Children with systemic autoinflammatory diseases have multiple, mixed ethnicities that reflect regional ethnic diversity

L.B. Tucker[1,2], I. Niemietz[3,4], P. Mangat[2], M. Belen[2], J. Tekano[2], D.A. Cabral[1,2], J. Guzman[1,2], K.M. Houghton[1,2], K.A. Morishita[1,2], M.O. Chan[1,2], A. Human[1,2], M. Sundqvist[1,3], K.L. Brown[1,3,5]

[1]Department of Paediatrics, The University of British Columbia, Vancouver; [2]Division of Rheumatology, British Columbia Children's Hospital, Vancouver; [3]British Columbia Children's Hospital Research Institute, Vancouver; [4]Department of Microbiology and Immunology, and [5]Centre for Blood Research, the University of British Columbia, Vancouver, BC, Canada.

Lori B. Tucker, MD, FRCPC, FAAP
Iwona Niemietz, MPharm
Preet Mangat
Maria Belen
Jenny Tekano
David A. Cabral, MBBS, FRCPC
Jaime Guzman, MD, MSc, FRCPC
Kristin M. Houghton, MD, FRCPC
Kimberly A. Morishita, MD, MSc, FRCPC
Mercedes O. Chan, MBBS, MHPE, FRCPC
Andrea Human, MD, FRCPC
Martina Sundqvist, PhD, MPharm
Kelly L. Brown, PhD

Please address correspondence to:
Kelly L. Brown,
Department of Paediatrics,
University of British Columbia and BC Children's Hospital Research Institute,
950 West 28th Avenue,
V5Z 4H4 Vancouver (BC), Canada.
E-mail: kbrown@bcchr.ca

ORCID iD: 0000-001-5385-3582

Received on March 23, 2021; accepted in revised form on September 1, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 132): S124-S128.

Key words: autoinflammatory disease, paediatric, ethnicity

Funding: page S128.

Competing interests: none declared.

ABSTRACT

Objective. *To evaluate the ethnic diversity of children with a systemic autoinflammatory disease (SAID) in a multi-ethnic Canadian province.*

Methods. *Self-reported ethnicity of 149 children and adolescents with a SAID in British Columbia, Canada, was analysed for ethnic representation among individual patients, across the cohort, within particular SAIDs, and compared to provincial census data on ethnic diversity.*

Results. *Half of reported cases had a diagnosis of either PFAPA (23.5%) or an unclassifiable autoinflammatory syndrome (31.5%), with a monogenic SAID diagnosed in only 12.8% of cases. The majority of participants (73.1%) were mixed ethnicity with European and Asian heritage reported most frequently (57.0% and 23.0% of all responses, respectively). Ethnic diversity reflected regional diversity except for West Asian, Arabic, Jewish, and Eastern European heritage, which were over-represented in SAID patients, and Chinese descent, which was under-represented in our cohort compared to the general population of British Columbia.*

Conclusion. *Results from this study show extensive multi-ethnic diversity in individual patients and across the various SAIDs inclusive of monogenic SAIDs that are frequently associated with particular ethnicities. Although not disproportionately represented, this is the first report of systemic autoinflammatory disease in Canadian children of Indigenous heritage.*

Introduction

Systemic autoinflammatory diseases (SAIDs) encompass a broad range of inflammatory conditions caused by dysregulation of the innate immune system (1). There are a number of monogenic SAIDs linked to pathogenic variants in genes involved in the regulation of innate immunity and inflammation; however a significant number of patients with SAIDs have no identifiable monogenic cause, or are found to have heterozygous gene mutations of uncertain significance. Several of the monogenic SAIDs have distinct ethnic patterns of occurrence. One of the most well-described of these is familial Mediterranean fever (FMF), which is most frequent in individuals from the Mediterranean region, including Armenian, Turkish, Arab, and Israeli populations (2-4). There are, however, patients of European and Asian ethnicity with FMF (4-8). Similarly, Behçet's disease is more common in individuals with Turkish, Iranian, Israeli, and Japanese ethnicity, but is also reported in Caucasian individuals (9, 10).

