

## Serum level and interleukin 9 genetic polymorphisms

### In patients with tonsillitis

Wasan A. Majeed<sup>1</sup>; Abdulwahab A. Jbara<sup>1</sup>; Ibtesam B. Hassan\*<sup>1</sup>; MohammedAli S. Mohammad; Bariq T. Khodaer<sup>1</sup>; Wurood K. Mohammed<sup>1</sup>

1-Department of Biology, College of Education for Pure Science, University of Diyala, Diyala-Iraq.

\*1 Corresponding author email: ibtesambh67@gmail.com

#### Abstract

The study investigated the relationship between the polymorphism of the IL-9 gene at position -6676 for the variation rs1799962 for tonsillitis among patients in Baquba, which included 31 male samples with an average age of (15.65 ± 1.79) years compared to 5 healthy males with an average age (14.66 ± 3.43) years enrolled in this study the polymorphism of IL9-6676 was data waved by polymerase chain reaction-specific sequence primer (PCR-SSP) assay. As the results of the electrophoresis of the IL- 9 gene at position -6676 showed a comparison *genotypes & alleles* between tonsillitis patients & controls frequencies of AA genotype & A *allele*, showed that a significant increase in patients with tonsillitis (45.16% and 72.58% P =1.000 respectively) Compared to the control (70% and 40% P= 0.431 respectively) and associated RR rates were(8.6% and 38.0% respectively.) and And the related EF values were (1.24 and 1.75). In contrast AG genotype & G *allele* (35.48 vs. 17.74, P =0.357 respectively). Decreased frequency was observed in patients compared to the control (30% and 60% P =0.431) , and the related PF values were (0.37 and 0.57 respectively). The results of the study indicate that IL9-6676 SNP may have a role in the mechanism of etiopathogenic. It was observed that it has a negative and positive role in the samples with tonsillitis in the samples of Iraqi patients

**Key words:** Single Nucleotide Polymorphism, *Interleukine-9*. Tonsillitis.

#### Introduction

The tonsils are the two lymph nodes that are located on either side of the back of the throat. They act as a defense mechanism, helping to prevent infection from entering the body. Tonsillitis is easy to diagnose and treat (Shantinath, 2015). Tonsillitis is common (15-40%) among children and (5- 15%) among adults (Shaikh, others 2010). About 11 million people annually in the United States become infected with pharyngitis. The largest group in which streptococcus pharyngitis is prevalent, by 15 to 40% among children and by 5 to 15% among adults, and these cases often occur in late winter and early spring. Tonsils are organs in which immunity is

regulated where allergen-specific regulatory T cells can be generated by mechanisms that rely on plasmadendritic cells (Choby, 2009; Shulman et al., 2012) and are considered the host's first line of defense against pathogens, but it is also a place with processes Recurrent chronic inflammatory.

It is predominant in tonsillitis, initiates production of Th1 cytokines, including IFN- $\alpha$  and TNF- $\alpha$ , and then on secretion of Th2 type cytokines the elevated concentration of TNF- $\alpha$ , IL-1, IL-6, IL-9, and IL-13 in tissues is As a result of the overproduction of inflammatory cytokines due to the activation of single-celled macrophages resulting from repeated stimulation by pathogenic agents (Mikola, 2018). IL-9 plays a critical role in inflammatory diseases such as asthma, atopic dermatitis, systemic lupus erythematosus and rheumatoid arthritis. The anti-inflammatory or anti-inflammatory function of the IL-9 source depends on the role of the IL-9 secretion source and the stage of the disease. For all previous information present study focused on Interleukins 9

## Materials and Methods

### Subjects

The current study was conducted on a group of patients attending Baqubah Teaching Hospital / Consulting Clinic. Blood samples were obtained for patients with tonsillitis from Baqubah district, and samples were collected for the period from 1-5-2020 until 1-8-2020, and the number was (31) samples, and all cases in the study included only males in addition to 5 healthy controls males. Blood samples were collected in EDTA. The specimens were stored in deep freeze at -20°C. tonsillitis patients and randomly collected healthy controls (HC). The patients age range was  $15.65 \pm 1.79$  years compared subject of health's controls was  $14.66 \pm 3.43$  years, were record in the study.

### Detection of IL9 rs1799962 Polymorphism

Genomic DNA was extracted from EDTA blood using G-spin TM Total DNA Purification Kit (G-SPIN USA) followed by electrophoresis on 2% agarose-gel by CTS-PCRSSP Tray Kit (Maxime PCR PreMix USA).

