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Integrated genomics and metabolomics to identify cause-specific biomarkers for chronic kidney disease in Korean population

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Objectives : The heterogeneity of chronic kidney disease (CKD) features and the fragmentary nature of analysis methods may impede the precise identification of novel biomarkers. Herein, we addressed this issue by utilizing two independent cohorts to integrate genomics and metabolomics, aiming to identify cause-specific biomarkers for CKD and its progression in Korean population.
Methods : A longitudinal genome-wide survival analysis was conducted using the Ansan and Ansung cohort (n=5,194), a part of Korean Genome and Epidemiology Study. To validate these genomic biomarkers and integrate them with metabolomic biomarker, we used a biopsy-confirmed CKD cohort from Seoul National University Hospital in Korea. In this cohort, we analyzed 4 disease groups matched for age and sex, namely type 2 diabetic kidney disease (DKD) (n=64), hypertensive nephropathy (HN) (n=24), immunoglobulin A nephropathy (IgAN) (n=66), and membranous nephropathy (MN) (n=66), and compared them with healthy individuals (n=66). In the biopsy cohort, significant SNPs and metabolites for each CKD subset were identified, and cause-specific biomarker pairs were selected using correlation-based network analysis. Subsequently, the risk of kidney progression associated with the identified pairs was assessed.
Results : From the Ansan and Ansung cohort, we analyzed 451,172 SNP variants, identifying a total of 448 variants significant for CKD development. Among these, 11, 10, 13, and 21 variants were selected as significant in DKD, HN, IgAN, and MN, respectively, in the biopsy cohort. Regarding plasma metabolomics, 51, 28, 29, and 71 metabolites in DKD, HN, IgAN, and MN, respectively, were identified. Accordingly, we identified 36 pairs of SNP variants and metabolites, and 5 pairs exhibited an association with only one specific disease subset. Within these pairs, the rs1025170 and tyrosine pair correlated with the progression of DKD.
Conclusions : Integrating both genomics and metabolomics with independent cohorts enables the discovery of cause-specific biomarkers for CKD and its progression in Korean population.

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Table 3. Validation of genetic biomarkers in the biopsy cohort

CKD subset	SNP	Gene	Minor allele	MAF	Odds ratio (95% CI)	*P**
DKD	rs41354447	IL17RA	T	0.050	0.222 (0.070–0.703)	0.011
	rs7222384	LOC100506974	A	0.494	0.486 (0.283–0.833)	0.009
	rs75478132	MAN2A2	G	0.035	14.660 (1.666–129.100)	0.016
	rs1125327	ZFP42	C	0.043	0.189 (0.040–0.895)	0.036
	rs4715580	COL21A1	T	0.186	0.413 (0.198–0.864)	0.019
	rs132351	EMID1	A	0.197	2.182 (1.085–4.388)	0.029
	rs12023515	ADSS	T	0.133	3.385 (1.390–8.246)	0.007
	rs10275530	CDK14	A	0.204	0.437 (0.226–0.846)	0.014
	rs17080554	RASEF	C	0.087	5.655 (1.673–19.110)	0.005
	rs1025170	FOXB1	A	0.113	2.678 (1.056–6.789)	0.038
	rs78355929	LOH12CR1	C	0.170	2.368 (1.184–4.736)	0.015
HN	rs4714273	DAAM2	A	0.440	2.132 (1.053–4.318)	0.036
	rs9563198	LINC00458	A	0.090	3.087 (1.321–7.212)	0.009
	rs4911532	MYLK2	C	0.424	0.446 (0.208–0.959)	0.039
	rs79445374	EYS	G	0.064	6.065 (1.185–31.040)	0.03
	rs189456593	LPPR1	T	0.019	6.988 (1.139–42.890)	0.036
	rs6060930	TPX2	G	0.421	0.427 (0.199–0.918)	0.029
	rs7769544	KLHL31	C	0.112	5.042 (1.409–18.050)	0.013
	rs78160911	DHX29	C	0.041	6.148 (1.359–27.800)	0.018
	rs12977409	LOC100128682	A	0.100	3.018 (1.025–8.887)	0.045
	rs75159273	VGLL4	A	0.053	5.398 (1.170–24.910)	0.031
IgAN	rs11145117	PRUNE2	A	0.288	1.934 (1.090–3.433)	0.024
	rs12681357	NKAIN3	A	0.383	0.439 (0.250–0.770)	0.004
	rs74426712	LOC101928241	T	0.213	2.201 (1.172–4.136)	0.014
	rs9886239	IKZF1	A	0.438	0.580 (0.340–0.989)	0.045
	rs2532925	SFTA2	G	0.234	0.354 (0.184–0.681)	0.002
	rs2253588	SFTA2	C	0.234	0.354 (0.184–0.681)	0.002
	rs2532941	VARS2	G	0.229	0.354 (0.184–0.681)	0.002
	rs9365689	QKI	A	0.075	3.076 (1.131–8.366)	0.028
	rs17075889	LOC105377732	C	0.380	1.951 (1.143–3.332)	0.014
	rs17080554	RASEF	C	0.087	4.692 (1.403–15.690)	0.012
	rs7769544	KLHL31	C	0.112	3.405 (1.160–10.000)	0.026
	rs17031161	LOC101927533	C	0.483	1.674 (1.007–2.784)	0.047
	rs4561414	LINC00924	A	0.203	2.222 (1.184–4.169)	0.013
MN	rs17016322	MMRN1	G	0.104	0.128 (0.027–0.605)	0.009
	rs2295894	SYNJ2	T	0.277	2.018 (1.118–3.643)	0.020
	rs7222384	LOC100506974	A	0.494	0.440 (0.245–0.790)	0.006
	rs12681357	NKAIN3	A	0.383	0.555 (0.329–0.937)	0.027
	rs375016	TLDC1	T	0.391	1.845 (1.045–3.259)	0.035
	rs1192415	HSP90B3P	G	0.135	2.167 (1.074–4.372)	0.031
	rs8119573	C20orf196	A	0.385	1.823 (1.006–3.304)	0.048
	rs2532925	SFTA2	G	0.234	0.399 (0.209–0.760)	0.005
	rs11639416	ATP10A	C	0.475	0.607 (0.375–0.982)	0.042
	rs11842112	ATP8A2	C	0.259	2.490 (1.364–4.547)	0.003
	rs2253588	SFTA2	C	0.234	0.399 (0.209–0.760)	0.005
	rs2532941	VARS2	G	0.229	0.399 (0.209–0.760)	0.005
	rs67175264	LOC105373559	C	0.457	2.068 (1.193–3.583)	0.010
	rs144942333	PRKCD	T	0.038	5.700 (1.123–28.920)	0.036
	rs17075889	LOC105377732	C	0.380	2.191 (1.172–4.098)	0.014
	rs9319510	ADAMTS18	G	0.179	2.417 (1.144–5.108)	0.021
	rs3787359	ADA	G	0.276	0.544 (0.298–0.992)	0.047
	rs1135411	LOC100507507	T	0.111	2.556 (1.104–5.916)	0.028
	rs17080554	RASEF	C	0.087	4.761 (1.452–15.610)	0.010
	rs993376	MIR3974	C	0.460	2.648 (1.438–4.879)	0.002
	rs12583550	MIR1297	T	0.057	7.418 (1.736–31.700)	0.007

