# Meta-Analyses of Epigenetics Risk Factors for Heart Disease Prevention: NOS3 HUMAN GENE VARIATIONS ACROSS DIFFERENT RACE-ETHNICITY GROUPS

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## Faculty Disclosure

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| *Conflicts of interest:* | None |
| *Employer:* | National Taiwan University |
| *Sponsorship / Commercial support* | None |

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| *Employer:* | Azusa Pacific University |
| *Sponsorship / Commercial support* | None |

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| *Conflicts of interest:* | None |
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| *Sponsorship / Commercial support* | None |

# Introduction

- Ischemic heart disease (IHD) is the major leading cause of death worldwide.
- Endothelial NOS3 gene mutation variations increase risks of IHD in various populations.
- NOS3 affects metabolism cycle, critical for preventing systematic inflammation as an epigenetics risk factor for heart health.

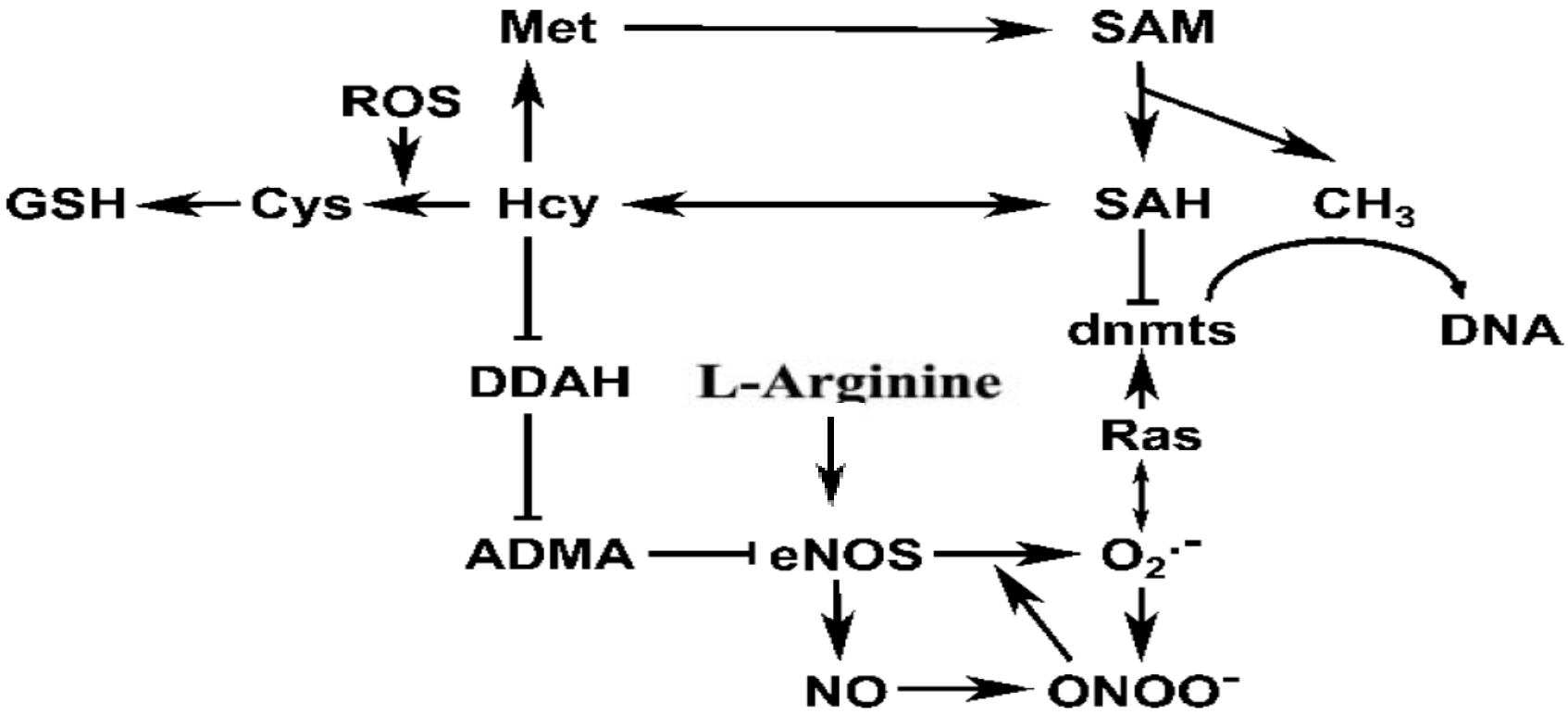
# Purpose

- The purpose of this meta-analysis is:
  - To identify the association of NOS3 894G>T gene variations with IHD in various populations
  - To identify the related lifestyle risk factors for IHD prevention.

# NOS3

- Nitric oxide: endothelium adhesion, platelet aggregation and vascular smooth muscle cell proliferation.
- Nitric oxide syntheses: neuronal NOS1, inducible NOS2 and endothelial NOS3 (eNOS).
- G894T SNP in the promoter region of the NOS3: endothelial dysfunction, early event in IHD.

