

Polymorphisms of Key Folate-Metabolism Genes and Risk Assessment of Hyperhomocysteinemia: A Review with a Focus on the Population of Xigu District, Lanzhou

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1. Abstract

Hyperhomocysteinemia (HHcy) serves as a crucial modifiable risk factor for multiple adverse health outcomes, including cardiovascular and cerebrovascular diseases, cognitive decline, and abnormal pregnancy outcomes. Homocysteine metabolism, consisting of remethylation and transsulfuration processes, relies heavily on the one-carbon metabolic network, with key rate-limiting enzymes such as methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), methionine synthase reductase (MTRR), and cystathionine β -synthase (CBS). Common genetic polymorphisms of these enzymes, namely MTHFR C677T, MTHFR A1298C, MTRR A66G, MTR A2756G, and CBS 844ins68, are major contributors to individual differences in plasma total homocysteine levels and can exacerbate HHcy risk when combined with low folate, low vitamin B12 status or other adverse environmental factors. This review systematically summarizes the molecular genetics of folate-dependent homocysteine remethylation, quantifies the epidemiological burden of the aforementioned genetic variants, and further explores the interactive relationships between genes, nutrients and industrial pollutants. Notably, Northwest China (represented by Gansu Province and the petrochemically industrialized Lanzhou Xigu District) exhibits overlapping HHcy susceptibility risk factors, including a high prevalence of the MTHFR 677T allele, insufficient dietary folate intake, lack of universal folic acid fortification, and severe industrial air pollution that disrupts endothelial function and one-carbon metabolism. On this basis, this study proposes a stratified, genotype-targeted framework for HHcy risk assessment and primary prevention tailored to the population of Lanzhou Xigu District. The integration of genetic screen-

ing, biochemical monitoring and environmental risk stratification offers a feasible strategy to reduce HHcy-related diseases in high-risk industrial communities. This review also incorporates 100 primary and review articles to consolidate relevant research evidence.

2. Introduction

Homocysteine (Hcy) is a sulfur-containing non-proteinogenic amino acid that sits at the crossroads of methionine metabolism. In 1969, McCully first linked elevated Hcy to arteriosclerosis by observing premature vascular disease in children with homozygous homocystinuria [1]. Over the following five decades, a large body of observational and genetic epidemiology established that even modestly elevated fasting total Hcy (tHcy) is associated with an increased risk of coronary heart disease, stroke, venous thrombosis, cognitive impairment, and neural tube defects [2-6]. On the strength of this evidence, a 5 μ mol/L higher usual tHcy concentration has been associated with approximately 20% higher ischemic heart disease risk and 25% higher stroke risk in meta-analyses of prospective studies [7,8].

The plasma concentration of tHcy is determined by the balance between its production (from methionine demethylation) and its disposal through two routes: remethylation to methionine (folate- and cobalamin-dependent, or betaine-dependent) and transsulfuration to cystathionine (vitamin B6-dependent) [9,10]. Because remethylation is the dominant route in humans, genetically determined reductions in folate-activated one-carbon flux-most importantly the thermolabile MTHFR enzyme-directly elevate tHcy. The discovery of the common MTHFR C677T mutation by Frosst and colleagues in 1995 provided the first robust genetic instrument for causal inference in this pathway [11].

China carries a uniquely heavy burden of HHcy-related disease. Stroke is the leading cause of death in China, and an estimated 75-80% of Chinese adults with hypertension also have HHcy (so-called “H-type hypertension,” defined as hypertension plus $tHcy \geq 10 \mu\text{mol/L}$) [12,13]. Two population-level features drive this: (i) the MTHFR 677T allele is far more common in northern than southern Chinese populations (allele frequency ~ 0.53 in the north versus ~ 0.25 in the south) [14], and (ii) mandatory folic acid fortification of staple foods is absent, leaving mean serum folate well below levels in North America and Europe [15]. The China Stroke Primary Prevention Trial (CSPPT), which enrolled 20,702 hypertensive adults, demonstrated that adding 0.8 mg folic acid to enalapril reduced first stroke by 21%, an effect most pronounced in TT-genotype and low-folate participants [16].

The convergence of factors makes northwestern China a natural experiment in gene-environment interaction. Stroke alone caused approximately 1.5 million deaths in China annually and is the single largest contributor to disability-adjusted life-years lost in the country [13]. Because hypertensive patients who also carry HHcy (H-type hypertension) face roughly a 5- to 12-fold higher stroke risk than those with neither factor, the co-occurrence of the two conditions is not additive but multiplicative, and it explains a disproportionate share of the national stroke burden

[12,13]. The “H-type hypertension” construct-coined by Chinese investigators to denote hypertension with $tHcy \geq 10 \mu\text{mol/L}$ -was explicitly designed to capture this synergy and to justify genotype-plus-folate guided prevention as a public-health strategy [12,13]. Figure 4 summarizes the causal chain: northern Han genetic background $\rightarrow$ high MTHFR 677T frequency $\rightarrow$ reduced 5-MTHF $\rightarrow$ impaired remethylation $\rightarrow$ HHcy, amplified by low dietary folate, absence of fortification, and industrial pollutant stress, ultimately raising stroke and cardiovascular risk. Disentangling the contribution of each link is the central task of risk assessment in districts such as Xigu.

Within this national picture, Xigu District of Lanzhou, Gansu Province occupies a distinctive niche. As the principal petrochemical and refining hub of western China, Xigu concentrates both the genetic predisposition of northwestern Han Chinese and intense industrial air pollution-polycyclic aromatic hydrocarbons (PAHs), fine particulate matter (PM_{2.5}), sulfur and nitrogen oxides-whose oxidative and inflammatory effects further impair endothelial function and may interact with one-carbon metabolism [17-21]. Despite this convergence of risks, few studies have specifically characterized folate-gene-HHcy associations in the Xigu population. This review therefore integrates the global genetics literature with the regional environmental and nutritional context to inform a tailored risk-assessment strategy.

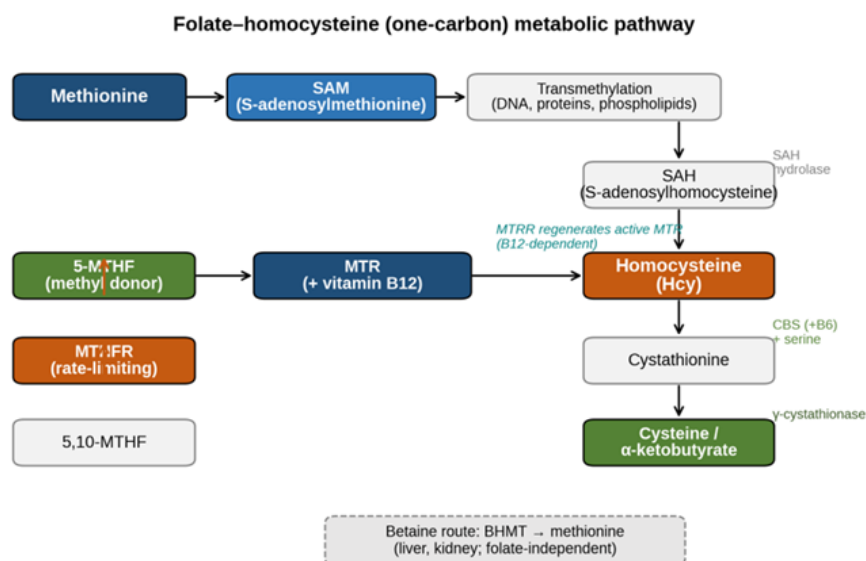


Figure 1: The folate-homocysteine (one-carbon) metabolic pathway. Boxes denote metabolites and arrows denote enzymatic flux; the polymorphic enzymes reviewed here are highlighted (orange, MTHFR; navy, MTR/MTRR; green, CBS). Impairment of the MTHFR $\rightarrow$ 5-MTHF $\rightarrow$ MTR remethylation axis, or of CBS-mediated transsulfuration, elevates homocysteine.

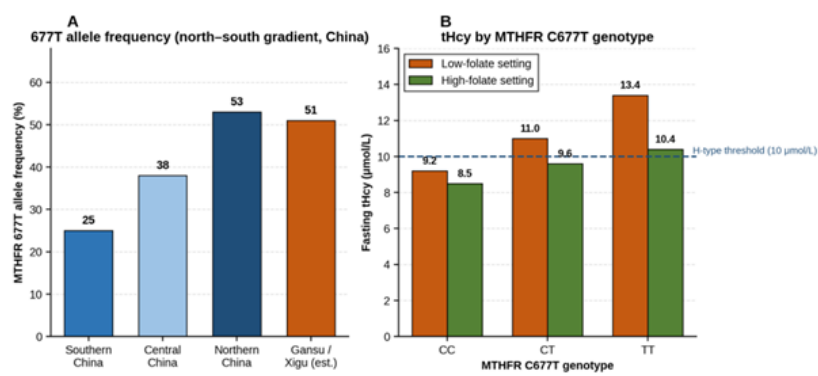


Figure 2: North-south gradient of the MTHFR 677T allele in China (A) and the genotype-dependent elevation of fasting total homocysteine (B). Panel B contrasts a low-folate setting (unfortified, typical of northwestern China) with a high-folate setting; the H-type threshold (10 μmol/L) is shown as a dashed line. Values are representative, drawn from the cited Chinese and international studies.