The largest published cohorts of children with SAIDs come from the EuroFever Registry (11,12), a multi-national clinical registry hosted by the Pediatric Rheumatology International Trials Organisation (PRINTO; www.printo.it) and the Pediatric Rheumatology European Society (PRES) since 2009. Although the patients enrolled in the EuroFever registry reside in many different countries, the majority are from Western Europe (11). Thus, it is possible that represented ethnicities in the EuroFever cohort are more homogeneous than those present, for example, in Canada and in the USA. Studies of cultural diversity and economic development provide evidence that North American countries, and in particular Canada, are far more culturally diverse (based on ethnicity, language and reli-

gion) than countries in Europe (13, 14). There are only a few studies addressing the prevalence of SAIDs in multi-ethnic communities and countries, and there are no reports of ethnicity of children with SAIDs in Canada. The objective of this study was to examine the ethnic background of a cohort of Canadian children with SAIDs and living in the multi-ethnic province of British Columbia.

Patients and methods

Ethics

This study complies with the Declaration of Helsinki and was approved by the University of British Columbia and the Children's and Women's Health Centre of British Columbia Research Ethics Board (H14-00272). Informed written consent was obtained from parents/guardians and, where appropriate, assent/consent from patients.

Study population

The study population included 149 children and adolescents in British Columbia (BC) that received clinical care for a systemic autoinflammatory disease (SAID) at the BC Children's Hospital (BCCH) paediatric rheumatology clinics. A diagnosis of a SAID was made by a paediatric rheumatologist based on clinical criteria, and molecular genetic testing where appropriate and possible. Genetic testing for FMF, TRAPS, and HIDS (*MEFV*, *TNFRSF1A* and *MVK* genes, respectively) was done by Sanger sequencing in the Division of Genome Diagnostics at BCCH.

Ethnicity of participants in the BCCH SAID registry

Eligible patients were enrolled between January 2016 and December 2019 and clinical information was entered into a BCCH SAID registry (15). Parents/guardians were asked to report the ethnicity of an affected child's four biologic grandparents, *i.e.* maternal grandmother and grandfather; paternal grandmother and grandfather. Ethnic groups (Supplementary Table S1) were derived from a Statistics Canada listing of ethnicity and modified to include Hutterite, Mennonite, Amish, Jewish, and 29 of BC's First Nations. Multiple ethnicities could be selected for each grandparent including 'other' and 'unknown'. Participants (n=2) with ethnicity data from less than two grandparents were excluded. From the remaining 149 participants, >700 expressions of ethnicity were recorded. To determine the relative contribution of each expressed ethnicity to individual patients, listed ethnicities for each grandparent were calculated as a fraction of their maximum (25%) contribution to the affected grandchild's overall ethnic composition. Ethnic representation was calculated from the sum of the individual fractions for each ethnicity and expressed as a percentage of the total sum of all ethnicities (Table I).

British Columbia census data

Statistics Canada census data on ethnicity in British Columbia and, specifically, the Greater Vancouver Area (GVA) was obtained from the 2016 Census of Population data on ethnic origin (16). To enable comparisons, BCCH SAID registry data was organised to mirror the census data: 'other' and 'unknown' responses were omitted and the remaining responses were categorised as a 'single' or 'multiple' response. For each ethnicity, a single response is recorded when only one ethnicity is reported (*i.e.* each affected child's reporting grandparent has the same (singular) ethnicity), and a multiple response is recorded when two or more ethnicities are reported (multi-ethnic). The combined response for each ethnicity is the sum of single and multiple responses and indicates the number of individuals in the population/study cohort that identify with a given ethnicity as their only ethnic origin or in addition to one or more other ethnic origins. A total of 396 and 221 combined responses were tabulated, respectively, across the entire BCCH SAID cohort (n=149) and from those participants (n=94) that reside in the GVA.