# DNA methylation pathway, NOS



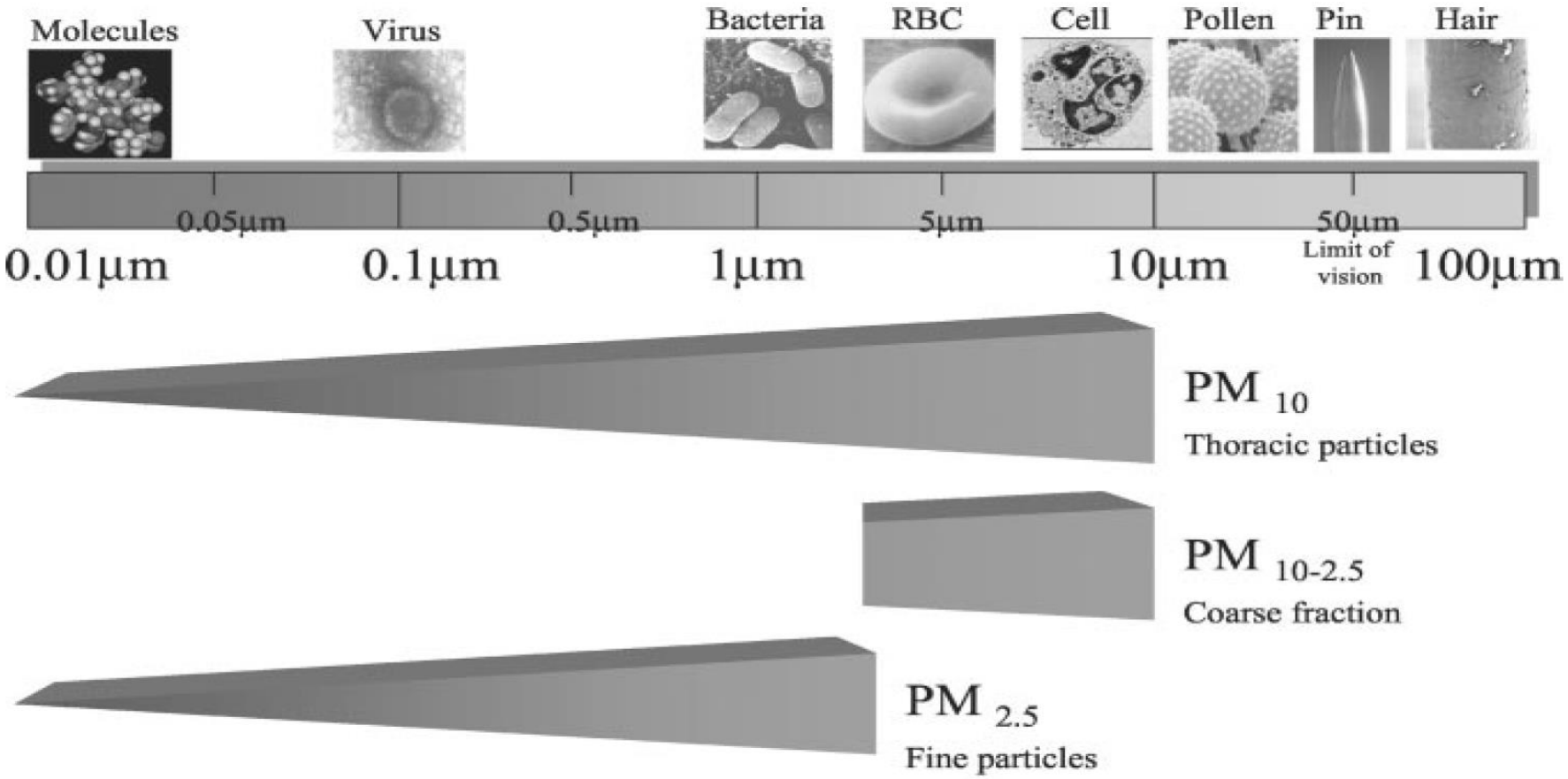

Adapted from Campos et al. [2007]

***Neoplasia 2007; 