SUPPLEMENTARY MATERIALS

Reverse Phenotypes of Patients with Genetically Confirmed Liddle's Syndrome

Authors

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Supplementary Table S1: Search string used on PubMed. First search was performed on March 16th 2022 and a re-run of the search was performed on December 20th 2022. All searches were performed with publication date filter from 1994 to the present.

#1	Liddle syndrome (MeSH Terms)	OR
#2	(Liddle syndrome) OR (Liddle's syndrome) OR (Liddle disease) OR (Liddle's disease) OR (SCNN1A) OR (SCNN1B) OR (SCNN1G)	

Supplementary Table S2: Search string used on Embase. First search was performed on March 16th 2022 and a re-run of the search was performed on December 20th 2022. All searches were performed with publication date filter from 1994 to the present.

#1	Exp Liddle syndrome/	OR
#2	(Liddle syndrome) OR (Liddle's syndrome) OR (Liddle disease) OR (Liddle's disease) OR (SCNN1A) OR (SCNN1B) OR (SCNN1G)	

Supplementary Table S3: Search string used on Scopus. First search was performed on March 16th 2022 and a re-run of the search was performed on December 20th 2022. All searches were performed with publication date filter from 1994 to the present.

#1	(Liddle syndrome) OR (Liddle's syndrome) OR (Liddle disease) OR (Liddle's disease) OR (SCNN1A) OR (SCNN1B) OR (SCNN1G)

Supplementary Table S4: Information used for variant classification in accordance with the ACMG guidelines[1].

1. Allele frequency in gnomAD Exomes version 2.1.1.[2]
2. Type of genetic variation
3. Involvement of the PY motif ("no", "loss" or "change")
4. *In silico* analysis using the prediction software in Varsome Premimum with default settings[3]
5. PhyloP100 convervation score via Varsome Premium
6. *In vitro* and *in vivo* functional data of the variant described in the literature
7. Segregation analysis within pedigrees. The PP1 criteria was only used, when a variant segregated with the phenotype over ≥ 5 meioses
8.Classification in the databases ClinVar (www.ncbi.nlm.nih.gov/clinvar), the Human Gene Mutation Database, and Varsome (www.varsome.com)
9. Number of reportings of the variant in affected individuals

Supplementary Table S5: Standardized table for phenotype data extraction and applied definitions.

	ID	Gender	Age	Age HT_D	Hypertension	Hypokalemia	Renin suppression	Aldosterone suppression	Metabolic alkalosis	Response to ENaC blocker	HT disposition	CVE disposition	Sys1	Dia1	K1	Sys2	Dia2	K2	Comorbidity
Index																			
Relative																			
Additional comments:																			

Abbreviations: ID = identification in article. HT_D = Diagnosis of hypertension. HT = hypertension. CVE = cerebrovascular event. Sys1 = systolic blood pressure before ENaC blocker. Dia1 = diastolic blood pressure before ENaC blocker. K1 = blood potassium before ENaC blocker. Sys2 = systolic blood pressure after ENaC blocker. Dia2 = diastolic blood pressure after ENaC blocker. K2 = blood potassium after ENaC blocker.

Applied definitions:

Hypertension is systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or the requirement of hypertensive medication to maintain normal blood pressure levels. Age-specific cut-off were used for patients < age 18, and hypertension was defined as either systolic or diastolic blood pressure higher than the sex-specific blood pressure 95%-quartile while assuming height in the 95% quartiles[4].

Hypokalemia is plasma or serum potassium < 3.5 mM.

Renin suppression is defined as plasma renin concentration (PRC) and/or plasma renin activity (PRA) below normal reference range of the applied assay. The description of PRC and/or PRA in the article was used when no normal level references were provided.

Aldosterone suppression is defined as plasma aldosterone level and/or urinary aldosterone level below normal reference range of the applied assay. The description of plasma aldosterone levels and/or urine aldosterone levels in the article was used when no normal level references were provided.

Metabolic alkalosis was defined by either (1) pH > 7.45, or (2) plasma bicarbonate concentration >28.0 mM, (3) pCO_2 > 6.0 kPa, or 4) standard base excess >2.0 mEq/L.

