

Conclusions and Recommendations

Conclusions

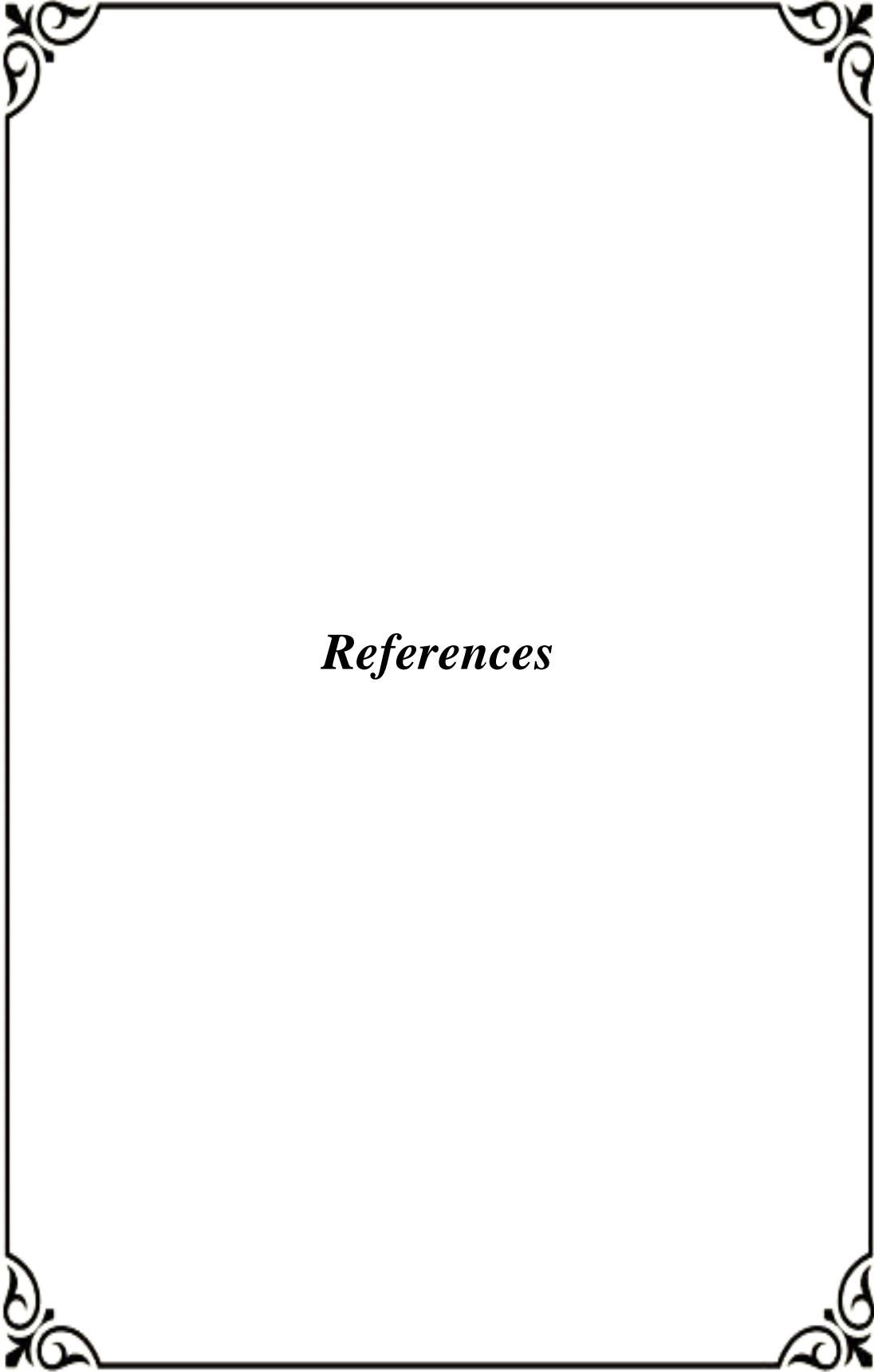
Based on the results of this study, the following conclusions can be drawn:

1. The present study provides an evidence that single nucleotide polymorphisms *rs320995* in the *cysteinyl leukotriene receptor 1* and *rs730012* in *leukotriene C4 synthase* are associated with asthma in an Iraqi population and that this effect is comparable in males and females.
2. Polymorphisms *rs320995* in the *cysteinyl leukotriene receptor 1* and *rs730012* in *leukotriene C4 synthase* are important risk factors for asthma and can be useful in understanding the pathways of asthma susceptibility.
3. The genotypes TC and CC of 927 T > *CYSLTR1 rs320995* significantly increase the risk of asthma and the C allele is a risk factor in asthma. Whereas, the only CC of 444A > *LTC4S rs730012* significantly increases the risk of asthma and the C allele is a risk factor in asthma.
4. Based on the association of 927 T > *CYSLTR1 rs320995* polymorphism with asthma, the susceptibility is different between males and females in relation to the effect of the genotype on the disease.

Recommendations

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1. Further investigation into the biological functions of the *Cysteinyl Leukotriene Receptor 1* gene and *Leukotriene C4 Synthase* in relation to asthma and its related phenotypes may provide new clues for asthma therapeutic and preventive strategies.
2. Multicentre studies with larger sample sizes are required in the future.
3. There is a necessity to send the results of these studies to Iraqi health institutions because of their great impact by adding new biomarkers that may contribute to the diagnosis and treatment of diseases.



References

References

- Abdulmutaleb, M. M. and Ahmed, I. H. (2023). 'Polymorphisms of 444A> C Leukotriene C4 Synthase (LTC4S) in Asthmatic Iraqi Patients'. *Central Asian Journal of Medical and Natural Science*, vol.4,pp. 659-666.
- Abrahamsson, T. R., Jakobsson, H. E., Andersson, A. F., Björkstén, B., Engstrand, L. and Jenmalm, M. C. (2012). 'Low diversity of the gut microbiota in infants with atopic eczema'. *Journal of allergy and clinical immunology*, vol.129,pp. 434-440.
- Ago, H., Kanaoka, Y., Irikura, D., Lam, B. K., Shimamura, T., Austen, K. F. and Miyano, M. (2007). 'Crystal structure of a human membrane protein involved in cysteinyl leukotriene biosynthesis'. *Nature*, vol.448,pp. 609-12.
- Agrawal, S., Pearce, N. and Ebrahim, S. (2013). 'Prevalence and risk factors for self-reported asthma in an adult Indian population: a cross-sectional survey'. *The international journal of tuberculosis and lung disease*, vol.17,pp. 275-282.
- Al-Alwan, A., Bates, J. H. T., Chapman, D. G., Kaminsky, D. A., Desarno, M. J., Irvin, C. G. and Dixon, A. E. (2014). 'The nonallergic asthma of obesity. A matter of distal lung compliance'. *American journal of respiratory and critical care medicine*, vol.189,pp. 1494-1502.
- Al-Kubaisy, W., Ali, S. H. and Al-Thamiri, D. (2005). 'Risk factors for asthma among primary school children in Baghdad, Iraq'. *Saudi Med J*, vol.26,pp. 460-6.
- Al-Muhsen, S., Johnson, J. R. and Hamid, Q. (2011). 'Remodeling in asthma'. *J Allergy Clin Immunol*, vol.128,pp. 451-62; quiz 463-4.
- Al-Thamiri, D., Al-Kubaisy, W. and Ali, S. H. (2005). 'Asthma prevalence and severity among primary-school children in Baghdad'. *East Mediterr Health J*, vol.11,pp. 79-86.
- Alcalá, S. E., Benton, A. S., Watson, A. M., Kureshi, S., Reeves, E. M., Damsker, J., Wang, Z., Nagaraju, K., Anderson, J., Williams, A. M., Lee, A. J., Hayes, K., Rose, M. C., Hoffman, E. P. and Freishtat, R. J. (2014). 'Mitotic asynchrony induces transforming growth factor- β 1 secretion from airway epithelium'. *Am J Respir Cell Mol Biol*, vol.51,pp. 363-9.
- Allen, M., Heinzmann, A., Noguchi, E., Abecasis, G., Broxholme, J., Ponting, C. P., Bhattacharyya, S., Tinsley, J., Zhang, Y. and Holt, R. (2003). 'Positional cloning of a novel gene influencing asthma from chromosome 2q14'. *Nature genetics*, vol.35,pp. 258-263.
- Alsamarai, A. M., Salih, M. A., AlObaidy, A. H., Alwan, A. M. and Abdulaziz, Z. H. (2009). 'Risk factors for asthma in Iraqi children'. *Journal of Rural and Tropical Public Health*, vol.8,pp. 45-52.

References

- Amelink, M., De Groot, J. C., De Nijs, S. B., Lutter, R., Zwinderman, A. H., Sterk, P. J., Ten Brinke, A. & Bel, E. H. 2013. 'Severe adult-onset asthma: A distinct phenotype'. *J Allergy Clin Immunol*, vol.132,pp. 336-41.
- Antó, J. M., Pearce, N., Douwes, J., Garcia-Aymerich, J., Pembrey, L., Richiardi, L. & Sunyer, J. 2023. 'Why has epidemiology not (yet) succeeded in identifying the origin of the asthma epidemic?'. *Int J Epidemiol*, vol.52,pp. 974-983.
- Arriba-Méndez, S., Sanz, C., Isidoro-García, M., Pascual, M., Avila, C., Dávila, I. & Lorente, F. 2008. 'Analysis of 927T> C CYSLTR1 and -444A> C LTC4S polymorphisms in children with asthma'. *Allergologia et immunopathologia*, vol.36,pp. 259-263.
- Arriba-Mendez, S., Sanz, C., Isidoro-Garcia, M., Davild, I., Laffond, E., Horeno, E., Avila, C. & Lorente, F. 2006. '927T> C polymorphism of the cysteinyl-leukotriene type-1 receptor (CYSLTR1) gene in children with asthma and atopic dermatitis'. *Pediatric allergy and immunology*, vol.17,pp. 323-328.
- Arrieta, M. C., Stiemsma, L. T., Dimitriu, P. A., Thorson, L., Russell, S., Yurist-Doutsch, S., Kuzeljevic, B., Gold, M. J., Britton, H. M. & Lefebvre, D. L. 2015. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 7: 307ra152.
- Arshad, S. H., Raza, A., Lau, L., Bawakid, K., Karmaus, W., Zhang, H., Ewart, S., Patil, V., Roberts, G. & Kurukulaaratchy, R. 2014. 'Pathophysiological characterization of asthma transitions across adolescence'. *Respir Res*, vol.15,pp. 153.
- Asano, K., Nakade, S., Shiomi, T., Nakajima, T., Suzuki, Y., Fukunaga, K., Oguma, T., Sayama, K., Fujita, H. & Tanigawara, Y. 2009. 'Impact of pharmacokinetics and pharmacogenetics on the efficacy of pranlukast in Japanese asthmatics'. *Respirology*, vol.14,pp. 822-827.
- Asano, K., Shiomi, T., Hasegawa, N., Nakamura, H., Kudo, H., Matsuzaki, T., Hakuno, H., Fukunaga, K., Suzuki, Y. & Kanazawa, M. 2002. 'Leukotriene C4 synthase gene A (-444) C polymorphism and clinical response to a CYS-LT1 antagonist, pranlukast, in Japanese patients with moderate asthma'. *Pharmacogenetics and Genomics*, vol.12,pp. 565-570.
- Austen, K. F., Maekawa, A., Kanaoka, Y. & Boyce, J. A. 2009. 'The leukotriene E4 puzzle: finding the missing pieces and revealing the pathobiologic implications'. *J Allergy Clin Immunol*, vol.124,pp. 406-14; quiz 415-6.
- Bacharier, L. B., Cohen, R., Schweiger, T., Yin-Declue, H., Christie, C., Zheng, J., Schechtman, K. B., Strunk, R. C. & Castro, M. 2012. 'Determinants of asthma after severe respiratory syncytial virus bronchiolitis'. *Journal of Allergy and Clinical Immunology*, vol.130,pp. 91-100.
- Bäck, M. 2002. 'Functional characteristics of cysteinyl-leukotriene receptor subtypes'. *Life Sci*, vol.71,pp. 611-22.

