

SUPPLEMENTAL MATERIAL

Table S1. Name, function, and category of urinary proteins associated with DHFA in our study in either non-adjusted or adjusted analyses.

Short name	Full name	Function	Biologic process
Albumin	Albumin	Binds water, electrolytes, hormones, drugs. Regulates colloid osmotic pressure in blood.	Transporter, osmotic regulator
ALDH1A1	Aldehyde dehydrogenase 1A1	Cytosolic dehydrogenase that catalyzes oxidation of a wide range of aldehydes to carboxylic acids	Lipid metabolism
AMY2A	Pancreatic alpha-amylase	Hydrolyzes 1,4-alpha-D-glucosidic bonds in oligosaccharides and polysaccharides	Carbohydrate metabolism
AMY2B	Pancreatic alpha-amylase 2B	Hydrolyzes 1,4-alpha--D-glucosidic bonds in oligosaccharides and polysaccharides	Carbohydrate metabolism
ANGPTL2	Angiopoietin-related protein 2	A member of the vascular endothelial growth factor family, promotes inflammation, potentially pleiotropic functions	Multicellular organism development
APCS	Serum amyloid P-component	Can interact with DNA and histones	Many (innate immune response, complement activation, chaperone-mediated protein complex assembly, negative regulation of monocyte differentiation, protein folding)
ATP1B1	Sodium/potassium-transporting ATPase subunit beta-1	Na ⁺ /K ⁺ ATPase is an important membrane protein responsible for the electrochemical gradients of sodium and potassium ions.	Cell adhesion, immunity, innate immunity, ion transport, potassium transport
ATP5F1A	ATP synthase subunit alpha, mitochondrial	A subunit of mitochondrial ATP synthase.	ATP synthesis, hydrogen ion transport, ion transport, transport
Attractin	Attractin	Involved in the initial immune inflammatory response and may regulate chemokines. May play a role in melanocortin signaling pathways involved in energy homeostasis and hair color.	Inflammatory response

B4GALT1	Beta-1,4-galactosyltransferase 1	Membrane-bound glycoproteins that transfer galactose to acceptor sugars.	lipid metabolism
C11orf54	Ester hydrolase C11orf54	Enables hydrolase activity. unknown biological role	Hydrolase
COL15A1	Collagen alpha-1(XV) chain	Collagen type XV is predominantly located in the basement membrane zones of microvessels and cardiac or skeletal myocytes	Fibrosis
COL6A1	Collagen alpha-1(VI) chain	Collagen VI is a major structural component of microfibrils	Fibrosis
CPE	Carboxypeptidase E	Involved in synthesis of neuropeptides and peptide hormones. Catalyzes the release of C-terminal arginine or lysine residues.	Many (cardiac LV morphogenesis, insulin processing, neuropeptide signaling pathway, peptide hormone secretion)
DNASE1	Deoxyribonuclease-1	Serum endonuclease. Involved in cell death by apoptosis	Apoptosis
EGF	Pro-epidermal growth factor	EGF stimulates the growth of various epidermal and epithelial tissues	Many (negative regulation of cholesterol efflux, endothelial cell migration, angiogenesis)
Haptoglobin	Haptoglobin	Haptoglobin binds free hemoglobin. It also has antibacterial activity and plays a role in many aspects of the acute phase reactions.	Acute phase response, immunity
HMCN1	Hemicentin-1	Involved in cytoskeleton development, basement membrane organization, and cell division.	Cell cycle, cell division, sensory transduction, vision
HSPD1	60 kDa heat shock protein, mitochondrial	Chaperonin associated with mitochondrial protein import. May also prevent misfolding and promote proper assembly of polypeptides generated under stress conditions in the mitochondria	Host-virus interaction
ICOSLG	ICOS ligand	Ligand for T-cell specific receptor ICOS	Inflammatory response

