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Cause-specific biomarker of chronic kidney disease by integrating genomics and metabolomics in Korean population

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Objectives: Heterogenous feature of chronic kidney disease (CKD) and fragmentary analysis method may hinder precise identification of its novel biomarkers. Herein, we addressed this issue using independent two cohorts to integrate genomics and metabolomics and to identify cause-specific biomarkers of CKD progression in Korean population.

Methods: For discovering the biomarker related with the risk of CKD, longitudinal study using the genomic data of KoGES cohort was conducted. To validate the genomic biomarkers resulted in KoGES cohort and identify the correlations of genomic markers and metabolites, Genome Wide Association Study (GWAS) and metabolomics study were conducted using Seoul National University Hospital (SNUH) cohort consisting of biopsy-confirmed patients. The SNUH cohort was divided into normal and subgroups of CKD, including diabetic nephropathy (DMN), hypertensive nephropathy (HN), IgA nephropathy (IgAN) and membranous nephropathy (MN), using propensity score matching.

Results: From the genomic data of the KoGES cohort, 7,943,674 SNPs were analyzed, and a total of 5,969 single nucleotide polymorphisms (SNPs) were statistically significant for CKD progression in both the discovery and replication sets. Among the 515,990 SNPs in the genomic data of the biopsy cohort, 325 SNPs overlapped with the results of the KoGES cohort. Compared with healthy individuals, 8, 6, 5, and 15 SNPs were selected as being significant in T2DN, HN, IgAN, and MN, respectively. Regarding plasma metabolomics, 51, 28, 29, and 71 metabolites in T2DN, HN, IgAN, and MN, respectively, were different from those from healthy individuals. Accordingly, 32, 16, 7, and 103 pairs of SNPs and metabolites had correlations in T2DN, HN, IgAN, and MN, respectively.

Conclusions: Integrating both GWAS and metabolomics with independent CKD cohorts enables to discover cause-specific biomarkers of CKD in Korean population.

Figure 1. statistically significant pairs of SNPs and metabolites

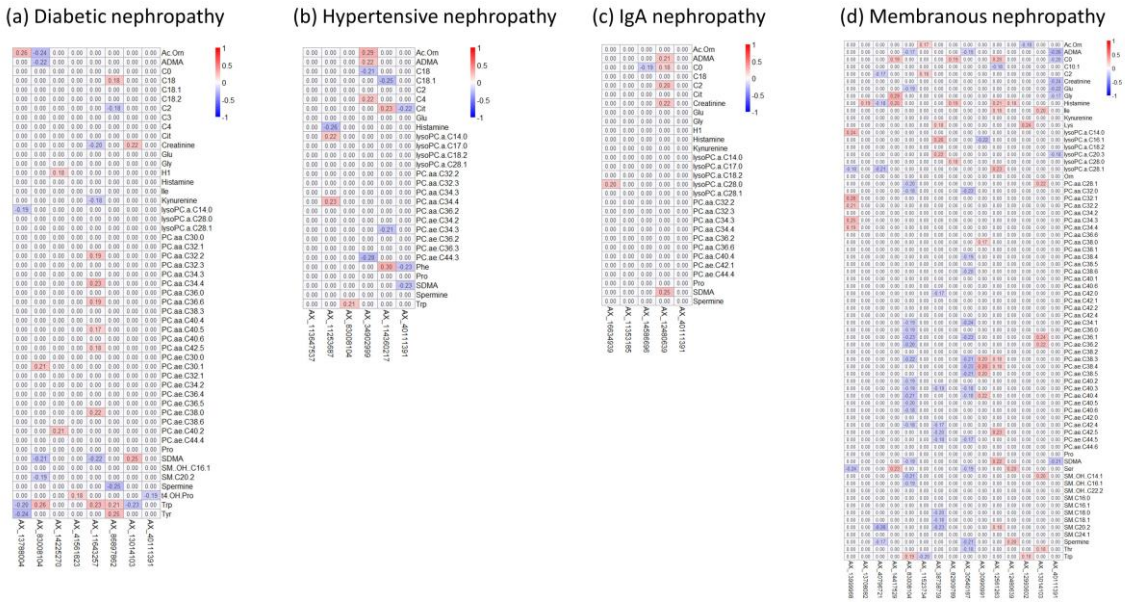

Table 1. CKD related SNPs in SNUH overlapped with KoGES data

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SNU SNP marker	dbSNP.RS.ID	Chromosom	Position	P (Hexa)	P (Ansan-Ansung)	P (SNUH)
Diabetic nephropathy						
AX-83008104	rs112399999	3	149238595	<0.001	0.040	0.001
AX-40111391	---	16	84367090	<0.001	0.004	0.005
AX-13014103	rs10459745	15	100799357	<0.001	0.028	0.019
AX-41561823	rs17155198	5	102618885	<0.001	0.044	0.024
AX-86897862	rs141003853	7	102332448	<0.001	0.024	0.031
AX-11643257	rs7753911	6	55884724	<0.001	0.036	0.034
AX-14225270	rs3821522	3	182933562	<0.001	0.043	0.038
AX-13788004	rs4992744	2	189181674	<0.001	0.042	0.045
Hypertensive nephropathy						
AX-11253687	rs13420911	2	207820276	<0.001	0.007	0.009
AX-40111391	---	16	84367090	<0.001	0.004	0.025
AX-83008104	rs112399999	3	149238595	<0.001	0.040	0.027
AX-113647537	---	2	116959608	<0.001	0.047	0.032
AX-114360217	rs151188446	8	115994899	<0.001	0.049	0.040
AX-34902999	rs4404604	4	66638393	<0.001	0.028	0.042
IgA nephropathy						
AX-16634939	rs2765497	1	157799973	<0.001	0.047	0.002
AX-40111391	---	16	84367090	<0.001	0.004	0.009
AX-12480639	rs16944863	15	91354782	<0.001	0.036	0.016
AX-11353185	rs1925327	1	196163629	<0.001	0.039	0.018
AX-14586696	rs13119610	4	174908521	<0.001	0.023	0.032
Membranous nephropathy						
AX-12480639	rs16944863	15	91354782	<0.001	0.036	0.002
AX-13999968	rs7572044	2	66083220	<0.001	0.012	0.003
AX-14417529	rs2228056	3	98307630	<0.001	0.041	0.008
AX-13708082	rs11687783	2	149358592	<0.001	0.011	0.009
AX-12561263	rs3783093	13	111860716	<0.001	0.032	0.010
AX-12993602	rs6496846	15	92174033	<0.001	0.004	0.012
AX-40111391	---	16	84367090	<0.001	0.004	0.015
AX-83008104	rs112399999	3	149238595	<0.001	0.040	0.017
AX-30990991	rs636138	13	110909043	<0.001	0.007	0.018
AX-38738739	rs10886937	10	123195615	<0.001	0.023	0.023
AX-30540187	rs7312850	12	125723098	<0.001	0.026	0.027
AX-13014103	rs10459745	15	100799357	<0.001	0.028	0.030
AX-82909789	rs56235610	11	128805557	<0.001	0.048	0.041
AX-11523734	rs475691	6	165633342	<0.001	0.032	0.046
AX-40796721	rs6434482	2	192423103	<0.001	0.028	0.050

Abbreviation: CKD, chronic kidney disease; SNUH, Seoul national university hospital; KoGES, Korean genome and epidemiology study