Shared genetic variants between serum levels of high-density lipoprotein cholesterol and wheezing in a cohort of children from Cyprus

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Abstract

Background: In a cohort of children in Cyprus, we recently reported low levels of high density lipoprotein cholesterol (HDL-C) to be associated with asthma. We examined whether genetic polymorphisms that were previously linked individually to asthma, obesity, or HDL-C are associated with both asthma and HDL-C levels in the Cyprus cohort.

Methods: We assessed genotypes frequencies in current-wheezers (n = 190) and non-asthmatic controls (n = 671) and HDL-C levels across several genotypes. Binary logistic regression models were used to assess the effect of genotypes on wheezing risk and examined whether this effect is carried out through changes of HDL-C.

Results: Of the 16 polymorphisms tested, two polymorphisms TNFa rs3093664 and PRKCA rs9892651 presented significant differences in genotype distribution among current-wheezers and controls. Higher HDL-C levels were noted in carriers of genotype GG of polymorphism TNFa rs3093664 that was protective for wheezing Vs AG and AA genotypes (65.3 Vs 51.8 and 53.3 mg/dl, p-value < 0.001 and p-value for trend = 0.028). In polymorphism PRKCA rs9892651, HDL-C levels were lower in carriers of CC and TC genotypes that were more frequent in current-wheezers Vs TT genotype (52.2 and 52.7 Vs 55.2 mg/dl, p-value = 0.042 and p-value for trend = 0.02). The association of TNFa rs3093664 with wheezing is partly mediated by its effect on HDL-C whereas association of PRKCA rs9892651 with wheezing appeared to be independent of HDL-C.

Conclusions: We found evidence that two SNPs located in different genetic loci, are associated with both wheezing and HDL-C levels, although more studies in other populations are needed to confirm our results.

Keywords: Asthma, Children, High density lipoprotein cholesterol, Polymorphisms, Genotypes

Background

High density lipoprotein cholesterol (HDL-C) is widely known to have systemic and vascular anti-inflammatory properties [1] and, as shown in vitro, also anti-inflammatory effects consistent with a protective role in asthma [2]. In a cohort of 3982 children in Cyprus, we recently reported low levels of HDL-C at age 11–12 years to be associated with active asthma five years later in adolescence, suggesting a potential role of this lipoprotein in the pathogenesis of pediatric asthma [3]. Obesity is also widely accepted to be related to asthma [4] as well as with low serum HDL-C levels [5] and consequently it may play a confounding or mediating role in the asthma – HDL-C association.

Numerous individual studies confirmed the implication of genetic factors in the development of asthma [6], obesity [7] or low HDL-C [8]. In addition, epidemiological studies in twins have suggested that the association of asthma and allergy with obesity or low HDL-C levels could, at least in part, be explained by the presence of shared genetic factors [9]. In the case of asthma and obesity, overlapping
genomic regions for common susceptibility genes on chromosomes 5, 6, 11 and 12 have been identified by linkage analysis studies [10]. Specifically, some of the most known candidate genes and genetic loci for asthma and allergy [6, 11] have already been linked [12] to the pathogenesis of obesity such as the tumor necrosis factor alpha (TNF-α) gene [12], the protein kinase C alpha (PRKCA) gene [13] and β2-adrenergic receptor (ADRB2) [14]. To date however, no common genetic loci were reported to be associated with asthma and HDL-C levels.

In this study, we selected 16 single nucleotide polymorphisms (SNPs) located in genes that were linked to asthma and/or obesity or HDL-C and examined in the Cyprus cohort of children a) whether they were associated with both asthma and HDL-C levels and b) explored, in the SNPs that were associated with both conditions, whether the association with asthma is mediated through changes in the levels of HDL-C.

**Methods**

**Study population**

The participants of this study were selected from a cohort of 3982 children who participated in two large school-based health surveys in Cyprus (Fig. 1). The first survey spanned years 2001–2003 and involved all children (n = 19,849) attending the 6th grade from all primary schools across Cyprus and focused on nutrition and physical fitness. The second survey was conducted in year 2007, followed-up 3982 of the subjects who took part in the first survey (20.1 %) and focused on respiratory health (International Study of Asthma and Allergies in Childhood – ISAAC) and risk factors for asthma. In a case-control design, we invited all those from the 3982 children who on the second survey (ISAAC questionnaire) reported wheezing in the past 12 months (n = 297) to participate in this study along with a triplicate number of healthy controls (n = 932).

