Brief Communication

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NOTCH1 Pathway is Involved in Polyhexamethylene Guanidine-Induced Humidifier Disinfectant Lung Injuries

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An outbreak of fatal humidifier disinfectant lung injuries (HDLI) occurred in Korea. Human studies on mechanisms underlying HDLI have yet to be conducted. This study aimed to investigate methylation changes and their potential role in HDLI after exposure to HDs containing polyhexamethylene guanidine-phosphate. DNA methylation analysis was performed in blood samples from 10 children with HDLI and 10 healthy children using Infinium Human MethylationEPIC BeadChip. Transcriptome analysis was performed using lung tissues from 5 children with HDLI and 5 controls. Compared to healthy controls, 92 hypo-methylated and 79 hyper-methylated CpG sites were identified in children with HDLI at the statistical significance level of $|\Delta\beta|>0.2$ and $p<0.05$. NOTCH1 was identified as a candidate network hub gene in cases. NOTCH1 transcripts significantly increased in lung tissues from HDLI cases compared to unexposed controls ($p=0.05$). NOTCH1 may play an important role in pulmonary fibrosis of HDLI.

Key Words: Humidifier disinfectant, pulmonary fibrosis, *NOTCH1*, methylation, polyhexamethylene guanidine

An outbreak of fatal lung injuries occurred in Korea between early 2000 and 2011, characterized by rapidly progressing respiratory failure with lung fibrosis, extensive air leak syndrome in many cases, a lack of responsiveness to any treatment, and high mortality rate.[1-5] This fatal interstitial lung disease (ILD) was distinct from previously identified ILDs in terms of clinical course as well as radiologic and pathologic findings; therefore, it was considered to be idiopathic.[1,2] Toxic chemicals, including polyhexamethylene guanidine (PHMG), in humidifier disinfectants (HDs) were subsequently identified as the cause.[1,2] The unique features of this fatal lung disease raised questions regarding the distinct mechanisms underlying the disorder.[6] However, there has been no report on the mechanisms underlying HD-associated lung injuries (HDLI) in humans. As altered DNA methylation is associated with development of idiopathic pulmonary fibrosis,[6,7] we investigated whether DNA methylation plays a

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•The authors have no potential conflicts of interest to disclose.

Table 1. Clinical Characteristics of the Study Population

Mean±SD or number	Methylation study from blood samples		Transcriptome study with lung tissues	
	Controls	Children with HDLI	Controls	Children with HDLI
Number	10	10	5	5
Age at sample collection (yr)	7.0±0.6	11.4±3.6	9.0±2.4	1.8±0.8
Age at diagnosis of HDLI (month)	NA	35.4±1.8	NA	30.2±9.5
Sex, male:female	7:3	7:3	2:3	2:3
Dyspnea at diagnosis	0/10	9/10	0/5	5/5
Pneumothorax during illness	0/10	4/10	0/5	5/5
Oxygen need	0/10	9/10	0/5	5/5
Ventilator care	0/10	2/10	0/5	0/5
Mortality	0/10	0/10	0/5	0/5

HDLI, humidifier disinfectant lung injuries; NA, not applicable.

role in HDLI using human samples.

Blood samples from 10 children with HDLI and 10 healthy control children with no exposure to HDs were used to analyze methylation profiles. Clinical characteristics of the study population are summarized in Table 1. The mean age at diagnosis of HDLI was 35.4 months (range, 12–81 months) and blood samples for methylation analysis were obtained at a mean age of 11.4 years (range, 7–15 years). Male-to-female rate was 7:3. None of the children in sex-matched control group had any respiratory diseases and their mean age was 7 years. DNA extracted from the peripheral blood mononuclear cells of each subject was analyzed using Infinium Human MethylationEPIC BeadChip (Illumina, San Diego, CA, USA). For quality check (QC) of the methylation data, beta-mixture quantile normalization, and Pearson's correlation (range: $-1 \leq r \leq 1$) for reproducibility between samples were performed. For QC of the transcriptome data, all data were normalized with the robust multi-average method implemented in in Affymetrix® Power Tools (Thermo Fisher Scientific, Waltham, MA, USA). Statistical significance for differentially methylated CpG sites was set at $|\Delta\beta|>0.2$ and $p<0.05$ using a t-test. Ingenuity® Pathway Analysis (IPA, Ingenuity Systems, Redwood City, CA, USA) was used to represent the functional networks of genes containing differentially methylated CpG sites. Transcriptome analysis was performed using lung tissues from five pediatric patients with HDLI and five control children. Lung tissue was obtained from children with no abnormal lung lesions from Bio-Resource Center at Asan Medical Center to form a control group. The Institutional Review Board of Asan Medical Center reviewed and approved the study protocol (IRB No. 2016-0885).

