearranged Ig heavy chain genes with a varying number of somatic mutations (Falini et al. 2000). In normal lymph nodes, Mum-1 immunostaining demonstrates that post-germinal center B cells gather in the interfollicular areas, including parafollicular sinusoids (Figures 4A and 4B). In our NF-kB1 deficient patient, immunostaining revealed a marked reduction in numbers of Mum-1-positive activated B cells in the germinal centers and the interfollicular zones (Figure 4C). The reduced development of secondary germinal centers (Figure 4D) indicates that the development of activated B cells is likely slowed although not completely absent, given the presence of Mum-1 positive cells in the lymph node sinusoids (Figure 4E).

Discussion

Multiple studies have described *NFKB1* mutations as a monogenic cause of immunodeficiency, mostly presenting in late childhood/early adulthood. Patients with *NFKB1* haploinsufficiency have a variety of clinical manifestations, including predominantly antibody deficiency, autoimmunity, and immune dysregulation. Autoinflammatory disorders including Bechet disease have been reported as well (Smart 2014; Kaustio et al. 2017; Tuijnenburg et al. 2018; Lorenzini et al. 2020).

Recently, a young pediatric patient who first presented with severe dermatitis, recurrent invasive and opportunistic infections, persistent EBV viremia, generalized lymphadenopathy and hepatosplenomegaly at the age of 9 months was diagnosed with a novel homozygous mutation in the *NFKB1* gene. This mutation predicted to cause a glycine to arginine substitution at position 960 (p.Gly960Arg). G960R is located in the C-terminal of p105, distal to the death domain and the Ser-903 and Ser-907 phosphorylation sites required for p105 proteolytic processing. Phosphorylation of p105 directly affects the formation of p50 which is required for downstream transcription, i.e. attenuated NF-kB1 phosphorylation on stimulation leads to reduced nuclear RelA translocation and target gene expression (Mandola et al. 2021). To our knowledge, this is the only case reported in the literature as causing a profound disruption of the classical NF-kB pathway resulting in SCID.

Lymph nodes are organized secondary lymphoid organs with a distinct architecture, containing structures comprising a reticular network packed with lymphocytes, macrophages, and dendritic cells. They are divided into microenvironments, such as lymphoid follicles and additional B and T cell areas, all surrounded by a fibrous capsule. A normal reactive lymph node histopathology is expected to consist of numerous follicles, prominent germinal centers, "tingible body

