Salt Intake, Blood Pressure, and the *AGT* Locus: Evidence for Gene–Sodium Interaction (Literature Review)

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ABSTRACT

Background:
High dietary sodium exposure increases blood pressure at the population level, yet the magnitude of the blood pressure response to sodium intake differs substantially between individuals. This heterogeneity, often described as salt sensitivity, reflects variation in renal sodium handling and neurohormonal control systems, including the renin–angiotensin system. The *AGT* gene encodes angiotensinogen, the precursor substrate for angiotensin peptides, which is a biologically plausible locus for sodium-related blood pressure responsiveness because *AGT* variation has been linked to essential hypertension susceptibility and to differences in circulating angiotensinogen concentrations (Jeunemaitre, 1992).

Methods:
A synthesis of peer-reviewed studies was conducted using a targeted literature search. Human case–control, cohort, and dietary intervention/feeding studies were included if they evaluated angiotensinogen (*AGT*) genetic variation (e.g., rs699/M235T) in relation to dietary sodium exposure (assessed by intake estimates, urinary sodium excretion, or controlled sodium manipulation) and blood pressure–related outcomes (resting blood pressure, salt sensitivity phenotypes, hypertension prevalence/incidence, or diet-induced blood pressure change).

Results:
Molecular genetic evidence established *AGT* as a hypertension susceptibility locus and connected *AGT* genotypes with circulating angiotensinogen concentrations, supporting a mechanistic intermediate phenotype for downstream hemodynamic effects (Jeunemaitre, 1992). In controlled dietary settings, *AGT* genotype stratified blood pressure responses to sodium reduction and to blood pressure–lowering dietary patterns; notably, Trials of Hypertension Prevention Phase II demonstrated genotype-dependent differences in long-term blood pressure change and incident hypertension under sodium reduction using an *AGT* promoter polymorphism, and a feeding study reported genotype-stratified blood pressure responses to dietary patterns

at controlled sodium intake (Hunt, 1998; Svetkey, 2001). In population studies with urinary sodium biomarkers, the sodium–blood pressure association was steeper among carriers of higher-risk *AGT* genotypes at higher sodium exposure, consistent with a gene–environment interaction model (Iso, 2000; Norat, 2008). In hypertensive cohorts, rs699 (*AGT* 704T>C) has been associated with blood pressure severity and metabolic comorbidity patterns, even when case–control frequency differences are not observed (Repchuk, 2021).

Discussion:
Across intervention and observational evidence, common *AGT* variants are consistently biologically plausible modifiers of salt-related blood pressure regulation, with strongest signals at higher sodium exposure and in specific populations (Jeunemaitre, 1992; Hunt, 1998; Norat, 2008; Iso, 2000).

Subjects: Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, NaCl

INTRODUCTION

Sodium is required daily to maintain extracellular fluid volume, transmembrane electrochemical gradients, neuromuscular excitability, and acid–base homeostasis. Nevertheless, sustained exposure to high dietary sodium increases extracellular volume burden and renal sodium load and can elevate blood pressure through compensatory natriuresis accompanied by hemodynamic and neurohormonal adaptations that, in susceptible individuals, favor higher vascular tone and higher blood pressure (Bie, 2004; Balafa, 2021). A defining feature of sodium-related blood pressure regulation is substantial inter-individual heterogeneity: salt sensitivity, commonly operationalized as a larger blood pressure change in response to sodium loading or restriction, is influenced by age, baseline blood pressure, renal function, and genetic variation in pathways governing vascular resistance and renal sodium handling (Balafa, 2021).

Among candidate pathways, the renin–angiotensin system is central to integrated control of vascular tone and renal sodium balance. Human genetic evidence implicating angiotensinogen (*AGT*) as a susceptibility locus for essential hypertension, and as a determinant of circulating angiotensinogen concentrations, provides a mechanistic rationale for *AGT*-dependent differences in blood pressure responsiveness to dietary sodium exposure (Jeunemaitre, 1992). Population studies further suggest that *AGT*-associated differences in hypertension risk and sodium–blood pressure relationships can be more evident under higher sodium exposure, consistent with gene–environment interaction (Iso, 2000; Norat, 2008). This review focuses on *AGT* variation — particularly rs699 (M235T) — and evaluates evidence from controlled interventions, biomarker-based population studies, and clinical cohorts regarding sodium-dependent blood pressure phenotypes (Hunt, 1998; Svetkey, 2001; Norat, 2008; Repchuk, 2021).