Statistical analyses

Combined responses were used for statistical calculations in GraphPad Prism version 8.0.2 (GraphPad Software, San Diego, CA, USA) to assess whether particular ethnicities were disproportionately associated with particular SAIDs (Suppl. Table S2) or under- or over-represented relative to the general population (Suppl. Table S3 and Table S4). The Wilson/Brown method (17) was used to calculate the 95% confidence interval (CI) for each ethnic origin in the BCCH SAID registry and a binomial test, with the null hypothesis that distribution in ethnic origin in the BCCH SAID registry (observed distribution) is not different to individual SAIDs or to the BC population (expected distribution). A two-tailed p-value <0.05 was regarded as statistically significant.

Results

Diverse and mixed ethnicities represented in BC SAID cases

Consistent with previous reports of autoinflammatory disease in children in BC (15) and in Canada (18), half (55.0%) of all cases in this cohort had a diagnosis of either PFAPA (35/149; 23.5%) or an unclassifiable autoinflammatory syndrome (47/149; 31.5%). Monogenic SAIDs inclusive of FMF, TRAPS, HIDS and CAPS collectively accounted for only 12.8% (19/149) of all cases. Diagnoses include: periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA, n=35), Behçet's disease (BD, n=8), chronic recurrent multifocal osteomyelitis (CRMO, n=39), tumor necrosis factor receptor-associated periodic syndrome (TRAPS, n=6), cryopyrin-associated periodic syndromes (CAPS, n=1), hyperimmunoglobulin D (IgD) syndrome (HIDS, n=2), Familial Mediterranean Fever (FMF, n=11), and unclassified autoinflammatory syndrome (UC SAID, n=47).

Using self-reported ethnicity of the affected child's maternal and paternal grandparents and equally weighted calculation of ethnic contribution stemming from each grandparent (see methods), results indicate extensive ethnic diversity across our SAID cohort (Table I, "all SAID"), with representation from every ethnic category (n=23 defined groups inclusive of 'other' and 'unknown'). This diversity was also present within individuals as evidenced by the majority of partici-

Table I. Percent ethnic representation across different SAIDs in the BCCH registry.

Ethnicity	[a]All SAID (n=149)	UC SAID (n=47)	CRMO (n=39)	PFAPA (n=35)	FMF (n=11)	Behçet's (n=8)	TRAPS (n=6)
First Nations	2.4	2.9	0.7	2.9	-	10.9	-
Black	1.1	0.7	1.3	-	-	4.2	7.6
Latin American	2.3	2.7	1.3	0.4	9.1	1.0	8.3
Chinese	3.6	4.3	2.6	2.5	4.5	12.5	-
Filipino	1.3	2.1	-	-	-	12.5	-
Korean	1.0	3.2	-	-	-	-	-
Japanese	1.1	1.1	2.6	-	-	1.0	-
Pacific Islander	0.3	-	1.0	-	-	-	-
South Asian	10.7	8.2	18.6	7.9	9.1	-	18.8
Southeast Asian	0.3	0.8	-	-	-	-	-
West Asian	5.0	7.2	-	1.8	31.8	-	-
Arabic	2.2	-	3.2	1.1	13.6	-	-
Jewish	1.9	1.9	2.6	-	9.1	-	-
British	15.2	14.1	13.8	20.5	1.1	29.7	11.8
Irish	5.3	5.3	4.1	7.1	5.7	3.1	6.9
Scottish	5.7	5.6	5.7	7.4	2.3	-	11.8
French	4.7	4.0	5.8	5.8	1.1	3.1	7.6
Eastern European	9.7	9.2	12.1	11.5	9.1	-	2.1
Northern European	4.5	2.6	4.2	8.5	1.1	6.3	4.2
Southern European	3.5	2.0	3.0	6.3	-	-	4.2
Western European	8.4	10.5	9.1	6.4	-	7.8	-
Other	5.2	4.5	5.4	7.0	-	-	16.7
Unknown	4.6	7.2	3.2	2.9	2.3	7.8	-

