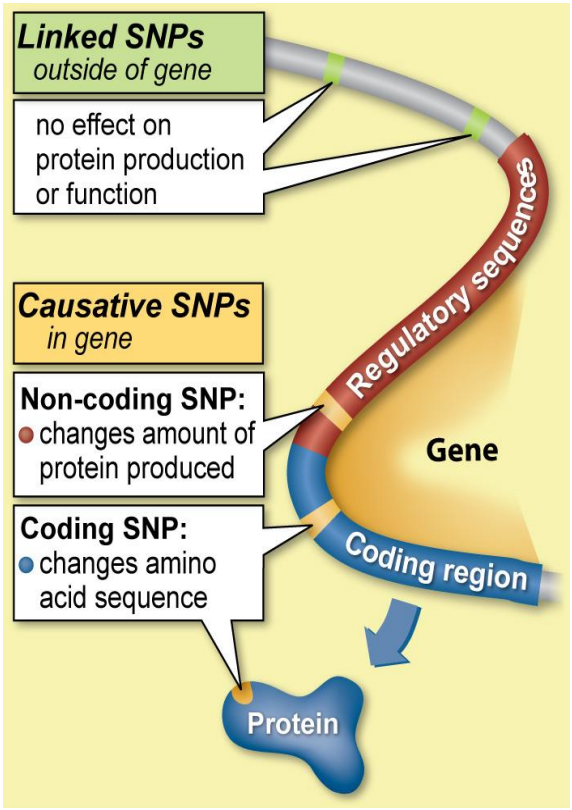
Single nucleotide polymorphism (SNP) studies for prediction, prognosis and prevention in female infertility, atherosclerotic vascular diseases and colorectal cancer

Department of Biomedical Science
CHA University

Nam Keun Kim, PhD

SNP in diseases

▪ Single nucleotide polymorphism (SNP)



- **SNPs are single-nucleotide substitutions of one base for another.**
- **2 or more versions (types) of a sequence must each be present in at >1% (MAF, minor allele frequency) of the population.**
- **SNPs occur throughout the human genome□about 1 in every 300 base pairs.**
- **Linked SNPs (also called indicative SNPs)**
  - located on out of a coding region.
  - do not affect protein function.
  - correspond to a drug response or to the risk for getting a certain disease.
- **Causative SNPs**
  - affect the way a protein functions / correlating with a disease.
  - **Coding SNPs**: located within the coding region of a gene.
  - **Non-coding SNPs**: located within the gene's regulatory sequences.

Non-protein-coding sequences and diseases

Clin Genet 2013: 84: 422–428
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CLINICAL GENETICS
doi: 10.1111/cge.12272

Review

Pathogenic variants in non-protein-coding sequences

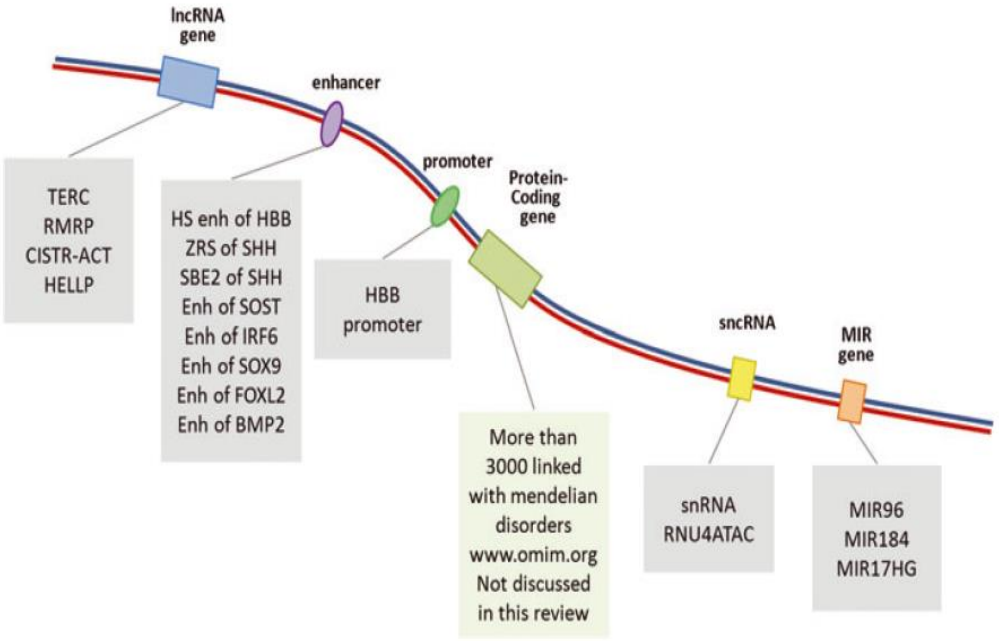

Table 1. Numbers of functional genomic elements.

Genomic element	Number	Source
Protein-coding genes	20330	GENCODE V17 (Feb2013, GRCh37) Ensembl 72
Long non-coding RNAs	13333	GENCODE V17
lincRNAs	6020	GENCODE V17
Pseudogenes	14154	GENCODE V17
Short non-coding RNAs	9078	GENCODE V17
miRNAs	3086	GENCODE V17
Promoters	70292	ENCODE (3)
Enhancers	399124	ENCODE (3)
TFBS (ChIP peaks)	636336	ENCODE (3)

lincRNAs, long intergenic non-coding RNAs; miRNAs, micro RNAs; TFBS, transcription factor binding sites.

Fig. 1. Schematic representation of the different functional genomic elements (shown as colored boxes and ovals), and some examples of pathogenic elements per element for Mendelian disorders. For description and references see text.

Makrythanasis P et al. Clin Genet 2013

SNP in diseases

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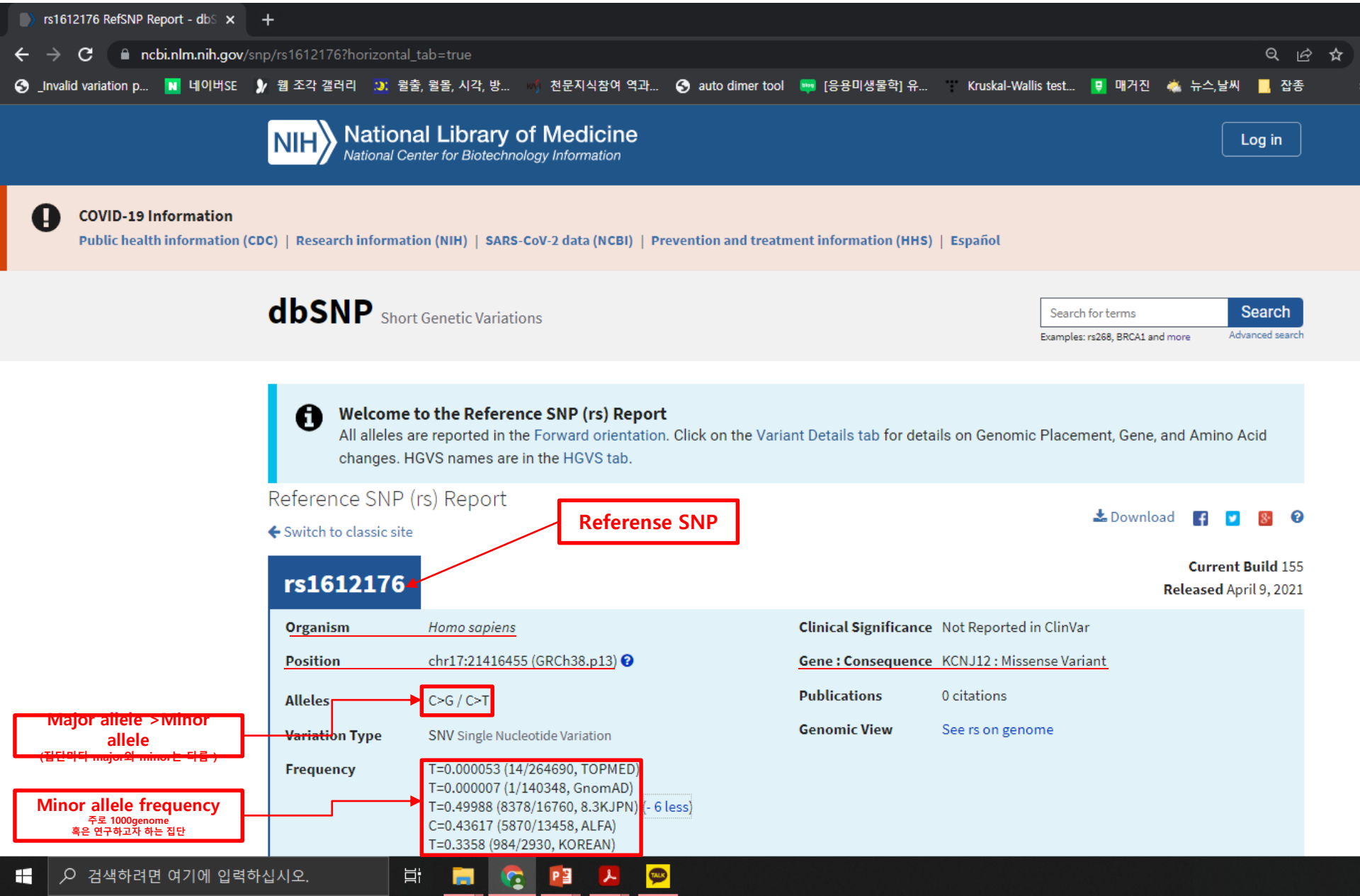


유전자 위치에 따른 SNP 표기법

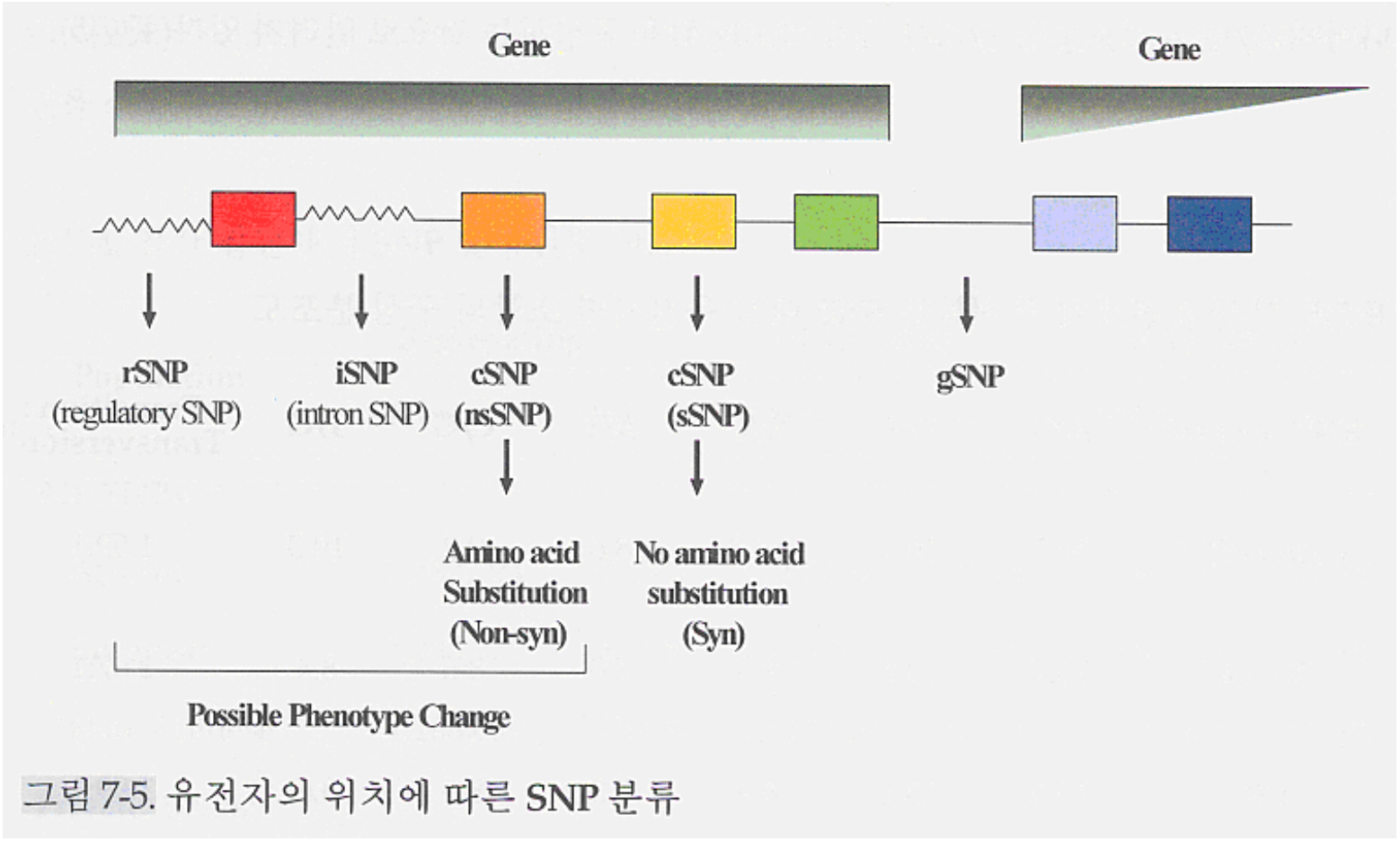
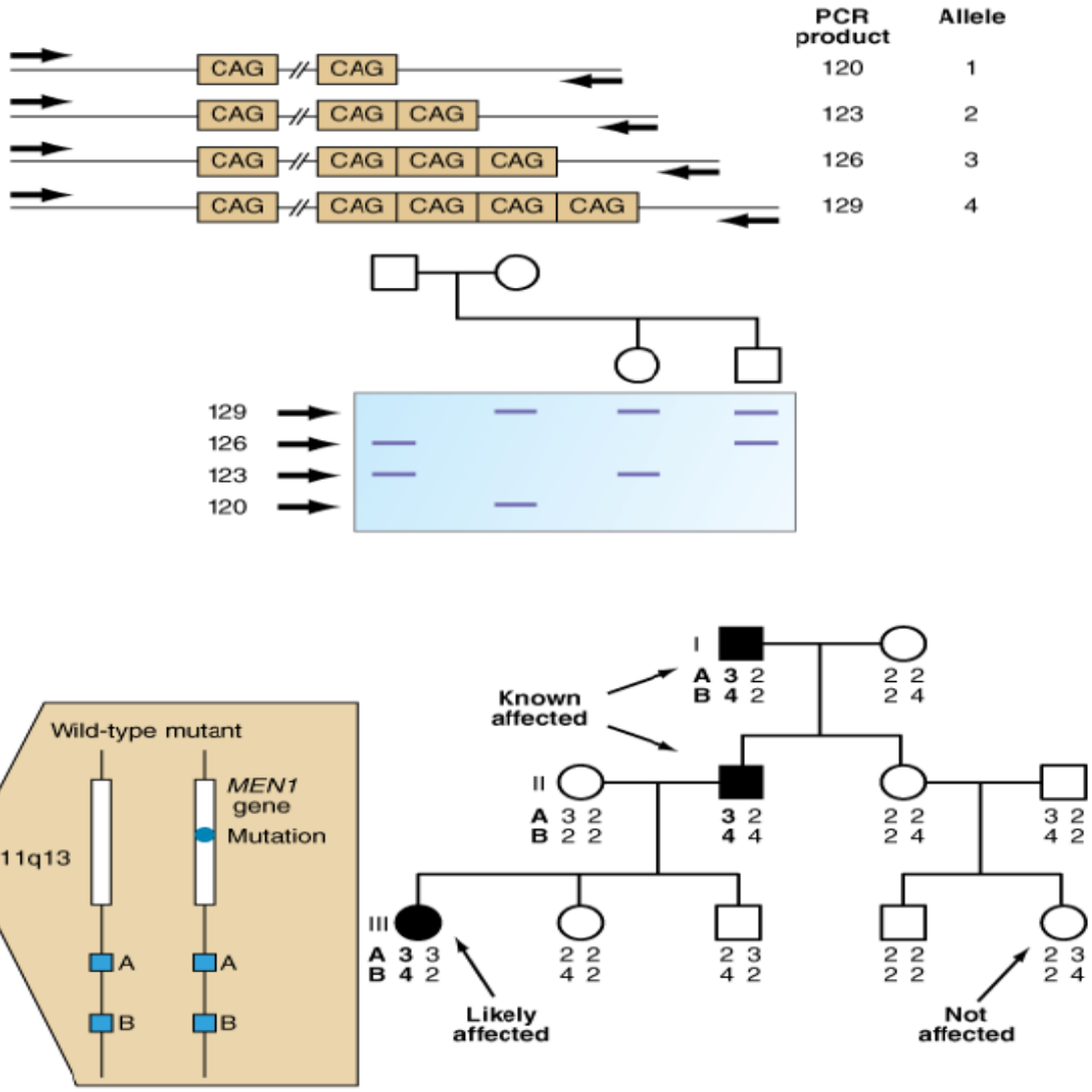


그림 7-5. 유전자의 위치에 따른 SNP 분류

CAG repeat length and linkage analysis in multiple endocrine neoplasia (MEN) type 1.

Figure 62-12.



Human Genome의 영역별 구성비율

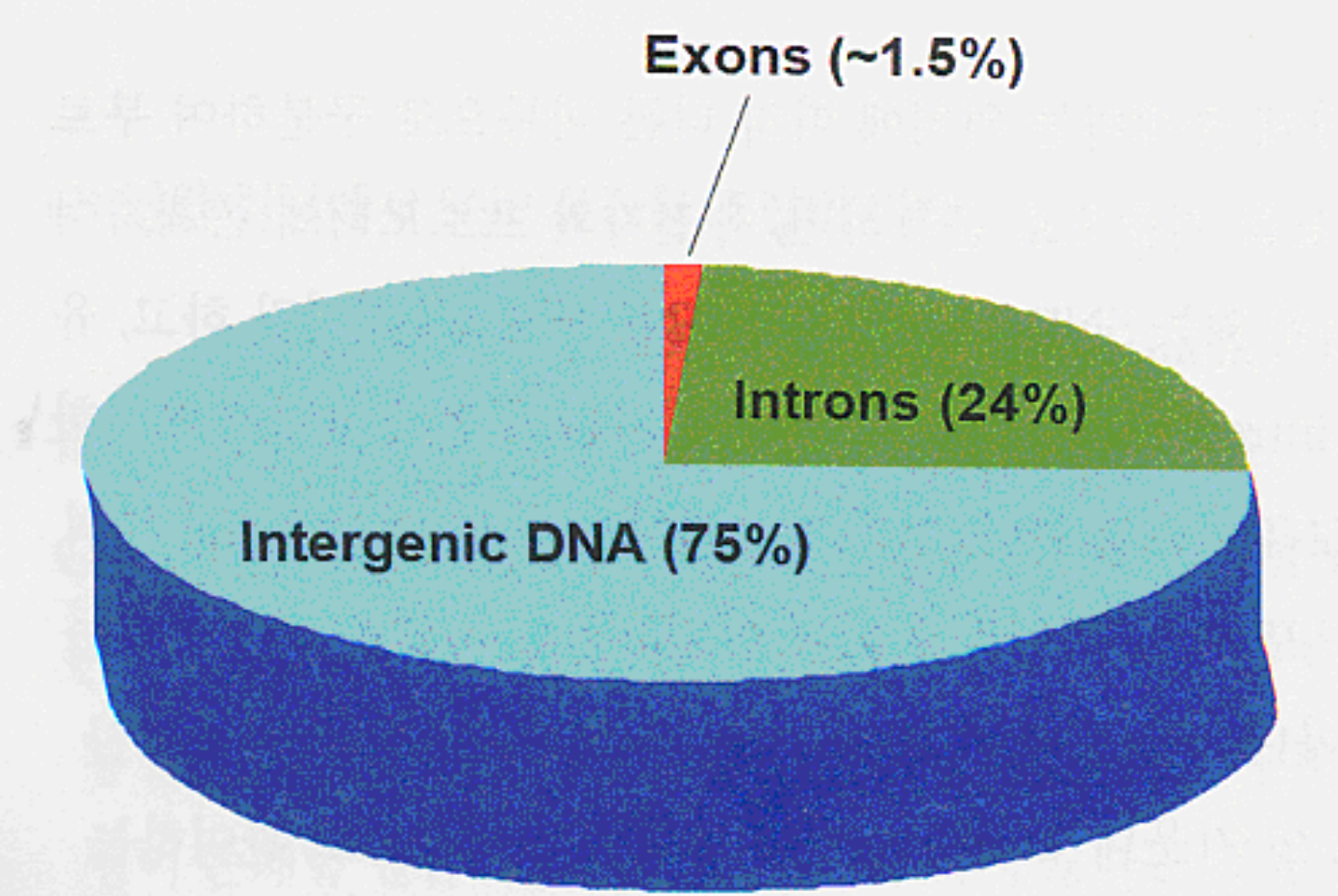


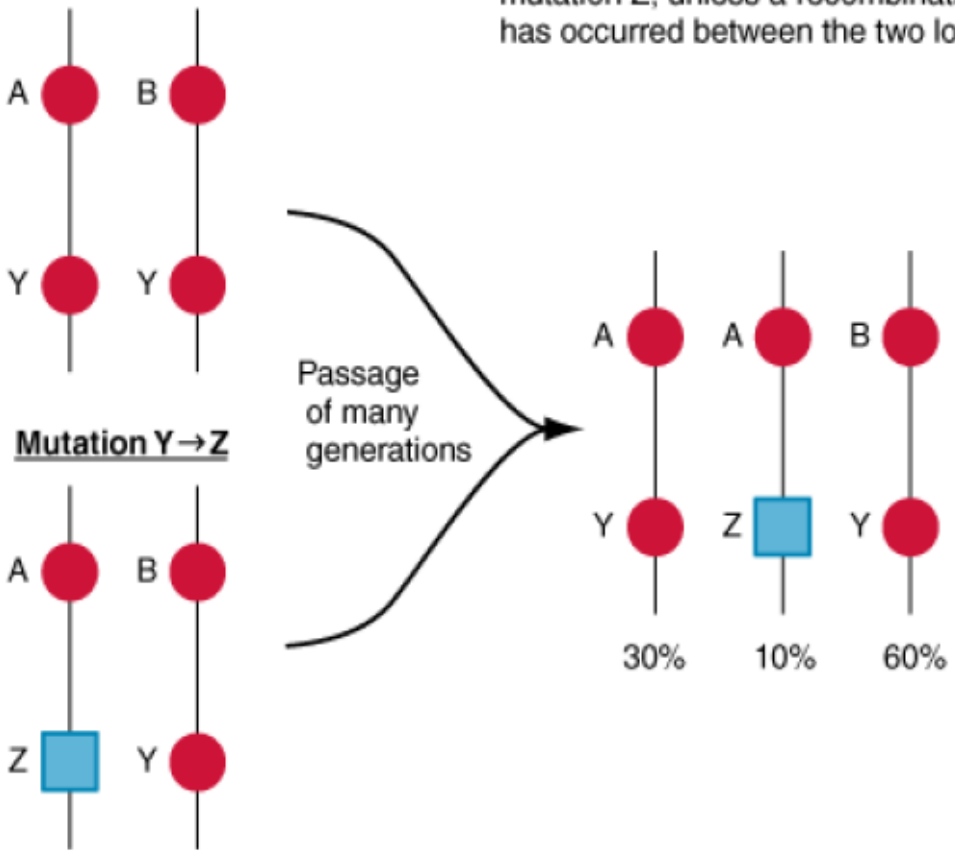
그림 7-6. 유전자 구조별 각 영역의 비율

Linkage disequilibrium

Figure 62-13

Wild-type: Polymorphic alleles
A = 40%; B = 60%
Wild-type allele Y = 100%

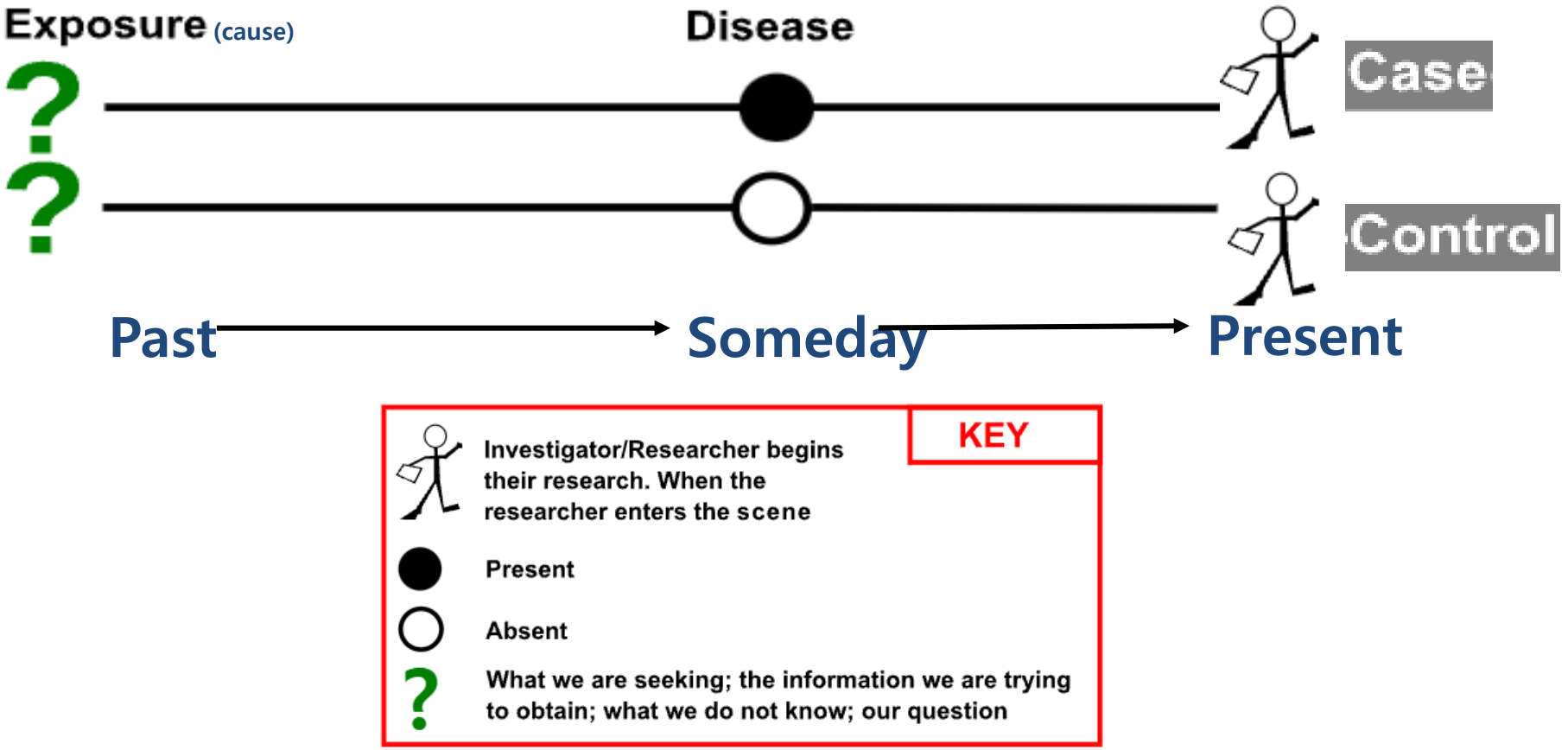
Linkage disequilibrium: Allele A is associated with the mutation Z in 10%. B is never associated with the mutation Z, unless a recombination has occurred between the two loci.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Study design & statistical analyze

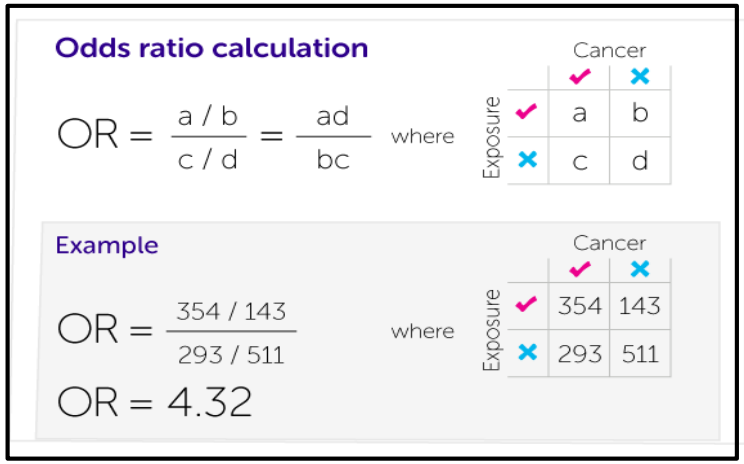
Case-control study



https://www.slideshare.net/tarekksalem1966/odds-ratios-basic-concepts
https://bioinformaticsandme.tistory.com/287