Angiotensinogen Genetics and Sodium-Dependent Blood Pressure Variation

The *AGT* gene encodes angiotensinogen, the precursor substrate for angiotensin peptides within the renin–angiotensin system, a core endocrine pathway regulating vascular resistance, intravascular volume, and renal tubular sodium handling. Foundational human genetic work linked common *AGT* variation to essential hypertension susceptibility and demonstrated genotype-related differences in circulating angiotensinogen concentrations, establishing a plausible intermediate phenotype through which downstream hemodynamic effects could occur (Jeunemaitre, 1992).

The polymorphism emphasized here is *AGT* rs699, a common biallelic coding variant historically described as M235T and, in some clinical genetics reports, as *AGT* 704T>C (rs699) (Norat, 2008; Repchuk, 2021). Depending on strand orientation and reporting conventions, rs699 may be displayed using complementary nucleotide labels; accordingly, genotype categories can appear as G/G, G/A, and A/A in some reporting frameworks, while the same locus may be described using alternative nucleotide notation (Repchuk, 2021). In translational contexts, rs699 genotypes are sometimes treated under an allele-dose model as an ordinal indicator of susceptibility to sodium-associated increases in blood pressure. From an epidemiologic standpoint, the defensible interpretation is probabilistic: rs699 is a common polymorphism that may shift the expected magnitude of blood pressure responsiveness to sodium exposure

rather than define a categorical “functional” versus “non-functional” physiological state (Norat, 2008; Schorr, 1999).

Table 1: Human Studies on *AGT* rs699 (M235T), Salt Intake, and Blood Pressure

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s)/Focus Investigated	Main Outcome(s)
Jeunemaitre et al., 1992	Family-based genetic study (hypertensive sibships)	Two geographically distinct panels of hypertensive sibships	*AGT* variants (paper is a foundational report for *AGT* M235T/rs699)	*AGT* variation linked to essential hypertension and angiotensinogen biology (Jeunemaitre, 1992).
Hunt et al., 1999	Randomized, placebo-controlled sodium-reduction trial (6 months)	86 untreated hypertensive adults	*AGT* M235T (rs699)	T-allele carriers (MT/TT) had larger BP reductions with sodium reduction vs MM (Hunt, 1999).
Schorr et al., 1999	Controlled feeding: high- vs low-salt (short-term), salt-sensitivity phenotyping	187 young normotensive men	*AGT* M235T (rs699)	No difference in BP salt-sensitivity by genotype; T allele associated with family history and higher angiotensinogen (Schorr, 1999).
Iso et al., 2000	Community case–reference study	229 hypertensives + 229 matched normotensives; lean, non-drinking Japanese adults (32–83y)	*AGT* M235T (rs699) *(co-assessed with T174M)*	M235T alone not associated; sodium–hypertension interaction observed mainly for a haplotype including 235T (Iso, 2000).
Norat et al., 2008	Cross-sectional population study	11,384 adults (45–79y), free-living population	*AGT* M235T (rs699) × urinary sodium	SBP–sodium slope stronger in MT/TT than MM, especially at higher sodium exposure (Norat, 2008).
Repchuk et al., 2021	Case–control	72 essential HTN (stage 2) vs 50 controls	*AGT* 704T>C / rs699	rs699 associated with HTN severity/phenotype (and metabolic comorbidity patterns), supporting broader gene–lifestyle context (Repchuk, 2021).
Svetkey et al., 2001	Randomized controlled dietary intervention trial	459 DASH participants,	*ACE* genotype and BP response.	AA genotype confers excess risk of hypertension and is associated with increased responsiveness to diet.

Evidence Base for *AGT* Sodium Interactions

Mechanistic Plausibility and Intermediate Phenotypes

Mechanistic plausibility for *AGT*-dependent sodium–blood pressure effects is supported by evidence that *AGT* variation relates both to hypertension susceptibility and to circulating angiotensinogen levels, providing an intermediate phenotype for downstream vascular and renal effects (Jeunemaitre, 1992). Because sodium balance and renin–angiotensin activity are tightly coupled, inter-individual differences in AGT expression or substrate availability offer a coherent biological pathway through which identical sodium exposures could translate into different blood pressure outcomes (Balafa, 2021).

Controlled Interventions and Feeding Studies

Evidence for gene–diet effect modification is supported by controlled dietary intervention trials. In Trials of Hypertension Prevention Phase II, a randomized prevention framework incorporating sodium reduction and weight loss, Hunt and colleagues evaluated an *AGT* promoter polymorphism (a locus distinct from rs699) and reported genotype-dependent differences in long-term blood pressure change and incident hypertension under sodium reduction, with the largest apparent benefit of sodium reduction among individuals carrying the higher-risk genotype at that promoter locus (Hunt, 1998). Importantly for translation, this study demonstrates that common regulatory variation within *AGT* can stratify the magnitude of blood pressure benefit from sustained sodium reduction.