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**Fig. 1** Course of the study: From the 19,849 participants (11–12 years) in Survey 1, a random sample of 3982 adolescents (15–17 years) participated in Survey 2. All (n = 297) subjects from the 3982 sample, who reported wheezing in the last 12 months were invited to participate as cases. A sample of 932 children with no diagnosis of asthma and no wheezing in the past 12 months were invited to participate as controls.
**Phenotype description**

Current wheezers (CUWH) were named those who reported wheezing in the past 12 months. For the purpose of performing a sensitivity analysis, the case definition was further refined to Active Asthma (ACAS), if also there was report of diagnosis of asthma ever. Controls were selected amongst the 3982 adolescents who did not report any wheezing or asthma ever (Never Wheezers Never Asthmatics - NWNA). NWNA were selected using a stratified random sampling approach in order to increase the probability of selection of children at the extremes of Body Mass Index (BMI) change between childhood and adolescence, in line with the scope of another study on the relation of adiposity and serum lipids with asthma [15]. The full scale of BMI change (and BMI) was represented in the final sample, just in slightly different proportions compared to the general population i.e. there was slight over-representation of participants whose BMI increased or decreased between childhood and adolescence and, equivalently slight under-representation of children whose BMI remained stable over this period. In all analyses normalized sampling weights based on inverse probability of selection from the original population were used.

In the asthmatic groups, information was also obtained regarding the presence of exercise induced wheezing and hospital admissions ever in hospital for an asthma attack. IgE sensitization was assessed with skin prick tests (SPT) to 8 common aeroallergens (Greer, USA), performed and interpreted according to the GA2LEN recommendations [16]. Children with a positive SPT to any of the 8 allergens tested were considered sensitized to IgE. Asthmatic children had measurements of forced expiratory volume in one second (FEV1) (Vitalograph, UK) and values were expressed as percent of predicted [17].

The adolescents had anthropometric measurements and assessments of serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), HDL-C and triglycerides (TG) after a 12-h fast. We calculated BMI (kg/m2) and expressed it as age- and gender-specific z-scores based on the United States’ Centers for Disease Control 2000 growth charts [18]. Lipids were determined with the ILab 600 analyzer using ILab Chemistry systems (Instrumentation Laboratory SpA, Monza, Milano, Italy). The assays’ coefficients of variation were 2.08 % for TC, 1.53 % for HDL-C, 1.15 % for LDL-C and 2.45 % for TG.

**SNPs selection, DNA extraction and genotyping**

Using the NCBI PubMed Entrez database, a total of 16 SNPs in ten genes that were previously reported [12–14, 19–30] to be associated individually with asthma, obesity or HDL-C were selected for genotyping (Table 1). Venous blood specimens were collected from participants in EDTA treated tubes that were transported on ice to the laboratory. DNA was extracted from peripheral blood lymphocytes using the standard phenol extraction method, and stored at −70 °C until genotyping. Genotyping was carried out using TaqMan Real-time PCR assay. Thirty ng of genomic DNA was used for each reaction and the end-point PCR was carried out on the ABI primer 7900 HT (Applied Biosystems, Foster City, CA).

| Gene | Chromosome | SNPs genotyped | dbsSNP# | Alleles | Published literature reference |
|------|------------|----------------|---------|---------|-------------------------------|
| IL1R1 | 2 | 1 | rs1420101 | C > T | Gudbjartsson 2009 [19] |
| ACP1 | 2 | 1 | rs12714402 | G > A | Bottini 2007 [20] |
| GNPDA2 | 4 | 1 | rs10938397 | A > G | Melen 2010 [21] |
| IL13 | 5 | 1 | rs20541 | C > T | Cui 2012 [22] |
| ADRB2 | 5 | 3 | rs1800888 | C > T | Hall 2006 [23] |
|         |         |       | rs1042714 | C > G | Park 2008 [24] |
|         |         |       | rs1042713 | G > A | Garenc 2002 [25] |
| TNF-a | 6 | 3 | rs3093664 | A > G | Joubert 2011 [26] |
|         |         |       | rs1800629 | G > A | Thomas 2001 [27] |
|         |         |       | rs361525 | G > A | Castro 2009; Joffe 2012 [12, 28] |
| LEP | 7 | 1 | rs2167270 | G > A | Ichihara 2008 [29] |
| ACE | 17 | 2 | rs4343 | A > G | Rankinen 2006 [14] |
|         |         |       | rs4311 | C > T | Halapi 2010 [30] |
| GSDMB | 17 | 1 | rs7216389 | T > C | Murphy 2009 [13] |
| PRKCA | 17 | 2 | rs9892651 | T > C | |
|         |         |       | rs9901804 | G > A | |
Statistical analysis

