The Effect of Mutations to Genes Associated with the Development of Pediatric Autoimmune Diseases on Patient Prognosis in Non-Hodgkin's Lymphoma

Shayan Siddiqui

Webber Academy, University of Calgary

Dr Narendran, Ms. Narendran, Dr Garcia-Diaz

June 5 2020

Abstract:

Autoimmune diseases currently affect over 10% of the global population. As well these individuals are at a higher risk of developing Non-Hodgkin's lymphoma, a type of cancer. We looked at mutations to genes that are associated with the development of autoimmune diseases and how they affected patient prognosis for Non-Hodgkin' lymphoma. This was done by utilizing two databases, the GAAD database for acquiring genes associated with the development of autoimmune disorders, and CBioPortal for mutations within the Non-Hodgkin's population. Overall 22 mutations were analysed. Five mutations to the gene BCL2 were found to correlate with a poor patient prognosis. One mutation to the STAT4 gene was found to be correlated with better patient prognosis. The other 16 mutations were to various genes and displayed expected patient outcome. This is useful as it can be used to give a more accurate prognosis for patients who develop Non-Hodgkin's lymphoma.

Introduction:

Autoimmune diseases are a category of diseases that currently affects over 10% of the global population, not including those affected by Rheumatoid Arthritis (RA) and Autoimmune Thyroiditis [1]. Within Canada, the incidence rate of autoimmune diseases are increasing with current statistics suggesting an annual increase of 7.5% [1]. These diseases are especially concerning as they affect both adults and children.

Most notably, Autoimmune diseases are associated with the development of Non-Hodgkin's lymphoma, a type of cancer. The American Cancer Society has identified autoimmune diseases

as a risk factor for developing Non-Hodgkin's lymphoma [2]. Currently, most of the research done associating autoimmune diseases with Non-Hodgkin's lymphoma has been conducted on the adult population, focusing on more common autoimmune diseases such as RA [3]. A study done by Smedby etal. at the Karolinska University Hospital identified that patients with RA, Systemic lupus erythematosus, Celiacs disease, Hashimoto's thyroiditis, and Sjorgens diesease have up to a 25-fold increased chance of developing a Non-Hodgkin's lymphoma [3,4]. Despite this, current research has been inconclusive about the specific genetic link between autoimmune diseases and Non-Hodgkin's lymphoma [4], furthermore no studies focusing on pediatric autoimmune diseases and the development of cancer later on in adulthood have been published.

Six autoimmune diseases which are most common in the pediatric population are: Systemic Lupus Erythematosus, Systemic scleroderma, Sjorgen's, Celiacs disease, Behcets disease, and Ankylosing Spondylitis.[5]

All of the autoimmune diseases mentioned above have risk factors associated with the human leukocyte antigen (HLA) complex. The HLA genes encode for the human major histocompatibility complex. It is found on the sixth chromosome [6]. Class I of HLA encompasses; HLA-A, HLA-B, and HLA C. whereas class II HLA genes comprises HLA-DR, HLA-DQ. HLA-DP [7]. Over 100 diseases including several autoimmune diseases have been associated with the HLA complex, however it is unclear how the complex influences the development of the diseases [8].

Systemic lupus erythematosus (SLE) manifests itself differently in different people. Typically it is characterized by the inflammation of connective tissues most notably of the cartilage and lining of blood vessels [9]. SLE heritability is just not from one gene variant/mutation, but through multiple genes variants/mutations.[10] The STAT4 gene has been identified as a gene that plays into the incurrence of SLE [11,12] The signal transducer and activator of transcription 4 (STAT4) gene encodes for a protein responsible for mediating responses to interleukin 12 in lymphocytes [12].

Systemic scleroderma (SS) is a disorder that affects the skin and internal organs characterized by a buildup of scar tissue [13]. Variations in several genes may influence the risk of SS such as the STAT4 gene [14] and interferon regulatory factor 5 (IRF5) gene and the associated polymorphism rs2004640 [15,16]. The IRF5 gene encodes a member of the interferon regulatory factor family. This group of transcription factors has diverse roles, including virus-mediated activation of interferon, and immune system activity [17].

Sjorgen's syndrome is characterized by the immune system attacking the lacrimal and salivary glands, impairing the ability of the glands to excrete fluid [18,19]. Sjorgen's is thought to be caused by a combination of genetic and environmental factors and variations in some genes affect the risk of developing Sjorgen's [19]. The variants of the interleukin 10 (IL10) gene may be considered as a genetic factor in developing mixed connective tissue diseases such as Sjorgen's [20]. The protein encoded by this gene is a cytokine produced primarily by monocytes and to a lesser extent by lymphocytes. This cytokine has pleiotropic effects in immunoregulation

and inflammation [21]. In addition, variant of the Methylene-tetrahydrofolate reductase (MTHFR) gene, which synthesizes an enzyme essential in DNA synthesis and methylation, have been associated with susceptibility to Non-Hodgkin's lymphoma in patients with Sjogren 's [20].

