A population-based approach to assess the heritability and distribution of renal handling of electrolytes

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The handling of electrolytes by the kidney is essential for homeostasis. However, the heritability of these processes, the first step in gene discovery, is poorly known. To help clarify this, we estimated the heritability of serum concentration, urinary excretion, renal clearance, and fractional excretion of sodium, potassium, magnesium, calcium, phosphate, and chloride in a population-based study. Nuclear families were randomly selected from the general population in Lausanne, Geneva, and Bern, Switzerland, and urine collected over 24-hour periods. We used the ASSOC program (S.A.G.E.) to estimate narrow sense heritability, including sex, age, body mass index, and study center as covariates in the model. The 1128 participants, from 273 families, had a mean age of 47 years, body mass index of 25.0 kg/m^2, and an estimated glomerular filtration rate (CKD-EPI) of 98 mL/min/1.73 m^2. The heritability of serum concentration was highest for calcium, 37% and lowest for sodium, 13%. The heritability of 24-hour urine clearances, excretions, and fractional excretions ranged from 15%, 10%, and 16%, respectively, for potassium to 45%, 44%, and 51%, respectively, for calcium. All probability values were significant. The heritability for phosphate-related phenotypes was lower than that for calcium. Thus, the serum and urine concentrations as well as urinary excretion and renal handling of electrolytes are heritable in the general adult population. The phenotypic variance attributable to additive genetic factors was variable and was higher for calcium. These results pave the way for identifying genetic variants involved in electrolyte homeostasis in the general population.

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The renal handling of electrolytes is essential for homeostasis. Electrolytes are freely filtered through the glomerular membrane, reabsorbed or secreted or both via specialized transport systems that operate in various tubular segments. Over the last 2 decades, the molecular counterpart of many of transport systems have been identified in the context of rare inherited tubulopathies associated with electrolyte disorders or defective blood pressure regulation.[1] Despite these advances, the genetic counterpart of electrolyte handling in the general population remains poorly characterized, with only few studies[2–5] on the heritability of the renal handling of sodium, calcium, and potassium that are not transferable to the general population because of their design (twin studies, clinical population, or monocentric). To our knowledge, no prior study reported the heritability of the renal handling of magnesium, chloride, and phosphate.

The serum concentration of most electrolytes is confined within narrow ranges, resulting from a tight regulation of their renal tubular handling and urinary excretion. Further levels of complexity include the influence of dietary intake and the regulation of intestinal absorption. Urinary sodium and chloride are fully absorbed in the intestine and are not stored in the body. Their urinary concentration therefore reflects dietary intake. Sodium and potassium are partly regulated by the renin-angiotensin-aldosterone system. Potassium and phosphate are intracellular ions with strong

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regulation for storage in muscles. Calcium and phosphate are stored in the bone and are tightly regulated by the vitamin D–parathyroid hormone axis and fibroblast growth factor 23. Furthermore, the net intestinal absorptions of calcium, phosphate, and magnesium are highly regulated, so that their urinary excretions do not merely reflect dietary intake.[6]

The heritabilities of serum electrolytes are usually moderate to high, with published estimates varying from 15% to 39% for magnesium, from 21% to 45% for calcium, from 53% to 62% for phosphate,[2] and from 0% to 38% for sodium, potassium, and chloride.[7–10] So far, these numbers originate from studies in twin pairs, in which reduced environmental variance inflates heritability estimates, or from studies with small sample sizes, and little data come from large-scale population-based family studies (except for sodium and potassium[9]).

A single twin study (N = 1747) explored the familial aggregation of multiple electrolytes in blood and urine.[2] Although evidence was provided for the importance of genetic factors in determining the heritability of blood and serum levels of electrolytes and creatinine clearance, this study was restricted to women.

We are not aware of any study presenting the heritability of renal clearances for electrolytes in the general population.

Estimating the relative contribution of genetic and environmental influences on serum and urinary electrolytes levels on renal function parameters is a prerequisite for genetic studies aiming at identifying genes involved in renal function or electrolyte unbalances or both. Some serum electrolyte concentration associations with common genetic variants have been reported.[11] In this study, we analyzed a large, family-based cohort from Switzerland, using the same standardized protocol across 3 centers, including 24-hour urine collection. We estimated the heritability of estimated glomerular filtration rate (eGFR) as well as of serum and urine concentrations, renal clearances, and fractional excretions of sodium, potassium, magnesium, calcium, phosphate, and chloride.