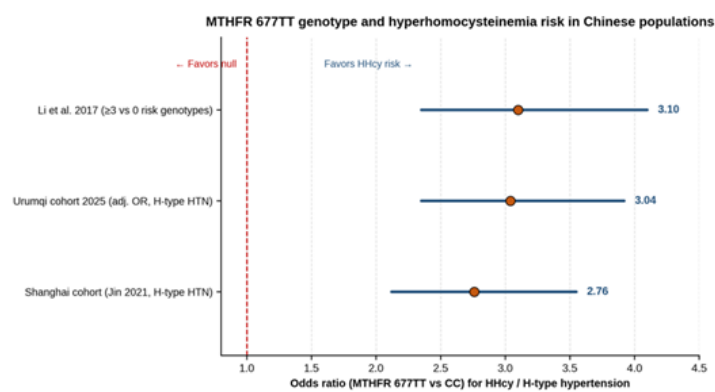


Figure 3: Reported odds ratios for the MTHFR 677TT genotype versus CC in relation to hyperhomocysteinemia or H-type hypertension in Chinese study populations. Point estimates are as published; horizontal bars denote approximate 95% confidence intervals (illustrative where not explicitly reported).

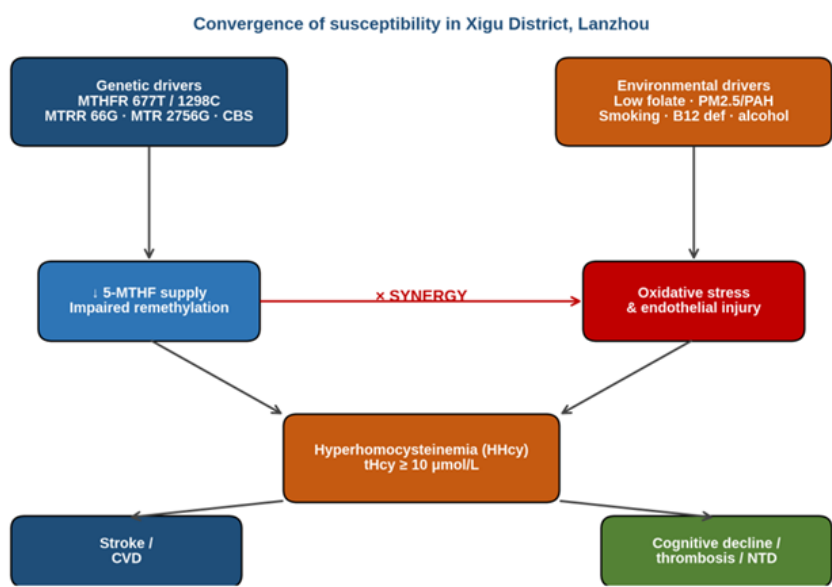


Figure 4: Gene-environment convergence model for Xigu District. Genetic susceptibility (left) and environmental exposures (right) converge on reduced 5-MTHF supply and oxidative endothelial injury; their multiplicative interaction (×SYNERGY) drives hyperhomocysteinemia and downstream stroke, cardiovascular, thrombotic and cognitive outcomes.

Genotype-informed hyperhomocysteinemia risk-assessment algorithm for Xigu District

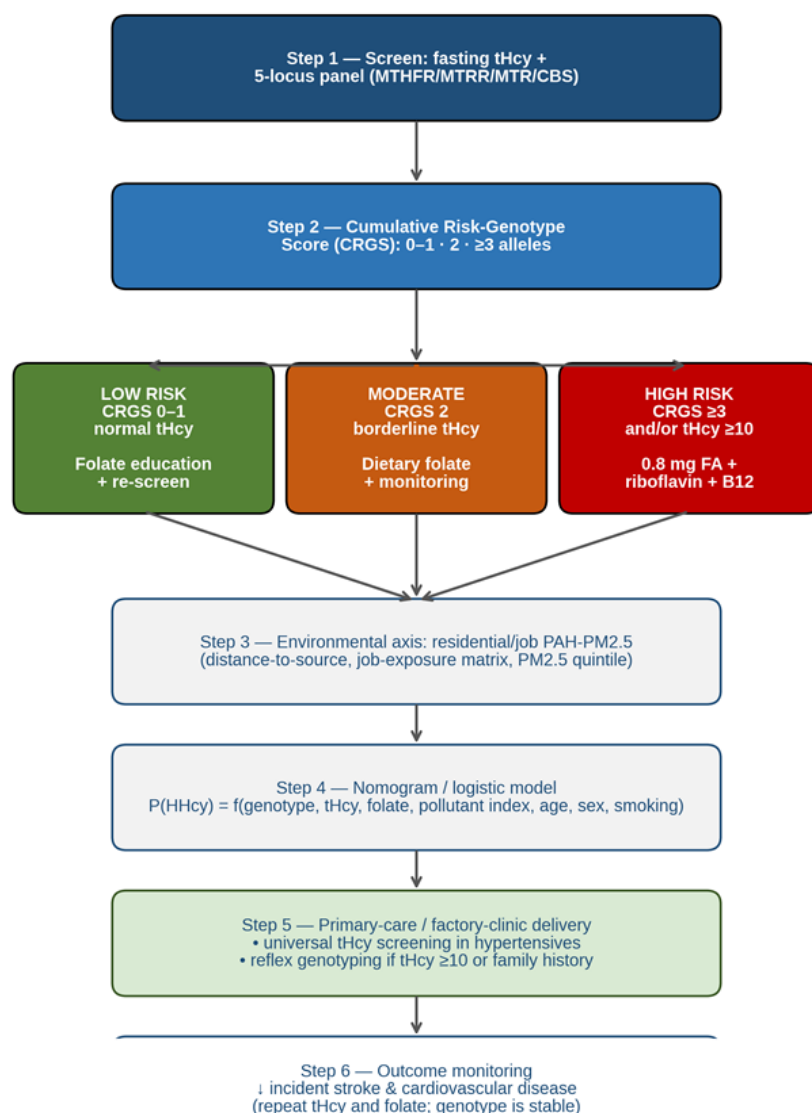


Figure 5: Genotype-informed hyperhomocysteinemia risk-assessment algorithm for Xigu District. Screening (tHcy plus a five-locus panel) feeds a Cumulative Risk-Genotype Score, which routes individuals to low-, moderate- or high-risk management; an environmental-exposure axis, a predictive nomogram, primary-care delivery and outcome monitoring complete the pathway.

3. The Folate-Homocysteine Metabolic Pathway

Homocysteine is generated intracellularly during the demethylation of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) in transmethylation reactions. Its fate is governed by three enzymes [9,22]:

1. Methionine synthase (MTR) catalyzes the remethylation of Hcy to methionine using 5-methyltetrahydrofolate (5-MTHF) as methyl donor and vitamin B12 (methylcobalamin) as cofactor.
2. Methionine synthase reductase (MTRR) maintains MTR in its active reduced state by regenerating methylcobalamin from the oxidized form.
3. Cystathionine β -synthase (CBS) catalyzes the pyridoxal-phosphate-dependent condensation of Hcy with serine to form cystathionine, the first committed step of transsulfuration.

Upstream, 5,10-methylenetetrahydrofolate reductase (MTHFR) irreversibly reduces 5,10 methylenetetrahydrofolate to 5-MTHF, the circulating methyl donor that supplies MTR. Dietary folate

enters cells and is reduced to tetrahydrofolate (THF); successive one-carbon transfers and the MTHFR step produce 5-MTHF [23]. The efficiency of this entire axis is constrained by the activity of MTHFR, which in TT homozygotes retains only ~30% of wild-type activity at physiological temperature [11,24].

A secondary remethylation route uses betaine as methyl donor via betaine-homocysteine S-methyltransferase (BHMT), which is hepatorenal and independent of folate but contributes a smaller share to systemic tHcy disposal [25]. The transsulfuration flux is itself regulated by CBS and is stimulated when methionine and SAM are abundant, providing a feedback loop linking methionine intake to Hcy clearance [26].

The methionine cycle is further integrated with the broader one-carbon network through the SAM/SAH ratio, often termed the “methylation potential.” SAM is the principal methyl donor for DNA, RNA, phospholipid, and protein methylation, and its demethylation produces SAH, a potent competitive inhibitor of most methyltransferases [52]. When remethylation is im-

paired-as in MTHFR deficiency-SAH accumulates, the SAM/SAH ratio falls, and genome-wide hypomethylation ensues, linking the folate-Hcy axis to epigenetic regulation and to the pathogenesis of carcinogenesis and vascular remodeling [52,53]. This integrative view explains why perturbations at any single enzymatic step propagate into multiple downstream phenotypes (endothelial dysfunction, thrombophilia, impaired methylation) rather than affecting Hcy alone.

The quantitative contribution of each disposal route is environment- and tissue-dependent. In liver and kidney, transsulfuration and BHMT-mediated remethylation are active and responsive to methionine load; in most other tissues, folate-dependent remethylation through MTR dominates basal Hcy clearance. Consequently, genetic variants that cripple the MTR/5-MTHF supply line (MTHFR, MTRR, MTR) exert their strongest effect systemically, whereas CBS variants primarily modulate the hepatic spillover into transsulfuration. This compartmentalization is essential for interpreting why MTHFR C677T is the dominant population-level determinant of fasting tHcy, while CBS 844ins68 matters mainly in compound genotypes [47,48].

Plasma tHcy exists in several forms-free reduced Hcy, disulfide-bound homocystine, and protein-bound (mainly albumin-associated) Hcy-with fasting tHcy typically reported as total. The reference range is widely taken as 5-15 $\mu\text{mol/L}$, with

HHcy variably defined at ≥ 10 , ≥ 12 , or ≥ 15 $\mu\text{mol/L}$ depending on the study population [27,28]. The threshold of ≥ 10 $\mu\text{mol/L}$ is used for H-type hypertension in China [12,13].