Study design & statistical analyze

Statistical analyze



an odds ration of

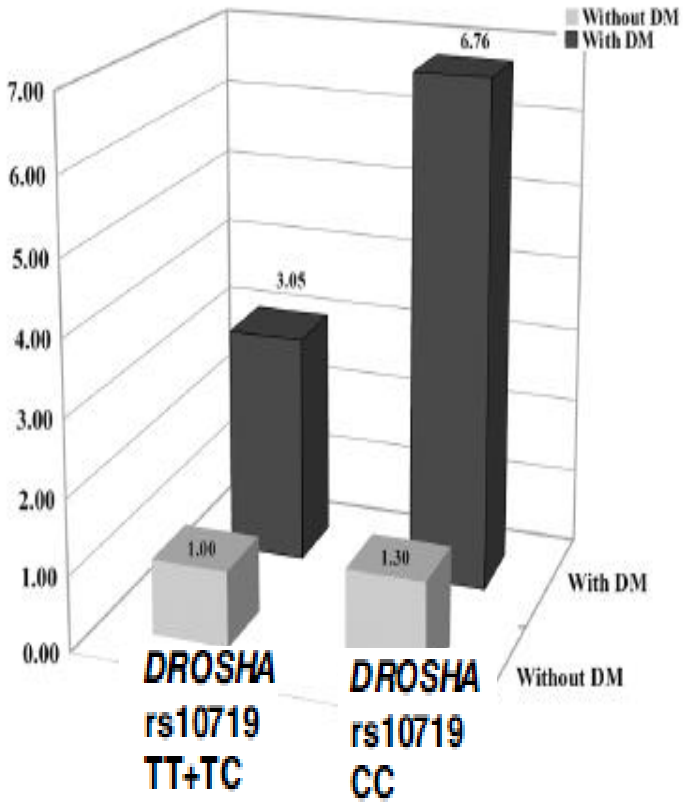
1.0	The exposure **is not associated** with the disease	Means that the odds of exposure among cases is **the same** as the odds of exposure among controls
>1.0	The exposure may be **a risk factor** for the disease	Means that the odds of exposure among cases is **greater than** the odds of exposure among controls
<1.0	The exposure may be **protective** against the disease	Means that the odds of exposure among cases is **lower than** the odds of exposure among controls

Genotypes	Controls (n = 409)	Stroke (n = 507)	AOR (95% CI)*	P†
TS 1100 T>C				
TT	218 (53.3)	215 (42.4)	1.000 (reference)	
TC	165 (40.3)	235 (46.4)	1.486 (1.115–1.980)	0.007
CC	26 (6.4)	57 (11.2)	2.151 (1.275–3.628)	0.004
TT vs TC+CC			1.576 (1.197–2.074)	0.001
TT +TC vs CC			1.758 (1.064–2.905)	0.028
HWE P	0.480	0.547		
TS 1170 A>G				
AA	190 (46.5)	320 (63.1)	1.000 (reference)	
AG	184 (45.0)	170 (33.5)	0.505 (0.377–0.676)	<0.0001
GG	35 (8.6)	17 (3.4)	0.284 (0.151–0.537)	<0.0001
AA vs AG+GG			0.472 (0.357–0.626)	<0.0001
AA +AG vs GG			0.382 (0.206–0.710)	0.002
HWE P	0.306	0.331		

Study design & statistical analyze

Statistical analyze

Factor	*DROSHA* rs10719 TT+TC	*DROSHA* rs10719 CC
DM		
No	1.000 (reference)	1.300 (0.660–2.561)
Yes	3.054 (2.095–4.452)	6.764 (1.424–32.126)



유전자형-환경 상호작용 분석

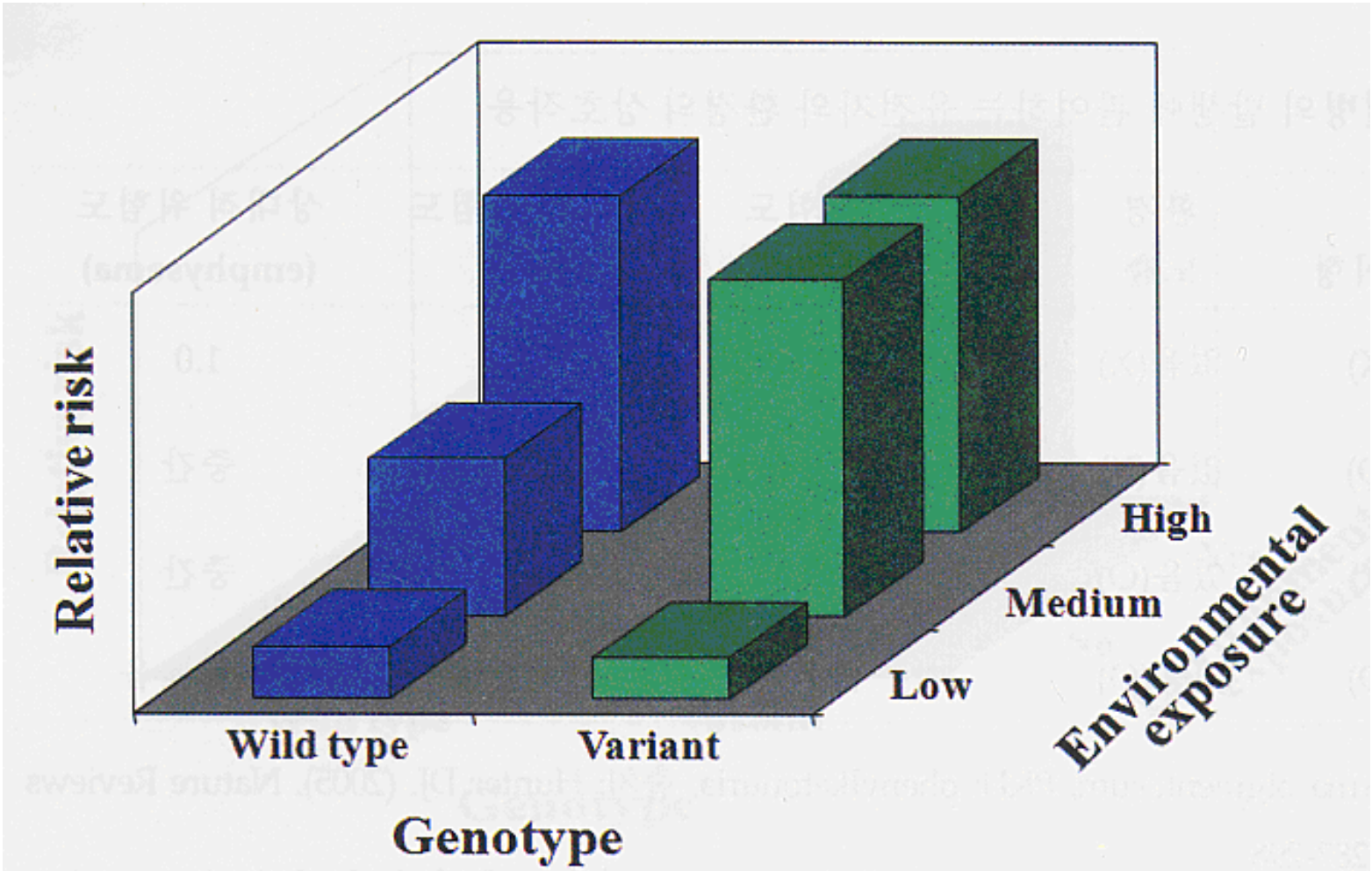
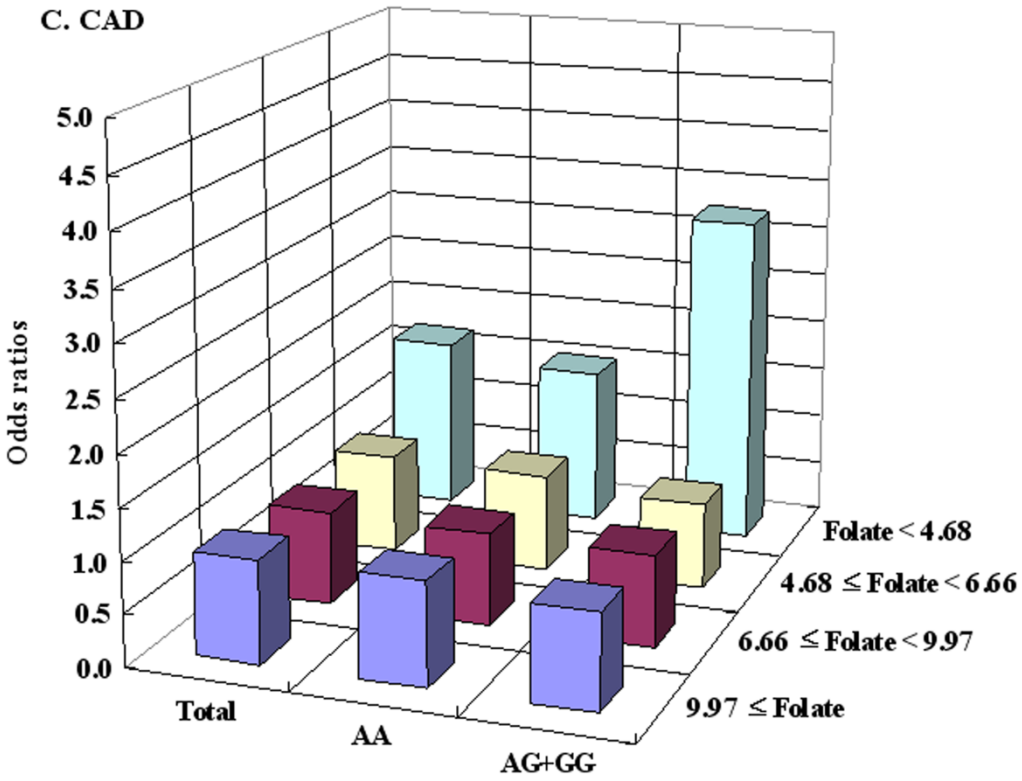


그림 15-5. 유전자-환경 상호작용: 2 × 3 모델

VKORC1 -1639A>G polymorphism & folate levels in CAD patients



Homocysteine and Vascular Disease

- Elevated levels of plasma homocysteine is an independent risk factor for both heart attack and stroke.

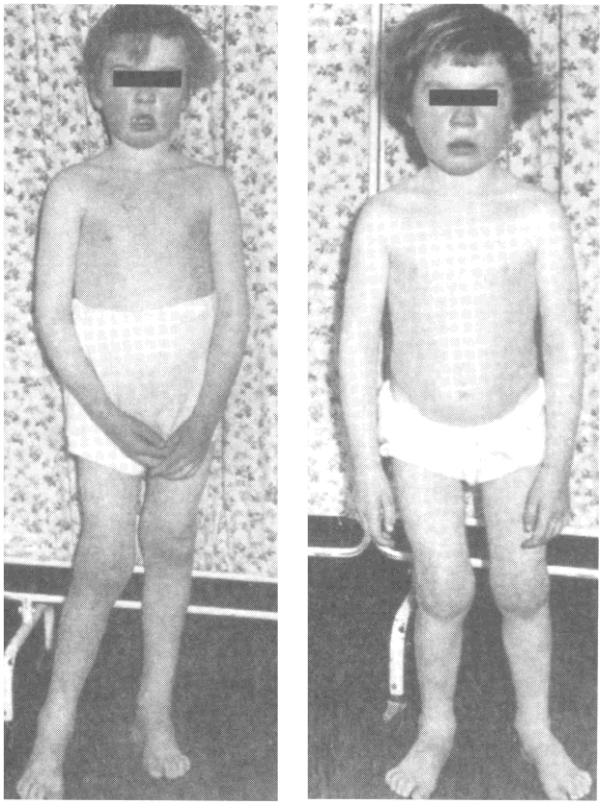
- A meta-analysis (JAMA 2002) suggests that 3 μmol/L reduction was associated with an 11% decrease heart attack and 18% decrease in stroke.

Homocystinuria(호모시스틴우리아 병)

CHA 의과학대학교 CHA 차병원

. ***Homocystinuria*** **is a metabolic disorder due to** ***Cystathionine b-synthase*** **(EC 4.2.1.23) deficiency** ***producing increased urinary homocysteine and methionine.*** **Major clinical manifestation involve the eyes and the central nervous, skeletal, and vascular system.**

The Homocystinuric Patients (호모시스틴우리아 환자)



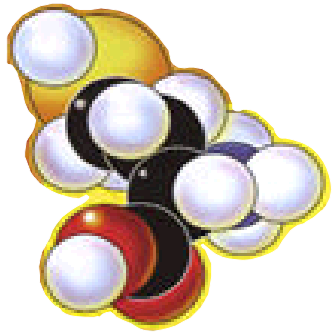
The two homocystinuric sisters identified by Carson et al. in the early 1960s 6-year-old sister on the left and 4-year-old on the right. The abnormalities included mental retardation, seizures, and dislocation of ocular lenses.
Visible features include mottled skin and " knock knees."
(4살과 6살의 자매환자는 정신지체, 간질증상,수정체이상, 굽은 다리와 망치모양의 무릎을 보이고 있다. 이들은 8살과 9살 때 동맥경화증으로 죽었다.)

Homocysteine

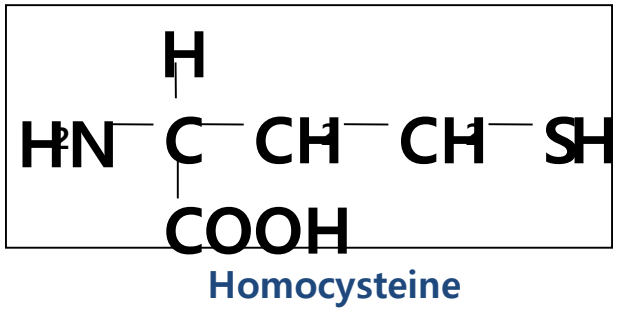
1. History

Finding and Synthesized -- 1932 (duVigneaud, V)
Homocystinuria -- 1964 (Mudd, S. H.)
Homocysteine theory -- 1969 (McCully, K)
"The Homocysteine Revolution"
"Beyond Cholesterol"
early 1990s, Harvard Medical School
Tuft University etc. support homocyteine theory

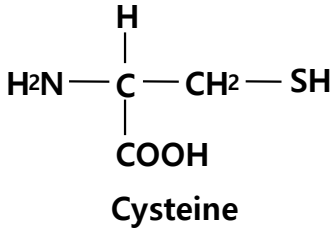
recently, Homocysteine protection formula



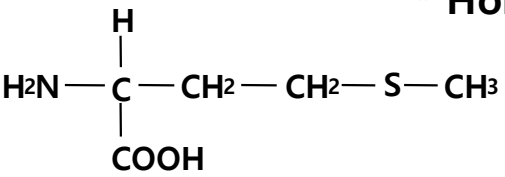
2. Structure



Homocysteine



Cysteine



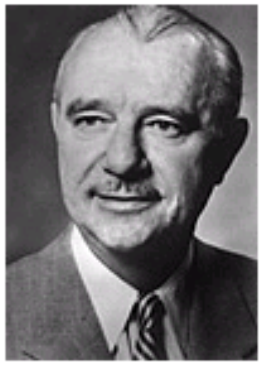
Methionine

3. Presence form in body

* Some free thiol
* Homocystine
* Homocyteine-cysteine mixed disulfide
* Homocyteine-protein

The Nobel Prize in Chemistry 1955

"for his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone"



Vincent du Vigneaud

USA

Cornell University
Ithaca, NY, USA

b. 1901
d. 1978

The Nobel Prize in Chemistry 1955
Presentation Speech

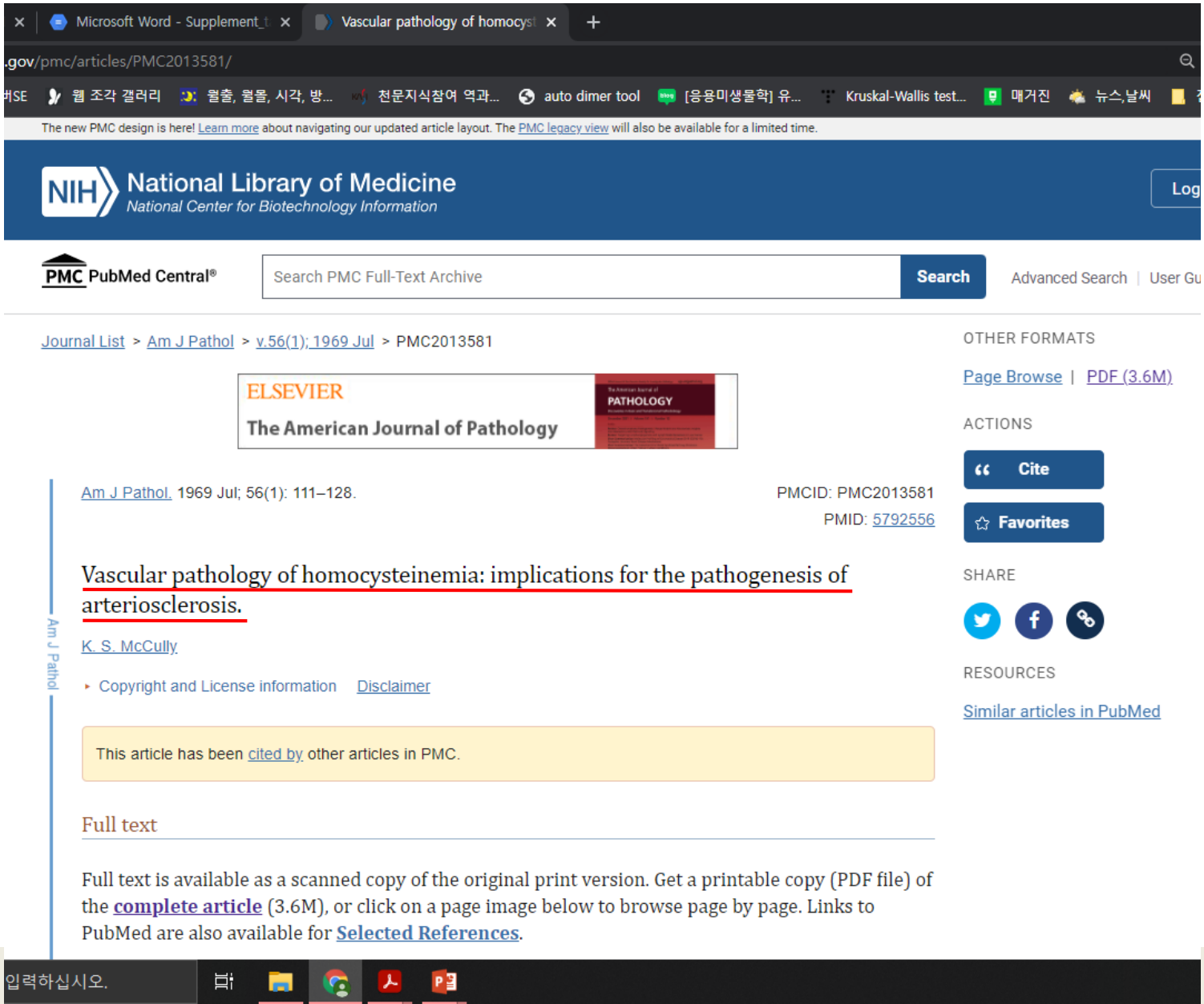
Vincent du Vigneaud
Biography
Nobel Lecture
Banquet Speech

1954 1956

The 1955 Prize in:
Physics
Chemistry
Physiology or Medicine
Literature
Peace

Find a Laureate:
Name GO

Prize Announcements
The latest information is found at Nobelprize.org »



Microsoft Word - Supplement_t | Vascular pathology of homocyst

.gov/pmc/articles/PMC2013581/

버SE | 웹 조각 갤러리 | 월출, 월몰, 시각, 방... | 천문지식참여 역과... | auto dimer tool | [응용미생물학] 유... | Kruskal-Wallis test... | 메거진 | 뉴스,날씨

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Journal List > Am J Pathol > v.56(1); 1969 Jul > PMC2013581

ELSEVIER
The American Journal of Pathology

Am J Pathol. 1969 Jul; 56(1): 111–128.

PMCID: PMC2013581
PMID: 5792556

Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis.

K. S. McCully

This article has been cited by other articles in PMC.

Full text

Full text is available as a scanned copy of the original print version. Get a printable copy (PDF file) of the complete article (3.6M), or click on a page image below to browse page by page. Links to PubMed are also available for Selected References.

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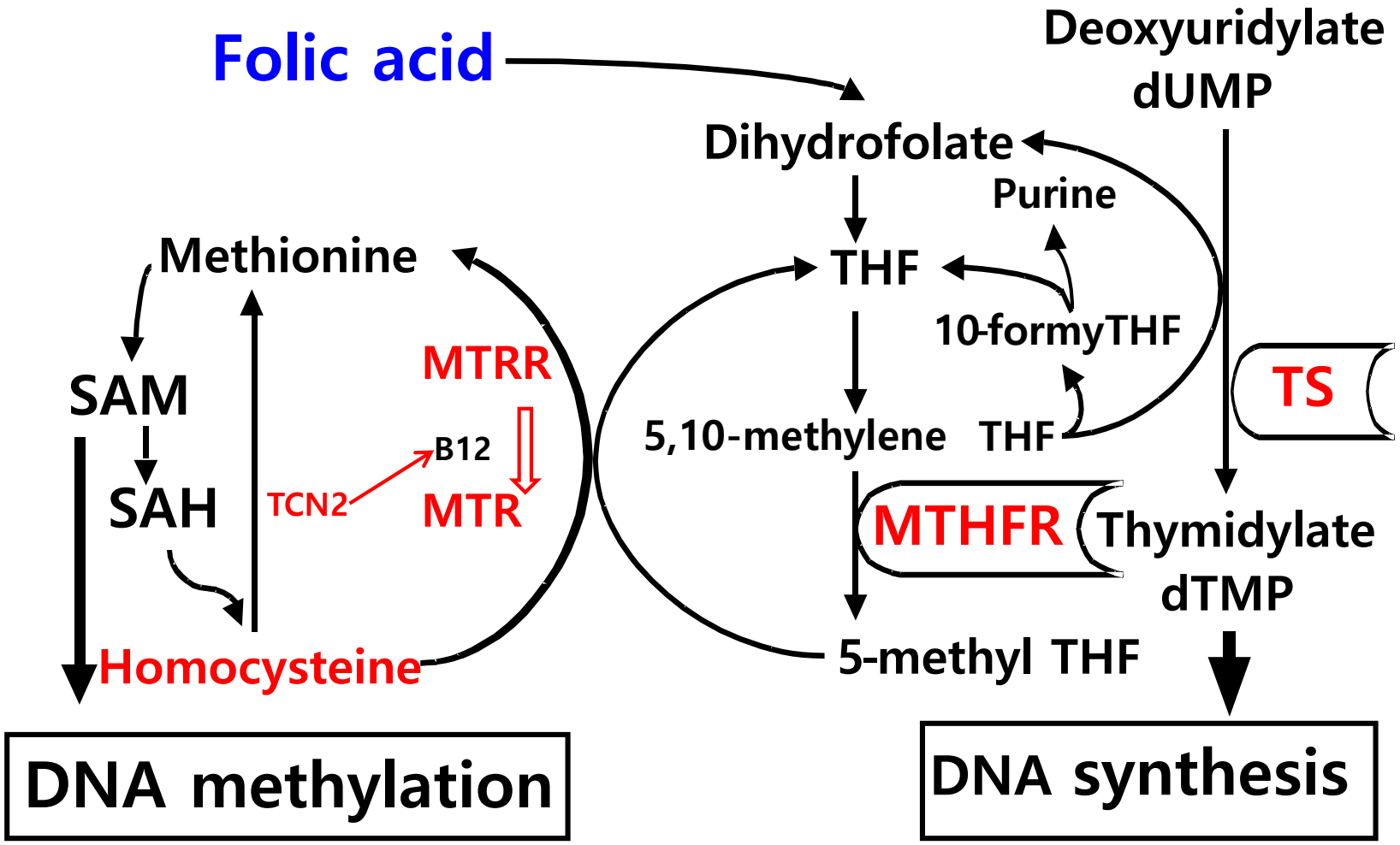
입력하십시오.

One-carbon metabolism



Hyperhomocysteinemia, oxidative stress, and cerebral vascular

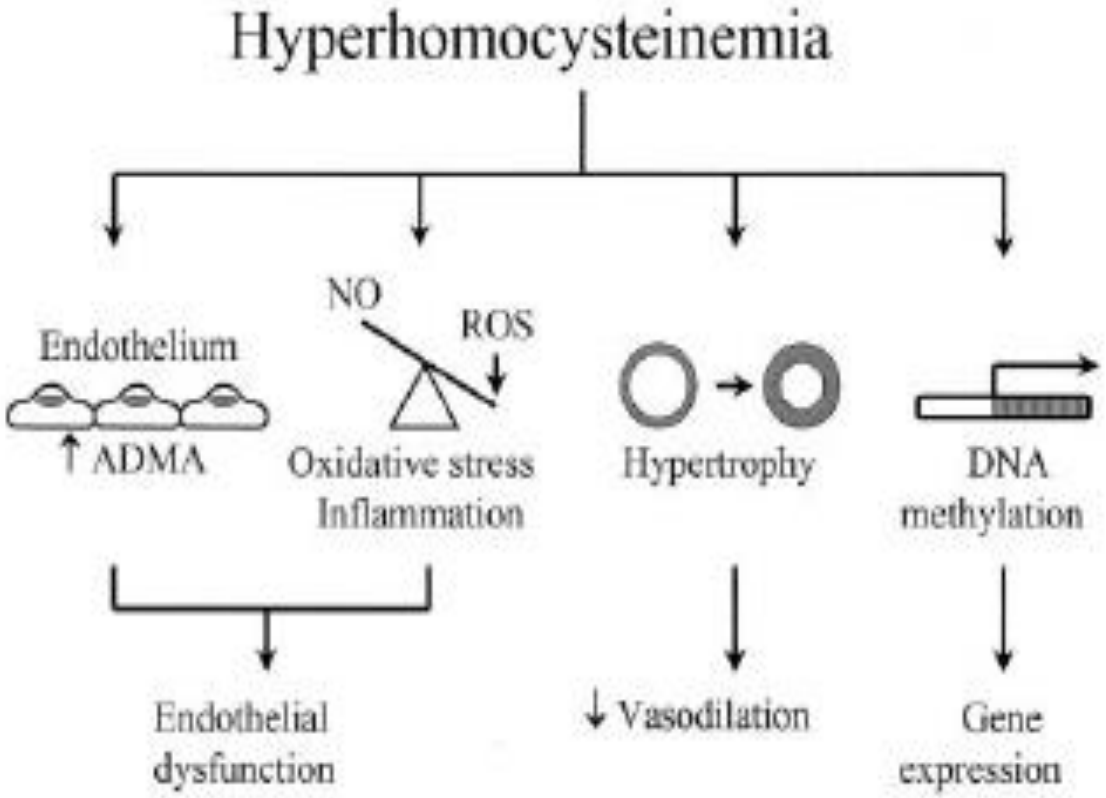
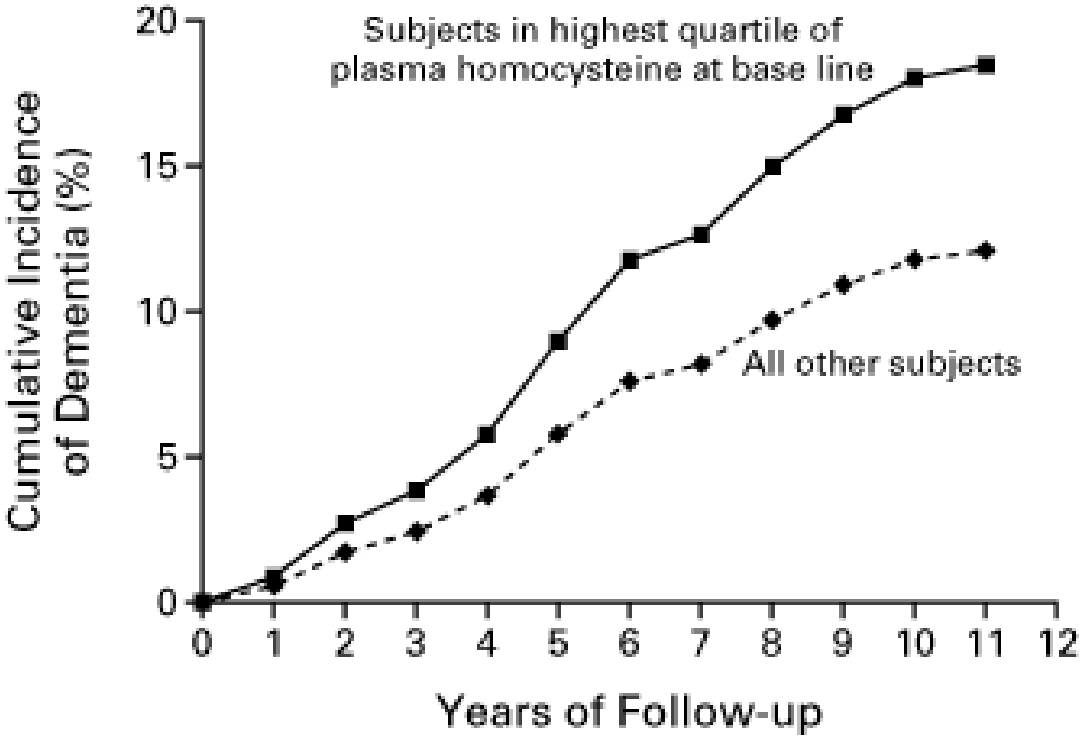


