

Table S1. Information of *NPRL3*, *MPG* polymorphisms for PCR-RFLP and real-time PCR analysis

Gene	rs number	CHR	Position	Primer sequence	Probe sequence	Annealing temperature	Restriction enzyme
<i>NPRL3</i>	rs2541618	ch16	142825	F: 5'- TCC AGG CTG GCT CTT CTA ATC CAC -3' R: 5'- TGA GAT GGG AAC TGG TGG GAG AAC -3'		58°C	<i>Sau96 I</i>
<i>NPRL3</i>	rs75187722	ch16	180529	F: 5'- ATC TGG GTG AAT AGG AGG GTG GGG -3' R: 5'- AAC CCT CCT GTG TGT GGA AGG ACC -3'		60°C	<i>HphI</i>
<i>MPG</i>	rs2562162	ch16	128179		Oligo 5'- TCA CTG CCC CCC CTC TCC CGG CTT C -3' Oligo 5' -TCA CTG CCC CCC TTC TCC CGG CTT C -3'	66°C	
<i>MPG</i>	rs710079	ch16	129223	F: 5' - ATC TGC TCC CCA GGT CAT GCA G - 3' R: 5' - GGG TGA CCA TCC TGT GGG TTG T - 3'		60°C	<i>BccI</i>

Note: PCR-RFLP, polymorphism chain reaction-restriction fragment length polymorphism; CHR, chromosome.

Table S2. Information of *NPRL3*, *MPG* gene polymorphisms from WES results

Gene	Location	Rs number	P-value
MPG	5_prime_UTR	rs76079375	>0.05
MPG	5_prime_UTR	rs2562162	0.00007259
MPG	5_prime_UTR	.	>0.05
MPG	5_prime_UTR	.	>0.05
MPG	5_prime_UTR	rs710079	>0.05
MPG	5_prime_UTR	rs3176380;rs2234890	>0.05
MPG	5_prime_UTR	rs710080	>0.05
MPG	synonymous	rs710081	>0.05
MPG	missense	rs201536549	>0.05
MPG	intron	.	>0.05
NPRL3	intron	rs743725	0.0002432
NPRL3	frameshift	rs57321480;rs397815833	>0.05
NPRL3	intron	rs559166204	>0.05
NPRL3	intron	rs2541618	0.0000468
NPRL3	intron	rs2541616	>0.05
NPRL3	intron	rs808892	0.0003943
NPRL3	intron	rs369659219	>0.05
NPRL3	intron	rs116993855	>0.05
NPRL3	intron	rs148796095	>0.05
NPRL3	intron	.	>0.05
NPRL3	intron	rs138059300	>0.05
NPRL3	splice_region & intron	rs61016911	>0.05
NPRL3	synonymous	rs75187722	0.01976
NPRL3	splice_acceptor & 5_prime_UTR & intron	.	>0.05

Note: NPRL3, nitrogen permease receptor like-3; MPG, N-methylpurine DNA glycosylase.

Table S3. Comparison of baseline characteristics between ischemic stroke patients, ischemic stroke subgroups, and controls