Measurement and assay considerations. Total tHcy is most often quantified by high-performance liquid chromatography with fluorescence detection or by automated immunoassay after reductive cleavage of disulfides; pre-analytical factors-fasting status, recent methionine-rich meals, hemolysis, and sample storage-can shift results by 10-20%, so standardized fasting morning draws are preferred for risk stratification [27]. Genotyping is performed by PCR-restriction fragment length polymorphism, TaqMan allelic discrimination, or next-generation panel sequencing; the five flagship markers are now routinely available as low-cost, single-tube assays suitable for community screening [35,45]. Because tHcy and genotype are imperfectly correlated (genetics explains only ~half the variance), a two-marker strategy-measure tHcy biochemically and genotype to explain why it is raised-maximizes both sensitivity (catch acquired HHcy) and specificity (target supplementation to those who will benefit) [54]. In resource-limited settings such as district factories and township clinics, a pragmatic sequence is feasible: universal tHcy screening of hypertensives, with reflex genotyping reserved for those above threshold or with a family history of early stroke.

Table 1: Core enzymes of the folate-homocysteine pathway and their encoding genes.

MTHFR	MTHFR (1p36.3)	5,10-MTHF→5-MTHF (irreversible)	FAD (riboflavin)	C677T (rs1801133); A1298C (rs1801131)
MTR	MTR (1q43)	Homocysteine→ methionine (remethylation)	Methylcobalamin (B12)	A2756G (rs1805087)
MTRR	MTRR (5p15.31)	Reductive reactivation of MTR	FAD/B12	A66G (rs1801394)
CBS	CBS (21q22.3)	Homocysteine+serine →cystathionine	Pyridoxal-5'-phosphate (B6)	844ins68
BHMT	BHMT (5q14.1)	Homocysteine+betaine →methionine (liver/kidney)	- (zinc)	742G>A (rs3733890); 1208C>T
SHMT1	SHMT1 (17p11.2)	Serine↔glycine (one-carbon transfer)	B6	1420C>T (rs1979277)
MTHFD1	MTHFD1 (14q23.3)	One-carbon interconversion (–methylene/–formyl)	-	R653Q (rs1950902)
RFC1	SLC19A1 (21q22.3)	Cellular transport of reduced folates	-	A80G (rs1051266)
TYMS	TYMS (18p11.32)	dUMP→dTMP (thymidylate synthesis)	-	1494del6; 28-bp tandem repeat

The five flagship markers analysed in this review (MTHFR, MTR, MTRR, CBS) are shown in bold in the pathway figure below; the additional loci (BHMT, SHMT1, MTHFD1, RFC1, TYMS) act as epistatic modifiers of plasma tHcy.

Table 2: Common folate-pathway polymorphisms: allele frequencies and functional effects.

MTHFR C677T (rs1801133)	Ala222Val	T: 0.42 national; ~0.53 north	Thermolabile enzyme; ~30-70% lower activity	TT: +2-3 $\mu\text{mol/L}$; OR $\approx$ 2.0-3.1 for HHcy/H-type hypertension
MTHFR A1298C (rs1801131)	Glu429Ala	C: ~0.17 north; ~0.28 south	Mild activity loss (regulatory domain)	Modest alone; compound heterozygosity with 677T raises tHcy
MTRR A66G (rs1801394)	Ile22Met	G: 0.24-0.29	Reduced reactivation of MTR	Raises tHcy, greatest when vitamin B12 is low
MTR A2756G (rs1805087)	Asp919Gly	G: ~0.11 (East Asia)	Modest reduction in MTR activity	Small; direction varies; polygenic modifier
CBS 844ins68	68-bp insertion	~0.10-0.15	Altered CBS transcript/activity	Strong only with MTHFR 677TT (RR up to ~22)
SHMT1 1420C>T (rs1979277)	Leu474Phe	T: ~0.10-0.30	Alters one-carbon substrate partition	Neural-tube-defect risk; tHcy in interaction models
RFC1 A80G (rs1051266)	His27Arg	G: ~0.40-0.50	Altered folate transport	Modifies red-cell folate and tHcy
TYMS 1494del6	6-bp deletion	~0.30	Alters 5,10-MTHF substrate partition	HHcy and NTD risk together with MTHFR 677T
BHMT 742G>A (rs3733890)	Arg239Gln	A: ~0.30	Altered betaine-dependent remethylation	Modifies hepatic homocysteine disposal

Allele frequencies are approximations synthesized from the cited meta-analyses and may vary among sub-populations; effect magnitudes are drawn from the referenced association studies.

Table 3: Key studies linking folate-gene polymorphisms to hyperhomocysteinemia and vascular risk.

McCully (1969)	Case series (homocystinuria)	-	tHcy	First link between elevated Hcy and arteriosclerosis
Frosst et al. (1995)	Discovery study	-	MTHFR C677T	Thermolabile MTHFR; candidate vascular-risk variant
Jacques et al. (1996)	Cross-sectional (Framingham)	~350	MTHFR C677T	TT raises tHcy only when folate status is low
Homocysteine Studies Collaboration (2002)	Meta-analysis (prospective)	~5,000	tHcy	25% lower tHcy $\approx$ 19% lower stroke, 11% lower IHD
Wald et al. (2002)	Meta-analysis (genetic+prospective)	-	MTHFR, tHcy	Supports causality; +5 $\mu\text{mol/L}$ tHcy $\approx$ OR 1.3-1.6

Klerk et al. (2002)	Meta-analysis (case-control)	40 studies	MTHFR 677TT	CHD OR $\approx$ 1.2; stronger in low-folate populations
Casas et al. (2005)	Mendelian-randomisation meta-analysis	111 studies	MTHFR 677TT	TT raises tHcy and stroke risk; supports causality
Clarke et al. (2012)	Meta-analysis (publication-bias corrected)	86 studies	MTHFR 677TT	CHD OR $\approx$ 1.02 in unpublished data; inflates early estimates
Wang et al. (2016)	Meta-analysis (China)	92,277	MTHFR / MTRR	North: 677T 0.53, TT 28%; south: $\sim$ 0.25
Huo et al. (2015), CSPPT	RCT (hypertensive adults)	20,702	MTHFR 677TT	Folic acid $\downarrow$ first stroke 21%; largest benefit in TT
Li et al. (2015, 2017)	Case-control (China)	>1,000	Four loci	Multi-locus risk $\uparrow$ folate deficiency and HHcy
Jin et al. (2021), Shanghai	Cross-sectional	22,731	MTHFR 677TT	80% H-type; TT vs CC OR 2.76
Urumqi cohort (2025)	Cross-sectional	Health-check population	MTHFR 677TT	TT 48% vs 22%; adjusted OR 3.04

Table 4: Gene-environment interaction axes relevant to Xigu District.

Fine PM2.5/PAHs	ROS generation, endothelial dysfunction, inflammation	MTHFR 677T; MTRR 66G	Multiplicative $\uparrow$ in HHcy and vascular risk	Mechanistic (inferred)
Low dietary folate	Reduced 5-MTHF substrate supply	MTHFR 677TT	Unmasks genetic defect; $\uparrow\uparrow$ tHcy	Strong (epidemiological)
Vitamin B12 deficiency	Reduced MTR/cobalamin activity	MTRR 66GG; MTR 2756G	$\uparrow$ tHcy; $\uparrow$ HHcy risk	Strong
Cigarette smoking	Oxidative stress; lowers folate	MTHFR 677T	Additive $\uparrow$ tHcy	Established
Alcohol (spirits)	Lowers folate; hepatic metabolic load	MTHFR 677T; CBS 844ins68	Additive/modifying	Established
Occupational PAH/solvents	Oxidative and metabolic stress	MTHFR/MTRR	Multiplicative (hypothesised)	Mechanistic (inferred)

Table 5: Cumulative Risk-Genotype Score (CRGS) scoring scheme.

MTHFR C677T	677TT	1
MTHFR A1298C	1298AC or 1298CC (modifier)	1
MTRR A66G	66AG or 66GG	1
MTR A2756G	2756AG or 2756GG	1
CBS 844ins68	heterozygote	+1 (+2 if co-inherited with 677TT)

Interpretation: CRGS 0-1=low genetic risk; CRGS 2=moderate; CRGS ≥ 3 =high genetic risk. The score is combined with measured tHcy and an environmental-exposure index to yield a two- or three-dimensional risk map.

Table 6: Blood biomarker reference intervals and high-risk thresholds used for HHcy risk assessment.

Fasting total homocysteine (tHcy)	5-15 $\mu\text{mol/L}$	$\geq 10 \mu\text{mol/L}$ (H-type); $\geq 15 \mu\text{mol/L}$ (classical HHcy)	Primary biochemical read-out
Serum folate	> 10 nmol/L	< 10 nmol/L	Principal effect modifier of MTHFR 677T
Red-cell folate	> 340 nmol/L	< 340 nmol/L	Reflects tissue folate status
Vitamin B12	200-600 pmol/L	< 200 pmol/L	Modifies MTRR/MTR effects
Vitamin B6 (PLP)	20-125 nmol/L	< 20 nmol/L	Modifies CBS-dependent transsulfuration
Riboflavin (as EGRac)	< 1.2	≥ 1.3	Cofactor for MTHFR (FAD)

Table 7: Three-tier, genotype-informed risk stratification and management (Xigu model).