### Statistical Analysis

Genotypes of IL9<sup>-6676</sup> SNP were presented as percentage frequencies, These estimations were calculated by using the WINPEPI computer programs for epidemiologists. The latest version of the WINPEPI package is available free online at <http://www.brixtonhealth.com>.

### Rustles:

SNP of IL9 gene was determined in the promoter region at position <sup>-6676</sup> (IL9<sup>-6676</sup> SNP), it was presented with three genotypes (AA, AG and GG) that correlate with two alleles (A and G). Among Tonsillitis patients, no significant difference was observed between the observed and expected frequencies of the three genotypes (a good agreement with Hardy-Weinberg equilibrium; HWE), However comparing patients to controls results some significant differences (Table -1).

The frequencies of AA genotype and A allele were significantly increased in patients (45.16% and 72.58%, respectively) compared to controls (70% and 40% respectively). The relative risks (RRs) of such positive associations were 8.6% and 38.0% respectively. In contrast, AG genotype & G allele frequencies were significantly decreased in patients (35.48 vs. 17.74, respectively) compared to controls (30% and 60%, respectively). The preventing fractions (PFs) of such negative associations were 0.37 and 0.57, respectively). (Table 2).

**Table 1:** numbers and percentage frequencies and Hardy-Weinberg (H-W) equilibrium of (IL9-6676 rs1799962 genotypes and alleles) in tonsillitis patients and controls.

Groups			IL9-6676 Genotypes or alleles					H-W $X^2 P \leq$
			AA	AG	GG	A	G	
tonsillitis (No. = 31)	Observed	No.	14	11	0	45	11	0.22
		%	45.16	35.48	0	72.58	17.74	
	Expected	No.	16.33	7.98	0.98	Not Estimated		
		%	52.68	25.75	3.15			
Controls (No. = 5)	Observed	No.	2	3	0	7	3	0.33
		%	60	40	0	70	30	
	Expected	No.	2.45	2.1	0.45	Not Estimated		
		%	49	42	9			

**Table 2-:** Statistical analysis of associations between IL9-6676 rs1799962 genotypes or alleles in tonsillitis patients and controls. .

Type Comparison of	Statistical Evaluation.				
	IL9-6676 Genotype or Allele	Relative Risk.	Preventive or Fraction Etiological.	Fisher's Exact Probability	95% Confidence Intervals
tonsillitis Disease Versus Controls.	AA	8.6%	1.24	1.000	7.07 -0.22
	AG	38.0%	0.37	0.357	2.12 -0.06
	GG	0	0	0	0
	A	34.5%	1.75	0.431	0.42 - 7.40
	G	12.9%	0.57	0.431	0.14 - 2.41

**Discussion:**

The results of the current study, as shown in Table (1-4), showed that the identical genotype AA and allele A recorded a significant increase in the group of patients with tonsillitis and present study illustrated that IL9-6676 rs1799962 important genetic marker in the “pathogenesis of tonsillitis especially if we consider RR values was

(8.6% and 38.0%), respectively, was showed that frequency of AA genotype and A allele (45.16% and 72.58%; P =1.000 respectively) were significantly rise in patients contrast to controls, (07% and 40% respectively; P=0.357), and the associated EF values were 1.24 & 1.75, respectively. In contrast, AG genotype and G allele (35.48 and 17.74, respectively P= 0.357 respectively) frequencies were significantly decreased in patients, compared to controls (30% and 60%, respectively; P=0.431), and the associated PF values” were 0.37 and 0.57 respectively. The presented results strongly suggest that IL9-6676 rs1799962 polymorphism is involved in tonsillitis in terms of susceptibility (positive association) and protection (negative association). The current study did not agree with the study conducted by the researcher (Fatahi et al. 2016), which indicated that the IL-9 in the homozygous genotype AA has a protective effect or protection from the risk of developing rhinitis respiratory disease in women in Iran because of its low frequency in infected patients. This mean genotype in this singlenucleotide polymorphisms can effect the level of IL-9 in serum in asthmatic patients (Turner et al.,2013). Unfortunately, such polymorphism has not been investigated in tonsillitis.