References

- Baffi, C. W., Wood, L., Winnica, D., Strollo Jr, P. J., Gladwin, M. T., Que, L. G. & Holguin, F. 2016. 'Metabolic syndrome and the lung'. *Chest*, vol.149,pp. 1525-1534.
- Balas, L., Rise, P., Gandrath, D., Rovati, G., Bolego, C., Stellari, F., Trenti, A., Buccellati, C., Durand, T. & Sala, A. 2019. 'Rapid metabolism of protectin D1 by β -oxidation of its polar head chain'. *Journal of medicinal chemistry*, vol.62,pp. 9961-9975.
- Balzar, S., Fajt, M. L., Comhair, S. A., Erzurum, S. C., Bleeker, E., Busse, W. W., Castro, M., Gaston, B., Israel, E., Schwartz, L. B., Curran-Everett, D., Moore, C. G. & Wenzel, S. E. 2011. 'Mast cell phenotype, location, and activation in severe asthma. Data from the Severe Asthma Research Program'. *Am J Respir Crit Care Med*, vol.183,pp. 299-309.
- Barbers, R. G., Papanikolaou, I. C., Koss, M. N., Patel, A., Katagihara, E., Arenas, M., Chan, K., Azen, C. G. & Sharma, O. P. 2012. 'Near fatal asthma: clinical and airway biopsy characteristics'. *Pulm Med*, vol.2012,pp. 829608.
- Barnig, C., Cernadas, M., Dutile, S., Liu, X., Perrella, M. A., Kazani, S., Wechsler, M. E., Israel, E. & Levy, B. D. 2013. 'Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma'. *Sci Transl Med*, vol.5,pp. 174ra26.
- Baur, X. & Bakehe, P. 2014. 'Allergens causing occupational asthma: an evidence-based evaluation of the literature'. *International Archives of Occupational and Environmental Health*, vol.87,pp. 339-363.
- Berghea, E. C., Popa, L. O., Dutescu, M. I., Meirosu, M., Farcasanu, I. C., Berghea, F., Bara, C. & Popa, O. M. 2015. 'Association of leukotriene C4 synthase A-444C polymorphism with asthma and asthma phenotypes in Romanian population'. *Maedica*, vol.10,pp. 91.
- Bernstein, J. A., Alexis, N., Barnes, C., Bernstein, I. L., Nel, A., Peden, D., Diaz-Sanchez, D., Tarlo, S. M. & Williams, P. B. 2004. 'Health effects of air pollution'. *Journal of allergy and clinical immunology*, vol.114,pp. 1116-1123.
- Bijanzadeh, M., Ramachandra, N. B., Mahesh, P. A., Savitha Mysore, R., Kumar, P., Manjunath, B. S. & Jayaraj, B. S. 2010. 'Association of IL-4 and ADAM33 gene polymorphisms with asthma in an Indian population'. *Lung*, vol.188,pp. 415-422.
- Birbian, N., Singh, J. & Jindal, S. K. 2013. 'Protective role of IL-18 -137G/C polymorphism in a North Indian population with asthma: a pilot study'. *Cytokine*, vol.61,pp. 188-93.
- Biscardi, S., Lorrot, M., Marc, E., Moulin, F., Boutonnat-Faucher, B., Heilbronner, C., Iniguez, J.-L., Chaussain, M., Nicand, E. & Raymond, J. 2004. 'Mycoplasma pneumoniae and asthma in children'. *J Clinical infectious diseases*, vol.38,pp. 1341-1346.

References

- Bisgaard, H. 2001. 'Leukotriene modifiers in pediatric asthma management'. *Pediatrics*, vol.107,pp. 381-390.
- Bjermer, L. 2014. 'The role of small airway disease in asthma'. *Curr Opin Pulm Med*, vol.20,pp. 23-30.
- Bønnelykke, K., Vissing, N. H., Sevelsted, A., Johnston, S. L. & Bisgaard, H. 2015. 'Association between respiratory infections in early life and later asthma is independent of virus type'. *Journal of Allergy Clinical Immunology*, vol.136,pp. 81-86. e4.
- Boucherat, O., Boczkowski, J., Jeannotte, L. & Delacourt, C. 2013. 'Cellular and molecular mechanisms of goblet cell metaplasia in the respiratory airways'. *Exp Lung Res*, vol.39,pp. 207-16.
- Bousquet, J., Bousquet, P. J., Godard, P. & Daures, J. P. 2005. 'The public health implications of asthma'. *Bull World Health Organ*, vol.83,pp. 548-54.
- Bousquet, J., Gern, J. E., Martinez, F. D., Anto, J. M., Johnson, C. C., Holt, P. G., Lemanske Jr, R. F., Le Souëf, P. N., Tepper, R. S. & Von Mutius, E. R. 2014. 'Birth cohorts in asthma and allergic diseases: report of a NIAID/NHLBI/MeDALL joint workshop'. *Journal of Allergy Clinical Immunology*, vol.133,pp. 1535-1546.
- Bouvier, M. 2001. 'Oligomerization of G-protein-coupled transmitter receptors'. *Nat Rev Neurosci*, vol.2,pp. 274-86.
- Boyce, J. A. 2008. 'Eicosanoids in asthma, allergic inflammation, and host defense'. *Curr Mol Med*, vol.8,pp. 335-49.
- Bradding, P., Walls, A. F. & Holgate, S. T. 2006. 'The role of the mast cell in the pathophysiology of asthma'. *J Allergy Clin Immunol*, vol.117,pp. 1277-84.
- Brightling, C. E., Bradding, P., Symon, F. A., Holgate, S. T., Wardlaw, A. J. & Pavord, I. D. 2002. 'Mast-cell infiltration of airway smooth muscle in asthma'. *N Engl J Med*, vol.346,pp. 1699-705.
- Bunyavanich, S. & Schadt, E. E. 2015. 'Systems biology of asthma and allergic diseases: a multiscale approach'. *Journal of Allergy Clinical Immunology*, vol.135,pp. 31-42.
- Burke, H., Leonardi-Bee, J., Hashim, A., Pine-Abata, H., Chen, Y., Cook, D. G., Britton, J. R. & McKeever, T. M. 2012. 'Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis'. *Pediatrics*, vol.129,pp. 735-744.
- Butland, B. K. & Strachan, D. P. 2007. 'Asthma onset and relapse in adult life: the British 1958 birth cohort study'. *Ann Allergy Asthma Immunol*, vol.98,pp. 337-43.
- Cai, C., Zhou, M. X., Li, Y. P. & Chen, C. S. 2011. 'Association of leukotriene gene polymorphisms with response to antileukotriene treatment in patients with asthma'. *Zhonghua jie he he hu xi za zhi= Zhonghua Jiehe*

References

- he Huxi Zazhi= Chinese Journal of Tuberculosis and Respiratory Diseases, vol.34,pp. 362-366.
- Cankaya, A. & Shankar, R. 2021. Phenome to Genome—Application of GWAS to Asthmatic Lung Biomarker Gene Variants. *Advances in Computer Vision and Computational Biology: Proceedings from IPCV'20, HIMS'20, BIOCOMP'20, and BIOENG'20*. Springer.
- Capra, V. 2004. 'Molecular and functional aspects of human cysteinyl leukotriene receptors'. *Pharmacol Res*, vol.50,pp. 1-11.
- Capra, V., Thompson, M. D., Sala, A., Cole, D. E., Folco, G. & Rovati, G. E. 2007. 'Cysteinyl-leukotrienes and their receptors in asthma and other inflammatory diseases: critical update and emerging trends'. *Med Res Rev*, vol.27,pp. 469-527.
- Caramori, G., Adcock, I. M., Barnes, P. J. & Chung, K. F. 2019. 'Drugs for the Treatment of Airway Disease'. *Nijkamp and Parnham's Principles of Immunopharmacology*,pp. 425-474.
- Cardet, J. C., Ash, S., Kusa, T., Camargo, C. A. & Israel, E. 2016. 'Insulin resistance modifies the association between obesity and current asthma in adults'. *European Respiratory Journal*, vol.48,pp. 403-410.
- Carion, T. W., Wang, Y., Stammersky, A., Ebrahim, A. S. & Berger, E. A. 2022. 'A dual role for cysteinyl leukotriene receptors in the pathogenesis of corneal infection'. *The Journal of Immunology*, vol.208,pp. 2331-2342.
- Chang, C. & Sun, Y. 2022. 'Global Strategy for Asthma Management and Prevention: Interpretation of the Updates in 2022'. *Chinese General Practice*, vol.25,pp. 4355.
- Chesné, J., Braza, F., Mahay, G., Brouard, S., Aronica, M. & Magnan, A. 2014. 'IL-17 in severe asthma. Where do we stand?'. *Am J Respir Crit Care Med*, vol.190,pp. 1094-101.
- Choi, J.-H., Park, H.-S., Oh, H.-B., Lee, J.-H., Suh, Y.-J., Park, C.-S. & Shin, H.-D. 2004. 'Leukotriene-related gene polymorphisms in ASA-intolerant asthma: an association with a haplotype of 5-lipoxygenase'. *Human genetics*, vol.114,pp. 337-344.
- Colazzo, F., Gelosa, P., Tremoli, E., Sironi, L. & Castiglioni, L. 2017. 'Role of the Cysteinyl Leukotrienes in the Pathogenesis and Progression of Cardiovascular Diseases'. *Mediators Inflamm*, vol.2017,pp. 2432958.
- Contopoulos-Ioannidis, D. G., Kouri, I. N. & Ioannidis, J. P. 2007. 'Genetic predisposition to asthma and atopy'. *Respiration*, vol.74,pp. 8-12.
- Cookson, W. O. & Moffatt, M. F. 2000. 'Genetics of asthma and allergic disease'. *Human molecular genetics*, vol.9,pp. 2359-2364.
- Croisant, S. 2014. 'Epidemiology of asthma: prevalence and burden of disease'. *Heterogeneity in asthma*,pp. 17-29.