Differences in participant characteristics between study groups were investigated in a pairwise manner (NWNA versus CUWH and NWNA versus ACAS) using chi square test in the case of categorical variables and t-test in the case of continuous variables. Furthermore, chi-squared testing was used for Hardy-Weinberg (HW) equilibrium determination and for the investigation of genotypes and allele frequencies associations with study groups. Mean HDL-C levels were compared across genotypes using the one-way ANOVA test and ρ and p values and ρ values for trend were reported. For SNPs that presented significant effects, two binary logistic regression models were used a) to assess the effect of genotypes on asthma risk and b) examine whether this effect is carried out through the change of HDL-C, after adjusting for age and sex (Model 1), age, sex and BMI (Model 2) and age, sex, BMI and HDL-C levels (Model 3). The genotype with the most protective effect for asthma was chosen as the reference in all cases. Binary logistic regression analysis was performed only among NWNA and CUWH as the ACAS group was very small and for most SNPs, at least one cell had no cases. Analysis was performed with SPSS statistical package, version 20.0 (IBM, SPSS Inc., Chicago, IL).

Results

A total of 190 subjects with CUWH (of whom 69 ACAS) and 671 NWNA participated in the study. This corresponds to 64 and 72 % response rates respectively of the targeted population for recruitment (Fig. 1). Participants were aged 17 years (SD 0.6) and the three groups did not differ significantly in terms of age, gender and BMI (Table 2). Mean HDL-C levels in the ACAS and CUWH were significantly lower than in the controls (47.9 and 49.1 Vs 53.4 mg/dl; p < 0.001 for both) (Table 2). Mean serum levels of TC, LDL-C and TG were similar in the three groups (results not shown in detail). The frequency of atopic sensitization was 52.0 % in ACAS and 41.4 % in CUWH (p-value = 0.073), whereas FEV1 was normal and not different between them (97.6 % Vs 99.1 % of predicted; p-value = 0.332) indicating that they were clinically stable. ACAS were experiencing more frequently exercise induced wheezing (83.6 % vs 67.6 %, p-value < 0.001) and lifetime hospitalizations for asthma attack (18.8 % vs 9.0 %, p-value = 0.003) than the CUWH (Table 2). Results of minor allele frequencies and HW equilibrium for genotype distribution are presented in Additional file 1: Table S1.

SNPs genotype distribution in CUWH Vs NWNA and HDL-C levels

Distribution of the genotypes of the 16 polymorphisms in CUWH Vs NWNA and the corresponding HDL-C levels can be found in Additional file 2: Table S2. Two polymorphisms, TNFa rs3093664 and PRKCA rs9892651 presented statistically significant and ADRB2 rs1800888 nearly significant differences in genotype distribution among NWNA and CUWH and are presented separately at Table 3.

The larger differences were exhibited in the genotype distribution of TNFa rs3093664 polymorphism, where the rare GG genotype appeared to offer a protective effect with a frequency of 4.1 % Vs 1.1 % in NWNA and CUWH respectively (p-value = 0.03, p-value for trend = 0.912). Significantly higher HDL-C levels were noted in subjects with GG genotype as opposed to those in AG and AA genotype carriers (65.3 mg/dl Vs 51.8 mg/dl and 53.3 mg/dl, p-value < 0.001 and p-value for trend = 0.028) (Table 3). The genotypes of polymorphism PRKCA rs9892651 were also found to be differentially distributed with the frequency of genotype CC to be higher in CUWH (19.2 %) compared to NWNA (14.3 %) (p-value = 0.141, p-value for trend = 0.048). HDL-C levels