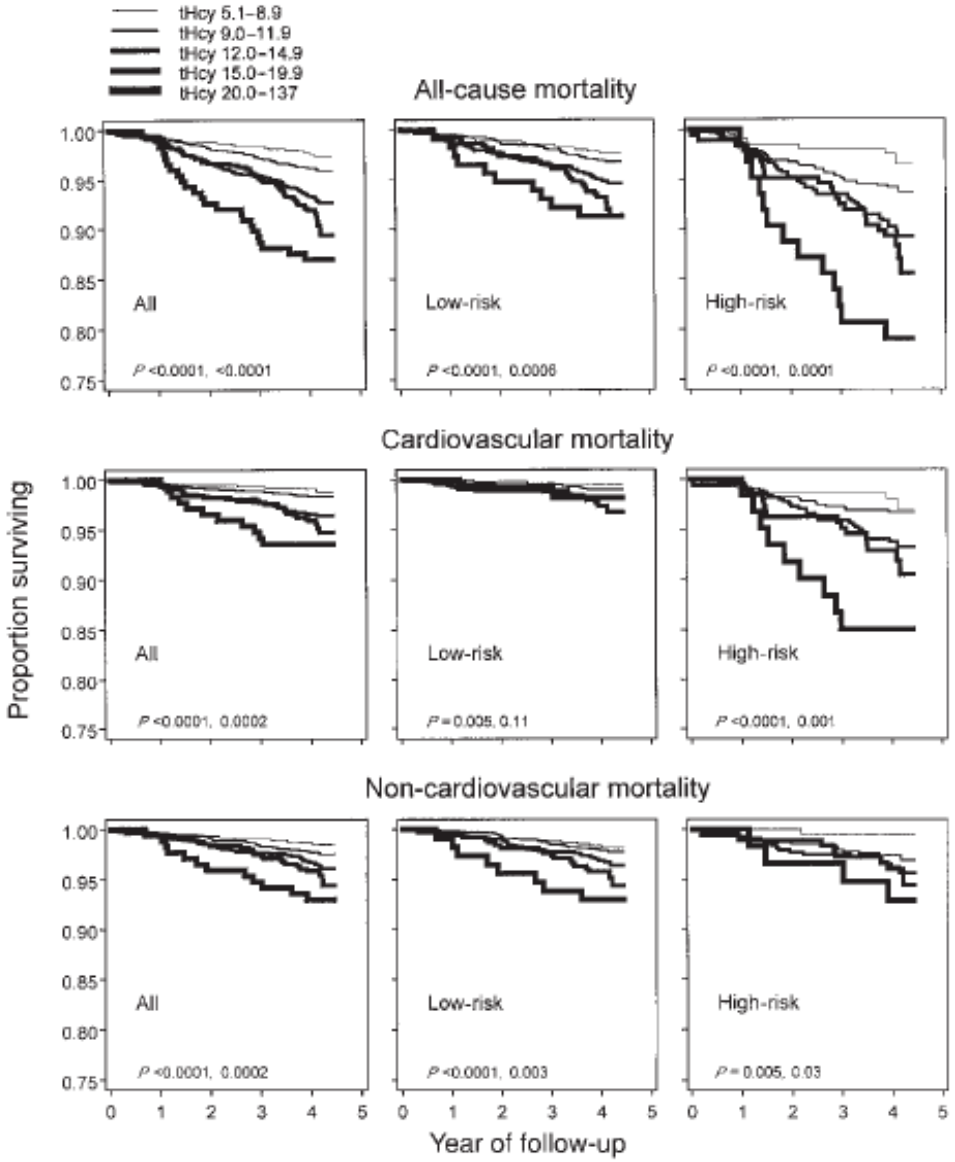
Fig. Schemic summary of selected changes within the vessel wall in response to hyperhomocysteinemia.

Faraci FM et al. Stroke 35:345-7, 2004.



A cohort of 1092 elderly subjects who were free of dementia were studied prospectively. After a median of eight years of follow-up, dementia had developed in 111 subjects. Even after adjustment for other known risk factors, an elevated plasma total homocysteine level at base line was an independent predictor of the development of clinical dementia, most cases of which were caused by Alzheimer's disease. The risk of Alzheimer's disease was nearly doubled for those with the highest plasma homocysteine levels.

Cardiovascular mortality associated with homocysteine level

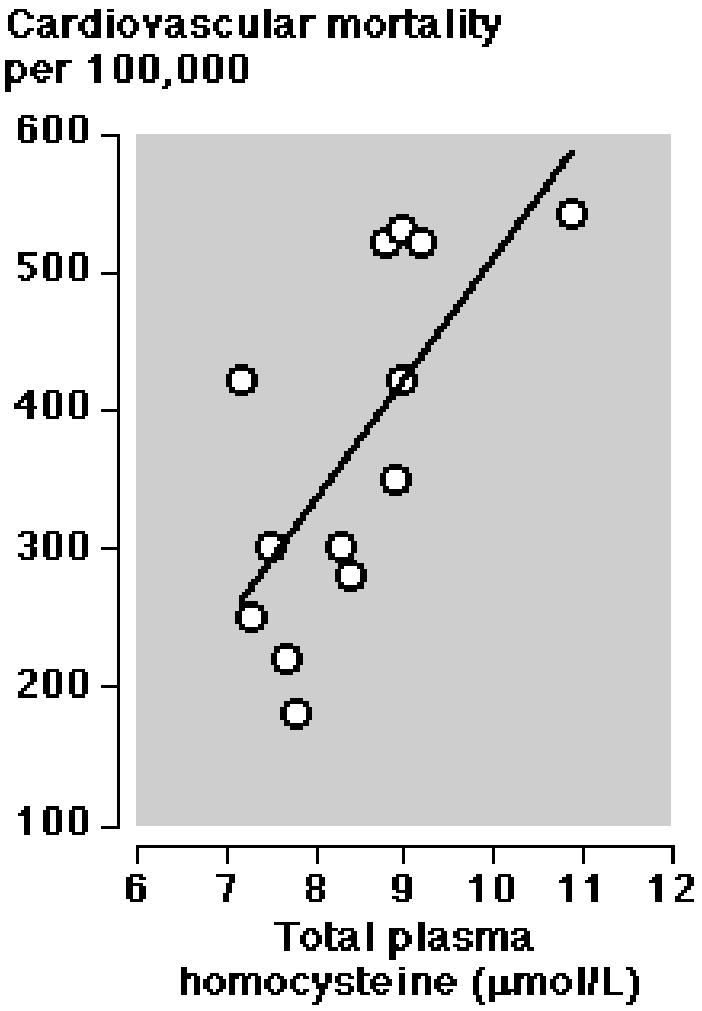


Vollset SE et al. Am J Clin Nutr 74:130-6, 2001.

Homocysteine and disease

혈장내에 (생체내에)
호모시스테인의 양이
많으면 심장병 및
뇌졸중 발병율도 증가.

Figure 1: Association between cardiovascular disease mortality and plasma total homocysteine [2]



- *McCully KS (Cell Mol Biol 2006;52:1)*

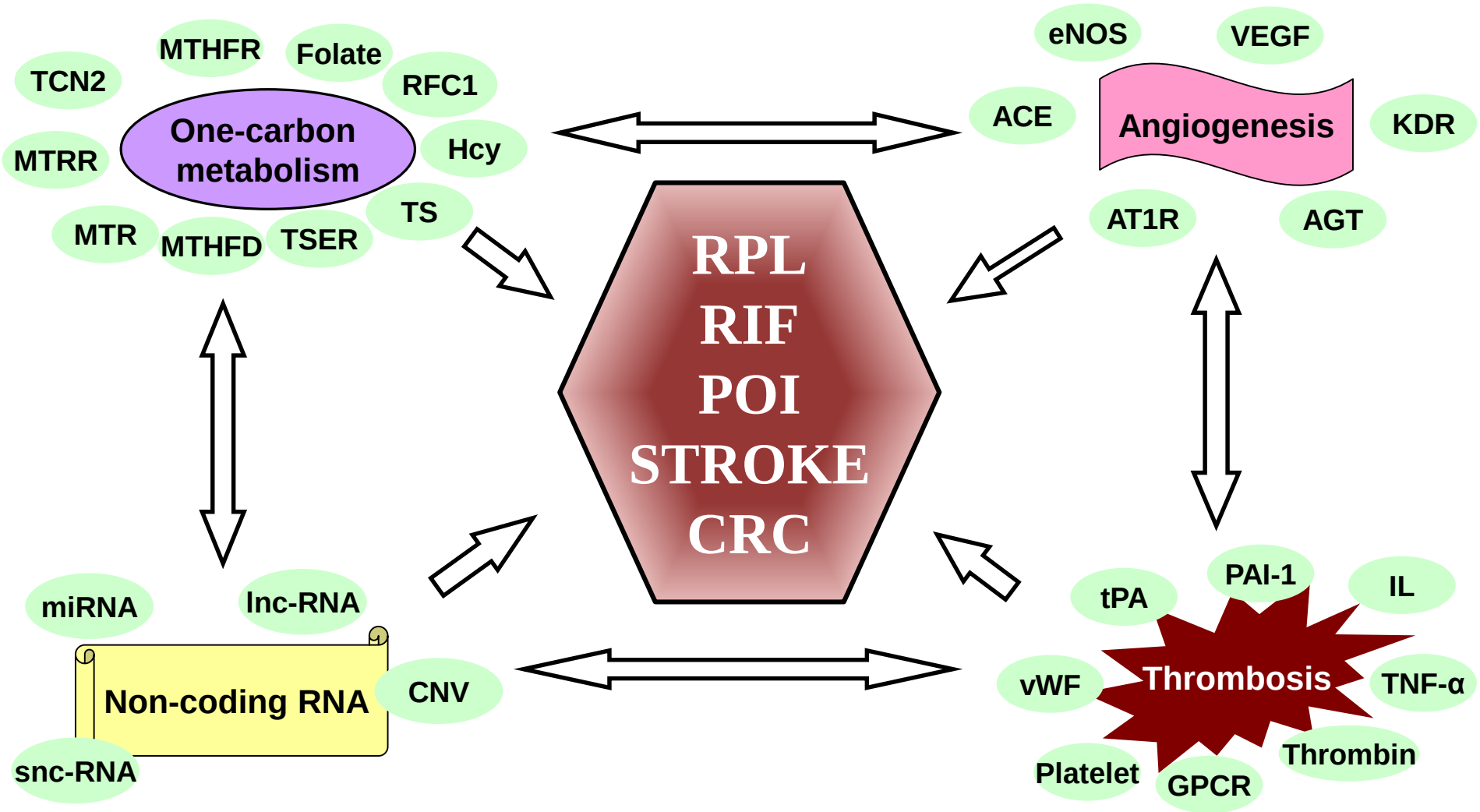
The purpose of this study

1. Identify disease-related genetic polymorphisms that affect the occurrence of 5 diseases.

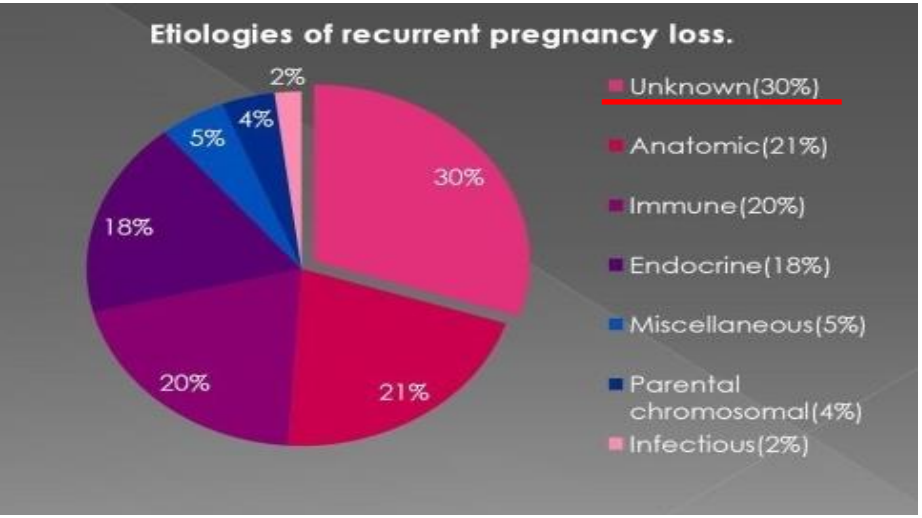
2. Find out the relationship with environmental factors (Nutritional factors, homocysteine, folate, Vitamin B12; Metabolic syndrome factors, DM, HTN, Hyperlipidemia, Obesity, thrombotic factors; PT, aPTT) that interact with genes and affect disease development.

3. Identify genetic variants that affect mortality (survival) in ischemic stroke and colorectal cancer.

Our study overview in diseases



The definitive etiologic factors for RPL



O'Connor et al. Maturitas 1998

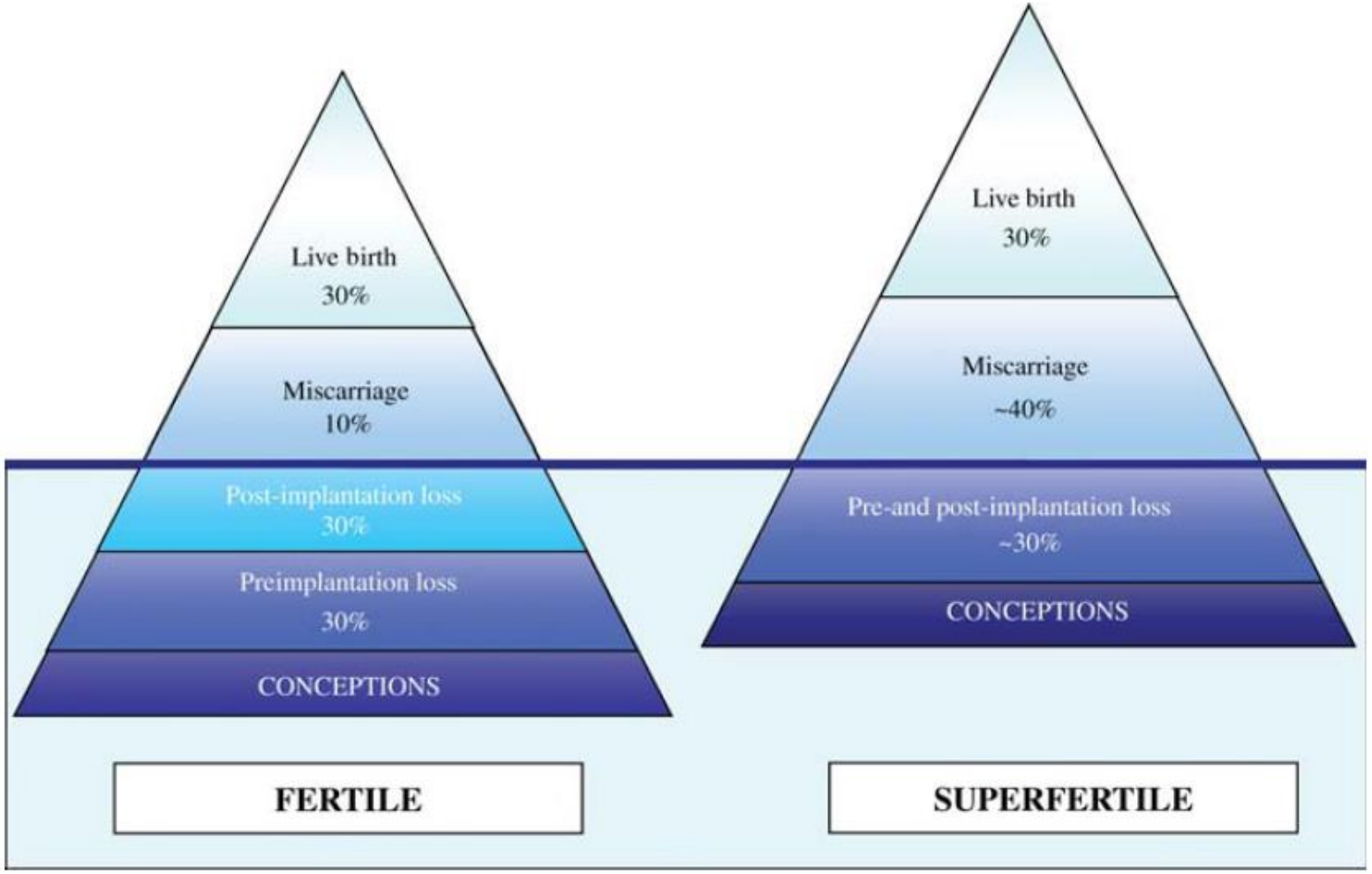
연도	구 분	계	19세이하	20대	30대	40대이상
2007년	분만인원(명)	418,445	1,072	162,541	248,656	6,176
	유산인원(명)	101,898	896	35,143	56,900	8,959
	유산율(%)	**19.6**	**45.5**	**17.8**	**18.6**	**59.2**
2008년	분만인원(명)	412,654	1,286	156,597	247,542	7,229
	유산인원(명)	103,662	876	34,534	58,331	9,921
	유산율(%)	**20.1**	**40.5**	**18.1**	**19.1**	**57.8**
2009년	분만인원(명)	393,447	1,329	139,837	244,316	7,965
	유산인원(명)	100,035	829	30,259	58,811	10,136
	유산율(%)	**20.3**	**38.4**	**17.8**	**19.4**	**56.0**

표 1. 국민건강보험공단 자료
'연도 • 연령 • 지역별 자연유산율 현황' (이철영, 2010)

- Recurrent pregnancy loss(RPL) is a disease distinct from infertility, defined by two or more failed pregnancies before 20 weeks of gestation.
  - It also called Recurrent Spontaneous Abortion (RSA), Recurrent Miscarriage (RM), Habitual Abortion (HA)

2013, ASRM

The definitive etiologic factors for RPL



Teklenburg G et al. The molecular basis of recurrent pregnancy loss: impaired natural embryo selection. Mol Hum Reprod 2010

To related factors for early pregnancy

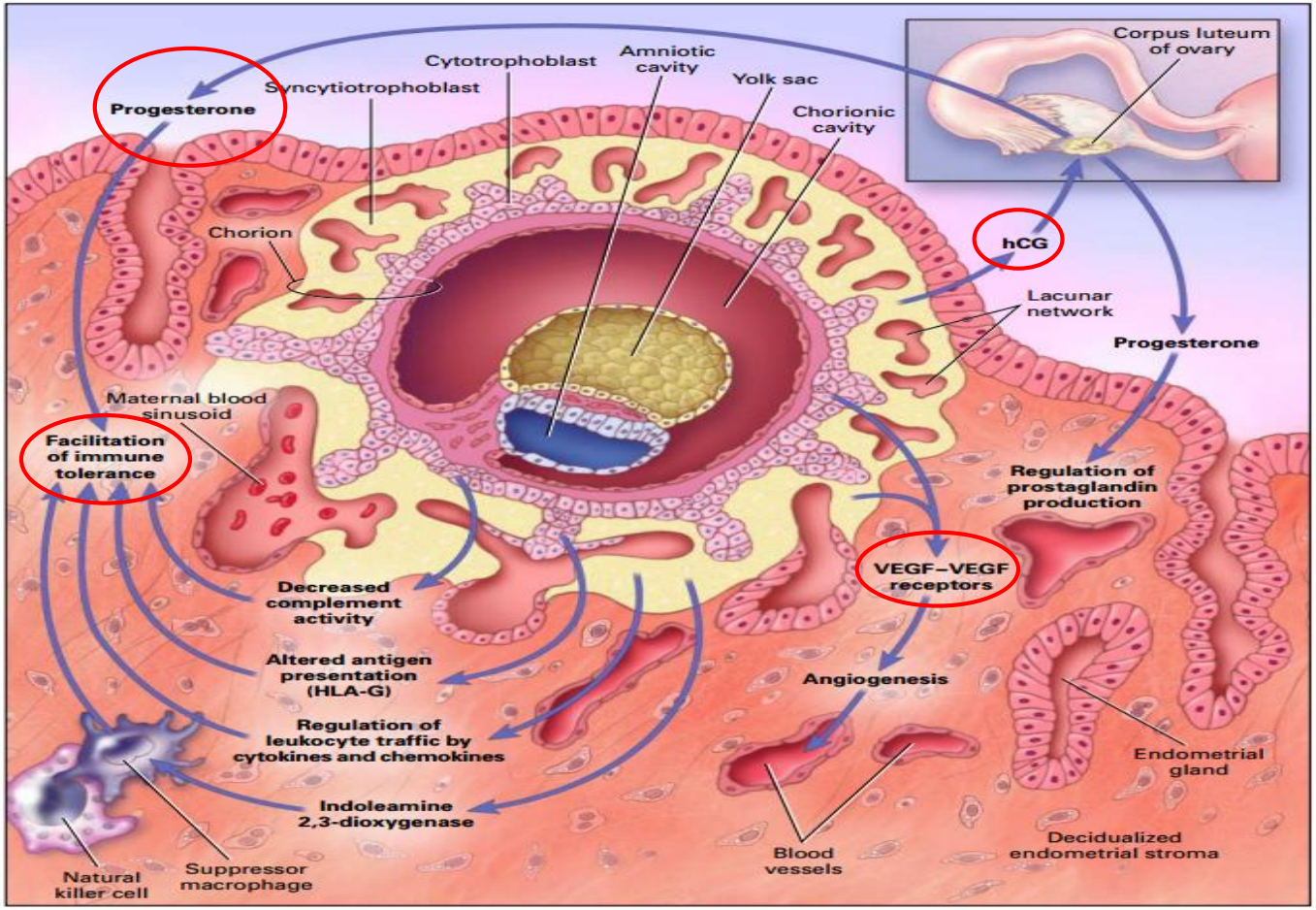


Figure 3. Maintenance of Early Pregnancy.
The diagram shows an implanted embryo (approximately 14 days after conception) and the processes necessary for the maintenance of an early pregnancy. VEGF denotes vascular endothelial growth factor, and hCG human chorionic gonadotropin.

Teklenburg G et al. Implantation and the survival of early pregnancy. N Engl J Med 2001

Riboflavin as a Determinant of Plasma Total Homocysteine: Effect Modification by the Methylenetetrahydrofolate Reductase C677T Polymorphism

Steinar Hustad,* Per Magne Ueland, Stein Emil Vollset, Ying Zhang, Anne Lise Bjørke-Monsen, and Jørn Schneede

Table 2. Plasma tHcy and vitamin status according to *MTHFR* C677T genotype.

	Genotype[a]			
	CC (n = 204)	CT (n = 182)	TT (n = 37)	P[b]
Plasma tHcy, μmol/L	8.6 (8.3–9.0)	9.1 (8.8–9.5)	11.5 (9.7–13.5)	0.03
Plasma riboflavin, nmol/L	13.3 (12.1–14.6)	13.7 (12.6–15.0)	12.1 (10.0–14.7)	0.6
Plasma FMN, nmol/L	7.5 (7.0–8.0)	7.9 (7.5–8.4)	7.1 (5.9–8.4)	0.2
Plasma FAD, nmol/L	59.3 (57.7–60.9)	60.7 (59.0–62.5)	56.6 (52.7–60.8)	0.2
Serum folate, nmol/L	16.4 (15.6–17.2)	15.0 (14.3–15.9)	13.2 (11.6–15.0)	0.02
Serum cobalamin, pmol/L	381 (365–397)	379 (362–398)	360 (325–400)	0.9

[a] Data are given as geometric mean with 95% confidence intervals in parentheses.
[b] By ANOVA, adjusted for age and sex.

Hustad S et al. Clin Chem 46:1065-1071, 2000.

One-carbon metabolism - RPL

CHA 의과학대학교 CHA 차병원

Neonatal and fetal MTHFR genetic polymorphisms: An examination of 677C>T and 1298A>C mutations

Table 2

Combined C677T/A1298C MTHFR Genotype Frequencies and Allele Frequencies for Neonatal and Fetal Groups

Genotype or Allele	Observed Frequency: Neonatal Group (*n* = 119)[a]	Observed Frequency: Fetal Group (*n* = 161)	Odds Ratio (95% CI)	*P*[b]
MTHFR C677T/A1298C genotype:				
CC/AA	.143	.155	1.1 (.57–2.2)	.866
CC/AC	.353	.335	.93 (.6–1.5)	.800
CC/CC	.076	.107	1.3 (.6–3.2)	.415
CT/AA	.117	.174	.2 (.8–3.2)	.237
CT/AC	.193	.168	.8 (.5–1.6)	.637
CT/CC	NO	.031	8.4 (.5–153.5)	.074
TT/AA	.101	.012	.1 (.02–.5)	.001
TT/AC	.017	.012	.7 (.1–5.3)	1.000
TT/CC	NO	.006	2.2 (.1–55.4)	1.000
Combined CT/CC and TT/CC	NO	.037	10.0 (.6–179.2)	.040
MTHFR allele:				
677C	.727	.783		
677T	.273	.217		
1298A	.643	.599		
1298C	.357	.401		

[a] NO = not observed.
[b] By Fisher's exact test.

Phillip A et al. Am J Hum Genet 2000

Prevalent genotypes of MTHFR 677C>T and 1298A>C in spontaneously aborted embryos

TABLE 1

Individual MTHFR genotype distributions for spontaneously aborted embryos and control groups.

Genotype	Abortus (n = 94) (%)	Controls (n = 549): Child (n = 100) (%)	Controls (n = 549): Adult (n = 449) (%)	Child control-based: Odds ratio (95% CI)	Child control-based: *P*[a]	Adult control-based: Odds ratio (95% CI)	Adult control-based: *P*[a]
MTHFR C677T							
CC	38 (40.4)	24 (24.0)	145 (32.3)	2.149 (1.164–3.967)	0.022	1.423 (0.903–2.247)	0.163
CT	39 (41.4)	55 (55.0)	239 (53.2)	0.570 (0.324–1.003)	0.071	0.612 (0.392–0.957)	0.041
TT	17 (18.1)	21 (21.0)	65 (14.5)	0.831 (0.411–1.680)	0.741	1.304 (0.730–2.334)	0.465
C allele	0.612	0.515	0.590				
T allele	0.388	0.485	0.410				
MTHFR A1298C							
AA	63 (67.0)	77 (77.0)	312 (69.5)	0.607 (0.320–1.139)	0.165	0.892 (0.557–1.430)	0.728
AC	28 (29.8)	21 (21.0)	129 (28.7)	1.596 (0.834–3.051)	0.214	1.052 (0.649–1.708)	0.936
CC	3 (3.2)	2 (2.0)	8 (1.8)	1.615 (0.315–8.263)	0.944	2.329 (0.656–8.317)	0.409
A allele	0.819	0.875	0.840				
C allele	0.181	0.125	0.160				
MTHFR C677T/A1298C							
CC/AA	17 (18.1)	14 (14.0)	85 (18.9)	1.356 (0.634–2.899)	0.562	0.945 (0.535–1.673)	0.964
CC/AC	18 (19.1)	8 (8.0)	52 (11.6)	2.724 (1.143–6.469)	0.039	1.808 (1.009–3.243)	0.068
CC/CC	3 (3.2)	2 (2.0)	8 (1.8)	1.815 (0.353–9.297)	0.843	1.817 (0.514–6.456)	0.631
CT/AA	28 (29.8)	42 (42.0)	162 (36.1)	0.586 (0.324–1.058)	0.105	0.752 (0.466–1.214)	0.296
CT/AC	11 (11.7)	13 (13.0)	77 (17.2)	0.887 (0.383–2.055)	0.955	0.640 (0.330–1.245)	0.250
TT/AA	17 (18.1)	21 (21.0)	65 (14.5)	0.864 (0.427–1.751)	0.864	1.304 (0.730–2.334)	0.465

[a] By Fisher's exact test.

