LETTER TO THE EDITOR

An association analysis to identify genetic variants linked to asthma and rhino-conjunctivitis in a cohort of Sicilian children

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Abstract

Asthma and rhino-conjunctivitis are common chronic diseases in childhood. In this cross-sectional study, we performed a gene association analysis with current asthma and rhino-conjunctivitis in a cohort of Sicilian children aged 10–15 years. Overall, our findings reveal the importance of different genetic variants at 4p14, 16p12.1, 17q12, 6p12.2 and 17q21.1, identifying possible candidate genes responsible for susceptibility to asthma and rhino-conjunctivitis.

Keywords: Asthma, Rhino-conjunctivitis, Sicilian children, Genetics, SNPs

To the Editor,

Asthma and rhino-conjunctivitis (RC) are common diseases worldwide that are frequently associated. Observed differences in prevalence of asthma and RC may be explained by genetic susceptibility, though environmental factors play a relevant role [1]. In order to increase genomic information on Sicilian children, this research has explored some genetic variants to discover possible association with asthma and RC.

A representative sample of 1050 children within the “Palermo Junior High School” (PJHS II) [2] study were investigated through questionnaires, spirometry, and skin prick test (SPT) to quantify the prevalence of asthma and RC, in association with allergic sensitization and respiratory function, and to evaluate the role of environmental and host risk factors for allergic respiratory diseases. The study was approved by the local Institutional Ethical Committee. All parents of the enrolled children signed a written informed consent.

Two different phenotypes were identified: Current Asthma (CA) defined as asthma ever plus at least a wheeze episode in the last 12 months, RC defined as sneezing, or runny, or blocked nose apart from common cold or flu in the last 12 months and nose problem accompanied by itching and/or watering eyes. The concomitant presence of CA and RC was merged into the CA group; children without CA and RC (nAnRC) were used as controls.

A total of 52 Single Nucleotide Polymorphisms (SNPs), involved in the innate immune system pathways were selected for genotyping by Matrix-Assisted Laser Desorption/Ionization (MALDI-TOF-MS). Out of the 52 initially selected SNPs, 7 were complete drop-outs and the remaining SNPs were successfully genotyped. The individuals were genotyped with the Illumina Bead-Chip (Illumina Inc., San Diego, CA, USA); the PLINK v1.07 software was used to perform standard quality control. SNPs were excluded if they had low call rates (proportion of genotyped called < 90%), were not in Hardy-Weinberg equilibrium (HWE, p < 0.001) on the nAnRC subjects, or had a low minor allele frequency (MAF < 1%). A total of 22 SNPs were used for further analyses.

Mean values were compared among children with CA, RC and nAnRC using the analysis of variance (ANOVA). Differences of categorical variables were evaluated using Chi-squared test. Associations between single SNPs and CA and RC were analysed by applying the case/control model of the SNPassoc R package, adjusting for sex, age, body mass index (BMI), SPT+ (at least one positive), exposure to current environmental tobacco smoke and traffic.

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The demographic and lung function characteristics of the 1050 subjects are shown in Table 1. The study sample was composed by 523 (49.8%) Female and 527 (50.2%) Male, aged 12.07 ± 0.74 years on average. Subjects were categorized into CA (n = 61), RC (n = 184) and nAnRC (n = 805). Subjects with CA and RC more frequently had SPT+, subjects with CA were younger than nAnRC and RC subjects.

Chromosome, gene, SNP name, quality control tag, alleles coding (Major/minor), minor allele frequency (MAF), test for Hardy-Weinberg Equilibrium, percentage of missing values (%) and genotyping distribution are reported in Table 2.