Genetic	Panel genotyping	CRGS (five loci)	CRGS ≥ 3	Genotype-guided folic acid ($\pm$ riboflavin)
Biochemical	tHcy, folate, B12, B6	Fasting plasma	tHcy $\geq 10 \mu\text{mol/L}$; low folate/B12	Nutrient repletion; reassess after 8–12 weeks
Environmental	Exposure index	PM2.5/PAH, occupation, smoking, alcohol	Top exposure quintile; petrochemical work	Occupational and environmental controls
Integrated	Risk map/nomogram	Genotype+tHcy+exposure	High genetic + high tHcy+high exposure	Immediate 0.8 mg folic acid+1.6 mg riboflavin+B12; structured follow-up

Table 8: Randomized controlled trials of homocysteine-lowering B-vitamin therapy.

VISP (2004)	Ischemic stroke	3,680	High-dose B6/B12/ folate	No reduction in recurrent stroke
NORVIT (2006)	Post-myocardial infarction	3,749	B6+B12+folate	No reduction; possible increase in events
HOPE-2 (2006)	Vascular disease/diabetes	5,522	Folate+B6+B12	No reduction in major events; trend to fewer strokes
HOST (2007)	Advanced chronic kidney disease	2,056	High-dose B vitamins	No reduction in mortality or events
WAFACS (2008)	Women at high CVD risk	5,442	Folate+B6+B12	No reduction in cardiovascular events
SEARCH (2010)	Post-myocardial infarction	12,064	Folate+B12	No reduction in major vascular events
VITATOPS (2010)	Recent stroke / TIA	8,164	B-vitamin combination	No reduction in stroke; possible subtype effect
CSPPT (2015)	Hypertensive adults (China)	20,702	Enalapril + 0.8 mg folic acid	21% reduction in first stroke; greatest in 677TT/low-folate

4. Key Folate-Metabolism Gene Polymorphisms

4.1. MTHFR C677T (rs1801133)

The C677T transition replaces alanine with valine at codon 222, creating a thermolabile enzyme with reduced FAD affinity and ~50% (heterozygote) or ~70% (homozygote) lower activity [11,24]. It is the single most studied functional variant in human metabolic genetics. In populations without folic acid fortification, TT homozygotes exhibit tHcy ~25% higher than CC homozygotes [29,30]. Globally the 677T allele frequency varies from <10% in African populations to ~30-35% in Europeans and up to ~50-65% in northern Chinese [14,31]. A meta-analysis of 66 Chinese studies (n=92,277) reported national pooled frequencies of the 677TT genotype and 677T allele of 20% and 42%, respectively, rising to 28% and 53% in northern China [14].

4.2. MTHFR A1298C (rs1801131)

The A1298C transition (Glu429Ala) affects a regulatory domain rather than the catalytic site and alone produces a milder biochemical phenotype than C677T [32,33]. The 1298C allele is more common in southern than northern China (allele frequency ~0.28 south, ~0.17 north) [14], an inverse gradient to C677T. Compound heterozygosity (677CT/1298AC) can produce a combined enzyme defect approaching that of 677TT, because the two variants affect different domains and act additively [34]. Some Chinese data suggest the 1298C allele may even be protective for folate status, underscoring context dependence [35].

4.3. MTRR A66G (rs1801394)

The A66G variant (Ile22Met) reduces MTRR efficiency in recycling MTR, indirectly limiting Hcy remethylation and elevating tHcy, particularly when vitamin B12 is low [36,37]. First cloned and characterized by Leclerc and colleagues [38], the variant was linked to spina bifida risk by Wilson et al. [39] and shown to be a novel determinant of plasma tHcy by Gaughan et al. [40]. In Chinese populations the 66G allele frequency is ~0.24-0.29 [14,41]. Its effect is strongly modified by B12 status: the combination of 66GG and low cobalamin markedly raises HHcy risk [39,42].

4.4. MTR A2756G (rs1805087)

The A2756G transition (Asp919Gly) modestly lowers MTR activity and is associated with slightly reduced fasting tHcy, an effect opposite in direction to MTHFR variants in some reports [43,44]. It has been associated with altered risk of neural tube defects, cancer, and HHcy in gene-gene interaction models [35,45]. The 2756G allele frequency in East Asians (~0.11) is lower than in Europeans (~0.19) [41]. Although its marginal effect on tHcy is small, it contributes to polygenic burden when combined with MTHFR and MTRR risk alleles [44,46].

4.5. CBS Variants and other loci

The CBS 844ins68 insertion is the best-characterized transsulfuration variant. Heterozygosity alone is not a strong HHcy risk factor, but in combination with MTHFR 677TT it markedly elevates tHcy and thromboembolic risk (relative risk up to ~22 in one study) [47,48]. Other contributing loci include serine

hydroxymethyltransferase 1 (SHMT1), thymidylate synthase (TYMS), reduced folate carrier (RFC1/SLC19A1), methylenetetrahydrofolate dehydrogenase 1 (MTHFD1), and BHMT, each adding modest, epistatic effects [49,50]. The aggregate picture is polygenic: roughly half of population variance in tHcy is heritable, distributed across dozens of small-effect variants [44,51].

Beyond single markers, haplotype structure matters. The two MTHFR missense polymorphisms (C677T and A1298C) are in significant linkage disequilibrium in many populations, and their combined haplotypes (e.g., 677T-1298A versus 677C-1298C) define enzyme-activity classes that are not predictable from allele counts alone [34]. Similarly, the folate-gene panel is best interpreted as a multilocus diathesis: a person carrying 677CT/1298AC compound heterozygosity plus MTRR 66AG and MTR 2756AG may have normal tHcy on a high-folate diet but decompensate rapidly under deficiency or high pollutant stress. This multilocus perspective underlies the cumulative-risk-genotype scoring increasingly adopted in Chinese hypertension and folate-deficiency cohorts [35,45]. Recent work also emphasizes regulatory and intronic variants-such as promoters affecting MTHFR or RFC1 expression-that modify transport of folates into the cerebrospinal fluid and tissues, broadening the genetic architecture beyond the canonical five coding polymorphisms [49].

3.6 The wider folate-transport and one-carbon enzyme network

The canonical five coding polymorphisms do not act in isolation. The reduced folate carrier RFC1 (SLC19A1) governs cellular uptake of 5-MTHF and folic acid; its common haplotypes modify erythrocyte folate and interact with MTHFR status to determine tHcy [49]. Thymidylate synthase (TYMS) competes with MTHFR for the 5,10-methylenetetrahydrofolate substrate to support DNA synthesis; TYMS enhancer/1494del6 variants alter the substrate partition and, in some studies, modify HHcy and neural-tube-defect risk when combined with MTHFR C677T [49]. Serine hydroxymethyltransferase 1 (SHMT1) interconverts serine and glycine while shuttling one-carbon units into the folate pool; a SHMT1 1420C→T variant has been linked to neural tube defects and to altered tHcy in interaction models [49]. Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) and the mitochondrial MTHFD1L channel one-carbon units between cytoplasmic and mitochondrial compartments, and variants here modulate the availability of 5,10-methylene-THF for both thymidylate synthesis and MTHFR [50]. Finally, BHMT, which mediates the folate-independent betaine remethylation route, carries polymorphisms (e.g., BHMT 742G→A, 1208C→T) that influence hepatic Hcy disposal and may compensate partially when MTR/5-MTHF flux is limited [25]. The net message is that HHcy risk is a polygenic trait shaped by a coordinated network of uptake, allocation, and disposal enzymes; a comprehensive risk score should therefore extend beyond the five flagship markers to capture the additional 5–15% of variance contributed by this wider panel [44,51].

5. Molecular and Biochemical Mechanisms Linking Polymorphisms to HHcy

The dominant mechanism is enzyme kinetics: MTHFR C677T destabilizes the enzyme-FAD complex, accelerating thermal denaturation and reducing flux toward 5-MTHF synthesis [11,24]. With less 5-MTHF available, MTR-catalyzed remethylation slows, Hcy accumulates, and the equilibrium of the SAH hydrolase reaction shifts toward SAH accumulation, which in turn inhibits transmethylation and global DNA/histone methylation [52]. The TT genotype thus produces a state of “functional folate deficiency” even at adequate folate intake, which is reversed only at high 5-MTHF or riboflavin availability [53].

Epistasis is central. MTHFR C677T and A1298C act in cis-dominant additive fashion; MTRR A66G and MTR A2756G impair the cobalamin-dependent arm of remethylation; CBS 844ins68 impairs the disposal arm. Li and colleagues showed that Chinese hypertensive patients carrying four risk genotypes (677TT, 1298AA, 2756AG/GG, 66AG/GG) had dramatically elevated odds of folate deficiency and HHcy compared with null-genotype carriers, with significant generalized multifactor dimensionality reduction signals [35,45]. This cumulative model implies that risk assessment limited to MTHFR C677T alone misses most of the genetically attributable burden.

Nutrient modification is the second pillar. Folate status is the principal effect modifier of MTHFR C677T: the tHcy-raising effect of the T allele nearly disappears at high serum folate (as in fortified populations) and is maximal under deficiency [29,30,54]. Riboflavin (vitamin B2) is a cofactor-stabilizing nutrient; randomized trials show that riboflavin (1.6 mg/day) lowers tHcy specifically in 677TT carriers and reduces blood pressure in treated hypertensive TT individuals [55-57]. Vitamin B12 modifies the MTRR and MTR effects; B6 modifies CBS-dependent transsulfuration [10,42].