## The References

- AL-Kinani, I. B .H ; Ad'hiah, A. H. and Shihab, B. A.(2015). Single Nucleotide polymorphisms of cytokines in inflammatory bowel disease of Iraqi patients. Thesis Baghdad University- College of Science for Women:23-102.
- Ansel, K. M., Djuretic, I., Tanasa, B. and Rao, A.( 2006). Regulation of Th2 differentiation and Il4 locus accessibility. *Annu. Rev. Immunol.*; 24:607.
- Barnas, J.L. and Ritchlin, C.T.(2015). Etiology and pathogenesis of psoriatic arthritis. *Rheum. Dis. Clin. North. Am.*; 41:643–63.
- Barreiro ,L. B.; Laval, G.; Quach, H.; Patin, E. and Quintana-Murci , L. (2008). "Natural selection has driven population differentiation in modern humans". *Nature Genetics*, ; 40 (3): 340–345.
- Basma, H. ; Norrby-Teglund, A. ; Guedez, Y. ; McGeer, A. ; Low, D. ; El-Ahmedy, O. ; Schwartz, B. and Kotb, M. (1999). Risk factors in the pathogenesis of invasive group A streptococcal infections : Role of protective humoral immunity. *Infect. Immun.*, 67(4):1871-1977.
- Beriou, G.; Bradshaw, E. M.; Lozano, E.; Costantino, C. M.; Hastings, W. D.; Orban, T.; Elyaman,W.; Khoury,S.J.; Kuchroo,V.K.; Baecher-Allan,C. and Hafler, D. A. (2010). TGF-Induces IL-9 Production from Human Th17 Cells. *The Journal of Immunology*, 185(1), 46–54.
- Butler and John, M. (2010). *Fundamentals of forensic DNA typing*. Burlington, MA. : Elsevier, Academic Press, ISBN. 9780080961767.
- Carlson and Bruce (2008). "SNPs — A Shortcut to Personalized Medicine". *Genetic Engineering & Biotechnology News*. Mary Ann Liebert, Inc. 28 (12). 07-06.

- Chakravarti , A.(2001). To a future of genetic medicine. *Nature*;409 (6822):822–3.
- Chen, D. Y. ; Chen, Y. M. ; Wen, M. C. ; Hsieh, T. Y. ; Hung, W. T and J. L. Lan, (2012). “The potential role of Th17 cells and Th17-related cytokines in the pathogenesis of lupus nephritis,” *Lupus*, vol. 21, no. 13, pp. 1385–1396.
- Choby BA (March 2009). "Diagnosis and treatment of streptococcal pharyngitis". *Am Fam Physician*. 79(5): 383–90.
- Dantas, A.T. ; Marques, C.D. ; da Rocha Junior, L.F.; Cavalcanti, M.B. ; Goncalves, S.M. ; Cardoso, P.R. ; Mariz Hde, A.; Rego, M.J. ; Duarte, A.L.; Pitta, I.da. and Pitta, M.G.(2015). Increased serum interleukin-9 levels in rheumatoid arthritis and systemic lupus erythematosus: pathogenic role or just an epiphenomenon? *Dis. Markers*, 51963-8.
- Davies, P. (1986) The genetics of Alzheimer's disease: a review and a discussion of the implications. *Neurobiol. Aging*. 7, 459-466.
- Elyaman, W.; Bradshaw, .; E.M. ; Uyttenhove, C.; Dardalhon, V.; Awasthi, A.; Imitola, J. ; Bettelli, E.; Oukka, M. ; van Snick, J.; Renauld, J. Ch.; Kuchroo, v. k. and Khoury, s. j.(2009). “IL-9 induces differentiation of TH17 cells and enhances function of FoxP3+ natural regulatory T cells,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 31, pp. 12885–12890.
- Fatahi, ARS Chaleshtori, K Ghatreh Samani, SM Mousavi, F Zandi, S Heydari, M Hashemzadeh Chaleshtori, M Amiri,<sup>1</sup> and H Khazraee.( 2016).Assessment of the Effects of *IL9*, *IL9R*, *IL17A*, and *IL17F* Gene Polymorphisms on Women with Allergic Rhinitis in Shahrekord, Iran [Ann Med Health Sci Res](#). 2016 Jul-Aug; 6(4): 216–223.
- Frazer, K.A.; Ballinger, D.G.; Cox ,D.R.; Hinds, D.A.; Stuve, L.L.; Gibbs, R.A.; Belmont, J.W.; Boudreau, A.; Hardenbol, P.; Leal, S.M; Pasternak, S.; Wheeler, D.A.; Jamieson, R.; Stewart, J. (2007). International Hap- Map Consortium. A second generation human haplotype map of over 3.1 million SNPs. *Nature*, ;449:851–61.
- Gabriel, S.B.; Schaffner, S.F.; Nguyen, H.; Moore, J.M.; Roy, J.; Blumenstie, B.; Higgins, J.; DeFelice, M.; Lochner, A.; Faggart, M.; Liu-Cordero, Sh. N.; Rotimi, Ch.; Adeyemo, A.; Cooper, R.; Ward, R.; Lander, E.S.; Daly, M.J. and Altshuler ,D.(2002).The structure of haplotype blocks in the human genome. *Science*, ;296:2225–9.
- Geißler, K., Weigel, C., Schubert, K. et al. Cytokine production in patients with recurrent acute tonsillitis: analysis of tonsil samples and blood. *Sci Rep* 10, 13006 (2020). <https://doi.org/10.1038/s41598-020-69981-1>.
- Gessner, A. ;Blum, H. and Röllinghoff, M.(1993). Differential regulation of IL-9-expression after infection with *Leishmania major* in susceptible and resistant mice. *Immunobiology*,189: (5) 419–435.

