Published in final edited form as:
Pharmacotherapy. 2008 December ; 28(12): 1495–1501. doi:10.1592/phco.28.12.1495.

Association of the Histamine *N*-methyltransferase C314T (Thr105Ile) Polymorphism with Atopic Dermatitis in Caucasian Children

Mary Jayne Kennedy, Pharm.D.[1,2], **Jennifer A. Loehle, M.S., M.D.**[1], **Angela R. Griffin, B.S.**[1], **Mark A. Doll, M.S.**[2], **Gregory L. Kearns, Pharm.D., Ph.D.**[3,4], **Janice E. Sullivan, M.D.**[1,2], and **David W. Hein, Ph.D.**[2]

1*Kosair Charities Pediatric Clinical Research Unit, Department of Pediatrics, School of Medicine, University of Louisville, Louisville, KY*

2*Department of Pharmacology and Toxicology, School of Medicine, University of Louisville, Louisville, KY*

3*Division of Pediatric Pharmacology and Medical Toxicology, Children's Mercy Hospitals and Clinics, Kansas City, MO*

4*Department of Pediatrics, School of Medicine, University of Missouri-Kansas City, Kansas City, MO.*

Abstract

Study Objective—To investigate potential associations between the histamine *N*-methyltransferase (HNMT) C314T (Thr105Ile) polymorphism and atopic dermatitis (AD) in a cohort of Caucasian children.

Design—Prospective, multi-center (n=4) genotype/association study.

Setting—Four academic, tertiary care, medical centers within the Pediatric Pharmacology Research Unit (PPRU) network

Patients or Participants—Caucasian children ages 6 months – 5 years with (n=129) and without (n=127) AD. All subjects completed the study although data from 6 subjects (n=2 AD and n=4 control) were excluded due to violations in inclusion/exclusion criteria (n=5) and the informed consent process (n=1).

Interventions—Information was collected regarding severity of AD, oral antihistamine treatment and treatment response via parental report. Buccal swabs (n=1 per cheek) were also performed to obtain epithelial cells for extraction of genomic DNA.

Measurements and Main results—HMNT genotypes were successfully obtained in 116 and 122 control and AD subjects, respectively. Frequencies of the T314 variant allele (0.12, p=0.04) and combined CT/TT genotype (0.24, p=0.02) were significantly higher in children with AD compared with controls (allele and genotype frequencies = 0.06 and 0.12). Children with genotypes conferring reduced HNMT activity were two times more likely to have AD than those who were homozygous for the C314 reference allele.

Conclusions—Increased histamine levels in patients with AD may result, at least in part, from reduced inactivation via HNMT. Genetically-associated reduction in histamine biotransformation

Address for reprint requests: Mary Jayne Kennedy, Pharm.D., Assistant Professor of Pediatrics and Pharmacology/Toxicology, Department of Pediatrics, University of Louisville, 231 E. Chestnut Street - N97, Louisville, KY 40202, Phone: (502) 629-5608, Facsimile: (502) 629-5285, Electronic mail: mjkenn07@louisville.edu.

Presented in part at the 2004 American College of Clinical Pharmacy Annual Meeting, Dallas, TX. October 2004.

may therefore contribute to the pathogenesis, persistence and progression of AD. If confirmed, these data indicate that HNMT might represent a common risk factor for development of AD, asthma and allergic rhinitis and may be useful in identifying individuals who are candidates for early preventative pharmacotherapeutic intervention. Additional longitudinal studies will be required in order to assess the relationship between genotype, disease severity and antihistamine response.

Keywords

atopic dermatitis; histamine *N*-methyltransferase; pediatric; pharmacogenetics

Introduction

Atopic dermatitis (AD) is a common condition in the pediatric population, affecting an estimated 15% of children greater than 18 months of age.[1] This chronic, relapsing-remitting skin disorder is characterized by classic symptoms including pruritus and a distinctive rash that exhibits an age-dependent distribution pattern. However, it is now recognized that AD is a disease of significant heterogeneity with respect to both severity and response to conventional pharmacologic treatment. With the recognition of this variability has come the understanding that, as with many allergic diseases, there exist specific disease phenotypes that ultimately govern response to pharmacologic intervention. Characterization of these unique phenotypes and their associated biologic mediators is therefore of critical importance in the development of disease- and patient-specific treatment strategies.