IGFALS	Insulin-like growth factor-binding protein complex acid labile subunit	Growth promoting peptides. Increases the half-life of insulin like growth factors.	Cell adhesion
IGHA2	Immunoglobulin heavy constant alpha 2 (IGHA2)	Constant region of immunoglobulin heavy chains.	Immune response
IGLV3-25	Immunoglobulin lambda variable 3-25	Region of the immunoglobulin light chains that participates in antigen recognition	Adaptive immunity, immunity
KIF3A	Kinesin-like protein	Microtubule-based anterograde translocator for membranous organelles, cilia formation, centriole cohesion.	Microtubule-based movement
LRRC19	Leucine-rich repeat-containing protein 19	Involved in signaling pathways, inflammation.	Host mediated regulation of intestinal microbiota composition, regulation of inflammatory response, toll-like receptor signaling pathway
MAGEA4	Melanoma-associated antigen 4	Regulates cell proliferation	Negative regulation of apoptotic process, negative regulation of transcription by RNA polymerase II, positive regulation of cell cycle
MAN1A1	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA	Involved in the synthesis of glycoproteins	Carbohydrate metabolism, golgi apparatus mannose trimming, protein targeting to ER, ubiquitin-dependent ERAD pathway
MBD1	Methyl-CpG-binding domain protein 1	Transcriptomal repressor	Cell replication, DNA transcription
MELTF	Melanotransferrin	Involved in cellular iron uptake. Present on melanoma cells	iron transport, coagulation, inflammation
PGKA	Phosphoglycerate kinase 1	Catalyzes one of the two ATP producing reactions in the glycolytic pathway	Glycolysis
PLAU	Urokinase-type plasminogen activator	Cleaves the zymogen plasminogen to form the active enzyme plasmin.	Blood coagulation, fibrinolysis, hemostasis, plasminogen activation

Prostasin	Prostasin	Trypsinogen, a serine protease.	Hydrolase, protease, serine protease
PROZ	Vitamin K-dependent protein Z	Involved in hemostasis. Inhibits coagulation factor Xa.	Blood coagulation, hemostasis
QPCT	Glutaminyl-peptide cyclotransferase	Catalyzes formation of N-terminal pyroglutamates in peptides and proteins.	Cellular protein modification process
SERPINA5	Plasma serine protease inhibitor	Inactivates serine proteases.	Fertilization, lipid transport, transport
SLC12A3	Solute carrier family 12 member 3	Sodium and chloride ion cotransporter. Receptor for the cytokine IL18	Ion transport, sodium transport, symport, transport, potassium ion homeostasis
SLC2A5	Solute carrier family 2, facilitated glucose transporter member 5	Fructose transporter. Plays a role in the regulation of salt uptake.	transport, sugar transport
X6R868	Bile salt activated lipase	Bile salt activated lipase	Digestion
XPNPEP2	Xaa-Pro aminopeptidase 2	Metalloprotease which catalyzes the removal of a residue from the N-termini of peptides. May play a role in the metabolism of the vasodilator bradykinin.	Protease
ZG16B	Zymogen granule protein 16 homolog B	Carbohydrate binding activity, retina homeostasis	Carbohydrate binding, retina homeostasis

Name, function, and category of proteins, as adapted from Uniprot (1) and Genecards (2).

Table S2. Urinary biomarkers associated with DHFA when adjusting for urine creatinine and eGFR. Urinary proteins significantly associated with the outcome when adjusting for total urine proteins include 23 significant proteins, all of which were present in our primary analyses.

