Allergy

WILEY

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

LETTER OPEN ACCESS

GWAS Identifies *CACNA2D3* Associated With Asthma and Atopic Dermatitis Multimorbidity in Children

Dong Yun Kim[1,2] | Soyeon Lee[1] | Jae Hwa Jung[3] | Yujin Sub[1] | Sumin Lee[3] | Eun Gyul Kim[3] | Mi Na Kim[3] | Soo Yeon Kim[3] | Yoon Hee Kim[3] | Myung Hyun Sohn[3] | Heon Yung Gee[1] | Kyung Won Kim[3]

[1]Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea | [2]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea | [3]Department of Pediatrics, Severance Hospital, Institute of Allergy, Institute for Innovation in Digital Healthcare, Yonsei University College of Medicine, Seoul, Korea

Correspondence: Heon Yung Gee (hygee@yuhs.ac) | Kyung Won Kim (kwkim@yuhs.ac)

Received: 3 July 2024 | **Revised:** 13 January 2025 | **Accepted:** 16 January 2025

Funding: This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (Nos. 2022R1A2C1010462 and 2018R1A5A2025079).

To the Editor,

Allergic diseases significantly impact children's health—especially asthma and atopic dermatitis (AD) multimorbidity [1]. Genome-wide association studies (GWASs) have revealed genetic variants linked to these conditions, elucidating disease mechanisms and potential therapeutic targets. However, most GWASs focus on European populations [2, 3]. We conducted a GWAS with 955 Korean children (mean age 8.4 years) to identify genetic variants associated with asthma and AD multimorbidity, and thereby improve our understanding of these conditions in diverse populations (Table S1).

We analyzed 6.6 million SNPs for asthma and AD multimorbidity. The genomic inflation factor (λ) was 1.03, indicating no systemic bias (Figure S1). Three loci reached genome-wide suggestive significance—*CACNA2D3* on chromosome 3p14.3 ($p = 5.03 \times 10^{-7}$), *SMYD2* on chromosome 1q32.3 ($p = 2.52 \times 10^{-7}$), and *SULF2* on chromosome 20q13.12 ($p = 6.50 \times 10^{-7}$) (Figure 1A and Table 1)—neither of which is reported in previous GWASs on asthma and AD multimorbidity. In our replication cohort of 274 individuals (mean age 8.5 years), we attempted to replicate 20 variants of these three novel loci (Figure S2). 16 SNPs in *CACNA2D3* were significantly associated with asthma and AD multimorbidity ($p = 0.003$), while the *SMYD2* and *SULF2* variants were not ($p = 0.418$ and $p = 0.109$, respectively; Table 1). The 16 significant SNPs in *CACNA2D3* were in the same LD block. (Figure S3) All 16 SNPs located in the *CACNA2D3* locus lost statistical significance after conditioning on the lead SNP, rs78970585, indicating a single association signal in this region (Figure S4). The CG and GG genotypes of rs78970585 were less common in the multimorbidity group ($p < 0.001$; Figure S5). We investigated 12 previously reported SNPs, finding significant associations at the 17q12 locus in *IKZF3* ($p = 4.76 \times 10^{-5}$), and 5q31.1 in *KIF3A* ($p = 0.01$; Table S2). We performed *in silico* analysis using HaploReg v4.2 to examine the function of the lead SNP in *CACNA2D3*. This revealed that rs78970585 is purportedly related with key regulatory motifs for NF-κB, PPARγ, and RREB1, which relate to inflammation, metabolic regulation, and cell growth, implying a possible functional influence on asthma and AD multimorbidity (Table S3).

To examine the function of *CACNA2D3*, we conducted functional studies by manipulating *CACNA2D3* expressions in both HaCaT and RAW 264.7 cell lines. Specifically, *CACNA2D3* overexpression in HaCaT cells (Figure S6A,B) and RAW 264.7 cells (Figure S6C,D) resulted in a marked upregulation of IL-6 and IL-1β mRNA levels compared to vehicle controls. These data support a pro-inflammatory role for *CACNA2D3*, potentially linking it to the pathophysiology of asthma and AD multimorbidity.