Increased systemic exposure to histamine has been demonstrated in individuals with atopy[2] and allergy[3] and also in children with AD and concomitant food allergies.[4, 5] This increased exposure leads to a pharmacodynamic effect that is both exaggerated and adverse, and constitutes a fundamental pathogenic mechanism of atopic conditions such as AD. Systemic exposure to histamine is determined by a balance between the processes of release from precursor cells (i.e., mast cells and basophils) and inactivation via endogenous metabolic pathways. A key pathogenic determinant of AD may reside with a disruption in the balance among those physiologic processes determining systemic exposure. Exaggerated histamine release from AD-derived precursor cells has been previously demonstrated.[6, 7] Whether the detoxification/inactivation of this important mediator is similarly affected, however, remains unclear.

Histamine *N*-methyltransferase (HNMT) is the primary enzyme responsible for histamine metabolism in the skin,[8] bronchial epithelia[9] and central nervous system.[10] Significant variability in the expression and activity of HNMT has been observed in healthy adults and this variability is mediated, in part, by genetic mechanisms.[11, 12] A single nucleotide polymorphism (SNP) located in exon 4 (C314T, Thr105Ile) of the HNMT gene has been identified and is associated with decreased enzyme activity (up to 50%) and immunoreactive protein in renal tissue and red blood cell lysates.[13] This allelic variant was also found to be relatively common, occurring in an estimated 5 to 10% of the healthy Caucasian population.[13, 14] Given the known functional consequences of the C314T (Thr105Ile) polymorphism on HNMT activity, it is possible that this allelic variant, when present, may contribute to the pathogenesis and heterogeneity of expression in diseases such as AD where histamine plays a fundamental biochemical role. It is also possible that genetic differences in HNMT activity may be responsible, in part, for the well-recognized inter-individual variability in response to antihistamines in children with atopic/allergic diseases. To begin exploring the link between genetics and AD disease pathogenesis / treatment response we therefore conducted this initial study to investigate potential associations between the HNMT C314T polymorphism and AD in a cohort of Caucasian children.

Methods

Study Sites

Four institutions within the Pediatric Pharmacology Research Unit (PPRU) network participated in this study: University of Louisville (Louisville, KY); Children's Mercy Hospitals and Clinics (Kansas City, MO), Baylor University College of Medicine (Houston, TX), and Arkansas Children's Hospital (Little Rock, AR). Children were enrolled between August 2003 and September 2004. The protocol received approval from the Institutional Review Boards of each participating site and the PPRU Network Steering Committee. Written informed consent was obtained from each subject's parent or guardian and required research authorization (i.e., HIPAA) was obtained. All study procedures were performed in accordance with ethical standards of each local Institutional Review Board and the Helsinki Declaration of 1975. The study was also registered with the clinical trials registry sponsored by the United States National Library of Medicine (www.clinicaltrials.gov, study identifier NCT00277433).

Study Subjects

Caucasian children ages 6 months to 5 years with a physician-confirmed clinical diagnosis of AD were eligible for study enrollment. Upon study entry, parents were asked about clinical symptoms during the 12 months prior to enrollment in order to confirm presence of active AD. Subjects with at least three of the following major diagnostic features were considered to have a confirmed clinical diagnosis of AD: pruritus, rash of typical morphology and distribution, chronic or relapsing-remitting presentation and/or family history of atopy.[15] Any child with AD and either a documented history of asthma or bronchospasm or a current need for treatment of either of these conditions was excluded. Healthy Caucasian children ages 6 months to 5 years without a personal and without a family (first degree relative) history of allergy, asthma or atopy were concurrently recruited as controls.

Estimation of Disease Severity and Treatment Response

Information was collected regarding severity of AD, current and prior antihistamine treatment and treatment response. Information regarding disease severity (mild, moderate or severe) and treatment response (good, fair or poor) was obtained via parental report and based on a subjective assessment by the parent or primary caregiver.