By applying the case/control model, no SNP reached the Bonferroni corrected significance threshold (P value < 0.002, i.e., 0.05/#tests), and only one SNP reached the Bonferroni corrected suggested significance threshold (P value < 0.005, i.e., 0.10/#tests). However, we also included those SNPs reaching the nominal significance threshold (P value < 0.05) just to highlight modest associations with the two studied phenotypes. CA was strongly associated only with rs4252665 and modestly with RC. The SNPs modestly associated with CA showed a high frequency of the major allele homozygote genotype compared with nAnRC, in which the genotypes were mostly characterized by the presence of the minor allele. Furthermore, with respect to nAnRC, SNPs modestly associated with RC showed small variations in the genotypic frequencies. In particular, the SNPs rs8079416, rs7741835 and rs3894194 showed high frequencies of heterozygote genotypes compared with nAnRC, which are frequently homozygous, whilst the SNPs rs7212938 and rs3859192 had high frequencies of the minor allele homozygote genotypes compared with nAnRC, in which genotypes are characterized by the presence of the major allele.

### Table 1 Baseline demographic and clinical characteristics of study population

|                | nAnRC n (805 (76.7%)) | CA n (61 (5.8%)) | RC n (184 (17.5%)) | p-value  |
|----------------|------------------------|------------------|---------------------|----------|
| Female, n (%)  | 390 (48.45)            | 29 (47.54)       | 104 (56.52)         | 0.133    |
| Age, mean (SD) | 12.06 (0.74)           | 11.90 (0.62)     | 12.18 (0.74)        | 0.025    |
| Height, mean (SD) | 152.58 (7.87)        | 151.52 (7.81)    | 153.51 (7.41)       | 0.168    |
| Weight, mean (SD) | 49.05 (12.07)         | 50.11 (12.65)    | 50.28 (13.52)       | 0.417    |
| BMI (kg/m²), mean (SD) | 20.92 (4.28)         | 21.62 (4.15)     | 21.16 (4.78)        | 0.426    |
| Skin Prick Test +, n (%) (%) | 274 (34.16)       | 43 (70.49)       | 76 (41.30)          | < 0.001  |

**Environmental exposure current**

| Tobacco smoke, n (%)  | 440 (54.93) | 27 (44.26) | 107 (58.15) | 0.167    |
| Traffic in the zone of residence, n (%) | 627 (77.99) | 41 (67.21) | 134 (72.83) | 0.071    |
| Mould/dampness, n (%) | 108 (13.47) | 7 (11.67)  | 31 (17.03)  | 0.396    |

**Spirometric values**

|                | nAnRC n (805 (76.7%)) | CA n (61 (5.8%)) | RC n (184 (17.5%)) | p-value  |
|----------------|------------------------|------------------|---------------------|----------|
| FEV₁/FVC % predicted, mean (SD) | 103.39 (11.80) | 96.96 (12.68) | 98.82 (11.34) | 0.035    |
| FEV₁, Z, mean (SD) | 0.04 (1.02) | −0.26 (1.09) | −0.09 (0.98) | 0.037    |
| FVC, Z, mean (SD) | 97.10 (13.29) | 97.60 (13.63) | 95.51 (12.44) | 0.304    |
| FEV₁/Z, mean (SD) | −0.27 (1.14) | −0.22 (1.17) | −0.40 (1.07) | 0.314    |
| FEV₁/FVC % predicted, mean (SD) | 103.28 (7.57) | 99.17 (8.11) | 103.33 (7.89) | < 0.001  |
| FEV₁, Z, mean (SD) | 0.60 (1.21) | −0.04 (1.20) | 0.60 (1.25) | < 0.001  |
| FEF₂₅₋₇₅, Z, mean (SD) | 102.10 (22.19) | 89.17 (21.67) | 101.76 (23.98) | < 0.001  |
| FEF₂₅₋₇₅, Z, mean (SD) | 0.05 (0.98) | −0.55 (1.02) | 0.02 (1.05) | < 0.001  |

CA current asthma, RC rhino-conjunctivitis, nAnRC not asthma and not rhino-conjunctivitis

*according to Allergy diagnostic testing: an updated practice parameter (2008); allergic sensitization was defined as at least one positive skin prick test (SPT)