We further analyzed data from the Genotype-Tissue Expression (GTEx) portal, which revealed *CACNA2D3*

Allergy, 2025; 80:1776–1781
https://doi.org/10.1111/all.16483

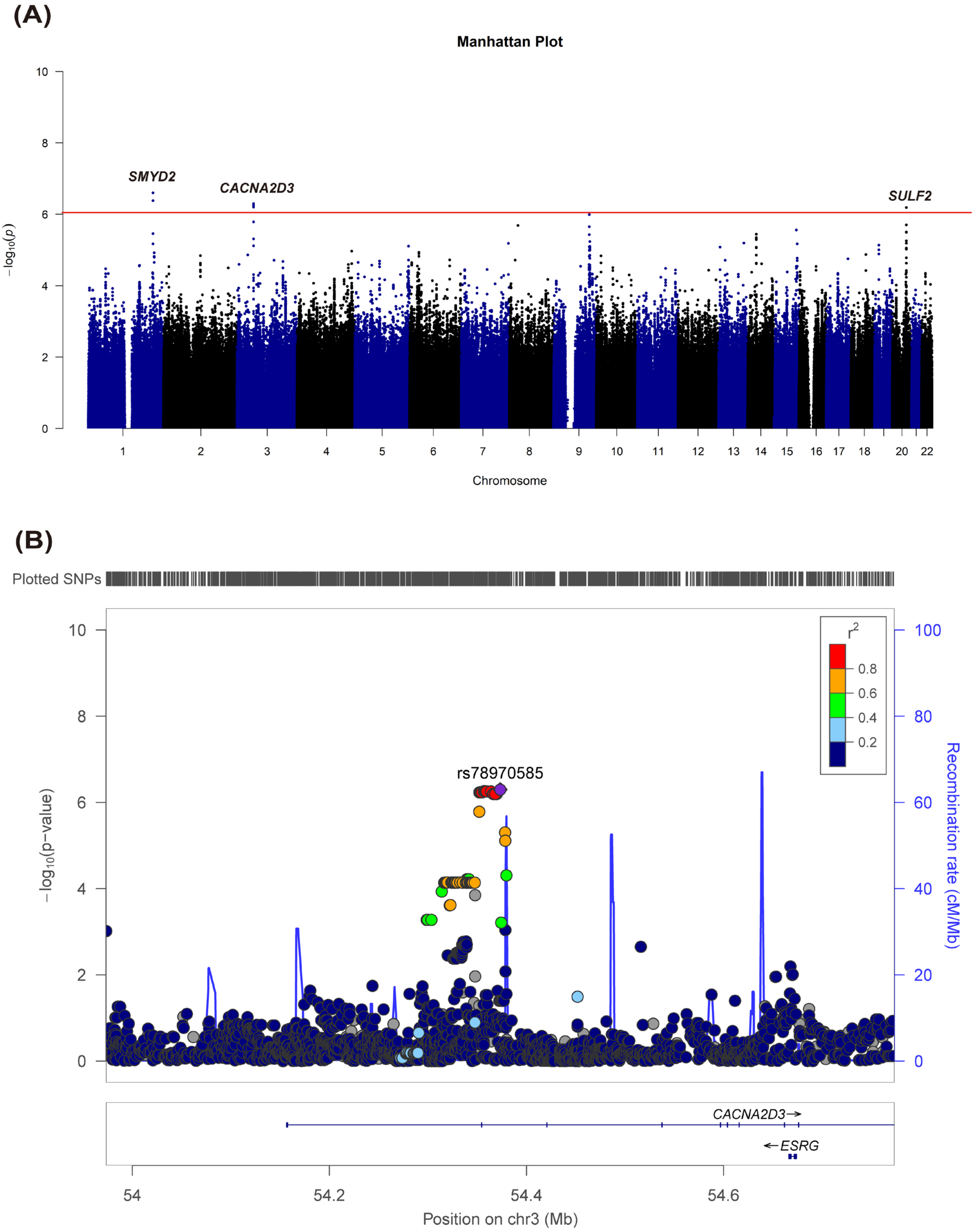

FIGURE 1 | Genome-wide association study (GWAS) reveals that *CACNA2D3* is associated with childhood asthma and AD multimorbidity. (A) Manhattan plot of GWAS on persistent asthma and AD multimorbidity with allergic sensitization in Korean children. Variants are plotted on the x-axis of the Manhattan plot according to their chromosomal position and their $-\log_{10}$ (p value) is shown on the y-axis. The red line shows the genome-wide significance threshold ($p < 5 \times 10^{-6}$). (B) Regional association plot at the *CACNA2D3* locus for persistent childhood asthma and AD multimorbidity. The genome builds and linkage disequilibrium used in this plot is from hg19/1000 Genomes Asian (Nov 2014); the blue line indicates the recombination rate based on HapMap data. The 10 most significant SNPs in *CACNA2D3* are labeled. Colors correspond to LD (r^2) with the lead SNP, rs78970585, as shown on the color scale in the upper right.