Characteristic	Controls (n=417)	Stroke patients (n=519)	<i>P</i> ^a	LAD patients (n=207)	<i>P</i> ^a	SVD patients (n=149)	<i>P</i> ^a	CE patients (n=53)	<i>P</i> ^a
BMI (kg/m ² , mean ±SD)	24.37±3.22	24.18±3.11	0.439	24.39±3.07	0.931	23.98±3.16	0.253	23.84±3.27	0.290
HDL-C (mg/dl, mean ±SD)	46.39±13.67	44.58±15.62	0.021^b	43.52±13.26	0.039	44.03±13.77	0.127	46.33±13.76	0.975
Homocysteine (μmol/L, mean ±SD)	10.07±4.18	11.21±7.34	0.005^b	11.40±7.95	0.047^b	10.89±5.67	0.085 ^b	9.44±3.75	0.294
Folate (nmol/L, mean±SD)	8.83±7.92	7.10±6.15	< 0.0001^b	6.40±4.21	< 0.0001^b	7.07±5.53	< 0.0001^b	9.73±11.53	0.309 ^b
Vitamin B12 (pg/ml, mean ±SD)	741.34±662.85	752.10±641.72	0.803	794.03±872.81	0.935 ^b	657.32±314.81	0.148 ^b	813.58±433.98	0.013^b
Total cholesterol (mg/dl, mean ±SD)	193.12±36.99	190.33±40.40	0.280	193.21±46.28	0.682 ^b	189.32±36.23	0.283	180.25±34.59	0.017
Triglyceride (mg/dl, mean ±SD)	146.69±89.81	152.82±114.81	0.761 ^b	152.10±100.27	0.500	169.29±125.53	0.099 ^b	134.02±181.59	0.007^b
PLT (10 ³ /μl, mean ±SD)	242.70±67.84	244.71±76.82	0.509 ^b	251.65±84.05	0.802 ^b	239.11±70.40	0.584	233.34±74.61	0.351
PT (sec, mean ±SD)	11.78±0.80	11.82±1.04	0.793 ^b	11.78±0.76	1.000	11.68±0.79	0.199	12.07±1.05	0.099 ^b
aPTT (sec, mean ±SD)	33.39±18.51	30.57±4.78	0.043^b	30.49±4.82	0.052 ^b	30.82±4.70	0.273 ^b	30.80±4.27	0.760 ^b
Fibrinogen (mg/dl, mean ±SD)	402.27±126.70	425.30±127.15	0.054	431.97±128.17	0.224	398.40±115.24	0.780 ^b	453.96±133.29	0.086
Antithrombin III (% , mean ±SD)	94.16±43.02	93.95±17.39	0.078 ^b	94.82±15.54	0.056 ^b	95.45±20.05	0.045^b	86.28±17.23	0.130 ^b
BUN (mg/dl, mean ±SD)	15.81±5.00	16.14±6.39	0.920 ^b	15.41±4.85	0.348	15.08±5.14	0.135	18.68±11.04	0.068 ^b
Uric Acid (mg/dl, mean ±SD)	4.64±1.47	4.70±1.52	0.561	4.67±1.42	0.811	4.62±1.36	0.905	4.54±1.56	0.644

Note: SD, standard deviation; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; PLT, platelet; PT, prothrombin time; aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; LAD, large artery disease; SVD, small vessel disease; CE, cardioembolism.

^a *P*-values were calculated by two-sided t-test for continuous variables and chi-square test for categorical variables.

^b *P*-values were calculated by Mann-Whitney-test for continuous variables.

***P*-values < 0,05 are bold**

Table S4. Stratified analysis of *NPRL3* genotypes and characteristics of ischemic stroke among individual risk factors