[a]Percent ethnic representation across the cohort (all SAID, n=149, >700 expressions of ethnicity) and within specific SAIDs where n = number of patients per SAID group.
UC SAID: unclassifiable SAID. Data not shown for patients with HIDS (n=2) and CAPS (n=1).

pants (73.1%) reporting mixed ethnicity, with a mean representation per individual of 3.6 distinct ethnic groups (range of 2–7 ethnicities per person). European (inclusive of British, Irish, Scottish, French, and Eastern, Western, Northern and Southern European), and Asian (inclusive of Chinese, Filipino, Korean, Japanese, and West, South and Southeast Asian) heritage were indicated, respectively, in approximately one half (57.0%) and one quarter (23.0%) of all responses. Although SAIDs have not been reported previously in Indigenous populations, First Nations were indicated in 2.4% of total responses and were associated with diagnoses of unclassified SAID, PFAPA, CRMO, and Beçhet's disease. Patients with FMF, Behçet's and TRAPS had less ethnic diversity compared to patients with unclassifiable SAID, CRMO, and PFAPA (Table I and Suppl. Fig. S1).

Although few in number, participants with FMF (n=11) and TRAPS (n=6), had over-representation (Supplementary Table S2), respectively of Middle Eastern (Arabic, West Asian), and South Asian/Black origins, which is consistent with previous reports of strong ethnic associations within the monogenic disorders. No other statistically significant differences in ethnic composition were observed in individual SAIDs compared to the collective SAID cohort.

Diverse ethnicities in BC children with SAID reflect regional ethnic diversity

To determine if the observed ethnic diversity in children and adolescents with a SAID in BC reflected regional ethnic diversity, we compared the BCCH SAID registry data to Statistics Canada population estimates of ethnicity (16) in the province of BC, and specifically in the Greater Vancouver Area (GVA; Suppl. Fig. S2) where approximately 48.6% of the population resides. In the BCCH SAID registry, ~60% of study participants (n=94) live in the GVA, suggesting a slight bias in the number of cases from this region.

The relative percentage of 16 out of 21 ethnic groups ('other' and 'unknown' excluded) was similar in the BCCH SAID registry participants and both the general populations of BC (Fig. 1A, 1B and Suppl. Table S3) and the GVA (Fig. 1C and Suppl. Table S4). Representation within five ethnic groups (Chinese, West Asian, Arabic, Jewish and Eastern European), however, was significantly different in the BCCH SAID registry compared to both the BC and GVA census data. Over represented ethnicities in SAID patients compared to the BC and GVA population included West Asian (for GVA, 2.7 fold higher, p-value = 0.002), Arabic (for GVA;, 3.4 fold higher, p-value = 0.011), Jewish (for GVA, 12.0 fold higher, p-value <0.0001), and Eastern European (for GVA, 1.6 fold higher, p-value = 0.010). Chinese was the only under represented ethnicity in SAID patients with ~3.9 and ~4.9 fold less representation (p-value <0.0001) compared, respectively, to the general population of BC and the GVA.

Discussion

In this manuscript, we report complex ethnic diversity within the majority of individual patients and across a provincial cohort of Canadian children and adolescents with a systemic autoinflammatory disease. From comparisons to Statistics Canada ethnicity data for the province of British Columbia and the Greater Vancouver area, our data demonstrate that the extensive ethnic diversity observed within the cohort reflects, for the most part, regional ethnic diversity in the province. There are notable exceptions, however, for particular ethnicities: this includes an over representation of individuals with West Asian, Arabic, Jewish, and Eastern European heritage, and under representation of Chinese ethnicity. Although not disproportionately represented, this is the first report of systemic autoinflammatory disease in Canadian children of Indigenous heritage.