A total of 171 CpG loci (79 hypermethylated, 92 hypomethylated) showed significantly differential methylation patterns in children with HDLI compared to the controls (Fig. 1A), with a distinctive clustering observed between the two groups (Fig. 1B) (Table 2). The top 25 hypomethylated and 25 hypermethylated CpG loci are listed in Table 2. *SYT8* cg09575189 showed the highest hypomethylation level ($|\Delta\beta|=0.433$, $p=0.003$), whereas cg26786615 (chr16: 86593603) had the highest hypermethylation level ($|\Delta\beta|=0.519$, $p=0.0006$). However, there are a few functional studies of these two genes and no reports in existing literature that provide any clues to the associations between them and fibrosis and/or lung diseases. Potential upstream and downstream regulators of NOTCH1 based on IPA network analysis and its signaling (https://www.rndsystems.com/pathwyas/notch-signaling-pathway) are described in Table 3.

NOTCH1 cg14065526 showed a significant degree of hypomethylation ($|\Delta\beta|=0.304$, $p=0.016$). In further network analysis of the genes containing differently methylated CpG sites, "cancer, organismal injury and abnormalities, reproductive system disease (score=41)" was identified as the top network for HDLI, indicating *NOTCH1* as a hub gene (Fig. 1C). The cg14065526 (chr9: 139406352) of *NOTCH1* showed a significantly hypomethylated level ($|\Delta\beta|=0.304$, $p=0.016$). *NOTCH1* transcripts from lung tissues were significantly elevated in HDLI cases compared to unexposed controls ($p=0.05$, each group n=5) (Fig. 1D).

Our present findings from methylation and transcriptome analysis of human blood and lung tissues have identified that *NOTCH1* is involved in the pathogenesis of HDLI. This is the first study to investigate DNA methylation changes and network analyses combined with transcriptomics in pediatric patients with HDLI, which may partially explain the underlying mechanisms of HDLI.

Although *NOTCH1* may be common to the mechanisms of other types of ILDs,[8] the results of our current analysis suggest that it also plays a central role in the mechanism of HDLI. Notch1 is involved in angiogenesis, abnormal remodeling of vessels, and mucus hypersecretion, and thereby is associated with pathogenesis of diverse lung diseases.[9] The apoptosis of bronchial epithelial cells following exposure to toxic chemicals affects the clearance of apoptotic debris combined with lung fibrosis.[10] The overexpression of *NOTCH1*, which is related to its gene hypomethylation, as shown in this study, promotes the differentiation of myofibroblasts, which is a critical step in pulmonary fibrosis.[3] NOTCH1 has been identified to be involved in bleomycin-induced lung diseases and paraquat poisoning, for which the main mechanism is pulmonary fibrosis.[11,12] The results of previous reports and our present findings provide strong evidence for the involvement of *NOTCH1* in the pathogenesis of