Characteristics	<i>NPRL3</i> rs2541618		<i>NPRL3</i> rs2541618		<i>NPRL3</i> rs75187722		<i>NPRL3</i> rs75187722	
	TT		CT+TT		GA		GA+AA	
	AOR(95% CI)*	<i>P</i>	AOR(95% CI)*	<i>P</i>	AOR(95% CI)*	<i>P</i>	AOR(95% CI)*	<i>P</i>
Age (936)								
<63	1.757 (0.853 - 3.620)	0.126	1.436 (0.951 - 2.167)	0.085	0.605 (0.350 - 1.044)	0.071	0.589 (0.343 - 1.014)	0.056
≥63	1.412 (0.710 - 2.810)	0.325	1.048 (0.723 - 1.519)	0.805	0.762 (0.468 - 1.241)	0.275	0.794 (0.493 - 1.281)	0.345
Sex (936)								
Male	1.858 (0.913 - 3.782)	0.088	1.581 (1.033 - 2.421)	0.035	0.544 (0.310 - 0.957)	0.035	0.544 (0.310 - 0.957)	0.035
Female	1.339 (0.673 - 2.667)	0.406	1.012 (0.708 - 1.448)	0.947	0.815 (0.504 - 1.318)	0.404	0.825 (0.517 - 1.316)	0.419
Hypertension (936)								
No	1.169 (0.586 - 2.333)	0.657	1.060 (0.714 - 1.574)	0.773	0.993 (0.598 - 1.650)	0.978	0.993 (0.598 - 1.650)	0.978
Yes	2.109 (1.005 - 4.427)	0.049	1.375 (0.944 - 2.002)	0.097	0.529 (0.321 - 0.872)	0.012	0.550 (0.339 - 0.893)	0.016
Diabetes mellitus (936)								
No	1.403 (0.824 - 2.392)	0.213	1.154 (0.853 - 1.561)	0.353	0.685 (0.454 - 1.033)	0.071	0.681 (0.454 - 1.020)	0.062
Yes	2.782 (0.702 - 11.017)	0.145	1.651 (0.863 - 3.160)	0.130	0.766 (0.349 - 1.683)	0.507	0.838 (0.385 - 1.822)	0.656
Hyperlipidemia (936)								
No	1.378 (0.805 - 2.361)	0.242	1.180 (0.862 - 1.616)	0.301	0.599 (0.394 - 0.909)	0.016	0.594 (0.394 - 0.897)	0.013
Yes	3.132 (0.786 - 12.479)	0.106	1.367 (0.791 - 2.362)	0.262	1.233 (0.574 - 2.651)	0.591	1.318 (0.619 - 2.805)	0.474
Smoking (930)								
No	1.771 (0.918 - 3.415)	0.088	1.225 (0.873 - 1.719)	0.241	0.775 (0.495 - 1.216)	0.268	0.767 (0.493 - 1.193)	0.240
Yes	1.504 (0.707 - 3.200)	0.289	1.181 (0.745 - 1.871)	0.479	0.535 (0.287 - 0.998)	0.049	0.568 (0.307 - 1.052)	0.072
HDL-c (671)								
≥40(M)/50(F)	1.083 (0.445 - 2.634)	0.860	0.945 (0.570 - 1.568)	0.827	0.510 (0.238 - 1.094)	0.084	0.510 (0.238 - 1.094)	0.084
<40(M)/50(F)	1.354 (0.556 - 3.295)	0.504	1.453 (0.877 - 2.405)	0.147	0.589 (0.324 - 1.070)	0.082	0.623 (0.345 - 1.127)	0.118
Folate * (927)								