Buccal Swab Collection, Processing and Storage

Buccal swabs (n=1 per cheek) were performed in all subjects using Catch-All® Sample Collection Swabs (Epicentre, Madison, WI) to obtain epithelial cells for extraction of genomic DNA. Samples were collected by rotating a collection swab on the surface of each cheek a minimum of 5 times. Following collection, samples were allowed to air dry for at least 20 minutes (maximum 1 hour), placed in their original packing and stored at −20° C for a maximum of 12 months.

DNA Isolation and Detection of HNMT C314T Polymorphism

Genomic DNA was isolated using the BuccalAmp® DNA extraction kit (Epicentre, Madison, WI). Swabs were allowed to thaw at room temperature, rotated at least 10 times in the commercially-available QuickExtract® Solution and heated to release DNA into the solution according to the following protocol: 65° C for 1 minute, 98° C for 15 minutes. Isolated DNA samples were then stored at −20°C for a maximum of 12 months before analysis.

The HNMT C314T polymorphism was determined via allele-specific restriction digestion after polymerase chain reaction (PCR) amplification of exon 4 according to the methods of Yan *et al.*.[14] DNA was amplified using the following primers: (5'- tgt aaa acg acg gcc agt gaa aaa cgt

tct ttc tat ctg ttt gta tat aa - 3') and (5'- cag gaa aca gct atg acc ttg gaa tgt taa aga aaa tct tag tat aat a - 3') (Midland Certified Reagent Company, Midland, TX). The PCR amplification included an initial denaturation step of at 94° C for 1 minute followed by 30 cycles at 94° C for 1 minute, 52° C for 1 minute and 72° C for 1 minute. Following a final 7 minute extension at 72° C the resulting PCR product was cooled to 4°C. The PCR product (25 μL) was then digested at 37° C for a minimum of 4 hours using EcoRV restriction enzyme (New England Biolabs, Ipswich, MA). The T314 allele was cleaved by EcoRV digestion while the C314 allele was not digested. Digests were subsequently run out on 2% agarose gel using ethidium bromide to visualize the fragments. Control samples with a known cleavage were included to ensure digestion had occurred. Given that gel-based genotyping methods were used, *HNMT* genotype assignments were determined independently by 2 separate research personnel.

Sample Size Estimation and Statistical Analysis

Sample size calculation was performed *a priori* using PS Power and Sample Size Calculation Software (version 2.1.31, Department of Biostatistics, Vanderbilt University, Nashville, TN).[16] Historical T314 allele frequencies in Caucasian adults with (0.14) and without (0.08) asthma were used to estimate frequencies of the T314 allele in children with (p_1) and without (p_0) AD.[14] Assuming $\alpha = 0.05$, $\beta=0.2$, $p_0 = 0.08$ and $p_1 = 0.14$, 213 subjects per group were projected as a requirement to detect a statistically significant difference in the frequency of the T314 allele between children with and without AD. Given the hypothesis generating and descriptive nature of this initial pilot study, however, it was neither practical nor feasible to conduct a study of this magnitude. Furthermore, the intent of the current study was not to compare allele frequencies between treatment groups, *per se*, but rather to investigate the potential association between AD and *HNMT* C314T genotype. Therefore, for this initial pilot investigation, we therefore chose to enroll 120 subjects per group and to perform an interim data analysis prior to enrollment of additional subjects. A sample size of 120 subjects per group was selected based on the anticipated subject enrollment rate at each participating site and the funds available to complete this pilot investigation. Assuming $\alpha = 0.05$, $p_0 = 0.08$, $p_1 = 0.14$ and $n = 120$ per group, the predicted *a priori* power to detect a statistically significant difference in the T314 allele frequency between children with and without AD was 0.50.

Statistical analyses were performed using SPSS® version 13.0 (SPSS, Chicago, IL). Subject demographics were compared using a two-sample, unpaired Student's t-test assuming equal variances. Allele and genotype frequencies were calculated in AD and control subjects and compared using χ^2 analysis. Given the small observed frequency of the TT genotype in both groups, combined frequencies for genotypes associated with reduced function (i.e., CT and TT) were used. Odds ratios and associated 95% confidence intervals were also calculated. The level of significance for all statistical tests was $\alpha = 0.05$.