Most published data on patients with SAIDs indicate relatively narrow ethnic diversity especially for certain SAIDs. Without studies of multi-ethnic populations, it is difficult to determine to what extent these associations may reflect the study population. Within the EuroFever registry, 93% of children with TRAPS (n=158) were of European Caucasian background (12), a finding that likely reflects the ethnicity of the participat-

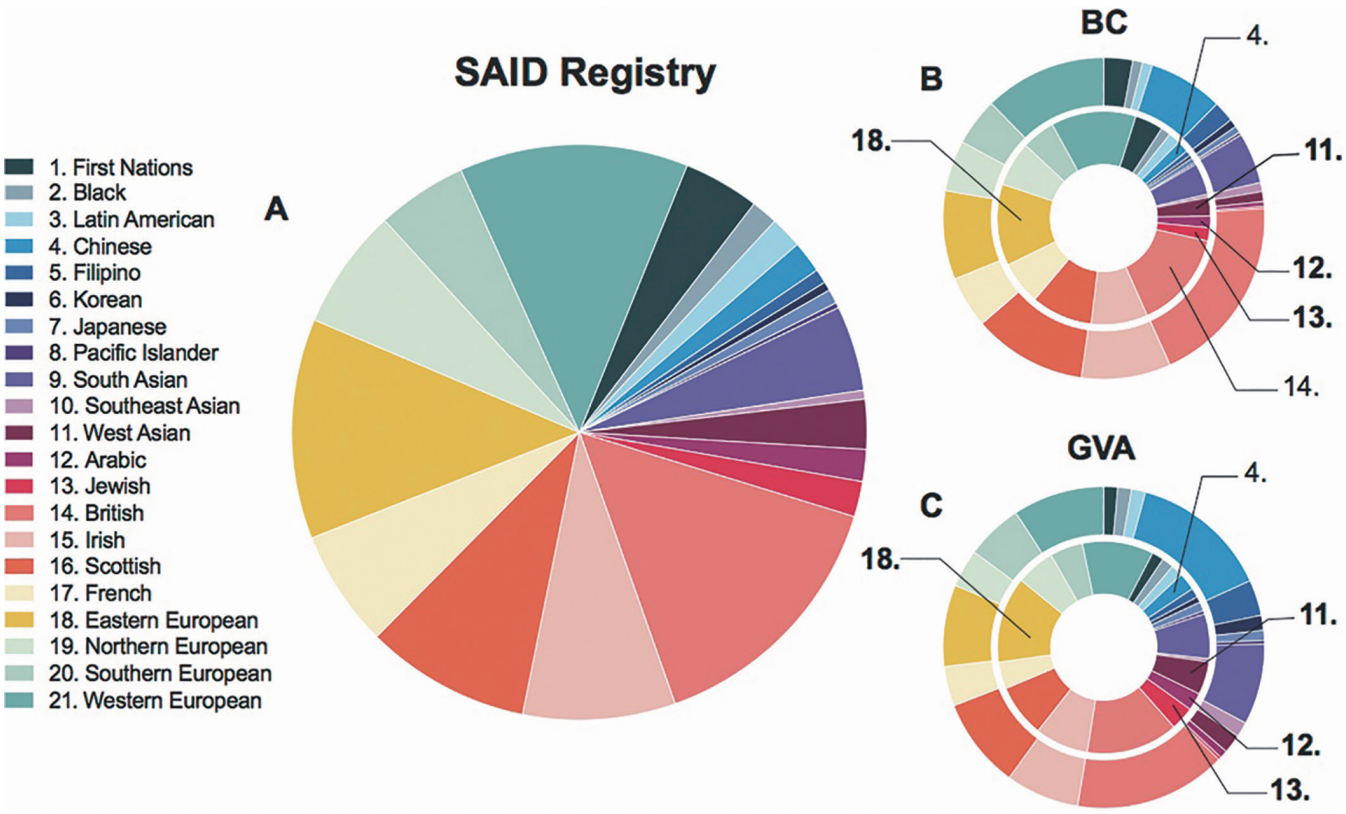

Fig. 1. Relative ethnic composition in BCCH SAID registry patients and BC residents.
A: Pie chart shows ethnic composition (relative percentage based on 396 combined responses) of participants (n=149) in the BCCH SAID registry cohort.
B: Doughnut chart compares the relative ethnic composition in the BCCH SAID registry (inner circle and shown in A) compared to the BC population (outer circle; BC Census 2016).
C: Doughnut chart shows the relative ethnic composition of (inner circle) BCCH SAID registry participants residing in the Greater Vancouver Area (GVA, n=94 participants, 221 responses) compared to (outer circle) the GVA population (GVA Census 2016). Annotated are ethnicities that are over- (bold) and under (plain text) -represented ($p<0.05$) in the BC SAID when compared to BC Census (see Suppl. Table S3) and GVA Census data (see Suppl. Table S4).

ing (European) countries in the study. In this respect, it may not be surprising that children with a SAID in our cohort are multi-ethnic and reflect the vast ethnic diversity in the BC population. Even patients in our cohort with FMF, a monogenic SAID that is common in people with Mediterranean background were multi-ethnic with Chinese, South Asian, European, Jewish, and British Isle origin represented. This heterogeneity in FMF is in line with our prevous report (15) and may warrant consideration of somatic mutations in the aetiology of SAIDs in different ethnic groups than those commonly expected.

In contrast, over representation of West Asian, Arabic, Jewish and Eastern European individuals in our cohort may not have been expected given that they are frequently associated with monogenic SAIDs, which were a large minority in our cohort. Likewise, the under representation of children of Chinese background in this SAID cohort was also surprising given that British Columbia, and the greater Vancouver region in particular, have a sizeable and varied