>3.54 nmol/L	1.387 (0.808 - 2.381)	0.235	1.176 (0.874 - 1.582)	0.285	0.917 (0.618 - 1.359)	0.665	0.910 (0.617 - 1.341)	0.633
≤3.54 nmol/L	2.949 (0.580 - 15.003)	0.193	1.408 (0.613 - 3.237)	0.420	0.137 (0.048 - 0.386)	0.0002	0.142 (0.051 - 0.399)	0.0002
Homocysteine † (931)								
<13.7 μmol/L	1.546 (0.917 - 2.605)	0.102	1.257 (0.936 - 1.687)	0.128	0.736 (0.493 - 1.098)	0.133	0.737 (0.497 - 1.093)	0.129
≥13.7 μmol/L	1.454 (0.295 - 7.171)	0.646	0.930 (0.432 - 2.001)	0.852	0.537 (0.217 - 1.329)	0.179	0.578 (0.237 - 1.411)	0.229
Platelet † (927)								
<305 10 ³ /μl	1.375 (0.812 - 2.330)	0.236	1.138 (0.847 - 1.531)	0.391	0.918 (0.610 - 1.381)	0.680	0.906 (0.606 - 1.355)	0.630
≥305 10 ³ /μl	3.847 (0.859 - 17.218)	0.078	1.814 (0.880 - 3.742)	0.107	0.291 (0.121 - 0.701)	0.006	0.322 (0.137 - 0.757)	0.009
PT * (801)								
>11.00 sec	1.197 (0.690 - 2.075)	0.523	1.157 (0.834 - 1.605)	0.382	0.577 (0.381 - 0.874)	0.009	0.560 (0.371 - 0.844)	0.006
≤11.00 sec	3.859 (0.627 - 23.766)	0.145	1.853 (0.851 - 4.037)	0.120	1.093 (0.365 - 3.280)	0.874	1.241 (0.426 - 3.614)	0.692
aPTT * (801)								
>26.30 sec	1.678 (0.928 - 3.035)	0.087	1.233 (0.890 - 1.709)	0.207	0.585 (0.385 - 0.889)	0.012	0.588 (0.389 - 0.890)	0.012
≤26.30 sec	0.568 (0.164 - 1.973)	0.373	1.559 (0.698 - 3.481)	0.279	0.744 (0.238 - 2.320)	0.610	0.666 (0.223 - 1.988)	0.466
Fibrinogen † (626)								
<537 mg/dl	1.685 (0.784 - 3.621)	0.181	1.334 (0.886 - 2.007)	0.167	0.692 (0.411 - 1.165)	0.166	0.720 (0.429 - 1.208)	0.213
≥537 mg/dl	0.948 (0.196 - 4.590)	0.947	1.280 (0.413 - 3.966)	0.669	0.176 (0.040 - 0.767)	0.021	0.176 (0.040 - 0.767)	0.021

Note: AOR, adjusted odds ratio; 95% CI, 95% confidence interval; HDL-c, high density lipoprotein cholesterol; PT, prothrombin time; aPTT, activated partial thromboplastin time; *NPRL3*, nitrogen permease receptor like-3. * The adjusted odds ratio on the basis of risk factors, such as age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking. *P*-values <0.05 are bold. The number of each subgroup is located next to each subgroup.