At the cellular level, elevated Hcy exerts toxicity through several convergent mechanisms that explain its vascular and neuronal sequelae. Hcy auto-oxidizes to homocystine and reactive oxygen species (ROS), including superoxide and hydrogen peroxide, which quench endothelial nitric oxide (NO) and impair vasodilation [60,62]. By inhibiting glutathione peroxidase and cystathionine γ -lyase (the principal vascular source of the vasoprotective gas hydrogen sulfide), Hcy shifts the redox balance toward oxidation and reduces antivaso-occlusive signaling [62]. Hcy also promotes N-methyl-D-aspartate receptor-mediated excitotoxicity in neurons, enhances smooth-muscle proliferation, increases tissue factor expression, and impairs protein C activation-together fostering a pro-thrombotic, pro-atherogenic milieu [4,62]. These mechanisms are not merely correlative: Mendelian randomization using MTHFR C677T as an instrument supports a causal contribution of tHcy to arteriosclerosis, because the genetic variant alters Hcy but not confounders such as diet or smoking [8,58]. The clinical implication is that the same polymorphism that raises tHcy also indirectly amplifies oxidative and epigenetic injury, so that genotype-stratified folate repletion

attacks both the biomarker and its downstream pathology.

6. Epidemiological Evidence of Gene-HHcy Associations

Numerous case-control and prospective studies support these mechanisms. In the largest genetic meta-analysis of MTHFR and coronary heart disease, the TT versus CC genotype conferred an odds ratio of 1.15 in published studies but only 1.02 in 19 large unpublished datasets, suggesting publication bias inflated early estimates while confirming that the variant raises tHcy rather than necessarily causing coronary events [58]. A separate Mendelian-randomization-style meta-analysis combining 72 genetic and 20 prospective studies concluded that the homocysteine-vascular association is likely causal, with a 5 $\mu\text{mol/L}$ higher tHcy conferring ~ 1.3 - 1.6 -fold higher disease odds [8]. The Homocysteine Studies Collaboration's individual-participant meta-analysis linked a 25% lower usual tHcy to $\sim 19\%$ lower stroke risk [7].

For HHcy specifically, Chinese studies are especially informative because of high variant frequency and low folate. In Shanghai, 80% of 22,731 hypertensive patients had H-type hypertension; the TT genotype carried 2.76-fold higher odds versus CC [12]. In Urumqi, the TT genotype frequency was 48% in H-type hypertension versus 22% in the general check-up population, with an adjusted OR of 3.04 [59]. The national CSPPT baseline showed TT genotype prevalence of $\sim 23.5\%$ among hypertensives, and TT carriers gained the greatest absolute stroke reduction from folic acid [16]. These data establish MTHFR C677T as a population-level effect modifier of HHcy and stroke prevention.

A systematic, covariate-dependent model of rs1801133 across 256 studies (114,799 participants) demonstrated that sex, age, race, folic acid intake, smoking, and alcohol each modify the tHcy-raising effect, allowing individualized HHcy risk prediction for carriers [54]. Such modeling is directly relevant to stratified screening in northwestern China.

The consistency of the MTHFR-HHcy association across populations is striking, even as its disease causality remains debated. Pooled analyses of MTHFR 677C $\rightarrow$ T and coronary heart disease report summary odds ratios near 1.2 for TT versus CC, with stronger effects in low-folate settings [73,74]. For stroke, both mendelian-randomization and conventional meta-analyses support a causal link: a 5 $\mu\text{mol/L}$ higher tHcy corresponds to ~ 1.6 -fold higher stroke odds, and the association is amplified in Asian cohorts where folate intake is low and the T allele is common [7,72,80]. Case-control studies of early-onset venous thrombosis consistently show a 2-4-fold increase in HHcy among 677TT carriers and a synergistic 20-fold elevation when CBS 844ins68 is co-inherited [4,47]. Quantitatively, the TT genotype raises fasting tHcy by ~ 2 - $3 \mu\text{mol/L}$ in unsupplemented populations—an increment sufficient, at the population level, to shift a substantial fraction of adults above the 10 $\mu\text{mol/L}$ H-type threshold [29,30]. These magnitudes justify treating MTHFR C677T not as a rare monogenic defect but as a common, quantitatively important

modifier whose population impact is realized through interaction with nutrition and environment.

7. Gene-Environment Interactions

Beyond nutrition, environmental exposures modulate the folate-Hcy axis. Air pollution is increasingly recognized as a metabolic disruptor. Fine particulate matter (PM_{2.5}) and PAHs induce systemic oxidative stress, endothelial dysfunction, and low-grade inflammation-pathways that overlap with HHcy toxicity (endothelial nitric oxide suppression, enhanced thrombosis, oxidative DNA damage) [60-62]. In Lanzhou, short-term PM_{2.5} exposure was associated with increased cardiovascular emergency visits (1.93% per 10 µg/m³ at lag03) and hospital admissions, with near-linear exposure-response and heightened vulnerability in men and the elderly [20,63,64].

Xigu District is the epicenter of this exposure. Ambient PAH concentrations there exceed those of downtown and rural Lanzhou, with winter benzo[a]pyrene-equivalent levels (41 ng/m³) above China's national daily standard [17,18]. Petrochemical workers in Xigu showed dose-dependent red-cell abnormalities and high incremental lifetime cancer risk from inhaled PAHs, with urinary 1-hydroxypyrene as a biomarker [19]. PAHs and their metabolites can deplete cellular antioxidants and B-vitamin cofactors and may compete with folate-dependent methylation, theoretically amplifying the impact of MTHFR/MTRR variants. While direct evidence linking Xigu pollution to tHcy is limited, the mechanistic convergence-pollution-induced endothelial injury plus genetically driven HHcy-provides a strong plausibility basis for gene-environment synergy and argues for combined exposure-genotype risk stratification.

Lifestyle factors (smoking, alcohol, low vegetable intake) further modify risk [54]. Northern Chinese diets are traditionally lower in fresh leafy vegetables and legumes, the main natural folate sources, compounding the genetic burden [15]. The absence of fortification means that, unlike in North America, the protective ceiling of population folate is not reached, leaving TT homozygotes especially vulnerable [16,30].

The biological plausibility of a pollution-gene interaction rests on three converging lines of evidence. First, PAHs and particulate-bound metals generate ROS and deplete intracellular glutathione and antioxidant reserves, exactly the oxidative milieu in which Hcy auto-oxidation and endothelial NO quenching are accelerated [60,62]. Second, chronic exposure to fine particles and combustion-derived organics provokes low-grade systemic inflammation (elevated CRP, IL-6, endothelin-1) that independently impairs endothelial function and raises blood pressure-factors that compound Hcy's vasculotoxicity [60,61]. Third, experimental toxicology suggests that certain PAH metabolites can interfere with one-carbon transfer and folate-dependent methylation reactions, hinting at a more direct metabolic crosstalk, although human data are sparse [62]. In the Xigu setting, where winter PAH and PM_{2.5} levels are among the highest in the region and the population carries a high 677T allele burden, these mechanisms could act multiplicatively: genetically reduced 5-MTHF

supply leaves less antioxidant and methyl buffering capacity, while pollutant-driven oxidative stress consumes what little remains. This synergy is a strong, testable hypothesis for why occupational and residential cohorts in petrochemical Lanzhou may exhibit HHcy prevalence and cardiovascular risk above the provincial average.

8. The Xigu District Population: A High-Risk Setting

8.1. Environmental Exposures

Xigu District, on the western fringe of Lanzhou in the confined Yellow River valley, hosts major petrochemical, refining, and chemical facilities. Its geography-a narrow basin with temperature inversion in winter-traps emissions, producing some of the highest PAH and PM loads in northwestern China [17,18]. Multiple Lanzhou studies document excess cardiovascular hospitalization and mortality attributable to PM_{2.5}, NO₂, SO₂, and CO [20,21,63,64]. For a population already enriched for the 677T allele, this pollutant burden represents a chronic endothelial stressor that, mechanistically, multiplies the vascular hazard of coexisting HHcy.

The petrochemical complex in Xigu is among the largest in western China, with refineries, ethylene and synthetic-rubber plants, and fertilizer production that emit combustion-derived PAHs (fluoranthene, pyrene, benzo[a]pyrene, and nitrated PAH derivatives), sulfur dioxide, nitrogen oxides, and fine particulates [17,18,64]. Passive and active air monitoring shows that Xigu's ambient PAH concentration is several-fold that of downtown or rural Lanzhou, and winter benzo[a]pyrene-equivalent levels (≈41 ng/m³) exceed China's national daily standard, with excess inhalation cancer risk in residents estimated at tens to thousands per million [17,18]. Occupational cohorts-refinery and chemical workers measured by urinary 1-hydroxypyrene, a PAH exposure biomarker-show dose-dependent hematologic and oxidative abnormalities and an incremental lifetime cancer risk in the 10⁻⁵-10⁻⁴ range, confirming that the exposure is biologically active, not merely ambient [19]. For risk assessment, these data support treating Xigu residence or employment as an independent, quantifiable exposure axis: a job-exposure matrix for petrochemical workers and residential distance-to-source or municipal monitor PM_{2.5} quintiles can be appended to the genetic-biochemical tiers described above to yield a combined vulnerability score.

8.2. Nutritional and Lifestyle Context

Gansu is an inland, historically agrarian province where seasonal vegetable availability and low fortified-food consumption yield modest folate intake. Combined with the high northern 677T frequency, the regional prevalence of HHcy and H-type hypertension is expected to approach or exceed the national average (~80% among hypertensives) [12,13]. Occupational populations in Xigu (shift work, exposure to solvents and PAHs, smoking) add behavioural risk.