Celiacs disease (CD) is a condition where the immune system is abnormally sensitive to gluten, causing inflammation of the gastrointestinal tract [22]. There has been a 35% increase in the incidence rate of CD in Canada per year [1]. People with CD have specific mutations to the HLA-DQA1 and HLA-DQB1 genes. However, only 3% of people with the mutations develop CD [23].

Behcets disease (BD) is a condition characterized by the inflammation of blood vessels. Usually it is localized to the small blood vessels of the mouth, genitals, skin, and eyes. The first sign of developing BD is the development of aphthous ulcers in the mouth and 75% of patients develop ulcers of the genitals [24]. It is reported that the HLA-B51 serotype is a genetic factor for BD [25]. Furthermore, associations with polymorphisms of the class II major histocompatibility complex transactivator (CIITA) and the nucleotide binding oligomerization domain containing 1 (NOD1) genes have been established [26]. The CIITA gene encodes a protein with an acidic transcriptional activation domain, 4 leucine-rich repeats and a GTP binding domain. The CIITA gene acts as a positive regulator of class II major histocompatibility complex gene transcription [27]. The NOD1 gene encodes a member of the nucleotide-binding oligomerization domain-like receptor family of proteins. This protein plays a role in innate immunity by acting as a pattern-recognition receptor that binds bacterial peptidoglycans and initiates inflammation [28].

Ankylosing Spondylitis (AS) is a disorder consisting of joint inflammation of the spine [29]. At first, inflammation of the sacroiliac joints occurs and over time, the vertebrae fuse together [29]. Variations in the HLA-B27, endoplasmic reticulum aminopeptidase 1 (ERAP1), interleukin 1 alpha (IL1A), and interleukin 23 receptor (IL23R) gene are associated with AS [30,31]. The ERAP1 encodes an aminopeptidase involved in trimming HLA class I-binding precursors so that they can be presented on major histocompatibility class I molecules [32] The IL1A gene encodes a pleiotropic cytokine involved in various immune responses, inflammatory processes, and hematopoiesis [33] The IL23R encoded a protein which is a subunit of the receptor for IL23A/IL23. This protein pairs with the receptor molecule IL12RB1/IL12Rbeta1, and both are required for IL23A signaling.[34] However it is not known how these genes increase the risk of developing AS [37].

This study aims to look into the effect of mutations on genes that are associated with the development of pediatric autoimmune diseases on patient prognosis for Non-Hodgkin's lymphoma.

Procedures:

Collection of Gene Associated with Pediatric Autoimmune Diseases

To begin the study, it was necessary to acquire all genes associated with the six pediatric autoimmune diseases mentioned in the background research section. To do this, the Gene & Autoimmune Disease Association Database (GAAD) was used [35]. This database text-mines

the entire PubMed database for studies that associated a specific gene with the development of a certain pediatric autoimmune disease [35]. All the diseases mentioned above were included in this database. An Excel sheet was downloaded of the associated genes from the GAAD database and they were put into one master spreadsheet (MS Excel, 2019). Genes that were associated with three or more pediatric Autoimmune Diseases were selected for the second part of the study.

Mutation Data

For this phase of the study, the CBioPortal database was used [36,37]. It provided access to 16 Non-Hodgkin's lymphoma studies with genomic information of the participants. The total sample size amounted to 3727 samples. All the genes previously selected were inputted into the database to find out the presence of a mutated version of the gene in the total sample size. Only genes with mutated versions present in more than 0.05% of the sample were further explored. All the mutation data for the selected genes were downloaded into individual Excel spreadsheets for each gene. The frequency of appearance (occurrence) of each mutation was determined. Double samples were accounted for. These double samples came from patients having multiple samples from different times or from a study that had built on from a previous study using the same patient cohort. Mutations where five or more patients had the mutation were further explored into.

Survival Data

Patient data was compiled in an Excel spreadsheet (MS Excel, 2019) including Patient ID, survival in month and survival status.For the statistical package, a zero or a one was put next to

the patient survival status where 1 stood for deceased. A separate spreadsheet was created for all patients who did not carry the mutations (control group).

Both spreadsheets were uploaded into GraphPad Prism 8 (Graphpad Prism 8, 8.3.1) statistical package and program and Kaplan-Meier survival curves were calculated.Two significance tests were conducted, a Mantel-Cox test and a Gehan Breslow-Wilcoxon test, with significance set to under 0.05 for both.

Results:

The screening of the GAAD database rendered 6 genes (BCL2, TP53, SOCS1, STAT3, FAS, & ETS1) that are associated with Juvenile idiopathic arthritis, Juvenile dermatomyositis, Systemic Lupus Erythematosus, Systemic scleroderma, Sjorgen's, CD, Behcets disease, and Ankylosing Spondylitis.

The CBioPortal database, containing genomic information for 3727 patients who have been diagnosed with a Non-Hodgkins Lymphoma, was probed for the presence of mutations in the BCL2, TP53, SOCS1, STAT3, FAS, & ETS1 genes. Table 1 shows a list of mutations found in 5 or more patients along with the statistical values calculated using the Mantel-Cox and the Gehan-Breslow-Wilcoxon tests.

Tabe 1. Statistical Significance of the Presence of a Mutation and Survival Rate. Two tests were performed to ascertain the statistical significance ($p<0.05$): Mantel-Cox test and Gehan-Breslow-Wilcoxon test.