Giacopelli, F.; Marciano ,R.; Pistorio, A.; Catarsi, P.; Canini, S.; Karsenty, G., et al.(2004). Polymorphisms in the osteopontin promoter affect its transcriptional activity. *Physiol. Genomics* affect its.20:87–96.

Goswami, R. and M. H. Kaplan, M. H. (2011). “A brief history of IL-9,” *Journal of Immunology*, vol. 186, no. 6, pp. 3283–3288.

Grohmann, U.; van Snick, J.; Campanile F.; Silla, S.; Giampietri, A.; Vacca, C.; Renauld, J. C.; Fioretti, M. C. and Puccetti, P.(2000). “IL-9 protects mice from gram-negative bacterial shock: suppression of TNF alpha, IL-12, and IFN-gamma, and induction of IL-10,” *The Journal of Immunology*, vol. 164, no. 8, pp. 4197–4203.

Hardy, J. and Singleton, A.(2009). Genome wide association studies and human disease. *human disease. N. Engl. J. Med.*360:1759–68.

Harrington, L. E.; Hatton, R. D.; Mangan, P. R. ;Turner, H. ;Murphy, Th. L. ;Murphy, K. M. and Weaver, C.T. (2005). Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat. Immunol.* ; 6:1123.

Hughes-Austin, J.M. ; Deane, K.D. ; Derber, L.A. ; Kolfenbach, J.R. ; Zerbe, G.O. ; Sokolove, J.; Lahey, L.J. ; Weisman, M.H.; Buckner, T.R. Mikuls, J.H.; O'Dell, J.R.; Keating, R.M.; Gregersen, P.K.; Robinson, W.H. ; Holers, V.M.; Norris, J.M. (2013).Multiple cytokines and chemokines are associated with rheumatoid arthritis-related autoimmunity in first-degree relatives without rheumatoid arthritis: Studies of the Aetiology of Rheumatoid Arthritis(SERA), *Ann. Rheum. Dis.* 72 (6) 901–907.

Hyde, R. M. (2000). *Immunology*. 4th ed. Lippincott Williams and Wilkins, Philadelphia, USA.Kaplan, M.H.(2017). The transcription factor network in Th9 cells. *Semin. Immunopathol*;39(1):11–20.

Kelleher, K.; Bean, K.; Clark, S.C.; Leung, W.Y.; Yang-Feng ,T.L.; Chen, J. ;WKelleher, K.; Bean, K.; Clark, S.C.; Leung ,W.Y. and Yang-Feng, T.L.(1991). Chen JWsequence, chromosomal location, and sequences expression in human T-cell leukemia virus (HTLV)-I-virus (HTLV)-I-transformed human T cells" .*Blood.* 77 (7): 1436–41.

Kim, J.; Kang, S.; Kwon, G. and SKoo, S.(2013). “Elevated levels ofT helper 17 cells are associated with disease activity in patientswith rheumatoid arthritis,” *Annals of Laboratory Medicine*, vol.33, no. 1, pp. 52–59.

Kundu-Raychaudhuri, S.; Abria, C.and Raychaudhuri S.P. .(2016). IL-9, a local growth factor for synovial T cells in inflammatory arthritis. *Cytokine*, ;79:45–51.