*according to ATS/ERS guidelines and normalized in accordance with the Global Lungs Initiative 2012

p-values come from Pearson’s test for categorical variable or ANOVA test for mean comparison; bold values indicate significance (p-values < 0.05)
| Chr | Gene   | SNP name | QC | Alleles (M/m) | MAF   | HWE p values | Missing (%) | GENO (AA/Aa/aa) |
|-----|--------|----------|----|---------------|-------|--------------|-------------|-----------------|
| 1   | SELE   | rs5361   | –  | T/G           | 9.9   | 0.005        | 5.4         | 814/161/18      |
| 2   | ORMDL1 | rs5742940 | –  | G/A           | 1.8   | 0.028        | 1.0         | 1004/33/2       |
| 3   | CACNA2D2 | rs12488468 | LCR | G/T          | 48.2  | 0.014        | 25.9        | 187/432/159     |
| 3   | DOCK3  | rs76699816 | –  | G/A           | 11.6  | <0.001       | 8.7         | 779/138/42      |
| 4   | TLR1   | rs7616434 | –  | T/C           | 47.1  | 0.020        | 5.6         | 295/459/237     |
| 4   | TLR1   | rs2101521 | LCR | G/A          | 34.4  | <0.001       | 15.6        | 444/274/168     |
| 4   | TLR1   | rs4843095 | –  | T/C           | 48.4  | 0.014        | 7.1         | 292/422/261     |
| 4   | TLR1   | rs5743595 | HWE | A/G          | 30.5  | <0.001       | 5.8         | 506/363/120     |
| 4   | TLR10  | rs10004195 | HWEd | T/A       | 46.2  | <0.001       | 11.0        | 309/387/238     |
| 4   | TLR10  | rs4274855 | LCR | C/T          | 29.4  | 1.000        | 22.5        | 408/334/72      |
| 4   | TLR2   | rs11736691 | GF  | –            | 14.5  | <0.001       | 7.1         | 455/442/118     |
| 4   | TLR6   | rs1039560 | –  | T/C           | 33.4  | <0.001       | 3.3         | 460/268/114     |
| 5   | IL13   | rs1800925 | –  | C/T           | 18.4  | 0.721        | 4.6         | 668/300/34      |
| 5   | IL13   | rs1881457 | –  | A/C           | 18.4  | 0.720        | 2.8         | 681/305/35      |
| 5   | IL13   | rs20541  | –  | C/T           | 14.5  | <0.001       | 7.1         | 734/200/41      |
| 5   | IL17   | rs7741835 | –  | C/T           | 19.4  | 0.371        | 5.0         | 659/291/48      |
| 5   | DMRT1  | rs3812523 | –  | A/G           | 15.6  | 0.074        | 3.4         | 733/245/36      |
| 5   | IL17   | rs1342326 | –  | A/C           | 21.8  | 0.174        | 3.5         | 627/331/55      |
| 5   | IL13   | rs928413 | –  | A/G           | 30.8  | 0.397        | 4.3         | 486/418/101     |
| 5   | ANO9   | rs7482596 | HWE | G/T          | 13.3  | <0.001       | 4.2         | 770/205/31      |
| 5   | ANO9   | rs7484182 | HWE | T/C          | 14.1  | <0.001       | 4.1         | 758/215/34      |
| 5   | CHCR7  | rs1044842 | GF  | –            | 29.5  | <0.001       | 19.8        | 460/268/114     |
| 5   | GST-P1 | rs1695   | HWE | A/G          | 29.9  | <0.001       | 6.2         | 521/338/126     |
| 5   | NADSYN1 | rs2186777 | –  | A/C           | 26.7  | 0.014        | 4.5         | 553/365/85      |
| 5   | SIGIRR | rs4074794 | HWE | G/A          | 19.5  | <0.001       | 6.3         | 659/266/59      |
| 11  | IRAK3  | rs1152918 | –  | C/T           | 6.9   | 0.295        | 2.1         | 893/128/7       |
| 11  | IRAK3  | rs2701652 | –  | G/C           | 22.0  | 0.256        | 4.1         | 620/330/57      |
| 11  | ORMDL2 | rs7954619 | GF  | –            | 29.9  | <0.001       | 6.2         | 521/338/126     |
| 11  | IL4R   | rs1801275 | –  | A/G           | 16.0  | 0.001        | 4.7         | 722/237/42      |
| 11  | IL4R   | rs1805012 | HWE | T/C          | 5.8   | <0.001       | 2.6         | 916/96/11       |
| 11  | IL4R   | rs3024548 | HWE | C/G          | 46.4  | <0.001       | 13.0        | 314/351/249     |
| 11  | ERBB2  | rs1058808 | –  | G/C           | 30.6  | 0.009        | 6.8         | 495/369/115     |
| 11  | ERBB2  | rs1136201 | HWE | A/G          | 13.8  | <0.001       | 4.1         | 767/203/37      |
| 11  | ERBB2  | rs2934797 | GF  | –            | 29.9  | <0.001       | 6.2         | 521/338/126     |
| 11  | ERBB2  | rs2952155 | GF  | –            | 29.9  | <0.001       | 6.2         | 521/338/126     |
| 11  | GSDMA  | rs3859192 | –  | C/T           | 37.9  | 0.028        | 6.5         | 398/423/161     |
| 11  | GSDMA  | rs3894194 | –  | G/A           | 41.6  | 0.005        | 5.3         | 359/442/193     |
| 11  | GSDMA  | rs7212938 | –  | T/G           | 44.2  | 0.039        | 4.8         | 326/463/211     |
| 11  | GSDMA  | rs2305479 | –  | C/T           | 42.0  | 0.166        | 1.9         | 355/485/190     |
| 11  | GSDMA  | rs2305480 | –  | G/A           | 40.2  | 0.088        | 3.6         | 371/466/173     |
| 11  | GSDMA  | rs7216389 | HWE | T/C          | 42.2  | <0.001       | 6.6         | 359/416/206     |
| 11  | LRRC3C | rs8065126 | HWE | C/T          | 38.3  | <0.001       | 12.5        | 386/362/171     |