UNIPROT ID	Short Name	Full name	Hazard Ratio	95% CI	P value
Q9UKU9	ANGPTL2	Angiopoietin-related protein 2	0.61	0.49-0.74	0.0006
P04746	AMY2A	Pancreatic alpha-amylase	0.57	0.45-0.71	0.0004
P24855	DNASE1	Deoxyribonuclease-1	0.56	0.45-0.7	0.0002
P00352	ALDH1A1	Aldehyde dehydrogenase 1A1	0.59	0.47-0.73	0.0004
P19961	AMY2B	Pancreatic alpha amylase 2B	0.58	0.45-0.73	0.0022
P00749	PLAU	Urokinase-type plasminogen activator	0.61	0.48-0.76	0.0062
P10809	HSP60	60 kDa heat shock protein, mitochondrial	0.60	0.49-0.74	0.0005
A0A0C4DGN4	ZG16B	Zymogen granule protein 16 homolog B	0.62	0.5-0.76	0.0023
K4DIA0	ICOSLG	ICOS ligand	0.64	0.51-0.79	0.0097
P00558	PGKA	Phosphoglycerate kinase 1	0.66	0.54-0.8	0.0067
P01133	EGF	Pro-epidermal growth factor	0.60	0.47-0.75	0.0032
Q9H0W9	C11orf54	Ester hydrolase C11orf54	0.64	0.51-0.8	0.0356
K7EPZ6	MBD1	Methyl-CpG-binding domain protein 1	1.62	1.29-2.02	0.0064
P22732	SLC2A5	Solute carrier family 2, facilitated glucose transporter member 5	0.64	0.51-0.78	0.0055
P25705	ATP5F1A	ATP synthase subunit alpha, mitochondrial	0.64	0.52-0.78	0.0056
P05026	ATP1B1	Sodium/potassium-transporting ATPase subunit beta-1	0.64	0.51-0.79	0.0149
P15291	B4GALT1	Beta-1,4-galactosyltransferase 1	0.62	0.49-0.77	0.0094
P02743	APCS	Serum amyloid P-component	1.50	1.23-1.81	0.0145
A0A087X0K0	COL15A1	Collagen alpha-1(XV) chain	0.65	0.52-0.79	0.0124
Q16769	QPCT	Glutaminy-peptide cyclotransferase	0.66	0.53-0.81	0.0344
P01717	IGLV3-25	Immunoglobulin lambda variable 3-25	1.53	1.24-1.88	0.0186
P43358	MAGEA4	Melanoma-associated antigen 4	1.51	1.24-1.84	0.0117
P06576	ATPB	ATP Synthase subunit beta	0.64	0.51-0.79	0.0136

HR = Hazard Ratio, CI = confidence interval, eGFR = estimated glomerular filtration rate

Table S3. Urinary biomarkers associated with DHFA adjusting for total urine protein.

Urinary proteins significantly associated with the outcome when adjusting for total urine proteins include 18 significant proteins, all of which were present in our main analyses.

Uniprot ID	Short name	Full name	HR	95%CI	P value
P02743	APCS	Serum amyloid P-component	1.63	1.34-2.00	0.0003
P01717	IGLV3-25	Immunoglobulin lambda variable 3-25	1.53	1.24-1.88	0.0176
Q16769	QPCT	Glutaminyl-peptide cyclotransferase	0.67	0.55-0.82	0.0318
P05026	ATP1B1	Sodium/potassium-transporting ATPase subunit beta-1	0.67	0.55-0.83	0.0500
A0A087X0K0	COL15A1	Collagen alpha-1(XV) chain	0.67	0.55-0.82	0.0301
P35858	IGFALS	Insulin-like growth factor-binding protein complex acid labile subunit	0.66	0.54-0.82	0.0288
P22732	SLC2A5	Solute carrier family 2, facilitated glucose transporter member 5	0.65	0.53-0.81	0.0226
K4DIA0	ICOSLG	ICOS ligand	0.65	0.53-0.79	0.0087
P00749	PLAU	Urokinase-type plasminogen activator	0.64	0.51-0.79	0.0113
P10809	HSP60	60 kDa heat shock protein, mitochondrial	0.63	0.52-0.78	0.0035
P19961	AMY2B	Alpha-amylase 2B	0.63	0.51-0.87	0.0067
P00352	ALDH1A1	Aldehyde dehydrogenase 1A1	0.63	0.52-0.77	0.0031
A0A0C4DGN4	ZG16B	Zymogen granule protein 16 homolog B	0.63	0.51-0.76	0.0013
P01133	EGF	Pro-epidermal growth factor	0.61	0.49-0.77	0.0062
P15291	B4GALT1	Beta-1,4-galactosyltransferase 1	0.62	0.50-0.75	0.0005

Q9UKU9	ANGPTL 2	Angiopoietin-related protein 2	0.61	0.50-0.75	0.0008
P24855	DNASE1	Deoxyribonuclease-1	0.60	0.49-0.74	0.0004
P04746	AMY2A	Pancreatic alpha-amylase	0.59	0.48-0.74	0.0010

HR = Hazard ratio, CI = confidence interval

Table S4. Urinary biomarkers associated with DHFA adjusting for the inverse of urine creatinine (1/urine creatinine). Urinary proteins significantly associated with the outcome when adjusting for total urine proteins include 43 significant proteins, of which three (TCN2, GSTM3, PDCD1LG2) are not represented in our main analyses.