TABLE 1 | Summary of significant SNPs for childhood asthma and AD multimorbidity with $p < 5.0 \times 10^{-6}$ in a Korean population.

Chromosome	Position	rs number	Closest gene[a]	Allele (minor allele)	MAF (discovery)	*OR*[b] (discovery)	*p*[c] (discovery)	MAF (replication)	*OR*[b] (replication)	*p*[c] (replication)	*OR*[b] (meta-analysis)	*p*[c] (meta-analysis)
1q32.3	214,419,971	rs72156013	*SMYD2*	ATCT>A (A)	0.080	0.311 (0.200–0.485)	2.52×10^{-7}	0.074	0.813 (0.376–1.760)	0.600	0.406 (0.283–0.584)	1.10×10^{-6}
	214,418,706	rs12748832	*SMYD2*	G > A (A)	0.079	0.318 (0.204–0.496)	4.17×10^{-7}	0.074	0.731 (0.343–1.561)	0.418	0.401 (0.279–0.579)	7.80×10^{-7}
	214,418,438	rs35466426	*SMYD2*	CTCTT>C (C)	0.079	0.318 (0.204–0.496)	4.17×10^{-7}	0.070	0.731 (0.343–1.561)	0.418	0.401 (0.279–0.579)	7.80×10^{-7}
3p14.3	54,373,419	rs78970585	*CACNA2D3*	C > G (G)	0.094	0.357 (0.239–0.534)	5.03×10^{-7}	0.103	0.358 (0.179–0.717)	0.003	0.370 (0.262–0.514)	4.72×10^{-9}
	54,357,015	rs59369555	*CACNA2D3*	T > C (C)	0.097	0.355 (0.237–0.533)	5.48×10^{-7}	0.105	0.462 (0.244–0.876)	0.017	0.386 (0.278–0.540)	1.26×10^{-8}
	54,357,768	rs112375002	*CACNA2D3*	C > T (T)	0.096	0.355 (0.237–0.533)	5.48×10^{-7}	0.10	0.462 (0.244–0.876)	0.017	0.386 (0.278–0.540)	1.26×10^{-8}
	54,358,793	rs118004755	*CACNA2D3*	T > A (A)	0.095	0.355 (0.237–0.533)	5.54×10^{-7}	0.105	0.433 (0.226–0.834)	0.013	0.380 (0.273–0.531)	8.63×10^{-8}
	54,359,558	rs79137690	*CACNA2D3*	G > C (C)	0.096	0.355 (0.237–0.533)	5.54×10^{-7}	0.103	0.433 (0.226–0.834)	0.013	0.380 (0.273–0.531)	8.63×10^{-8}
	54,364,017	rs117430322	*CACNA2D3*	A > T (T)	0.095	0.355 (0.237–0.533)	5.54×10^{-7}	0.103	0.433 (0.266–0.834)	0.013	0.380 (0.273–0.531)	8.63×10^{-8}
	54,353,240	rs7431992	*CACNA2D3*	T > A (A)	0.098	0.358 (0.240–0.536)	5.75×10^{-7}	0.103	0.445 (0.235–0.843)	0.013	0.385 (0.278–0.537)	9.91×10^{-8}
	54,353,711	rs78775756	*CACNA2D3*	C > T (T)	0.098	0.358 (0.240–0.536)	5.75×10^{-7}	0.102	0.445 (0.235–0.843)	0.013	0.385 (0.278–0.537)	9.91×10^{-8}
	54,353,814	rs11716076	*CACNA2D3*	G > A (A)	0.098	0.358 (0.240–0.536)	5.75×10^{-7}	0.102	0.445 (0.235–0.843)	0.013	0.385 (0.278–0.537)	9.91×10^{-8}
	54,352,296	rs4077645	*CACNA2D3*	T > C (C)	0.097	0.358 (0.240–0.536)	5.82×10^{-7}	0.102	0.417 (0.217–0.802)	0.008	0.379 (0.272–0.528)	6.80×10^{-9}
	54,354,696	rs117395094	*CACNA2D3*	T > A (A)	0.097	0.358 (0.240–0.536)	5.82×10^{-7}	0.100	0.417 (0.217–0.802)	0.008	0.379 (0.272–0.528)	6.80×10^{-9}