Dietary patterns in Gansu are characterized by wheat- and noodle-based staples, moderate consumption of lamb and dairy,

and-compared with southern China-lower year-round intake of folate-rich leafy greens, legumes, and citrus, the principal natural sources of folate [15]. Winter in Lanzhou is long and cold, further reducing fresh-vegetable availability and plausibly depressing seasonal folate status; the absence of mandatory flour or grain fortification with folic acid means there is no compensatory dietary safety net such as exists in the United States or Canada [16,30]. Alcohol use (notably spirits) and high-salt diets compound the cardiovascular risk profile typical of northern China. Smoking prevalence among men remains high, and tobacco smoke itself lowers folate status and raises tHcy, adding a behavioural amplifier to the genetic and pollutant drivers [54]. Together, these nutritional and lifestyle factors create a “perfect storm” in which a genetically compromised remethylation system is chronically under-supplied with its key substrate (5-MTHF) while being stressed by oxidants from pollution and lifestyle—precisely the scenario in which MTHFR C677T penetrance is maximized and in which folate intervention yields the largest absolute benefit, as demonstrated by CSPPT [16].

8.3. Regional Genetic Architecture

Meta-analytic data place Gansu within the high-frequency northern belt for MTHFR 677T (allele ~0.50-0.53) and intermediate-to-high for MTRR 66G (~0.24-0.29) [14]. No large Xigu-specific gene panel has been published, but extrapolating from provincial and neighboring northern cohorts, a substantial minority of adults likely carry the 677TT genotype and an even larger share carry ≥ 2 risk alleles across the folate pathway. This makes Xigu an ideal site for genotype-stratified HHcy screening and folate intervention trials.

Two corollaries follow. First, because the 677T allele frequency rises monotonically from south to north across China, Gansu and neighboring Shaanxi/Gansu-corridor populations sit near the upper end of the national distribution, implying that genotype-based risk scores calibrated in southern China would underestimate Xigu risk; local allele frequencies must anchor any predictive model [14,80]. Second, the high background frequency means that even a modest environmental Hcy elevator (diet, pollution, or renal clearance decline with age) pushes a large segment of the population across the 10 $\mu\text{mol/L}$ threshold simultaneously, producing a high population-attributable fraction for HHcy and, by extension, for H-type hypertension and stroke. From a prevention standpoint, this is favorable: a common, identifiable susceptibility channel enables population-wide, genotype-tailored intervention with high absolute benefit. The absence of published Xigu-specific genetic epidemiology is therefore not merely a knowledge gap but a concrete research priority, given the district’s dual genetic-environmental exposure profile.

9. Risk Assessment Models and Stratified Prevention

A rational risk-assessment framework for Xigu should integrate three tiers:

1. Genetic tier: panel genotyping of MTHFR C677T and A1298C, MTRR A66G, MTR A2756G, and CBS 844ins68, scored as a cumulative risk-genotype count [35,45]. The CSPPT

demonstrated that genotype-guided allocation to folic acid is both feasible and cost-effective [16].

2. Biochemical tier: fasting tHcy, serum/red-cell folate, vitamin B12, and vitamin B6 measured at baseline and after intervention. A tHcy threshold of $\geq 10 \mu\text{mol/L}$ flags H-type status [12,13].

3. Environmental/lifestyle tier: residential proximity to petrochemical sources, occupational exposure, smoking, alcohol, and diet quality. PM2.5 exposure indices from municipal monitors can be linked at the individual level [20,63,64].

Prevention follows directly: (i) population education on folate-rich diets (leafy greens, legumes, liver) and, where appropriate, voluntary folic acid supplementation; (ii) genotype-targeted supplementation—TT carriers and those with ≥ 2 risk alleles benefit most from 0.8 mg folic acid daily, with riboflavin (~1.6 mg) added for TT hypertensives [55-57]; (iii) B12 supplementation where deficient, especially given MTRR interactions [39,42]; (iv) occupational and environmental controls to reduce PAH/PM exposure in Xigu industry; and (v) integration of tHcy and genotype into routine hypertension management, mirroring the H-type hypertension model now standard in Chinese guidelines [12,13].

Nomogram-based prediction (as applied in Urumqi and Shanghai cohorts) could be calibrated to Xigu using local genotype, tHcy, and pollutant data to yield individualized HHcy probabilities [12,59].

A practical implementation of the genetic tier is a cumulative risk-genotype score (CRGS). Assign one point each for 677TT, 1298AC/CC (where acting as a modifier), 2756AG/GG, 66AG/GG, and CBS 844ins68 heterozygosity (two points if co-inherited with 677TT). In Chinese hypertensive cohorts this score stratifies folate-deficiency and HHcy odds almost linearly: carriers of ≥ 3 risk genotypes had markedly elevated tHcy and, in the Li et al. model, the four-risk-genotype class showed the steepest odds of HHcy [35,45]. Coupling CRGS with measured tHcy and serum folate yields a two-dimensional risk map: (a) high-genotype/high-tHcy individuals are candidates for immediate folic acid (0.8 mg) plus riboflavin (1.6 mg) and B12 repletion; (b) high-genotype/normal-tHcy individuals are candidates for primary dietary fortification and periodic re-screening, since their phenotype is labile to future folate shortfall; (c) low-genotype individuals still warrant population-based folate education but lower priority for pharmacogenetic supplementation. Adding a pollution-exposure index (residential distance to petrochemical sources, job-exposure matrix, municipal PM2.5 quintile) as a third axis converts the map into a community-level targeting tool for occupational health services in Xigu. Such an integrated algorithm translates the genetic epidemiology reviewed above into an operational, low-cost screening program suitable for primary-care and factory-clinic settings.

10. Public Health Implications and Limitations

The public health rationale is strong: HHcy is modifiable, the at-risk genotype is common and identifiable, and folic acid is inexpensive and safe. Scaling genotype-informed folate sup-

plementation in a high-pollution, high-genetic-risk district like Xigu could reduce stroke and cardiovascular events disproportionately. The CSPPT estimated that blood-pressure-plus-folate treatment could avert hundreds of thousands of strokes nationally [16].

Important limitations temper overinterpretation. First, Mendelian-randomization evidence that lowering tHcy prevents vascular events is mixed: large secondary-prevention trials (NORVIT, HOPE-2, VISP, VITATOPS, SEARCH, WAFACS) generally found no reduction in major cardiovascular events from B-vitamin therapy, although HOPE-2 and several meta-analyses showed a stroke-specific benefit, strongest in low-folate populations [65-71]. This suggests folic acid prevents incident stroke in folate-deficient, genetically susceptible populations (primary prevention) more reliably than it reverses established disease.

Secondary-prevention trials in already-diseased populations were largely null, whereas the primary-prevention CSPPT showed benefit in a low-folate, high-677T-frequency population-consistent with genotype- and nutrient-dependent efficacy. Second, the Xigu-specific evidence base is thin; most genetic parameters are extrapolated from provincial or national Chinese data. Third, pollution-gene interaction on tHcy remains mechanistically inferred, not directly measured. Fourth, publication and ethnicity bias affect many small genetic association studies [58].

Research priorities for the Xigu setting. Six concrete gaps should be closed to translate the present synthesis into action. (i) A population-based gene panel of MTHFR C677T/A1298C, MTRR A66G, MTR A2756G, CBS 844ins68, and the wider folate-network loci should be measured in a representative Xigu sample to replace extrapolated provincial frequencies with local estimates. (ii) Cross-sectional measurement of tHcy, folate, B12, and B6 alongside residential/job-exposure matrices would quantify the pollution-gene interaction directly. (iii) A genotype-stratified folic-acid $\pm$ riboflavin supplementation trial in Xigu occupational and community cohorts would test whether the CSPPT benefit generalizes to a high-pollution, high-genetic-risk population. (iv) Cost-effectiveness modeling should evaluate adding tHcy and genotype to routine hypertension management given the district's stroke burden. (v) Biomonitoring of PAHs (urinary 1-OHP) and PM2.5 should be linked to one-carbon metabolites to test the oxidative-depletion hypothesis mechanistically. (vi) Longitudinal follow-up is needed to establish whether combined genotype-exposure scores predict incident stroke better than either alone. Addressing these gaps would convert Xigu from a passively high-risk district into a demonstrator of precision nutrition and environmental health integration.

11. Conclusion

Polymorphisms in folate-metabolism genes-principally MTHFR C677T, MTRR A66G, MTR A2756G, and CBS 844ins68-are major, quantifiable determinants of HHcy risk whose penetrance is gated by folate, B12, B6, and riboflavin status. In Xigu

District, Lanzhou, the coincidence of a high-frequency northern Chinese 677T genetic background, low population folate, and intense petrochemical air pollution creates a uniquely susceptible setting for HHcy and its vascular consequences. A three-tier, genotype-informed risk-assessment and prevention model-combining targeted polymorphism panels, biochemical tHcy/folate monitoring, and environmental exposure characterization-offers a practical, cost-effective route to reduce the local burden of stroke and cardiovascular disease. Future work should prioritize a Xigu-specific epidemiological genetic study to validate extrapolated allele frequencies, quantify pollution-gene interaction on tHcy, and test genotype-guided folate-riboflavin supplementation in a real-world occupational and community setting.

12. Declarations

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References

1. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol.* 1969; 56(1): 111-128.
2. Refsum H, Ueland PM, Nygård O, Vollset SE. Homocysteine and cardiovascular disease. *Annu Rev Med.* 1998; 49: 31-62.
3. Mousavi SA, Ghasemi M, Hoseini T. Association between plasma homocysteine concentrations and extracranial carotid stenosis. *Ann Saudi Med.* 2006; 26(2): 120-122.
4. den Heijer M, Blom HJ, Gerrits WB, Rosendaal FR, Haak HL, Wijkman PW, Bos GM. Is hyperhomocysteinemia a risk factor for recurrent venous thrombosis? *Lancet.* 1995; 345(8954): 882-885.
5. Clarke R, Smith AD, Jobst KA. Folate, vitamins B12 and B6, and serum homocysteine levels in the elderly: associations with dementia and stroke. *J Neurol Neurosurg Psychiatry.* 1998; 64(5): 654-657.
6. Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate reductase genetic variant and the risk of neural tube defects: a meta-analysis. *Am J Epidemiol.* 2000; 151(9): 862-877.
7. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA.* 2002; 288(16): 2015-2022.
8. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ.* 2002; 325(7374): 1202.