Results

A total of 255 children were enrolled during the 13 month study period (129 AD and 126 control). All subjects completed the buccal swab procedure. However, due to violations of the inclusion/exclusion criteria (n = 5) and informed consent process (n = 1), 2 AD and 4 control subjects were excluded from analysis. Subject demographics, AD disease severity and antihistamine treatment / response information are presented in Table 1. Control subjects were slightly older than those with AD (2.9 vs. 2.5 years, respectively, p = 0.03) although the difference is of minimal clinical importance. The majority of children with AD were treated (either currently or in the past) with antihistamines (57%) and, in subjects in whom disease severity data was obtained from the parent (n=117), had either mild (51%) or moderate (43%) disease. Parental report of a good treatment response (based on their own subjective

assessment) was noted in 71% (n=41) of antihistamine treated subjects with evaluable response data (n=58/73).

HNMT genotypes were successfully obtained in 116 and 122 control and AD subjects, respectively. Allele and genotype frequencies of control subjects were in Hardy-Weinberg equilibrium and are presented in Table 2. The frequency of the T314 variant allele in children with AD was significantly higher than in controls (0.12 *vs.* 0.06, p = 0.04). The combined frequency of genotypes associated with reduced HNMT activity (i.e., CT or TT) was also significantly increased in children with AD (0.24) compared with controls (0.12) (p = 0.02). Children with genotypes conferring reduced HNMT activity were 2 times more likely to have AD than those who were homozygous for the C314 allele (odds ratio 2.3, 95% confidence interval 1.1 – 4.6).

Discussion

Histamine is an important biochemical mediator that regulates numerous processes involved in both the pathogenesis and symptomatology of AD. Through its interaction with the H_1 receptor, histamine plays a central role in mediating AD-induced pruritus, a common symptom that if inadequately controlled, can significantly impact quality of life.[17, 18] Histamine also acts as a chemical mediator of inflammation exerting pro-inflammatory and immunomodulatory effects which contribute to AD disease pathogenesis.[19–21] Increased local (i.e., skin) [22, 23] and systemic [2, 4, 5] histamine levels have been consistently noted in patients with AD suggesting that alterations in the synthesis, release and/or degradation of this biochemical mediator may be important in the pathogenesis, persistence and progression of disease.

HNMT is the primary enzyme responsible for histamine metabolism in human skin and its activity is, in part, mediated by genetic mechanisms. The *HNMT* gene, located on the long arm of chromosome 2 (q22.1) is approximately 34 kb in length, consists of 6 exons and has a second intron that is approximately 15 kb in length.[24] To date, a total of 8 SNPs in the *HNMT* gene have been identified although of these, only 3 occur with frequencies of greater than 5%. [25] The current study, which investigated associations between one of these *HMNT* variants (C314T) and AD, provides initial insight into how alterations in the physiologic processes determining histamine exposure might influence disease pathogenesis.

This is the first study to demonstrate a significant association between AD and the *HNMT* C314T (Thr105Ile) polymorphism. This relatively common SNP, which occurs in 5–10% of the Caucasian population,[13] results in decreased catalytic activity in the primary enzymatic pathway of histamine elimination in human skin. Our data are consistent with the hypothesis that genetically-associated reductions in histamine metabolism may contribute to AD disease pathogenesis and suggest that increased histamine levels in patients with AD may result, at least in part, from reduced inactivation via HNMT. They are also concordant with a recently published investigation in adults with atopic eczema which demonstrated reduced functional activity of diamine oxidase, a cytosolic protein that, although inactive in human skin, is thought to play an important role in the degradation of circulating histamine.[26] Our finding of a significant association of HNMT genotype with AD provides additional support for the hypothesis that impaired histamine metabolism may be a common pathogenic disease mechanism among the classic “atopic triad” of asthma, allergic rhinitis and AD given that similar associations with HNMT genotype also been observed in Caucasian adults with asthma.[14] Observation of a significant gene-disease association also indicates that *HNMT* genotype might represent a risk factor for AD and consequently, that genotyping may be useful to identify individuals who may be at increased risk of developing disease. This has potentially important therapeutic implications given the natural history of AD, the characteristic pattern of disease

progression to asthma and/or allergic rhinitis (i.e., the "atopic march")[27] and the possibility to delay and/or prevent disease progression via early pharmacologic intervention with oral antihistamines.[28–31]