Reference: Sottile et al. Italian Journal of Pediatrics (2019) 45:16
The detected association signals for CA were located within the Toll-like receptor (TLR1) on chromosome 4, the interleukin 4 receptor (IL4R) on chromosome 16 and the Erb-b2 receptor tyrosine kinase 2 (ERBB2) on chromosome 17. It is known that Toll-like receptors (TLRs) represent a major group of receptors for the specific recognition of pathogen-associated molecular patterns of microbes capable of activating innate and adaptive immunity that reduce the risk for asthma [3]. The IL4R gene is known to encode a protein that regulates IgE production and it has been shown that allelic variations in this gene are associated with atopy, allergic rhinitis and asthma [4]. Recently, some loci of ERBB2, which belong to the encoding region 17q12, have been reported to be in linkage disequilibrium with loci in the region 17q21 encoding gasdermin A (GSDMA) gene, previously associated with childhood asthma [5–7].

With regard to the RC, the modestly associated genes were interleukin 17 (IL17) on chromosome 6, leucine rich repeat containing 3C (LRRC3C), and GSDMA on chromosome 17. IL17 is a pro-inflammatory cytokine that targets epithelial cells [48] and its expression in the nasal mucosa has been associated with allergic rhinitis and its degree of severity [8, 9]. To our knowledge, no functional studies have been published on LRRC3C, although, within the human genome, the gene LRRC32 has been associated with eczema and allergic rhinitis [10], and probably some similarities between the two proteins encoded by LRRC3C and LRRC32 exist. Finally, GSDMA gene has been associated with childhood asthma and allergic disease in many populations. In particular, region 17q21 has been originally identified in the first GWAS on childhood asthma [6], and GSDMA

| Chr | Gene | SNP name | QC | Alleles (M/m) | MAF | HWE p values | Missing (%) | GENO (AA/Aa/aa) |
|-----|------|----------|----|--------------|-----|--------------|-------------|----------------|
| 17  | LRRC3C | rs8079416 | –  | T/C          | 45.2 | 0.013        | 4.5         | 315/469/219   |
| 17  | MAP2K3 | rs10468608 | HWE/LCR | C/T       | 30.2 | < 0.001      | 19.8        | 462/251/129   |
| 17  | MAP2K3 | rs2363226 | GF  | –            | –   | –            | 100.0       | –             |
| 17  | MAP2K4 | rs3760201 | HWE/LCR | A/G       | 32.9 | < 0.001      | 34.6        | 343/236/108   |
| 17  | ORMDL3 | rs8076131 | HWE/LCR | A/G       | 40.7 | < 0.001      | 15.9        | 333/382/168   |
| 17  | PGAP3  | rs1495102 | HWE/LCR | C/T       | 14.0 | < 0.001      | 17.7        | 697/92/75     |
| 17  | ZBPBP2 | rs11557467 | GF  | –            | –   | –            | 100.0       | –             |
| X   | IRAK1  | rs1059703 | HWE  | A/G         | 25.5 | < 0.001      | 4.2         | 679/140/187   |