|              | NWNA (Controls) (n = 671) | CUWH (Current Wheezers) (n = 190) | p-value | ACAS (Active Asthmatics) (n = 69) | p-value |
|---------------|---------------------------|-------------------------------|---------|--------------------------------|---------|
| Age (yrs)a   | 16.95 (15.91–18.00)       | 17.00 (16.00–18.11)           | 0.309   | 16.91 (15.91–18.07)             | 0.567   |
| Sex (% female)b | 57.4 %                    | 56.9 %                        | 0.914   | 56.5 %                          | 0.894   |
| BMI z scoresb | 0.358 (–2.13–2.16)        | 0.288 (–1.73–2.20)            | 0.396   | 0.340 (–1.87–2.37)              | 0.896   |
| HDL (mg/dl)c | 53.4 (30.00–86.50)        | 49.1 (30.00–71.55)            | <0.001  | 47.9 (31.73–73.75)              | <0.001  |
| Atopic Sensitization (% positive)b | -                        | 41.4 %                        | -       | 520.0 %                        | 0.073e  |
| FEV1 (% predicted)a | -                       | 99.1 (72.9–130.5)            | -       | 97.6 (62.0–125.6)               | 0.332a  |
| Exercise Induced Wheezing (% positive)b | -                       | 67.6 %                        | -       | 83.6 %                         | <0.001c |
| Hospitalization (% positive)b | -                       | 9.0 %                         | -       | 18.8 %                         | 0.003d  |

aMean and 95 % CI, Independent sample t test for equality of means (2-sited significance)
bPercentage, χ² test (asymptomatic 2-sited significance)
cComparison between NWNA and CUWH
dComparison between NWNA and ACAS
eComparison between CUWH and ACAS
were also significantly lower in subjects with the CC and TC genotype compared to TT genotype (52.2 mg/dl and 52.7 mg/dl Vs 55.2 mg/dl, \(p\)-value = 0.042 and \(p\)-value for trend = 0.02).

The only other SNP that displayed nearly significant differences in genotype frequencies was \(ADRB2\) rs1800888, where the heterozygous genotype CT had a higher frequency in NWNA compared to CUWH (5 % Vs 2.2 %, \(p\)-value = 0.076) thus exhibiting a protective effect compared with the homozygote CC genotype. HDL-C levels in the protective CT genotype carriers were not significantly higher at the 5 % level to those in CC, probably due to the small size of the CT genotype group (57.24 mg/dl Vs 53.28 mg/dl, \(p\)-value = 0.092).

SNPs genotype distribution in ACAS Vs NWNA and HDL-C levels

As a sensitivity analysis, the same investigations were performed between the more strictly defined asthmatic phenotype ACAS and NWNA. In general, the magnitude and direction of the relationships of the three SNPs genotypes in ACAS and NWNA remained consistent with the findings of the NWNA Vs CUWH analysis although these were not always significant probably due to the smaller size of the ACAS study-group. A detailed description of these findings is presented with Additional file 3: Table S3. Allelic associations of the 16 tested SNPs with study groups were not statistically different and are presented in Additional file 4: Table S4.

**Table 3** SNPs genotype distribution in Current Wheezers (CUWH) Vs Controls (NWNA) and HDL-C levels

| SNP (genotype) | NWNA (n, %) | CUWH (n, %) | \(\chi^2\) | \(p\) value | HDL mg/dl (mean, 95 % CI) | F | \(p\) value | \(p\) trend |
|----------------|-------------|-------------|----------|----------|-------------------------|---|----------|----------|
| \(ADRB2\) rs1800888 |             |             |          |          |                         |   |          |          |
| CC             | 609 (95 %) | 175 (97.8 %) |          |          | 53.3 (52.3–54.2) | 5.72 (51.7–62.8) | 2.840 | 0.092 |
| CT             | 32 (5.0 %) | 4 (2.2 %) | 2.535 | 0.076 | 57.2 (51.7–62.8) | - | - |
| \(TNFa\) rs3093664 |             |             |          |          |                         |   |          |          |
| AA             | 500 (79.6) | 134 (76.1) |          |          | 53.3 (52.2–54.3) | 5.17 (49.4–54.1) | 17.87 | >0.001 |
| AG             | 102 (16.2) | 40 (22.7) |          |          | 51.7 (49.4–54.1) | - | - |
| GG             | 26 (4.1) | 2 (1.1) | 7.047 | 0.03 | 65.3 (59.2–71.4) | - | - |
| \(PRKCA\) rs9892651 |             |             |          |          |                         |   |          |          |
| TT             | 230 (37.0) | 52 (30.2) |          |          | 55.2 (53.4–56.9) | 52.7 (51.4–54.1) | 3.179 | 0.042 |
| CT             | 302 (48.6) | 87 (50.6) |          |          | 52.7 (51.4–54.1) | - | - |
| CC             | 89 (14.3) | 33 (19.2) | 3.921 | 0.14 | 52.2 (50.0–54.5) | - | - |