Asian population. These results suggest that even within a multi-ethnic population, particular ethnicities may enhance the risk for certain SAIDs. Along these lines, in a multi-ethnic French population, disease risk in 79 individuals with Behçet's disease was more strongly associated with ethnicity than the geographic environment (19), and Mediterranean descent was more common in individuals in Israel with PFAPA, a SAID of unknown aetiology (20).

In summary, our results demonstrate that children with SAIDs in British Columbia have complex, multi-ethnic origins. A limitation of this study is parent-reported ethnicity. Although data on all four grandparents provides a richer picture of a child's ethnic background than would be obtained if families were asked to select one ethnicity, a better understanding of the ethnic contributions to SAIDs in Canadian children will require application of ancestry genetic marker testing.

Acknowledgements
The authors thank Jessica Tang, Sophia Noles, Nathaniel Tok, Joey Fu, Stephanie Hughes and Dr Lovro Lamot for assistance with patient recruitment, registry data entry, and data curation. The authors also recognise Dr William Gibson, Dr Linlea Armstrong, Simone Race and Christopher Elsner for expertise and advice on ethnicity data collection, and Dr Michael Irvine for statistical support.

Key messages
- Complex ethnic diversity is seen in Canadian children with systemic autoinflammatory diseases.
- Systemic autoinflammatory disease is seen in Canadian children of Indigenous heritage.

Funding

This work was supported by research funds from The Arthritis Society – Ross Petty Chair in Paediatric Rheumatology start-up fund [KLB] and a Novartis educational grant [KLB and LBT]. Work by D.A. Cabral is supported by The Arthritis Society (TAS) Canada through the Ross Petty Arthritis Society Chair. L.B. Tucker is supported by a Clinical Investigator Award from the BC Children's Hospital Research Foundation. K.L. Brown is supported by the Michael Smith Foundation for Health Research and Cassie & Friends Society Scholar Award. I. Niemietz is supported by a UBC-affiliated Award: Andrew Nord Fellowship in Rheumatology. M. Sundqvist is supported by the Elisabeth and Alfred Ahlqvist Foundation - Swedish Pharmacy Society grant, the Rune and Ulla Almlövs Foundation grant and the Magnus Bergwall Foundation grant (ID: 2018–02579, to M. Sundqvist).