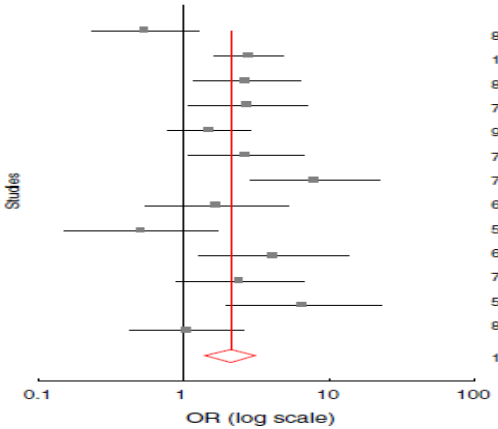
Bae. Prevalent MTHFR genotypes in abortus. Fertil Steril 2007.

Bae JH et al. Fertil and Steril 2007

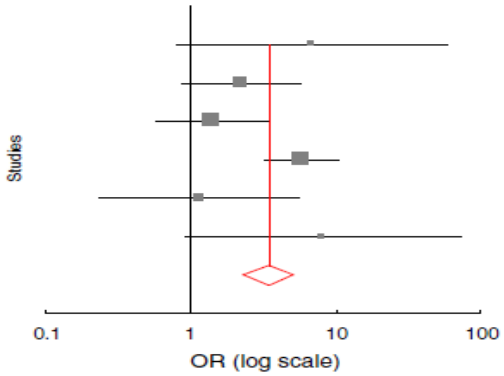
One-carbon metabolism with RPL risk

Association study between methylenetetrahydrofolate reductase polymorphisms and unexplained recurrent pregnancy loss: A meta-analysis.

Study ID	Year	Exposed n[e](E=1)/n[e]	Control n[c](E=1)/n[c]	Weight (%)	Association measure with 95% CI
Makino et al.	2004	10/85	15/76	8.38%	0.5422 (0.2275 to 1.2924)
Guan et al.	2005	55/127	25/117	10.69%	2.8111 (1.5986 to 4.9433)
Dong et al.	2006	20/36	18/57	8.42%	2.7083 (1.1431 to 6.4169)
Ma et al.	2008	16/60	7/60	7.64%	2.7532 (1.0396 to 7.292)
Mitic et al.	2009	36/222	14/122	9.95%	1.4931 (0.7707 to 2.8926)
Zhang et al.	2009	19/56	8/50	7.90%	2.6959 (1.0565 to 6.8797)
Wang et al.	2002	16/62	5/119	7.08%	7.9304 (2.745 to 22.9117)
Li et al.	2004	9/57	5/50	6.44%	1.6875 (0.5256 to 5.4176)
Kobashi et al.	2005	3/38	25/174	5.97%	0.5109 (0.1459 to 1.7882)
Song et al.	2005	12/50	4/56	6.22%	4.1053 (1.2286 to 13.7178)
Wang et al.	2006	20/147	5/82	7.34%	2.4252 (0.8745 to 6.7259)
Zhong et al.	2010	16/141	3/160	5.95%	6.6987 (1.9091 to 23.5049)
Shin et al.	2011	7/33	32/155	8.01%	1.0349 (0.4121 to 2.5987)
META-ANALYSIS:		239/1114	166/1278	100%	2.1124 (1.4005 to 3.1862)



Study ID	Year	Exposed n[e](E=1)/n[e]	Control n[c](E=1)/n[c]	Weight (%)	Association measure with 95% CI
Nair et al.	2012	5/106	1/140	3.07%	6.8812 (0.7918 to 59.8035)
M.R.R.G et al.	2009	10/23	19/74	19.03%	2.2267 (0.8395 to 5.9066)
Couto et al.	2005	12/88	9/88	29.04%	1.386 (0.5524 to 3.4773)
Mtiraoui et al.	2006	61/200	14/200	36.36%	5.8304 (3.1333 to 10.8493)
Vettriselvi et al.	2008	3/104	3/120	10.11%	1.1584 (0.2287 to 5.867)
Settin et al.	2011	4/70	1/136	2.39%	8.1818 (0.8967 to 74.6571)
Excluded	*	0/24	0/24	*	* (*)
META-ANALYSIS:		95/615	47/782	100%	3.4701 (2.3136 to 5.2048)



Cao Y et al. Gene 2013

Association study of vascular endothelial growth factor polymorphisms with the risk of recurrent spontaneous abortion

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TABLE 1

Genotype frequencies of VEGF -2578C > A, -1154G > A, -634G > C, and 936C > T polymorphisms in Korean patients with recurrent spontaneous abortion and in controls.

Genotype	No. of controls (%)	No. of cases (%)	AOR (95% CI)*
VEGF -2578C>A			
CC	60 (53.1)	107 (49.8)	1.000
CA	45 (39.8)	94 (43.7)	1.191 (0.703–2.016)
AA	8 (7.1)	14 (6.5)	0.794 (0.284–2.218)
CA+AA	53 (46.9)	108 (50.2)	0.906 (0.547–1.501)
Allele frequency (A)	0.27	0.28	
VEGF -1154G>A			
GG	81 (71.7)	130 (60.5)	1.000
GA	23 (20.4)	80 (37.2)	2.774 (1.512–5.092)
AA	9 (8.0)	5 (2.3)	0.287 (0.077–1.070)
GA+AA	32 (28.3)	85 (39.5)	2.006 (1.158–3.473)
Allele frequency (A)	0.18	0.21	
VEGF -634G>C			
CC	21 (18.6)	34 (15.8)	1.000
GC	54 (47.8)	114 (53.0)	2.074 (0.970–4.436)
GG	38 (33.6)	67 (31.2)	1.634 (0.765–3.493)
GC+GG	92 (81.4)	181 (84.2)	1.826 (0.913–3.653)
Allele frequency (G)	0.57	0.58	
VEGF 936C>T			
CC	82 (72.6)	149 (69.3)	1.000
CT	29 (25.7)	63 (29.3)	1.047 (0.597–1.838)
TT	2 (1.8)	3 (1.4)	1.876 (0.189–18.581)
CT+TT	31 (27.4)	66 (30.7)	1.082 (0.622–1.882)
Allele frequency (T)	0.15	0.16	
Total	113 (100.0)	215 (100.0)	

*Adjusted by age and body mass index.

TABLE 2

Frequencies of VEGF -2578C > A, -1154G > A, -634G > C and 936C > T haplotypes in patients with recurrent spontaneous abortion and in controls.

Haplotype	Cases	Controls	*P*
VEGF -2578C>A/-1154G>A/- 634G>C/936C>T			
C-G-C-C	0.355	0.377	0.573
C-G-G-C	0.263	0.261	0.965
A-A-G-C	0.128	0.113	0.566
A-G-G-C	0.059	0.057	0.901
A-G-G-T	0.040	0.071	0.092
C-G-C-T	0.048	0.026	0.165
A-A-G-T	0.050	0.019	0.051
C-G-G-T	0.019	0.016	0.784
C-A-G-C	0.015	0.024	0.417
C-A-C-C	0.013	0.011	0.832
A-G-C-C	6.31E-03	0.011	0.520
C-A-G-T	2.43E-03	0.015	0.060
C-A-C-T	1.14E-03	2.98E-59	0.612
VEGF -1154G>A/-634G>C/936C>T			
G-G-T	0.052	0.092	0.050
G-C-T	0.052	0.023	0.081
VEGF -2578C>A/-1154G>A/936C>T			
A-A-T	0.051	0.021	0.063

Lee HH et al. Fertil Steril 2010

Reproductive Sciences
20(4) 408-413

DOI: 10.1177/1933719112459237
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Tumor Necrosis Factor-α Gene Polymorphisms in Korean Patients With Recurrent Spontaneous Abortion

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Table 1. Genotype Frequencies of *TNF-α* -1031T>C, -376G>A, -308G>A, and -238G>A Polymorphisms in Korean Patients With Recurrent Spontaneous Abortion and in Controls.

Characteristics	Controls, n = 236	Patients With RSA, n = 357	COR (95% CI)	AOR (95% CI)	P[a]
TNF-α -1031T>C					
TT	191 (80.9)	230 (64.4)	1.000		
TC	45 (19.1)	115 (32.2)	2.122 (1.430-3.149)	2.071 (1.392-3.081)	<.001
CC	–	12 (3.4)	20.770 (1.221-353.330)	NA	NA
TC+CC			2.344 (1.586-3.463)	2.292 (1.547-3.395)	<.001
HWE P	0.105	0.605			
TNF-α -376G>A					
GG	236 (100.0)	357 (100.0)			
GA	–	–	NA	NA	NA
AA	–	–	NA	NA	NA
TNF-α -308G>A					
GG	213 (90.3)	319 (89.4)	1.000		
GA	21 (8.9)	36 (10.1)	1.145 (0.650-2.015)	1.149 (0.652-2.024)	.631
AA	2 (0.8)	2 (0.5)	0.668 (0.093-4.779)	0.713 (0.099-5.119)	.737
GA+AA			1.103 (0.639-1.905)	1.111 (0.643-1.920)	.705
HWE P	0.083	0.379			
TNF-α -238G>A					
GG	228 (96.6)	330 (92.4)	1.000		
GA	8 (3.4)	26 (7.3)	2.245 (0.999-5.050)	2.237 (0.994-5.033)	.052
AA	–	1 (0.3)	2.074 (0.084-51.182)	NA	NA
GA+AA			2.332 (1.040-5.226)	2.327 (1.038-5.217)	.040
HWE P	0.791	0.526			

Abbreviations: HWE, Hardy-Weinberg equilibrium; COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval; NA, not applicable; RSA, recurrent spontaneous abortion; TNF-α, tumor necrosis factor α.
[a] Adjusted by age of all participants.

Table 2. Combination Analysis of *TNF-α* -1031T>C, -308G>A, and -238G>A Polymorphisms in Korean Patients With Recurrent Spontaneous Abortion and in Controls.

Characteristics	Controls, n = 236	Patients With RSA, n = 357	AOR (95% CI)	P[a]
TNF-α -1031T>C/-308G>A				
TT/GG	171 (72.5)	197 (55.2)	1.000	
TT/GA+AA	20 (8.4)	33 (9.2)	1.425 (0.786-2.583)	.243
TC+CC/GG	42 (17.8)	122 (34.2)	2.467 (1.639-3.714)	<.001
TC+CC/GA+AA	3 (1.3)	5 (1.4)	1.420 (0.334-6.044)	.635
TNF-α -1031T>C/-238G>A				
TT/GG	188 (79.7)	228 (63.9)	1.000	
TT/GA+AA	3 (1.3)	2 (0.5)	0.526 (0.087-3.187)	.485
TC+CC/GG	40 (16.9)	102 (28.6)	2.037 (1.343-3.090)	.001
TC+CC/GA+AA	5 (2.1)	25 (7.0)	4.054 (1.520-10.812)	.005
TNF-α -308G>A/-238G>A				
GG/GG	205 (86.9)	292 (81.8)	1.000	
GG/GA+AA	8 (3.4)	27 (7.6)	2.366 (1.053-5.317)	.037
GA+AA/GG	23 (9.7)	38 (10.6)	1.169 (0.675-2.023)	.577

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; RSA, recurrent spontaneous abortion; TNF-α, tumor necrosis factor-α.
[a] Adjusted by age of all participants.

Lee BE et al. Reprod Sci 2012

Interleukin-1beta-511T > C genetic variant contributes to recurrent pregnancy loss risk and peripheral natural killer cell proportion

Jung O Kim, M.S.,[a,b] Woo Sik Lee, M.D., Ph.D.,[c] Bo Eun Lee, M.S.,[a,b] Young Joo Jeon, Ph.D.,[a,b] Young Ran Kim, M.D., Ph.D.,[d] Sang Hee Jung, M.D., Ph.D.,[d] Sung Woon Chang, M.D., Ph.D.,[d] and Nam Keun Kim, Ph.D.[a,b]

TABLE 2

Genotype frequencies of interleukin gene polymorphisms between controls and RPL patients.

Characteristic	Controls (n = 232), n (%)	RPL patients (n = 385), n (%)	AOR (95% CI)	P[a]	P[b]
IL-1β -511T>C					
TT	73 (31.5)	99 (25.7)	1.000 (reference)		
TC	120 (51.7)	190 (49.4)	1.168 (0.799–1.706)	.423	.657
CC	39 (16.8)	96 (24.9)	1.826 (1.130–2.953)	.014	.028
Dominant			1.327 (0.927–1.901)	.123	.369
Recessive			1.648 (1.089–2.495)	.018	.036
T allele	266 (57.3)	388 (50.4)	1.000 (reference)		
C allele	198 (42.7)	382 (49.6)	1.324 (1.050–1.670)	.018	.054
HWE *P*	.384	.800			
IL-4 intron3 VNTR					
B1B1	149 (64.2)	238 (61.8)	1.000 (reference)		
B1B2	74 (31.9)	128 (33.2)	1.083 (0.762–1.540)	.657	.657
B2B2	9 (3.9)	19 (4.9)	1.364 (0.598–3.115)	.461	.461
Dominant			1.110 (0.791–1.556)	.546	.698
Recessive			1.292 (0.574–2.906)	.536	.536
B1 allele	372 (80.2)	604 (78.4)	1.000 (reference)		
B2 allele	92 (19.8)	166 (21.6)	1.113 (0.836–1.481)	.464	.696
HWE *P*	.960	.739			
IL-10 -1082A>G					
AA	198 (85.3)	333 (86.5)	1.000 (reference)		
AG	34 (14.7)	50 (13.0)	0.877 (0.548–1.403)	.583	.657
GG	0	2 (0.5)	NA	NA	NA
Dominant			0.912 (0.572–1.454)	.698	.698
Recessive			NA	NA	NA
A allele	430 (92.7)	716 (93.0)	1.000 (reference)		
G allele	34 (7.3)	54 (7.0)	0.957 (0.613–1.494)	.845	.845
HWE *P*	.228	.934			

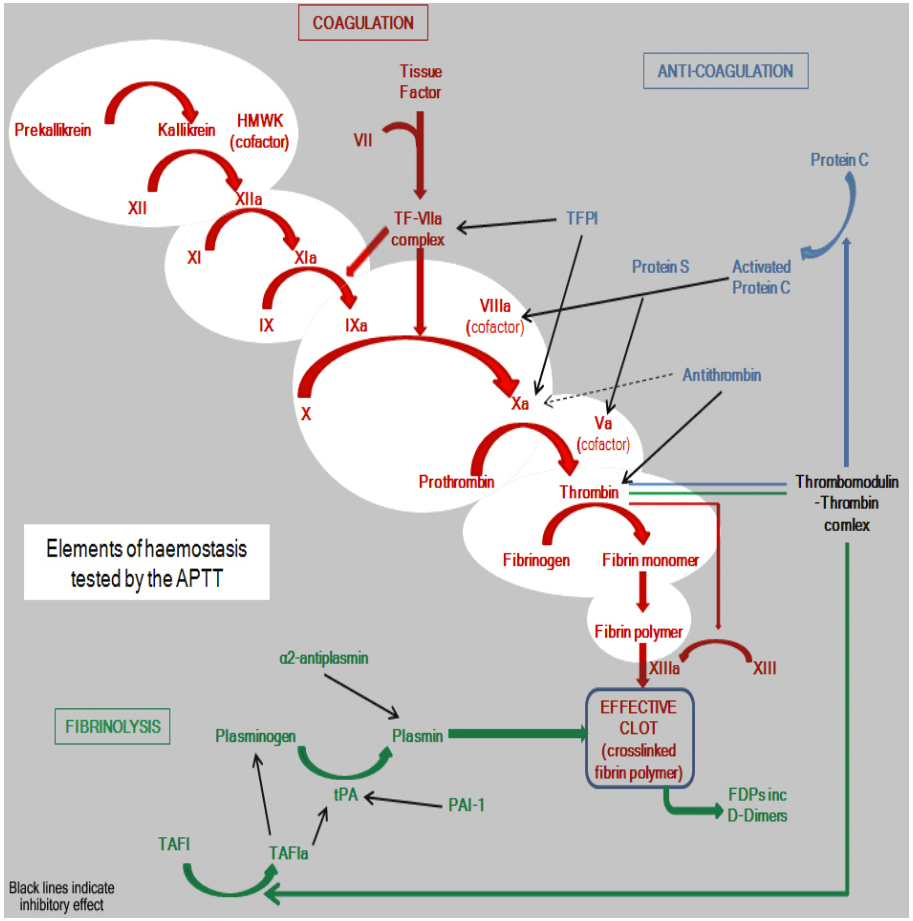
SUPPLEMENTAL TABLE 2

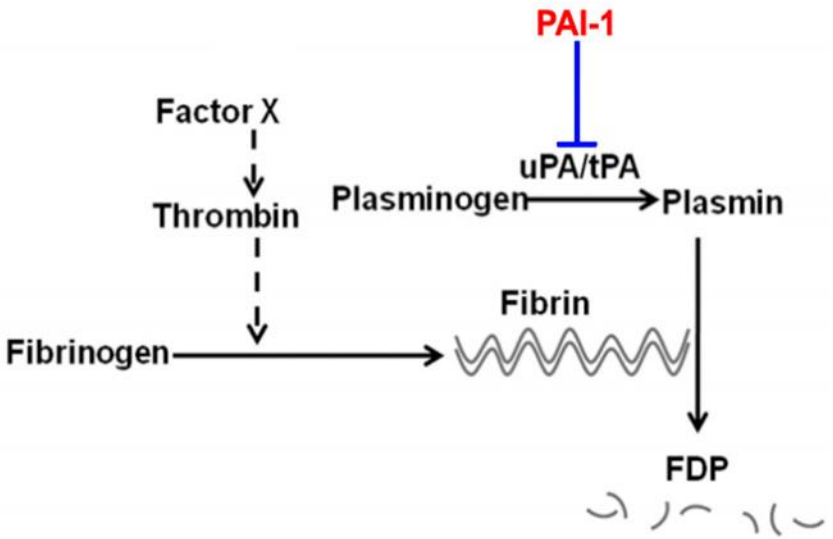
Allelic gene–gene interactions of interleukin polymorphisms according to the number of pregnancy losses.

Allelic combinations	Controls (2n = 464), n (%)	PL = 2 (2n = 360), n (%)	OR (95% CI)	P[a]	P[b]	PL ≥ 3 (2n = 410), n (%)	OR (95% CI)	P[a]	P[b]
IL-1β/IL-4/IL-10									
T-B1-A	201 (43.3)	130 (36.1)	1.000 (reference)			161 (39.3)	1.000 (reference)		
T-B1-G	22 (4.7)	9 (2.5)	0.633 (0.282–1.417)	.335	.531	5 (1.2)	0.284 (0.105–0.766)	.009	.032
T-B2-A	43 (9.3)	29 (8.1)	1.043 (0.620–1.754)	.895	1.000	40 (9.8)	1.161 (0.720–1.873)	.544	.699
T-B2-G	0 (0.0)	7 (1.9)	23.161 (1.311–409.258)	.002	.014	7 (1.7)	18.715 (1.060–330.376)	.004	.028
C-B1-A	142 (30.6)	135 (37.5)	1.470 (1.064–2.030)	.022	.077	145 (35.4)	1.275 (0.934–1.739)	.133	.310
C-B1-G	7 (1.5)	10 (2.8)	2.209 (0.820–5.950)	.131	.306	8 (2.0)	1.427 (0.507–4.019)	.599	.699
C-B2-A	45 (9.7)	37 (10.3)	1.271 (0.781–2.071)	.379	.531	39 (9.5)	1.082 (0.672–1.742)	.808	.808
C-B2-G	4 (0.9)	3 (0.8)	1.160 (0.255–5.268)	1.000	1.000	5 (1.2)	1.561 (0.412–5.909)	.521	.699
IL-1β/IL-4									
T-B1	223 (48.1)	139 (38.6)	1.000 (reference)			166 (40.5)	1.000 (reference)		
T-B2	43 (9.3)	35 (9.7)	1.306 (0.797–2.140)	.309	.309	48 (11.7)	1.500 (0.948–2.371)	.101	.152
C-B1	149 (32.1)	146 (40.6)	1.572 (1.151–2.146)	.004	.012	153 (37.3)	1.379 (1.020–1.866)	.038	.114
C-B2	49 (10.6)	40 (11.1)	1.310 (0.820–2.092)	.278	.309	43 (10.5)	1.179 (0.747–1.861)	.485	.485

Kim JO et al. Fertil Steril 2014

Coagulation & Thrombosis





Morange PE et al.
Arterioscler Thromb Vasc Biol 2007

Genetic association of five plasminogen activator inhibitor-1 (PAI-1) polymorphisms and idiopathic recurrent pregnancy loss in Korean women

Young Joo Jeon[1,*]; Young Ran Kim[2,*]; Bo Eun Lee[1]; Yi Seul Choi[1]; Ji Hyang Kim[2]; Ji Eun Shin[2]; HyungChul Rah[1]; Sun Hee Cha[2]; Woo Sik Lee[3]; Nam Keun Kim[1]

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Characteristics	Controls (n=227, %)	RPL patients (n=308, %)	AOR (95% CI)	P[a]
PAI-1 –844G>A				
GG	72 (31.7)	115 (37.3)	1.000 (reference)	
GA	120 (52.9)	133 (43.2)	0.692 (0.471 – 1.017)	0.061
AA	35 (15.4)	60 (19.5)	1.079 (0.647 – 1.798)	0.772
Dominant (GG vs GA+AA)			0.776 (0.540 – 1.115)	0.171
Recessive (GG+GA vs AA)			1.322 (0.836 – 2.090)	0.232
HWE *P*	0.194	0.058		
PAI-1 –675 4G/5G				
5G5G	39 (17.2)	47 (15.3)	1.000 (reference)	
4G5G	117 (51.5)	132 (42.9)	0.935 (0.571 – 1.530)	0.788
4G4G	71 (31.3)	129 (41.9)	1.496 (0.894 – 2.505)	0.125
Dominant (5G5G vs 4G5G+4G4G)			1.151 (0.724 – 1.831)	0.553
Recessive (5G5G+4G5G vs 4G4G)			1.578 (1.100 – 2.264)	0.013
HWE *P*	0.436	0.174		
PAI-1 43G>A				
GG	193 (85.0)	270 (87.7)	1.000 (reference)	
GA	34 (15.0)	38 (12.3)	0.797 (0.484 – 1.312)	0.372
AA	0 (0.0)	0 (0.0)	NA	NA
Dominant (GG vs GA+AA)			0.797 (0.484 – 1.312)	0.372
Recessive (GG+GA vs AA)			NA	NA
HWE *P*	0.223	0.249		
PAI-1 9785G>A				
GG	218 (96.0)	286 (92.9)	1.000 (reference)	
GA	9 (4.0)	22 (7.1)	1.849 (0.834 – 4.098)	0.130
AA	0 (0.0)	0 (0.0)	NA	NA
Dominant (GG vs GA+AA)			1.849 (0.834 – 4.098)	0.130
Recessive (GG+GA vs AA)			NA	NA
HWE *P*	0.761	0.516		
PAI-1 11053T>G				
TT	65 (28.6)	84 (27.3)	1.000 (reference)	
TG	101 (44.5)	140 (45.5)	1.071 (0.709 – 1.618)	0.745
GG	61 (26.9)	84 (27.3)	1.067 (0.671 – 1.696)	0.786
Dominant (TT vs TG+GG)			1.071 (0.731 – 1.569)	0.725
Recessive (TT+TG vs GG)			1.020 (0.693 – 1.501)	0.920
HWE *P*	0.098	0.111		

HWE, Hardy-Weinberg equilibrium; NA, not applicable; RPL, recurrent pregnancy loss. [a] Adjusted by age of female participants.

PAI-1 genotypes	Plasma PAI-1 (ng/ml)	PLT (10^3 cells/μl)	PT (sec)	aPTT (sec)
-844GG	10.37 ± 6.23 (n=41)	244.28 ± 60.56	11.71 ± 0.69	32.63 ± 4.29
-844GA	10.80 ± 5.54 (n=42)	248.45 ± 53.24	11.49 ± 0.80	32.02 ± 4.24
-844AA	13.12 ± 5.49 (n=21)	278.86 ± 59.69	11.25 ± 0.91	31.48 ± 4.68
P[a]	0.198	0.011	0.013	0.403
5G5G	9.82 ± 6.33 (n=21)	218.19 ± 42.78	11.76 ± 0.71	33.34 ± 4.33
4G5G	10.93 ± 5.55 (n=40)	253.29 ± 61.60	11.81 ± 0.63	32.30 ± 3.88
4G4G	11.88 ± 5.91 (n=43)	265.29 ± 56.15	11.13 ± 0.83	31.48 ± 4.74
P[a]	0.412	0.001	<0.001	0.122
43GG	11.05 ± 5.86 (n=90)	256.42 ± 59.03	11.47 ± 0.81	31.96 ± 4.30
43GA	11.45 ± 5.99 (n=14)	228.47 ± 50.21	11.85 ± 0.63	33.41 ± 4.61
P[b]	0.813	0.040	0.035	0.135
9785GG	10.92 ± 5.70 (n=96)	255.41 ± 58.81	11.51 ± 0.82	32.16 ± 4.45
9785GA	13.25 ± 7.60 (n=8)	218.27 ± 44.69	11.69 ± 0.47	31.85 ± 3.13
P[b]	0.283	0.042	0.407	0.799
11053TT	10.25 ± 6.13 (n=28)	230.63 ± 50.86	11.85 ± 0.59	33.71 ± 4.24
11053TG	11.08 ± 5.94 (n=49)	248.26 ± 60.02	11.50 ± 0.77	31.40 ± 3.83
11053GG	12.07 ± 5.47 (n=27)	279.27 ± 52.81	11.25 ± 0.93	32.02 ± 3.83
P[a]	0.534	<0.001	0.001	0.013

PLT, platelet; PT, prothrombin time; aPTT, activated partial thromboplastin time. [a] One-way analysis of variance test. [b] Independent two-sample t-test.

Jeon YJ et al. Thromb Haemost 2013

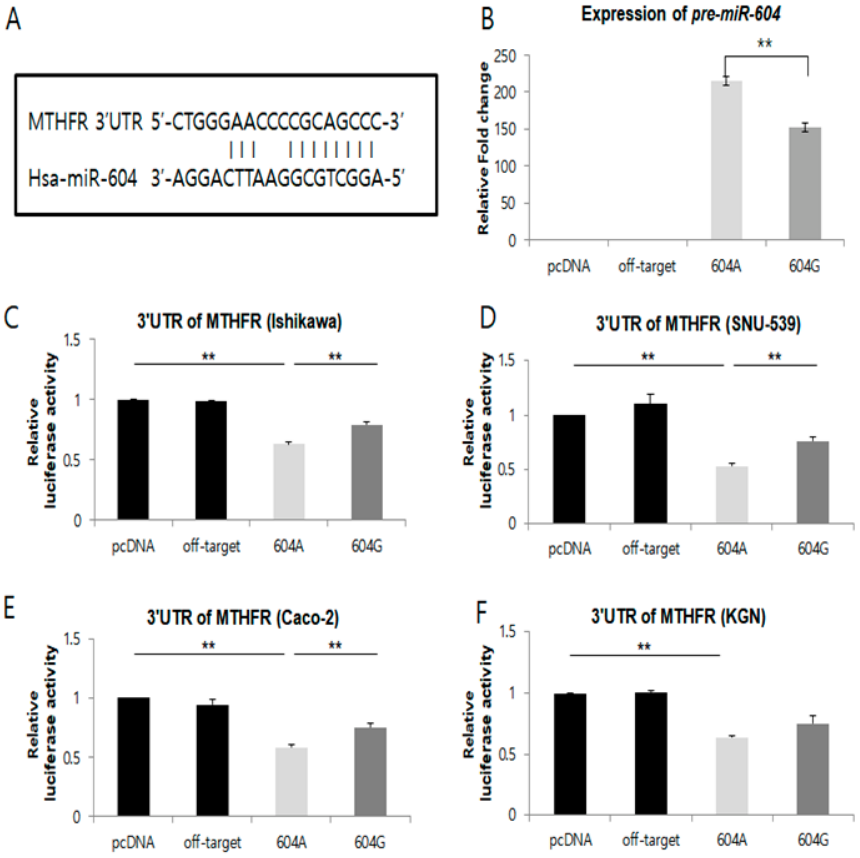
Article

Genetic Polymorphisms in *miR-604*A>G, *miR-938*G>A, *miR-1302-3*C>T and the Risk of Idiopathic Recurrent Pregnancy Loss

Sung-Hwan Cho [1,†], Ji-Hyang Kim [2,†], Hui-Jeong An [1,3], Young-Ran Kim [2], Eun-Hee Ahn [2], Jung-Ryeol Lee [4], Jung-Oh Kim [1], Jung-Jae Ko [1] and Nam-Keun Kim [1,*]

Table 2. Comparison of microRNA polymorphic genotype frequencies in controls and RPL patients.