While statistically significant, our findings do not appear to represent a major disease locus for AD given the relatively low frequency of the variant T314 allele in the AD group (0.12). However, recognizing that AD is a polygenic disorder,[32] it is possible that many different combinations of genes could result in clinically similar phenotypes. Potential candidate genes which may also influence histamine exposure and/or action include those involved in the synthesis (histidine decarboxylase)[33], release (IgE receptor polymorphisms)[34] and degradation (diamine oxidase, N-acetyltransferase)[33]. In addition, several SNPs in the H_1 receptor gene have been identified[35] and may similarly affect disease phenotype. Other functionally-significant SNPs in the *HNMT* gene (e.g., A939G)[25] may also play an important role. We also cannot exclude the possibility that our observations might result from linkage to additional polymorphisms within the *HNMT* gene and/or other genes important in the histamine biosynthetic pathway and AD pathogenesis.

Given the significant variability in clinical presentation, disease severity and response to conventional pharmacologic treatment among patients with AD, it is becoming increasingly apparent that there are specific disease phenotypes whose expression may be significantly influenced by inherited differences in disease pathogenesis. It is therefore possible that *HNMT* genotype may contribute to development of one such phenotype where histamine predominates as the primary biochemical mediator and consequently, where antagonism of its physiologic effects with antihistamines would be more likely to confer therapeutic benefit. Specifically, in individuals with genotypes conferring reduced HNMT activity (i.e., CT or TT), reduced histamine metabolism via HNMT may, in turn, result in a disease phenotype in which histamine predominates as a biochemical mediator. It is anticipated that these individuals would be more responsive to antihistamine treatment. However, additional longitudinal studies, in which standardized assessments are performed prior to and following an adequate trial of antihistamine therapy will be required in order to sufficiently characterize the relationship between genotype and treatment response. As with disease expression, treatment response to antihistamines may be polygenically determined (e.g., genes controlling expression of both histamine and drug biotransformation); a factor that must be considered in studies designed to examine associations between disease expression and antihistamine response.

In conclusion, these data suggest that the frequency of an allelic variant of HNMT associated with reduced enzyme activity is higher in children with AD as compared to those who are unaffected by the disease. In such patients, increased persistence of histamine in tissues resulting from reduced inactivation via HNMT may contribute to the pathogenesis, persistence and progression of AD. If these results are confirmed in subsequent investigations, HNMT genotype might represent a common risk factor for development of allergic disease and also, could permit identification of patients who are candidates for early preventative pharmacotherapeutic intervention. The current data do not rule out the potential for involvement of multiple candidate genes in disease pathogenesis, severity and treatment response in AD and thus, future investigations should consider multiple pharmacogenetic associations in relevant candidate genes. Finally, potential influences of genetic differences in the histamine biosynthetic pathway should be considered in future investigations of antihistamine response as well as in the development of novel antihistamine agents (e.g., H4 receptor antagonists).

Acknowledgements

Supported by the Aventis Asthma/Allergy Investigator Development Award and the National Institute of Child Health and Human Development (NICHD) Pediatric Pharmacology Research Unit (PPRU) Network (grant numbers 1 U10 HD 0495934-04 and 1 U10 HD31313-15).

We gratefully acknowledge the financial support provided by the Aventis Asthma/Allergy Investigator Development Award through the ACCP Research Institute. We also would like to thank the research personnel and support staff of the Kosair Charities Pediatric Clinical Research Unit and the following collaborating PPRU network sites: Children's Mercy Hospitals and Clinics, Kansas City, MO (Sub-Investigators: Amy Nopper, M.D., Kim Horii, M.D.); Baylor College of Medicine, Houston, TX (PI: Moise Levy, M.D.); Arkansas Children's Hospital (PI: Stacie Jones, M.D.). We also thank Elizabeth McDowell, RN, CCRC, Jackie Bourke, RN, CCRC, Laura McDowell, RN, Faye Jones, M.D., Tom Badgett, M.D., Jim Sublett, M.D., Mary Jane Smith, NP and Joseph Fowler, M.D. for their assistance with subject identification and recruitment and Doug Lorenz, MA, MSPH for his assistance with data analysis.