9:1118***

***Circulation 2004;109:1813***

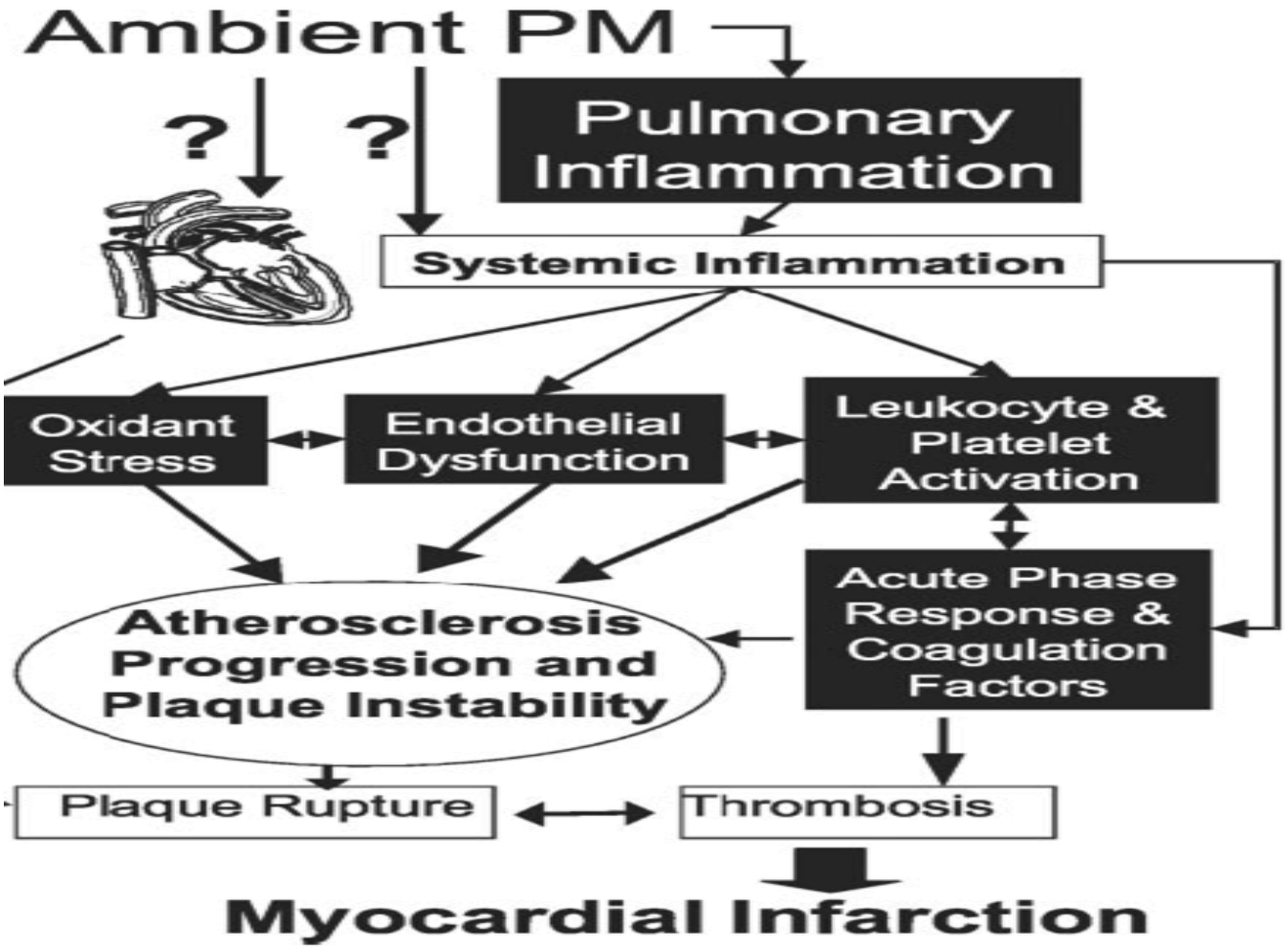
http://www.heartfixer.com/AMRI-Nutrigenomics.htm