References

1. KRAINER J, SIEBENHANDL S, WEINHÄUSEL A: Systemic autoinflammatory diseases. *J Autoimmun* 2020; 109: 102421.
2. OZEN S, KARAASLAN Y, OZDEMIR O *et al*.: Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. *J Rheumatol* 1998; 25: 2445–9.
3. DANIELS M, SHOHAT T, BRENNER-ULLMAN A, SHOHAT M: Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish populations in Israel. *Am J Med Genet* 1995; 55: 311-4.
4. SAMUELS J, OZEN S: Familial Mediterranean fever and the other autoinflammatory syndromes: evaluation of the patient with recurrent fever. *Curr Opin Rheumatol* 2006; 18: 108-17.
5. KISHIDA D, NAKAMURA A, YAZAKI M, TSUCHIYA-SUZUKI A, MATSUDA M, IKEDA S-I: Genotype-phenotype correlation in Japanese patients with familial Mediterranean fever: differences in genotype and clinical features between Japanese and Mediterranean populations. *Arthritis Res Ther* 2014; 16: 439.
6. WU D, SHEN M, ZENG X: Familial Mediterranean fever in Chinese adult patients. *Rheumatology* 2018; 57: 2140-4.
7. HUA Y, WU D, SHEN M, YU K, ZHANG W, ZENG X: Phenotypes and genotypes of Chinese adult patients with systemic autoinflammatory diseases. *Semin Arthritis Rheum* 2019; 49: 446-52.
8. BEN-CHETRIT E, TOUITOU I: Familial Mediterranean fever in the world. *Arthritis Rheum* 2009; 61: 1447-53.
9. SAVEY L, RESCHE-RIGON M, WECHSLER B *et al*.: Ethnicity and association with disease manifestations and mortality in Behçet's disease. *Orphanet J Rare Dis* 2014; 9: 42.
10. LEONARDO NM, MCNEIL J: Behçet's disease: Is there geographic variation? A review far from the silk road. *Int J of Rheumatol* 2015; 2015: 945262.
11. TOPLAK N, FRENKEL J, OZEN S *et al*.: An international registry on autoinflammatory diseases: the Eurofever experience. *Ann Rheum Dis* 2012; 71: 1177-82.
12. LACHMANN HJ, PAPA R, GERHOLD K *et al*.: The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. *Ann Rheum Dis* 2014; 73: 2160-7.
13. ALESINA A, DEVLEESCHAUWER A, EASTERLY W *et al*.: Fractionalization. *J Econ Growth* 2003; 8: 155-84.
14. GÖREN E: How ethnic diversity affects economic growth. *World Development* 2014; 59: 275-97.
15. WESTWELL-ROPER C, NIEMIETZ I, TUCKER LB, BROWN KL: Periodic fever syndromes: beyond the single gene paradigm. *Pediatr Rheumatol Online J* 2019; 17: 22.
16. Statistics Canada: 2017. Immigration and Ethnocultural Diversity Highlight Tables. 2016 Census. Statistics Canada Catalogue no. 98-402-X2016007. Ottawa. Released October 25, 2017. http://www12.statcan.gc.ca/census-recensement/2016/dp-pd/hlt-fst/imm/index-eng.cfm
17. BROWN L, CAI T, DASGUPTA A: Interval estimation for a binomial proportion. *Statist Sci* 2008; 16: 101-33.
18. DANCEY P, BESNELER S, GATTORNO M *et al*.: Surveillance of periodic fever syndromes in Canada [abstract]. *Arthritis Rheumatol* 2015; 67 (Suppl. 10).
19. MAHR A, BELARBI L, WECHSLER B *et al*.: Population-based prevalence study of Behçet's disease: differences by ethnic origin and low variation by age at immigration. *Arthritis Rheum* 2008; 58: 3951-9.
20. AMARILYO G, HAREL L, ABU AHMAD S *et al*.: Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome - is it related to ethnicity? An Israeli multicenter cohort study. *J Pediatr* 2020; 227: 268-73.