Response to ENaC blocker was defined as normalization of high blood pressure and low plasma potassium.

Hypertension disposition was defined as reporting of 1) first-degree relative with hypertension under the age of 40 or 2) three first-degree relatives with hypertension.

Cerebrovascular disposition was defined as reporting of any cerebrovascular event (e.g. stroke or cerebrovascular hemorrhage) in the family regardless of age.

Supplementary Table 6: List of the 62 studies included in the review (references 5-67). *Initially 63 studies were included, but one study[52] was subsequently excluded because the reported genetic and protein variants did not exist in the transcript.

First author	Year of publication	Journal	Title
Bao	2020	J Med Genet	Genetic screening for monogenic hypertension in hypertensive individuals in a clinical setting
Bogdanović	2012	Eur J Pediatr	Liddle syndrome in a Serbian family and literature review of underlying mutations
Brower	2020	AACE Clin Case Rep	Liddle syndrome due to a novel c.1713 deletion in the epithelial sodium channel β-subunit in a normotensive adolescent
Büyükkaragöz	2016	Pediatr Int	Liddle syndrome in a Turkish family with heterogeneous phenotypes
Caretto	2014	Case Rep Obstet Gynecol	A therapeutic challenge: Liddle's syndrome managed with amiloride during pregnancy
Chen	2022	Scand J Clin Lab Invest	Clinical and genetic characteristics of the patients with hypertension and hypokalemia carrying a novel *SCNN1A* mutation
Ciechanowicz	2005	Pediatr Nephrol	Liddle syndrome caused by P616R mutation of the epithelial sodium channel beta subunit
Cui	2017	J Clin Hypertens (Greenwich)	Liddle syndrome: clinical and genetic profiles
Ding	2019	Exp Ther Med	A family with Liddle's syndrome caused by a new c.1721 deletion mutation in the epithelial sodium channel β-subunit
Fan	2019	Kidney Blood Press Res	Truncating epithelial sodium channel β subunit responsible for Liddle syndrome in a Chinese family
Fan	2018	Endocrine Connect	Liddle syndrome misdiagnosed as primary aldosteronism resulting from a novel frameshift mutation of SCNN1B
Fan	2020	Am J Hypertens	Pediatric Liddle syndrome caused by a novel SCNN1G variant in a Chinese family and characterized by early-onset hypertension
Fan	2020	Kidney Blood Press Res	Premature stroke secondary to severe hypertension results from Liddle syndrome caused by a novel SCNN1B mutation
Fan	2019	Am J Hypertens	A novel frameshift mutation of SCNN1G causing Liddle syndrome with normokalemia
Findling	1997	J Clin Endocirnol Metab	Liddle's syndrome: prospective genetic screening and suppressed aldosterone secretion in an extended kindred
Freercks	2017	Cardiovasc J Afr	Liddle's syndrome in an African male due to novel frameshift mutation in the beta-subunit of the epithelial sodium channel gene

Freundlich	2005	Pediatr Nephrol	A novel epithelial sodium channel beta-subunit mutation associated with hypertensive Liddle syndrome
Furuhashi	2005	J Clin Endocrinol Metab	Liddle's syndrome caused by a novel mutation in the proline-rich PY motif of the epithelial sodium channel beta-subunit
Gao	2013	J Pediatr	A family with Liddle syndrome caused by a novel missense mutation in the PY motif of the beta-subunit of the epithelial sodium channel
Gao	2001	J Hypertens	Diagnosis of Liddle syndrome by genetic analysis of beta and gamma subunits of epithelial sodium channel – a report of five affected family members
Gong	2014	Mol Biol Rep	Phenotype-genotype analysis in two Chinese families with Liddle syndrome
Hansson	1995	Nat Genet	Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome
Hansson	1995	Proc Natl Acad Sci U S A	A de novo missense mutation of the beta subunit of the epithelial sodium channel causes hypertension and Liddle syndrome, identifying a proline-rich segment critical for regulation of channel activity
Hiltunen	2002	J Hypertens	Liddle's syndrome associated with a point mutation in the extracellular domain of the epithelial sodium channel gamma subunit
Inoue	1998	J Clin Endocrinol Metab	A family with Liddle's syndrome caused by a new missense mutation in the beta subunit of the epithelial sodium channel
Inoue	1998	Eur J Endocrinol	Identification of a single cytosine base insertion mutation at Arg-597 of the beta subunit of the human epithelial sodium channel in a family with Liddle's disease
Jackson	1998	J Med Genet	The diagnosis of Liddle syndrome by identification of a mutation in the beta subunit of the epithelial sodium channel
Jeunemaitre	1997	J Hypertens	Genotype-phenotype analysis of a newly discovered family with Liddle syndrome
Jin	2022	J Pediatr Endrocrinol Metab	A case report of a young boy with low renin and high aldosterone levels induced by Liddle syndrome who was previously misdiagnosed with primary aldosteronism
Jones	2011	Cardiovasc J Afr	The R563Q mutation of the epithelial sodium channel beta-subunit is associated with hypertension
Kozina	2019	BMC Nephrol	Liddle syndrome due to a novel mutation in the γ subunit of the epithelial sodium channel (ENaC) in family from Russia: a case report
Kuang	2017	J Am Soc Hypertens	The importance of genetic counseling and genetic screening: a case report of a 16-year-old boy with resistant hypertension and severe hypokalemia

