長庚大學醫學院臨床醫學研究所
畢業生研究成果

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畢業論文題目（中文）：探討臺灣兒童維生素D路徑基因之常見與罕見遺傳變異和氣喘及過敏疾病之關聯

畢業論文題目（英文）：Association of common and rare genetic variants on vitamin D pathway genes with asthma and allergic diseases in Taiwanese children

BACKGROUND

- It has been reported that genes encoded in vitamin D pathway were associated with transcriptional regulations of vitamin D, and associated with asthma, atopy, and eczema as well.
- However, there were contradictory results of genetic associations with allergic diseases for variants on vitamin D pathway genes in different populations from previous literature.
- Evidence of association between asthma and allergic diseases and rare and low-frequency variants and common variants on vitamin D pathway genes is still limited.

Figure 1. The number of cases and controls in asthma, atopy, eczema and rhinitis

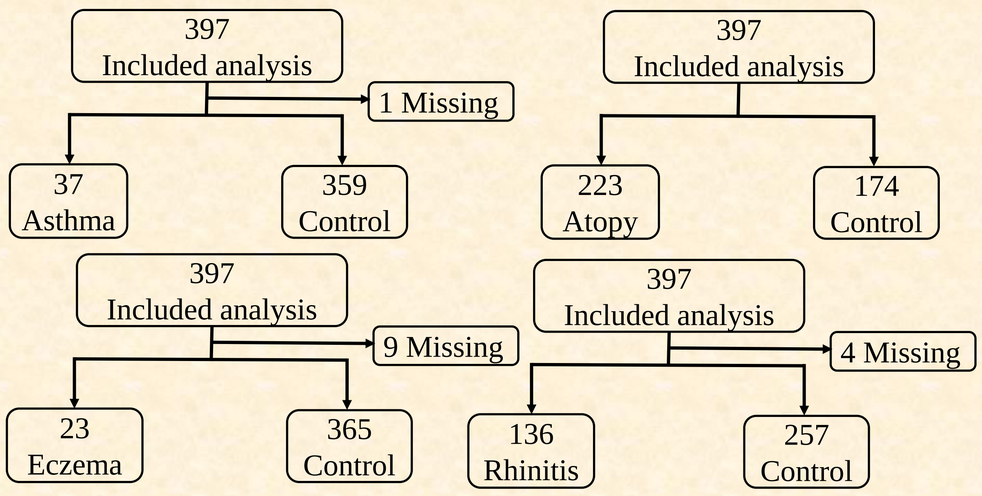

Table 1. Rare and low-frequency variants count and statistical results of asthma, atopy, eczema, and rhinitis with CYP2R1, CYP27A1, VDR, and CD28

Phenotype	SNP	p-value
Asthma	CYP27A1	3.7×10^{-3}
	VDR	6.7×10^{-3}
	CD28	0.0335
eczema	CYP2R1	1.1×10^{-3}
rhinitis	CD28	0.0104

OBJECTIVE

- To investigate whether rare and low-frequency variants of the 12 candidate genes (CYP2R1, CYP27A1, CYP27B1, GC, VDR, CYP24A1, IL10, IL1RL1, CD28, CD86, IL8, and SKIIP) on the vitamin D pathway are associated with asthma and allergic diseases.
- To examinine whether common variants of the 12 candidate genes (CYP2R1, CYP27A1, CYP27B1, GC, VDR, CYP24A1, IL10, IL1RL1, CD28, CD86, IL8, and SKIIP) on the vitamin D pathway are associated with asthma and allergic diseases.
- To calculate odds ratio and 95% confidence interval between risk alleles and disease in the common genetic variation and to explore what types of SNP genotypes contribute a higher risk of disease.
- Based on 2, to analyze haplotypic associations of significantly associated common variants. We aim to explore whether haplotypes are associated with asthma and allergic diseases. In addition, to determine whether the contribution of individual common variants to the risk of diseases is independent or related to each other.
- To explore gene-gene interactions. We seek to investigate what combinations of SNPs on different genes contribute a higher risk of disease.