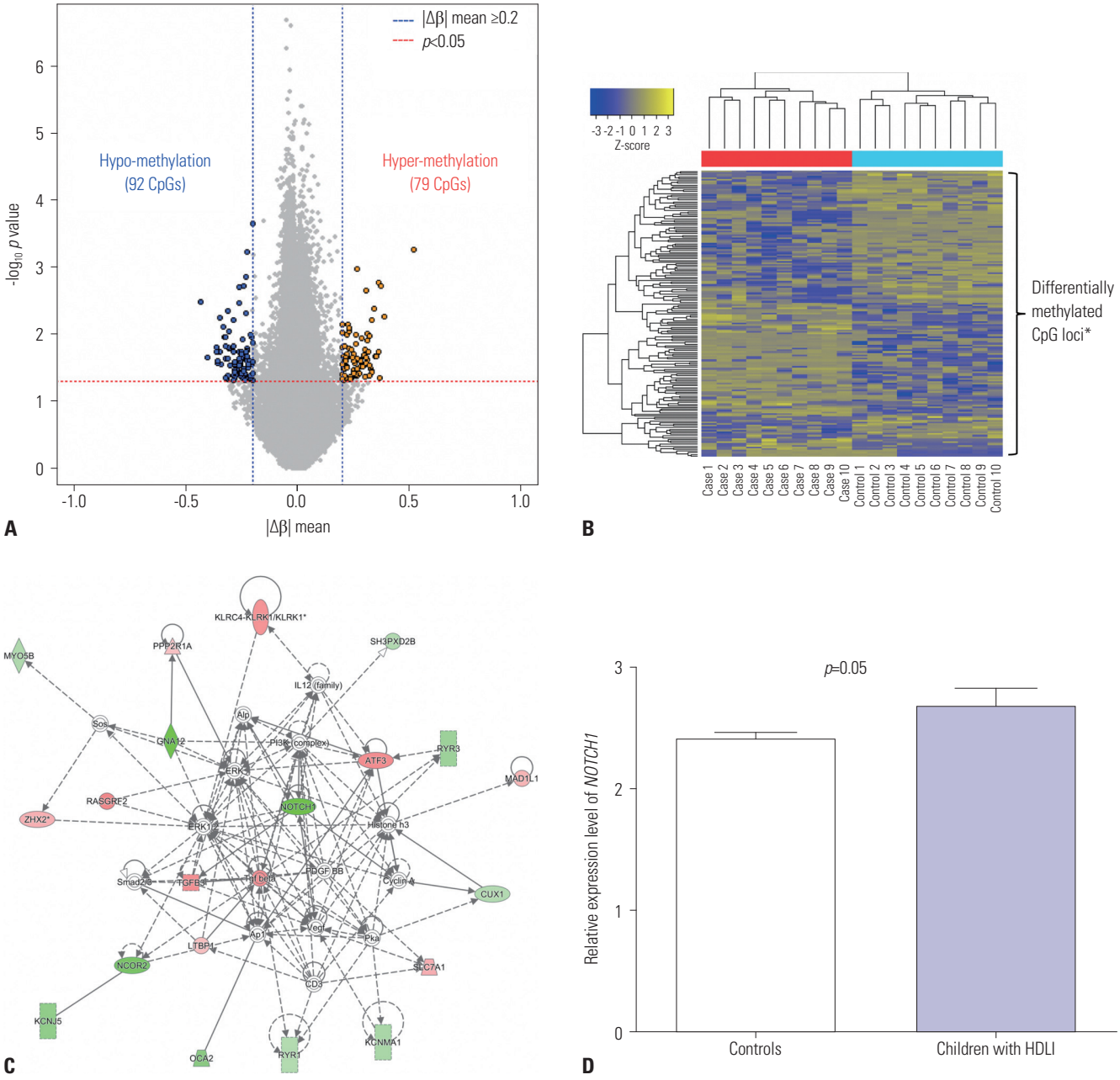

Fig. 1. Results of methylation, network, and *NOTCH1* expression analysis in pediatric HDLI cases. (A) Volcano plot of differentially methylated CpG sites. (B) Heatmap of differentially methylated CpG sites between children with humidifier disinfectant associated lung injuries and unexposed healthy controls. Differentially methylated CpG loci indicated by asterisk. (C) The top network of differentially methylated CpG sites was found to be "cancer, organismal injury and abnormalities, reproductive system disease" and was derived from genes containing hyper-/hypo-methylated CpG sites associated with HDLI. (D) The transcriptional expression of *NOTCH1* between HDLI cases and the control group (p=0.05, t-test, nonparametric methods were applied, and no correction for multiple testing was done due to the small sample size of each group, n=5 for each group). HDLI, humidifier disinfectant lung injuries.

fatal fibrotic lung diseases and give new insights into the possible mechanisms of lung injuries caused by inhalation of unidentified but harmful chemicals that are commonly used.