Chr: chromosome, MAF: minor allele frequency, GF: genotyping failing, LCR: low call rate, HWE: deviation from the Hardy-Weinberg equilibrium; A: major allele; a: minor allele; bold values indicate significance (p-values < 0.001)

Table 3 Genotypic frequencies of the associated SNPs in CA/RC and nAnRC groups

| Gene  | Region | SNP name | Alleles | Group | AA (%) | Aa (%) | aa (%) | OR (95% CI) |
|-------|--------|----------|---------|-------|--------|--------|--------|-------------|
| TLR1  | 4p14   | rs17616434 | T/C     | nAnRC | 29.4   | 45.6   | 25.0   | –           |
|       |        |          |         |       | 42.4   | 44.1   | 13.5   | –           |
| IL4R  | 16p12.1| rs1801275 | A/G     | nAnRC | 71.0   | 24.5   | 4.5    | –           |
|       |        |          |         |       | 80.0   | 20.0   | 0.0    | –           |
| ERBB2 | 17q12  | rs4252665 | C/T     | nAnRC | 97.4   | 2.5    | 0.1    | 5.75 (2.03–16.29) |
|       |        |          |         |       | 90.2   | 9.8    | 0.0    | –           |
| IL17  | 6p12.2 | rs7741835 | C/T     | nAnRC | 64.3   | 31.2   | 4.5    | –           |
|       |        |          |         | RC    | 69.1   | 25.5   | 5.4    | –           |
| LRR3C | 17q21.1| rs8079416 | T/C     | nAnRC | 32.8   | 45.0   | 22.2   | –           |
|       |        |          |         | RC    | 33.9   | 42.4   | 23.7   | –           |
| GSDMA | 17q21.1| rs7212938 | T/G     | nAnRC | 34.1   | 45.4   | 20.5   | –           |
|       |        |          |         | RC    | 32.8   | 41.4   | 25.8   | –           |
| GSDMA | 17q21.1| rs3859192 | C/T     | nAnRC | 42.2   | 42.6   | 15.2   | –           |
|       |        |          |         | RC    | 40.7   | 40.7   | 18.6   | –           |
| GSDMA | 17q21.1| rs3894194 | G/A     | nAnRC | 37.9   | 43.3   | 18.8   | –           |
|       |        |          |         | RC    | 39.0   | 37.3   | 23.7   | –           |

A: major allele; a: minor allele
Adjusted odds ratios (OR) and 95% confidence interval (CI) of the logistic regression models
variants were suggested to be strong risk factors for asthma and airway inflammation \[7\].

Overall, our findings reveal the importance of different genetic variants at 4p14, 16p12.1, 17q12, 6p12.2 and 17q21.1, identifying possible candidate genes responsible for CA and RC in the Sicilian child population. These results are a preliminary step in understanding the pathophysiology of asthma and rhino-conjunctivitis in a paediatric population in the Mediterranean area and need to be verified by further studies using more advanced technologies. Furthermore, novel methodologies combining genome-wide association study (GWAS; \[11\]) and expression quantitative trait locus (eQTL \[12\]) such as summary-data based Mendelian randomization (SMR; \[13\]), PrediXcan \[14\], MetaXcan \[15\], would be useful in discovering new genetic variants linked to these allergic respiratory diseases in this geographic area. Unlike traditional single-variant tests, these innovative approaches based on SNP-gene linkage will provide valuable insights on disease causality. Noteworthy, the integrative analysis of GWAS and eQTL studies, by identifying gene-trait-associated changes in the expression, would mitigate some tasks associated with a GWAS approach, allowing the discover of genetic variants which can affect gene expression \[16\]. Moreover, since some gene functions are often pleiotropic, this combined approach would allow a better comprehension of the pathways through which pleiotropy can affect clinical phenotypes.