In the Dietary Approaches to Stop Hypertension feeding study, Svetkey and colleagues likewise reported that *AGT* genotype stratified blood pressure responses to dietary patterns under controlled feeding conditions, supporting the concept that *AGT*-linked biology can influence diet responsiveness even when sodium intake is held constant within the protocol (Svetkey, 2001

Taken together, controlled interventions support a model in which *AGT* variation modifies the magnitude of blood pressure change achievable through sodium reduction and related dietary modifications. (Hunt, 1998; Hunt, 1999; Svetkey, 2001).

Population Studies with Urinary Sodium Biomarkers

Observational evidence using objective biomarkers strengthens external validity. In EPIC-Norfolk, urinary sodium was used as a biomarker of sodium exposure in a large free-living cohort, and sodium–blood pressure associations were observed across genotypes; however, the slope of the sodium-associated increase in systolic blood pressure was steeper among M235T MT and TT carriers compared with MM carriers, with differences most evident at higher sodium exposure (Norat, 2008). These findings support a dose-dependent gene–environment interaction model in which genotype differences may be modest at low sodium exposure but become more apparent when sodium intake is high.

Clinical Cohort Evidence and rs699-Labeled Phenotypes

Clinical cohort studies provide additional perspective on disease expression. In a contemporary hypertensive cohort, Repchuk and colleagues analyzed *AGT* 704T>C (rs699) and reported that genotype frequencies did not differ significantly between hypertensive patients and controls, but the T allele was associated with increased likelihood of higher blood pressure severity categories, and the heterozygous genotype correlated with obesity risk (Repchuk, 2021). This pattern is compatible with a model in which rs699 is not a sole determinant of hypertension presence but may relate to severity, phenotype clustering, or comorbidity structure within hypertensive populations.

Reconciling Heterogeneity and Null Findings

A balanced interpretation requires recognition that *AGT*-defined salt sensitivity is not uniformly observed across all settings. In young, normotensive Caucasian men, Schorr and colleagues reported that the *AGT* 235T genotype was not a determinant of salt sensitivity when defined by short-term blood pressure responses to salt restriction, despite associations with family history of hypertension and higher plasma angiotensinogen concentrations (Schorr, 1999). This discordance illustrates a recurring issue in the field: salt sensitivity phenotypes can vary substantially according to the duration and magnitude of sodium manipulation, baseline sodium exposure, participant age and baseline blood pressure, and the outcome window selected for blood pressure measurement.

Systematic review evidence has emphasized that heterogeneity in sodium exposure assessment (dietary recall versus urinary biomarkers), salt-loading and restriction protocols, outcome definitions, and analytic strategies limits comparability across studies and complicates quantitative pooling, thereby reinforcing the need for standardized phenotyping in gene–sodium interaction research (Beeks, 2004). Gene–environment interactions are also expected to differ by ancestry due to linkage disequilibrium structure and allele frequency differences, as well as by kidney function and cardiometabolic context, all of which influence sodium handling and vascular responsiveness (Balafa, 2021; Beeks, 2004).

Translational Interpretation of rs699 and Related *AGT* Variation

In translational contexts, rs699 (M235T) is sometimes presented as stratifying expected blood pressure responsiveness to sodium exposure. The most defensible framing, based on intervention and population evidence, is that *AGT* variation shifts the expected magnitude of blood pressure change with sodium modification rather than producing deterministic outcomes (Norat, 2008; Schorr, 1999). Consistent patterns across multiple study types — greater blood pressure response to sodium reduction in carriers of higher-risk *AGT* genotypes in some trials and a steeper sodium–blood pressure association among higher-risk genotypes in biomarker-based cohorts — support risk enrichment, particularly at higher sodium exposure (Hunt, 1999; Norat, 2008; Iso, 2000). Nonetheless, heterogeneity in findings indicates that genotype should be interpreted alongside

clinical context, including baseline blood pressure, kidney function, and overall dietary pattern, rather than as a standalone predictor (Schorr, 1999; Beeks, 2004).

From a clinical prevention standpoint, dietary sodium reduction remains broadly beneficial for lowering blood pressure at the population level, and the presence of a higher-responsiveness *AGT* genotype can be conceptualized as increasing the likelihood of a larger individual blood pressure benefit from sodium reduction rather than changing the direction of effect (Hunt, 1998; Norat, 2008). In this framework, genotype-informed messaging is best used to support adherence and set expectations about response magnitude, while avoiding categorical "permission/forbidden" interpretations of sodium exposure.