CKD, chronic kidney disease; SNP, single nucleotide polymorphism; MAF, minor allele frequency; CI, confidence interval; DKD, diabetic kidney disease; HN, hypertensive nephropathy; IgAN, immunoglobulin A nephropathy; MN, membranous nephropathy.
*Adjusted for age and sex.

Table 4. Hazard ratio of single nucleotide polymorphism for kidney progression

Associated disease	SNP	Associated gene of SNP	Hazard ratio (95% CI)	*P**
DKD	rs1025170	FOXB1	2.683 (1.383–5.204)	0.004
DKD	rs1125327	ZFP42	0.860 (0.465–1.591)	0.404
MN	rs17016322	MMRN1	0.841 (0.456–1.551)	0.579
MN	rs2295894	SYNJ2	0.774 (0.417–1.439)	0.196

SNP, single nucleotide polymorphism; CI, confidence interval; DKD, diabetic kidney disease; MN, membranous nephropathy.
*Adjusted for age, sex, estimated glomerular filtration, and random urine protein-to-creatinine ratio.

Table 5. The risk for kidney progression based on the minor allele count of rs1025170 (FOXB1) and plasma tyrosine levels

Minor allele counts	L-Tyrosine level	Subject no.	Hazard ratio (95% CI)	*P**
1 or 2	Lower level	32	3.470 (1.420–8.483)	0.006
1 or 2	Upper level	9	2.911 (0.616–13.743)	0.177
0	Lower level	125	1.420 (0.642–3.141)	0.387
0	Upper level	117	1 (reference)	

CI, confidence interval.
*Adjusted for age, sex, estimated glomerular filtration, and random urine protein-to-creatinine ratio.

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Figure 1. Study subjects of the KoGES cohort

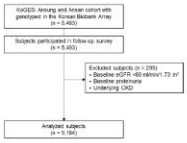

Figure 2. Study subjects of the biopsy cohort

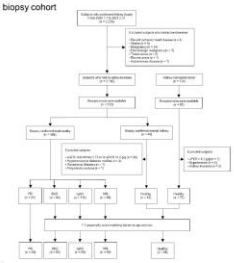

Figure 3. Flow chart of the analysis

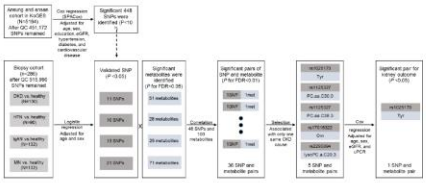

Figure 4. Correlation-based network of SNPs and metabolites according to the kidney disease cause in biopsy cohort

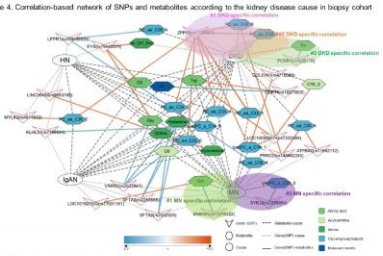

Figure 5. Unadjusted and adjusted survival curves for kidney outcome