Characteristics	Controls *n* = 227 *n* (%)	PL ≥ 2 *n* = 388 *n* (%)	AOR (95% CI) [a]	*p* [b]	FDR-*p* [c]	PL ≥ 3 *n* = 206 n (%)	AOR (95% CI) [a]	*p* [b]	FDR-*p* [c]
miR-604A>G									
AA	73 (32.2)	171 (44.1)	1.000 (reference)			86 (41.7)	1.000 (reference)		
AG	115 (50.7)	173 (44.6)	0.640 (0.445–0.920)	0.016	0.061	95 (46.1)	0.686 (0.452–1.04)	0.076	0.126
GG	39 (17.2)	44 (11.3)	**0.496 (0.296–0.832)**	**0.008**	**0.024**	25 (12.1)	**0.532 (0.292–0.970)**	**0.04**	0.12
Dominant (AA vs. AG + GG)			**0.606 (0.429–0.856)**	**0.005**	**0.025**		0.650 (0.438–0.965)	0.033	0.055
Recessive (AA + AG vs. GG)			0.621 (0.389–0.992)	0.046	0.138		0.646 (0.374–1.117)	0.118	0.276
miR-608C>G									
CC	48 (21.1)	93 (24.0)	1.000 (reference)			51 (24.8)	1.000 (reference)		
CG	109 (48.0)	189 (48.7)	0.885 (0.581–1.349)	0.57	0.57	103 (50.0)	0.867 (0.536–1.401)	0.559	0.559
GG	70 (30.8)	106 (27.3)	0.789 (0.497–1.252)	0.314	0.471	52 (25.2)	0.702 (0.411–1.199)	0.195	0.292
Dominant (CC vs. CG + GG)			0.850 (0.572–1.261)	0.419	0.419		0.805 (0.513–1.263)	0.345	0.345
Recessive (CC + CG vs. GG)			0.847 (0.591–1.214)	0.366	0.549		0.751 (0.492–1.146)	0.184	0.276
miR-631I/D									
II	204 (89.9)	357 (92.0)	1.000 (reference)			193 (93.7)	1.000 (reference)		
ID	23 (10.1)	31 (8.0)	0.778 (0.441–1.372)	0.385	0.481	13 (6.3)	0.577 (0.283–1.178)	0.131	0.163
DD	0 (0.0)	0 (0.0)	N/A	N/A	N/A	0 (0.0)	N/A	N/A	N/A
Dominant (II vs. ID + DD)			0.778 (0.441–1.372)	0.385	0.419		0.577 (0.283–1.178)	0.131	0.163
Recessive (II + ID vs. DD)			N/A	N/A	N/A		N/A	N/A	N/A
miR-938G>A									
GG	215 (94.7)	380 (97.9)	1.000 (reference)			204 (99.0)	1.000 (reference)		
GA	12 (5.3)	8 (2.1)	0.375 (0.151–0.933)	0.035	0.061	2 (1.0)	0.179 (0.040–0.811)	0.026	0.087
AA	0 (0.0)	0 (0.0)	N/A	N/A	N/A	0 (0.0)	N/A	N/A	N/A
Dominant (CC vs. CT + TT)			0.375 (0.151–0.933)	0.035	0.061		0.179 (0.040–0.811)	0.026	0.055
Recessive (CC + CT vs. TT)			N/A	N/A	N/A		N/A	N/A	N/A



What is Recurrent Implantation Failure (RIF)?

CHA 의과학대학교 CHA 차병원

•RIF be defined as the failure to achieve a clinical pregnancy after transfer of at least 4 good-quality embryos in a minimum of two or three (fresh or frozen) IVF cycles in a woman.

• RIF may simply be defined as two or more continuous implantation failures

•Based on the definition proposed above, RIF is primarily due to uterine factors.

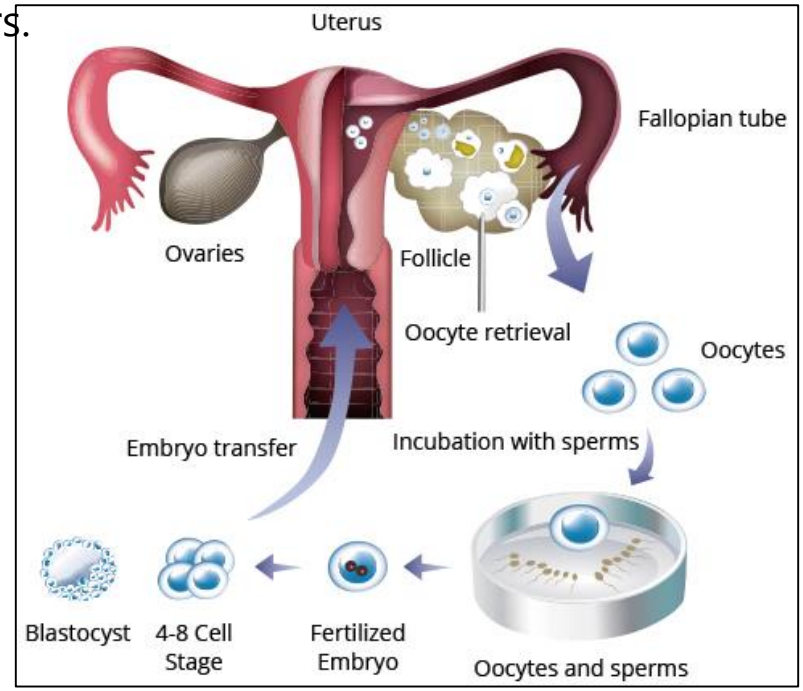
•Proportion of cases due to gamete or embryo factors.

- Oocyte quality
- Sperm quality
- Parental chromosomal anomalies

•Uterine factors

- Congenital uterine anomalies
- Hydrosalpinx
- Immunological factors
- Thrombotic conditions

•Genetic factors



COUGHLAN, Carol, et al. Recurrent implantation failure: definition and management. *Reprod. Biomed. online*, 2014, 28.1: 14-38.

RESEARCH ARTICLE

Genetic Variation of Methylenetetrahydrofolate Reductase (*MTHFR*) and Thymidylate Synthase (*TS*) Genes Is Associated with Idiopathic Recurrent Implantation Failure

Youngsok Choi[1,2☯], Jung Oh Kim[1,3☯], Sung Han Shim[1,2], Yubin Lee[2], Ji Hyang Kim[4], Young Joo Jeon[1,3], Jung Jae Ko[1], Woo Sik Lee[2]*, Nam Keun Kim[1,3]*

Table 2. Genotype frequencies of one-carbon metabolism-related gene polymorphisms between controls and RIF patients.

Genotype	Controls	RIF patients	Reference allele	Models	AOR (95% CI)	*P*	FDR-*P*
MTHFR 677C>T	n = 125	n = 120					
CC	46 (36.8)	35 (29.2)	677C	Additive	1.394 (0.957–2.030)	0.083	0.332
CT	64 (51.2)	60 (50.0)	677C	Dominant	1.384 (0.807–2.375)	0.238	0.476
TT	15 (12.0)	25 (20.8)	677C	Recessive	1.834 (0.908–3.705)	0.091	0.364
HWE *P*	0.308	0.939					
MTHFR 1298A>C							
AA	79 (63.2)	78 (65.0)	1298A	Additive	1.005 (0.631–1.600)	0.984	0.984
AC	43 (34.4)	38 (31.7)	1298A	Dominant	0.977 (0.576–1.657)	0.931	0.931
CC	3 (2.4)	4 (3.3)	1298A	Recessive	1.273 (0.277–5.851)	0.756	0.907
HWE *P*	0.306	0.810					
TSER 2R/3R							
3R3R	82 (65.6)	81 (67.5)	3R	Additive	0.958 (0.615–1.493)	0.850	0.984
2R3R	37 (29.6)	34 (28.3)	3R	Dominant	0.953 (0.558–1.628)	0.860	0.931
2R2R	6 (4.8)	5 (4.2)	3R	Recessive	0.930 (0.275–3.143)	0.907	0.907
HWE *P*	0.497	0.811					
TS 1494 0bp/6bp							
0bp0bp	70 (56.0)	59 (49.2)	14940bp	Additive	1.242 (0.835–1.848)	0.285	0.570
0bp6bp	45 (36.0)	51 (42.5)	14940bp	Dominant	1.391 (0.836–2.316)	0.204	0.476
6bp6bp	10 (8.0)	10 (8.3)	14940bp	Recessive	1.091 (0.435–2.739)	0.852	0.907
HWE *P*	0.471	0.826					

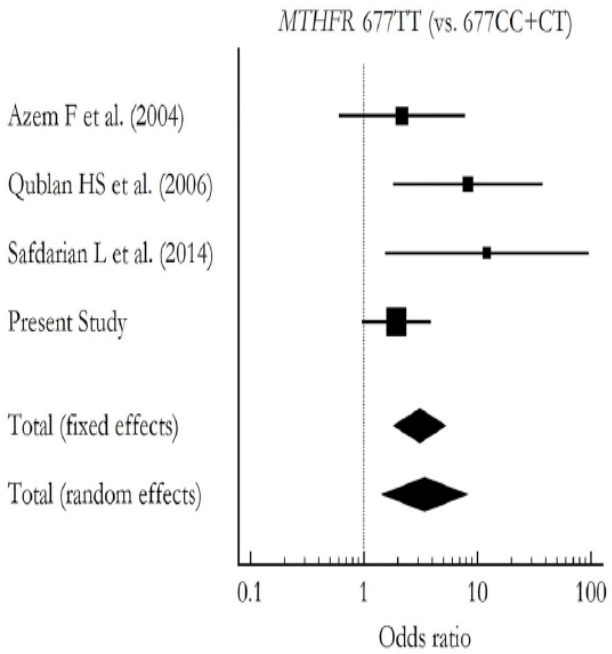


Fig 1. A meta-analysis of *MTHFR* 677C>T in RIF. A meta-analysis of the association between carriers of the T allele (individuals with TT genotype) in the *MTHFR* 677C>T polymorphism and recurrent implantation failure (RIF). The fixed and random effects models were used to calculate the pooled weighted odds ratios (ORs).

Association of *miR-27a*A>G, *miR-423*C>a, *miR-449b*A>G, and *miR-604*A>G Polymorphisms with Risk of Recurrent Implantation Failure

Jung Oh Kim[1] · Eun Hee Ahn[2] · Jung Hyun Sakong[1] · Hui Jeong An[1] · Han Sung Park[1] · Young Ran Kim[2]
Jung Ryeol Lee[3] · Woo Sik Lee[4] · Nam Keun Kim[1]

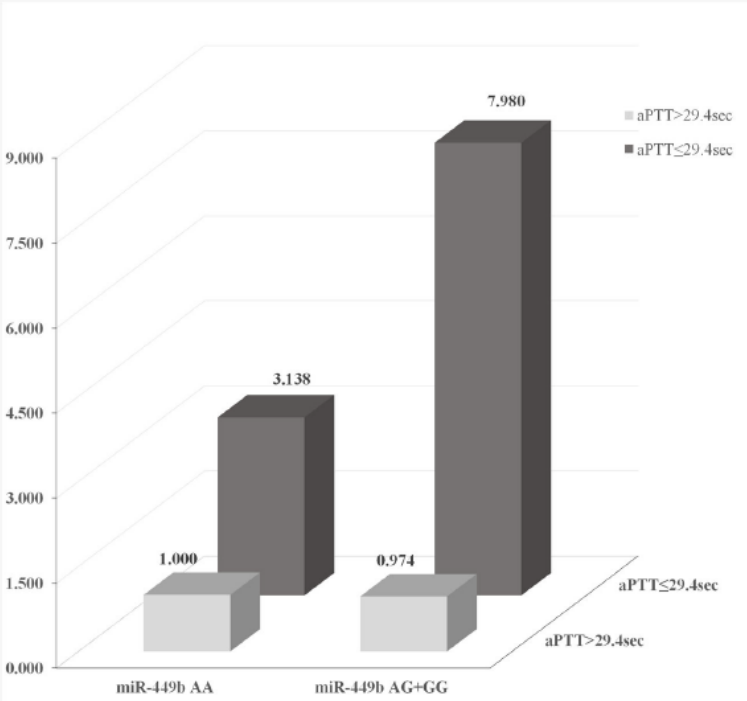
Sakong JH et al. Reprod Sci. 2019

Table 2 Genotype frequencies of miRNA four gene polymorphisms between controls and RIF patients

Genotypes	Controls (n = 219)	RIF ≥ 2 (n = 120)	AOR (95% CI)	P	FDR-P	RIF ≥ 3 (n = 107)	AOR (95% CI)	P	FDR-P[a]	RIF ≥ 4 (n = 75)	AOR (95% CI)	P	FDR-P[a]
miR-27a rs895819 A>G													
AA	72 (32.9)	59 (49.2)	1.000 (reference)			53 (49.5)	1.000 (reference)			39 (52.0)	1.000 (reference)		
AG	117 (53.4)	47 (39.2)	0.480 (0.296–0.781)	0.003	0.012	42 (39.3)	0.477 (0.288–0.789)	0.004	0.016	25 (33.3)	0.383 (0.213–0.689)	0.001	0.004
GG	30 (13.7)	14 (11.7)	0.564 (0.273–1.164)	0.121	0.242	12 (11.2)	0.535 (0.250–1.147)	0.108	0.159	11 (14.7)	0.670 (0.302–1.486)	0.325	0.433
Dominant (AA vs. AG+GG)			0.499 (0.316–0.789)	0.003	0.012		0.491 (0.305–0.789)	0.003	0.012		0.444 (0.260–0.759)	0.003	0.012
Recessive (AA+AG vs. GG)			0.829 (0.420–1.636)	0.588	0.588		0.790 (0.386–1.618)	0.519	0.519		1.078 (0.510–2.281)	0.844	0.844
miR-423 rs6505162 C>A													
CC	142 (64.8)	70 (58.3)	1.000 (reference)			63 (58.9)	1.000 (reference)			46 (61.3)	1.000 (reference)		
CA	64 (29.2)	45 (37.5)	1.464 (0.906–2.367)	0.119	0.119	41 (38.3)	1.501 (0.914–2.465)	0.109	0.145	26 (34.7)	1.303 (0.737–2.304)	0.363	0.363
AA	13 (5.9)	5 (4.2)	0.792 (0.271–2.316)	0.670	0.670	3 (2.8)	0.536 (0.147–1.952)	0.344	0.344	3 (4.0)	0.735 (0.200–2.702)	0.643	0.643
Dominant (CC vs. CA+AA)			1.356 (0.856–2.149)	0.195	0.195		1.342 (0.831–2.169)	0.229	0.229		1.211 (0.701–2.093)	0.493	0.493
Recessive (CC+CA vs. AA)			0.707 (0.245–2.036)	0.520	0.588		0.472 (0.131–1.696)	0.250	0.333		0.679 (0.188–2.458)	0.556	0.741
miR-449b rs10061133 A>G													
AA	120 (54.8)	53 (44.2)	1.000 (reference)			45 (42.1)	1.000 (reference)			30 (40.0)	1.000 (reference)		
AG	86 (39.3)	57 (47.5)	1.536 (0.961–2.454)	0.073	0.109	52 (48.6)	1.667 (1.021–2.722)	0.041	0.082	39 (52.0)	1.903 (1.088–3.329)	0.024	0.048
GG	13 (5.9)	10 (8.3)	1.721 (0.708–4.185)	0.231	0.308	10 (9.3)	2.040 (0.832–4.998)	0.119	0.159	6 (8.0)	1.850 (0.644–5.313)	0.253	0.433
Dominant (AA vs. AG+GG)			1.584 (1.008–2.490)	0.046	0.061		1.747 (1.088–2.803)	0.021	0.042		1.932 (1.122–3.327)	0.018	0.036
Recessive (AA+AG vs. GG)			1.477 (0.626–3.483)	0.373	0.588		1.692 (0.715–4.006)	0.232	0.333		1.439 (0.525–3.949)	0.479	0.741
miR-604 rs2368393 A>G													
AA	71 (32.4)	53 (44.2)	1.000 (reference)			45 (42.1)	1.000 (reference)			31 (41.3)	1.000 (reference)		
AG	110 (50.2)	54 (45.0)	0.650 (0.400–1.056)	0.082	0.109	49 (45.8)	0.695 (0.419–1.154)	0.160	0.160	33 (44.0)	0.678 (0.380–1.207)	0.186	0.248
GG	38 (17.4)	13 (10.9)	0.415 (0.196–0.878)	0.021	0.084	13 (12.1)	0.483 (0.226–1.033)	0.061	0.159	11 (14.7)	0.590 (0.259–1.346)	0.210	0.433
Dominant (AA vs. AG+GG)			0.596 (0.377–0.945)	0.028	0.056		0.648 (0.402–1.047)	0.076	0.101		0.667 (0.388–1.148)	0.144	0.192
Recessive (AA+AG vs. GG)			0.544 (0.274–1.081)	0.082	0.328		0.613 (0.307–1.224)	0.165	0.333		0.769 (0.366–1.616)	0.488	0.741

Note: For AOR was adjusted by age of participants. *RIF*, recurrent implantation failure; *AOR*, adjusted odds ratio; *CI*, confidence interval

[a] *FDR-P*, false discovery rate, adjusted *P* value



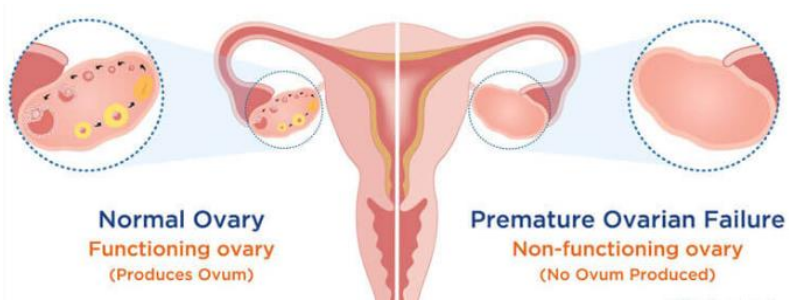
activated Partial Thromboplastin Time (aPTT)

What is primary ovarian insufficiency (POI)?

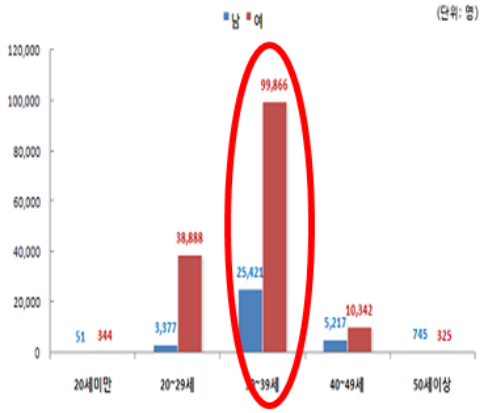
CHA 의과학대학교 CHA 차병원

Primary Ovarian Failure / Insufficiency

1. **Cessation of normal ovarian function by amenorrhea before 40 years old**
2. **Elevated gonadotropin levels: serum FSH >40 IU/L**
   Recently proposed guideline: serum FSH >30 IU/L
3. Prevalence: approximately 1% of women
4. Majority of cases: post-pubertal POI onset
5. 90% of post-pubertal POI
   at the time of diagnosis: nulliparous (without menstruation)



Average age of mothers giving birth to child (Birth Statistics in 2020)



Treatment status of Infertility in each age/gender in 2010 (HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE, 2011)

Association of methylenetetrahydrofolate reductase (*MTHFR* 677C>T) and thymidylate synthase (*TSER* and *TS* 1494del6) polymorphisms with premature ovarian failure in Korean women

HyungChul Rah, DVM, PhD,[1,2] Young Joo Jeon, MS,[1,2] Youngsok Choi, PhD,[1,3] Sung Han Shim, PhD,[1,3] Tae Ki Yoon, MD, PhD,[3] Dong Hee Choi, MD, PhD,[4] Sun Hee Cha, MD, PhD,[4] and Nam Keun Kim, PhD[1,2]

Rah et al. Menopause 2012

TABLE 2. *Genotype frequencies of the MTHFR 677C>T, TSER, and TS 1494del6 polymorphisms in Korean POF patients and controls*

Genotypes	Controls (n = 236), %	POF patients (n = 136), %	OR (95% CI)	*P*	FDR
MTHFR 677C>T					
CC	74 (31.4)	24 (17.7)	1.000 (reference)		
CT	122 (51.7)	89 (65.4)	2.249 (1.317-3.843)	0.003	0.009
TT	40 (16.9)	23 (16.9)	1.773 (0.890-3.533)	0.102	0.306
Dominant (CC vs CT + TT)	162 (68.6)	112 (82.3)	2.132 (1.268-3.585)	0.004	0.012
T allele	0.428	0.496			
HWE *p*	0.391	<0.001			
TSER					
3R3R[a]	156 (66.1)	94 (69.1)	1.000 (reference)		
2R3R	72 (30.5)	39 (28.7)	0.899 (0.565-1.433)	0.654	0.654
2R2R	8 (3.4)	3 (2.2)	0.622 (0.161-2.405)	0.751[b]	0.751
Dominant (3R3R vs 2R+)[c]	80 (33.9)	42 (30.9)	0.871 (0.554-1.370)	0.551	0.551
2R allele	0.186	0.165			
HWE *p*	0.930	0.654			
TS 1494del6					
del6/del6	125 (53.0)	78 (57.4)	1.000 (reference)		
del6/ins6	99 (41.9)	52 (38.2)	0.842 (0.543-1.306)	0.442	0.654
ins6/ins6	12 (5.1)	6 (4.4)	0.801 (0.289-2.223)	0.670	0.751
Dominant (del6/del6 vs del6/ins6 + ins6/ins6)	111 (47.0)	58 (42.6)	0.837 (0.547-1.281)	0.413	0.551
ins6 allele	0.261	0.235			
HWE *p*	0.174	0.466			

MTHFR, methylenetetrahydrofolate reductase; *TSER*, *TS* enhancer region; *TS*, thymidylate synthase; POF, premature ovarian failure; OR, odds ratio; FDR, false discovery rate; HWE *p*, Hardy-Weinberg equilibrium *p* value.
[a]One 3R4R included.
[b]*P* value by Fisher's exact test; otherwise, *p* value by χ^2 test.
[c]2R+: *TSER* 2R2R and 2R3R genotypes.

TABLE 3. *Combination analysis of the MTHFR 677C>T, TSER, and TS 1494del6 polymorphisms in Korean POF patients and controls*

Genotypes	Controls (n = 236), %	POF patients (n = 136), %	OR (95% CI)	*P*	FDR
MTHFR 677/*TSER*					
CC/3R3R	50 (21.2)	16 (11.8)	1.000 (reference)		
CC/2R+	25 (10.6)	8 (5.9)	1.000 (0.377-2.652)	1.000	1.000
CT + TT/3R3R	106 (44.9)	78 (57.3)	2.300 (1.219-4.337)	0.009	0.014
CT + TT/2R+	55 (23.3)	34 (25.0)	1.932 (0.953-3.918)	0.066	0.099
MTHFR 677/*TS* 1494del6					
CC/del6/del6	47 (19.9)	12 (8.8)	1.000 (reference)		
CC/del6/ins6 + ins6/ins6	28 (11.9)	12 (8.8)	1.679 (0.664-4.242)	0.271	0.713
CT + TT/del6/del6	78 (33.1)	66 (48.6)	3.314 (1.623-6.767)	<0.001	0.003
CT + TT/del6/ins6 + ins6/ins6	83 (35.1)	46 (33.8)	2.171 (1.047-4.501)	0.035	0.099
TSER/*TS* 1494del6					
3R3R/del6/del6	101 (42.8)	65 (47.8)	1.000 (reference)		
3R3R/del6/ins6 + ins6/ins6	55 (23.3)	29 (21.3)	0.819 (0.474-1.416)	0.475	0.713
2R+/del6/del6	24 (10.2)	13 (9.6)	0.842 (0.400-1.770)	0.649	0.649
2R+/del6/ins6 + ins6/ins6	56 (23.7)	29 (21.3)	0.805 (0.466-1.389)	0.435	0.435

MTHFR, methylenetetrahydrofolate reductase; *TSER*, *TS* enhancer region; *TS*, thymidylate synthase; POF, premature ovarian failure; OR, odds ratio; FDR, false discovery rate.

Vascular endothelial growth factor gene polymorphisms in Korean patients with premature ovarian failure

Young Joo Jeon [a], Youngsok Choi [b], Sung Han Shim [b], Yi Seul Choi [a], Jung Jae Ko [a], Tae Ki Yoon [c], Sun Hee Cha [d], Nam Keun Kim [a,*]

Jeon YJ, et al.. Eur J Obstet Gynecol Reprod Biol. 2011

Table 1

Genotype frequencies of VEGF −2578C>A, −1154G>A, −634G>C, and 936C>T in premature ovarian failure (POF) patients and control subjects.

Characteristics	Controls (n=120)	POF patients (n=135)	OR (95% CI)	P[a]
VEGF −2578C>A				
CC	68 (56.7)	64 (47.4)	1.000 (Ref.)	
CA	45 (37.5)	63 (46.7)	1.488 (0.891–2.484)	0.128
AA	7 (5.8)	8 (5.9)	1.214 (0.416–3.542)	0.722
CA+AA	52 (43.3)	71 (52.6)	1.451 (0.885–2.379)	0.140
VEGF −1154G>A				
GG	90 (75.0)	86 (63.7)	1.000 (Ref.)	
GA	23 (19.2)	44 (32.6)	2.002 (1.116–3.592)	0.019
AA	7 (5.8)	5 (3.7)	0.746 (0.228–2.446)	0.629
GA+AA	30 (25.0)	49 (36.3)	1.709 (0.994–2.940)	0.052
VEGF −634G>C				
GG	38 (31.7)	39 (28.9)	1.000 (Ref.)	
GC	59 (49.2)	71 (52.6)	1.173 (0.667–2.063)	0.581
CC	23 (19.1)	25 (18.5)	1.059 (0.515–2.179)	0.876
GC+CC	82 (68.3)	96 (71.1)	1.141 (0.668–1.948)	0.630
VEGF 936C>T				
CC	87 (72.5)	89 (65.9)	1.000 (Ref.)	
CT	31 (25.8)	40 (29.6)	1.261 (0.724–2.196)	0.411
TT	2 (1.7)	6 (4.4)	2.933 (0.576–14.934)	0.280[b]
CT+TT	33 (27.5)	46 (34.1)	1.363 (0.797–2.329)	0.257

[a] Chi-square test.

[b] Fisher's exact test.

Table 3

Frequencies of VEGF −2578C>A, −1154G>A, −634G>C, and 936C>T haplotypes in patients with POF and in control subjects.

Characteristics	Overall (n=255)	Controls (n=120)	POF patients (n=135)	OR (95% CI)	P[a]
VEGF −2578/−1154/−634/936					
C-G-C-C	0.3974	0.4059	0.3907	0.922 (0.646–1.315)	0.654
C-G-G-C	0.2328	0.2747	0.1931	0.629 (0.416–0.952)	0.028
A-A-G-C	0.1263	0.1087	0.1477	1.431 (0.845–2.426)	0.181
A-G-G-C	0.0593	0.0450	0.0718	1.576 (0.734–3.383)	0.240
C-G-G-T	0.0454	0.0277	0.0620	2.237 (0.911–5.490)	0.072
A-G-G-T	0.0431	0.0654	0.0249	0.373 (0.151–0.922)	0.027
C-G-C-T	0.0407	0.0218	0.0575	2.961 (1.068–8.208)	0.029
A-A-G-T	0.0389	0.0214	0.0482	2.377 (0.835–6.770)	0.095
VEGF −2578/−1154/936					
C-G-T	0.0856	0.0505	0.1174	2.555 (1.284–5.082)	0.006
A-G-T	0.0433	0.0643	0.0264	0.399 (0.160–0.997)	0.042
VEGF −2578/−634/936					
C-G-C	0.2394	0.2828	0.1978	0.618 (0.410–0.932)	0.021
C-C-T	0.0408	0.0214	0.0578	2.961 (1.068–8.208)	0.029
VEGF −1154/−634/936					
G-C-T	0.0406	0.0212	0.0578	2.961 (1.068–8.208)	0.029
VEGF −2578/−1154					
A-A	0.1653	0.1312	0.1959	1.647 (1.017–2.667)	0.041
VEGF −2578/936					
C-C	0.6400	0.6936	0.5902	0.639 (0.443–0.921)	0.016
C-T	0.0894	0.0606	0.1172	2.017 (1.064–3.824)	0.029
VEGF −634/936					
C-T	0.0406	0.0215	0.0577	2.961 (1.068–8.028)	0.029

Note: Haplotypes for VEGF −2578/−1154/−634, −2578/−634, −1154/−634, and −1154/936 were not statistically significant (P>0.05).