(Continues)

TABLE 1 | (Continued)

Chromosome	Position	rs number	Closest gene[a]	Allele (minor allele)	MAF (discovery)	*OR*[b] (discovery)	*p*[c] (discovery)	MAF (replication)	*OR*[b] (replication)	*p*[c] (replication)	*OR*[b] (meta-analysis)	*p*[c] (meta-analysis)
3p14.3	54,366,259	rs75921549	*CACNA2D3*	T > G (G)	0.094	0.357 (0.238–0.536)	6.33×10^{-7}	0.100	0.445 (0.231–0.859)	0.015	0.388 (0.278–0.541)	1.97×10^{-8}
	54,366,433	rs145322591	*CACNA2D3*	CAT>C (C)	0.097	0.357 (0.238–0.536)	6.33×10^{-7}	0.101	0.445 (0.231–0.858)	0.015	0.388 (0.279–0.54)	1.97×10^{-8}
	54,366,610	rs73841974	*CACNA2D3*	C > T (T)	0.097	0.357 (0.238–0.536)	6.33×10^{-7}	0.097	0.439 (0.228–0.848)	0.014	0.386 (0.277–0.540)	1.78×10^{-8}
	54,368,315	rs59922903	*CACNA2D3*	T > C (C)	0.097	0.357 (0.238–0.536)	6.33×10^{-7}	0.097	0.363 (0.181–0.728)	0.004	0.369 (0.262–0.516)	5.50×10^{-9}
	54,369,855	rs200863842	*CACNA2D3*	A > AC (AC)	0.099	0.357 (0.238–0.536)	6.33×10^{-7}	0.098	0.363 (0.181–0.728)	0.004	0.369 (0.264–0.516)	5.50×10^{-9}
20q13.12	46,369,114	rs4810677	*SULF2*	A > G (G)	0.237	1.968 (1.507–2.569)	6.50×10^{-7}	0.275	1.639 (1.083–2.481)	0.109	1.668 (1.352–2.058)	1.81×10^{-6}

Abbreviations: AD, atopic dermatitis; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism.
[a] The closest gene was annotated using the UCSC Genome Browser (GRCh37/hg19).
[b] Odds ratio and 95% confidence interval (CI) of the minor allele.
[c] *p* Values were determined by logistic regression analysis using an additive model.

expression in lungs, skin, and whole blood (Figure S7A). Single-cell analysis demonstrated *CACNA2D3* expressions were identified including in lung immune cells (Figure S7B). We investigated *CACNA2D3* expression in skin at the single-cell level, using a publicly available scRNA-seq dataset (GSE230575) including samples from 4 healthy controls and 10 AD patients (Figure S8A–C). Cluster analysis identified nine distinct cell types, with epithelial cells most abundant in AD patients, and fibroblasts predominant in healthy controls (Figure S8D–G). *CACNA2D3* expression in macrophages was significantly lower in AD patients versus healthy controls (Figure S8H,I). Similarly, *CACNA2D3* expression was dynamically elevated in the lung's mononuclear phagocytic system in response to allergen-induced inflammation, reinforcing its potential involvement in the asthma and AD multimorbidity (Figure S9A–J). This study elucidates the genetic underpinnings of asthma and AD multimorbidity in a Korean pediatric population, identifying a novel locus, *CACNA2D3*, associated with decreased risk. In the replication cohort, 16 genome-wide suggestive variants in *CACNA2D3* exhibited significant associations ($p = 0.003$) and retained the same effects in the phenotype homogeneity test (Table S4). The consistent association across various control groups highlights its specific influence on the multimorbid condition, distinct from asthma or AD alone. *CACNA2D3* encodes a subunit of voltage-dependent calcium channels, and is crucial in calcium signaling, impacting immune cell functions and inflammatory responses. Calcium channels play pivotal roles in immune cell activation and function [4, 5]. Calcium influx modulation can influence cytokine production, cell proliferation, and apoptosis, which are critical in allergic response development [6]. Variants in *CACNA2D3* are associated with lung function metrics [7] (e.g., FEV1, FVC, and FEV1/FVC ratio) and airway inflammation markers (e.g., exhaled nitric oxide [8]), suggesting a possible involvement in asthma severity, progression, and exacerbation risk, even in patients receiving ICS therapy [9].