Kyuma	2001	Clin Exp Hypertens	A family with Liddle's syndrome caused by a mutation in the beta subunit of the epithelial sodium channel
Lata	2018	Ann Intern Med	Whole-exome sequencing in adults with chronic kidney disease: a pilot study
Liu	2018	J Hypertens	Analysis of the genes involved in Mendelian forms of low-renin hypertension in Chinese early-onset hypertensive patients
Lu	2022	Front Cardiovasc Med	A novel frame-shift mutation in novel frame-shift mutation in *SCNN1B* identified in a Chinese family characterized by early-onset hypertension
Mareš	2021	Blood Press	A nonsense mutation in the β-subunit of the epithelial sodium channel causing Liddle syndrome
Melander	1998	Hypertension	Mutations and variants of the epithelial sodium channel gene in Liddle's syndrome and primary hypertension
Nakano	2002	J Hypertens	A frameshift mutation of beta subunit of epithelial sodium channel in a case of isolated Liddle syndrome
Phoojaroenchanachai	2015	J Med Assoc Thai	Liddle's syndrome: a case report.
Polfus	2016	Cold Spring Harb Mol Case Stud	Whole-exome sequencing reveals an inherited R566X mutation of the epithelial sodium channel β-subunit in a case of early-onset phenotype of Liddle syndrome
Rayner	2003	J Hypertens	A new mutation R563Q of the beta subunit of the epithelial sodium channel associated with low-renin, low-aldosterone hypertension
Rossi	2008	J Hypertens	Liddle's syndrome caused by a novel missense mutation (P617L) of the epithelial sodium channel beta subunit
Rossi	2011	Am J Hypertens	A clinical phenotype mimicking essential hypertension in a newly discovered family with Liddle's syndrome
Salih	2017	J Am Soc Nephrol	A missense mutation in the extracellular domain of αENaC causes Liddle syndrome
Sawathiparnich	2009	J Pediatr Endocrinol Metab	A novel mutation in the beta-subunit of the epithelial sodium channel gene (SCNN1B) in a Thai family with Liddle's syndrome
Shimkets	1994	Cell	Liddle's syndrome: Heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel
Suman	2021	Saudi J Kidney Dis Transpl	A rare case of familiar hypertension presenting with hypertensive encephalopathy in an elderly patient: a diagnostic dilemma: a presentation of Liddle's syndrome due to a novel mutation in SCNN1G gene
Tamura	1996	J Clin Invest	Liddle disease caused by a missense mutation of beta subunit of the epithelial sodium channel gene
Teoh	2020	Clin Nephrol Case Stud	A case report of three children with secondary hypertension caused by Liddle syndrome