† Folate 3.54nmol/L, PT 11.00 sec, and aPTT 26.30 sec were lower 15% cut-off each level in ischemic stroke patients and controls.

† Homocysteine 13.7 μmol/L, Platelet 305 103/μℓ, and fibrinogen 537 mg/dl were upper 15% cut-off each level in ischemic stroke patients and controls.

Table S5. Stratified analysis of MPG genotypes and characteristics of ischemic stroke among individual risk factors

Characteristics	MPG rs2562162		MPG rs2562162		MPG rs710079		MPG rs710079	
	CT		CT+TT		CT		CT+TT	
	AOR(95% CI)*	P						
Age (936)								
<63	1.339 (0.876 - 2.045)	0.177	1.435 (0.952 - 2.164)	0.085	0.938 (0.592 - 1.486)	0.784	0.903 (0.573 - 1.424)	0.661
≥63	1.255 (0.835 - 1.885)	0.275	1.157 (0.792 - 1.689)	0.451	0.950 (0.628 - 1.436)	0.808	0.915 (0.612 - 1.367)	0.664
Sex (936)								
Male	1.407 (0.899 - 2.203)	0.135	1.461 (0.953 - 2.239)	0.082	0.931 (0.575 - 1.508)	0.771	0.866 (0.540 - 1.388)	0.549
Female	1.229 (0.839 - 1.800)	0.289	1.168 (0.814 - 1.676)	0.399	0.924 (0.618 - 1.380)	0.698	0.914 (0.618 - 1.352)	0.652
Hypertension (936)								
No	1.357 (0.893 - 2.063)	0.153	1.415 (0.948 - 2.110)	0.089	1.201 (0.780 - 1.847)	0.406	1.093 (0.715 - 1.672)	0.680
Yes	1.191 (0.802 - 1.769)	0.387	1.127 (0.774 - 1.640)	0.534	0.779 (0.508 - 1.195)	0.252	0.798 (0.526 - 1.210)	0.288
Diabetes mellitus (936)								
No	1.188 (0.862 - 1.636)	0.293	1.184 (0.873 - 1.605)	0.277	0.859 (0.614 - 1.202)	0.376	0.829 (0.596 - 1.154)	0.266
Yes	1.875 (0.945 - 3.719)	0.072	1.830 (0.954 - 3.512)	0.069	1.728 (0.757 - 3.946)	0.194	1.570 (0.728 - 3.388)	0.250
Hyperlipidemia (936)								
No	1.373 (0.980 - 1.923)	0.065	1.340 (0.976 - 1.839)	0.071	0.863 (0.608 - 1.226)	0.412	0.821 (0.582 - 1.159)	0.262
Yes	1.108 (0.634 - 1.936)	0.719	1.113 (0.646 - 1.917)	0.700	1.321 (0.701 - 2.489)	0.390	1.309 (0.709 - 2.418)	0.389
Smoking (930)								
No	1.283 (0.896 - 1.838)	0.174	1.238 (0.880 - 1.741)	0.221	1.004 (0.683 - 1.477)	0.983	0.952 (0.654 - 1.387)	0.799
Yes	1.302 (0.800 - 2.119)	0.289	1.341 (0.845 - 2.126)	0.213	0.795 (0.477 - 1.327)	0.380	0.779 (0.469 - 1.292)	0.333
HDL-c (671)								
≥40(M)/50(F)	1.345 (0.790 - 2.289)	0.276	1.358 (0.819 - 2.253)	0.236	0.997 (0.562 - 1.769)	0.992	0.966 (0.547 - 1.706)	0.904
<40(M)/50(F)	1.311 (0.763 - 2.252)	0.328	1.276 (0.765 - 2.127)	0.350	0.571 (0.334 - 0.976)	0.040	0.589 (0.347 - 0.999)	0.050
Folate * (927)								
>3.54 nmol/L	1.277 (0.936 - 1.741)	0.123	1.235 (0.917 - 1.663)	0.165	1.026 (0.733 - 1.437)	0.879	0.969 (0.698 - 1.347)	0.852
≤3.54 nmol/L	1.391 (0.538 - 3.598)	0.496	1.555 (0.654 - 3.698)	0.318	0.635 (0.257 - 1.572)	0.326	0.714 (0.293 - 1.738)	0.458
Homocysteine † (931)								
<13.7 μmol/L	1.438 (1.054 - 1.960)	0.022	1.455 (1.083 - 1.956)	0.013	0.909 (0.652 - 1.268)	0.573	0.864 (0.624 - 1.195)	0.377
≥13.7 μmol/L	0.536 (0.236 - 1.215)	0.135	0.496 (0.229 - 1.070)	0.075	1.347 (0.590 - 3.076)	0.480	1.407 (0.618 - 3.203)	0.415
Platelet † (927)								
<305 10 ³ /μℓ	1.159 (0.846 - 1.586)	0.358	1.140 (0.846 - 1.535)	0.390	1.032 (0.738 - 1.443)	0.854	0.996 (0.717 - 1.383)	0.980
≥305 10 ³ /μℓ	2.137 (1.007 - 4.533)	0.048	2.278 (1.106 - 4.691)	0.026	0.691 (0.317 - 1.505)	0.352	0.654 (0.303 - 1.412)	0.279
PT* (801)								
>11.00 sec	1.154 (0.815 - 1.635)	0.420	1.121 (0.808 - 1.555)	0.496	0.857 (0.598 - 1.229)	0.401	0.813 (0.571 - 1.158)	0.251
≤11.00 sec	1.976 (0.864 - 4.518)	0.106	1.798 (0.812 - 3.980)	0.148	1.349 (0.550 - 3.309)	0.513	1.349 (0.559 - 3.252)	0.506
aPTT* (801)								
>26.30 sec	1.125 (0.798 - 1.587)	0.502	1.121 (0.809 - 1.555)	0.493	0.908 (0.630 - 1.307)	0.602	0.857 (0.599 - 1.224)	0.396
≤26.30 sec	2.228 (0.916 - 5.417)	0.077	1.662 (0.731 - 3.775)	0.225	0.998 (0.424 - 2.348)	0.996	0.969 (0.419 - 2.239)	0.941
Fibrinogen † (626)								
< 537 mg/dl	1.552 (0.999 - 2.413)	0.051	1.598 (1.050 - 2.433)	0.029	0.839 (0.535 - 1.314)	0.443	0.834 (0.535 - 1.298)	0.421
≥ 537 mg/dl	1.314 (0.408 - 4.232)	0.647	1.259 (0.419 - 3.778)	0.682	0.601 (0.190 - 1.901)	0.386	0.601 (0.190 - 1.901)	0.386