Gene	Mutation	Mantel-Cox Test p=	Gehan-Breslow -Wilcoxon test p=
BCL2	X96 Splice	0.0014	0.0007
	X195 Splice	0.7797	0.5300
	A131V	0.7962	0.5358
	A60V	0.0840	0.0480
	R129H	0.0767	0.1002
	H20Q	0.1259	0.1761
	P59S	0.1535	0.5487
	G33R	0.8526	0.9970
	G8E	<0.0001	<0.0001
	H120Y	0.4744	0.4810
	L86F	0.4170	0.5419
	T56M	0.0163	0.0117
	G8R	0.0205	0.0111
TP53	R175H	0.3411	0.3295
	R248Q	0.2972	0.4040
	N239D	0.4072	0.4013
SOCS1	S125T	0.3667	0.3198
	S116N	0.1758	0.1013
	A16T	0.7878	0.8253
STAT3	Y640F	0.00369	0.086

FAS	**V220Gfs*6**	**0.6643**	**0.8707**
ETS1	**E17K**	**0.796**	**0.6199**

BCL2

Thirteen mutations for the BCL2 gene were found to be present in more than 5 patients among the samples tested.The Mantel-Cox and the Gehan-Breslow-Wilcoxon tests revealed that that presence of five of those BCL2 mutations (A60V, G8R, X96 Splice, G8E, and T56M) significantly decreases ($p<0.05$) the survival rates of these patients. (Table 1) Figure 1 shows the Kaplan Meier survival curves of patients carrying each of these mutations (red curves) compared to patients carrying the wild type gene (blue curves).

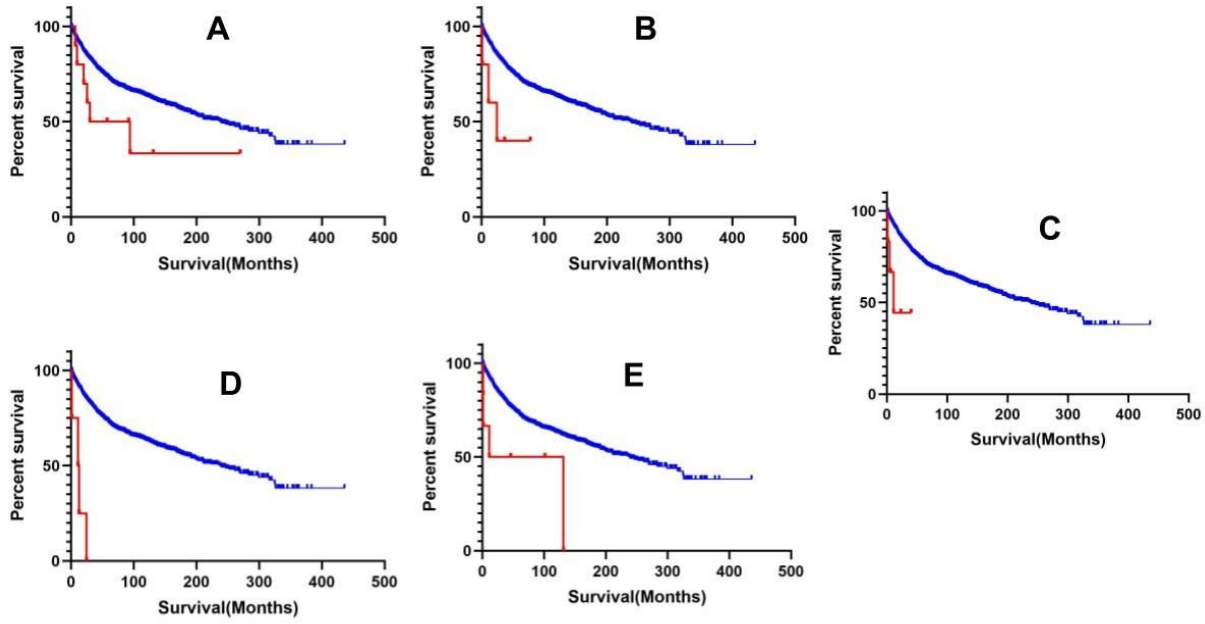

Figure 1. Kaplan-Meier Survival Curve of Patients Carrying different BCL2 Mutations. Among the thirteen different BCL2 mutations studied, patients carrying A60V (Panel A), G8R (Panel B), X96 Splice (Panel C), G8E

(Panel D) and T56M (Panel E) displayed decreased survival rates (red curves) when compared with the control group carrying the wild type BCL2 gene (blue curves)..