# Environment, Particulate matter, & IHD




*Circulation.* 2004;109:2655

# Biological mechanisms linking PMx & IHD




Adapted from Brook et al. [2004]

# NOS3, IHD, and Lifestyle

- In humans, variations of the NOS3 gene have been found to be increasing the risk of IHD across country groups and subsequently.
- Life style risk factors: smoking, air pollution, nutritional intake were associated with increased risks for IHD.

# Publication search and inclusion criteria

- Key words: NOS3, G894T, CAD, IHD, case control, meta-analysis = 229 articles
- Studies Excluded for
  - not case-control (n=11)
  - not IHD (n=106)
  - no NOS3 894G>T gene count (n=34).
  - Duplicate (n=29)
- Studies Included =49

# Preliminary Analyses

- 49 studies,13,830 cases and 10,595 controls.
- Gene mutation variations (GT and TT subtypes) - Caucasians (47.5-64.8%), Africans (42.9-55.9%), Eurasians (33.9-45.1%), and Asians (13.5–30.7%) for control and case groups.
- Inter-rater evaluations- search progression, quality scores, data coding were completed to ensure data accuracy for pooled meta-analyses.

# Relative risk: NOS G894T (49 studies)

| NOS3 G894T | IHD Cases (%) | Controls (%) | RR (95% CI) | p-value |
|---|---|---|---|---|
| GG | 7260 (52.5) | 6288 (59.3) | 0.92 (0.89-0.96) | p<0.001 |
| GT | 5135 (37.1) | 3390 (32.0) | 1.11 (1.04-1.18) | p=0.002 |
| TT | 1435 (10.4) | 892 ( 8.4) | 1.32 (1.13-1.56) | p<0.001 |

