or environmental factors should be carried out. Among the environmental factors, increased fluid intake and urine
alkalinization are the most successful preventive recommendations. Cystinuria is not very frequent, but there are
other genetic alterations that may result in stone formation and consequently nephrolithiasis, both of which can be
improved with greater hydration. Likewise, some interactions between genes associated with vasopressin and liquid
intake on blood pressure and other phenotypes of cardiovascular risk are becoming known.

Key words: Mediterranean, lifestyle, genetics, gene-diet interactions, cardiovascular.

Water is life: an evolutionary perspective of hydration-related gene-
environment interactions

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Since the time that archaic species left the water to live on land, the essential evolutionary demand was to provide
the organism’s cells with an aqueous environment similar to the one that was left behind in the oceans. The impor-
tance of proper hydration continues to be manifested in modern humans that can survive weeks without food but
only a few days without water. It was in 2004 when the Food and Nutrition Board at the Institute of Medicine of the
National Academies released the Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate
Report. In this report, we find a brief but comprehensive description about the importance of appropriate hydration
to maintain health: “The largest single constituent of the human body, water, is essential for cellular homeostasis and
life. It provides the solvent for biochemical reactions, is the medium for material transport, and has unique physical
properties (high specific heat) to absorb metabolic heat. Water is essential to maintain vascular volume, to support
the supply of nutrients to tissues, and to remove waste via the cardiovascular system and renal and hepatic clearance.
Body water deficits challenge the ability of the body to maintain homeostasis during perturbations (e.g., sickness,
physical exercise, or climatic stress) and can impact functions and health. Total water intake includes drinking wa-
ter, water in other beverages, and water in food.” However, despite the paramount role of hydration we don’t have
well-defined and soundly supported figures regarding daily water requirements for the general population. This is
partially due to the many factors involved in defining the individual’s needs (i.e., age, sex, dietary habits, physical
activity, climate, seasonality and geographical and cultural environment) and related mechanisms (i.e., thirst, gene-
tic background).

Apart from the hydration-related functions outlined above, a major driver through human evolution has been the
correct maintenance of osmolality and vascular volume in changing environments. This is prior to the out-of-Africa
dispersion (included the initial hot and humid forest, followed by the hot and dry savannah) where members of the
homo genus survived and thrived thanks to a highly efficient heat dissipation mechanism, achieved through eva-
porative heat loss (sweat). However, sweating leads to loss of water and salt, which triggers thirst, salt appetite and
renal sodium conservation, essential for survival in that ancestral environment. The downside of this evolutionary
adaptation is the current prevalence of hypertension and other common diseases, characteristic of the modern socie-
ty exposed to such different environmental and behavioral conditions.

Despite the relevance of hydration in relation to human evolution, metabolic homeostasis and its potential in-
volve in most common chronic diseases, the field of gene-environment interactions and more specifically,
the area of nutrigenetics, has focused exclusively on gene-(solid)nutrient interactions, with a blatant absence of
gen-hydration interactions. Withstanding the fuzziness involved in collecting drinking information and the lack
of practical biomarkers of hydration status, there is enough evidence to support that individuals in the general
population can maintain homeostasis, and apparently good health, with reported water intakes that differ as much
as one order of magnitude (i.e., between 400 and 4000 ml/day). This suggests different individual needs and sus-
cceptibilities (i.e., perspiration, urination or thirst) that could have a significant genetic component. For example, it
is known that subjects in northern latitudes sweat more under similar environmental conditions than people in the
tropics. Moreover, it is also known that the susceptibility to hypertension in blacks leaving in the US is higher than
in US whites. Whereas no genome wide association studies have been reported related to hydration factors (i.e.,
thirst, water intake and water loss), there are a number of alleles at candidate genes related to blood pressure, renal
function and arterial and cardiac contractility that were potentially advantageous in our ancestral African habitat

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but deleterious in today’s world. This may be the case of the A-6G (rs5051) genetic variant in the proximal promoter region of the angiotensinogen (AGT) gene in the renin-angiotensin-aldosterone system (RAAS) pathway. The ancestral allele, shared with non-human primates, has been associated with elevated AGT gene transcription and plasma AGT levels and with essential hypertension. Other alleles related to hypertension are present only in humans and increased in frequency, most probably due to the positive selection, during the adaptation to the hot and dry environment characteristic of the African savannah. Some of the best characterized include: AGT G-217A (rs5049); G protein β3 subunit (GNB3) C825T (rs5433); β2 adrenergic receptor (ADRB2) G47A and G79C; and Sodium Channel, Non Voltage Gated 1 Alpha Subunit (SCNN1A) A-946G.

We need to keep in mind the evidence from most other dietary components studied so far, showing that the relation between intake and disease risk follows a J or U shape curve, and that the optimal intake may vary from one individual to another depending on genetic factors. Therefore, much more research is needed to elucidate individual hydration levels in order to achieve optimal homeostasis through life. This is especially important at a time in which hedonic, cultural and social factors contribute substantially to our current habits, overriding the ancestral endogenous thirst mechanism and potentially driving us outside of our specific “genomic” comfort zone.

Key words: hydration, nutrigenetics, positive selection, hypertension, evolution.

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