References

1. Munday J, Bloomfield R, Goldman M, et al. Chlorpheniramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis with a nocturnal itching and scratching component. Dermatology 2002;205(1):40–45. [PubMed: 12145433]
2. Fujisawa T, Komada M, Iguchi K, Uchida Y. Plasma histamine levels in normal and atopic children. Ann Allergy 1987;59(4):303–306. [PubMed: 3662132]
3. Kimura K, Adachi M, Kubo K, Ikemoto Y. The basal plasma histamine level and eosinophil count in allergic and non-allergic patients. Fukuoka Igaku Zasshi 1999;90(12):457–463. [PubMed: 10655666]
4. Ring J. Plasma histamine concentrations in atopic eczema. Clin Allergy 1983;13(6):545–552. [PubMed: 6640890]
5. Sampson HA, Broadbent KR, Bernhisel-Broadbent J. Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. N Engl J Med 1989;321(4):228–232. [PubMed: 2473400]
6. May CD. High spontaneous release of histamine in vitro from leukocytes of persons hypersensitive to food. J Allergy Clin Immunol 1976;58(3):432–437. [PubMed: 61221]
7. Shichijo M, Ebisawa M, Miura K, et al. Relationship between histamine release and leukotrienes production from human basophils derived from atopic dermatitis donors. Int Arch Allergy Immunol 1995;107(4):587–591. [PubMed: 7542518]
8. Francis D, Greaves MW, Yamamoto S. Enzymatic histamine degradation by human skin. Br J Pharmacol 1977;60(4):583–587. [PubMed: 907871]
9. Okinaga S, Ohrui T, Nakazawa H, et al. The role of HMT (histamine N-methyltransferase) in airways: a review. Methods Find Exp Clin Pharmacol 1995;17:16–20. [PubMed: 8750789]
10. Schwartz J, MM A, M G, H P, M R. Histaminergic transmission in the mammalian brain. Physiological Reviews 1991;17(1):1–51. [PubMed: 1846044]
11. Girard B, Otterness DM, Wood TC, Honchel R, Wieben ED, Weinshilboum RM. Human histamine N-methyltransferase pharmacogenetics: cloning and expression of kidney cDNA. Mol Pharmacol 1994;45(3):461–468. [PubMed: 8145732]
12. Price RA, Scott MC, Weinshilboum RM. Genetic segregation analysis of red blood cell (RBC) histamine N-methyltransferase (HNMT) activity. Genet Epidemiol 1993;10(2):123–131. [PubMed: 8339926]
13. Preuss CV, Wood TC, Szumlanski CL, et al. Human histamine N-methyltransferase pharmacogenetics: common genetic polymorphisms that alter activity. Mol Pharmacol 1998;53(4): 708–717. [PubMed: 9547362]
14. Yan L, Galinsky RE, Bernstein JA, Liggett SB, Weinshilboum RM. Histamine N-methyltransferase pharmacogenetics: association of a common functional polymorphism with asthma. Pharmacogenetics 2000;10(3):261–266. [PubMed: 10803682]
15. Hanifin J, Rajka G. Diagnostic Features of Atopic Dermatitis. Acta Derm Venereol 1980;92:44–47.
16. Dupont W, Plummer W. PS power and sample size program available for free on the internet 1997;18:274.

17. Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB Jr, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. Pediatr Dermatol 2005;22(3):192–199. [PubMed: 15916563]

18. Stander S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. Exp Dermatol 2002;11(1):12–24. [PubMed: 11952824]

19. Akdis CA, Blaser K. Histamine in the immune regulation of allergic inflammation. J Allergy Clin Immunol 2003;112(1):15–22. [PubMed: 12847474]

20. MacGlashan D Jr. Histamine: A mediator of inflammation. J Allergy Clin Immunol 2003;112(4 Suppl):S53–S59. [PubMed: 14530789]

21. Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H1 and H4 receptors in allergic inflammation: the search for new antihistamines. Nat Rev Drug Discov 2008;7(1):41–53. [PubMed: 18172439]