Dietary Implications

Across populations, lowering dietary sodium reduces blood pressure on average, and the available human evidence suggests that common *AGT* variation may modify the magnitude of this reduction in some settings rather than reverse its direction (Hunt, 1998; Hunt, 1999; Norat, 2008). From an implementation perspective, this implies that sodium reduction remains a rational strategy for blood pressure control broadly, while individuals with higher-responsiveness genetic profiles may, on average, experience a larger blood pressure benefit when sodium intake is reduced or when dietary patterns supportive of lower blood pressure are adopted (Svetkey, 2001; Norat, 2008). Importantly, genotype-based expectations should be integrated with established clinical determinants of sodium sensitivity — baseline blood pressure, renal function, age, and cardiometabolic status — because these factors frequently account for a substantial portion of response variability and may confound or modify apparent genetic associations (Balafa, 2021; Beeks, 2004).

In practical dietary terms, sodium exposure is driven largely by the food environment, particularly commercially processed and prepared foods, and sustained reduction typically requires changes in food selection rather than discretionary salt use alone (U.S. Food and Drug Administration, 2024). Public health guidance has therefore emphasized quantitative sodium targets and food-pattern approaches that facilitate lower sodium intake while maintaining overall dietary quality (World Health Organization, 2025). Within controlled feeding conditions, dietary pattern interventions such as the Dietary Approaches to Stop Hypertension have produced clinically meaningful blood pressure reductions and demonstrated that genotype at *AGT* can stratify the magnitude of dietary response, supporting an integrative view in which sodium intake and broader dietary composition jointly influence blood pressure outcomes (Svetkey, 2001). Translationally, the most defensible use of rs699 information is to support adherence and expectation-setting — for example, by reinforcing that a substantial blood pressure response to sodium reduction is plausible in some genotype groups — while avoiding deterministic interpretations that imply inevitable harm from modest sodium intake or guaranteed benefit from dietary change (Schorr, 1999; Beeks, 2004).

CONCLUSION

The collective evidence supports a biologically coherent role for *AGT* variation in shaping sodium-related blood pressure heterogeneity, with rs699 (M235T) representing a commonly studied marker of inter-individual differences within the renin–angiotensin system. The mechanistic rationale is grounded in foundational human genetic observations linking *AGT* variation to essential hypertension susceptibility and to differences in circulating angiotensinogen concentrations, an intermediate phenotype with direct relevance to vascular tone and renal sodium handling (Jeunemaitre, 1992).

Across study designs, the most consistent pattern is one of effect modification that becomes clearer under conditions of higher sodium exposure or under controlled dietary manipulation. In intervention settings, genetic variation within *AGT* has been associated with differential blood pressure responses to sustained sodium reduction and to blood pressure–lowering dietary patterns, indicating that genotype can influence the magnitude of achievable blood pressure change through lifestyle modification (Hunt, 1998; Svetkey, 2001). More directly relevant to rs699/M235T, a controlled sodium reduction trial reported larger blood pressure reductions among carriers of the 235T allele, consistent with genotype-stratified sodium responsiveness in hypertensive adults (Hunt, 1999). In free-living populations, urinary sodium biomarker studies provide ecologically valid evidence that the sodium–blood pressure relationship can be steeper among higher-risk M235T genotype carriers, with differences most apparent at higher sodium exposure (Norat, 2008). Parallel results from Japanese community data further support a sodium-dependent genetic risk model, suggesting that high sodium exposure may amplify genotype-associated differences in hypertension risk or expression within specific populations (Iso, 2000).

At the same time, discordant findings and heterogeneity in salt sensitivity phenotyping underscore the limits of inference from any single study and argue against deterministic interpretations. Evidence from controlled short-term feeding protocols indicates that M235T genotype does not uniformly predict salt sensitivity across populations and experimental paradigms, even when associated intermediate phenotypes are present (Schorr, 1999). Systematic appraisal of the broader salt sensitivity genetics literature further indicates substantial heterogeneity in exposure measurement, protocol design, and analytic approaches, which likely contributes to variability in observed gene–sodium interaction effects and limits straightforward quantitative synthesis (Beeks, 2004). These considerations highlight several priorities for future research, including standardized and reproducible salt sensitivity phenotyping, improved exposure assessment using urinary sodium biomarkers, and adequately powered multi-ancestry studies capable of resolving ancestry-specific linkage disequilibrium patterns and interaction effects (Beeks, 2004; Norat, 2008).

From a translational perspective, rs699 should therefore be framed as a common polymorphism that may shift the expected magnitude of blood pressure responsiveness to dietary sodium rather than define categorical physiological competence. In clinical and public health contexts, sodium reduction remains broadly beneficial for blood pressure control, and rs699-informed messaging is best positioned as a tool for expectation-setting and adherence support, integrated with individual clinical characteristics and overall dietary quality (Svetkey, 2001; Balafa, 2021; U.S. Food and Drug Administration, 2024; World Health Organization, 2025).

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