Tetti	2018	Int J Mol Sci	Liddle syndrome: review of the literature and description of a new case
Tolu	2021	Cureus	A search for secondary hypertension: “Where’s Waldo?”
Uehara	1998	J Hypertens	Genetic analysis of the epithelial sodium channel in Liddle’s syndrome
Wang	2012	Chine Med J (Engl)	Genetic diagnosis of Liddle’s syndrome by mutation analysis of SCNN1B and SCNN1G in a Chinese family
Wang	2015	J Clin Hypertens	Prevalence of Liddle syndrome among young hypertension patients of undetermined cause in a Chinese population
Wang	2006	Endocrine	Mutation analysis of SCNN1B in a family with Liddle syndrome
Wang	2022	Nephron	A family with Liddle syndrome caused by a novel stop-gain mutation in the γ subunit of the epithelial sodium channel
Wang	2007	Clin Endocrinol (Oxf)	A novel epithelial sodium channel gamma-subunit de novo frameshift mutations leads to Liddle syndrome
Yamashita	2001	Am J Kidney Dis	Two sporadic cases of Liddle’s syndrome caused by de novo ENaC mutations
Yang	2018	Clin Exp Hypertens	Genetic screening of SCNN1B and SCNN1G genes in early-onset hypertensive patients helps to identify Liddle syndrome
Yang	2015	Clin Endocrinol (Oxf)	A novel frameshift mutation of epithelial sodium channel β-subunit leads to Liddle syndrome in an isolated case
Yang	2022	Blood Press	Liddle syndrome misdiagnosed a primary aldosteronism is caused by inaccurate aldosterone-rennin detection while a novel *SCNN1G* mutation is discovered
Zhang	2022	Front Pediatr	Pathogenicity and long-term outcomes of Liddle syndrome caused by a nonsense mutation of SCNN1G in a Chinese family

Supplementary Table S7: Disease-causing coding variants in *SCNN1A*, *SCNN1B*, and *SCNN1G* associated with pseudohypoaldosteronism type 1 reported in the Human Gene Mutation Database (Accessed 31st July 2023).

Gene	Gene variant	Exon	Protein variant	Reference
SCNN1A	c.166C>T	2	p.Arg56*	68
SCNN1A	c.189C>A	2	p.Cys63*	69
SCNN1A	c.203_204delTC	2	p.Ile68Thrfs*76	70
SCNN1A	c.206A>G	2	p.His69Arg	71
SCNN1A	c.217C>T	2	p.Arg73Cys	72
SCNN1A	c.301C>A	2	p.Gln101Lys	73
SCNN1A	c.398G>A	2	p.Cys133Tyr	74
SCNN1A	c.505_506delAC	3	p.Thr169Serfs*36	68
SCNN1A	c.574delA	3	p.Arg192Glyfs*57	75
SCNN1A	c.587dupC	3	p.Pro197Alafs*9	69
SCNN1A	c.598dupG	3	p.Ala200Glyfs*6	71
SCNN1A	c.604C>T	3	p.Arg202*	76
SCNN1A	c.677T>G	3	p.Phe226Cys	77
SCNN1A	c.727T>C	4	p.Ser243Pro	78
SCNN1A	c.729delA	4	p.Val245Trpfs*4	79
SCNN1A	c.729_730delAG	4	p.Val245Glyfs*65	80
SCNN1A	c.742delG	4	p.Val248*	69
SCNN1A	c.814dupG	4	p.Glu272Glyfs*39	81
SCNN1A	c.979G>T	5	p.Gly327Cys	82
SCNN1A	c.1305delC	8	p.Tyr436Ilefs*46	68
SCNN1A	c.1311delG	8	p.Arg438Glyfs*44	81
SCNN1A	c.1322delA	8	p.Asn441Thrfs*41	83
SCNN1A	c.1339dupT	8	p.Tyr447Leufs*13	84
SCNN1A	c.1339_1342dupTACA	8	p.Arg448Ilefs*13	69
SCNN1A	c.1356delC	8	p.Trp453Glyfs*29	82
SCNN1A	c.1449delC	10	p.Tyr484Thrfs*13	79
SCNN1A	c.1453C>T	10	p.Gln485*	83
SCNN1A	c.1474C>T	10	p.Arg492*	74
SCNN1A	c.1496A>G	10	p.Gln499Arg	83
SCNN1A	c.1522C>T	11	p.Arg508*	70
SCNN1A	c.1582_1584delTTC	12	p.Phe528del	85
SCNN1A	c.1678G>A	13	p.Gly560Ser	86
SCNN1A	c.1685C>T	13	p.Ser562Leu	79
SCNN1A	c.1684T>C	13	p.Ser562Pro	87
SCNN1B	c.87C>A	2	p.Tyr29*	71
SCNN1B	c.109G>A	2	p.Gly37Ser	70
SCNN1B	c.519_520insA	3	p.Leu174Ilefs*12	68
SCNN1B	c.637C>T	4	p.Gln213*	88
SCNN1B	c.648dupA	4	p.Glu217Argfs*38	89
SCNN1B	c.682delG	4	p.Ala228Hisfs*8	90
SCNN1B	c.789delC	5	p.Ile264Serfs*16	68
SCNN1B	c.915delC	6	p.Tyr306Thrfs*13	89
SCNN1B	c.978C>A	6	p.Tyr326*	91