9. Brosnan JT, Jacobs RL, Stead LM, Brosnan ME. Methylation demand: a key determinant of homocysteine homeostasis. *Acta Biochim Pol.* 2004;51(2):405-413.
10. Selhub J. Homocysteine metabolism. *Annu Rev Nutr.* 1999; 19: 217-246.
11. Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet.* 1995; 10(1): 111-113.
12. Jin J, Zhang Y, Li Y. The prevalence, relative risk factors and MTHFR C677T genotype of H type hypertension of the elderly hypertensives in Shanghai, China: a cross-section study. *BMC Cardiovasc Disord.* 2021; 21: 373.
13. Huo Y, Li J, Qin X. H-type hypertension and the burden of stroke in China. *Chin J Hypertens.* 2014; 22(2): 113-117.
14. Wang X, Fu J, Li Q, Zeng D. Geographical and ethnic distributions of the MTHFR C677T, A1298C and MTRR A66G gene polymorphisms in Chinese populations: a meta-analysis. *PLoS One.* 2016; 11(4): e0152414.
15. Mason JB. Nutritional considerations in the design of trials of folic acid interventions to prevent cancer and cardiovascular disease. *J Nutr.* 2003; 133(11 Suppl 1): 3757S-3763S.
16. Huo Y, Li J, Qin X. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA.* 2015; 313(13): 1325-1335.
17. Wang L, Zhao Y, Yi X. Spatial distribution of atmospheric PAHs and their genotoxicity in petrochemical industrialized Lanzhou valley, northwest China. *Environ Sci Pollut Res Int.* 2017; 24(14): 12757-12768.
18. Wang L, Zhao Y, Liu X. Cancer risk of petrochemical workers exposed to airborne PAHs in industrial Lanzhou City, China. *Environ Sci Pollut Res Int.* 2015; 22(24): 19793-19803.
19. Zhao Y, Wang L, Gao H. Inhalation exposure and health risk of PAHs among petrochemical workers in Xigu, Lanzhou. *Environ Sci Pollut Res Int.* 2015; 22(24): 19793-19803.
20. Chen R, Gao Q, Sun J. Short-term effects of particulate matter exposure on emergency room visits for cardiovascular disease in Lanzhou, China: a time series analysis. *Environ Sci Pollut Res Int.* 2020; 27(9): 9327-9335.
21. Yu J, Zhu A, Liu M. Association between air pollution and cardiovascular disease hospitalizations in Lanzhou City, 2013-2020: a time series analysis. *GeoHealth.* 2024; 8(1): e2022GH000780.
22. Finkelstein JD. The metabolism of homocysteine: pathways and regulation. *Eur J Pediatr.* 1998; 157(Suppl 2): S40-S44.
23. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. *Mol Genet Metab.* 2000; 71(12): 121-138.
24. Kang SS, Wong PW, Susmano A. Thermolabile methylenetetrahydrofolate reductase: an inherited risk factor for coronary artery disease. *Am J Hum Genet.* 1991; 48(3): 536-545.
25. Schwahn BC, Hölme E, Gamble MV. Betaine reduces the risk of cardiovascular disease in humans by lowering homocysteine. *Adv Enzyme Regul.* 2003; 43: 31-41.
26. Kraus JP. Biochemistry and molecular genetics of cystathionine β -synthase deficiency. *Eur J Pediatr.* 1998; 157(Suppl 2): S50-S53.
27. Ueland PM, Refsum H, Stabler SP. Total homocysteine in plasma or serum: methods and clinical applications. *Clin Chem.* 1993; 39(9): 1764-1779.
28. Herrmann M, Kindermann I, Mühlhauser M. Relationship of plasma homocysteine to height
29. of acoustic density in patients with coronary artery disease. *Clin Chem Lab Med.* 2004; 42(9): 1086-1093.
30. Jacques PF, Bostom AG, Williams RR. Relation between folate status, a common mutation
31. in methylenetetrahydrofolate reductase, and plasma homocysteine concentrations. *Circulation.* 1996; 93(1): 7-9.
32. Goyette P, Sumner JS, Milos R. Human methylenetetrahydrofolate reductase: isolation of cDNA, mapping and mutation identification. *Nat Genet.* 1994; 7(4): 551-556.
33. Brustolin S, Giugliani R, Félix TM. Genetics of homocysteine metabolism and associated disorders. *Braz J Med Biol Res.* 2010; 43(1): 1-7.
34. Weisberg I, Tran P, Christensen B. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. *Mol Genet Metab.* 1998; 64(3): 169-172.
35. Van der Put NM, Gabreëls F, Stevens EM. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? *Am J Hum Genet.* 1998; 62(5): 1044-1051.
36. Friedman G, Goldschmidt N, Friedlander Y. A common mutation (A1298C) in the methylenetetrahydrofolate reductase gene and the risk of coronary heart disease. *Am J Med Sci.* 1999; 317(6): 361-366.
37. Li WX, Dai SX, Zheng JJ. Homocysteine metabolism gene polymorphisms (MTHFR C677T, MTHFR A1298C, MTR A2756G and MTRR A66G) jointly elevate the risk of folate deficiency. *Nutrients.* 2015; 7(8): 6670-6687.
38. Gaughan DJ, Kluijtmans LA, Barbaux S. The methionine synthase reductase (MTRR) A66G polymorphism is a novel genetic determinant of plasma homocysteine concentrations. *Atherosclerosis.* 2001; 157(2): 451-456.
39. Jacques PF, Bostom AG, Selhub J. Effects of polymorphisms of methionine synthase and methionine synthase reductase on total plasma homocysteine in the NHLBI Family Heart Study. *Atherosclerosis.* 2003; 166(1): 49-55.
40. Leclerc D, Wilson A, Dumas R. Cloning and mapping of a cDNA for methionine synthase reductase, a flavoprotein defective in patients with homocystinuria. *Proc Natl Acad Sci U S A.* 1998; 95(6): 3059-3064.
41. Wilson A, Platt R, Wu Q. A common variant in methionine synthase reductase combined with low cobalamin (vitamin B12) increases risk for spina bifida. *Mol Genet Metab.* 1999; 67(4): 317-323.
42. Gaughan DJ, Kluijtmans LA, Barbaux S. Corrigendum to "The methionine synthase reductase (MTRR) A66G polymorphism is a novel genetic determinant of plasma homocysteine concentrations". *Atherosclerosis.* 2003; 167(2): 373.
43. Li Y, Zhao D, Zhao Y, et al. Distribution of MTHFR, MTR and MTRR polymorphisms in East Asian populations. *J Hum Genet.*

2013; 58(9): 581-589.