References

- Cruz, A. A. 2007. *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach*, World Health Organization.
- Cui, L., Jia, J., Ma, C.-F., Li, S.-Y., Wang, Y.-P., Guo, X.-M., Li, Q., Yu, H.-B., Liu, W.-H. & Gao, L.-B. 2012. 'IL-13 polymorphisms contribute to the risk of asthma: a meta-analysis'. *Clinical biochemistry*, vol.45,pp. 285-288.
- D'amato, G., Vitale, C., De Martino, A., Viegi, G., Lanza, M., Molino, A. & D'amato, M. 2015. Effects On Asthma and Respiratory Allergy of Climate Change and Air Pollution. *Multidisciplinary respiratory medicine*, 10, 39.
- Dabuo, B., Xorlali, N., Amoliga, N. T., Atibodu, Z. K., Newman, P. M., Mohammed, A., Ali, R. A. & Abudu, A. 2023. 'Aspergillus and Aspergillosis in People with Chronic Diseases'.
- Davoodi, P., Mahesh, P. A., Holla, A. D. & Ramachandra, N. B. 2015. 'A preliminary study on the association of single nucleotide polymorphisms of interleukin 4 (IL4), IL13, IL4 receptor alpha (IL4Ra) & Toll-like receptor 4 (TLR4) genes with asthma in Indian adults'. *The Indian journal of medical research*, vol.142,pp. 675.
- Diamant, Z., Gauvreau, G. M., Cockcroft, D. W., Boulet, L. P., Sterk, P. J., De Jongh, F. H., Dahlén, B. & O'byrne, P. M. 2013. 'Inhaled allergen bronchoprovocation tests'. *J Allergy Clin Immunol*, vol.132,pp. 1045-1055.e6.
- Dinakar, C. & O'connor, G. T. 2016. 'The health effects of electronic cigarettes'. *New England Journal of Medicine*, vol.375,pp. 1372-1381.
- Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N. & Knight, R. 2010. 'Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns'. *Proceedings of the National Academy of Sciences*, vol.107,pp. 11971-11975.
- Dumas, O., Laurent, E., Bousquet, J., Metspalu, A., Milani, L., Kauffmann, F. & Le Moual, N. 2014. 'Occupational irritants and asthma: an Estonian cross-sectional study of 34,000 adults'. *Eur Respir J*, vol.44,pp. 647-56.
- Dunn, R. M., Busse, P. J. & Wechsler, M. E. 2018. 'Asthma in the elderly and late-onset adult asthma'. *Allergy*, vol.73,pp. 284-294.
- Duroudier, N. P., Sayers, I., Castagna, C. C., Fenech, A. G., Halapi, E., Swan, C. & Hall, I. P. 2007. 'Functional polymorphism and differential regulation of CYSLTR1 transcription in human airway smooth muscle and monocytes'. *Cell biochemistry and biophysics*, vol.47,pp. 119-129.
- Edwards, M. R., Bartlett, N. W., Hussell, T., Openshaw, P. & Johnston, S. L. 2012. 'The microbiology of asthma'. *Nature Reviews Microbiology*, vol.10,pp. 459-471.

References

- Ege, M. J., Mayer, M., Normand, A.-C., Genuneit, J., Cookson, W. O. C. M., Braun-Fahrlander, C., Heederik, D., Piarroux, R. & Von Mutius, E. 2011. 'Exposure to environmental microorganisms and childhood asthma'. *New England Journal of Medicine*, vol.364,pp. 701-709.
- Evans, J. F. 2002. 'Cysteinyl leukotriene receptors'. *Prostaglandins & other lipid mediators*, vol.68,pp. 587-597.
- Evans, J. F. 2003. 'The cysteinyl leukotriene receptors'. *Prostaglandins Leukot Essent Fatty Acids*, vol.69,pp. 117-22.
- Fahy, J. V. 2015. 'Type 2 inflammation in asthma--present in most, absent in many'. *Nat Rev Immunol*, vol.15,pp. 57-65.
- Fajt, M. L. & Wenzel, S. E. 2013. 'Mast cells, their subtypes, and relation to asthma phenotypes'. *Ann Am Thorac Soc*, vol.10 Suppl,pp. S158-64.
- Ferreira, M. A., Vonk, J. M., Baurecht, H., Marenholz, I., Tian, C., Hoffman, J. D., Helmer, Q., Tillander, A., Ullemar, V. & Van Dongen, J. 2017. 'Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology'. *Nature genetics*, vol.49,pp. 1752-1757.
- Figueroa, D. J., Breyer, R. M., Defoe, S. K., Kargman, S., Daugherty, B. L., Waldburger, K., Liu, Q., Clements, M., Zeng, Z., O'neill, G. P., Jones, T. R., Lynch, K. R., Austin, C. P. & Evans, J. F. 2001. 'Expression of the cysteinyl leukotriene 1 receptor in normal human lung and peripheral blood leukocytes'. *Am J Respir Crit Care Med*, vol.163,pp. 226-33.
- Finlay, B. B. & Finlay, J. M. 2019. *The Whole-Body Microbiome: How to Harness Microbes—Inside and Out—for Lifelong Health*, The Experiment.
- Forno, E., Han, Y.-Y., Muzumdar, R. H. & Celedón, J. C. 2015. 'Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma'. *Journal of Allergy and Clinical Immunology*, vol.136,pp. 304-311.
- Freidin, M. B. & Puzyrev, V. P. 2010. 'Syntropic genes of allergic diseases'. *Russian journal of genetics*, vol.46,pp. 224-229.
- Fu, L., Freishtat, R. J., Gordish-Dressman, H., Teach, S. J., Resca, L., Hoffman, E. P. & Wang, Z. 2014. 'Natural progression of childhood asthma symptoms and strong influence of sex and puberty'. *Ann Am Thorac Soc*, vol.11,pp. 939-44.
- Funk, C. D. 2001. 'Prostaglandins and leukotrienes: advances in eicosanoid biology'. *Science*, vol.294,pp. 1871-5.
- Fuseini, H. & Newcomb, D. C. 2017. 'Mechanisms Driving Gender Differences in Asthma'. *Curr Allergy Asthma Rep*, vol.17,pp. 19.
- Gaga, M., Papageorgiou, N., Yiourgioti, G., Karydi, P., Liapikou, A., Bitsakou, H., Zervas, E., Koulouris, N. G., Holgate, S. T. & Group, E. S. 2005. 'Risk factors and characteristics associated with severe and difficult to treat asthma phenotype: an analysis of the ENFUMOSA group of patients

References

- based on the ECRHS questionnaire'. *Clinical & Experimental Allergy*, vol.35,pp. 954-959.
- García, E. C. 2020. 'Anti-IL-4,-IL-13 and-IgE vaccination for the treatment of allergic diseases'.
- Genuneit, J. 2014. 'Sex-specific development of asthma differs between farm and nonfarm children: a cohort study'. *American journal of respiratory and critical care medicine*, vol.190,pp. 588-590.
- Gern, J. E. 2010. 'The urban environment and childhood asthma study'. *Journal of Allergy and Clinical Immunology*, vol.125,pp. 545-549.
- Ghosh, A., Coakley, R. C., Mascenik, T., Rowell, T. R., Davis, E. S., Rogers, K., Webster, M. J., Dang, H., Herring, L. E. & Sassano, M. F. 2018. 'Chronic e-cigarette exposure alters the human bronchial epithelial proteome'. *American journal of respiratory and critical care medicine*, vol.198,pp. 67-76.
- Gibson, P. G., McDonald, V. M. & Marks, G. B. 2010. 'Asthma in older adults'. *Lancet*, vol.376,pp. 803-13.
- Gilmour, M. I., Jaakkola, M. S., London, S. J., Nel, A. E. & Rogers, C. A. 2006. 'How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma'. *Environmental health perspectives*, vol.114,pp. 627-633.
- Godtfredsen, N. S., Lange, P., Prescott, E., Osler, M. & Vestbo, J. 2001. 'Changes in smoking habits and risk of asthma: a longitudinal population based study'. *European respiratory journal*, vol.18,pp. 549-554.
- Graff, S., Bricmont, N., Moermans, C., Henket, M., Paulus, V., Guissard, F., Louis, R. & Schleich, F. 2020. 'Clinical and biological factors associated with irreversible airway obstruction in adult asthma'. *Respiratory medicine*, vol.175,pp. 106202.
- Granell, R., Henderson, A. J., Timpson, N., Pourcain, B. S., Kemp, J. P., Ring, S. M., Ho, K., Montgomery, S. B., Dermitzakis, E. T. & Evans, D. M. 2013. 'Examination of the relationship between variation at 17q21 and childhood wheeze phenotypes'. *J Journal of allergy clinical immunology*, vol.131,pp. 685-694.
- Gray-Ffrench, M., Fernandes, R. M., Sinha, I. P. & Abrams, E. M. 2022. 'Allergen Management in Children with Type 2-High Asthma'. *Journal of Asthma and Allergy*,pp. 381-394.
- Green, M. R. & Sambrook, J. 2019. 'Agarose Gel Electrophoresis'. *Cold Spring Harb Protoc*, vol.2019.
- Gupta, A., Chakraborty, S. & Agrawal, A. 2020. Molecular and genomic basis of bronchial asthma. *Clinical Molecular Medicine*. Elsevier.
- Haeggstrom, J. Z. & Funk, C. D. 2011. 'Lipoxygenase and leukotriene pathways: biochemistry, biology, and roles in disease'. *Chemical reviews*, vol.111,pp. 5866-5898.