SCNN1B	c.1245dupC	8	p.Asn416Glnfs*35	92
SCNN1B	c.1288delC	9	p.Leu430Tyrfs*3	93
SCNN1B	c.1290delA	9	p.Gln431Argfs*2	94
SCNN1B	c.1350_1363del14	10	p.Thr451Aspfs*6	94
SCNN1B	c.1559C>A	13	p.Ser520*	83
SCNN1G	c.109_114delAACACC	2	p.Asn37_Thr38del	95
SCNN1G	c.116A>G	2	p.His39Arg	96
SCNN1G	c.187G>C	2	p.Ala63Pro	85
SCNN1G	c.527_528delCA	3	p.Thr176Argfs*9	83
SCNN1G	c.1057A>C	6	p.Thr353Pro	97
SCNN1G	c.1318C>T	9	p.Arg440*	88
SCNN1G	c.1415C>T	10	p.Pro472Leu	96
SCNN1G	c.1627delG	13	p.Val543Leufs*56	98

Supplementary Table S8: Characteristics of 268 individuals with Liddle syndrome diagnostic variants reported in the literature. Adults only were calculated by removing individuals with age unknown or <18

*Statistically significant change with student's paired t-test.

Hypertension • Whole cohort, frequency (%) • Adults only, frequency (%)	 247 of 268 (92) 173 of 178 (97)
Age in years Missing observations, frequency. mean ±SD Median (range)	 69 of 268 32 ±18 30 (2-82)
Age of hypertension diagnosis in years Missing observations, frequency. mean ±SD Median (range)	 69 of 268 21 ±11 18 (2-64)
Systolic blood pressure before ENaC blocker in mmHg, mean ±SD (no. of observations) • Whole cohort • Adults only	 164 ±28 (219) 169 ±24 (161)
Systolic blood pressure after ENaC blocker in mmHg, mean ±SD (no. of observations) • Whole cohort • Adults only	 125 ±11 (126) 127 ±9 (96)
Change in systolic blood pressure after ENaC blocker in mmHg, mean ±SD (no. of observations) • Whole cohort • Adults only	 -48 ±23 (122)* -51 ±22 (93)*
Diastolic blood pressure before ENaC blocker in mmHg, mean ±SD (no. of observations) • Whole cohort • Adults only	 103 ±19 (219) 106 ±16 (161)
Diastolic blood pressure after ENaC blocker in mmHg, mean ±SD (no. of observations) • Whole cohort • Adults only	 80 ±9 (126) 82 ±8 (96)
Change in diastolic blood pressure after ENaC blocker in mmHg, mean ±SD (no. of observations) • Whole cohort • Adults only	 -20 ±17 (122)* -30 ±16 (93)*
Blood potassium level before ENaC blocker in mM, mean ±SD (no. of observations)	3.3 ±0.7 (219)
Blood potassium level after ENaC blocker in mM, mean ±SD (no. of observations)	4.2 ±0.5 (120)
Change in blood potassium level after ENaC blocker in mmHg, mean ±SD (no. of observations)	1.1 ±0.6 (117)*

Supplementary Table S9: Comparison of categorical phenotypic traits between patients with *SCNN1B* vs. *SCNN1G* variants. Missing observations are excluded. P-values are calculated using Fisher's exact test with * denoting statistical significance.