In contrast, the presence of BCL2 mutations X195 Splice, R129H, A131V, G33R, P59S, L86F, H20Q, and H120Y did not significantly decrease/increase the survival rate of patients compared to the control group (Fig 2) as indicated by the p-values larger than 0.05 calculated by the Mantel-Cox and the Gehan-Breslow-Wilcoxon tests. (Table 1)

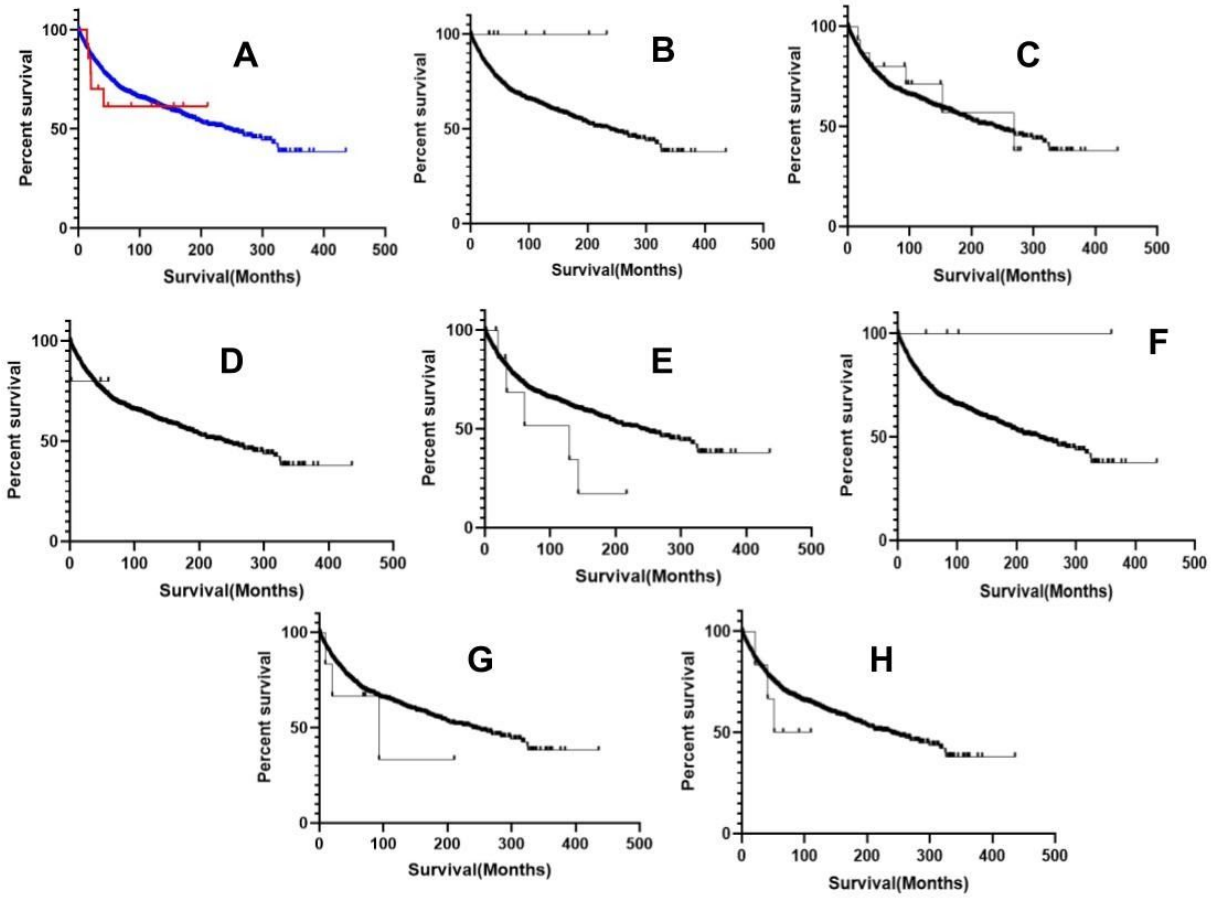

Figure 2. Kaplan-Meier Survival Curve of Patients Carrying different BCL2 Mutations. Among the thirteen different BCL2 mutations studied, patients carrying X195 Splice (Panel A), R129H (Panel B), A131V (Panel C), G33R

(Panel D), P59S (Panel E), H20Q (Panel F), H120Y(Panel G), and L86F (Panel H) displayed survival rates (red/thin curves) comparable with the control group carrying the wild type BCL2 gene (blue/thick curves).

TP53

Three mutations for the TP53 gene were found to be present in more than 5 patients among the samples tested.The Mantel-Cox and the Gehan-Breslow-Wilcoxon tests revealed that that presence these three TP53 mutations (R175H, R248Q, and N239D) did not significantly decrease/increase ($p>0.05$) the survival rates of these patients. (Table 1) Figure 3 shows the Kaplan Meier survival curves of patients carrying each of these mutations (red/thin curves) compared to patients carrying the wild type gene (blue/thick curves).