References

- Halwani, R., Vazquez-Tello, A., Sumi, Y., Pureza, M. A., Bahammam, A., Al-Jahdali, H., Soussi-Gounni, A., Mahboub, B., Al-Muhsen, S. & Hamid, Q. 2013. 'Eosinophils induce airway smooth muscle cell proliferation'. *Journal of clinical immunology*, vol.33,pp. 595-604.
- Hammad, H. & Lambrecht, B. N. 2021. 'The basic immunology of asthma'. *Cell*, vol.184,pp. 1469-1485.
- Hao, L., Sayers, I., Cakebread, J. A., Barton, S. J., Beghé, B., Holgate, S. T., Sampson, A. P. & Holloway, J. W. 2006. 'The cysteinyl-leukotriene type 1 receptor polymorphism 927T/C is associated with atopy severity but not with asthma'. *Clinical & Experimental Allergy*, vol.36,pp. 735-741.
- Hardin, M., Cho, M., McDonald, M.-L., Beaty, T., Ramsdell, J., Bhatt, S., Van Beek, E. J. R., Make, B. J., Crapo, J. D. & Silverman, E. K. 2014. 'The clinical and genetic features of COPD-asthma overlap syndrome'. *European Respiratory Journal*, vol.44,pp. 341-350.
- Harkness, L. M., Ashton, A. W. & Burgess, J. K. 2015. 'Asthma is not only an airway disease, but also a vascular disease'. *Pharmacol Ther*, vol.148,pp. 17-33.
- Hedi, H. & Norbert, G. 2004. '5-Lipoxygenase pathway, dendritic cells, and adaptive immunity'. *BioMed Research International*, vol.2004,pp. 99-105.
- Heise, C. E., O'dowd, B. F., Figueroa, D. J., Sawyer, N., Nguyen, T., Im, D. S., Stocco, R., Bellefeuille, J. N., Abramovitz, M., Cheng, R., Williams, D. L., Jr., Zeng, Z., Liu, Q., Ma, L., Clements, M. K., Coulombe, N., Liu, Y., Austin, C. P., George, S. R., O'neill, G. P., Metters, K. M., Lynch, K. R. & Evans, J. F. 2000. 'Characterization of the human cysteinyl leukotriene 2 receptor'. *J Biol Chem*, vol.275,pp. 30531-6.
- Hernandez, M. L., Dhingra, R., Burbank, A. J., Todorich, K., Loughlin, C. E., Frye, M., Duncan, K., Robinette, C., Mills, K. & Devlin, R. B. 2018. 'Low-level ozone has both respiratory and systemic effects in African American adolescents with asthma despite asthma controller therapy'. *Journal of Allergy and Clinical Immunology*, vol.142,pp. 1974-1977.
- Holgate, S. T. 2012. 'Innate and adaptive immune responses in asthma'. *Nat Med*, vol.18,pp. 673-83.
- Holgate, S. T., Holloway, J., Wilson, S., Buccieri, F., Puddicombe, S. & Davies, D. E. 2004. 'Epithelial-mesenchymal communication in the pathogenesis of chronic asthma'. *Proc Am Thorac Soc*, vol.1,pp. 93-8.
- Holgate, S. T., Wenzel, S., Postma, D. S., Weiss, S. T., Renz, H. & Sly, P. D. 2015. 'Asthma'. *Nat Rev Dis Primers*, vol.1,pp. 15025.
- Hong, X., Zhou, H., Tsai, H. J., Wang, X., Liu, X., Wang, B., Xu, X. & Xu, X. 2009. 'Cysteinyl leukotriene receptor 1 gene variation and risk of asthma'. *European Respiratory Journal*, vol.33,pp. 42.

References

- Horioka-Duplix, M. 2022. 'Biased Constitutive Activity in the Uveal Melanoma Oncogene CYSLTR2 is Unique in CYSLTR2 Germline and Pan-Cancer Human Variome'.
- Hsieh, F. H., Lam, B. K., Penrose, J. F., Austen, K. F. & Boyce, J. A. 2001. 'T Helper Cell Type 2 Cytokines Coordinate Regulate Immunoglobulin E-dependent Cysteinyl Leukotriene Production by Human Cord Blood-derived Mast Cells: Profound Induction of Leukotriene C4 Synthase Expression by Interleukin 4'. *The Journal of Experimental Medicine*, vol.193,pp. 123-134.
- Hui, Y. & Funk, C. D. 2002. 'Cysteinyl leukotriene receptors'. *Biochemical pharmacology*, vol.64,pp. 1549-1557.
- Hui, Y., Yang, G., Galczenksi, H., Figueroa, D. J., Austin, C. P., Copeland, N. G., Gilbert, D. J., Jenkins, N. A. & Funk, C. D. 2001. 'The murine cysteinyl leukotriene 2 (CysLT2) receptor. cDNA and genomic cloning, alternative splicing, and in vitro characterization'. *J Biol Chem*, vol.276,pp. 47489-95.
- Im, D. S. 2009. 'New intercellular lipid mediators and their GPCRs: an update'. *Prostaglandins Other Lipid Mediat*, vol.89,pp. 53-6.
- Jackman, J. K., Stockwell, A., Choy, D. F., Xie, M. M., Lu, P., Jia, G., Li, H., Abbas, A. R., Bronson, P. G. & Lin, W.-Y. 2022. 'Genome-wide association study identifies kallikrein 5 in type 2 inflammation-low asthma'. *Journal of Allergy and Clinical Immunology*, vol.150,pp. 972-978.
- Jackson, D. J., Hartert, T. V., Martinez, F. D., Weiss, S. T. & Fahy, J. V. 2014. 'Asthma: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases'. *Ann Am Thorac Soc*, vol.11 Suppl 3,pp. S139-45.
- Jain, V. V., Perkins, D. L. & Finn, P. W. 2008. 'Costimulation and allergic responses: immune and bioinformatic analyses'. *Pharmacol Ther*, vol.117,pp. 385-92.
- Jakobsson, P.-J., Morgenstern, R., Mancini, J., Ford-Hutchinson, A. & Persson, B. 1999. 'Common structural features of MAPEG—a widespread superfamily of membrane associated proteins with highly divergent functions in eicosanoid and glutathione metabolism'. *Protein Science*, vol.8,pp. 689-692.
- Jakobsson, P.-J., Morgenstern, R., Mancini, J., Ford-Hutchinson, A. & Persson, B. 2000. 'Membrane-associated proteins in eicosanoid and glutathione metabolism (MAPEG) a widespread protein superfamily'. *American journal of respiratory and critical care medicine*, vol.161,pp. S20-S24.
- Jarjour, N. N., Erzurum, S. C., Bleeker, E. R., Calhoun, W. J., Castro, M., Comhair, S. a. A., Chung, K. F., Curran-Everett, D., Dweik, R. A. & Fain, S. B. 2012. 'Severe asthma: lessons learned from the national heart, lung,

References

- and blood institute severe asthma research program'. *American journal of respiratory and critical care medicine*, vol.185,pp. 356-362.
- Jayalatha, A. K. S., Hesse, L., Ketelaar, M. E., Koppelman, G. H. & Nawijn, M. C. 2021. 'The central role of IL-33/IL-1RL1 pathway in asthma: From pathogenesis to intervention'. *Pharmacology & therapeutics*, vol.225,pp. 107847.
- Jin, Z., Pan, Z., Wang, Z., Kong, L., Zhong, M., Yang, Y., Dou, Y. & Sun, J. L. 2022. 'CYSLTR1 rs320995 (T927C) and GSDMB rs7216389 (G1199A) Gene Polymorphisms in Asthma and Allergic Rhinitis: A Proof-of-Concept Study'. *J Asthma Allergy*, vol.15,pp. 1105-1113.
- Jindal, S. K. 2007. 'Bronchial asthma: the Indian scene'. *Current opinion in pulmonary medicine*, vol.13,pp. 8-12.
- Jindal, S. K., Aggarwal, A. N., Gupta, D., Agarwal, R., Kumar, R., Kaur, T., Chaudhry, K. & Shah, B. 2012. 'Indian study on epidemiology of asthma, respiratory symptoms and chronic bronchitis in adults (INSEARCH)'. *The international journal of tuberculosis and lung disease*, vol.16,pp. 1270-1277.
- Johnson, J. R., Folestad, E., Rowley, J. E., Noll, E. M., Walker, S. A., Lloyd, C. M., Rankin, S. M., Pietras, K., Eriksson, U. & Fuxe, J. 2015. 'Pericytes contribute to airway remodeling in a mouse model of chronic allergic asthma'. *Am J Physiol Lung Cell Mol Physiol*, vol.308,pp. L658-71.
- Kalayci, O., Miligkos, M., Beltrán, C. F. P., El-Sayed, Z. A., Gómez, R. M., Hossny, E., Le Souef, P., Nieto, A., Phipatanakul, W. & Pitrez, P. M. 2022. 'The role of environmental allergen control in the management of asthma'. *World Allergy Organization Journal*, vol.15,pp. 100634.
- Kaliner, M. & Lemanske, R. 1992. 'Rhinitis and asthma'. *JAMA*, vol.268,pp. 2807-2829.
- Kanemitsu, Y., Ito, I., Niimi, A., Izuhara, K., Ohta, S., Ono, J., Iwata, T., Matsumoto, H. & Mishima, M. 2014. 'Osteopontin and periostin are associated with a 20-year decline of pulmonary function in patients with asthma'. *Am J Respir Crit Care Med*, vol.190,pp. 472-4.
- Kang, M.-J., Kwon, J.-W., Kim, B.-J., Yu, J., Choi, W.-A., Shin, Y.-J. & Hong, S.-J. 2011. 'Polymorphisms of the PTGDR and LTC4S influence responsiveness to leukotriene receptor antagonists in Korean children with asthma'. *Journal of human genetics*, vol.56,pp. 284-289.
- Kay, A. B. 2006. 'The role of T lymphocytes in asthma'. *Chem Immunol Allergy*, vol.91,pp. 59-75.
- Kazani, S., Sadeh, J., Bunga, S., Wechsler, M. E. & Israel, E. 2011. 'Cysteinyl leukotriene antagonism inhibits bronchoconstriction in response to hypertonic saline inhalation in asthma'. *Respiratory medicine*, vol.105,pp. 667-673.

References

- Kim, H. Y., Dekruyff, R. H. & Umetsu, D. T. 2010. 'The many paths to asthma: phenotype shaped by innate and adaptive immunity'. *Nat Immunol*, vol.11,pp. 577-84.
- Kim, K.-H., Jahan, S. A. & Kabir, E. 2013. 'A review on human health perspective of air pollution with respect to allergies and asthma'. *Environment international*, vol.59,pp. 41-52.
- Kim, S.-H., Yang, E.-M., Park, H.-J., Ye, Y.-M., Lee, H.-Y. & Park, H.-S. 2007a. 'Differential contribution of the CysLTR1 gene in patients with aspirin hypersensitivity'. *Journal of clinical immunology*, vol.27,pp. 613-619.
- Kim, S. H., Oh, J. M., Kim, Y. S., Palmer, L. J., Suh, C. H., Nahm, D. H. & Park, H. S. 2006. 'Cysteinyl leukotriene receptor 1 promoter polymorphism is associated with aspirin-intolerant asthma in males'. *Clinical & Experimental Allergy*, vol.36,pp. 433-439.
- Kim, S. H., Ye, Y. M., Hur, G. Y., Lee, S. K., Sampson, A. P., Lee, H. Y. & Park, H. S. 2007b. 'CysLTR1 promoter polymorphism and requirement for leukotriene receptor antagonist in aspirin-intolerant asthma patients'. *Pharmacogenomics*, vol.8,pp. 1143-50.
- Kmyta, V., Cherednichenko, N. & Prystupa, L. 2018. -444 A/C polymorphism in the leukotriene-C4 synthase gene in patients with bronchial asthma. Eur Respiratory Soc.
- Laitinen, T., Polvi, A., Rydman, P., Vendelin, J., Pulkkinen, V., Salmikangas, P., Makela, S., Rehn, M., Pirskanen, A. & Rautanen, A. 2004. 'Characterization of a common susceptibility locus for asthma-related traits'. *Science*, vol.304,pp. 300-304.
- Lambrecht, B. N. & Hammad, H. 2015. 'The immunology of asthma'. *Nat Immunol*, vol.16,pp. 45-56.
- Landrigan, P. J., Fuller, R., Acosta, N. J. R., Adeyi, O., Arnold, R., Baldé, A. B., Bertollini, R., Bose-O'reilly, S., Boufford, J. I. & Breysse, P. N. 2018. 'The Lancet Commission on pollution and health'. *The lancet*, vol.391,pp. 462-512.
- Lee, S. Y., Kim, H. B., Kim, J. H., Kim, B. S., Kang, M. J., Jang, S. O., Seo, H. J. & Hong, S. J. 2007. 'Responsiveness to montelukast is associated with bronchial hyperresponsiveness and total immunoglobulin E but not polymorphisms in the leukotriene C4 synthase and cysteinyl leukotriene receptor 1 genes in Korean children with exercise-induced asthma (EIA)'. *Clinical & Experimental Allergy*, vol.37,pp. 1487-1493.
- Lee, T. H., Woszczeck, G. & Farooque, S. P. 2009. 'Leukotriene E4: perspective on the forgotten mediator'. *J Allergy Clin Immunol*, vol.124,pp. 417-21.
- Levin, A. M., Gui, H., Hernandez-Pacheco, N., Yang, M., Xiao, S., Yang, J. J., Hochstadt, S., Barczak, A. J., Eckalbar, W. L., Rynkowski, D., Samedy, L. A., Kwok, P. Y., Pino-Yanes, M., Erle, D. J., Lanfear, D. E., Burchard,