[a] Permutation test. Overall haplotype frequencies below 0.03 were excluded. In cases where the expected value was <5, results were confirmed by Fisher's exact test.

Association of five common polymorphisms in the plasminogen activator inhibitor-1 gene with primary ovarian insufficiency

Young Joo Jeon, M.S.,[a] Young Ran Kim, M.D.,[b] Bo Eun Lee, M.S.,[a] Sun Hee Cha, M.D., Ph.D.,[b] Myoung-Jin Moon, M.D., Ph.D.,[b] Doyeun Oh, M.D., Ph.D.,[c] Woo Sik Lee, M.D., Ph.D.,[d] and Nam Keun Kim, Ph.D.[a]

Jeon et al. Fertil Steril 2014

TABLE 2

Genotype frequencies of *PAI-1* polymorphisms in POI patients and controls.

Characteristic	Controls (n = 227), n (%)	POI patients (n = 137), n (%)	OR (95% CI)	*P* value[a]	FDR-*P*
PAI-1 −844G>A					
GG	72 (31.7)	58 (42.3)	1.000 (reference)		
GA	120 (52.9)	58 (42.3)	0.600 (0.376–0.957)	.033	.083
AA	35 (15.4)	21 (15.3)	0.745 (0.392–1.416)	.420	.450
Dominant (GG vs. GA+AA)			0.633 (0.408–0.982)	.043	.108
Recessive (GG+GA vs. AA)			0.993 (0.551–1.788)	1.000	1.000
A allele frequency	0.419	0.365			
HWE *P*	.194	.310			
PAI-1 −675 4G/5G					
5G5G	39 (17.2)	32 (23.4)	1.000 (reference)		
4G5G	117 (51.5)	59 (43.1)	0.615 (0.350–1.079)	.109	.182
4G4G	71 (31.3)	46 (33.6)	0.790 (0.435–1.434)	.450	.450
Dominant (5G5G vs. 4G5G+4G4G)			0.681 (0.403–1.151)	.172	.215
Recessive (5G5G+4G5G vs. 4G4G)			1.111 (0.707–1.746)	.645	.806
4G allele frequency	0.570	0.551			
HWE *P*	.436	.129			
PAI-1 43G>A					
GG	193 (85.0)	120 (87.6)	1.000 (reference)		
GA	34 (15.0)	15 (10.9)	0.710 (0.371–1.358)	.343	.343
AA	0 (0.0)	2 (1.5)	8.029 (0.382–168.796)	.149	.328
Dominant (GG vs. GA+AA)			0.804 (0.430–1.503)	.536	.536
Recessive (GG+GA vs. AA)			8.395 (0.400–176.298)	.141	.353
A allele frequency	0.075	0.069			
HWE *P*	.223	.076			
PAI-1 9785G>A					
GG	218 (96.0)	111 (81.0)	1.000 (reference)		
GA	9 (4.0)	24 (17.5)	5.237 (2.354–11.652)	<.001	<.001
AA	0 (0.0)	2 (1.5)	9.798 (0.466–205.999)	.116	.328
Dominant (GG vs. GA+AA)			5.674 (2.570–12.525)	<.001	<.001
Recessive (GG+GA vs. AA)			8.395 (0.400–176.298)	.141	.353
A allele frequency	0.020	0.102			
HWE *P*	.761	.596			
PAI-1 11053T>G					
TT	65 (28.6)	50 (36.5)	1.000 (reference)		
TG	101 (44.5)	56 (40.9)	0.721 (0.440–1.180)	.210	.263
GG	61 (26.9)	31 (22.6)	0.661 (0.374–1.166)	.197	.328
Dominant (TT vs. TG+GG)			0.698 (0.444–1.097)	.131	.215
Recessive (TT+TG vs. GG)			0.796 (0.484–1.307)	.386	.643
G allele frequency	0.491	0.431			
HWE *P*	.098	.051			

Note: FDR-P = false-positive discovery rate-corrected; HWE = Hardy-Weinberg equilibrium.
[a] Fisher's exact test.

Jeon. PAI-1 and primary ovarian insufficiency. Fertil Steril 2014.

TABLE 3

Combination analysis of *PAI-1* polymorphisms in POI patients and controls.

Combined genotypes		Controls (n = 227), n (%)	POI patients (n = 137), n (%)	OR (95% CI)	*P* value[a]	FDR-*P*
−844G>A	9785G>A					
GG+GA	GG	184 (81.1)	94 (68.6)	1.000 (reference)		
GG+GA	GA+AA	8 (3.5)	22 (16.1)	5.383 (2.308–12.553)	<.001	<.001
AA	GG	34 (15.0)	17 (12.4)	0.979 (0.520–1.843)	1.000	1.000
AA	GA+AA	1 (0.4)	4 (2.9)	7.830 (0.862–71.082)	.050	.075
4G/5G	9785G>A					
5G5G+4G5G	GG	147 (64.8)	73 (53.3)	1.000 (reference)		
5G5G+4G5G	GA+AA	9 (4.0)	18 (13.1)	4.027 (1.725–9.405)	.001	.002
4G4G	GG	71 (31.3)	38 (27.7)	1.078 (0.664–1.748)	.805	.805
4G4G	GA+AA	0 (0.0)	8 (5.8)	34.116 (1.941–599.639)	<.001	.001
43G>A	9785G>A					
GG	GG	185 (81.5)	98 (71.5)	1.000 (reference)		
GG	GA+AA	8 (3.5)	22 (16.1)	5.191 (2.229–12.093)	<.001	<.001
GA+AA	GG	33 (14.5)	13 (9.5)	0.744 (0.374–1.478)	.502	.502
GA+AA	GA+AA	1 (0.4)	4 (2.9)	7.551 (0.832–68.523)	.055	.083
9785G>A	11053T>G					
GG	TT+TG	157 (69.2)	85 (62.0)	1.000 (reference)		
GG	GG	61 (26.9)	26 (19.0)	0.787 (0.464–1.337)	.428	.428
GA+AA	TT+TG	9 (4.0)	21 (15.3)	4.310 (1.890–9.829)	<.001	.002
GA+AA	GG	0 (0.0)	5 (3.6)	20.263 (1.106–371.122)	.006	.009

Note: Nonsignificant combinations are not presented.
[a] Fisher's exact test.

Jeon. PAI-1 and primary ovarian insufficiency. Fertil Steril 2014.

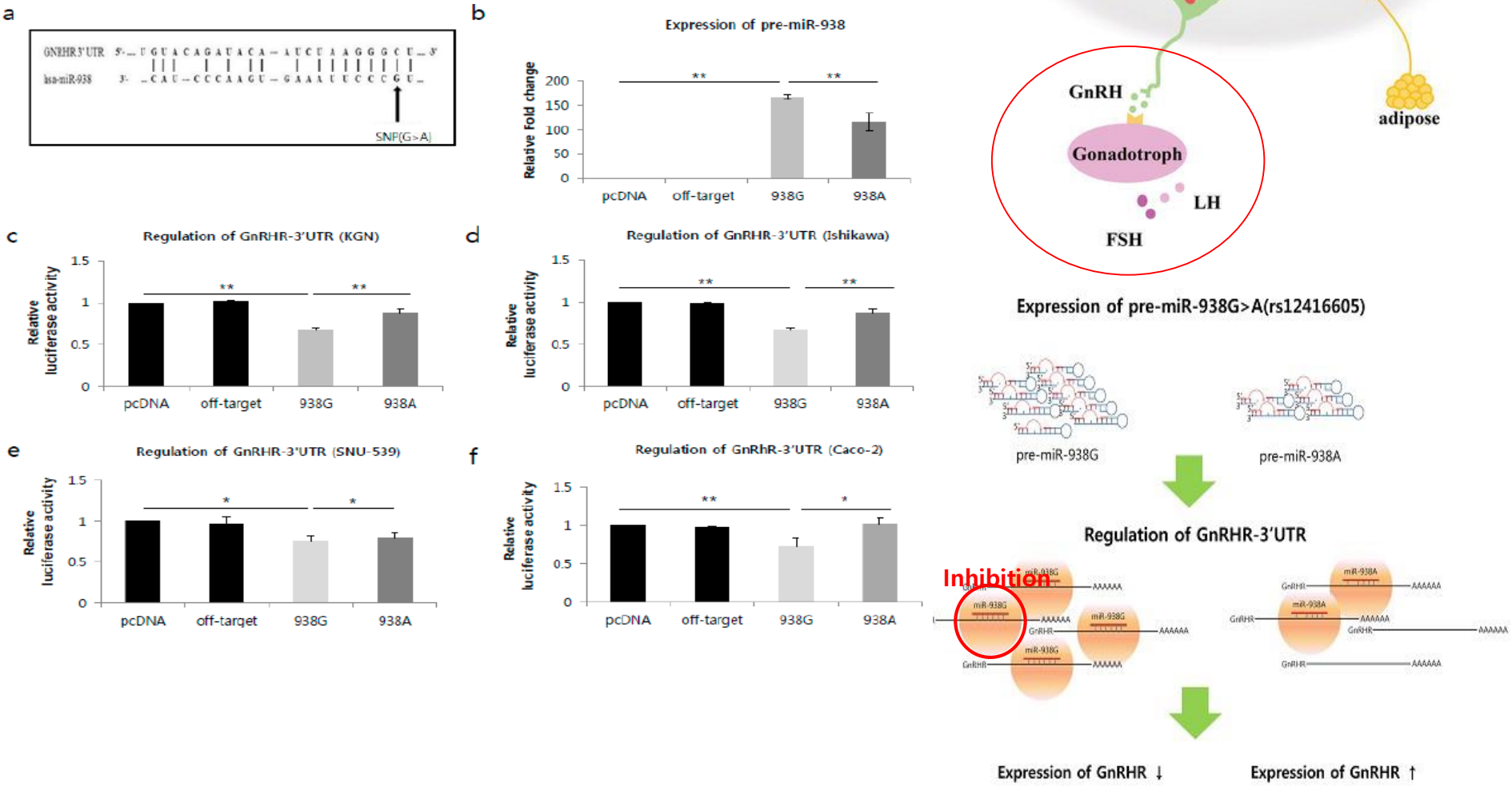
Haplotype analysis of *PAI-1* polymorphisms in POI patients and controls.

Haplotype	Controls (2n = 454), (n %)	POI patients (2n = 274), n (%)	OR (95% CI)	*P* value[a]	FDR-*P*
PAI-1 −675/9785					
5G-G	186 (41.0)	116 (42.3)	1.058 (0.780–1.434)	.756	.756
5G-A	9 (2.0)	7 (2.6)	1.296 (0.477–3.522)	.611	.756
4G-G	259 (57.0)	130 (47.4)	0.680 (0.503–0.919)	.014	.028
4G-A	0 (0.0)	21 (7.7)	77.095 (4.647–1278.942)	<.001	<.001

Article

Association of *miR-938*G>A Polymorphisms with Primary Ovarian Insufficiency (POI)-Related Gene Expression

Sung Hwan Cho [1,†], Eun Hee Ahn [2,†], Hui Jeong An [1], Ji Hyang Kim [2], Jung Jae Ko [1], Young Ran Kim [2], Woo Sik Lee [3] and Nam Keun Kim [1,*]



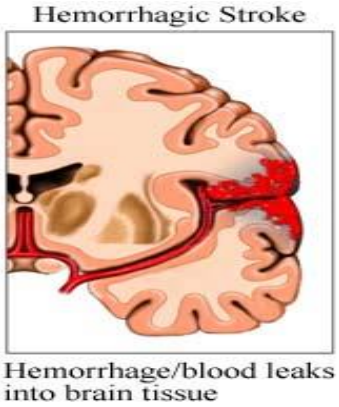
Cho SH, et al. Int J Mol Sci. 2017

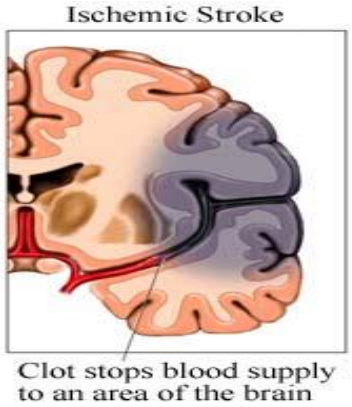
Ischemic stroke

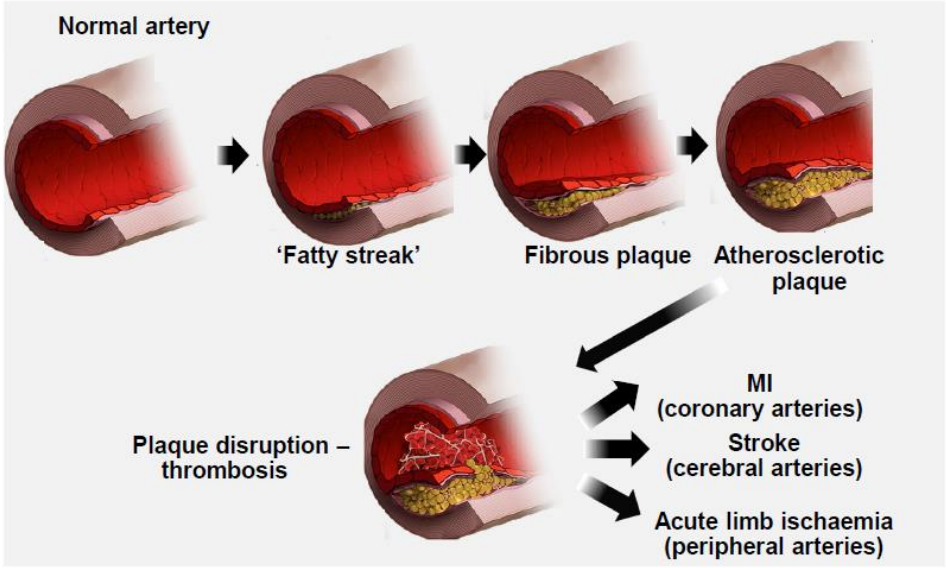
CHA 의과학대학교 CHA 차병원

Vascular rupture
: hemorrhagic stroke

Vascular occlusion
: ischemic stroke







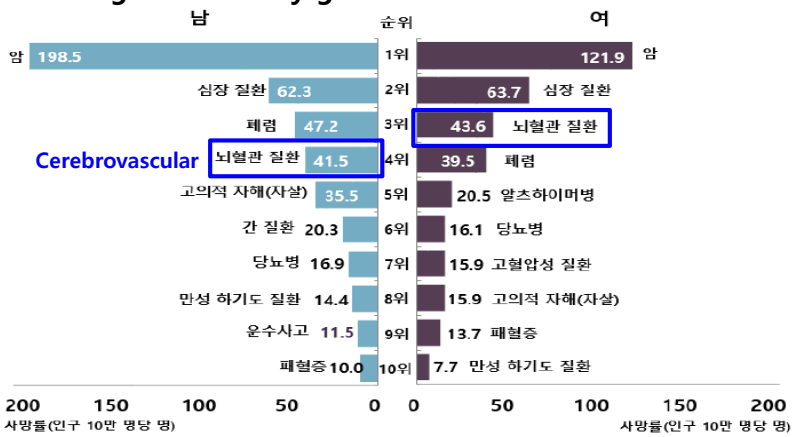
Insull W Jr, *Am J Med* 2009;122(1 Suppl):S3–S14; Bradberry JC *et al*, *J Am Pharm Assoc* 2004;44:S37–S45

Ranking of deaths in 2020

(단위: 인구 10만 명당 명)

순위	사망원인	사망률	'19년 순위 대비
1	악성신생물(암)	160.1	-
2	심장 질환	63.0	-
3	폐렴	43.3	-
4	뇌혈관 질환	42.6	-
5	고의적 자해(자살)	25.7	-
6	당뇨병	16.5	-
7	알츠하이머병	14.7	-
8	간 질환	13.6	-
9	고혈압성 질환	11.9	⬆(+1)
10	패혈증	11.9	⬆(+1)

Ranking of deaths by gender in 2020



CHA 의과학대학교 CHA 차병원

Homozygous C677T mutation in the MTHFR gene as an independent risk factor for multiple small-artery occlusions

B.O. Choi[a,1], N.K. Kim[b], S.H. Kim[b], M.S. Kang[b], S. Lee[b], J.Y. Ahn[b], O.J. Kim[a], S. Kim[b], D. Oh[b,*]

Table 3
Adjusted odds ratio assessment of the MTHFR 677TT genotype for subtypes of ischemic stroke compared to both no mutation, such as the CC (normal) genotype, and non-homozygous mutations including the CC and the CT (heterozygous) genotypes

MTHFR	Controls ($n=198$)	Total patients ($n=195$)	Large-artery* ($n=55$)	Small-artery** ($n=72$)	Cardioembolism ($n=41$)	Other etiology ($n=6$)	Unknown ($n=21$)
677 CC	73 (36.9)	62 (31.8)	20 (36.4)	20 (27.8)	12 (29.3)	2 (33.3)	8 (38.1)
677 CT	100 (50.5)	97 (49.7)	30 (54.5)	32 (44.4)	22 (53.6)	3 (50.0)	10 (47.6)
677 TT	25 (12.6)	36 (18.5)	5 (9.1)	20 (27.8)	7 (17.1)	1 (16.7)	3 (14.3)
AOR (CI),*** TT vs. CC	1.00	1.06 (0.49–2.29)	1.29 (0.31–5.34)	2.92 (1.01–8.48)	3.60 (0.80–16.26)	0.48 (0.02–11.35)	4.41 (0.63–31.04)
AOR (CI),*** TT vs. CC/CT	1.00	0.99 (0.53–1.86)	0.91 (0.28–2.97)	2.85 (1.24–6.54)	2.18 (0.73–6.57)	1.77 (0.16–20.26)	4.18 (0.80–21.76)

* Large-artery atherosclerosis.
** Small-artery occlusion.
*** Adjusted odds ratio and 95% confidence intervals, adjusted for age, sex, hypertension, diabetes mellitus, and smoking.

Choi B O. et al. Thromb Res. 2003

Gene–environment interactions between methylenetetrahydrofolate reductase (*MTHFR*) 677C>T and metabolic syndrome for the prevalence of ischemic stroke in Koreans

Ok Joon Kim[a,b,1], Seung Ho Hong[c,1], Young Joo Jeon[b], Seung Hun Oh[a], Hyun Sook Kim[a], Young Seok Park[d], Eo Jin Kim[e], Nam Keun Kim[b,*]

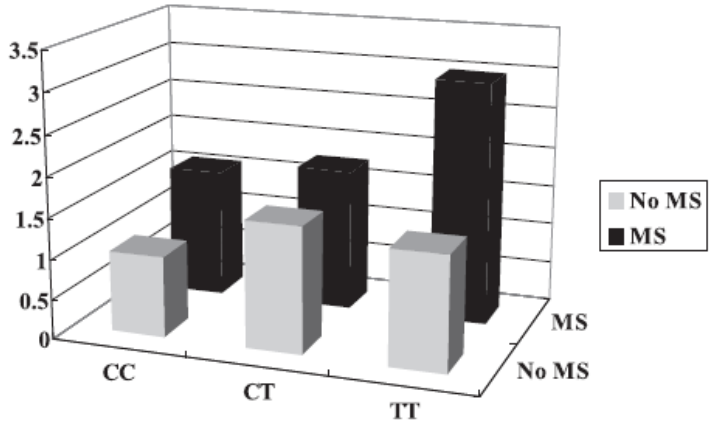
OJ Kim et al. Neurosci. Lett. 2012

Table 2
Prevalence of metabolic syndrome in ischemic stroke patients and controls and its association with ischemic stroke, including specific subtypes.

	Prevalence of metabolic syndrome (%)	COR (95% CI)	*P*	AOR[a] (95% CI)	*P*
Total stroke	243/404 (60.2)	1.415 (1.015–1.973)	0.040	1.420 (1.017–1.982)	0.040
SAO	79/123 (64.2)	1.683 (1.068–2.653)	0.024	1.707 (1.081–2.695)	0.022
LAO	103/160 (64.4)	1.694 (1.114–2.576)	0.013	1.661 (1.089–2.534)	0.019
CE	20/50 (40.0)	0.625 (0.334–1.168)	0.139	0.580 (0.306–1.101)	0.096
UD	41/71 (57.8)	1.281 (0.746–2.201)	0.369	1.281 (0.746–2.202)	0.370
Control	112/217 (51.6)				

Abbreviations: COR, crude odds ratio; CI, confidence interval; AOR, adjusted odds ratio; SAO, small artery occlusion; LAO, large artery occlusion; CE, cardioembolism; UD, undetermined causes.

[a] The adjusted odds ratio on the basis of risk factors, such as age and gender.



	CC	CT	TT
No MS	1.000 (reference)	1.559 (0.894 - 2.720)	1.418 (0.643 - 3.126)
MS	1.602 (0.885 - 2.902)	1.772 (1.053 - 2.983)	3.001 (1.487 - 6.057)

*The adjusted odds ratio on the basis of risk factors, such as age and gender.

Journal of Personalized Medicine

MDPI

Article

The 3′-UTR Polymorphisms in the Thymidylate Synthase (TS) Gene Associated with the Risk of Ischemic Stroke and Silent Brain Infarction

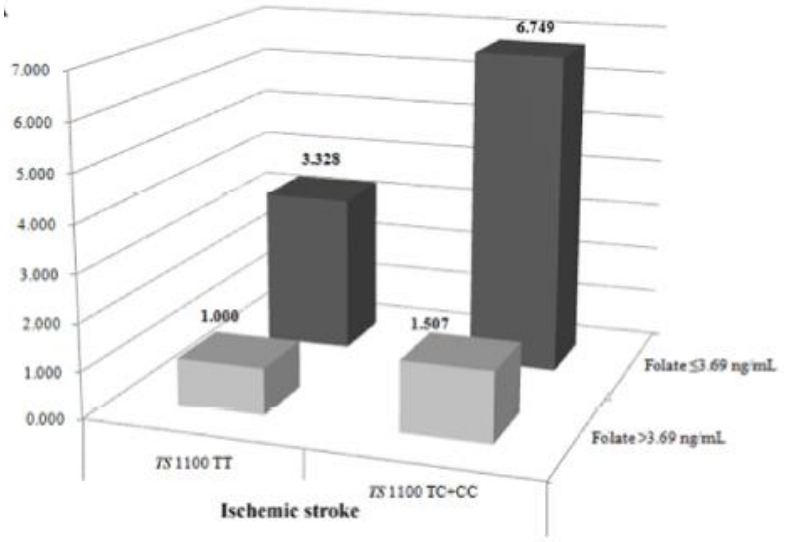
Jung Oh Kim [1,2], Han Sung Park [2], Eun Ju Ko [2], Jung Hoon Sung [3], Jinkwon Kim [3], Seung Hun Oh [3], Ok Joon Kim [3,*] and Nam Keun Kim [2,*]

JO Kim et al. J. Pers. Med. 2021

Table 2. Genotype frequencies of *TS* gene polymorphisms in control subjects, ischemic stroke patients, and silent brain infarction patients.

Genotypes	Controls (n = 409)	Stroke (n = 507)	AOR (95% CI) *	P †	P ‡	SBI (n = 383)	AOR (95% CI) *	P †	P ‡
TS 1100 T>C									
TT	218 (53.3)	215 (42.4)	1.000 (reference)			176 (45.9)			
TC	165 (40.3)	235 (46.4)	1.486 (1.115–1.980)	0.007	0.011	173 (45.2)	1.397 (0.961–2.031)	0.080	0.120
CC	26 (6.4)	57 (11.2)	2.151 (1.275–3.628)	0.004	0.006	34 (8.9)	1.740 (0.879–3.443)	0.112	0.168
TT vs. TC+CC			1.576 (1.197–2.074)	0.001	0.002		1.443 (1.009–2.063)	0.045	0.068
TT+TC vs. CC			1.758 (1.064–2.905)	0.028	0.042		1.489 (0.783–2.833)	0.225	0.338
HWE *P*	0.480	0.547				0.354			
TS 1170 A>G									
AA	190 (46.5)	320 (63.1)	1.000 (reference)			316 (82.5)			
AG	184 (45.0)	170 (33.5)	0.505 (0.377–0.676)	<0.0001	0.0003	61 (15.9)	0.198 (0.127–0.309)	<0.0001	0.0003
GG	35 (8.6)	17 (3.4)	0.284 (0.151–0.537)	<0.0001	0.0003	6 (1.6)	0.070 (0.016–0.298)	0.0002	0.0006
AA vs. AG+GG			0.472 (0.357–0.626)	<0.0001	0.0003		0.179 (0.117–0.276)	<0.0001	0.0003
AA +AG vs. GG			0.382 (0.206–0.710)	0.002	0.006		0.121 (0.029–0.514)	0.004	0.012
HWE *P*	0.306	0.331				0.135			
TS 1494 del>ins									
0bp0bp	197 (48.2)	232 (45.8)	1.000 (reference)			184 (48.0)			
0bp6bp	180 (44.0)	228 (45.0)	1.127 (0.847–1.500)	0.411	0.411	170 (44.4)	1.121 (0.774–1.623)	0.546	0.546
6bp6bp	32 (7.8)	47 (9.3)	1.256 (0.754 2.091)	0.381	0.381	29 (7.6)	1.124 (0.570–2.217)	0.736	0.736
0bp0bp vs. 0bp6bp+6bp6bp			1.147 (0.872–1.509)	0.326	0.326		1.122 (0.786–1.602)	0.527	0.527
0bp0bp +0bp6bp vs. 6bp6bp			1.302 (0.928–1.825)	0.506	0.506		1.040 (0.543–1.994)	0.905	0.905
HWE *P*	0.300	0.398				0.228			

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HWE, Hardy–Weinberg Equilibrium; SBI, silent brain infarction. Note; The 'reference' means that it is the standard for analysis by genotype in the table. * AORs were adjusted for these risk factors: age, gender, hypertension, diabetes mellitus, hyperlipidemia, and smoking. † *p*-value calculated by multivariable logistics regression. ‡ False discovery rate-adjusted *p*-value for multiple hypotheses testing using the Benjamini-Hochberg method.



Association of *miR-34a*, *miR-130a*, *miR-150* and *miR-155* polymorphisms with the risk of ischemic stroke

GUN HO CHOI[1*], KI HAN KO[1*], JUNG OH KIM[1], JINKWON KIM[2], SEUNG HUN OH[2], IN BO HA
KYUNG GI CHO[3], OK JOON KIM[2], JINKUN BAE[4] and NAM KEUN KIM[1]

Table II. Comparison of genotype frequencies of microRNA polymorphisms between ischemic stroke subtype and the controls.