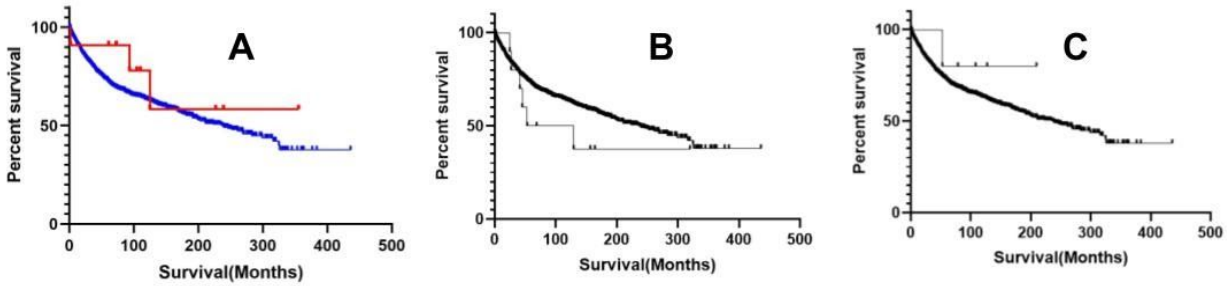

Figure 3. Kaplan-Meier Survival Curve of Patients Carrying different TP53 Mutations. Among the three different TP53 mutations studied, patients carrying R175H (Panel A), R248Q (Panel B), N239D (Panel C) displayed survival rates (red/thin curves) comparable with the control group carrying the wild type TP53 gene (blue/thick curves).

SOCS1

Three mutations for the SOCS1 gene were found to be present in more than 5 patients among the samples tested.The Mantel-Cox and the Gehan-Breslow-Wilcoxon tests revealed that the presence of these three SOCS1 mutations (S125T, S116N, and A16T) did not significantly

decrease/increase ($p>0.05$) the survival rates of these patients. (Table 1) Figure 4 shows the Kaplan Meier survival curves of patients carrying each of these mutations (thin curves) compared to patients carrying the wild type gene (thick curves).

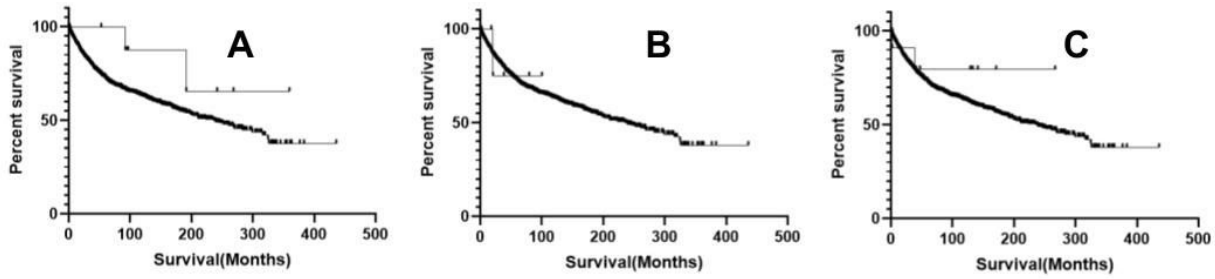

Figure 4. Kaplan-Meier Survival Curve of Patients Carrying different SOCS1 Mutations. Among the three different SOCS1 mutations studied, patients carrying S116N (Panel A), A16T (Panel B), S125T (Panel C) displayed survival rates (thin curves) comparable with the control group carrying the wild type SOCS1 gene (thick curves).

STAT3, FAS, & ETS1

One mutation for each of the STAT 3, FAS and ETS1 genes was found to be present in more than 5 patients. The Mantel-Cox and the Gehan-Breslow-Wilcoxon tests revealed that presence of the FAS mutation (V220Gfs*6) and ETS1 mutation (E17K) did not significantly decrease/increase ($p>0.05$) the survival rates of these patients. (Table 1) However the same tests revealed that the presence of the STAT3 mutation (Y640F) increased the survival rate of patients ($p<0.05$) when compared to the wild type. (Fig 5) (Table 1)

.

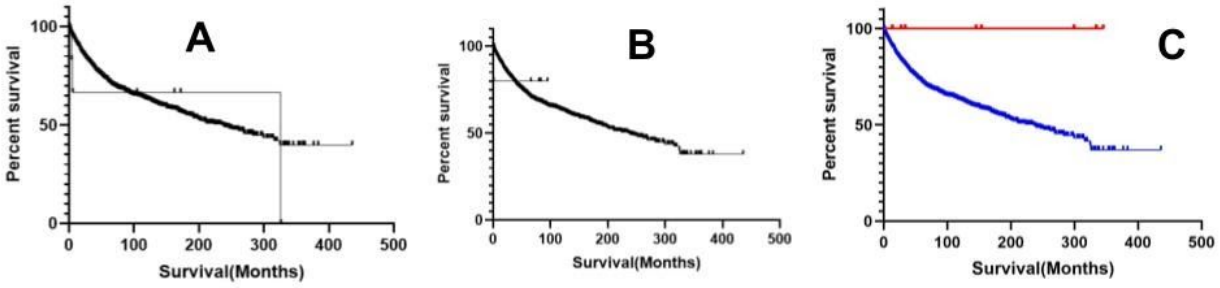

Figure 5. Kaplan-Meier Survival Curve of Patients Carrying either a FAS, ETS1, or STAT3 Mutations. Among the ETS1 and FAS mutations studied, patients carrying E17K(Panel A), V220Gfs*6 (Panel B), displayed survival rates (thin curves) comparable with the control group carrying the wild type ETS1 or FAS gene (thick curves). For the STAT3 mutation, patients carrying the mutation Y640F (Panel C) displayed an increased survival rate(red curve) compared with the control group carrying the wild type STAT3 Gene (blue curve)

Discussion:

This study aimed to explore the relationship between mutations in genes associated with the development of six pediatric autoimmune diseases and the prognosis these mutations have in Non-Hodgkin's Lymphoma. Overall 22 mutations in genes associated with the development of pediatric autoimmune diseases were analysed for their effect on patient outcome.