References

- E. G. & Williams, L. K. 2019. 'Integrative approach identifies corticosteroid response variant in diverse populations with asthma'. *J Allergy Clin Immunol*, vol.143,pp. 1791-1802.
- Li, J., Zhao, Q., Huang, J.-P., Jia, J.-Y., Zhu, T.-F., Hong, T. & Su, J. 2022. 'The functional microbiota of on-and off-year moso bamboo (*Phyllostachys edulis*) influences the development of the bamboo pest Pantana *phyllostachysae*'. *BMC Plant Biology*, vol.22,pp. 1-10.
- Liang, L., Willis-Owen, S. A., Laprise, C., Wong, K. C., Davies, G. A., Hudson, T. J., Binia, A., Hopkin, J. M., Yang, I. V. & Grundberg, E. 2015. 'An epigenome-wide association study of total serum immunoglobulin E concentration'. *Nature*, vol.520,pp. 670-674.
- Liccardi, G., Salzillo, A., Calzetta, L., Piccolo, A., Menna, G. & Rogliani, P. 2016. 'Can the presence of cat/dog at home be considered the only criterion of exposure to cat/dog allergens? A likely underestimated bias in clinical practice and in large epidemiological studies'. *European Annals of Allergy and Clinical Immunology*, vol.48,pp. 61-64.
- Liesker, J. J., Ten Hacken, N. H., Zeinstra-Smith, M., Rutgers, S. R., Postma, D. S. & Timens, W. 2009. 'Reticular basement membrane in asthma and COPD: similar thickness, yet different composition'. *Int J Chron Obstruct Pulmon Dis*, vol.4,pp. 127-35.
- Lima, J. J., Zhang, S., Grant, A., Shao, L., Tantisira, K. G., Allayee, H., Wang, J., Sylvester, J., Holbrook, J. & Wise, R. 2006. 'Influence of leukotriene pathway polymorphisms on response to montelukast in asthma'. *American journal of respiratory and critical care medicine*, vol.173,pp. 379-385.
- Liu, A. H., Babineau, D. C., Krouse, R. Z., Zoratti, E. M., Pongracic, J. A., O'connor, G. T., Wood, R. A., Hershey, G. K. K., Kercsmar, C. M. & Gruchalla, R. S. 2016. 'Pathways through which asthma risk factors contribute to asthma severity in inner-city children'. *Journal of Allergy Clinical Immunology*, vol.138,pp. 1042-1050.
- Lodge, C. J., Lowe, A. J., Gurrin, L. C., Hill, D. J., Hosking, C. S., Khalafzai, R. U., Hopper, J. L., Matheson, M. C., Abramson, M. J. & Allen, K. J. 2011. 'House dust mite sensitization in toddlers predicts current wheeze at age 12 years'. *Journal of Allergy Clinical Immunology*, vol.128,pp. 782-788. e9.
- Luginina, A., Gusach, A., Lyapina, E., Khorn, P., Safranova, N., Shevtsov, M., Dmitirieva, D., Dashevskii, D., Kotova, T. & Smirnova, E. 2023. 'Structural diversity of leukotriene G-protein coupled receptors'. *Journal of Biological Chemistry*,pp. 105247.
- Lukkarinen, M., Koistinen, A., Turunen, R., Lehtinen, P., Vuorinen, T. & Jartti, T. 2017. 'Rhinovirus-induced first wheezing episode predicts atopic but not nonatopic asthma at school age'. *Journal of Allergy and Clinical Immunology*, vol.140,pp. 988-995.

References

- Lundstrom, K. 2004. 'Structural genomics on membrane proteins: mini review'. *Combinatorial chemistry & high throughput screening*, vol.7,pp. 431-439.
- M Muhammed, S., M Sultan, K. & Y Abdulrazaq, M. 2012. 'Asthma in adults; epidemiology, risk factor and patterns of presentation: a cross sectional, questionnaire based study in Baghdad Teaching'. *Kerbala Journal of Medicine*, vol.5,pp. 1255-1261.
- Maalmi, H., Beraies, A., Charad, R., Ammar, J., Hamzaoui, K. & Hamzaoui, A. 2014. 'IL-17A and IL-17F genes variants and susceptibility to childhood asthma in Tunisia'. *J Asthma*, vol.51,pp. 348-54.
- Madore, A. M., Bossé, Y., Margaritte-Jeannin, P., Vucic, E., Lam, W. L., Bouzigon, E., Bourbeau, J. & Laprise, C. 2022. 'Analysis of GWAS-nominated loci for lung cancer and COPD revealed a new asthma locus'. *BMC Pulm Med*, vol.22,pp. 155.
- Mahesh, P. A., Moitra, S., Mabalirajan, U., Garg, M., Malamardi, S., Vedanthan, P. K., Christopher, D. J., Agrawal, A. & Krishna, M. T. 2023. 'Allergic diseases in India—Prevalence, risk factors and current challenges'. *Clinical & Experimental Allergy*, vol.53,pp. 276-294.
- Makoui, M. H., Imani, D., Motallebnezhad, M., Azimi, M. & Razi, B. 2020. 'Vitamin D receptor gene polymorphism and susceptibility to asthma: meta-analysis based on 17 case-control studies'. *Annals of Allergy, Asthma & Immunology*, vol.124,pp. 57-69.
- Mandelcwajg, A., Moulin, F., Menager, C., Rozenberg, F., Lebon, P. & Gendrel, D. 2010. 'Underestimation of influenza viral infection in childhood asthma exacerbations'. *The Journal of pediatrics*, vol.157,pp. 505-506.
- March, M. E., Sleiman, P. M. A. & Hakonarson, H. 2013. 'Genetic polymorphisms and associated susceptibility to asthma'. *International journal of general medicine*,pp. 253-265.
- Martinez-Gonzalez, I., Steer, C. A. & Takei, F. 2015. 'Lung ILC2s link innate and adaptive responses in allergic inflammation'. *Trends Immunol*, vol.36,pp. 189-95.
- Martinez Molina, D., Wetterholm, A., Kohl, A., McCarthy, A. A., Niegowski, D., Ohlson, E., Hammarberg, T., Eshaghi, S., Haeggström, J. Z. & Nordlund, P. 2007. 'Structural basis for synthesis of inflammatory mediators by human leukotriene C4 synthase'. *Nature*, vol.448,pp. 613-6.
- Matsui, E. C., Wood, R. A., Rand, C., Kanchanaraksa, S., Swartz, L., Curtin-Brosnan, J. & Eggleston, P. A. 2003. 'Cockroach allergen exposure and sensitization in suburban middle-class children with asthma'. *Journal of Allergy Clinical Immunology*, vol.112,pp. 87-92.
- Mattiuzzi, C. & Lippi, G. Worldwide asthma epidemiology: insights from the Global Health Data Exchange database. 2020. Wiley Online Library, 75-80.

References

- Mccarthy, J. J. & Hilfiker, R. 2000. 'The use of single-nucleotide polymorphism maps in pharmacogenomics'. *Nature biotechnology*, vol.18,pp. 505-508.
- Méndez-Enríquez, E. & Hallgren, J. 2019. 'Mast cells and their progenitors in allergic asthma'. *Frontiers in immunology*, vol.10,pp. 821.
- Micheal, S., Minhas, K., Ishaque, M., Ahmed, F. & Ahmed, A. 2013. 'IL4 gene polymorphisms and their association with atopic asthma and allergic rhinitis in Pakistani patients'.
- Mims, J. W. Asthma: definitions and pathophysiology. International forum of allergy & rhinology, 2015. Wiley Online Library, S2-S6.
- Miyake, Y., Tanaka, K. & Arakawa, M. 2013. 'Relationship between polymorphisms in IL4 and asthma in Japanese women: the Kyushu Okinawa Maternal and Child Health Study'. *J Investig Allergol Clin Immunol*, vol.23,pp. 242-247.
- Moore, W. C., Meyers, D. A., Wenzel, S. E., Teague, W. G., Li, H., Li, X., D'agostino Jr, R., Castro, M., Curran-Everett, D. & Fitzpatrick, A. M. 2010a. 'Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program'. *American journal of respiratory critical care medicine*, vol.181,pp. 315-323.
- Moore, W. C., Meyers, D. A., Wenzel, S. E., Teague, W. G., Li, H., Li, X., D'agostino Jr, R., Castro, M., Curran-Everett, D., Fitzpatrick, A. M. J. a. J. O. R. & Medicine, C. C. 2010b. 'Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program'. *American journal of respiratory critical care medicine*, vol.181,pp. 315-323.
- Morales, D. R., Jackson, C., Lipworth, B. J., Donnan, P. T. & Guthrie, B. 2014. 'Adverse respiratory effect of acute β -blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials'. *Chest*, vol.145,pp. 779-786.
- Morgan, W. J., Crain, E. F., Gruchalla, R. S., O'connor, G. T., Kattan, M., Evans Iii, R., Stout, J., Malindzak, G., Smartt, E. & Plaut, M. 2004. 'Results of a home-based environmental intervention among urban children with asthma'. *New England Journal of Medicine*, vol.351,pp. 1068-1080.
- Muller, G. 2000. 'Towards 3d structures of g protein-coupled receptors a multidisciplinary approach'. *Current medicinal chemistry*, vol.7,pp. 861-888.
- Neill, D. R., Wong, S. H., Bellosi, A., Flynn, R. J., Daly, M., Langford, T. K., Bucks, C., Kane, C. M., Fallon, P. G., Pannell, R., Jolin, H. E. & Mckenzie, A. N. 2010. 'Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity'. *Nature*, vol.464,pp. 1367-70.
- Niegowski, D., Kleinschmidt, T., Olsson, U., Ahmad, S., Rinaldo-Matthis, A. & Haeggström, J. Z. 2014. 'Crystal structures of leukotriene C4 synthase in complex with product analogs: implications for the enzyme mechanism'. *Journal of Biological Chemistry*, vol.289,pp. 5199-5207.