Levinson, W. and Jawetz, E.(2000). *Medical Microbiology and Immunology*,6th ed. Mc Graw-Hill.Co.New York.

Li, G. and Pan, T.(2014). One of the earliest successes in this field was finding a single base mutation in the non-coding region of the APOC3 (apolipoprotein C3 gene) that associated with higher risks of hyper triglyceridemia and atherosclerosis . *Mol. Biol. Int.* : 967565.

Lu, Y.F.; Mauger, D.M.; Goldstein, D. B.; Urban, Th. J.; Weeks, K. M. and Bradrick, S.S. (2015). "IFNL3 mRNA structure is remodeled by a functional non-coding polymorphism associated with hepatitis C virus clearance". *Scientific Reports*, . 5: 16037.

Maeda, S.; Hayami, Y.; Naniwa ,T. and Ueda ,R.(2012). The Th17/IL-23 axis and natural immunity in psoriatic arthritis. *Int. J. Rheumatol.* :539683.

Maniatis, T. ; Fritsch, E. F. and Sambrook, J. (1982). *Molecular cloning :Laboratory Manual*. Cold Spring Harbor Laboratory. New York,458pp.

Mikola, E., Elenius, V., Saarinen, M. et al. Tonsillar cytokine expression between patients with tonsillar hypertrophy and recurrent tonsillitis. *Clin Transl Allergy* 8, 22 (2018).

Mock, B.A. ; Krall, M. and Kozak, C.A. (1990). M.N. Nesbitt, O.W. McBride, J.C. Renauld, J. Van Snick, IL9 maps to mouse chromosome 13 and human chromosome 5, *Immunogenetics*, 31: (4) 265–270.

Murphy, K. M. and Reiner, S. L.( 2002). The lineage decisions of helper Tcells. *Nat. Rev. Immunol.* 2:933.

Nachman, and Michael, W. (2001). "Single-nucleotide polymorphisms and recombination rate in humans". *Trends in Genetics*. 17 (9): 481–485.

Nicolaides, N.C. ; Holroyd, K.J. ; S.L. Ewart, S.L. ; Eleff, S.M. ; Kiser, M.B. ; Dragwa, C.R. ; Sullivan, C.D. ; Grasso, L.; Zhang, L.Y. ; Messler, C.J. ; Zhou, T.; Kleeberger, S.R. ; Buetow, K.H. ; Levitt, R.C. (1997). Interleukin 9: a candidate gene for asthma, *Proc. Natl. Acad.Sci. U. S. A.* 94(24) 13175–13180.

Okada, Y.; Wu, D.; Trynka, G.; Raj, T.; Terao, C. ;Ikari, K. ;Kochi, Y. ;Ohmura, K. ;Suzuki, A. ;Yoshida, S.; Graham, R.R.; Manoharan,A.; Ortmann, W.; Bhangale, T. ; Denny, J. C. ; Carroll, R. J.; Eyler, A.E.; Greenberg, J.D.; Kremer, J. M.; and Plenge,R.M. (2013). Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*, 506(7488), 376–381.

Olivieri, I; D'Angelo, S.; Palazzi, C. and Padula ,A.(2014). Advances in the management of psoriatic arthritis. *Nat. Rev. Rheumatol.* ; 10: 531–42.

Ouyang, H. ; Shi, Y. ; Liu, Z.; Feng,Sh.; Li ,L.; Su ,N.; Lu ,Y. and Kong , Sh.(2013). "Increased Interleukin-9 and CD4+IL-9+ T cells in patients with Systemic lupus erythematosus," *Molecular Medicine Reports*, vol. 7, no. 3, pp. 1031–1037.

Perumal, N. B. and Kaplan, M. H.( 2011). Regulating IL9 transcription in T helper cells. *Trends. Immunol.*; 32:146.

Pilette, C. ; Ouadrhiri, Y.; J. van Snick, J.; Renauld, J. Ch.; Staquet, Ph.; Vaerman, j. p. and Sibille, Y.(2002). "IL-9 inhibits oxidative burst and TNF- $\alpha$  release in lipopoly saccharide-stimulated human monocytes Putto , A.(1987). Febrile exudativ tonsillitis : Viral or Streptococcal .J.Pediatr ., 80:6-11.