Note: AOR, adjusted odds ratio; 95% CI, 95% confidence interval; HDL-c, high density lipoprotein cholesterol; PT, prothrombin time; aPTT, activated partial thromboplastin time; MPG, N-methylpurine DNA glycosylase. * The adjusted odds ratio on the basis of risk factors, such as age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking. P-values <0.05 are bold. The number of each subgroup is located next to each subgroup.

[†] Folate 3.54nmol/L, PT 11.00 sec, and aPTT 26.30 sec were lower 15% cut-off each level in ischemic stroke patients and controls.

[‡] Homocysteine 13.7 μ mol/L, Platelet 305 103/ μ l, and fibrinogen 537 mg/dl were upper 15% cut-off each level in ischemic stroke patients and controls.

Table S6. Ischemic stroke incidence by interaction analysis between *NPRL3*, *MPG* genotypes and environmental factors

Characteristics	<i>NPRL3</i> rs2541618 CC	<i>NPRL3</i> rs2541618 CT+TT	<i>NPRL3</i> rs75187722 GG	<i>NPRL3</i> rs75187722 GA+AA	<i>MPG</i> rs2562162 CC	<i>MPG</i> rs2562162 CT+TT	<i>MPG</i> rs710079 CC	<i>MPG</i> rs710079 CT+TT
HDL-c (671)								
≥40(M)/50(F)	1.000 (reference)	1.089 (0.758 - 1.565)	1.000 (reference)	0.508 (0.297 - 0.870)	1.000 (reference)	1.449 (1.007 - 2.085)	1.000 (reference)	1.078 (0.718 - 1.619)
<40(M)/50(F)	4.529 (2.900 - 7.074)	6.364 (4.103 - 9.869)	5.541 (3.880 - 7.912)	3.699 (2.099 - 6.520)	5.718 (3.754 - 8.709)	7.330 (4.564 - 11.773)	6.449 (4.384 - 9.487)	3.929 (2.412 - 6.400)
Folate * (927)								
>3.54 nmol/L	1.000 (reference)	1.187 (0.883 - 1.596)	1.000 (reference)	0.911 (0.619 - 1.340)	1.000 (reference)	1.254 (0.932 - 1.686)	1.000 (reference)	0.953 (0.687 - 1.322)
≤3.54 nmol/L	3.235 (1.739 - 6.019)	4.866 (2.527 - 9.370)	5.427 (3.151 - 9.347)	0.696 (0.282 - 1.717)	3.347 (1.892 - 5.919)	5.601 (2.651 - 11.836)	3.925 (2.270 - 6.785)	2.622 (1.247 - 5.517)
Homocysteine † (931)								
<13.7 μmol/L	1.000 (reference)	1.261 (0.940 - 1.691)	1.000 (reference)	0.738 (0.499 - 1.092)	1.000 (reference)	1.463 (1.088 - 1.965)	1.000 (reference)	0.860 (0.621 - 1.190)
≥13.7 μmol/L	1.727 (0.976 - 3.056)	1.839 (1.057 - 3.201)	1.639 (1.041 - 2.581)	0.857 (0.391 - 1.875)	2.365 (1.374 - 4.071)	1.301 (0.731 - 2.318)	1.281 (0.797 - 2.059)	1.747 (0.882 - 3.462)
Platelet † (927)								
<305 10 ³ /μℓ	1.000 (reference)	1.140 (0.849 - 1.530)	1.000 (reference)	0.870 (0.585 - 1.296)	1.000 (reference)	1.158 (0.861 - 1.557)	1.000 (reference)	0.991 (0.716 - 1.373)
≥305 10 ³ /μℓ	0.670 (0.379 - 1.187)	1.205 (0.711 - 2.042)	1.170 (0.749 - 1.829)	0.356 (0.163 - 0.776)	0.658 (0.385 - 1.123)	1.348 (0.770 - 2.357)	1.033 (0.650 - 1.643)	0.662 (0.342 - 1.281)
PT* (801)								
>11.00 sec	1.000 (reference)	1.113 (0.831 - 1.491)	1.000 (reference)	0.666 (0.454 - 0.976)	1.000 (reference)	1.182 (0.882 - 1.585)	1.000 (reference)	0.900 (0.653 - 1.240)
≤11.00 sec	1.067 (0.606 - 1.881)	2.192 (1.241 - 3.872)	1.319 (0.855 - 2.035)	1.579 (0.608 - 4.099)	1.201 (0.690 - 2.088)	2.071 (1.164 - 3.682)	1.364 (0.858 - 2.170)	1.564 (0.744 - 3.290)
aPTT* (801)								
>26.30 sec	1.000 (reference)	1.176 (0.879 - 1.573)	1.000 (reference)	0.679 (0.463 - 0.996)	1.000 (reference)	1.215 (0.907 - 1.627)	1.000 (reference)	0.910 (0.660 - 1.257)
≤26.30 sec	1.190 (0.668 - 2.121)	1.731 (0.971 - 3.086)	1.273 (0.812 - 1.996)	1.255 (0.489 - 3.222)	1.210 (0.696 - 2.105)	1.832 (0.996 - 3.372)	1.312 (0.801 - 2.149)	1.292 (0.648 - 2.579)
Fibrinogen † (626)								
< 537 mg/dl	1.000 (reference)	1.204 (0.904 - 1.603)	1.000 (reference)	0.804 (0.553 - 1.168)	1.000 (reference)	1.272 (0.954 - 1.696)	1.000 (reference)	0.982 (0.717 - 1.346)
≥ 537 mg/dl	2.690 (1.276 - 5.670)	3.464 (1.698 - 7.065)	3.535 (1.972 - 6.335)	0.702 (0.223 - 2.209)	2.926 (1.483 - 5.770)	3.460 (1.580 - 7.578)	3.481 (1.838 - 6.595)	1.716 (0.727 - 4.049)

Note: *NPRL3*, nitrogen permease receptor like-3; *MPG*, N-methylpurine DNA glycosylase; PT, prothrombin time; aPTT, activated partial thromboplastin time. *P*-values <0.05 are bold. The number of each subgroup is located next to each subgroup.

* Folate 3.54nmol/L, PT 11.00 sec, and aPTT 26.30 sec were lower 15% cut-off each level in ischemic stroke patients and controls.

† Homocysteine 13.7 umol/L, Platelet 305 10³/μℓ, and Fibrinogen 537 mg/dl were upper 15% cut-off each level in ischemic stroke patients and controls.