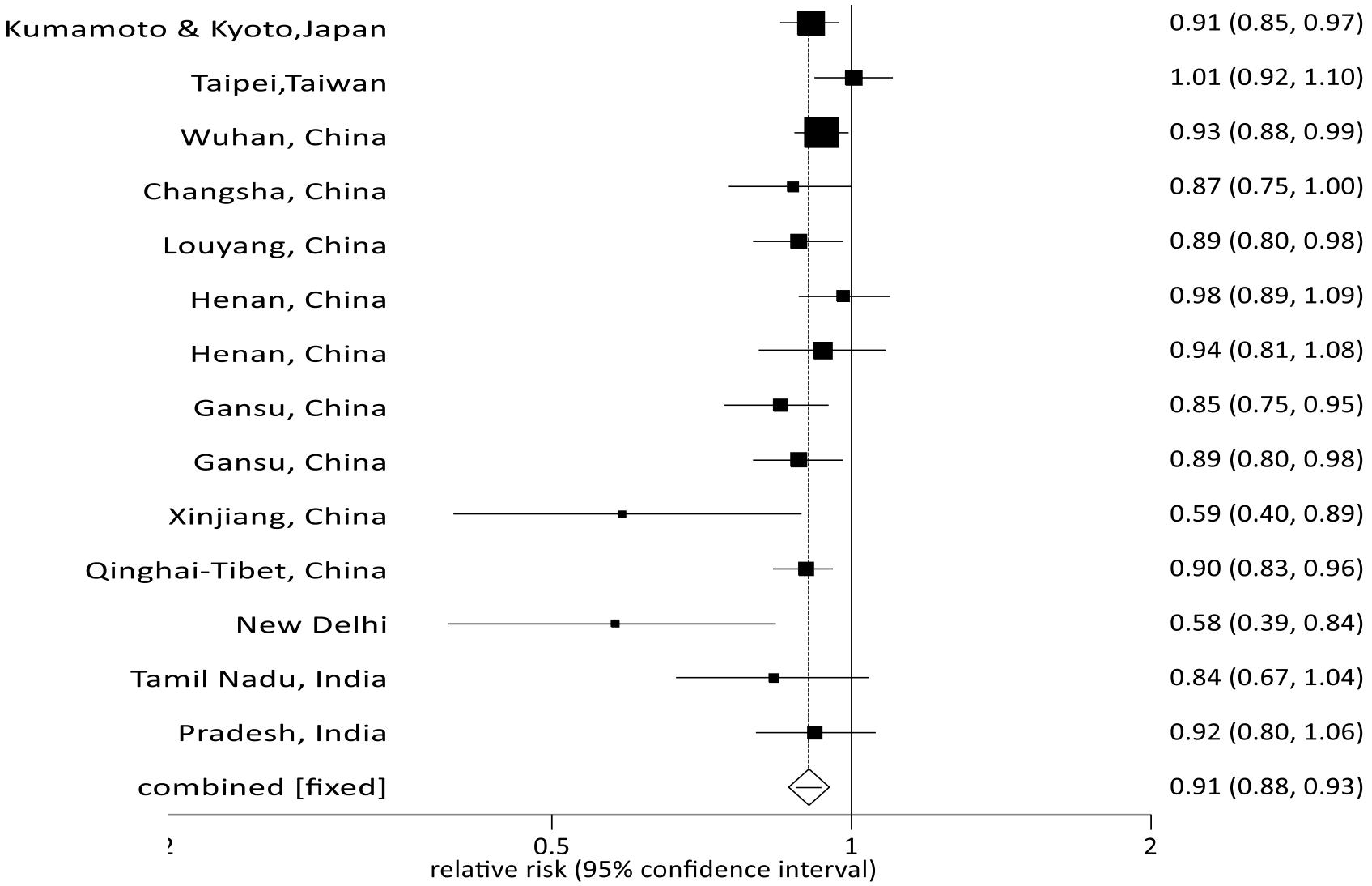
# Relative risk: **Eurasian population** (9 studies)

| NOS3 G894T | IHD Cases n (%) | Controls n (%) | RR (95% CI) | p-value |
|---|---|---|---|---|
| GG | 860 (49.5) | 805 (56.7) | 0.85 (0.76-0.96) | p=0.068 |
| GT | 668 (38.5) | 513 (36.2) | 1.07 (0.97-1.17) | p=0.155 |
| TT | 208 (12.0) | 101 ( 7.1) | 1.82 (1.18-2.80) | p=0.007 |

# Relative risk - **Asian & Caucasian population**

| G894T (n, studies) | IHD Cases n (%) | Controls n (%) | **RR** (95% CI) * P < 0.05 |
|---|---|---|---|
| GG Caucasian (16) | 3268 (44.0) | 1842 (43.5) | **0.97** (0.93-1.014) |
| **GG** Asian (22) | 2626 (88.7) | 3277 (83.6) | **0.91*** (0.88-0.93) |
| GT Caucasian (16) | 3160 (32.3) | 1785 (42.2) | **0.97** (0.92-1.01) |
| **GT** Asian (22) | 818 (27.6) | 603 (15.4) | **1.39**** (1.26-1.52) |
| TT Caucasian (16) | 997 (13.4) | 607 (14.3) | **1.18** (0.96-1.45) |
| **TT** Asian (22) | 102 ( 3.4) | 42 (1.1) | **1.82**** (0.38-0.98) |