RESULTS

The 273 pedigrees had mean size of 5.1 ± 2.29 that included 883 parent-offspring pairs, 424 sibling-sibling pairs, 75 grandparent-grandchild pairs, 183 avuncular pairs (i.e., aunt/uncle-niece/nephew), 37 cousin pairs, and 10 half-sibling pairs.

The main characteristics of the study participants are presented in Table 1. The descriptive data for electrolytes' urinary excretions, renal clearances, and fractional excretions are listed in Supplementary Table S1. The proportion of missing values ranged from 0% for body mass index to 3.2% for creatinine clearance. The mean value for eGFR was 98 ml/min per 1.73 m^2, determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; the mean value for serum creatinine was 73 μmol/l; the mean value for serum urea was 4.9 mmol/l; and the mean value for albuminuria was 10.9 mg/min ±56.8.

Table 1 | Participants characteristics, overall and by sex

Characteristic	Overall N = 1128	Male n = 537	Female n = 591
Age (yr)	47.4 ± 17.5	47.1 ± 17.8	47.2 ± 17.2
BMI (kg/m^2)	24.9 ± 4.52	25.9 ± 4.21	24.1 ± 4.63
Diabetes	51 (4.52)	35 (6.52)	16 (2.71)
Hypertension	260 (23.15)	148 (27.61)	112 (19.08)
CKD-EPI (ml/min per 1.73 m^2)	98.04 (18.49)	94.84 (18.49)	94.81 (17.63)
Albuminuria (mg/min)	10.9 (56.8)	10.9 (57.9)	10.8 (55.8)
Serum measurements			
Creatinine (μmol/l)	73 (14.15)	81 (13.73)	66 (10.19)
Urea (mmol/l)	4.9 (1.56)	5.3 (1.69)	4.5 (1.31)
Na (mmol/l)	140.4 (2.4)	141.3 (2.4)	140.5 (2.4)
K (mmol/l)	4.0 (0.33)	4.1 (0.31)	4.0 (0.28)
Ca (mmol/l)	2.29 (0.08)	2.28 (0.04)	2.29 (0.03)
Cl (mmol/l)	105 (2.54)	105 (2.53)	105 (2.52)
PO_4 (mmol/l)	1.01 (0.16)	0.99 (0.16)	1.10 (0.15)
Mg (mmol/l)	0.84 (0.06)	0.84 (0.06)	0.85 (0.05)
Urinary 24-hour excretion rates			
Na (mmol/min)	9.9 (4.43)	11.4 (4.63)	8.4 (3.52)
K (mmol/min)	4.25 (1.60)	4.83 (1.62)	3.86 (1.46)
Ca (mmol/min)	0.002 (0.001)	0.003 (0.001)	0.002 (0.001)
Cl (mmol/min)	0.08 (0.03)	0.10 (0.04)	0.07 (0.05)
PO_4 (mmol/min)	0.01 (0.006)	0.02 (0.004)	0.01 (0.007)
Mg (mmol/min)	0.28 (0.11)	0.30 (0.09)	0.25 (0.11)

BMI, body mass index; CKD-EPI, glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula; MDRD, glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula. Values are mean ± SD or n (%).

We found moderate to high heritability estimates, ranging from 16% to 49%, for renal function parameters, with similar estimates for serum creatinine, serum urea, and GFR estimated using the CKD-EPI (46%) equation (Table 2). By contrast, heritability estimates were lower, albeit significantly higher than 0 for creatinine clearances (18%) and urinary albumin excretion (23%). For all traits presented in Table 2, the sibship component of variance was not significant.

The distributions of serum electrolytes for men and women are shown in Figure 1. The distributions of 24-hour clearances are presented in Figure 2. Overall, men tend to have higher clearances than women and serum concentrations were similar for men and women, with the exception of phosphate. The distribution of 24-hour fractional excretions and urinary excretions for sodium, potassium, magnesium, calcium, phosphate, and chloride can be found in Supplementary Figure S1. The fractional excretions (Supplementary Table S1) were similar in men and women, with the exception of phosphate.

Heritability estimates for serum concentrations (Figure 3), ranged from 39% for serum calcium to 12% for serum sodium. All these heritability estimates were significantly different from 0. Adding a sibship component of variance did not substantially alter these estimates, which suggests that there is no substantial dominance variance effect nor shared sibship environmental component.

Heritability estimates for renal clearances were moderate to high (5% to 49%), with the highest values for calcium and