Table S7. Clinical variables of ischemic stroke patients and subtypes stratified according to *NPRL3* and *MPG* polymorphisms

Genotypes	PLT (10 ³ /μL)		Uric acid (mg/dL)		LAD patients Platelets (10 ³ /μL)		LAD patients Uric acid (mg/dL)		LAD patients HDL-c (mg/dL)		SVD patients Fibrinogen (mg/dL)	
	Mean±SD	<i>P</i> *	Mean±SD	<i>P</i> *	Mean±SD	<i>P</i> *	Mean±SD	<i>P</i> *	Mean±SD	<i>P</i> *	Mean±SD	<i>P</i> *
<i>NPRL3</i> rs2541618C>T												
CC	238.37±81.92	0.256	4.58±1.50	0.455	245.99±100.50	0.682	4.46±1.39	0.157	45.68±16.13	0.110	393.32±112.43	0.103
CT	249.98±71.92		4.76±1.57		255.96±66.07		4.83±1.50		41.52±10.56		387.55±113.65	
TT	247.66±75.39		4.90±1.35		257.40±75.36		4.87±1.18		42.55±8.42		450.26±120.70	
Dominant (CC vs CT+TT)	249.54±72.47	0.101	4.79±1.53	0.114	256.27±67.87	0.030 [†]	4.84±1.43	0.055	41.76±10.08	0.038	401.57±117.51	0.684
Recessive (CC+CT vs TT)	247.66±75.39	0.761	4.90±1.35	0.282	257.40±75.36	0.646 [†]	4.87±1.18	0.444	42.55±8.42	0.696	450.26±120.70	0.034
<i>NPRL3</i> rs7518772G>A												
GG	245.19±78.12	0.916	4.70±1.49	0.028	253.51±83.97	0.423	4.76±1.46	0.023 [†]	43.31±10.28	0.364 [†]	397.16±118.19	0.922
GA	241.61±70.88		4.58±1.58		239.79±85.13		4.08±0.94		44.98±26.14		407.14±93.19	
AA	251.75±50.07		6.65±2.67		-		-		-		429.00±0.00	
Dominant (GG vs GA+AA)	242.11±69.79	0.741	4.68±1.68	0.927	239.79±85.13	0.152 [†]	4.08±0.94	0.023 [†]	44.98±26.14	0.364 [†]	408.60±89.98	0.718
Recessive (GG+GA vs AA)	251.75±50.07	0.854	6.65±2.67	0.098 [†]	-		-		-		429.00±0.00	0.791
<i>MPG</i> rs2562162C>T												
CC	237.17±76.06	0.071	4.74±1.50	0.710	242.25±91.32	0.247	4.60±1.28	0.586	43.49±15.36	0.858	391.96±110.84	0.702
CT	253.07±75.91		4.63±1.53		260.11±72.14		4.78±1.61		43.24±11.10		406.78±120.93	
TT	249.89±84.18		4.76±1.54		269.00±94.22		4.48±1.24		45.37±8.72		383.83±110.54	
Dominant (CC vs CT+TT)	252.61±76.97	0.022	4.65±1.53	0.499	261.33±75.07	0.103	4.74±1.56	0.875 [†]	43.55±10.78	0.977	403.50±119.08	0.561
Recessive (CC+CT vs TT)	249.89±84.18	0.675	4.76±1.54	0.789	269.00±94.22	0.425	4.48±1.24	0.607	45.37±8.72	0.589	383.83±110.54	0.664
<i>MPG</i> rs710079C>T												
CC	245.56±78.74	0.629	4.69±1.48	0.937	254.09±86.26	0.316	4.74±1.50	0.342	43.06±10.48	0.406	395.93±118.45	0.874
CT	243.76±72.65		4.71±1.62		247.13±77.30		4.49±1.17		45.11±19.31		406.91±105.49	
TT	217.71±46.82		4.87±1.54		132.00±0.00		3.30±0.00		30.80±0.00		429.00±0.00	
Dominant (CC vs CT+TT)	242.47±71.71	0.684	4.72±1.62	0.809	245.07±78.12	0.595 [†]	4.47±1.17	0.227	44.83±19.22	0.413	407.67±103.67	0.628
Recessive (CC+CT vs TT)	217.71±46.82	0.350	4.87±1.54	0.758	132.00±0.00	0.090 [†]	3.30±0.00	0.336	30.80±0.00	0.337	429.00±0.00	0.791

Note: ANOVA, analysis of variance; HDL-c, high density lipoprotein cholesterol; LAD, large artery disease; SVD, small vessel disease; CE, cardioembolism; SD, standard deviation;

NPRL3, nitrogen permease receptor like-3; *MPG*, N-methylpurine DNA glycosylase.