References

- Nyenhuis, S. M., Schwantes, E. A., Evans, M. D. & Mathur, S. K. 2010. 'Airway neutrophil inflammatory phenotype in older subjects with asthma'. *J Allergy Clin Immunol*, vol.125,pp. 1163-5.
- O'byrne, P. M., Gauvreau, G. M. & Murphy, D. M. 2009. 'Efficacy of leukotriene receptor antagonists and synthesis inhibitors in asthma'. *J Allergy Clin Immunol*, vol.124,pp. 397-403.
- Ober, C. 2016. 'Asthma genetics in the post-GWAS era'. *Annals of the American Thoracic Society*, vol.13,pp. S85-S90.
- Ober, C. & Yao, T. C. 2011. 'The genetics of asthma and allergic disease: a 21st century perspective'. *Immunological reviews*, vol.242,pp. 10-30.
- Olgart Höglund, C., De Blay, F., Oster, J. P., Duvernelle, C., Kassel, O., Pauli, G. & Frossard, N. 2002. 'Nerve growth factor levels and localisation in human asthmatic bronchi'. *Eur Respir J*, vol.20,pp. 1110-6.
- Olivieri, M., Zock, J. P., Accordini, S., Heinrich, J., Jarvis, D., Künzli, N., Antó, J. M., Norbäck, D., Svanes, C. & Verlato, G. 2012. 'Risk factors for new-onset cat sensitization among adults: a population-based international cohort study'. *J Allergy Clin Immunol*, vol.129,pp. 420-5.
- Oren, E., Gerald, L., Stern, D. A., Martinez, F. D. & Wright, A. L. 2017. 'Self-Reported Stressful Life Events During Adolescence and Subsequent Asthma: A Longitudinal Study'. *J Allergy Clin Immunol Pract*, vol.5,pp. 427-434.e2.
- Ownby, D. R. 2013. 'Will the real inner-city allergen please stand up?'. *Journal of Allergy Clinical Immunology*, vol.132,pp. 836-837.
- Padrón-Morales, J., García-Solaesa, V., Isidoro-García, M., Hernández-Hernández, L., García-Sánchez, A., Hincapié-López, G., Lorente-Toledano, F., Dávila, I. & Sanz, C. 2014. 'Implications of cytokine genes in allergic asthma'. *Allergol Immunopathol (Madr)*, vol.42,pp. 603-8.
- Palmer, L. J., Burton, P. R., Faux, J. A., James, A. L., William Musk, A. & Cookson, W. O. C. M. 2000. 'Independent inheritance of serum immunoglobulin E concentrations and airway responsiveness'. *American journal of respiratory and critical care medicine*, vol.161,pp. 1836-1843.
- Pan, M.-M., Sun, T.-Y. & Zhang, H.-S. 2006. 'Association between leukotrieneC4 synthase A-444C polymorphism and asthma in Chinese Han population in Beijing'. *Chinese medical journal*, vol.119,pp. 1834-1838.
- Parameswaran, K., Cox, G., Radford, K., Janssen, L. J., Sehmi, R. & O'byrne, P. M. 2002. 'Cysteinyl leukotrienes promote human airway smooth muscle migration'. *American journal of respiratory and critical care medicine*, vol.166,pp. 738-742.
- Penders, J., Gerhold, K., Stobberingh, E. E., Thijs, C., Zimmermann, K., Lau, S. & Hamelmann, E. 2013. 'Establishment of the intestinal microbiota and its

References

- role for atopic dermatitis in early childhood'. *Journal of Allergy and Clinical Immunology*, vol.132,pp. 601-607.
- Pepe, C., Foley, S., Shannon, J., Lemiere, C., Olivenstein, R., Ernst, P., Ludwig, M. S., Martin, J. G. & Hamid, Q. 2005. 'Differences in airway remodeling between subjects with severe and moderate asthma'. *J Allergy Clin Immunol*, vol.116,pp. 544-9.
- Permaul, P., Hoffman, E., Fu, C., Sheehan, W., Baxi, S., Gaffin, J., Lane, J., Bailey, A., King, E., Chapman, M., Gold, D. & Phipatanakul, W. 2012. 'Allergens in urban schools and homes of children with asthma'. *Pediatr Allergy Immunol*, vol.23,pp. 543-9.
- Peters-Golden, M. & Henderson Jr, W. R. 2007. 'Leukotrienes'. *New England Journal of Medicine*, vol.357,pp. 1841-1854.
- Peters, U., Dixon, A. E. & Forno, E. 2018. 'Obesity and asthma'. *Journal of Allergy and Clinical immunology*, vol.141,pp. 1169-1179.
- Phan, J. A., Kicic, A., Berry, L. J., Fernandes, L. B., Zosky, G. R., Sly, P. D. & Larcombe, A. N. 2014. 'Rhinovirus exacerbates house-dust-mite induced lung disease in adult mice'. *PLoS One*, vol.9,pp. e92163.
- Phipatanakul, W., Eggleston, P. A., Wright, E. C. & Wood, R. A. 2000. 'Mouse allergen. I. The prevalence of mouse allergen in inner-city homes'. *Journal of allergy clinical immunology*, vol.106,pp. 1070-1074.
- Pite, H., Pereira, A. M., Moraes-Almeida, M., Nunes, C., Bousquet, J. & Fonseca, J. A. 2014. 'Prevalence of asthma and its association with rhinitis in the elderly'. *Respir Med*, vol.108,pp. 1117-26.
- Pitruzzella, A., Modica, D. M., Burgio, S., Gallina, S., Manna, O. M., Intili, G., Bongiorno, A., Saguto, D., Marchese, R. & Nigro, C. L. 2020. 'THE ROLE OF EMTU IN MUCOSAE REMODELING: FOCUS ON A NEW MODEL TO STUDY CHRONIC INFLAMMATORY LUNG DISEASES'. *Euromediterranean Biomedical Journal*, vol.15.
- Portelli, M. A., Hodge, E. & Sayers, I. 2015. 'Genetic risk factors for the development of allergic disease identified by genome-wide association'. *Clin Exp Allergy*, vol.45,pp. 21-31.
- Prince, A., Norris, M. R. & Bielory, L. 2018. 'Seasonal ocular allergy and pollen counts'. *Current Opinion in Allergy and Clinical Immunology*, vol.18,pp. 387-392.
- Puddicombe, S. M., Polosa, R., Richter, A., Krishna, M. T., Howarth, P. H., Holgate, S. T. & Davies, D. E. 2000. 'Involvement of the epidermal growth factor receptor in epithelial repair in asthma'. *Faseb j*, vol.14,pp. 1362-74.
- Puddicombe, S. M., Torres-Lozano, C., Richter, A., Bucchieri, F., Lordan, J. L., Howarth, P. H., Vrugt, B., Albers, R., Djukanovic, R., Holgate, S. T., Wilson, S. J. & Davies, D. E. 2003. 'Increased expression of p21(waf)

References

- cyclin-dependent kinase inhibitor in asthmatic bronchial epithelium'. *Am J Respir Cell Mol Biol*, vol.28,pp. 61-8.
- Raissy, H. & Blake, K. 2015. 'Vitamin D and asthma: association, causality, or intervention?'. *Pediatric allergy, immunology, pulmonology*, vol.28,pp. 60-62.
- Ramphul, M., Lo, D. K. H. & Gaillard, E. A. 2021. 'Precision Medicine for Paediatric Severe Asthma: Current Status and Future Direction'. *J Asthma Allergy*, vol.14,pp. 525-538.
- Reyes-Garcia, J., Montano, L. M., Carbajal-Garcia, A. & Wang, Y.-X. 2021. Sex hormones and lung inflammation. *Lung Inflammation in Health and Disease, Volume II*. Springer.
- Ricciardolo, F. L., Sorbello, V., Silvestri, M., Giacomelli, M., Debenedetti, V. M., Malerba, M., Ciprandi, G., Rossi, G. A., Rossi, A. & Bontempelli, M. 2013. 'TNF-alpha, IL-4R-alpha and IL-4 polymorphisms in mild to severe asthma from Italian Caucasians'. *Int J Immunopathol Pharmacol*, vol.26,pp. 75-84.
- Rinaldo-Matthis, A. & Haeggström, J. Z. 2010. 'Structures and mechanisms of enzymes in the leukotriene cascade'. *Biochimie*, vol.92,pp. 676-681.
- Rinaldo-Matthis, A., Wetterholm, A., Molina, D. M., Holm, J., Niegowski, D., Ohlson, E., Nordlund, P., Morgenstern, R. & Haeggström, J. Z. 2010. 'Arginine 104 is a key catalytic residue in leukotriene C4 synthase'. *Journal of Biological Chemistry*, vol.285,pp. 40771-40776.
- Rodriguez, R., Ventura-Martinez, R., Santiago-Mejia, J., Avila-Costa, M. R. & Fortoul, T. I. 2006. 'Altered responsiveness of the guinea-pig isolated ileum to smooth muscle stimulants and to electrical stimulation after in situ ischemia'. *British journal of pharmacology*, vol.147,pp. 371-378.
- Rönmark, E., Andersson, C., Nyström, L., Forsberg, B., Järvholt, B. & Lundbäck, B. 2005. 'Obesity increases the risk of incident asthma among adults'. *European Respiratory Journal*, vol.25,pp. 282-288.
- Rosenberg, S. L., Miller, G. E., Brehm, J. M. & Celedón, J. C. 2014. 'Stress and asthma: novel insights on genetic, epigenetic, and immunologic mechanisms'. *J Allergy Clin Immunol*, vol.134,pp. 1009-15.
- Rosenwasser, L. J. & Boyce, J. A. 2003. 'Mast cells: beyond IgE'. *Journal of Allergy and Clinical Immunology*, vol.111,pp. 24-32.
- Rovati, G. E. & Capra, V. 2007. 'Cysteinyl-leukotriene receptors and cellular signals'. *TheScientificWorldJournal*, vol.7,pp. 1375-1392.
- Rubner, F. J., Jackson, D. J., Evans, M. D., Gangnon, R. E., Tisler, C. J., Pappas, T. E., Gern, J. E. & Lemanske Jr, R. F. 2017. 'Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence'. *Journal of Allergy Clinical Immunology*, vol.139,pp. 501-507.
- Saino, H., Ukita, Y., Ago, H., Irikura, D., Nisawa, A., Ueno, G., Yamamoto, M., Kanaoka, Y., Lam, B. K., Austen, K. F. & Miyano, M. 2011. 'The