The presence of five of the BCL2 mutations (A60V, G8R, X96 Splice, G8E, and T56M) significantly decreased ($p<0.05$) the survival rates of these patients. Overexpression of BCL2 proteins in Non-Hodgkin's Lymphoma have been associated with a poorer prognosis for patients [38,39]. The mutations A60V, G8R, X96 Splice, and G8E could promote the aforementioned role which in return would explain the poor patient outcomes. In addition, T56M residue is phosphorylated in BCL2. [40] The effects of modification are unknown but it is suggested that

this provides a binding site for anti-apoptosis proteins which effectively delays cell death.[40] The inhibition of cell death by BCL2 has been associated with tumorigenesis which could explain the reason for poor patient survival. [40]. However not enough research has been done on how these aforementioned mutations affect BCL2 pathways and the production of BCL2 proteins.

The presence of the STAT3 mutation Y640F increased the survival rate of patients ($p<0.05$) when compared to the wild type. STAT3 Y640F is known to be oncogenic [41]. Furthermore STAT3 is overexpressed in Non-Hodgkin's Lymphoma which has been observed to result in poorer patient outcomes [42,43]. However the Y640F mutation causes a change in the protein's interaction with TYK2 enzyme which results in underexpression of STAT3 [44]. This could explain the increased survival rate observed in our study.

In contrast, the presence of eight BCL2 mutations (X195 Splice, A131V, R129H, H20Q, P59S, G33R, H120Y, and L86F) did not significantly decrease or increase ($p>0.005$) patient survival. The mutations H120Y, L86F, G33R, P59S, H20Q, R129H, have been observed not to significantly change patient outcomes in follicular lymphomas (a type of Non-Hodgkin's Lymphoma) with a specific treatment course [45]. More research is needed to explain the role of the BCL2 X195 Splice mutation because due to its similar patient outcome to the wild type, it would suggest that X195 Splice does not cause a higher expression of BCL2 proteins, or a binding site for anti-apoptosis proteins.

The presence of the three TP53 mutations; R175H, R249Q, N239D, three SOCS1 mutations; S116N,S125Y, and A16T, one FAS mutation: V220Gfs*6, and one ETS1 mutation: E17K displayed average patient outcome. It has been observed that TP53 mutations are prognostic indicators for Non-Hodgkins Lymphoma prognosis. [46] Deletion mutations in SOCS1 have been associated with high patient survival [47-50] , however S116N, S125Y, and A16T are missense mutations which could indicate that they have average outcomes. It has been suggested the downregulation of FasR (the protein produced by FAS) on B cells can help B cell lymphomas go undetected which worsens patient prognosis. [51] This would suggest that this mutation does not induce the underexpression of FasR. As well, it has been observed that high expression of ETS1 worsens patient prognosis, which would suggest E17K does not cause ETS1 to be overexpressed. [52] More research into the effect of these mutations on their respective gene would have to be conducted to provide better analysis..

In conclusion there were three distinct groups of mutations that this study found, those that improved patient prognosis, those which decreased, and those on par. These findings can be used as purely prognostic information for people who develop Non-Hodgkin's lymphoma. In conjunction with the genetic profile of a patient, doctors will be able to better give patients a more accurate prognosis. In relation to the aim of the study; patients with pediatric autoimmune diseases would be more likely to have mutations to the genes explored in this study as mutations to the genes and these genes themselves are also associated with the development of pediatric autoimmune diseases. Depending on the mutation of the patient, this would mean that if they develop Non-Hodgkin's lymphoma, they are at a risk of a poorer prognosis.

Reference List:

1. Lerner A, Jeremias P, Matthias T. The world incidence and prevalence of autoimmune diseases is increasing. *Int J Celiac Dis*. 2015;3(4):151-155. doi:10.12691/ijcd-3-4-8

2. The American Cancer Society. Non-Hodgkin Risk Factors. https://www.cancer.org/cancer/non-hodgkin-lymphoma/causes-risks-prevention/risk-factors.html

3. Kleinstern G, Maurer MJ, Liebow M, et al. History of autoimmune conditions and lymphoma prognosis. *Blood Cancer J*. 2018;8(8). doi:10.1038/s41408-018-0105-4

4. Smedby KE, Askling J, Mariette X, Baecklund E. Autoimmune and inflammatory disorders and risk of malignant lymphomas - An update. In: *Journal of Internal Medicine*. Vol 264. ; 2008:514-527. doi:10.1111/j.1365-2796.2008.02029.x

5. Dalrymple AM, Moore TL. Laboratory evaluation in pediatric autoimmune diseases. Pediatr Rev. 2015;36(11):496-501. doi:10.1542/pir.36-11-496

6. Turner D. ES07.02 The human leucocyte antigen (HLA) system. Vox Sang. 2004;87(s1):87-90. doi:10.1111/j.1741-6892.2004.00438.x