Categorical phenotype traits	***SCNN1B* frequency (%)**	***SCNN1G* frequency (%)**	**P-value**
Hypertension	213 of 231 (92)	34 of 37 (92)	1.000
Hypokalemia	140 of 199 (70)	24 of 36 (67)	0.695
Renin suppression	119 of 159 (75)	30 of 33 (91)	0.064
Aldosterone suppression	102 of 180 (57)	10 of 33 (30)	0.007*
Metabolic alkalosis	33 of 50 (66)	2 of 7 (29)	0.095
Complete treatment response with ENaC blocker	139 of 148 (94)	17 of 18 (94)	1.000
Hypertension disposition	57 of 78 (73)	33 of 37 (89)	0.755

Supplementary Table S10: Comparison of numeric phenotypic traits between patients with *SCNN1B* vs. *SCNN1G* variants. Missing observations are excluded. Blood pressure observations includes only adults. P-values are calculated using student's paired t-test or unpaired t-test as appropriate, and * denotes statistical significance.

Variable	***SCNN1B*** **Mean ±SD (no. of observations)**	***SCNN1G*** **Mean ±SD (no. of observations)**	**P-value**
Age in years	32 ±18 (176)	32 ±18 (23)	0.969
Age of hyperten diagnosis in years	21 ±11 (166)	21 ±11 (33)	0.960
Systolic blood pressure before ENaC blocker in mmHg	170 ±25 (138)	167 ±23 (23)	0.627
Systolic blood pressure after ENaC blocker in mmHg	127 ±10 (86)	129 ±8 (10)	0.534
Change in systolic blood pressure after ENaC blocker in mmHg	-51 ±22 (83)	-51 ±25 (10)	0.938
Diastolic blood pressure before ENaC blocker in mmHg	107 ±17 (138)	106 ±10 (23)	0.675
Diastolic blood pressure after ENaC blocker in mmHg	82 ±8 (86)	79 ±6 (10)	0.219
Change in diastolic blood pressure after ENaC blocker in mmHg	-30 ±17 (83)	-34 ±8 (10)	0.500
Blood potassium level before ENaC blocker in mM	3.3 ±0.7 (186)	3.3 ±0.7 (33)	0.840
Blood potassium level after ENaC blocker in mM	4.2 ±0.5 (104)	4.2 ±0.3 (16)	0.882
Change in blood potassium level after ENaC blocker in mM	1.1 ±0.6 (101)	1.1 ±0.6 (16)	0.957

Supplementary Table S11: Comparison of categorical phenotypic traits between patients with missense vs. truncating variants (i.e. frameshift or nonsense variants). Missing observations are excluded. P-values are calculated using Fisher's exact test with * denoting statistical significance.

Categorical phenotype traits	Missense frequency (%)	Truncating frequency (%)	P-value
Hypertension	97 of 103 (94)	150 of 165 (91)	0.484
Hypokalemia	71 of 90 (79)	93 of 145 (64)	0.019*
Renin suppression	71 of 83 (86)	78 of 109 (72)	0.024*
Aldosterone suppression	43 of 83 (52)	69 of 130 (53)	0.889
Metabolic alkalosis	15 of 20 (75)	20 of 37 (54)	0.159
Complete treatment response with ENaC blocker	71 of 72 (99)	85 of 94 (90)	0.044*
Hypertension disposition	94 of 103 (91)	150 of 165 (90)	1.000

Supplementary Table S12: Comparison of numeric phenotypic traits between patients with missense vs. truncating variants (i.e. frameshift or nonsense variants). Missing observations are excluded. Blood pressure observations includes only adults. P-values are calculated using student's paired t-test or unpaired t-test as appropriate, and * denotes statistical significance.