The inhalation of toxic chemicals damages the epithelial lining in the airway, initiating a series of processes including disruption of epithelial lining, alterations of diverse mediators and chemokine levels, and induction of epithelium-to-mesenchymal transition (EMT).[13] NOTCH1 regulates EMT through various signaling factors, such as TGF-β, NF-κB, and β-catenin.[10] It has been reported that exposure to PHMG phosphate can induce EMT in a dose-dependent manner.[14] A previous study identified that PHMG could induce EMT through the Akt/Notch signaling pathway.[15] This prior evidence, in combination with our current data, further supports the notion that *NOTCH1* plays a role in the pathogenesis of HDLI via EMT following exposure to HDs that contain PHMG.

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Table 2. Top 25 Hypomethylated and Top 25 Hypermethylated Sites Showing Significantly Different Levels in Pediatric Patients with HDLI Compared to Unexposed Healthy Control Children

Methylation type*	Illumina ID	Chr.	CpG coordinate	(Nearest) gene	Position†	Beta value (average)		Δβ	*p* value
						Patients (n=10)	Controls (n=10)		
Hypo-	cg09575189	11	1855561	*SYT8*	TSS200	0.376	0.808	-0.433	0.003
Hypo-	cg05751055	6	33036504	*HLA-DPA1*	Gene body	0.520	0.922	-0.402	0.022
Hypo-	cg11437465	6	33036958	*HLA-DPA1*	Gene body	0.442	0.806	-0.364	0.018
Hypo-	cg05340866	7	148032668	*CNTNAP2*	Gene body	0.200	0.563	-0.363	0.016
Hypo-	cg07474670	12	124831017	*NCOR2*	Gene body	0.357	0.714	-0.357	0.027
Hypo-	cg07791065	6	113786051	*(LINC02518)*		0.370	0.726	-0.356	0.025
Hypo-	cg13318082	1	19669688	*CAPZB*	Gene body	0.616	0.965	-0.348	0.006
Hypo-	cg05526809	4	1309416	*MAEA*	Gene body	0.508	0.855	-0.346	0.018
Hypo-	cg05554406	7	2834869	*GNA12*	Gene body	0.419	0.760	-0.340	0.028
Hypo-	cg20976286	15	28054345	*OCA2*	Gene body	0.405	0.735	-0.330	0.008
Hypo-	cg06378142	19	50119633	*PRR12*	Gene body	0.409	0.737	-0.328	0.011
Hypo-	cg11074353	6	153066907	*(VIP)*		0.488	0.811	-0.323	0.023
Hypo-	cg20981163	6	33049983	*HLA-DPB1*	Gene body	0.369	0.691	-0.323	0.015
Hypo-	cg12858166	6	33033176	*HLA-DPA1*	3′UTR	0.415	0.738	-0.322	0.045
Hypo-	cg24906015	2	58482767	*(FANCL)*		0.540	0.862	-0.321	0.011
Hypo-	cg07846874	7	11568529	*THSD7A*	Gene body	0.512	0.830	-0.318	0.048
Hypo-	cg17635970	8	133117602	*HHLA1*	TSS200	0.548	0.861	-0.313	0.023
Hypo-	cg10978613	8	117473031	*(LINC00536)*		0.561	0.874	-0.313	0.041
Hypo-	cg19484093	4	119990940	*(SYNP02)*		0.417	0.727	-0.310	0.016