22. Johnson HH Jr, Deoreo GA, Lascheid WP, Mitchell F. Skin histamine levels in chronic atopic dermatitis. J Invest Dermatol 1960;34:237–238. [PubMed: 14407457]

23. Juhlin L. Localization and content of histamine in normal and diseased skin. Acta Derm Venereol 1967;47(6):383–391. [PubMed: 4168800]

24. Aksoy S, Raftogianis R, Weinshilboum R. Human histamine N-methyltransferase gene: structural characterization and chromosomal location. Biochem Biophys Res Commun 1996;219(2):548–554. [PubMed: 8605025]

25. Wang L, Thomae B, Eckloff B, Wieben E, Weinshilboum R. Human histamine N-methyltransferase pharmacogenetics: gene resequencing, promoter characterization, and functional studies of a common 5'-flanking region single nucleotide polymorphism (SNP). Biochem Pharmacol 2002;64 (4):699–710. [PubMed: 12167489]

26. Maintz L, Benfadal S, Allam JP, Hagemann T, Fimmers R, Novak N. Evidence for a reduced histamine degradation capacity in a subgroup of patients with atopic eczema. J Allergy Clin Immunol 2006;117 (5):1106–1112. [PubMed: 16675339]

27. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003;112(6 Suppl):S118–S127. [PubMed: 14657842]

28. Bustos GJ, Bustos D, Romero O. Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. Clin Exp Allergy 1995;25(6):568–573. [PubMed: 7648464]

29. ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. Early Treatment of the Atopic Child. Pediatr Allergy Immunol 1998;9(3):116–124.

30. Iikura Y, Naspitz CK, Mikawa H, et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. Ann Allergy 1992;68(3):233–236. [PubMed: 1546818]

31. Warner JO. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. J Allergy Clin Immunol 2001;108(6):929–937. [PubMed: 11742270]

32. Kiyohara C, Tanaka K, Miyake Y. Genetic susceptibility to atopic dermatitis. Allergol Int 2008;57 (1):39–56. [PubMed: 18209506]

33. Igaz P, Fitzimons CP, Szalai C, Falus A. Histamine genomics in silico: polymorphisms of the human genes involved in the synthesis, action and degradation of histamine. Am J Pharmacogenomics 2002;2(1):67–72. [PubMed: 12083955]

34. Palikhe NS, Kim SH, Cho BY, Ye YM, Hur GY, Park HS. Association of three sets of high-affinity IgE receptor (FcepsilonR1) polymorphisms with aspirin-intolerant asthma. Respir Med. 2008

35. Garcia-Martin E, Ayuso P, Luengo A, Martinez C, Agundez JA. Genetic variability of histamine receptors in patients with Parkinson's disease. BMC Med Genet 2008;9:15. [PubMed: 18366640]

Table 1

Subject demographics, AD disease severity and antihistamine response

	AD (n = 127)	Control (n = 122)
Age (years)	2.5 ± 1.5 (0.3 – 5.9)	2.9 ± 1.7 (0.5 – 5.9)[A]
Male (n, %)	71 (56%)	64 (52%)
Disease Severity (n=117)	60 Mild / 50 Moderate / 7 Severe	N/A
Antihistamine Use (n, %)	73 (57%)	
Antihistamine Response (n = 58)	41 Good / 9 Fair / 8 Poor	

[A] p = 0.03, data presented as mean ± SD (range)

Table 2

HNMT allele and genotype frequencies in AD and control subjects

Study Group	Allele Frequency (number of alleles)		Odds Ratio (95% CI)	Genotype Frequency (number of subjects)				Odds Ratio (95% CI)
	C	T		CC	CT	TT	Combined CT and TT	
Control (n=116)	0.94	0.06	1.1	0.88	0.11	0.009	0.12	2.3
	(217)	(15)	(0.6, 2.1)	(102)	(13)	(1)	(14)	(1.1, 4.6)
AD (n=122)	0.88	0.12		0.76	0.24	0	0.24	
	(215)	(29)		(93)	(29)	(0)	(29)	
		$\chi^2 = 4.2$					$\chi^2 = 5.5$	
		p = 0.04					p = 0.02	