In conclusion, the present study could facilitate the application of novel therapeutics and preventive strategies arising from the genomics era of precision medicine.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
FC and SLG designed the study. Gianluca Sottile, GC, GF, and SLG wrote the initial draft and had final responsibility for the decision to submit for publication. Gianluca Sottile, GC and SF conducted the statistical analyses. RA and Gregorio Seditta contributed to the collection of samples. MT performed genotyping of the DNA samples. GV, FC and SLG performed a critical revision of the manuscript and offered precious technical advice on how the study might be improved. All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the paper, revised the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate
The study was approved by the local ethics committee (A.O.U. “Paolo Giacccone”, Palermo, Italy), and written informed consent was provided by parents of all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References
1. Galassi C, De Sario M, Biggeri A, et al. Changes in prevalence of asthma and allergies among children and adolescents in Italy: 1994–2002. Pediatrics. 2006;117(1):334–42.
2. Cicella F, Cuttitta G, La Grutta S, et al. Proportional Venn diagram and determinants of allergic respiratory diseases in Italian adolescents. Pediatr Allergy Immunol. 2011;22(6):386–92.
3. Kornmann MS, Depner M, Hartl D, et al. Toll-like receptor heterodimer variants protect from childhood asthma. J Allergy Clin Immunol. 2008;122(1):86–92.
4. Huang ZY, Cheng BJ, Cai GJ, et al. Association of the IL-4R Q576R polymorphism and asthma in the Chinese Han population: a meta-analysis. Genet Mol Res. 2015;14(1):2900–11.
5. Stein MM, Thompson EE, Schottler N, et al. A decade of research on the 17q12–21 asthma locus: Piecing together the puzzle. J Allergy Clin Immunol. 2018;142(3):649–66.e3.
6. Verlaan DJ, Berlivet S, Hunninghake GM, et al. Allele-specific chromatin remodeling in the ZBP12/GZMB/BOR3D3 locus associated with the risk of asthma and autonomic disease. Am J Hum Genet. 2009;85(3):377–93.
7. Feneoni MA, Matheson MC, Tang CS, et al. Genome-wide association analysis identifies 11 risk variants associated with the asthma with hay fever phenotype. J Allergy Clin Immunol. 2014;133(6):1564–71.
8. Albano GD, Di Sano C, Bonanno A, et al. TH17 immunity in children with allergic asthma and rhinitis: a pharmacological approach. PloS One. 2013;8(4):e58892.
9. Ramasamy A, Curjuric I, Coin LJ, et al. A genome-wide meta-analysis of genetic variants associated with allergic rhinitis and grass sensitization and their interaction with birth order. J Allergy Clin Immunol. 2011;128(5):1096–1005.
10. Beneske EP, Todo-Bom A, Loureiro C, et al. Asthma and rhinitis have different genetic profiles for IL13, IL17A and GSTP1 polymorphisms. Rev Port Pneumol. 2017;23(1):10–6.
11. Ozaki K, Nohira Y, Iida A, et al. Functional SNPs in the lymphotaxin-alpha gene that are associated with susceptibility to myocardial infarction. Nat Genet. 2002;32(4):650–4.
12. Brem RB, Yvert G, Clinton R, et al. Genetic dissection of transcriptional regulation in budding yeast. Science. 2002;296(5568):752–5.
13. Zhu Z, Zhang F, Hu H, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet. 2016;48(5):481–7.
14. Gamazon ER, Wheeler HE, Shah NP, et al. A gene-based association method for mapping traits using reference transcriptome data. Nat Genet. 2015;47(9):1091–8.
15. Barbeira AN, Dickinson SP, Bonazzola R, et al. Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. Nat Commun. 2018;9(1):1825.
16. Hauberg ME, Zhang W, Giambartolomei C, et al. Large-scale identification of common trait and disease variants affecting gene expression. Am J Hum Genet. 2017;100:885–94.