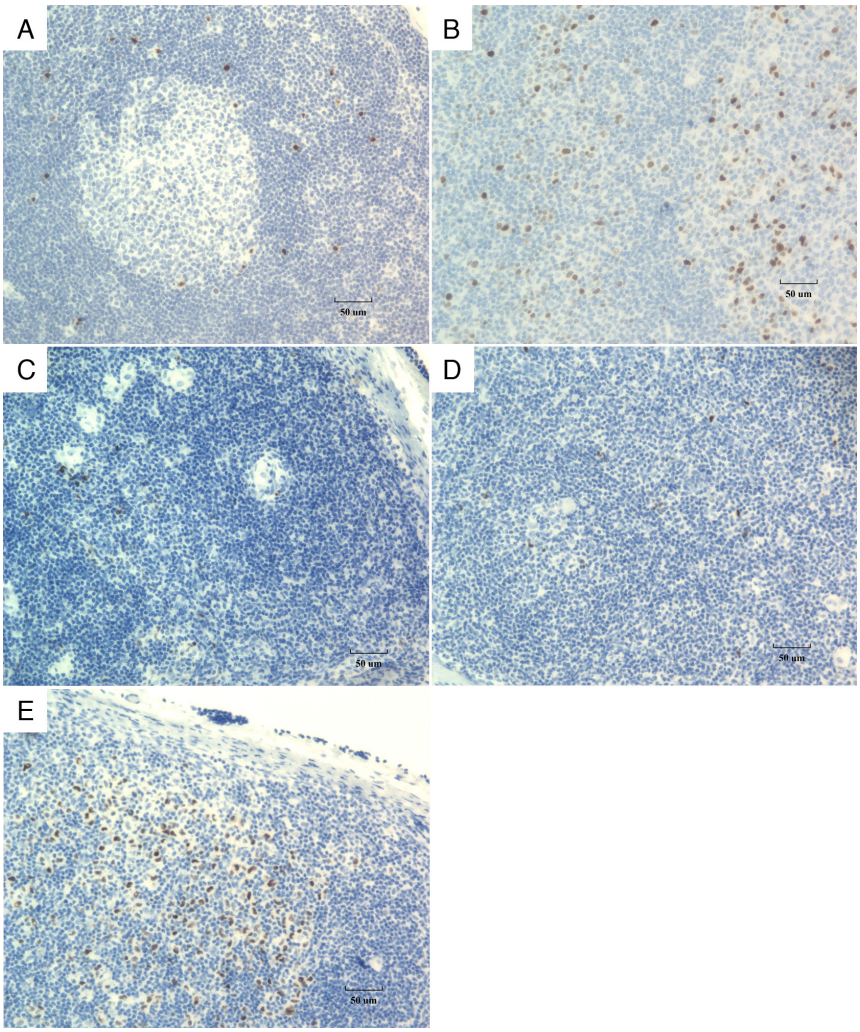

Figure 4: Mum-1 immunostain for activated B cells. In control lymph nodes, Mum-1 positive post-germinal center B cells (activated B cells that arise the in the germinal center) gather in the interfollicular areas (A). A secondary germinal center is shown on the right and perifollicular sinusoids on the left of (B), illustrating the development of activated B cells in the germinal center and their exit into the para-follicular sinusoids. Lymph node biopsy of our patient (C) shows a reduction of Mum-1-positive activated B cells in the germinal centers and the interfollicular zones. The reduced development of secondary germinal centers and activated B cells is shown in (D) with the primary germinal center on the left and parafollicular area to the right. (E) Some activated B cells are formed, as indicated by the presence of Mum-1-positive cells in the lymph node sinusoid.

macrophages", i.e., prominent macrophages with irregular cellular debris. These macrophages process antigens to pass to lymphocytes to stimulate a specific immune response (Willard-Mack 2006).

Our patient has normal lymphoid tissue development as determined by CD20, CD21 and CD3 staining, however, histopathological findings revealed atrophic germinal centers, thick concentric mantle zones and nonreactive marginal zones. The areas within the germinal center where centrocytes and centroblasts reside were small, and there was a lack of tingible body macrophages in comparison to the normal control. Immunostains targeting the B cells identified B cell follicles that were small and lacked expansion of germinal center domains. Furthermore, B cells failed to mature and emigrate at a regular rate.

Together, the histopathological observations are in keeping with combined immunodeficiency and likely

explain this patient's inability to clear EBV infection as well as the very high levels of EBV copy number in the blood of the patient. Moreover, our findings may suggest that the failure to develop a normal nodal architecture is related to a particularly severe T cell defect and thereby impairment of the T-B cell interaction. Failure to develop normal germinal center structure of this patient is also an indication of the important role of the NF-κB1 pathway in normal lymphoid architecture development.

NF-κB1 gene knockout studies have demonstrated the critical role of NF-κB1 in the development of lymphoid tissue. NF-κB1-/- mice display markedly disrupted lymphoid tissue architecture with flat Payer patches and lack of clear follicular structures (Willard-Mack 2006). In our patient, while lymphoid tissue development was normal, the development of the B cell response during EBV infection was observed to be markedly hindered.

Conclusion

Although homozygous NF-kB1 mutation in our patient resulted in a normal lymphatic tissue development, the loss of NF-kB activation mechanism has a significant impact on the development of B cell immunoproliferative responses within the germinal centers.

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Canadian resource guides for individuals and families affected by primary immunodeficiency

Wendy Shama[a,b,c*]

ABSTRACT

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 health care 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. 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.

Statement of novelty: National and provincial resources guides have been created for families and individuals affected by primary immunodeficiency.