METHOD

- This study was based on the genetic data from 397 Taiwanese children aged 5-18 years who have completed questionnaires regarding asthma and allergic diseases (Figure 1).
- We used minor allele frequency to differentiate rare and low-frequency variants and common variants and performed different comparative analyses.
- For rare and low-frequency variants, we carried out SNP-Set (Sequence) Kernel Association Test (SKAT), including Burden test, SKAT, and SKATO.
- For common variants, we performed case/control association analysis, Fisher's exact test, and Alternate/full model association tests. Furthermore, we performed haplotype block and haplotype-trait association analyses.
- Gene-gene interaction analysis was also performed to explore association between genes on vitamin D pathway for asthma and allergy diseases.

RESULT

- According to the results of SKAT, rare and low-frequency variants on the genes CYP27A1 and VDR were associated with asthma; CYP2R1 was associated with eczema; and CD28 was associated with asthma and rhinitis (Table 1).
- In the single-locus association analysis of common variants, four SNPs on GC rs16847015, rs60349934, rs113574864, and rs59241277 were the most significantly associated with atopy (Figure 2).
- In addition, the subjects who carried TT haplotype formed by rs6741592 and rs691066 on CYP27A1 and GGT haplotype formed by rs9729, rs7305032, and rs11168274 on VDR had 2.61 times higher and 3.28 times asthmatic risk respectively compared with those without carrying the haplotypes (Figure 3).
- Moreover, epistatic interactions associated with rhinitis were identified among rs55927292 on IL1RL1, rs3181113 on CD28, and rs751090 on CYP24A1 (Table 2).

Figure 2. Alternate/full model association test sand logistic regression analysis of common variants of GC with atopy

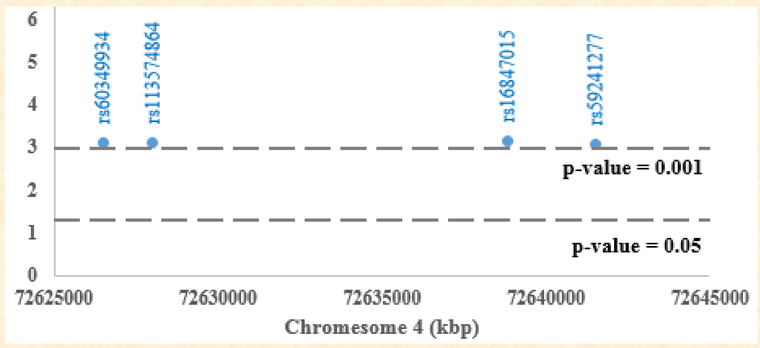

Figure 3. Linkage disequilibrium (LD) and haplotype block structures of CYP27A1, and VDR genes with asthma control were mapped by Haploview.

(a) CYP2R1 haplotype　　(b) CYP27A1 haplotype

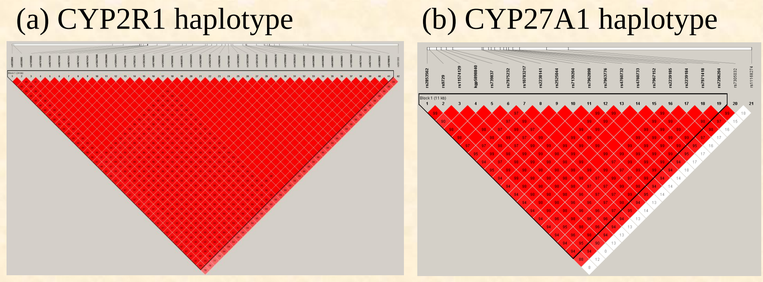

Table 2. Gene–gene interaction analysis for rhinitis by generalized multifactor dimensionality reduction method

Model	Gene	TA	CVC	p-value
rs55927292,rs3181113,rs751090	IL1RL1,CD28,CYP24A1	0.6065	10/10	0.0038

CONCLUSION

This study showed that rare and low-frequency genetic variants and common genetic variants of CYP2R1, CYP27A1, GC, VDR, CYP24A1, IL10, IL1RL1, CD28, CD86, and IL8 on vitamin D pathway were associated with asthma and allergic diseases in Taiwanese children.

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