7. Marsh SGE, Albert ED, Bodmer WF, et al. Nomenclature for factors of the HLA system, 2004. *Tissue Antigens*. 2005;65(4):301-369. doi:10.1111/j.1399-0039.2005.00379.x

8. Shiina T, Inoko H, Kulski JK. An update of the HLA genomic region, locus information and disease associations: 2004. *Tissue Antigens*. 2004;64(6):631-649. doi:10.1111/j.1399-0039.2004.00327.x

9. Cui Y, Sheng Y, Zhang X. Genetic susceptibility to SLE: Recent progress from GWAS. *J Autoimmun*. 2013;41:25-33. doi:10.1016/j.jaut.2013.01.008

doi:10.1016/j.semnephrol.2010.01.007

10. Costa-Reis P, Sullivan KE. Genetics and epigenetics of systemic lupus erythematosus. *Curr Rheumatol Rep*. 2013;15(9). doi:10.1007/s11926-013-0369-4

11. Amos CI, Chen WV, Lee A, Li W, Kern M, Lundsten R, et al. High-density SNP analysis of 642 Caucasian families with rheumatoid arthritis identifies two new linkage regions on 11p12 and 2q33. Genes Immun. 2006;7:277-86.

12. Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. N Engl J Med. 2007;357:977-86.

13. Hachulla E, Launay D. Diagnosis and classification of systemic sclerosis. *Clin Rev Allergy Immunol*. 2011;40(2):78-83. doi:10.1007/s12016-010-8198-y

14. Rueda B, Broen J, Simeon C, et al. The STAT4 gene influences the genetic predisposition to systemic sclerosis phenotype. *Hum Mol Genet*. 2009;18(11):2071-2077. doi:10.1093/hmg/ddp119

15. Dieudé P, Guedj M, Wipff J, et al. Association between the IRF5 rs2004640 functional polymorphism and systemic sclerosis: A new perspective for pulmonary fibrosis. *Arthritis Rheum*. 2009;60(1):225-233. doi:10.1002/art.24183

16. Ito I, Kawaguchi Y, Kawasaki A, et al. Association of a functional polymorphism in the IRF5 region with systemic sclerosis in a Japanese population. *Arthritis Rheum*. 2009;60(6):1845-1850. doi:10.1002/art.24600

17. IRF5 interferon regulatory factor 5 [Homo sapiens (human)] - Gene - NCBI. https://www.ncbi.nlm.nih.gov/gene/3663. Accessed December 19, 2019.

18. Mavragani CP, Moutsopoulos HM. Sjögren syndrome. *Can Med Assoc J*. 2014;186(15):E579-E586. doi:10.1503/cmaj.122037

19. De Paiva CS, Rocha EM. Sjögren syndrome: What and where are we looking for? *Curr Opin Ophthalmol*. 2015;26(6):517-525. doi:10.1097/ICU.0000000000000208

20.Fragkioudaki, S., Nezos, A., Souliotis, V.L. *et al.* MTHFR gene variants and non-MALT lymphoma development in primary Sjogren's syndrome. *Sci Rep* 7, 7354 (2017) doi:10.1038/s41598-017-07347-w

21. IL10 interleukin 10 [Homo sapiens (human)] - Gene - NCBI. https://www.ncbi.nlm.nih.gov/gene/3586. Accessed December 19, 2019.

22. Crowe SE. Celiac Disease. *Ann Intern Med*. 2011;154(9):ITC5. doi:10.7326/0003-4819-154-9-201105030-01005

23. Abadie V, Sollid LM, Barreiro LB, Jabri B. Integration of Genetic and Immunological Insights into a Model of Celiac Disease Pathogenesis. *Annu Rev Immunol*. 2011;29(1):493-525. doi:10.1146/annurev-immunol-040210-092915

24. Davatchi F, Assaad-Khalil S, Calamia KT, et al. The International Criteria for Behçet's Disease (ICBD): A collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatology Venereol*. 2014;28(3):338-347. doi:10.1111/jdv.12107

25. De Menthon M, LaValley MP, Maldini C, Guillevin L, Mahr A. HLA-B51/B5 and the risk of Behçet's disease: A systematic review and meta-analysis of case-control genetic association studies. *Arthritis Care Res*. 2009;61(10):1287-1296. doi:10.1002/art.24642

26. Li, L., Yu, H., Jiang, Y. *et al.* Genetic Variations of NLR family genes in Behcet's Disease. *Sci Rep* 6, 20098 (2016) doi:10.1038/srep20098

27. CIITA class II major histocompatibility complex transactivator [Homo sapiens (human)] - Gene - NCBI. https://www.ncbi.nlm.nih.gov/gene/4261. Accessed December 19, 2019.