Rawlings, D. J.; Dai, X., and Buckner, J. H. (2015). The Role of PTP N22 Risk Variant in the Development of Autoimmunity: Finding Common Ground between Mouse and Human. *The Journal of Immunology*, 194(7), 2977–2984.

Raychaudhuri, S.K.; Saxena, A. and Raychaudhuri, S.P.(2015). Role of IL-17 in the pathogenesis of psoriatic arthritis and axial spondylo arthritis. *Clin. Rheumatol.*; 34:1019–23.

Renauld, J. (1995). *Cytokines: Interleukins and Their Receptors. Cancer Treatment and Research. Springer, Boston, MA. pp. 287–303.*

Roediger, B. and Weninger, W. (2015). Group 2 innate lymphoid cells in the regulation of immune responses, *Advances in Immunology, Elsevier*, pp. 111–154.

Rojas-Zuleta ,W.G. and Sanchez, E. (2017). "IL-9: Function, Sources, and Detection". *Methods in Molecular, Biology* , ; 1585: 21–35.

Roy, D.N. and Goswami, R.(2017). IL-9 signaling pathway: an update, *Th9 Cells, Met. Protocols*, 37–50.

Sachidandam, R.; Weissman, D.; Schmidt, S. C.; Kakol, J. M.; Stein, L. D.; Marth, G.; Sherry, S.; Mullikin, J. C.; Mortimore, B. J.; Willey, D. L.; Hunt, S. E.; Cole, C. G.; Coggill, P. C.; Rice, C. M.; Ning, Z.; Rogers, J.; Bentley, and Altshuler, D. (2001). A map of human genome sequence Working Group and a map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature*, 409: 928-933.

Shaikh N, Leonard E, Martin JM (September 2010). "Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis". *Pediatrics*. 126 (3): e557–64.

Scott, L. J.; Mohlke , K. L.; Bonnycastle, L.L.; Willer, C.J.; Duren, W,L.; Erdos, M.R.; Stringham, H.M.; Chines, P.S.; Jackson, A.U.; Prokunina-Olsson ,L.; Ding, Ch.-J.; Swift, A.J.; Narisu, N.; Hu, T.; Pruim, R.; Xiao, R.; Li, X.Y.; Collins, F.C.; Boehnke, M. (2007). A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science*, ;316:1341–5.

Shah,U.K. (2004). Tonsillitis and peritonsillar abscess. <http://www.emedicine.com>.

Shantinath, D. Sajane. (2015) Tonsillitis. *Int. J. Adv. Nur. Management* 3(4): Oct. - Dec.; Page 372-376.



Shulman,ST; Bisno, AL; Clegg, HW; Gerber, MA; Kaplan, EL; Lee, G; Martin, JM; Van Beneden, C (Sep 9, 2012). "Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America". *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 55 (10): e86–102.

*Singh, M. ; Singh, P. ; Juneja, P. K. ; Singh, S. ; Kaur, T. (2010). SNP interactions within APOE gene influence plasma lipids in postmenopausal osteoporosis". Rheumatology International. 31 (3): 421–3.*

Sismanopoulos, N. ; Delivanis, D. A.; Alysandratos, K. D. ; Angelidou, A. ; Vasiadi, M.; Therianou, A. and Theoharides, Th. C.(2012). "IL-9 induces VEGF secretion from human mast cells and IL-9/IL-9 receptor genes are overexpressed in atopic dermatitis," *PLoS. ONE*, vol. 7, no. 3,Article ID e33271.

Spellberg, B. and Edwards, J. E.( 2001). *Type 1/Type 2 Immunity in Infectious Diseases*. *CID*:32 (1 January),p76-102.

Stassen, M.; Arnold, M.; Hultner, L.; Muller, C.; Neudorfl, C.; Reineke, T. and Schmitt, E. (2000).Murine bone marrow-derived mast cells as potent producers of IL-9: costimulatory function of IL-10 and kit ligand in the presence of IL-1. *J. Immunol*. 164 (11) 5549–5555.

Stassen, M.; Schmitt, E. and Bopp, T.(2012). "From interleukin-9 to T helper 9 cells," *Annals of the New York Academy of Sciences*, vol.1247, no. 1, pp. 56–68.

Stassen, M.; Schmitt, E. and Bopp, T.(2012). "From interleukin-9 to T helper 9 cells," *Annals of the New York Academy of Sciences*, vol. 1247, no. 1, pp. 56–68.