\(\chi^2\) test (asymptomatic 2-sided significance)

Fisher Exact test (exact 1-sided significance)

Comparisons of means (One way ANOVA)

**Discussion**

In this case-control study, we examined the effect of 16 genetic variants on asthma phenotypes and identified two SNPs that were simultaneously associated with the wheezing and HDL-C levels. Although many studies have examined separately the relationship of genetic loci with respiratory outcomes, only few have searched for common genetic variants between asthma and metabolic markers [12, 13, 21, 31]. Skaaby et al. studied loss-of-function mutations in the filaggrin gene, which are known to be associated with asthma and allergies and higher vitamin D, and found higher vitamin D status to...
be associated with higher HDL-C levels [32], suggesting an indirect potential genetic link between asthma and allergies with high HDL-C levels. In our cohort, we have not examined polymorphisms in the filaggrin gene, but to the best of our knowledge, this is the only study so far which, in the same population, assessed simultaneously the direct association of selected SNPs with wheezing and HDL-C levels. Interestingly, in our study the direction of the association of wheezing and HDL-C levels is in the opposite direction from the one implied in the Skaaby et al. study. More importantly, our results provide preliminary evidence that the association of TNFa rs3093664 with wheezing is mediated in part by its effect on HDL-C levels.

Evidence for underlying mechanisms of action

TNF-α gene codes for a highly pro-inflammatory cytokine [33] involved in many pathophysiological mechanisms of asthma [34, 35]. TNF-α is also known to affect lipid metabolism and lipid serum levels [36, 37]. Specific polymorphisms of the TNFa gene have been reported to affect HDL-C levels [38] and have been proposed as risk factors towards obesity, metabolic syndrome and type 2 diabetes mellitus [39]. Our findings point towards a novel protective effect of genotype GG of TNFa rs3093664 against wheezing but also at the same time suggest a strong association of this genotype with higher levels of HDL-C. To date, only few studies have examined the association of this particular polymorphism with asthma [26] or any metabolic condition [40]. Although TNF-α serum levels were not assessed in this study, previous reports have documented that TNF-α serum levels are inversely associated with serum HDL-C in the general population [41], whereas administration of anti TNF-α agents in patients with rheumatic diseases has been shown to result in elevated HDL-C levels [42, 43].

Coupled with these observations, our results suggest that in this small group of carriers of the GG genotype we may have a compromised TNF-α pro-inflammatory activity, manifesting as significantly lower risk for wheezing. At the same time, the direct protective effect of genotype GG for wheezing is further enhanced by the higher HDL-C levels that result from the reduced activity of TNF-α and its inflammatory properties [1].

Enzyme PKC-α has been proposed to be involved in asthma pathogenesis [44], in adipogenesis [45] and lipid mediated insulin resistance [46]. The potential pleiotropic effect of PRKCA gene on asthma and BMI was demonstrated by different SNPs influence on asthma or obesity [13, 21], including rs9892651. Our findings also support a pleiotropic effect of PRKCA rs9892651 as the minor C allele appeared to be more prevalent among current wheezers and also associated with lower HDL-C levels, although the effect on the risk of wheezing appeared to be very modest.

Polymorphisms of ADRB2 gene have been studied extensively in asthma but also in lipolysis of the adipose tissue [47]. We examined three of the most well studied polymorphisms of ADRB2 gene, the common rs1042714 and rs1042713 and the rarer rs1800888 [48, 49]. Our study provides evidence in support of a modest protective role for wheezing of T allele of the rare polymorphism rs1800888 but also for a modest association with higher HDL-C levels. This is the first study which evaluated the effects of rs1800888 on HDL-C levels since previous studies mainly examined cardiovascular outcomes with conflicting results [50–52].

Study limitations

The use of self-reported questionnaire data obtained from a young population to define wheezing and select cases and controls is not as accurate as the use of
Conclusions

In conclusion, this study provides a first indication that two SNPs located in different genetic loci, TNFa rs3093664 and PRKCA rs9892651, are associated with both the wheezing and HDL-C levels. The association of TNFa rs3093664 with wheezing was mediated in part by its effect on HDL-C levels whereas the associations of PRKCA rs9892651 with wheezing appeared to be independent of HDL-C levels. Further studies are needed to confirm these findings and reveal the functional mechanisms implicated in the interactions of HDL with wheezing and genetic loci expression.