28. Keestra-Gounder AM, Tsolis RM. NOD1 and NOD2: Beyond Peptidoglycan Sensing. Trends Immunol. 2017;38(10):758-767. doi:10.1016/j.it.2017.07.004

29. Shamji MF, Bafaquh M, Tsai E. The pathogenesis of ankylosing spondylitis. *Neurosurg Focus*. 2008;24(1):E3. doi:10.3171/FOC/2008/24/1/E3

30. Khan MA. HLA-B27 and its pathogenic role. *J Clin Rheumatol*. 2008;14(1):50-52. doi:10.1097/RHU.0b013e3181637a38

31. Ceccarelli F, Agmon-Levin N, Perricone C. *Editorial Genetic Factors of Autoimmune Diseases 2017*. 2017. doi:10.1155/2017/2789242

32. Riahi P, Kazemnejad A, Mostafaei S, et al. ERAP1 polymorphisms interactions and their association with Behçet's disease susceptibility: Application of model-based multifactor dimension reduction algorithm (MB-MDR). PLoS One. 2020;15(2). doi:10.1371/journal.pone.0227997

33. Malik A, Kanneganti TD. Function and regulation of IL-1α in inflammatory diseases and cancer. Immunol Rev. 2018;281(1):124-137. doi:10.1111/imr.12615

34.Duvallet E, Semerano L, Assier E, Falgarone G, Boissier MC. Interleukin-23: A key cytokine in inflammatory diseases. Ann Med. 2011;43(7):503-511. doi:10.3109/07853890.2011.577093

35. Lu G, Hao X, Chen WH, Mu S. GAAD: A Gene and Autoimmune Disease Association Database. Genomics, Proteomics Bioinforma. 2018;16(4):252-261. doi:10.1016/j.gpb.2018.05.001

36. Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data [published correction appears in Cancer

Discov. 2012 Oct;2(10):960]. Cancer Discov. 2012;2(5):401‑404. doi:10.1158/2159-8290.CD-12-0095

37. Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013;6(269):pl1. Published 2013 Apr 2. doi:10.1126/scisignal.2004088

38.Schuetz JM, Johnson NA, Morin RD, et al. BCL2 mutations in diffuse large B-cell lymphoma. Leukemia. 2012;26(6):1383-1390. doi:10.1038/leu.2011.378

39. Makino K, Nakamura H, Shinojima N, et al. BCL2 expression is associated with a poor prognosis independent of cellular origin in primary central nervous system diffuse large B-cell lymphoma. J Neurooncol. 2018;140(1):115-121. doi:10.1007/s11060-018-2940-3

40. Correia C, Lee SH, Meng XW, et al. Emerging understanding of Bcl-2 biology: Implications for neoplastic progression and treatment. Biochim Biophys Acta - Mol Cell Res. 2015;1853(7):1658-1671. doi:10.1016/j.bbamcr.2015.03.012

41. Gene: STAT3, Alteration: Y640F. https://www.oncokb.org/gene/STAT3/Y640F/. Accessed February 17, 2020.

42. Wu ZL, Song YQ, Shi YF, Zhu J. High nuclear expression of STAT3 is associated with unfavorable prognosis in diffuse large B-cell lymphoma. J Hematol Oncol. 2011;4(1):31. Published 2011 Aug 1. doi:10.1186/1756-8722-4-31

43.Huang X, Meng B, Iqbal J, et al. Activation of the STAT3 signaling pathway is associated with poor survival in diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol. 2013;31(36):4520‑4528. doi:10.1200/JCO.2012.45.6004

44. Mori R, Wauman J, Icardi L, et al. TYK2-induced phosphorylation of Y640 suppresses STAT3 transcriptional activity. Sci Rep. 2017;7(1):1-12. doi:10.1038/s41598-017-15912-6

45. Huet S, Szafer-Glusman E, Tesson B, et al. BCL2 mutations do not confer adverse prognosis in follicular lymphoma patients treated with rituximab. Am J Hematol. 2017;92(6):515-519. doi:10.1002/ajh.24701

46. Xu P, Liu X, Ouyang J, Chen B. TP53 mutation predicts the poor prognosis of non-Hodgkin lymphomas: Evidence from a meta-analysis. PLoS One. 2017;12(4). doi:10.1371/journal.pone.0174809

47. Mellert K, Martin M, Lennerz JK, et al. The impact of SOCS1 mutations in diffuse large B‐cell lymphoma. Br J Haematol. 2019;187(5):627-637. doi:10.1111/bjh.16147

48. Mutation overview page SOCS1 - p.S125T (Substitution - Missense). https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=113283644. Accessed May 26, 2020.

49. Mutation overview page SOCS1 - p.A16T (Substitution - Missense). https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=113282929. Accessed May 26, 2020.

50. Mutation overview page SOCS1 - p.S116N (Substitution - Missense). https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=113283553. Accessed May 26, 2020.

51. Rys RN, Venkataraman M, Zeng J, Mann KK, Johnson N. Fas Mutations in Non-Hodgkin's Lymphoma (Non-Hodgkin's lymphoma): Implications for Disease Progression and Therapeutic Resistance. Blood. 2019;134(Supplement_1):1520-1520. doi:10.1182/blood-2019-130602

52. Bonetti P, Testoni M, Scandurra M, et al. Deregulation of ETS1 and FLI1 contributes to the pathogenesis of diffuse large B-cell lymphoma. Blood. 2013;122(13):2233-2241. doi:10.1182/blood-2013-01-475772