Characteristics	Controls (n=404)	Stroke patients (n=596)	AOR (95% CI)[a]	P-value	P-value[b]	LAD (n=202)	AOR (95% CI)[a]	P-value	P-value[b]	SVD (n=143)	AOR (95% CI)[a]	P-value	P-value[b]	CE (n=57)	AOR (95% CI)[a]	P-value	P-value[b]
miR-34a																	
rs6577555C>A																	
CC	239 (59.2)	323 (54.2)	1.000 (reference)			107 (53.0)	1.000 (reference)			75 (52.4)	1.000 (reference)			34 (59.6)	1.000 (reference)		
CA	143 (35.4)	229 (38.4)	1.211 (0.915-1.603)	0.181	0.362	82 (40.6)	1.326 (0.911-1.930)	0.140	0.280	58 (40.6)	1.294 (0.852-1.967)	0.227	0.772	19 (33.3)	0.987 (0.537-1.813)	0.965	0.965
AA	22 (5.4)	44 (7.4)	1.384 (0.787-2.431)	0.259	0.389	13 (6.4)	1.347 (0.622-2.919)	0.450	0.675	10 (7.0)	1.244 (0.525-2.949)	0.621	0.621	4 (7.0)	1.432 (0.444-4.617)	0.548	0.822
Dominant			1.226 (0.938-1.602)	0.136	0.276		1.329 (0.927-1.905)	0.122	0.244		1.292 (0.864-1.932)	0.212	0.552		1.032 (0.581-1.834)	0.915	0.915
Recessive			1.252 (0.718-2.183)	0.429	0.562		1.192 (0.563-2.522)	0.646	0.969		1.123 (0.494-2.552)	0.782	0.782		1.277 (0.412-3.952)	0.672	0.672
miR-130a																	
rs731384C>T																	
CC	328 (81.2)	479 (80.4)	1.000 (reference)			162 (80.2)	1.000 (reference)			116 (81.1)	1.000 (reference)			45 (78.9)	1.000 (reference)		
CT	74 (18.3)	110 (18.5)	1.008 (0.715-1.420)	0.966	0.966	39 (19.3)	1.095 (0.696-1.723)	0.696	0.696	24 (16.8)	0.925 (0.545-1.570)	0.772	0.772	10 (17.5)	0.975 (0.465-2.044)	0.947	0.965
TT	2 (0.5)	7 (1.2)	1.611 (0.309-8.412)	0.572	0.572	1 (0.5)	1.079 (0.095-12.24)	0.951	0.951	3 (2.1)	4.006 (0.616-26.050)	0.146	0.219	2 (3.5)	6.229 (0.835-46.48)	0.074	0.222
Dominant			1.027 (0.733-1.439)	0.879	0.879		1.091 (0.696-1.709)	0.704	0.939		1.012 (0.608-1.686)	0.962	0.962		1.124 (0.562-2.248)	0.742	0.915
Recessive			1.630 (0.312-8.519)	0.562	0.562		0.961 (0.085-10.84)	0.974	0.974		3.907 (0.604-25.28)	0.153	0.230		5.919 (0.797-43.97)	0.082	0.246
miR-150																	
rs73056059G>A																	
GG	380 (94.1)	544 (91.3)	1.000 (reference)			181 (89.6)	1.000 (reference)			132 (92.3)	1.000 (reference)			48 (84.2)	1.000 (reference)		
GA	24 (5.9)	52 (8.7)	1.485 (0.881-2.504)	0.138	0.362	21 (10.4)	**1.922 (1.003-3.681)**	**0.049**	0.196	11 (7.7)	1.223 (0.558-2.683)	0.615	0.772	9 (15.8)	**2.996 (1.293-6.939)**	**0.011**	0.044
AA	0 (0.0)	0 (0.0)	N/A	N/A	N/A	0 (0.0)	N/A	N/A	N/A	0 (0.0)	N/A	N/A	N/A	0 (0.0)	N/A	N/A	N/A
Dominant			1.485 (0.881-2.504)	0.138	0.276		**1.922 (1.003-3.681)**	**0.049**	0.196		1.223 (0.558-2.683)	0.615	0.820		**2.996 (1.293-6.939)**	**0.011**	0.044
Recessive			N/A	N/A	N/A		N/A	N/A	N/A		N/A	N/A	N/A		N/A	N/A	N/A
miR-155																	
rs767649T>A																	
TT	117 (29.0)	167 (28.0)	1.000 (reference)			58 (28.7)	1.000 (reference)			46 (32.2)	1.000 (reference)			13 (22.8)	1.000 (reference)		
TA	191 (47.3)	311 (52.2)	1.141 (0.835-1.558)	0.409	0.545	105 (52.0)	1.168 (0.766-1.781)	0.472	0.629	69 (48.3)	0.873 (0.548-1.388)	0.565	0.772	34 (59.6)	1.508 (0.753-3.019)	0.246	0.492
AA	96 (23.8)	118 (19.8)	0.794 (0.546-1.155)	0.228	0.389	39 (19.3)	0.710 (0.420-1.200)	0.201	0.603	28 (19.6)	0.638 (0.360-1.131)	0.124	0.219	10 (17.5)	0.932 (0.385-2.258)	0.876	0.876
Dominant			1.024 (0.765-1.370)	0.876	0.879		1.006 (0.676-1.496)	0.977	0.977		0.786 (0.509-1.213)	0.276	0.552		1.280 (0.657-2.492)	0.468	0.915
Recessive			0.728 (0.529-1.002)	0.052	0.156		0.676 (0.435-1.050)	0.082	0.246		0.651 (0.395-1.074)	0.093	0.230		0.659 (0.317-1.368)	0.263	0.395

[a]Adjusted by age, gender, hypertension, diabetes mellitus, hyperlipidemia and smoking; [b]False discovery rate-adjusted P-value for multiple hypotheses testing using the Benjamini-Hochberg method. Values in bold font indicate statistical significance. AOR, adjusted odds ratio; 95% CI, 95% confidence interval; LAD, large-artery disease; SVD, small-vessel disease; CE, cardioembolism; N/A, not applicable.

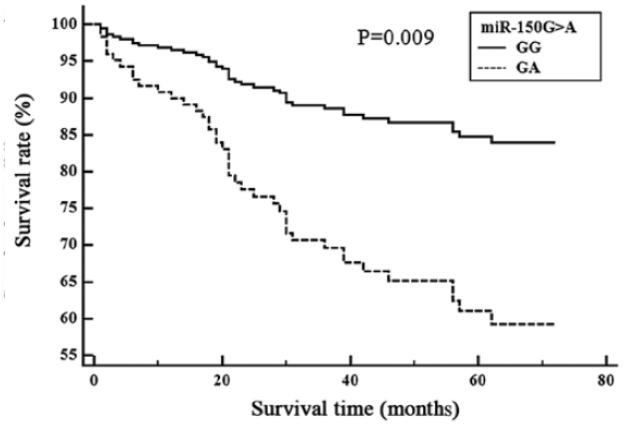


Figure 2. Cox proportional hazards regression of survival of patients with large-artery disease (LAD) according to *miR-150*G>A polymorphisms. Survival curves for the *miR-150*G>A polymorphism (GG vs. GA) (P=0.009).

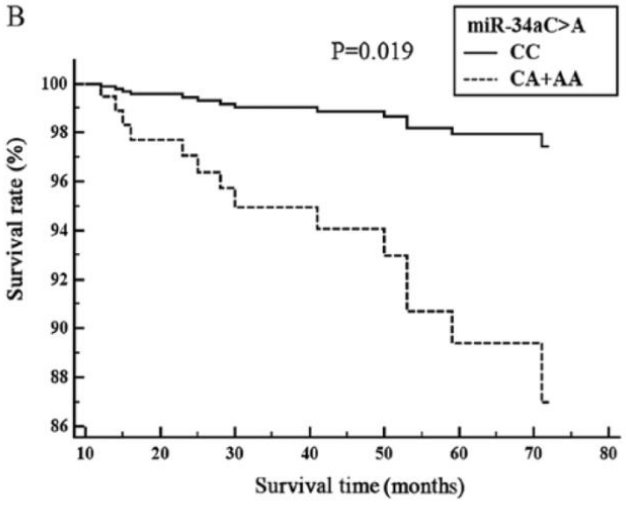


Figure 1. Cox proportional hazards regression of survival of patients with small-vessel disease (SVD) according to *miR-34a*C>A polymorphisms. (A) Survival curves for the *miR-34a*C>A polymorphism (CC vs. CA) (P=0.016). (B) Survival curves for the *miR-34a*C>A polymorphism (CC vs. CA+AA) (P=0.019).

Association of MicroRNA Biogenesis Genes Polymorphisms with Ischemic Stroke Susceptibility and Post-Stroke Mortality

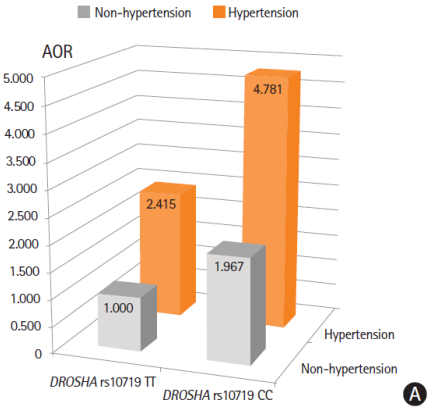
JO Kim et al. J. Stroke. 2018

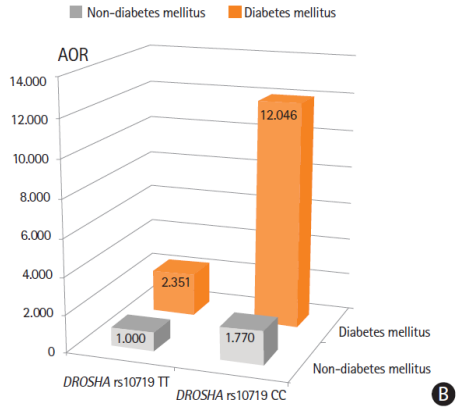
Jung Oh Kim,[a*] Jinkun Bae,[b*] Jinkwon Kim,[c] Seung Hun Oh,[c] Hui Jeong An,[a] In Bo Han,[d] Doyeun Oh,[e] Ok Joon Kim,[c] Nam Keun Kim[a]

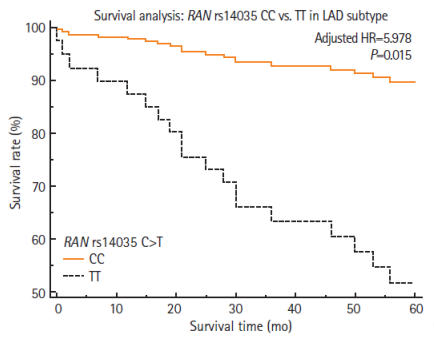
Table 2. Comparison of *DICER*, *DROSHA*, *RAN*, and *XPO5* polymorphisms between ischemic stroke patients and controls subjects

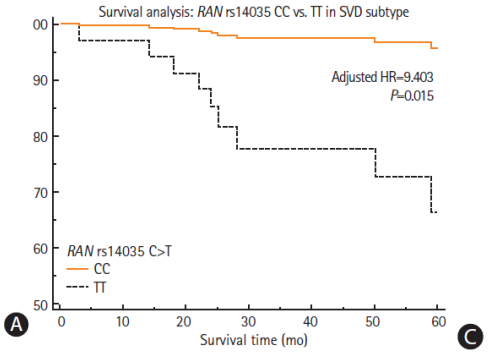
Genotype	Controls (n=403)	Cases (n=585)	COR (95% CI)	P*	P†	AOR (95% CI)‡	P§	P†
DICER rs13078 A>T								
AA	360 (89.3)	527 (90.1)	1.000 (reference)			1.000 (reference)		
AT	43 (10.7)	55 (9.4)	0.874 (0.574–1.331)	0.530	0.530	0.926 (0.596–1.439)	0.733	0.733
TT	0	3 (0.5)	NA			NA	0.994	0.994
Dominant (AA vs. AT+TT)			0.921 (0.608–1.398)	0.700	0.700	0.978 (0.633–1.511)	0.920	0.920
Recessive (AA+AT vs. TT)			NA			NA	0.994	0.994
HWE-*P*	0.258	0.238						
DICER rs3742330 A>G								
AA	148 (36.7)	169 (28.9)	1.000 (reference)			1.000 (reference)		
AG	180 (44.7)	280 (47.9)	1.362 (1.020–1.820)	0.036	0.129	1.313 (0.969–1.779)	0.079	0.237
GG	75 (18.6)	136 (23.2)	1.588 (1.110–2.272)	0.011	0.043	1.459 (1.000–2.126)	0.050	0.100
Dominant (AA vs. AG+GG)			1.429 (1.090–1.872)	0.010	0.057	1.360 (1.024–1.807)	0.034	0.102
Recessive (AA+AG vs. GG)			1.325 (0.966–1.817)	0.081	0.135	1.254 (0.902–1.745)	0.178	0.356
HWE-*P*	0.125	0.337						
DROSHA rs6877842 C>G								
CC	371 (92.1)	548 (93.7)	1.000 (reference)			1.000 (reference)		
CG	31 (7.7)	36 (6.2)	0.786 (0.478–1.294)	0.344	0.503	0.785 (0.467–1.320)	0.361	0.542
GG	1 (0.2)	1 (0.2)	0.677 (0.042–10.858)	0.783	0.783	0.769 (0.046–12.813)	0.855	0.994
Dominant (CC vs. CG+GG)			0.783 (0.479–1.279)	0.328	0.394	0.784 (0.470–1.309)	0.352	0.422
Recessive (CC+CG vs. GG)			0.688 (0.043–11.038)	0.792	0.792	0.766 (0.046–12.743)	0.852	0.994
HWE-*P*	0.680	0.614						
DROSHA rs10719 T>C								
TT	228 (56.6)	304 (52.0)	1.000 (reference)			1.000 (reference)		
TC	158 (39.2)	235 (40.2)	1.116 (0.856–1.454)	0.419	0.503	1.102 (0.835–1.455)	0.492	0.590
CC	17 (4.2)	46 (7.9)	2.029 (1.134–3.633)	0.017	0.043	2.038 (1.113–3.730)	0.021	0.994
Dominant (TT vs. TC+CC)			1.204 (0.933–1.554)	0.153	0.306	1.193 (0.913–1.558)	0.196	0.294
Recessive (TT+TC vs. CC)			1.938 (1.094–3.432)	0.023	0.115	2.001 (1.106–3.621)	0.022	0.132
HWE-*P*	0.107	0.950						
RAN rs14035 C>T								
CC	240 (59.6)	369 (63.1)	1.000 (reference)			1.000 (reference)		
CT	149 (37.0)	192 (32.8)	0.838 (0.641–1.097)	0.198	0.396	0.803 (0.606–1.064)	0.127	0.254
TT	14 (3.5)	24 (4.1)	1.115 (0.566–2.198)	0.753	0.783	1.106 (0.545–2.244)	0.780	0.994
Dominant (CC vs. CT+TT)			0.862 (0.664–1.118)	0.263	0.394	0.830 (0.632–1.091)	0.181	0.294
Recessive (CC+CT vs. TT)			1.189 (0.607–2.327)	0.614	0.768	1.198 (0.597–2.403)	0.611	0.917
HWE-*P*	0.114	0.876						
XPO5 rs11077 A>C								
AA	319 (79.2)	497 (85.0)	1.000 (reference)			1.000 (reference)		
AC	79 (19.6)	87 (14.9)	0.707 (0.505–0.989)	0.043	0.129	0.707 (0.497–1.005)	0.053	0.237
CC	5 (1.2)	1 (0.2)	0.128 (0.015–1.104)	0.062	0.103	0.101 (0.011–0.951)	0.045	0.100
Dominant (AA vs. AC+CC)			0.672 (0.483–0.936)	0.019	0.057	0.669 (0.473–0.945)	0.023	0.102
Recessive (AA+AC vs. CC)			0.136 (0.016–1.171)	0.069	0.135	0.116 (0.013–1.078)	0.058	0.174
HWE-*P*	0.965	0.161						

Values are presented as number (%).
RAN, Ran GTPase; XPO5, exportin 5; COR, crude odds ratio; CI, confidence interval; AOR, adjusted odds ratio; NA, not available; HWE, Hardy-Weinberg equilibrium.
*Calculated by chi-square test according to genotype frequencies; †*P*-value calculated by false discovery rate test; ‡Odds ratios adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, and smoking status; §*P*-value calculated by logistics regression analysis.

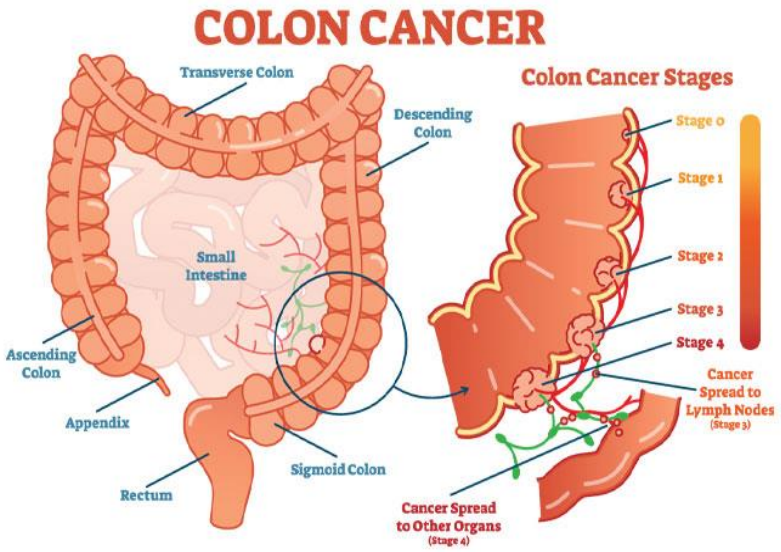








What is colorectal cancer?



Three elements

- T= tumor
  - how large is the tumor?
- N= node
  - Are cancer cells in the lymph nodes?
- M= metastases
  - Has the cancer spread to other organs?

Table. Colon and Rectum Cancer Staging[a]

AJCC Stage	TNM Stage	Description
0	Tis N0 M0	Tumor is confined to mucosa
I	T1 N0 M0	Tumor invades submucosa
I	T2 N0 M0	Tumor invades muscularis propria
IIA	T3 N0 M0	Tumor invades subserosa or beyond, no other organs involved
IIB	T4 N0 M0	Tumor invades adjacent organs or perforates visceral peritoneum
IIIA	T1-2 N1 M0	Metastasis to 1-3 regional lymph nodes with tumor invasion of submucosa and/or muscularis
IIIB	T3-4 N1 M0	Metastasis to 1-3 regional lymph nodes with tumor invasion of subserosa or adjacent organs
IIIC	Any T, N2 M0	Metastasis to 4 or more lymph nodes
IV	Any T, any N, M1	Metastasis to distant organs

Abbreviations: AJCC, American Joint Committee on Cancer; Tis, tumor (carcinoma) in situ.

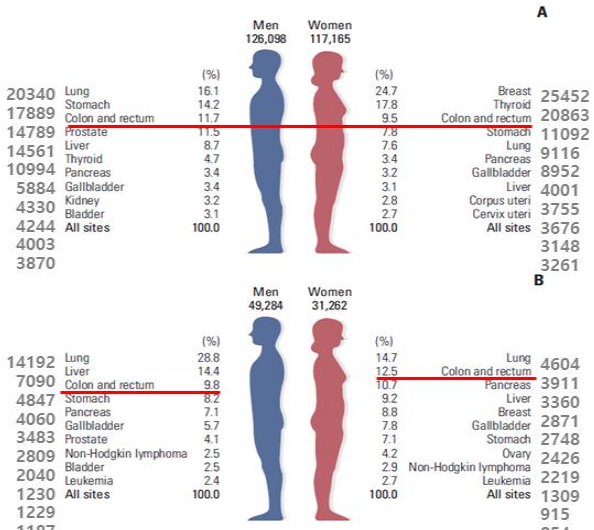


Fig. 1. The 10 leading types of estimated new cancer cases and deaths by sex in 2020. (A) Estimated new cases. (B) Estimated deaths.

Jung KW, et al. Cancer Res Treat. 2020

https://www.mountelizabeth.com.sg/healthplus/article/super-foods-colon-cancer

Polymorphisms in genes involved in folate metabolism and plasma DNA methylation in colorectal cancer patients

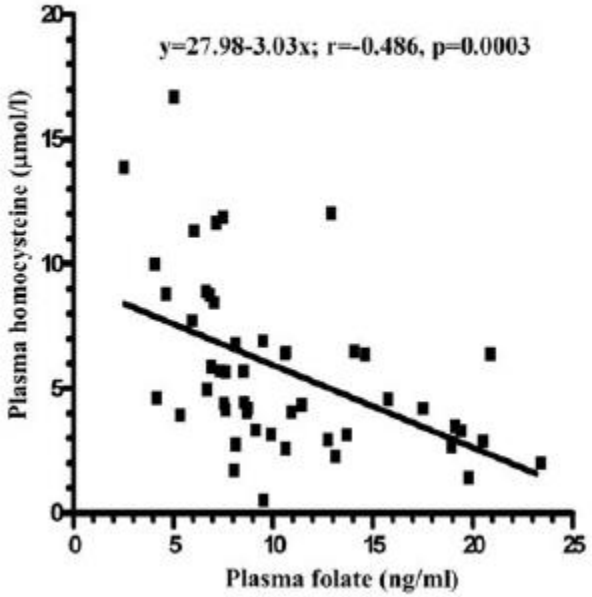
JONG WOO KIM[1*], HYE MI PARK[2*], YOUNG-KOOK CHOI[2*], SO YOUNG CHONG[3], DOYEUN OH[2,3] and NAM KEUN KIM[2,3]

JW Kim et al. Oncol. Rep. 2011

Table II. Genotype distribution of *MTHFR* 677C→T, 1298A→C, *MTR* 2756A→G polymorphisms in colorectal cancer patients.

Genotype	Control (%)	Cases (%)	OR (95% CI)	P-value
MTHFR 677				
CC	15 (28.3)	30 (44.8)	1.000 (Reference)	
CT	21 (39.6)	30 (44.8)	0.714 (0.310-1.645)	0.527
TT	17 (32.1)	7 (10.4)	0.206 (0.070-0.604)	0.005
MTHFR 1298				
AA	36 (67.9)	44 (65.7)	1.000 (Reference)	
AC	16 (30.2)	22 (32.8)	1.125 (0.516-2.455)	0.844
CC	1 (1.9)	1 (1.5)	0.818 (0.050-13.55)	1.000
MTR 2756				
AA	42 (79.2)	51 (76.1)	1.000 (Reference)	
AG	9 (17.0)	16 (23.9)	1.464 (0.587-3.469)	0.498
GG	2 (3.8)	0 (0.0)	0.165 (0.007-3.535)	0.212

A



Genetic variants in 3′-UTRs of methylenetetrahydrofolate reductase (*MTHFR*) predict colorectal cancer susceptibility in Koreans

Young Joo Jeon[1,*], Jong Woo Kim[2,*], Hye Mi Park[1], Jung O Kim[1], Hyo Geun Jang[1], Jisu Oh[3], Seong Gyu Hwang[3], Sung Won Kwon[2], Doyeun Oh[3] & Nam Keun Kim[1]

YJ Jeon et al. Sci Rep. 20.15

Characteristics	Control (n=400)	CRC (n=450)	AOR (95% CI)	*P*	*FDR-P*
MTHFR 2572C>A					
CC	278 (69.5)	276 (61.3)	1.00 (ref)		
CA	113 (28.3)	157 (34.9)	1.44 (1.05–1.98)	0.022	0.029
AA	9 (2.3)	17 (3.8)	2.03 (0.85–4.86)	0.110	0.348
Dominant			1.49 (1.10–2.03)	0.010	0.013
Recessive			1.87 (0.77–4.51)	0.166	0.348
HWE *P*	0.529	0.357			
MTHFR 4869C>G					
CC	360 (90.0)	365 (81.1)	1.00 (ref)		
CG	40 (10.0)	83 (18.4)	2.12 (1.37–3.26)	<.001	0.002
GG	0 (0.0)	2 (0.4)	NA	>.999	0.999
Dominant			2.17 (1.41–3.33)	<.001	0.001
Recessive			NA	>.999	>.999
HWE *P*	0.293	0.234			
MTHFR 5488C>T					
CC	340 (85.0)	352 (78.2)	1.00 (ref)		
CT	59 (14.8)	96 (21.3)	1.64 (1.12–2.41)	0.011	0.022
TT	1 (0.3)	2 (0.4)	2.54 (0.19–34.43)	0.483	0.644
Dominant			1.66 (1.13–2.42)	0.010	0.013
Recessive			2.40 (0.17–33.05)	0.514	0.685
HWE *P*	0.347	0.090			
MTHFR 6685T>C					
TT	319 (79.8)	361 (80.2)	1.00 (ref)		
TC	79 (19.8)	82 (18.2)	0.95 (0.65–1.37)	0.767	0.767
CC	2 (0.5)	7 (1.6)	3.12 (0.61–16.07)	0.174	0.348
Dominant			1.00 (0.70–1.44)	0.999	0.999
Recessive			3.13 (0.60–16.24)	0.174	0.348
HWE *P*	0.215	0.352			

	≥5.77 ng/mL of folate		<5.77 ng/mL of folate		
	AOR(95% CI)	*P*	AOR(95% CI)	*P*	$RERI_{OR}$(95% CI)
MTHFR 2572CC	1.00 (ref)		1.49 (0.95–2.32)	0.079	
MTHFR 2572CA + AA	1.13 (0.72–1.75)	0.597	3.74 (2.04–6.87)	<0.001	2.12 (1.37–3.80)
MTHFR 4869CC	1.00 (ref)		1.84 (1.25–2.73)	0.002	
MTHFR 4869CG + GG	1.97 (1.08–3.59)	0.027	4.41 (1.71–11.35)	0.002	1.60 (0.38–6.03)
MTHFR 5488CC	1.00 (ref)		1.72 (1.16–2.54)	0.007	
MTHFR 5488CT + TT	1.34 (0.79–2.27)	0.286	4.40 (1.74–11.11)	0.002	2.34 (0.79–7.30)
MTHFR 6685TT	1.00 (ref)		1.44 (0.97–2.16)	0.074	
MTHFR 6685TC + CC	0.67 (0.38–1.17)	0.160	3.31 (1.60–6.86)	0.001	2.20 (1.25–4.53)

Association of *VEGF* and *KDR* Single Nucleotide Polymorphisms With Colorectal Cancer Susceptibility in Koreans

Moon Ju Jang,[1] Young Joo Jeon,[2] Jong Woo Kim,[3] Yun Kyung Cho,[4] Seung Ku Lee,[5] Seong Gyu Hwang,[1,2] Doyeun Oh,[1,2] and Nam Keun Kim[2]*

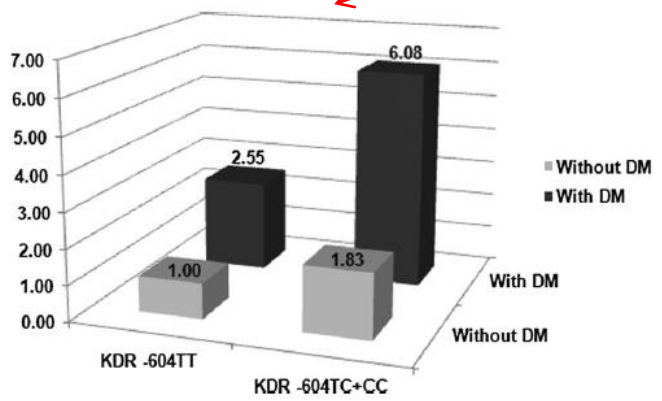
MJ Jang et al. Mol. Carcinog. 2013

Table 2. Genotype Frequencies of *VEGF* and *KDR* Polymorphisms Between Control and CRC Patients

Genotypes	Controls (n = 492)	CRC patients (n = 390)	OR (95% CI)[a]	AOR (95% CI)[b]	P[c]	P[d]
VEGF −2578C > A						
CC	260 (52.8)	217 (55.6)	1.00 (reference)	1.00 (reference)		
CA	201 (40.9)	148 (37.9)	0.88 (0.67–1.17)	0.88 (0.66–1.18)	0.394	0.591
AA	31 (6.3)	25 (6.4)	0.97 (0.55–1.69)	1.06 (0.59–1.90)	0.840	0.855
Dominant (CC vs. CA + AA)			0.89 (0.68–1.17)	0.91 (0.69–1.20)	0.491	0.737
Recessive (CC + CA vs. AA)			1.02 (0.59–1.76)	1.15 (0.65–2.02)	0.629	0.922
VEGF −1154G > A						
GG	349 (70.9)	279 (71.5)	1.00 (reference)	1.00 (reference)		
GA	130 (26.4)	98 (25.1)	0.94 (0.69–1.28)	0.99 (0.72–1.35)	0.927	0.927
AA	13 (2.6)	13 (3.3)	1.25 (0.57–2.74)	1.48 (0.66–3.32)	0.342	0.820
Dominant (GG vs. GA + AA)			0.97 (0.72–1.30)	1.03 (0.76–1.40)	0.852	0.852
Recessive (GG + GA vs. AA)			1.27 (0.58–2.77)	1.52 (0.68–3.40)	0.306	0.918
VEGF −634G > C						
GG	151 (30.7)	122 (31.3)	1.00 (reference)	1.00 (reference)		
GC	246 (50.0)	201 (51.5)	1.01 (0.75–1.37)	0.97 (0.71–1.33)	0.848	0.927
CC	95 (19.3)	67 (17.2)	0.87 (0.59–1.29)	0.84 (0.56–1.27)	0.410	0.820
Dominant (GG vs. GC + CC)			0.97 (0.73–1.30)	0.94 (0.70–1.27)	0.679	0.815
Recessive (GG + GC vs. CC)			0.87 (0.61–1.22)	0.88 (0.61–1.25)	0.468	0.922
VEGF 936C > T						
CC	349 (70.9)	244 (62.6)	1.00 (reference)	1.00 (reference)		
CT	130 (26.4)	135 (34.6)	1.49 (1.11–1.99)	1.38 (1.02–1.86)	0.039	0.080
TT	13 (2.6)	11 (2.8)	1.21 (0.53–2.75)	1.15 (0.49–2.73)	0.751	0.855
Dominant (CC vs. CT + TT)			1.46 (1.11–1.94)	1.36 (1.01–1.82)	0.040	0.084
Recessive (CC + CT vs. TT)			1.07 (0.47–2.41)	1.06 (0.45–2.47)	0.898	0.922
KDR −604T > C						
TT	312 (63.4)	185 (47.4)	1.00 (reference)	1.00 (reference)		
TC	151 (30.7)	173 (44.4)	1.93 (1.45–2.57)	1.96 (1.46–2.63)	<0.0001	0.000
CC	29 (5.9)	32 (8.2)	1.86 (1.09–3.18)	2.00 (1.15–3.47)	0.014	0.084
Dominant (TT vs. TC + CC)			1.92 (1.47–2.52)	1.96 (1.48–2.60)	<0.0001	0.000
Recessive (TT + TC vs. CC)			1.43 (0.85–2.40)	1.51 (0.88–2.59)	0.133	0.798
KDR 1192G > A						
GG	396 (80.5)	291 (74.6)	1.00 (reference)	1.00 (reference)		
GA	92 (18.7)	96 (24.6)	1.42 (1.03–1.96)	1.42 (1.02–1.99)	0.040	0.080
AA	4 (0.8)	3 (0.8)	1.02 (0.23–4.60)	1.16 (0.24–5.50)	0.855	0.855
Dominant (GG vs. GA + AA)			1.40 (1.02–1.93)	1.41 (1.01–1.96)	0.042	0.084
Recessive (GG + GA vs. AA)			0.95 (0.21–4.25)	1.08 (0.23–5.16)	0.922	0.922