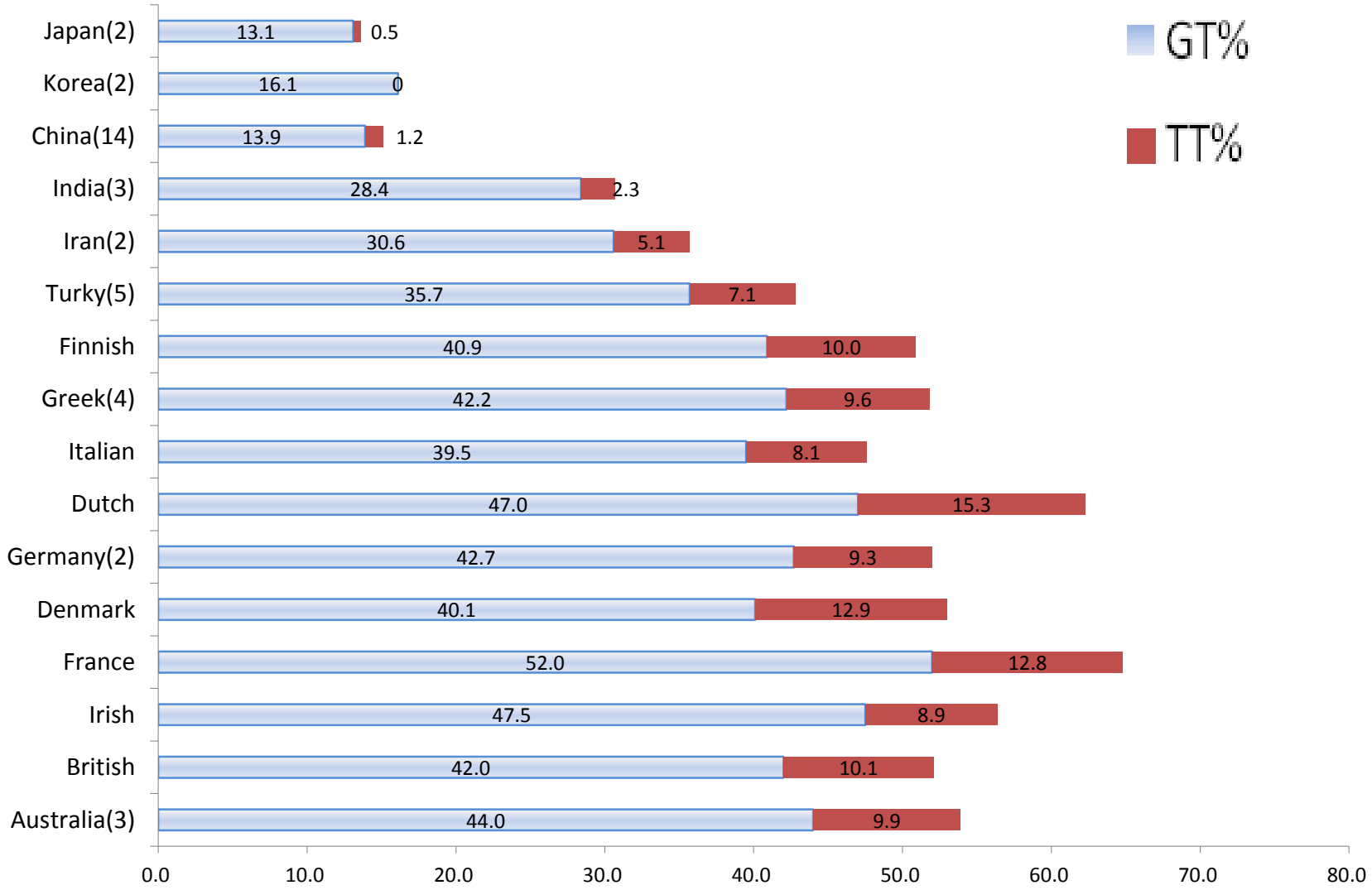
# NOS3 GG Asian



# Lifestyle Analyses

| Lifestyle | Cases | Control | RR (95% CI) | P-value |
|---|---|---|---|---|
| Smoking (24) | 4118 (59.8) | 3212 (56.5) | 1.68 (1.39 to 2.04) | p<0.0001 |
| DM (19) | 1706 (24.2) | 414 ( 8.9) | 3.16 (2.40 to 4.17) | p<0.0001 |
| Hyper-lipidemia (8) | 1551 (51.3) | 505 (21.9) | 2.92 (1.97 to 4.33) | p<0.0001 |

# Gene mutation (GT+TT) variations, control group



Variation displays
- Explore this variation
- Genomic context
  - Genes and regulation (5)
  - Flanking sequence
- **Population genetics**
- Individual genotypes (1785)
- Linkage disequilibrium
- Phenotype Data (7)
- Phylogenetic Context (6)
- Citations (145)
- External Data
  - LOVD

Configure this page

Add your data

Export data

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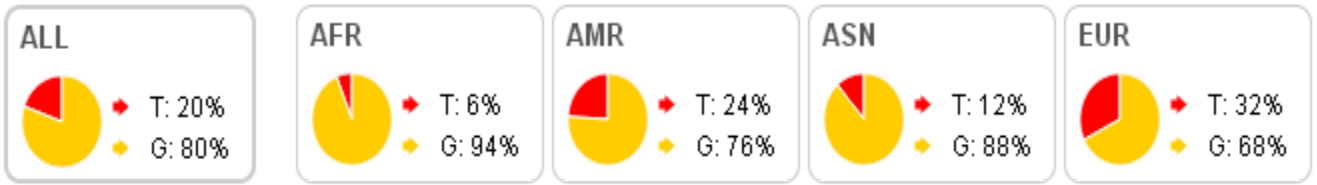
# rs1799983 SNP

| | |
|---|---|
| **Original source** | Variants (including SNPs and indels) imported from dbSNP (release 138) \| View in |
| **Alleles** | **T/G** \| Ambiguity code: **K** \| MAF: **0.20** (T) |
| **Location** | Chromosome **7:150696111** (forward strand) \| View in location tab |
| **Co-located** | with **HGMD-PUBLIC** CM981388 |