Additional files

**Additional file 1: Table S1.** Hardy – Weinberg equilibrium and MAF results. (DOCX 15 kb)

**Additional file 2: Table S2.** Genotype distribution of all 16 SNPs in Current Wheezers (CUWH) Vs Controls (NWNA) and HDL-C levels. (DOCX 28 kb)

**Additional file 3: Table S3.** SNPs genotype distribution in Active Asthmatics (ACAS) Vs Controls (NWNA) and HDL-C levels. (DOCX 16 kb)

**Additional file 4: Table S4.** Allelic comparisons for 16 SNPs in Never Wheezers Never Asthmatics (NWNA) Vs Current Wheezers (CUWH) and in Never Wheezers Never Asthmatics (NWNA) Vs Active Asthmatics (ACAS). (DOCX 21 kb)

Abbreviations

ACAS, active asthmatics; ADRB2, β2-adrenergic receptor; CUWH, current wheezers; HDL-C, high density lipoprotein cholesterol; NWNA, never wheezers never asthmatics; OR, odds ratio; PRKCA, protein kinase C alpha; SNPs, single nucleotide polymorphisms; TNF-a, tumor necrosis factor alpha

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Availability of data and material

The dataset supporting the conclusions of this article is available in the Figshare repository. https://dx.doi.org/10.6084/m9.figshare.3462782.v1.

Authors’ contributions

PY conceived, designed the study, secured the funding and prepared the first draft of the manuscript. PK performed the statistical analysis under NM supervision and contributed towards the preparation of the first draft of the manuscript. OK coordinated the field study. SY performed the genetic analysis under the guidance of PZ. KD and AZ performed the serum lipids assessment. SS, DP, NM and PZ contributed towards the interpretation of the findings. All authors read and approved the final manuscript.

Authors’ information

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Competing interests

The author(s) declare that they have no competing interests.

Ethics approval and consent to participate

The study has been performed in accordance with the declaration of Helsinki and was approved by the Cyprus National Bioethics Committee (ref: EEBK/EP/2009/18). Written informed consent was obtained from each participant and their guardian.