References

- catalytic architecture of leukotriene C4 synthase with two arginine residues'. *J Biol Chem*, vol.286,pp. 16392-401.
- Salem, M. B., Al-Sadoon, I. O. & Hassan, M. K. 2002. 'Prevalence of wheeze among preschool children in Basra governonate, southern Iraq'. *East Mediterr Health J*, vol.8,pp. 503-8.
- Sampson, A. P., Siddiqui, S., Buchanan, D., Howarth, P. H., Holgate, S. T., Holloway, J. W. & Sayers, I. 2000. 'Variant LTC4 synthase allele modifies cysteinyl leukotriene synthesis in eosinophils and predicts clinical response to zafirlukast'. *Thorax*, vol.55,pp. S28-S31.
- Samuelsson, B. 2012. 'Role of basic science in the development of new medicines: examples from the eicosanoid field'. *J Biol Chem*, vol.287,pp. 10070-10080.
- Sanak, M., Levy, B. D., Clish, C. B., Chiang, N., Gronert, K., Mastalerz, L., Serhan, C. N. & Szczeklik, A. 2000a. 'Aspirin-tolerant asthmatics generate more lipoxins than aspirin-intolerant asthmatics'. *European Respiratory Journal*, vol.16,pp. 44-49.
- Sanak, M., Pierzchalska, M., Bazan-Socha, S. & Szczeklik, A. 2000b. 'Enhanced expression of the leukotriene C4 synthase due to overactive transcription of an allelic variant associated with aspirin-intolerant asthma'. *American Journal of Respiratory Cell and Molecular Biology*, vol.23,pp. 290-296.
- Sanz, C., Isidro-Garcia, M., Davila, I., Moreno, E., Laffond, E. & Lorente, F. 2006. 'Patients with Asthma'. *J Investig Allergol Clin Immunol*, vol.16,pp. 331-337.
- Sarau, H. M., Ames, R. S., Chambers, J., Ellis, C., Elshourbagy, N., Foley, J. J., Schmidt, D. B., Muccitelli, R. M., Jenkins, O., Murdock, P. R., Herrity, N. C., Halsey, W., Sathe, G., Muir, A. I., Nuthulaganti, P., Dytko, G. M., Buckley, P. T., Wilson, S., Bergsma, D. J. & Hay, D. W. 1999. 'Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor'. *Mol Pharmacol*, vol.56,pp. 657-63.
- Savari, S., Vinnakota, K., Zhang, Y. & Sjölander, A. 2014. 'Cysteinyl leukotrienes and their receptors: bridging inflammation and colorectal cancer'. *World journal of gastroenterology: WJG*, vol.20,pp. 968.
- Sharma, S., Chhabra, D., Kho, A. T., Hayden, L. P., Tantisira, K. G. & Weiss, S. T. 2014. 'The genomic origins of asthma'. *Thorax*, vol.69,pp. 481-7.
- Shirakawa, T., Deichmann, K. A., Izuhara, K., Mao, X.-Q., Adra, C. N. & Hopkin, J. M. 2000. 'Atopy and asthma: genetic variants of IL-4 and IL-13 signalling'. *Immunology today*, vol.21,pp. 60-64.
- Singh, R. K., Gupta, S., Dastidar, S. & Ray, A. 2010. 'Cysteinyl Leukotrienes and Their Receptors: Molecular and Functional Characteristics'. *Pharmacology*, vol.85,pp. 336-349.
- Smith, A. M. 2011. 'The epidemiology of work-related asthma'. *Immunology and Allergy Clinics*, vol.31,pp. 663-675.

References

- Snelgrove, R. J., Gregory, L. G., Peiró, T., Akthar, S., Campbell, G. A., Walker, S. A. & Lloyd, C. M. 2014. 'Alternaria-derived serine protease activity drives IL-33-mediated asthma exacerbations'. *Journal of allergy and clinical immunology*, vol.134,pp. 583-592.
- Sokolowska, M., Rovati, G. E., Diamant, Z., Untersmayr, E., Schwarze, J., Lukasik, Z., Sava, F., Angelina, A., Palomares, O. & Akdis, C. A. 2021. 'Current perspective on eicosanoids in asthma and allergic diseases: EAACI Task Force consensus report, part I'. *Allergy*, vol.76,pp. 114-130.
- Sood, A., Qualls, C. & Schuyler, M. 2010. 'Leptin, adiponectin, and asthma: findings from a population-based cohort study'. *Annals of Allergy, Asthma & Immunology*, vol.104,pp. 355.
- Sousa, A. R., Parikh, A., Scadding, G., Corrigan, C. J. & Lee, T. H. 2002. 'Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis'. *N Engl J Med*, vol.347,pp. 1493-9.
- Spindel, E. R. & McEvoy, C. T. 2016. 'The role of nicotine in the effects of maternal smoking during pregnancy on lung development and childhood respiratory disease. Implications for dangers of e-cigarettes'. *American journal of respiratory and critical care medicine*, vol.193,pp. 486-494.
- Sporik, R., Holgate, S. T., Platts-Mills, T. A. & Cogswell, J. J. 1990. 'Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study'. *N Engl J Med*, vol.323,pp. 502-7.
- Stein, M. M., Hrusch, C. L., Gozdz, J., Igartua, C., Pivniouk, V., Murray, S. E., Ledford, J. G., Marques Dos Santos, M., Anderson, R. L. & Metwali, N. 2016. 'Innate immunity and asthma risk in Amish and Hutterite farm children'. *New England journal of medicine*, vol.375,pp. 411-421.
- Stein, R. T. & Martinez, F. D. 2004. 'Asthma phenotypes in childhood: lessons from an epidemiological approach'. *Paediatric respiratory reviews*, vol.5,pp. 155-161.
- Stern, J., Pier, J. & Litonjua, A. A. 2020. *Asthma epidemiology and risk factors*. 2020 2020. Springer, 5-15.
- Subbarao, P., Mandhane, P. J. & Sears, M. R. 2009. 'Asthma: epidemiology, etiology and risk factors'. *Cmaj*, vol.181,pp. E181-E190.
- Takasaki, J., Kamohara, M., Matsumoto, M., Saito, T., Sugimoto, T., Ohishi, T., Ishii, H., Ota, T., Nishikawa, T., Kawai, Y., Masuho, Y., Isogai, T., Suzuki, Y., Sugano, S. & Furuichi, K. 2000. 'The molecular characterization and tissue distribution of the human cysteinyl leukotriene CysLT(2) receptor'. *Biochem Biophys Res Commun*, vol.274,pp. 316-22.
- Takkouche, B., González-Barcala, F. J., Etminan, M. & Fitzgerald, M. 2008. 'Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis'. *Allergy*, vol.63,pp. 857-864.
- Tan, W. C. 2005. 'Viruses in asthma exacerbations'. *Current opinion in pulmonary medicine*, vol.11,pp. 21-26.

References

- Tavendale, R., Macgregor, D. F., Mukhopadhyay, S. & Palmer, C. N. 2008. 'A polymorphism controlling ORMDL3 expression is associated with asthma that is poorly controlled by current medications'. *Journal of Allergy Clinical Immunology*, vol.121,pp. 860-863.
- Teague, W. G. 2017. 'Up in smoke: accelerated loss of lung function in two clusters of smokers identified in a longitudinal cohort study of adult-onset asthma'. *The Journal of Allergy and Clinical Immunology: In Practice*, vol.5,pp. 979-980.
- Tischer, C., Weikl, F., Probst, A. J., Standl, M., Heinrich, J. & Pritsch, K. 2016. 'Urban dust microbiome: impact on later atopy and wheezing'. *Environmental Health Perspectives*, vol.124,pp. 1919-1923.
- Torrent, M., Sunyer, J., Garcia, R., Harris, J., Iturriaga, M. V., Puig, C., Vall, O., Anto, J. M., Newman Taylor, A. J. & Cullinan, P. 2007. 'Early-life allergen exposure and atopy, asthma, and wheeze up to 6 years of age'. *American journal of respiratory critical care medicine*, vol.176,pp. 446-453.
- Toskala, E. & Kennedy, D. W. Asthma risk factors. 2015. Wiley Online Library, S11-S16.
- Trivedi, M. & Denton, E. 2019. 'Asthma in children and adults—what are the differences and what can they tell us about asthma?'. *Frontiers in pediatrics*, vol.7,pp. 256.
- Truyen, E., Coteur, L., Dilissen, E., Overbergh, L., Dupont, L. J., Ceuppens, J. L. & Bullens, D. M. 2006. 'Evaluation of airway inflammation by quantitative Th1/Th2 cytokine mRNA measurement in sputum of asthma patients'. *Thorax*, vol.61,pp. 202-8.
- Tsai, C. H., Tung, K. Y., Su, M. W., Chiang, B. L., Chew, F. T., Kuo, N. W. & Lee, Y. L. 2013. 'Interleukin-13 genetic variants, household carpet use and childhood asthma'. *PLoS One*, vol.8,pp. e51970.
- Ualiyeva, S., Lemire, E., Aviles, E. C., Wong, C., Boyd, A. A., Lai, J., Liu, T., Matsumoto, I., Barrett, N. A. & Boyce, J. A. 2021. 'Tuft cell-produced cysteinyl leukotrienes and IL-25 synergistically initiate lung type 2 inflammation'. *Science immunology*, vol.6,pp. eabj0474.
- Unoki, M., Furuta, S., Onouchi, Y., Watanabe, O., Doi, S., Fujiwara, H., Miyatake, A., Fujita, K., Tamari, M. & Nakamura, Y. 2000. 'Association studies of 33 single nucleotide polymorphisms (SNPs) in 29 candidate genes for bronchial asthma: positive association of a T924C polymorphism in the thromboxane A2 receptor gene'. *Human genetics*, vol.106,pp. 440-446.
- Van Eerdewegh, P., Little, R. D., Dupuis, J., Del Mastro, R. G., Falls, K., Simon, J., Torrey, D., Pandit, S., McKenny, J. & Braunschweiger, K. 2002. 'Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness'. *Nature*, vol.418,pp. 426-430.