These findings suggest that *CACNA2D3* genetic variants that reduce calcium channel function and/or expression can promote a tempered immune response, thereby mitigating the risk and severity of asthma and AD multimorbidity. The G allele of rs78970585 in *CACNA2D3*, the identified signal for asthma and AD multimorbidity, is more prevalent in East Asians (0.08) compared to Finnish (0.03) or non-Finnish European (0.01) populations (gnomAD), potentially explaining why it has been underrecognized in European-based studies. The limitations of this study encompass the use of the Infinium HumanCoreExome-24 BeadChip, which has incomplete genomic coverage focused on exonic variants; the relatively small sample size for multimorbidity GWAS; and single-cell validation data derived from an Austrian cohort, which may restrict generalizability to the Korean population; and the absence of an assessment of environmental interactions. While our *in silico* research indicates a possible regulatory function for rs78970585, we recognize that the lack of direct evidence, such as expression quantitative trait loci (eQTL) data, constitutes a drawback. Nevertheless, our findings underscore a significant genetic marker for asthma and AD multimorbidity in East-Asian populations and support the potential role of *CACNA2D3* in immune regulation.

Author Contributions

All authors made substantial contributions to the conception or design and data acquisition of the work. D.Y.K., K.W.K., and H.Y.G. designed the study, enrolled the patients, and wrote the paper. Y.S., S.L. contributed to the analysis of single-cell RNA-sequencing. J.H.J. analyzed the clinical data. S.L., E.G.K., M.N.K., S.Y.K., and M.H.S. made substantial contributions to the literature review and data collection. D.Y.K., K.W.K., and H.Y.G. performed the analysis and interpretation of data. D.Y.K., K.W.K., and H.Y.G. drafted the work, and reviewed and edited the manuscript. All authors revised the manuscript for relevant content and gave final approval of the version submitted for publication.

Acknowledgments

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2022R1A2C1010462 and 2018R1A5A2025079).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Dong Yun Kim
Soyeon Lee
Jae Hwa Jung
Yujin Sub
Sumin Lee
Eun Gyul Kim
Mi Na Kim
Soo Yeon Kim
Yoon Hee Kim
Myung Hyun Sohn
Heon Yung Gee
Kyung Won Kim

References

1. S. C. Dharmage, A. Lowe, M. C. Matheson, J. Burgess, K. Allen, and M. J. Abramson, "Atopic Dermatitis and the Atopic March Revisited," *Allergy* 69, no. 1 (2014): 17–27.

2. I. Marenholz, J. Esparza-Gordillo, F. Rüschendorf, et al., "Meta-Analysis Identifies Seven Susceptibility Loci Involved in the Atopic March," *Nature Communications* 6 (2015): 8804.

3. P. Margaritte-Jeannin, A. Budu-Aggrey, M. Ege, et al., "Identification of OCA2 as a Novel Locus for the Co-Morbidity of Asthma-Plus-Eczema," *Clinical & Experimental Allergy* 52, no. 1 (2022): 70–81.

4. C. T. Berry, M. J. May, and B. D. Freedman, "STIM-and Orai-Mediated Calcium Entry Controls NF-κB Activity and Function in Lymphocytes," *Cell Calcium* 74 (2018): 131–143.

5. N. Manolios, J. Papaemmanouil, and D. J. Adams, "The Role of Ion Channels in T Cell Function and Disease," *Frontiers in Immunology* 14 (2023): 1238171.

6. A. Jairaman, C. H. Maguire, R. P. Schleimer, and M. Prakriya, "Allergens Stimulate Store-Operated Calcium Entry and Cytokine Production in Airway Epithelial Cells," *Scientific Reports* 6, no. 1 (2016): 32311.

7. N. Shrine, A. L. Guyatt, A. M. Erzurumluoglu, et al., "New Genetic Signals for Lung Function Highlight Pathways and Chronic Obstructive

Pulmonary Disease Associations Across Multiple Ancestries," *Nature Genetics* 51, no. 3 (2019): 481–493.

8. R. J. Van Der Valk, L. Duijts, N. J. Timpson, et al., "Fraction of Exhaled Nitric Oxide Values in Childhood Are Associated With 17q11. 2-q12 and 17q12-q21 Variants," *Journal of Allergy and Clinical Immunology* 134, no. 1 (2014): 46–55.

9. N. Hernandez-Pacheco, S. J. Vijverberg, E. Herrera-Luis, et al., "Genome-Wide Association Study of Asthma Exacerbations Despite Inhaled Corticosteroid Use," *European Respiratory Journal* 57, no. 5 (2021): 2003388.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.