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 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 during 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

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Submitted 23 February 2021
Accepted 24 February 2021
Available online 25 February 2021

LymphoSign Journal 8:19–33 (2021)
dx.doi.org/10.14785/lymphosign-2021-0015

Disability tax credit (DTC)

The 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. 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; Forms 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

Employment Insurance (EI) caregiving benefits and leave

Through EI, 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 2 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 1 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

Caregiving 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/forms-publications/publications/rc4065/medical-expenses-2016.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 (IDF)

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.

www.primaryimmune.org/idf.htm

Jeffrey Modell Foundation—Friends of John for Life Kids Wish Fund

Friends of John for Life Kids Wish Fund is a special "set aside" fund by the Jeffrey Modell Foundation. The fund is designed simply to bring joy and happiness to the lives of kids with immune deficiencies. The fund sponsors tickets for sporting events, concerts, the theatre, days at the zoo, the circus and more. These funds are not for research, doctors, or administration.

www.jmfworld.com/howtohelp/friends.cfm

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/1568396042341/1568396 1559824#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 Canada or Starlight Children's Foundation.

https://makeawish.ca/

Medic Alert Foundation of Canada

Canada Medic Alert 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), *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 (NORD)

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.

Children may only have ONE wish either through Make-A-Wish Canada, or Starlight Children's 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?
- 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

Accommodation

Ronald McDonald House of Southern Alberta

111 West Campus Place NW Calgary, Alberta T3B 2R6
Phone: 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 (available 24 hr/day, 7 days/wk). 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. 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.

www.humanservices.alberta.ca/disability-services

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

"Established in 1977 as the Calgary Immigrant Aid Society, for the past 30 years we have helped over 250 000 immigrants settle into their new life and home in Calgary, Alberta, Canada. As one of Calgary's most comprehensive immigrant serving agencies, our focus is on the individual and families first, providing a sense of community and connection".

9107 Ave SW,
Calgary, Alberta T2P 3N8
Phone: 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
Phone: 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
Phone: 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
Phone: 403-234-7876

www.pacekids.ca

British Columbia

Accommodation

Ronald McDonald House British Columbia

4567 Heather Street
Vancouver, British Columbia V5Z 0C9
Phone: 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
Phone: 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 BC 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

Manitoba

Accommodation

Ronald McDonald House Manitoba

566 Bannatyne Avenue
Winnipeg, Manitoba R3A 0G7
Phone: 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. Referral needed by the bone marrow transplant 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/ThirdPartyFundraisers?px=1048242&pg=personal&fr_id=1100#.XgOPfxybb0

Employment and Income Assistance

Employment and Income Assistance 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 3 areas; (*i*) 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, (*ii*) non-medical costs for treatment not available in the province, and (*iii*) 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/

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 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

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 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 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/

Newfoundland and Labrador

Accommodation

Ronald McDonald House Newfoundland & Labrador

P.O. Box 28091
St. John's, Newfoundland A1B 1X0
Phone: 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 18 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)

MTAP 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/

Nova Scotia

Accommodation

Ronald McDonald House Atlantic Canada

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

www.rmhatlantic.ca

Halifax Haven

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

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.

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 $1000 in travel assistance (round trip) and $125 per night up to $1500 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 (IA)

For families that collect 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 IA) 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 (eg. 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 and 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/

Ontario

Accommodation

Ronald McDonald House Toronto

240 McCaul St.
Toronto, Ontario M5T 1L1
Phone: 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:
Phone: 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)

Who is eligible:

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.

Jennifer Ashleigh Foundation
10800 Concession 5
Uxbridge, Ontario L9P 1R1
Phone: 905-852-1799

https://jenash.org/

Easter Seals Incontinence Supplies Grant

The program is for children and youth between the ages of 3–18 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
Phone: 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%–4% 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
Phone: 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
Phone: 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 6, 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
Ontario Early Years

Respites 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 lower 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 1 second is <1 L.
- 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° 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 4400 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, contact 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

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

Financial Assistance Drug Program

In Prince Edward Island, eligible Islanders and families with a valid PEI Health Card can get help to pay for prescription drugs. There are several drug programs that can save you money. You may qualify based on your age, health condition and (or) income.

https://www.princeedwardisland.ca/en/information/health-pei/get-help-with-prescription-drug-costs#utm_source=promo&utm_medium=url&utm_campaign=drugprograms

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 5 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 MTAP 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

Quebec

Accommodation

Ronald McDonald House Montreal

5800 Hudson Road
Montreal, Quebec H3S 2G5
Phone: 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

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

APIQ is a non-profit organization comprised of patients with immunodeficiencies and patients with hereditary angioedema, 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.