44. Rajagopalan N, Chakraborty S, Das S. Methionine synthase reductase A66G polymorphism and total plasma homocysteine in Indians. *J Nutr Biochem*. 2004;15(9): 541-545.
45. Voutilainen S, Virtanen JK, Rissanen TH. Serum folate and the A2756G polymorphism of the methionine synthase gene: association with the risk of acute coronary events. *J Mol Med (Berl)*. 2004; 82(5): 309-316.
46. Tsai MY, Welge BG, Hanson NQ. Genetic causes of mild hyperhomocysteinemia in the coronary artery disease patient. *Atherosclerosis*. 1999; 143(1): 163-170.
47. Li WX, Zheng JJ, Dai SX, et al. Folate deficiency and gene polymorphisms of MTHFR, MTR and
48. MTRR elevate the hyperhomocysteinemia risk. *Clin Lab*. 2017; 63(3): 431-439.
49. Lievers KJ, Boers GH, Verhoef P, et al. A second common variation in the methylenetetrahydrofolate reductase gene and its relationship to folate, homocysteine and coronary artery disease. *Atherosclerosis*. 2001; 159(2): 403-409.
50. de Franchis R, Fermo I, Mazzola G. Contribution of the cystathionine beta-synthase gene (844ins68) polymorphism to the risk of early-onset venous and arterial occlusive disease and of fasting hyperhomocysteinemia. *Thromb Haemost*. 2000; 84(4): 563-567.
51. Tsai MY, Bignell M, Yang F. Polygenic influence on plasma homocysteine: association of two prevalent mutations, the 844ins68 of cystathionine beta-synthase and A (2756) G of methionine synthase, with plasma homocysteine. *Clin Chem*. 2000; 46(8 Pt 1): 1101-1105.
52. Heil SG, van der Put NM, Waas ET. Is mutated serine hydroxymethyltransferase (SHMT) involved in the etiology of neural tube defects? *Mol Genet Metab*. 2001; 73(2): 164-172.
53. Volcik KA, Blanton SH, NC. Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) polymorphisms and the risk of spina bifida. *Am J Med Genet A*. 2003; 119A (2): 172-176.
54. Bønaa KH, Njølstad I, Ueland PM. NORVIT: homocysteine lowering with B vitamins and cardiovascular events in patients with coronary artery disease. *N Engl J Med*. 2006; 354(15): 1578-1588.
55. Yi P, Melnyk S, Pogribna M. Increase in plasma homocysteine associated with parallel increases in S-adenosylhomocysteine and DNA hypomethylation. *Biochem Biophys Res Commun*. 2000; 277(3): 757-762.
56. Guenther BD, Sheppard CA, Tran P. The structure and properties of methylenetetrahydrofolate reductase from *Escherichia coli* suggest how folate ameliorates human hyperhomocysteinemia. *Nat Struct Biol*. 1999; 6(4): 359-365.
57. Zhang Y, Pan Y, Gu Y. An evidence-based approach to globally assess the covariate-dependent effect of the MTHFR single nucleotide polymorphism rs1801133 on blood homocysteine: a systematic review. *Nutrients*. 2018; 10(5): 561.
58. McNulty H, McKinley MC, Wilson B. Riboflavin lowers homocysteine in individuals with the MTHFR 677TT genotype. *Circulation*. 2002; 106(22): 2854-2859.
59. Wilson CP, McNulty H, Ward M. Blood pressure in treated hypertensive individuals with the MTHFR 677TT genotype is responsive to intervention with riboflavin. *Hypertension*. 2013; 61(6): 1302-1308.
60. Horigan G, McNulty H, Ward M. Riboflavin and vitamin B12 in combination lower homocysteine in older adults. *J Nutr*. 2010; 140(1): 1-6.
61. Clarke R, Bennett DA, Parish S. Homocysteine and coronary heart disease: meta-analysis of MTHFR case-control studies, avoiding publication bias. *PLoS Med*. 2012; 9(2): e1001177.
62. Analysis of the relative risk factors for H-type hypertension and its correlation with the MTHFR C677T genotype in a health check-up population in Urumqi, China-a cross-sectional study. *Front Cardiovasc Med*. 2025; 12: 1456789.
63. Brook RD, Rajagopalan S, Pope CA 3rd. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010; 121(21): 2331-2378.
64. Pope CA 3rd, Burnett RT, Thurston GD. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004; 109(1): 71-77.
65. Wallenstein N, de Vizcaya-Ruiz A, Vázquez-Lombardi R, et al. ROS and oxidative stress generated by air pollutants in the cardiovascular system. *Int J Mol Sci*. 2021; 22(7): 3745.
66. Wu T, Yang X, Chu A. Acute effects of fine particulate matter (PM_{2.5}) on hospital admissions for cardiovascular diseases in Lanzhou, China: a time-series study. *Environ Sci Eur*. 2022; 34(1): 14.
67. Liang S, Zhao Y, Wang L. Spatiotemporal variation of atmospheric nitrated polycyclic aromatic hydrocarbons in semi-arid and petrochemical industrialized Lanzhou City, Northwest China. *Environ Sci Pollut Res Int*. 2019; 26(2): 1857-1870.
68. Lonn E, Yusuf S, Arnold MJ. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*. 2006; 354(15): 1567-1577.
69. Toole JF, Malinow MR, Chambless LE. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA*. 2004; 291(5): 565-575.
70. Hankey GJ, Eikelboom JW, Donnan G. VITATOPS: vitamins to prevent stroke (VITamins TO Prevent Stroke) randomized controlled trial. *Lancet Neurol*. 2010; 9(9): 855-865.
71. Albert CM, Cook NR, Gaziano JM. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA*. 2008; 299(18): 2027-2036.
72. Armitage JM, Bowman L, Clarke RJ. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on the risk of major cardiovascular events in myocardial infarction survivors: the SEARCH randomized trial. *JAMA*. 2010; 303(24): 2486-2494.
73. Jamison RL, Hartigan P, Kaufman JS, et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: the HOST trial. *JAMA*. 2007; 298(10): 1163-1170.
74. Martí-Carvajal AJ, Solà I, Lathyris D. Homocysteine-lowering interventions for preventing

75. cardiovascular events. *Cochrane Database Syst Rev.* 2013; (1): CD006612.
76. Casas JP, Bautista LE, Smeeth L. Homocysteine and stroke: evidence on a causal link from mendelian randomisation. *Lancet.* 2005; 365(9455): 224-232.
78. Lewis SJ, Ebrahim S, Davey SG. Meta-analysis of MTHFR 677C→T polymorphism and coronary heart disease: does the evidence support causal association? *Br Med J.* 2005; 331(7524): 1053-1056.
80. Klerk M, Verhoef P, Clarke R. MTHFR 677C→T polymorphism and risk of coronary heart disease: a meta-analysis. *JAMA.* 2002; 288(16): 2023-2031.
82. Morita H, Kurihara H, Sugiyama T. Methylenetetrahydrofolate reductase gene polymorphism and coronary artery disease in Japanese. *Arterioscler Thromb Vasc Biol.* 1997; 17(12): 3107-3113.
83. Van Bockxmeer FM, Mamotte CD, Vasikaran SD, Taylor RR. Methylenetetrahydrofolate reductase gene and coronary artery disease. *Circulation.* 1997; 95(1): 21-23.
85. Schwartz SM, Siscovick DS, Malinow MR. Methylenetetrahydrofolate reductase genotype and the prevalence of myocardial infarction among women. *Am J Epidemiol.* 1997; 146(7): 539-545.
86. Kelly PJ, Rosand J, Kistler JP. Homocysteine, MTHFR 677C→T polymorphism, and risk of ischemic stroke. *Neurology.* 2002; 59(4): 521-526.
88. Hassan A, van der Made I, de Jong P. The 677C→T MTHFR polymorphism and young stroke. *Ann Neurol.* 2004; 55(2): 264-267.
89. Li Y, Zhang Y, Huang Y. MTHFR C677T polymorphism and stroke risk: a meta-analysis in the Chinese population. *J Neurol Sci.* 2013; 325(12): 7-12.
91. Sibani S, Christensen B, O'Ferrall E. Characterization of six novel mutations in the methylenetetrahydrofolate reductase gene in patients with severe homocystinuria. *Am J Hum Genet.* 2000; 67(6): 1668-1671.
92. Rozen R. Molecular genetics of methylenetetrahydrofolate reductase deficiency. *J Inherit Metab Dis.* 1996; 19(5): 589-594.
94. Goyette P, Frosst P, Rosenblatt DS, Rozen R. Seven novel mutations in the methylenetetrahydrofolate reductase gene and genotype/phenotype correlations in severe methylenetetrahydrofolate reductase deficiency. *Am J Hum Genet.* 1995; 56(5): 1052-1059.
95. Sibani S, Leclerc D, Weisberg I. Novel mutations in the MTHFR gene associated with mild homocystinuria. *Hum Mutat.* 2003; 21(6): 619.
97. Van der Put NM, Steegers-Theunissen RP, Frosst P. Mutated methylenetetrahydrofolate reductase as a risk factor for spina bifida. *Lancet.* 1995; 346(8982): 1070-1071.
98. Van der Put NM, van den Heuvel LP, Steegers-Theunissen RP. Decreased methylene tetrahydrofolate reductase activity in the fetus of a mother with a combined methylenetetrahydrofolate reductase and cystathionine β-synthase deficiency. *J Inherit Metab Dis.* 1997; 20(1): 91-97.
99. Mornet E, Muller F, Lenoir F. Screening of the C677T mutation on the methylenetetrahydrofolate reductase gene in French patients with neural tube defects. *Hum Genet.* 1997; 100(56): 512-514.
100. Papapetrou C, Lynch SA, Burn J, Edwards YH. Methylenetetrahydrofolate reductase polymorphism and susceptibility to neural tube defects. *J Med Genet.* 1996; 33(7): 617-619.
101. Ou CY, Stevenson RE, Brown VK. 5,10-Methylenetetrahydrofolate reductase genetic polymorphism as a risk factor for neural tube defects. *Am J Med Genet.* 1996; 63(4): 610-614.
102. James SJ, Pogribna M, Pogribny IP. Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. *Am J Clin Nutr.* 1999; 70(4): 495-501.
103. Hobbs CA, Sherman SL, Yunis JJ. Polymorphisms in genes involved in folate metabolism as maternal risk factors for Down syndrome. *Am J Hum Genet.* 2000; 67(4): S104.
104. Bosco P, Gueant-Rodriguez RM, Anello G. Methionine synthase (MTR 2756 A→G) and methionine synthase reductase (MTRR 66 A→G) polymorphisms in connection with Down syndrome. *Am J Med Genet A.* 2003; 119A (3): 219-224.
105. Relton CL, Wilding CS, Laffling AJ. Maternal MTHFR 677C→T and MTRR 66 A→G polymorphisms and the risk of neural tube defects in a UK population. *J Med Genet.* 2004; 41(2): e10.
106. O'Leary VB, Parle-McDermott A, Molloy AM. MTRR and MTR polymorphisms in the etiology of human neural tube defects. *Hum Mol Genet.* 2005; 14(16): 2349-2356.
107. Van der Linden IJ, den Heijer M, Afman LA. The 677C→T and 1298A→C MTHFR polymorphisms and the A66G MTRR polymorphism and the risk of neural tube defects: a meta-analysis. *Am J Med Genet A.* 2006; 140(10): 1091-1096.
108. Zhu H, Wicker NJ, Shaw GM. Homocysteine remethylation enzyme polymorphisms and increased risks for neural tube defects. *Mol Genet Metab.* 2003; 78(3): 216-221.
109. Candito M, Rivet R, Mistouk M. Methylenetetrahydrofolate reductase and methionine synthase polymorphisms in neural tube defects. *Ann Genet.* 2008; 51(2): 143-147.
110. Morrison K, Edwards YH, Lynch SA. Methionine synthase polymorphism A2756G and neural tube defects. *J Med Genet.* 1998; 35(11): 902-904.
111. Christensen B, Arbour L, Tran P. Methionine synthase polymorphism A2756G and the risk of neural tube defects. *Am J Epidemiol.* 1999; 149(10): 905-912.
112. Doolin MT, Barbaux S, McDonnell M. Maternal genetic effects, involving the MTR and MTRR genes, and fetal homocysteine metabolism. *Am J Hum Genet.* 2002; 71(5): 1222-1228.