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References

1. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antinflammatory properties of HDL. Circ Res. 2004;95(8):764–72.
2. Otera H, Ishida T, Nishiuma T, Kobayashi K, Kotani Y, Yasuda T, Kandu RK, Quertermous T, Hirota K, Nishiuma Y. Targeted inactivation of endothelial lipase attenuates lung allergic inflammation through plasma HDL level and inhibiting eosinophil infiltration. Am J Physiol Lung Cell Mol Physiol. 2009;296(4):L594–602.
3. Yiallouros P, Savva S, Kolokotroni O, Behbud B, Zeniou M, Economou M, Chadjigeorgiou C, Noursides Y, Tamositis M, Lamnios D. Low serum high-density lipoprotein cholesterol in childhood is associated with adolescent asthma. Clin Exp Allergy. 2012;42(3):423–31.
4. Salome C, Marks G. Sex, asthma and obesity: an intimate relationship? Clin Exp Allergy. 2011;41(1):13–6.
5. Eisenmann JC, Welk GJ, Ihmels M, Dollman J. Fatness, fitness, and cardiovascular disease risk factors in children and adolescents. Med Sci Sports Exerc. 2007;39(8):1251–6.
6. Vercelli D. Discovering susceptibility genes for asthma and allergy. Nat Rev Immunol. 2009;9(8):570.
7. Eisenmann JC, Welk GJ, Ihmels M, Dollman J. Fatness, fitness, and cardiovascular disease risk factors in children and adolescents. Med Sci Sports Exerc. 2007;39(8):1251–6.
8. Weissglas-Volkov D, Pajukanta P. Genetic causes of high and low serum HDL-cholesterol. J Lipid Res. 2010;51(8):2032–57.
9. Becker KG. The common variants/multiple disease hypothesis of common complex genetic disorders. Eur Respir J. 2009;33(5):1003–10.
10. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun. 2008;12(1):1075–84.
11. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun. 2008;12(1):1075–84.
12. Castro-Giner F, Kogevinos M, Imboden M, de Cid R, Jarvis D, Machler M, Berger W, Burney P, Franklin KA, Gonzalez JR, Heinrich J, Janson C, Omenaas E, Pin I, Rochat T, Sunyer J, Wijt M, Anto JM, Estivill X, Pérusse L, Bouchard C. The human obesity gene map: the 2005 update. Obesity. 2006;14(4):529–644.
13. Yiallouros PK, Savva SC, Kolokotroni O, Dinu M, Zerva A, Kouis P, Bouquet J, Middleton N. Asthma: The Role of Low High-Density-Lipoprotein Cholesterol in Childhood and Adolescence. Int Arch Allergy Immunol. 2014;165(2):91–9.
14. Bouquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bouquet PJ, Burney PG, Canonica GW, Carlsten C, Cox L, Haathoel T, Lodrup Carlsten KC, Price D, Solominski B, Simons ER, Ferrer M, Wickman M, Annessi-Maeso I, Baena-Cagnani CE, Bergmann KC, Bindslev-Jensen C, Casale TB, Chiriac A, Cruz AA, Dubaque R, Durham SR, Fokkens WJ, Gerth-van-Wijk R, Kalyazi O, Kowalski ML, Mari A, Mulloli P, Nazmanova-Barnava L, O’Hehir RE, Ohts K, Panzer P, Passalacqua G, Ring J, Rogala B, Romano A, Ryan D, Schmid-Grendelmeier P, Todo-Bom A, Valenta R, Woehrl S, Yusuf OM, Zuberbier T, Demoly P. Practical guide to skin prick tests in allergy to aeroallergens. Allergy. 2012;67(8):1086–98.
15. Rankinen T, Zuberi A, Chagnon YC, Rankinen T, Zuberi A, Chagnon YC, Rankinen T, Zuberi A, Chagnon YC, Rankinen T, Zuberi A, Chagnon YC. Genetic factors for human obesity. Cell Mol Life Sci. 2008;65(7):1295–302.
16. Ichihara S, Yamada Y. Genetic factors for human obesity. Cell Mol Life Sci. 2008;65(7):1295–302.
17. Thomas PS. Tumour necrosis factor-alpha: The role of this multifunctional cytokine in asthma. Immunol Cell Biol. 2001;79(2):132–40.
18. Joffe YT, Van der Merwe E, Collins M, Lambert E, September A, Goedecke J. The tumor necrosis factor-a gene – 238 G > A polymorphism, dietary fat intake, obesity risk and serum lipid concentrations in black and white South African women. Eur J Clin Nutr. 2012;66:1295–302.
19. Siczekarkiewicz A, Berekowicz A, Sobkowiak P, Popiel A. Are genes associated with energy metabolism important in asthma and BM? J Asthma. 2009;46(1):153–8.
20. Skabas T, Husemøen LL, Martinsen T, Thysen JP, Meegaard M, Thuesen BH, Pisinger C, Jørgensen P, Johansen JD, Mennel T, Carlsten B, Szczek PB, Sønder S, Fenger RV, Fenger M, Linneberg A. Vitamin D status, filaggrin genotype, and cardiovascular risk factors: a Mendelian randomization approach. PloS One. 2013;8(3):e57647. doi:10.1371/journal.pone.0057647.
21. Deay D, Brightling C. Cytokines and cytokine-specific therapy in asthma. Adv Clin Chem. 2012;57:59.
22. Thomas PS, Yates DH, Barnes PJ. Tumor necrosis factor-alpha increases airway responsiveness and sputum neutrophilia in normal human subjects. Am J Respir Crit Care Med. 1995;152(1):76–80.
23. Brightling C, Berry M, Arzani Y. Targeting TNF-a: a novel therapeutic approach for asthma. J Allergy Clin Immunol. 2008;121(1):10–15.
24. van Sijl AJM, Peters MJL, Knol DL, de Vet RHG, Sattar N, Bijnensh BAC, Smulders YM, Nurmondhe MT. The effect of TNF-alpha blocking therapy on lipid levels in rheumatoid arthritis: a meta-analysis. Semin Arthritis Rheum. 2011;41(3):393–400.
25. Glass CK, Olfeky JM. Inflammation and lipid signaling in the etiology of insulin resistance. Curr Metab. 2012;15(5):635–45.
26. Fontaine-Bisson B, El-Sohemy A. Genetic polymorphisms of tumor necrosis factor-alpha modify the association between dietary polyunsaturated fatty acids and plasma high-density lipoprotein-cholesterol concentrations in a population of young adults. J Nutrigenet Nutrigenomics. 2008;5(3):215–23.
27. Sobti RC, Kher R, Sharma YP, Talwar KK, Singh N. Risk of obesity and type 2 diabetes with tumor necrosis factor-a 308G/A gene polymorphism in metabolic syndrome and coronary artery disease subjects. Mol Cell Biochem. 2012;360(1–2):1–7.
28. Boraska V, Rayner NW, Groves CJ, Frayling TM, Diakite M, Rockett KA, Kwiatkowski DP, Day-Williams AG, McCarthy MI, Zeggini E. Large-scale association analysis of TNF-alfa gene region polymorphisms in type 2 diabetes. BMC Med Genet. 2010;11(1):69.
41. Yamagishi S, Adachi H, Matsui T, Nakamura K, Enomoto M, Fukami A, Otsuka M, Kunage S, Nanjo Y, Imaizumi T. Decreased High-Density Lipoprotein Cholesterol Level is an Independent Correlate of Circulating Tumor Necrosis Factor-α in a General Population. Clin Cardiol. 2009;32(9):E29–32.