Staudt, V.; Bothur, E.; Klein, M.; Linghau, K. ;Reuter, S. ;Grebe, N.; Gerlitzki, B. ;Hoffmann, M. ;Ulges, Al. ;Taube, Ch. ;Dehzad, N. ;Becker, M. ;Jtassen, M. ;Steinborn, A. ;Lohoff, M. ; Jchild, H. ;Schild, E. and Bopp, T.( 2010). Interferon-regulatory factor 4 is essential for the developmental program of T helper 9 cells. *Immunity*, 33:192.

Stenfors, L.E.; Fredriksen , F.; Raisanen, S. and Myklebust, S.(1997).Identification of *Streptococcus pyogenes* on tonsillar epithelium during infection . *Acta Otolaryngol . (Stockn)*,529(Suppl):212-214.

Temann, U. A. ; Ray, P. and R. A. Flavell, R. A. (2002). "Pulmonary overexpression of IL-9 induces Th2 cytokine expression, leading toimmune pathology, " *TJournal of Clinical Investigation*, vol. 109, no. 1, pp. 29–39.

Temann, U.-A. ; Geba, G. P.; Rankin, J. A. and Flavell, R. A.(1998). "Expression of interleukin 9 in the lungs of transgenic mice causes airway inflammation, mast cell hyperplasia, and bronchial hyperresponsiveness, " *The Journal of Experimental Medicine*, vol. 188, no. 7, pp. 1307–1320.

Testa, J. M. ; Montoya-Lerma, J. ; Cadena, H.; Oviedo, M. and Ready, P. D. (2002).Molecular identification of vectors of *Leishmania* in Colombia: Mitochondrial introgression in the *Lutzomyia townsendi* series. *Acta . Tropica* ,84: 205- 218.

*Thomas, P. E.; Klinger, R.; Furlong, L. I.; Hofmann-Apitius, M. and Friedrich, C. M. (2011). "Challenges in the association of human single-nucleotide polymorphism mentions with unique database identifiers". B.M.C. Bioinformatics, ; 12: S4.*

Turner, J. E.,Morrison, P. J., Wilhelm, C., Wilson, M., Ahlfors, H., Renauld, J. C. and Stockinger, B. (2013). IL-9–mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *Journal of Experimental Medicine*, 210(13), 2951-2965.

through TGF- $\beta$ ,”*The Journal of Immunology*, vol. 168, no. 8, pp. 4103–4111.

van de Sande, M.G. and Baeten, D.L.(2016). Immunopathology of synovitis: from histology to molecular pathways. *Rheumatology*, (Oxf) ; 55:599–606.

Van Praet, L.; Van den Bosch, F.E.; Jacques, P.; Carron, Ph. ;Jans, L.; Colman, R. ;Glorieus, E.; Peeters, H.; Mielants, H.; De Vos, M.; Cuvelier, C. and Elewaut, D.(2013). Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. *Ann. Rheum. Dis.* ; 72:414–7.

*Varela, M. A. and Amos, W. (2010). "Heterogeneous distribution of SNPs in the human genome: Microsatellites as predictors of nucleotide diversity and divergence". Genomics, ; 95 (3): 151–159.*

Wilhelm, C.; Hirota, K.; Stieglitz, B.; Van Snick, J. ;Tolaini, M. ;Lahl, K. ;Sparwasser, T. ;Helmby, H. ;Stockinger, B . ( 2011). An IL-9 fate reporter demonstrates the induction of an innate IL-9 response in lung inflammation. *Nat. Immunol.* ;12:1071.

Wong, C. K.; Lit, L. C. W. ; am, L. S. T; Li, E. K. M. ; Wong, P. T. Y. and Lam, C. W. K. (2008). “Hyper production of IL-23 and IL-17 in patients with systemic lupus erythematosus: implications forTh17-mediated inflammation in auto-immunity,” *Clinical Immunology*, vol. 127, no. 3, pp. 385–393.

Yamamoto, K.; Okada, Y.; Suzuki, A.; and Kochi, Y. (2015). Genetics of rheumatoid arthritis in Asia—present and future. *Nature Reviews Rheumatology*, 11(6), 375–379.

Zhang, Y.; Zhao, Y.; Li, J.; Wang, S.; Liu, Y.;L. Nie, L. and Cheng, L.(2016). Interleukin-9 promotes TNF- $\alpha$  and PGE2 release in human degenerated intervertebral disc tissues, *Spine* 41 (21) 1631–1640