References

- Vink, N. M., Postma, D. S., Schouten, J. P., Rosmalen, J. G. & Boezen, H. M. 2010. 'Gender differences in asthma development and remission during transition through puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study'. *J Allergy Clin Immunol*, vol.126,pp. 498-504.e1-6.
- Von Mutius, E. 2009. 'Gene-environment interactions in asthma'. *Journal of Allergy and Clinical Immunology*, vol.123,pp. 3-11.
- Wan, S.-W., Wu-Hsieh, B. A., Lin, Y.-S., Chen, W.-Y., Huang, Y. & Anderson, R. 2018. 'The monocyte-macrophage-mast cell axis in dengue pathogenesis'. *Journal of biomedical science*, vol.25,pp. 1-10.
- Wang, D., Xiao, W., Ma, D., Zhang, Y., Wang, Q., Wang, C., Ji, X., He, B., Wu, X., Chen, H., Zhang, Y., Jiang, Y. & Yin, J. 2013a. 'Cross-sectional epidemiological survey of asthma in Jinan, China'. *Respirology*, vol.18,pp. 313-22.
- Wang, Z.-D., Lian, D., Shen, J.-L., Sun, R., Xu, W., Xin, Z., Lei, L., Jin, L.-H. & Jin, S.-D. 2013b. 'Association between the interleukin-4, interleukin-13 polymorphisms and asthma: a meta-analysis'. *Molecular biology reports*, vol.40,pp. 1365-1376.
- Wenzel, S. E. 2012. 'Asthma phenotypes: the evolution from clinical to molecular approaches'. *Nature medicine*, vol.18,pp. 716-725.
- Whelan, G. J., Blake, K., Kissoon, N., Duckworth, L. J., Wang, J., Sylvester, J. E. & Lima, J. J. 2003. 'Effect of montelukast on time-course of exhaled nitric oxide in asthma: Influence of LTC4 synthase A- 444C polymorphism'. *Pediatric pulmonology*, vol.36,pp. 413-420.
- Wjst, M., Sargurupremraj, M. & Arnold, M. 2013. 'Genome-wide association studies in asthma: what they really told us about pathogenesis'. *Current opinion in allergy and clinical immunology*, vol.13,pp. 112-118.
- Wlasiuk, G. & Vercelli, D. 2012. 'The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease'. *Current opinion in allergy and clinical immunology*, vol.12,pp. 461-466.
- Wu, M., Zheng, X., Huang, J. & Hu, X. 2021. 'Association of IL33, IL1RL1, IL1RAP Polymorphisms and Asthma in Chinese Han Children'. *Front Cell Dev Biol*, vol.9,pp. 759542.
- Wu, W., Bleeker, E., Moore, W., Busse, W. W., Castro, M., Chung, K. F., Calhoun, W. J., Erzurum, S., Gaston, B., Israel, E., Curran-Everett, D. & Wenzel, S. E. 2014. 'Unsupervised phenotyping of Severe Asthma Research Program participants using expanded lung data'. *J Allergy Clin Immunol*, vol.133,pp. 1280-8.
- Wu, Y.-H., Liu, C.-T., Wang, K. & Geng, Y.-M. 2008. 'The relevance of leukotriene C (4) synthase gene A (-444) C polymorphism to clinical responsiveness to montelukast in patients with asthma'. *Zhonghua jie he*

References

- he hu xi za zhi= Zhonghua Jiehe he Huxi Zazhi= Chinese Journal of Tuberculosis and Respiratory Diseases*, vol.31,pp. 806-810.
- Xu, Z., Pei, L., Zhang, F., Hu, X., Gui, Y., Wang, L. & Wu, B. 2013. 'A functional variant in IL12B promoter modulates its expression and associates with increased risk of allergic asthma'. *Genes Immun*, vol.14,pp. 238-43.
- Yang, I. V., Pedersen, B. S., Liu, A., O'connor, G. T., Teach, S. J., Kattan, M., Misiak, R. T., Gruchalla, R., Steinbach, S. F., Szeffler, S. J. J. J. O. A. & Immunology, C. 2015. 'DNA methylation and childhood asthma in the inner city'. *Journal of Allergy Clinical Immunology*, vol.136,pp. 69-80.
- Yang, X. X., Li, F. X., Wu, Y. S., Wu, D., Tan, J. Y. & Li, M. 2011. 'Association of TGF-beta1, IL-4 and IL-13 gene polymorphisms with asthma in a Chinese population'. *Asian Pac J Allergy Immunol*, vol.29,pp. 273-7.
- Yuan, N. Y., Maung, R., Xu, Z., Han, X. & Kaul, M. 2022. 'Arachidonic Acid Cascade and Eicosanoid Production Are Elevated While LTC4 Synthase Modulates the Lipidomics Profile in the Brain of the HIVgp120-Transgenic Mouse Model of NeuroHIV'. *Cells*, vol.11,pp. 2123.
- Zein, J. G. & Erzurum, S. C. 2015. 'Asthma is Different in Women'. *Current Allergy and Asthma Reports*, vol.15,pp. 28.
- Zhang, J., Migita, O., Koga, M., Shibasaki, M., Arinami, T. & Noguchi, E. 2006. 'Determination of structure and transcriptional regulation of CYSLTR1 and an association study with asthma and rhinitis'. *Pediatr Allergy Immunol*, vol.17,pp. 242-9.
- Zhang, Y., Huang, H., Huang, J., Xiang, Z., Yang, M., Tian, C. & Fan, H. 2012. 'The -444A/C Polymorphism in the LTC4S Gene and the Risk of Asthma: A Meta-analysis'. *Archives of Medical Research*, vol.43,pp. 444-450.
- Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y. & Li, Y. 2021. 'Inflammation and tumor progression: signaling pathways and targeted intervention'. *Signal transduction and targeted therapy*, vol.6,pp. 263.
- Zhao, Y., Zhang, X., Han, C., Cai, Y., Li, S., Hu, X., Wu, C., Guan, X., Lu, C. & Nie, X. 2022. 'Pharmacogenomics of Leukotriene Modifiers: A Systematic Review and Meta-Analysis'. *Journal of Personalized Medicine*, vol.12,pp. 1068.
- Zhu, J., Qiu, Y. S., Figueroa, D. J., Bandi, V., Galczenki, H., Hamada, K., Guntupalli, K. K., Evans, J. F. & Jeffery, P. K. 2005. 'Localization and upregulation of cysteinyl leukotriene-1 receptor in asthmatic bronchial mucosa'. *Am J Respir Cell Mol Biol*, vol.33,pp. 531-40.
- Zhu, N., Gong, Y., Chen, X.-D., Zhang, J., Long, F., He, J. & Xia, J.-W. 2013. 'Association between the polymorphisms of interleukin-4, the interleukin-

References

- 4 receptor gene and asthma'. *Chinese medical journal*, vol.126,pp. 2943-2951.
- Ziska, L., Knowlton, K., Rogers, C., Dalan, D., Tierney, N., Elder, M. A., Filley, W., Shropshire, J., Ford, L. B. & Hedberg, C. 2011. 'Recent warming by latitude associated with increased length of ragweed pollen season in central North America'. *Proceedings of the National Academy of Sciences*, vol.108,pp. 4248-4251.
- Ziska, L. H. & Beggs, P. J. 2012. 'Anthropogenic climate change and allergen exposure: the role of plant biology'. *Journal of Allergy and Clinical Immunology*, vol.129,pp. 27-32.

الخلاصة

تناول هذه الدراسة استكشاف الارتباطات المحتملة بين اثنين من التعدد الجيني، وهما $T > 927$ و $C (LTC4S) rs730012 > C (CYSLTR1) rs320995 and 444A > C$ ، وعلاقتها بمخاطر الإصابة بالربو في سكان العراق، على وجه الخصوص داخل محافظة واسط. تضمنت الدراسة مجموعة من ٤٥ مريضاً بالربو، مكونة من ٢٣ ذكرًا و ٢٢ أنثى، ومجموعة السيطرة تضمنت ٣٥ فرداً صحيًا، بما في ذلك ١٨ ذكرًا و ١٧ أنثى. تمت إجراء عمليات التمييز الجيني لهذه التعديلات باستخدام اختبارات تمييز TaqMan المخصصة لتحليل الأحادي النيوكليوتيد.

فيما يتعلق بتعدي $C (CYSLTR1) rs320995 > C$ ظهرت الدراسة أن النمط الوراثي الأكثر شيوعاً في المرضى وفي مجموعة المقارنة هو TT. بالإضافة إلى ذلك، أتضح أن الأنماط الوراثية CC و TC أكثر انتشاراً بين المرضى بالربو بالمقارنة مع الأفراد الأصحاء. وأشارت النتائج إلى أن النمط الوراثي T قد يلعب دوراً وقائياً ضد الربو، بينما يمكن اعتبار النمط الوراثي C عامل خطر. وعلاوة على ذلك، ارتبط الأنماط الوراثية CC و TC بزيادة مخاطر الإصابة بالربو، في حين كان النمط الوراثي TT مرتبطة بانخفاض احتمالية الإصابة بالربو. وفي تحليل الفرعيات، لوحظ أن النمط الوراثي CC زاد بشكل ملحوظ مخاطر الإصابة بالربو بين الإناث، بينما كان النمط الوراثي TT مرتبطة بانخفاض مخاطر الإصابة بالربو. بالنسبة للذكور، زاد النمط الوراثي TT مخاطر الإصابة بالربو، ولكن يجدر بالذكر أنه لم يتم العثور على ذكور يحملون النمط الوراثي TC.

أما بالنسبة لتعدي $A > C (LTC4S) rs730012 > A$ ، فإن النمط الوراثي الأكثر شيوعاً في المرضى وفي مجموعة المقارنة هو CA. أظهرت النتائج أن المرضى بالربو كانوا يتميزون بانتشار أعلى للنمط الوراثي CC، بينما كان النمط الوراثي AA أقل شيوعاً بينهم. وأشارت الدراسة إلى أن النمط الوراثي C قد يمثل عاملًا خطراً على الإصابة بالربو، بينما قد يكون النمط الوراثي A له دور وقائي. وبشكل ملحوظ، ارتبط النمط الوراثي CC بزيادة ملحوظة في مخاطر الإصابة بالربو، بينما كان النمط الوراثي CA و AA مرتبطين بانخفاض احتمالية الإصابة بالربو. في تحليل الفرعيات، لوحظ أن النمط الوراثي CC زاد بشكل ملحوظ مخاطر الإصابة بالربو بين الإناث، بينما كان النمط الوراثي CA مرتبطة بانخفاض مخاطر الإصابة بالربو. بالنسبة للذكور، زاد النمط الوراثي CC مخاطر الإصابة بالربو، وكان النمطان الوراثيان CA و AA مرتبطين بانخفاض احتمالية الإصابة بالربو.

في الختام، تحددت هذه الدراسة ارتباطات بين تعدادات جينية محددة ومخاطر الإصابة بالربو، مع ملاحظة وجود تباينات بين الذكور والإناث. طالما أن النمط الوراثي T لـ *CYSLTR1 rs320995* والنمط الوراثي A لـ *LTC4S rs730012* يبدو أن لهما دوراً وقائياً، بينما يتعلق النمط الوراثي C لـ *LTC4S rs730012* بزيادة مخاطر الإصابة بالربو.

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة واسط / كلية التربية للعلوم الصرفة

قسم علوم الحياة



تعدد الاشكال الوراثية في مستقبلات النوع الاول للوكتراينات
السيستينيل $T^{927} < C$ ومخلق لوكتريين سي $4^4 - 4^4 < A$ في
مرضى الربو في محافظة واسط، العراق

رسالة

مقدمة الى مجلس كلية التربية للعلوم الصرفة جامعة واسط وهي جزء من متطلبات نيل
درجة الماجستير في علوم الحياة-علم الحيوان

من قبل

مسار عبد مناف عبد المطلب

بكالوريوس في علوم الحياة ٢٠٠٤/جامعة واسط

بإشراف

أ.د. إنتصار حسين احمد

تشرين الأول ٢٣٢٠

ربيع الأول ١٤٤٥ هـ