42. Yeh K, Lee C, Chang C, Lin Y, Huang J. Lipid Profiles Alter from Pro-Atherogenic into Less Atherogenic and Proinflammatory in Juvenile Idiopathic Arthritis Patients Responding to Anti TNF-α Treatment. PLoS One. 2014;9(3):e90757.

43. Di Minno MN, Ambrosino P, Peluso R, Di Minno A, Lupoli R, Dentali F. Lipid profile changes in patients with rheumatic diseases receiving a treatment with TNF-α blockers: A meta-analysis of prospective studies. Ann Med. 2014;46(7–8):73–83.

44. McGraw DW, Elving JM, Fogel KM, Wang WC, Glinka CB, Mihlbachler KA, Rothenberg ME, Liggett SB. Crosstalk between Gi and Gq/Gs pathways in airway smooth muscle regulates bronchial contractility and relaxation. J Clin Invest. 2007;117(5):1391–8.

45. Artemenko Y, Gagnon A, Aubin D, Sorisky A. Anti-adipogenic effect of PDGF is reversed by PKC inhibition. J Cell Physiol. 2005;204(2):646–53.

46. Schmitz-Peiffer C. Protein Kinase C and lipid-induced insulin resistance in skeletal muscle. Ann N Y Acad Sci. 2002;967(1):146–57.

47. Amer P. Genetic variance and lipolysis regulation: implications for obesity. Ann Med. 2001;33(8):542–6.

48. Jalba MS, Rhoads GG, Demissie K. Association of Codon 16 and Codon 27 β2-Adrenergic Receptor Gene Polymorphisms with Obesity: A Meta-analysis. Obesity. 2008;16(9):1096–106.

49. Kontopoulos-Ioannidis DG, Manoli EN, Ioannidis J. Meta-analysis of the association of β2-adrenergic receptor polymorphisms with asthma phenotypes. J Allergy Clin Immunol. 2005;115(5):963–72.

50. Thomsen M, Dahl M, Tylbjærg-Hansen A, Nordestgaard B. β2-adrenergic receptor Thr164Ile polymorphism, blood pressure and ischaemic heart disease in 66 750 individuals. J Intern Med. 2012;271(3):305–14.

51. Thomsen M, Dahl M, Tylbjærg-Hansen A, Nordestgaard BG. β2-adrenergic receptor Thr164Ile polymorphism, obesity, and diabetes: comparison with FTO, MC4R, and TMEM18 polymorphisms in more than 64,000 individuals. J Clin Endocrinol Metab. 2012;97(6):E1074–9.

52. Schurks M, Kurth T, Ridker PM, Buring JE, Zee KY. Association between polymorphisms in the beta2-adrenergic receptor gene with myocardial infarction and ischaemic stroke in women. Thromb Haemost. 2009;101(2):351–8.

53. Montella S, Baraldi E, Cazzato S, Arrizza R, Berardi M, Brunetti LM, Cardinale F, Cutera R, de Benedictis FM, di Palmo E, Di Pillo S, Fenu G, La Grutta S, Lombardi E, Pacentini G, Santamaria F, Ullmann N, Rusconi F. Italian Pediatric Severe Asthma Network (IPSAN) on behalf of the Italian Society of Pediatric Respiratory Diseases (SIMRI). Severe asthma features in children: a case–control online survey. Ital J Pediatr. 2016;42:9. doi:10.1186/s13052-016-0217-z.