Hypo-	cg16715186	22	45981385	*FBLN1*	Gene body	0.522	0.832	-0.309	0.004
Hypo-	cg16776298	1	4784556	*AJAP1*	Gene body	0.499	0.805	-0.306	0.009
Hypo-	cg14065526	9	139406352	*NOTCH1*	Gene body	0.168	0.473	-0.304	0.016
Hypo-	cg17348244	7	786861	*HEATR2*	Gene body	0.624	0.926	-0.303	0.029
Hypo-	cg07336544	10	79194347	*KCNMA1*	Gene body	0.430	0.717	-0.287	0.019
Hypo-	cg04869491	15	33757740	*RYR3; RYR3*	Gene body	0.643	0.929	-0.286	0.015
Hyper-	cg04105547	16	965857	*LMF1*	Gene body	0.557	0.254	0.303	0.043
Hyper-	cg07093060	3	174092757	*(NAALADL2)*		0.751	0.447	0.304	0.017
Hyper-	cg18932722	12	94987650	*TMCC3*	5′UTR	0.864	0.557	0.307	0.022
Hyper-	cg06264089	12	10563947	*KLRC4-KLRK1*	TSS1500	0.686	0.378	0.307	0.002
Hyper-	cg04263740	7	65375514	*VKORC1L1*	Gene body	0.737	0.430	0.308	0.027
Hyper-	cg01359658	7	2426868	*(EIF3B)*		0.633	0.321	0.312	0.010
Hyper-	cg27114706	12	92527244	*LOC256021*	Gene body	0.778	0.465	0.312	0.012
Hyper-	cg01235375	2	66836203	*LOC100507073*	Gene body	0.804	0.490	0.315	0.024
Hyper-	cg13910001	20	31622082	*BPIFB6*	Exon	0.453	0.135	0.319	0.018
Hyper-	cg17155524	4	2305734	*ZFYVE28*	Gene body	0.747	0.426	0.321	0.030
Hyper-	cg18828306	11	17555864	*USH1C*	Gene body	0.605	0.284	0.321	0.041
Hyper-	cg05971102	2	3753297	*DCDC2C*	Gene body	0.616	0.293	0.323	0.011
Hyper-	cg01463139	1	158435277	*OR10K1*	TSS200	0.756	0.429	0.327	0.033
Hyper-	cg08880082	14	90165664	*(FOXN3)*		0.876	0.542	0.334	0.036
Hyper-	cg15570860	11	8986840	*TMEM9B; TMEM9B-AS1*	TSS1500; body	0.701	0.368	0.334	0.038
Hyper-	cg05961492	22	47459539	*TBC1D22A*	Gene body	0.467	0.133	0.334	0.006
Hyper-	cg14080585	20	60639721	*TAF4*	Exon	0.550	0.208	0.342	0.004
Hyper-	cg01886237	4	122378794	*(QRFPR)*		0.675	0.329	0.346	0.022
Hyper-	cg04234412	22	24373322	*LOC391322*	Gene body	0.834	0.481	0.353	0.022
Hyper-	cg21193926	14	76443578	*TGFB3*	Gene body	0.694	0.331	0.363	0.018
Hyper-	cg04531182	12	10563981	*KLRC4-KLRK1*	TSS1500	0.619	0.256	0.363	0.002
Hyper-	cg25099095	6	156954565	*(ARID1B)*		0.735	0.367	0.369	0.045
Hyper-	cg08041188	12	10564015	*KLRC4-KLRK1*	TSS1500	0.698	0.326	0.372	0.002
Hyper-	cg11547201	5	80501337	*RASGRF2; RNU5E; RNU5D*	Body; TSS200; TSS200	0.866	0.477	0.389	0.005
Hyper-	cg26786615	16	86593603	*(MTHFSD)*		0.779	0.261	0.519	0.0006

HDLI, humidifier disinfectant lung injuries; TSS, transcription start site; UTR, untranslated region.
*Hyper- and hypo- indicate the methylation levels of patients compared to controls, †TSS200 and TSS1500 indicate the distance within 200 bp and 1500 bp from TSS, respectively.