| **Most severe consequence** | Missense variant \| See all predicted consequences [Genes and regulation] |
| **Evidence status** |  |
| **Clinical significance** |  |
| **Synonyms** | This variation has **10** synonyms - click the plus to show |
| **HGVS names** | This variation has **9** HGVS names - click the plus to show |
| **Genotyping chips** | This variation has assays on **4** chips - click the plus to show |

## Population genetics

### 1000 Genomes allele frequencies




Sub-populations | Sub-populations | Sub-populations | Sub-populations

1000 Genomes (19)

http://uswest.ensembl.org/index.htm

## AMR sub-populations

### CLM


### MXL


### PUR


## ASN sub-populations

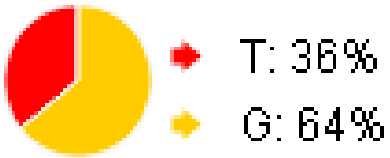
### CHB


### CHS

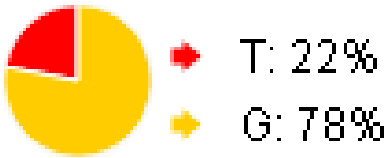

### JPT


## EUR sub-populations

### CEU




### FIN




### GBR


### IBS

# Conclusion and Discussion

- NOS3 GG (wild type) is protective from IHD; GT and TT gene variations are associated with increased IHD risk; Subgroups: Eurasian and Asians significant.
- Smoking, DM and hyperlipidemia increased IHD risk.
- Future studies: epigenetic factors for population health, gene variations in the prevention of IHD.

# *THANK YOU FOR YOUR ATTENTION*