Table 6. Colorectal Cancer Risk by Combined Gene-Environmental Effects

	Without HTN	With HTN	Without DM	With DM
Genotypes	AOR (95% CI)[a]	AOR (95% CI)[a]	AOR (95% CI)[a]	AOR (95% CI)[a]
VEGF −2578CC	1.00 (reference)	1.84 (1.24–2.75)	1.00 (reference)	2.94 (1.85–4.68)
VEGF −2578CA + AA	0.91 (0.60–1.38)	1.61 (1.06–2.45)	0.93 (0.68–1.27)	2.44 (1.52–3.94)
VEGF −1154GG	1.00 (reference)	1.94 (1.37–2.74)	1.00 (reference)	2.31 (1.56–3.41)
VEGF −1154GA + AA	1.23 (0.78–1.92)	1.83 (1.15–2.90)	0.91 (0.65–1.29)	3.96 (2.09–7.49)
VEGF −634GG	1.00 (reference)	1.99 (1.19–3.33)	1.00 (reference)	2.37 (1.28–4.39)
VEGF −634GC + CC	0.93 (0.59–1.45)	1.64 (1.06–2.53)	0.88 (0.63–1.24)	2.56 (1.62–4.06)
VEGF 936CC	1.00 (reference)	1.82 (1.27–2.61)	1.00 (reference)	3.43 (2.23–5.28)
VEGF 936CT + TT	1.53 (0.98–2.40)	2.61 (1.69–4.04)	1.61 (1.15–2.25)	2.86 (1.73–4.74)
KDR −604TT	1.00 (reference)	1.46 (0.98–2.16)	1.00 (reference)	2.55 (1.64–3.97)
KDR −604TC + CC	1.51 (0.99–2.30)	3.63 (2.37–5.55)	1.83 (1.33–2.52)	6.08 (3.55–10.41)
KDR 1192GG	1.00 (reference)	1.63 (1.18–2.26)	1.00 (reference)	2.60 (1.79–3.79)
KDR 1192GA + AA	1.19 (0.71–1.99)	2.63 (1.62–4.27)	1.34 (0.92–1.95)	4.24 (2.07–8.70)



Association between Five Common Plasminogen Activator Inhibitor-1 (*PAI-1*) Gene Polymorphisms and Colorectal Cancer Susceptibility

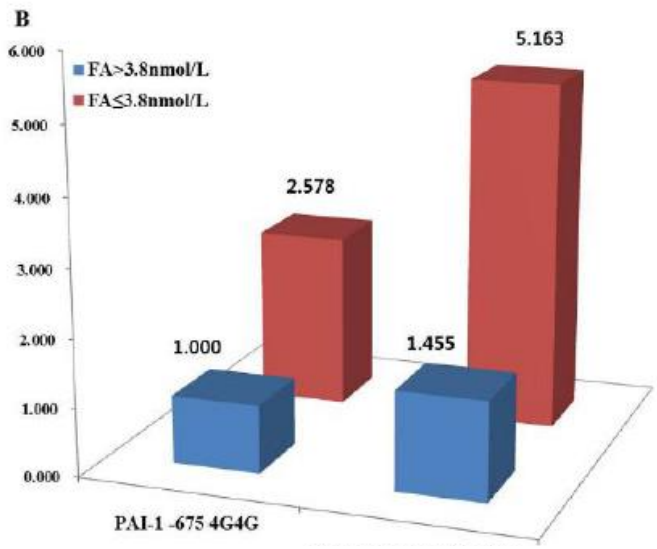
Jisu Oh [1,†], Hui Jeong An [2,†], Jung Oh Kim [2], Hak Hoon Jun [3], Woo Ram Kim [3], Eo Jin Kim [4], Doyeun Oh [1], Jong Woo Kim [3,*] and Nam Keun Kim [2,*]

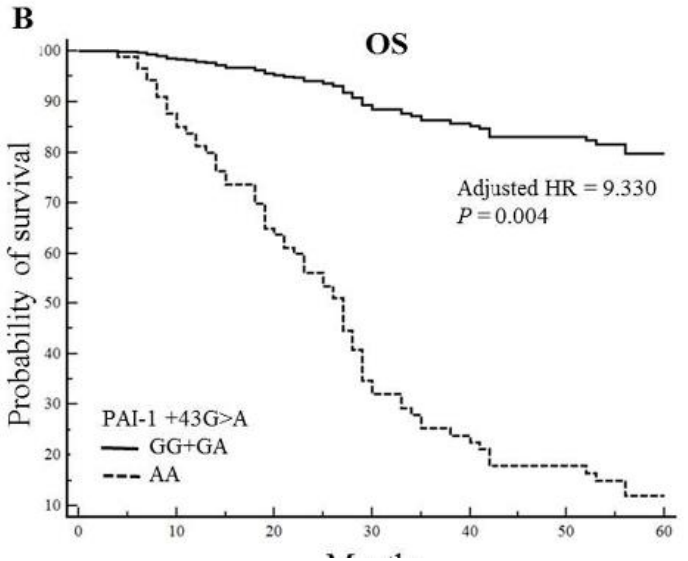
JS Oh et al. Oncol. Rep. 2014

Table 2. Comparison of the genotype frequencies and AOR (adjusted odds ratio) values of *PAI-1* gene polymorphisms between the colorectal cancer and control subjects.

Genotype	Controls (n = 416)	CRC Patients (n = 459)	AOR (95% CI) *	p [a]	p [b]
PAI-1 -844G > A					
GG	136 (32.7)	154 (33.6)	1.000 (reference)		
GA	199 (47.8)	230 (50.1)	1.000 (0.730–1.370)	1.00	1.00
AA	81 (19.5)	75 (16.3)	0.779 (0.508–1.195)	0.25	0.42
Dominant (GG vs. GA + AA)			0.937 (0.695–1.262)	0.67	0.83
Recessive (GG + GA vs. AA)			0.806 (0.559–1.164)	0.25	0.42
HWE-*P*	0.592	0.415			
PAI-1-675 4G > 5G					
4G4G	180 (43.3)	171 (37.3)	1.000 (reference)		
4G5G	180 (43.3)	206 (44.9)	1.212 (0.890–1.651)	0.22	1.00
5G5G	56 (13.5)	82 (17.9)	1.556 (1.012–2.391)	0.04	0.11
Dominant (4G4G vs. 4G5G + 5G5G)			1.284 (0.963–1.714)	0.09	0.45
Recessive (4G4G + 4G5G vs. 5G5G)			1.385 (0.938–2.044)	0.10	0.26
HWE-*P*	0.306	0.128			
PAI-1 +43G > A					
GG	335 (80.5)	375 (81.7)	1.000 (reference)		
GA	75 (18.0)	70 (15.3)	0.890 (0.612–1.296)	0.54	1.00
AA	6 (1.4)	14 (3.1)	0.647 (0.155–2.694)	0.55	0.69
Dominant (GG vs. GA + AA)			0.875 (0.606–1.261)	0.47	0.79
Recessive (GG + GA vs. AA)			0.670 (0.161–2.779)	0.58	0.73
HWE-*P*	0.447	0.851			
PAI-1 +9785G > A					
GG	383 (92.1)	417 (90.8)	1.000 (reference)		
GA	31 (7.5)	42 (9.2)	1.079 (0.629–1.849)	0.78	1.00
AA	2 (0.5)	0 (0.0)	N/A	1.00	1.00
Dominant (GG vs. GA + AA)			1.000 (0.588–1.700)	1.00	1.00
Recessive (GG + GA vs. AA)			N/A	1.00	1.00
HWE-*P*	0.124	0.329			
PAI-1 +11053T > G					
TT	107 (25.7)	133 (29.0)	1.000 (reference)		
TG	204 (49.0)	241 (52.5)	0.966 (0.692–1.349)	0.84	1.00
GG	105 (25.2)	85 (18.5)	0.620 (0.413–0.932)	**0.02**	0.11
Dominant (TT vs. TG + GG)			0.850 (0.620–1.165)	0.31	0.78
Recessive (TT + TG vs. GG)			0.662 (0.469–0.933)	**0.02**	0.10
HWE-*P*	0.695	0.200			

* The adjusted odds ratio on the basis of risk factors, such as age, gender, hypertension, and diabetes mellitus.
[a] p-value calculated by multiple logistics regression analysis. [b] False-positive discovery rate (FDR)-adjusted p-value.





Genetic associations between the miRNA polymorphisms miR-130b (rs373001), miR-200b (rs7549819), and miR-495 (rs2281611) and colorectal cancer susceptibility

Eun-Gyo Kim[1], Jung Oh Kim[1], Han Sung Park[1], Chang Soo Ryu[1], Jisu Oh[2], Hak Hoon Jun[3], Jong Woo Kim[3*] and Nam Keun Kim[1*]

EG Kim et al. BMC Cancer (2019)

Table 1 Baseline characteristics between controls and CRC patients

Characteristic	Controls (n = 399)	CRC Patients (n = 472)	P	Colon cancer (n = 268)	P	Rectal cancer (n = 193)	P
Age (years, mean ± SD)	61.15 ± 10.93	61.99 ± 12.32	0.129	61.44 ± 12.88	0.464	62.28 ± 11.54	0.153
Male (%)	173 (43.4)	212 (44.9)	0.645	118 (44.0)	0.915	88 (45.6)	0.750
Hypertension (%)	155 (38.8)	281 (59.5)	< 0.0001	157 (58.6)	0.003	117 (60.6)	0.003
HDL-C (mg/dL, mean ± SD)	45.91 ± 13.48	42.18 ± 13.05	0.001	42.82 ± 13.00	0.013	41.27 ± 13.07	0.001
LDL-C (mg/dL, mean ± SD)	115.87 ± 40.28	101.31 ± 28.62	0.003	98.55 ± 28.01	0.002	104.32 ± 29.54	0.142
Diabetes mellitus (%)	52 (13.0)	156 (33.1)	< 0.0001	92 (34.3)	< 0.0001	64 (33.2)	< 0.0001
Smoking (%)	138 (34.6)	92 (19.5)	< 0.0001	55 (20.5)	0.003	35 (18.1)	0.002
Folate (nmol/L, mean ± SD)	8.64 ± 6.13	7.94 ± 7.13	< 0.0001	8.12 ± 7.36	0.001	7.70 ± 6.86	0.000
Triglyceride (mg/dL, mean ± SD)	146.79 ± 89.33	129.00 ± 86.30	0.0003	126.93 ± 84.48	0.001	132.48 ± 90.86	0.015
Homocysteine (μmol/L, mean ± SD)	9.96 ± 4.27	10.68 ± 7.83	0.671	10.47 ± 8.21	0.572	10.88 ± 7.32	0.215
Total cholesterol (mg/dL, mean ± SD)	192.00 ± 37.32	178.76 ± 40.56	0.0001	178.73 ± 38.88	0.001	176.69 ± 42.89	0.002

Table 5 Multivariate survival analysis of polymorphisms in CRC patients

Genotype	CRC(n = 472)	Death(n = 85)	Adjusted HR[a](95% CI)	P
miR-130b rs373001T > C				
TT	269 (57.0)	47 (55.3)	1.000 (reference)	
TC	168 (35.6)	29 (34.1)	0.810 (0.491–1.338)	0.411
CC	35 (7.4)	9 (10.6)	1.345 (0.632–2.864)	0.442
Dominant (TT vs TC + CC)			0.910 (0.575–1.438)	0.685
Recessive (TT + TC vs CC)			1.435 (0.688–2.990)	0.336
miR-200b rs7549819T > C				
TT	216 (45.7)	48 (56.5)	1.000 (reference)	
TC	200 (42.4)	26 (30.6)	0.522 (0.307–0.888)	0.017
CC	56 (11.9)	11 (12.9)	0.781 (0.393–1.555)	0.482
Dominant (TT vs TC + CC)			0.592 (0.373–0.940)	0.026
Recessive (TT + TC vs CC)			0.994 (0.509–1.944)	0.987
miR-495 rs2281611A > C				
AA	125 (26.5)	23 (27.1)	1.000 (reference)	
AC	222 (47.0)	37 (43.5)	1.077 (0.618–1.879)	0.794
CC	125 (26.5)	25 (29.4)	1.167 (0.628–2.170)	0.625
Dominant (AA vs AC + CC)			1.126 (0.672–1.886)	0.652
Recessive (AA+AC vs CC)			1.147 (0.691–1.903)	0.595

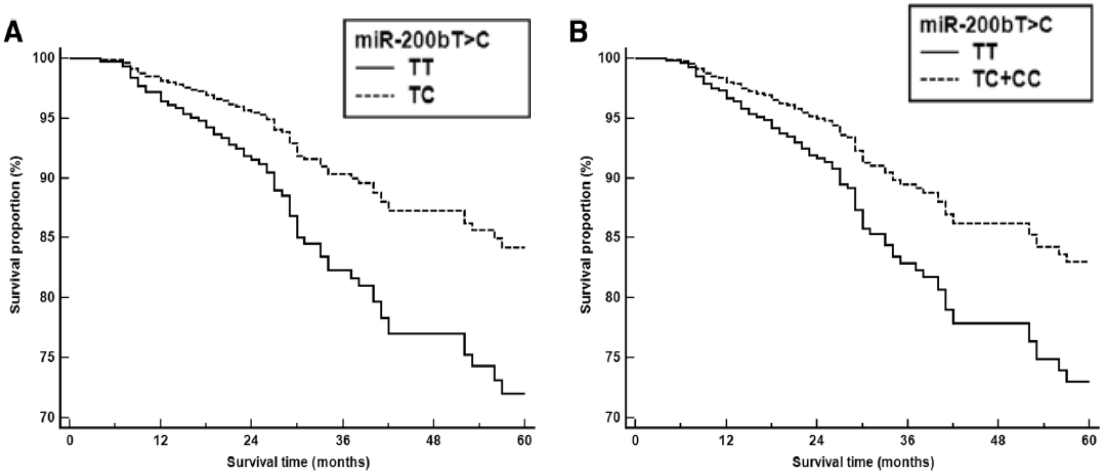


Fig. 2 Survival curves depicting the relationship between the *miR-200b*T > C polymorphism and CRC patients. Cox proportional-hazards regression model of CRC patient survival. Patients carrying the *miR-200b* (A) TC and (B) TC + CC genotypes had a reduced risk of death when compared with the TT genotype (P = 0.017 and P = 0.026, respectively)

Genetic Variants of *HOTAIR* Associated With Colorectal Cancer Susceptibility and Mortality

Jung Oh Kim[1†], Hak Hoon Jun[2†], Eo Jin Kim[3†], Jeong Yong Lee[1], Han Sung Park[1], Chang Soo Ryu[1], Seungki Kim[2], Doyeun Oh[4], Jong Woo Kim[2] and Nam Keun Kim[1*]*

Kim JO, et al. Front Oncol. 2020

TABLE 1 | Baseline characteristics between CRC patients and healthy control subjects.

Characteristic	Control ($n = 416$)	CRC ($n = 474$)	P^*	Colon ($n = 272$)	P^*	Rectum ($n = 189$)	P^*
Male, *n* (%)	173 (41.6)	214 (45.1)	0.317	122 (44.9)	0.443	84 (44.4)	0.568
Age (mean ± SD)	61.2 ± 11.38	62.1 ± 12.48	0.230	61.9 ± 12.97	0.267	62.1 ± 11.81	0.344
HTN, n (%)	168 (40.4)	157 (33.1)	0.030	86 (31.6)	0.025	68 (36)	0.347
DM, n (%)	55 (13.2)	76 (16.0)	0.277	46 (16.9)	0.220	30 (15.9)	<0.0001
Folate (mean ± SD)	9.0 ± 8.05	7.8 ± 6.82	<0.0001	7.9 ± 6.77	<0.0001	7.7 ± 6.97	<0.0001
Hcy (mean ± SD)	9.8 ± 4.25	10.7 ± 7.8	0.330	10.4 ± 8.12	0.870	10.9 ± 7.34	0.096
TNM stage							
I		45 (9.5)		20 (7.4)		24 (12.7)	
II		188 (39.7)		115 (42.3)		70 (37)	
III		189 (39.9)		109 (40.1)		78 (41.3)	
IV		46 (9.7)		27 (9.9)		16 (8.5)	
Tumor size							
T < 5 cm		275 (58)		176 (64.7)		96 (50.8)	
T ≥ 5 cm		187 (39.5)		92 (33.8)		93 (49.2)	

*CRC, colorectal cancer; SD, standard deviation; HTN, hypertension; DM, diabetes mellitus; Hcy, plasma homocysteine; TNM, tumor node metastasis. *P-values were calculated using chi-squared tests for categorical data and two-sided t-tests for continuous data.*

TABLE 2 | Comparison of *HOTAIR* polymorphism genotype frequencies between CRC patients and healthy controls.

Genotypes	Controls ($n = 416$)	CRC ($n = 474$)	AOR (95% CI)[a]	P^a	Colon ($n = 272$)	AOR (95% CI)[a]	P^a	Rectum ($n = 189$)	AOR (95% CI)[a]	P^a
***HOTAIR* rs7958904 G>C**										
GG	249 (59.9)	244 (51.5)	1.000 (reference)		151 (55.5)	1.000 (reference)		89 (47.1)	1.000 (reference)	
GC	140 (33.7)	191 (40.3)	1.352 (1.014–1.801)	0.040	102 (37.5)	1.202 (0.859–1.681)	0.283	84 (44.4)	1.559 (1.076–2.258)	0.019
CC	27 (6.5)	39 (8.2)	1.399 (0.802–2.443)	0.237	19 (7)	1.364 (0.7–2.66)	0.362	16 (8.5)	1.516 (0.751–3.062)	0.246
Dominant			1.351 (1.027–1.777)	0.032		1.206 (0.875–1.663)	0.252		1.547 (1.085–2.205)	0.016
Recessive			1.168 (0.681–2.002)	0.573		1.144 (0.602–2.175)	0.682		1.235 (0.626–2.435)	0.543
HWE-*P*	0.230	0.850			0.755			0.538		
***HOTAIR* rs1899663 G>T**										
GG	271 (65.1)	264 (55.7)	1.000 (reference)		161 (59.2)	1.000 (reference)		101 (53.4)	1.000 (reference)	
GT	132 (31.7)	186 (39.2)	1.338 (1.004–1.784)	0.047	100 (36.8)	1.219 (0.871–1.707)	0.248	76 (40.2)	1.404 (0.968–2.038)	0.074
TT	13 (3.1)	24 (5.1)	1.783 (0.86–3.698)	0.120	11 (4)	1.608 (0.671–3.854)	0.287	12 (6.3)	2.141 (0.906–5.06)	0.083
Dominant			1.378 (1.043–1.822)	0.024		1.244 (0.897–1.725)	0.191		1.481 (1.035–2.12)	0.032
Recessive			1.559 (0.764–3.182)	0.223		1.387 (0.591–3.256)	0.452		1.958 (0.849–4.515)	0.115
HWE-*P*	0.523	0.228			0.350			0.646		
***HOTAIR* rs4759314 A>G**										
AA	358 (86.1)	395 (83.3)	1.000 (reference)		229 (84.2)	1.000 (reference)		159 (84.1)	1.000 (reference)	
AG	55 (13.2)	71 (15)	1.062 (0.717–1.574)	0.763	39 (14.3)	1.031 (0.651–1.632)	0.898	28 (14.8)	1.026 (0.611–1.721)	0.924
GG	3 (0.7)	8 (1.7)	1.017 (0.201–5.139)	0.984	4 (1.5)	0.622 (0.063–6.126)	0.684	2 (1.1)	1.722 (0.28–10.577)	0.557
Dominant			1.059 (0.721–1.557)	0.770		1.012 (0.644–1.591)	0.960		1.056 (0.639–1.746)	0.831
Recessive			0.994 (0.197–5.016)	0.994		0.62 (0.063–6.091)	0.682		1.658 (0.27–10.172)	0.585
HWE-*P*	0.581	0.027			0.130			0.545		
***HOTAIR* rs920778 T>C**										
TT	241 (57.9)	258 (54.4)	1.000 (reference)		149 (54.8)	1.000 (reference)		102 (54)	1.000 (reference)	
TC	149 (35.8)	180 (38)	1.115 (0.838–1.484)	0.457	103 (37.9)	1.152 (0.825–1.607)	0.407	73 (38.6)	1.075 (0.74–1.56)	0.706
CC	26 (6.3)	36 (7.6)	1.222 (0.699–2.135)	0.482	20 (7.4)	1.353 (0.704–2.599)	0.365	14 (7.4)	1.118 (0.54–2.317)	0.763
Dominant			1.124 (0.855–1.477)	0.402		1.167 (0.849–1.604)	0.342		1.076 (0.754–1.535)	0.688
Recessive			1.139 (0.661–1.962)	0.640		1.228 (0.653–2.307)	0.524		1.058 (0.519–2.159)	0.876
HWE-*P*	0.645	0.555			0.706			0.851		

CRC, colorectal cancer; AOR, adjusted odds ratio; 95% CI, 95% confidence interval.
[a] Adjusted by age, gender, HTN, DM.

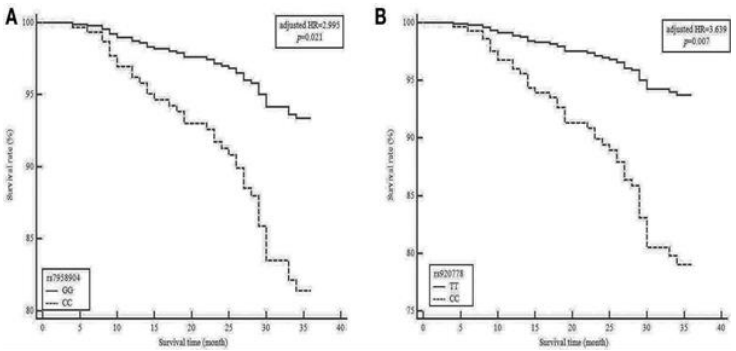


FIGURE 1 | Survival plot from a Cox proportion a hazards model with HOTAIR rs7958904G>C and rs920778T>C polymorphisms in colorectal cancer (CRC).

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Comparison of Odds ratio (over 2.5) for the gene polymorhisms in each disease

Disease	Category	Gene	Sequence variation	Genotype	AOR (95% CI)	References
RPL	Angiogenesis	VEGF	Rs25703xxG>A	GA	2.774 (1.512–5.092)	Lee HH et al. Fertil Steril 2010
	Endothelial function	AT1R	rs51xxA>C	AC	3.171 (1.562-6.436)	Jeon YJ, et al. Am J Reprod Immunol. 2013
	Fibrinolysis	PAI-1	rs22276xxG>A/ rs7998xx 4G>5G/ rs72xxT>G	A-5G-G	0.033 (0.002 – 0.573)	Jeon YJ et al. Thromb Haemost 2013
	Homocysteine	TCN2	rs96067xxA>G	AG+GG	3.110 (1.277–7.570)	Kim HS et al. Am J Reprod Immunol 2014
	miRNA	miR-150	rs730560xxG>A	GA	2.502 (1.555–4.025)	Park HS et al. Reprod Biomed Online. 2019
	miRNA biogenesis	AGO1	rs5959xx	AA	4.146 (1.075–15.996)	Kim YR et al. Sci Rep. 2019
RIF	Angiogenesis	VEGF	Rs8330xxT>C	CC	2.667 (1.002–7.095)	Jung YW et al. Reprod Biomed Online 2016
	Homocysteine	TCN2	rs96067xxA>G	AG	4.732 (1.220-18.356)	Park HS et al. J Assist Reprod Genet. 2019
	miRNA	miR-1302-3	rs75893xxC>T	CT	0.237 (0.090-0.624)	Lee HA et al. Reprod Sci 2018
POI	Angiogenesis	MMP-2	rs2438xxC>T	CT	2.651 (1.406–4.998)	Kim et al. Maturitas 2015
	Fibrinolysis	PAI-1	rs22276xxG>A	GA	5.237 (2.354–11.652)	Jeon et al. Fertil Steril 2014
	Cytokine	TNF-α	rs17999xxT>C	CC	40.204 (2.314–698.415)	Kim et al. Fertil Steril 2012
Stroke	Homocysteine	eNOS	1 intron VNTR	4a4b	2.769 (1.233-6.220)	OJ Kim et al. Mol. Med. Rep. 2010
		TS	rs27xx A>G	GG	0.284 (0.151–0.537)	JO Kim et al. J. Pers. Med. 2021
		MTHFR	rs48460xx T>C	CC	10.146 (1.297–79.336)	JO Kim et al. Sci Rep. 2017
	miRNA biogenesis	XPO5	rs110xx A>C	CC	0.101 (0.011–0.951)	JO Kim et al. J. Stroke. 2018
CRC	Angiogenesis	VEGF	rs30250xx C>T	CT+TT	4.156 (1.885-9.163)	SJ Bae et al. Anticancer Res. 2008
			rs15703xx G>A	AA	2.735 (1.243–6.015)	YS Choi et al. Genes Genom. 2011
	Homocysteine	MTHFR	rs18011xx C>T	TT	0.206 (0.070-0.604)	JW Kim et al. Oncol. Rep. 2011
		TS	rs27xx A>G	GG	3.19 (1.91–5.34)	YJ Jeon et al. J. Pers. Med. 2021

Conclusion

1. Interestingly, most of the four mechanism-related genes of the five diseases studied were found to be related to the development of the diseases.

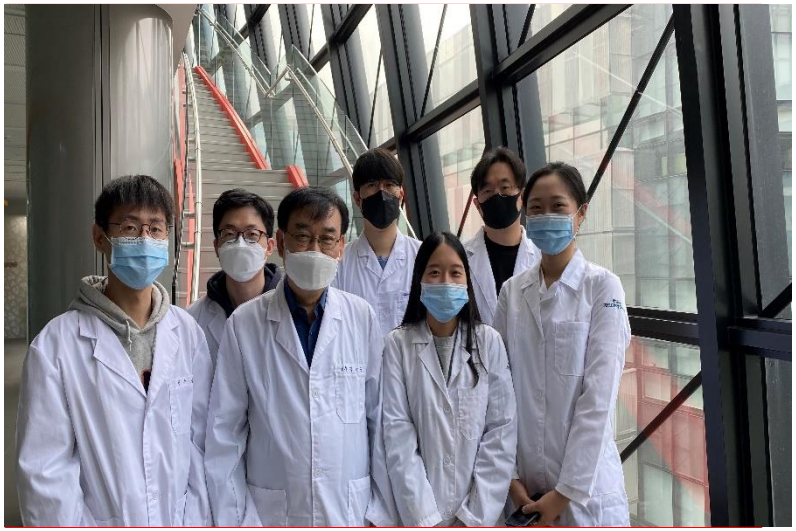
2. In addition, the types and risks of gene mutations as risk factors in each disease were very similar. Moreover, five genes were found to be common risk factors in two or more diseases. And it was found that various nutritional factors or risk factors of lifestyle-type diseases increase the risk of disease development.

3. Therefore, it was found that common SNPs normally play essential roles like proto-oncogenes, but when risk factors such as malnutrition, hypertension or diabetes act as promoters, they change into oncogene-like pathogens.

4. In microRNA and lncRNA, HOTAIR, etc., it was found that SNP not only acts as a disease risk factor, but also affects the survival rate of stroke and colorectal cancer patients.

5. Therefore, continuous researches on SNPs using NGS and bioinformatics study is required in the future.

Acknowledgements



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