Table 3. Gene Expression of Potential Upstream and Downstream Regulators of NOTCH1 in Formalin-Fixed, Paraffin-Embedded Lung Tissue Specimens from Children with HDLI and the Control Group

Category	Gene	mRNA accession	Fold change	*p* value
Upstream regulators				
	DAP3	NM_001199849	1.41	0.017
	ACTN1	NM_001102	1.56	0.003
	ACTN2	NM_001103	-1.23	0.213
	ACTN3	NM_001104	-1.02	0.812
	ACTN4	NM_004924	1.07	0.590
	LONP1	NM_001276479	-1.17	0.235
	ALKBH1	NM_006020	-1.27	0.046
Downstream regulators				
Canonical pathway	*HES1*	NM_005524	-1.12	0.119
	HEY1	NM_001040708	1.09	0.317
	MYC	NM_002467	-1.02	0.841
	BCL2	NM_000633	1.24	0.024
	CCND1	NM_053056	1.38	0.031
Non-canonical pathway	*CHUK*	NM_001278	1.25	0.138
	NFKB1	NM_001165412	1.18	0.124
	PIK3CA	NM_006218	1.11	0.457
	AKT1	NM_001014431	1.12	0.338
	AKT2	NM_001243027	1.07	0.107
	AKT3	NM_001206729	-1.02	0.884
	CTNNB1	NM_001098209	1.10	0.570
Lysosomal degradation	*NUMB*	NM_001005743	1.11	0.406

HDLI, humidifier disinfectant lung injuries.
Upstream regulators are predicted using Ingenuity Pathway Analysis. Downstream regulators of *NOTCH1* are notified from (https://www.rndsystems.com/pathways/notch-signaling-pathway). Formalin-Fixed Paraffin-Embedded lung tissue specimens from HDLI cases (n=5) and controls (n=5).

Our study had some limitations, including its small sample size. However, the results of the current study are significant in that HDLI is an exceptional disease, and the acquisition of blood and lung tissue in our patients was not easy. In our present cohort, there were time lags with a mean of 9 years between diagnosis of HDLI and blood sampling. The methylation patterns in the blood obtained after a time lag of 9 years may have been affected by diverse factors.[16] A previous study showed that less than 30% of individuals showed methylation changes in epigenome-wide DNA methylation analysis on average 11 years apart, even with intra-individual variations.[16] We could not perform methylation analysis in human lung tissues in the current study, as these samples were not available. In spite of the limitations, methylation changes observed in the present study could be helpful to elucidate the mechanisms underlying HDLI with stable disease state.

In conclusion, we have identified *NOTCH1* pathways as one of the possible main fibrogenetic mechanisms of HDLI in children following exposure to PHMG phosphate. Further identification and elucidation of the mechanisms underlying this fatal lung disease are essential for the future development of therapeutics and prevention of lung diseases after exposure to harmful domestic chemicals.

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AUTHOR CONTRIBUTIONS

Conceptualization: Eun Lee, Mi Jin Kang, Jeong-Hyun Kim, and Soo-Jong Hong. Data curation: Seung-Hwa Lee, So-Yeon Lee, Hyun-Ju Cho, Jisun Yoon, Sungsu Jung, Yangsoon Park, Dong Kyu Oh, and Sang-Bum Hong. Formal analysis: Mi Jin Kang and Jeong-Hyun Kim. Funding acquisition: Eun Lee and Soo-Jong Hong. Investigation: Eun Lee, Mi Jin Kang, Jeong-Hyun Kim, Dong Kyu Oh, Sang-Bum Hong, and Soo-Jong Hong. Methodology: Mi Jin Kang, Jeong-Hyun Kim, Seung-Hwa Lee, and Yangsoon Park. Project administration: Eun Lee, Mi Jin Kang, Jeong-Hyun Kim, and Soo-Jong Hong. Resources: Eun Lee and Soo-Jong Hong. Software: Mi Jin Kang and Jeong-Hyun Kim. Supervision: Soo-Jong Hong. Validation: Eun Lee, Mi Jin Kang, Jeong-Hyun Kim, Seung-Hwa Lee, and Yangsoon Park. Writing—original draft: Eun Lee. Writing—review & editing: Eun Lee, Jeong-Hyun Kim, and Soo-Jong Hong. Approval of final manuscript: all authors.

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