*Calculated using ANOVA. [†]Calculated using the Kruskal-Wallis test. *P*-values< 0,05 are bold

Table S8. Results of stepwise Cox regression analysis for ischemic stroke survival

Covariate	β	SEM	HR (95% CI)	<i>P</i> *
<i>MPG</i> rs2562162 CC vs CT in SVD group				
Age	0.078	0.026	1.081 (1.028 - 1.137)	0.003
<i>MPG</i> rs2562162 CC vs CT+TT in SVD group				
Age	0.078	0.024	1.082 (1.032 - 1.133)	0.001
<i>MPG</i> rs2562162 CC vs CT+TT in SVD group/with hypertension				
Genetic variant (CC vs CT+TT)	1.686	0.810	0.185 (0.038 - 0.899)	0.037
Age	0.100	0.035	1.105 (1.032 - 1.183)	0.001
<i>MPG</i> rs710079 CC vs CT with diabetes mellitus				
Genetic variant (CC vs CT)	0.788	0.381	2.200 (1.046 - 4.625)	0.039
Age	0.052	0.019	1.054 (1.016 - 1.093)	0.005
<i>NPRL3</i> rs2541618 CC vs CT+TT with hyperlipidemia				
Genetic variant (CC vs CT+TT)	1.134	0.556	3.107 (1.051 - 9.183)	0.041
Age	0.076	0.019	1.079 (1.040 - 1.120)	<0.001
<i>MPG</i> rs710079 CC vs CT in male				
Genetic variant (CC vs CT)	0.825	0.370	2.282 (1.109 - 4.696)	0.026
Age	0.075	0.015	1.078 (1.047 - 1.109)	<0.0001

Note: SEM, standard error of the mean; HR, hazard ratio; CI, confidence interval; NPRL3, nitrogen permease receptor like-3; MPG, N-methylpurine DNA glycosylase; SVD, small vessel disease.

**P*-value calculated by Cox proportional-hazards regression based on stepwise method. *P*-values < 0,05 are bold

Table S9. Statistical power to detect various genetic associations in the present case-control study

Characteristics	Table	AOR (95% CI)	Statistical power (%)
<i>NPRL3</i> rs75187722 Dominant model	Table 2 (LAD)	0.599 (0.370 - 0.968)	51.44
<i>NPRL3</i> rs2541618TT	Table 2 (SVD)	2.406 (1.225 - 4.725)	54.13
<i>NPRL3</i> rs2541618 Dominant model	Table 2 (SVD)	1.524 (1.019 - 2.279)	61.58
<i>NPRL3</i> rs75187722GA	Table 2 (SVD)	0.474 (0.261 - 0.860)	53.77
<i>NPRL3</i> rs75187722 Dominant model	Table 2 (SVD)	0.495 (0.277 - 0.886)	50.62
<i>MPG</i> rs2562162CT	Table 2 (SVD)	1.569 (1.038 - 2.372)	78.95
<i>MPG</i> rs2562162 Dominant model	Table 2 (SVD)	1.589 (1.069 - 2.363)	80.70

Note: AOR, adjust odds ratio; 95% CI, 95% confidence interval.

Table S10. The results of meta-analysis restricted to Europeans in the MEGASTROKE GWAS loci of *NPRL3* and *MPG* genes polymorphisms

SNP	Chr	Gene	Ischemic stroke patients & controls				LAD patients & controls				SVD patients & controls				CE patients & controls				
			Risk allele	MAF	Effect	StdErr	<i>P</i> -value	MAF	Effect	StdErr	<i>P</i> -value	MAF	Effect	StdErr	<i>P</i> -value	MAF	Effect	StdErr	<i>P</i> -value
rs2541618	16	NPRL3	T	0.142	0.019	0.015	0.203	0.146	0.007	0.038	0.855	0.141	0.078	0.035	0.024	0.144	0.025	0.029	0.400
rs75187722	16	NPRL3	A	0.016	-0.069	0.057	0.222	0.015	-0.097	0.158	0.537	0.016	0.133	0.142	0.350	0.017	-0.123	0.109	0.257
rs2562162	16	MPG	T	0.134	0.033	0.019	0.080	0.137	0.078	0.047	0.093	0.133	0.084	0.042	0.045	0.136	0.041	0.037	0.271
rs710079	16	MPG	T	0.017	0.035	0.052	0.509	0.018	0.016	0.141	0.913	0.017	0.101	0.121	0.407	0.018	0.031	0.103	0.764

Note: GWAS, genome-wide association study; SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; StdErr, standard error; NPRL3, nitrogen permease receptor like-3; MPG, N-methylpurine DNA glycosylase; LAD, large artery disease; SVD, small vessel disease; CE, cardioembolism. *P*-values < 0,05 are bold