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

Acknowledgements

The author would like to thank and acknowledge Social Workers from the PI Social Work Network that contributed to their respective Provincial Guides; Susan Ng, MSW, RSW, Alberta Children's Hospital, Laurie Weir, MSW, RSW, BC Children's Hospital, Cindy Falconer, BA, BSW, Winnipeg Health Science Center, Jacklynn Pidduck, MSW, RSW, IWK Health Centre, Linda Blanchette, MSW, Social Worker, Montreal Children's Hospital, Geneviève Rabouin, BSW, Social Worker, Sainte-Justine's Hospital & Suzanne Laplante, BSW, Social Worker, Sainte-Justine's Hospital.

Funding

This resource guide is compiled by Immunodeficiency Canada with generous support from Grifols and Takeda.

Content statement

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

Disclaimer

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Spotlight on women in science

Linda Vong*

February 11, 2021 marked the sixth annual International Day of Women and Girls in Science—a day commemorating the global effort to increase the advancement and engagement of women and girls in science and technology fields. Women play critical roles in STEM (science, technology, engineering, math) fields, however gender equity is yet to reach parity, with women accounting for only one third of researchers worldwide (UNESCO 2019).

Today, women graduating from higher education hold no <50% of MD degrees and PhDs in the life sciences and social sciences—a marked increase in comparison to statistics from decades earlier (Burrelli 2008). Yet, there remains an under representation of women in higher level tenure-track or professorship roles. Many aspects of societal structure and cultural beliefs constrain the choices that women make, from deferring careers to raise children or caring for elderly family members, through to prioritization of spouses' careers or geographical location over one's own. Critically, the choice to start a family can impact the decision to apply for and withdraw from tenured roles (Faculty Committee on Women in Science, Engineering, and Medicine 2010). Rather than penalizing female academic scientists for taking family leave, an approach towards attaining gender equity that many academic institutions have implemented include pausing the so-called "tenure clock", making accommodations or allowances for productivity during child-rearing, reduced teaching load, and extensions for grant and funding proposals.

Efforts directed towards overcoming barriers that women in academia have historically faced, including discrimination in grant funding, publication bias, and hiring practices, have largely been successful (Ceci and Williams 2011). However, in addressing the number of women entering and staying within STEM fields, other factors, such as gender pay gap, cultural beliefs, and biases (whether implicit or explicit) remain challenges that we must overcome to allow women to participate fully in science.

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Burrelli, J. 2008. Thirty-three years of women in S&E faculty positions. Natural Science Foundation, Division of Resources Statistics, Arlington, Va., USA [online]. Available from https://wayback.archive-it.org/5902/20160210152800/http://www.nsf.gov/statistics/infbrief/nsf08308/.

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Submitted 22 February 2021
Accepted 25 February 2021
Available online 26 February 2021

LymphoSign Journal 8:34–35 (2021)
dx.doi.org/10.14785/lymphosign-2021-0016

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Pediatric Clinical Immunology and Infectious Disease, Stollery Children's Hospital
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Biography

Sneha completed her pediatric residency and pediatric infectious disease fellowship at the University of Alberta. She received a Stollery Children's Foundation Fellowship to complete a fellowship in Clinical Immunology and Transplantation at the Hospital for Sick Children, University of Toronto. She currently works at the Stollery Children's Hospital as the clinical lead for the Pediatric Immune Deficiency clinic, serving patients in Northern Alberta, the Northwest Territories, and Nunavut. By combining her expertise in Infectious Disease and Immunology, her research focuses on vaccination and protection of immunocompromised hosts, both with primary and secondary immunodeficiency. She is also involved in the postgraduate and undergraduate education of residents and medical students in the field of Clinical Immunology.

Perspective on women in science

"As a woman in my particular field, pediatric Immunology and Infectious Disease, I have been incredibly lucky to have been mentored by both men and women who respect and value the contribution of women to science. Whether it is supervisors who consistently employ and give opportunities to women in their lab or fellowship programs, or women in the field themselves who understand the multifaceted roles that women in science or academia must balance; these mentors are wonderful role models of professionalism, dedication and balance that I have been so fortunate to learn from. The best advice I can give to women (and anyone!) starting their careers, is give yourself time to figure out what gives you a sense of balance and contentment. Whether that is time with family, children, pursuit of a sport or hobby, travel, or pursuit of further academic work in your field, figure out what that is and give it time and importance in your busy life. A sense of internal balance and fulfillment can only improve our external contributions to our respective fields."

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