Variable	Missense Mean ±SD (no. of observations)	Truncating Mean ±SD (no. of observations)	P-value
Age in years	31 ±15 (85)	33 ±19 (114)	0.358
Age of hyperten diagnosis in years	20 ±10 (82)	21 ±12 (117)	0.815
Systolic blood pressure before ENaC blocker in mmHg	170 ±24 (64)	169 ±25 (97)	0.725
Systolic blood pressure after ENaC blocker in mmHg	126 ±10 (45)	128 ±9 (51)	0.185
Change in systolic blood pressure after ENaC blocker in mmHg	-52 ±21 (42)	-51 ±23 (51)	0.888
Diastolic blood pressure before ENaC blocker in mmHg	107 ±16 (64)	107 ±17 (97)	0.995
Diastolic blood pressure after ENaC blocker in mmHg	82 ±8 (45)	81 ±8 (51)	0.882
Change in diastolic blood pressure after ENaC blocker in mmHg	-29 ±14 (42)	-32 ±18 (51)	0.463
Blood potassium level before ENaC blocker in mM	3.1 ±0.7 (86)	3.4 ±0.7 (133)	0.003*
Blood potassium level after ENaC blocker in mM	4.2 ±0.4 (53)	4.2 ±0.5 (67)	0.751
Change in blood potassium level after ENaC blocker in mM	1.2 ±0.5 (50)	1.0 ±0.6 (67)	0.041*

Supplementary Table S13: Comparison of categorical phenotypic traits between probands vs. relatives. Missing observations are excluded. P-values are calculated using Fisher's exact test with * denoting statistical significance.

Categorical phenotype traits	Proband frequency (%)	Relative frequency (%)	P-value
Hypertension	77 of 78 (99)	170 of 190 (90)	0.010*
Hypokalemia	69 of 78 (89)	95 of 157 (61)	0.000*
Renin suppression	64 of 72 (89)	85 of 120 (71)	0.004*
Aldosterone suppression	38 of 76 (50)	63 of 137 (46)	0.668
Metabolic alkalosis	13 of 19 (68)	22 of 38 (58)	0.567
Complete treatment response with ENaC blocker	67 of 73 (92)	89 of 93 (96)	0.338
Hypertension disposition	57 of 78 (73)	187 of 190 (98)	0.000*

Supplementary Table S14: Comparison of numeric phenotypic traits between probands vs. relatives. Missing observations are excluded. Blood pressure observations includes only adults. P-values are calculated using student's paired t-test or unpaired t-test as appropriate, and * denotes statistical significance.

Variable	Proband Mean ±SD (no. of observations)	Relative Mean ±SD (no. of observations)	P-value
Age in years	23 ±12 (68)	37 ±18 (131)	0.000*
Age of hypertension diagnosis in years	16 ±5 (74)	24 ±13 (125)	0.000*
Systolic blood pressure before ENaC blocker in mmHg	181 ±25 (46)	165 ±23 (115)	0.000*
Systolic blood pressure after ENaC blocker in mmHg	126 ±9 (32)	128 ±9 (64)	0.388
Change in systolic blood pressure after ENaC blocker in mmHg	-59 ±25 (32)	-47 ±20 (61)	0.015*
Diastolic blood pressure before ENaC blocker in mmHg	114 ±16 (46)	104 ±16 (115)	0.001*
Diastolic blood pressure after ENaC blocker in mmHg	81 ±8 (32)	82 ±8 (64)	0.531
Change in diastolic blood pressure after ENaC blocker in mmHg	-36 ±17 (32)	-28 ±15 (61)	0.019*
Blood potassium level before ENaC blocker in mM	2.9 ±0.6 (73)	3.4 ±0.7 (146)	0.000*
Blood potassium level after ENaC blocker in mM	4.1 ±0.4 (47)	4.3 ±0.5 (73)	0.104
Change in blood potassium level after ENaC blocker in mM	1.2 ±0.6 (47)	1.0 ±0.6 (70)	0.104

Supplementary Figure 1: PRISMA flow-chart of study selection adapted from the PRIMSMA guideline[99]. *Two studies identified causative genetic variants without reporting them in the article, and one study reported a variant that did not exist in the applied transcript.

Supplementary Figure 2: Distribution of missing data (%) in A) the whole cohort, B) *SCNN1B* vs. *SCNN1G* variants, C) missense vs. truncating variants, and D) probands vs. relatives.

Supplementary Figure 3: Systolic blood pressure across age groups. A) The whole cohort. B) *SCNN1B* vs. *SCNN1G* variants. C) Missense vs. truncating variants. D) Probands vs. relatives.

Supplementary Figure 4: Systolic blood pressure by age with linear trend lines when comparing A) *SCNN1B* vs. *SCNN1G* variants and B) missense vs. truncating variants.

References

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