Uniprot ID	Short name	Full name	HR	95%CI	P value
P24855	DNASE1	Deoxyribonuclease-1	0.51	0.41-0.64	4.79E-07
P04746	AMY2A	Pancreatic alpha-amylase	0.54	0.43-0.67	8.00E-06
P00352	ALDH1A1	Aldehyde dehydrogenase 1A1	0.54	0.44-0.67	9.01E-06
Q9UKU9	ANGPTL2	Angiopoietin-related protein 2	0.56	0.46-69	9.77E-06
P01133	EGF	Pro-epidermal growth factor	0.55	0.45-0.68	1.52E-05
A0A0C4DGN4	ZG16B	Zymogen granule protein 16B	0.57	0.46-0.70	2.42E-05
P19961	P19961	Alpha-amylase 2B	0.55	0.43-0.68	5.35E-05
P00749	PLAU	Urokinase-type plasminogen activator	0.57	0.46-71	7.32E-05
K4DIA0	K4DIA0	Inducible T cell costimulator ligand	0.60	0.49-0.73	1.26E-04
P15291	B4GALT1	Beta-1,4-galactosyltransferase 1	0.58	0.47-0.72	1.45E-04
P10809	HSPD1	60 kDa heat shock protein, mitochondrial	0.59	0.48-0.73	1.49E-04
P22732	SLC2A5	Solute carrier family 2, facilitated glucose transporter member 5	0.61	0.50-0.74	3.51E-04
A0A087X0K0	COL15A1	Collagen type XV alpha 1 chain	0.61	0.50-0.74	3.73E-04
Q16769	QPCT	Glutaminyl-peptide cyclotransferase	0.58	0.47-0.73	5.83E-04
X6R868	X6R868	X6R868	0.61	0.50-0.75	7.27E-04
P05026	ATP1B1	Sodium/potassium-transporting ATPase subunit beta-1	0.61	0.49-0.75	8.11E-04
P33908	P33908	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA	0.60	0.48-0.74	8.14E-04
A0A087X0S5	COL6A1	Collagen type VI alpha 1 chain	0.61	0.49-0.75	1.05E-03
Q16651	PRSS8	Prostasin	0.61	0.49-0.75	1.29E-03

P00558	PGK1	Phosphoglycerate kinase 1	0.64	0.53-0.78	2.19E-03
P25705	ATP5F1A	ATP synthase subunit alpha, mitochondrial	0.63	0.51-0.77	3.04E-03
P02743	APCS	Serum amyloid P-component	1.55	1.28-1.89	4.24E-03
Q9H756	LRRC19	Leucine-rich repeat-containing protein 19	0.64	0.52-0.79	6.24E-03
P01717	IGLV3-25	Immunoglobulin lambda variable 3-25	1.58	1.23-1.95	6.29E-03
P08582	MELTF	Melanotransferrin	0.64	0.53-0.79	6.32E-03
P16870	CPE	Carboxypeptidase E	0.64	0.51-0.78	7.14E-03
P22891	PROZ	Vitamin K-dependent protein Z	0.66	0.54-0.80	9.73E-03
Q9H0W9	C11orf54	Ester hydrolase C11orf54	0.63	0.50-0.78	1.03E-02
P35858	IGFALS	Insulin-like growth factor-binding protein complex acid labile subunit	0.65	0.53-0.80	1.49E-02
P02768	ALB	Albumin	1.50	1.23-1.83	1.70E-02
P05154	SERPINA5	Plasma serine protease inhibitor	0.65	0.53-0.80	1.84E-02
O43895	XPNPEP2	Xaa-Pro aminopeptidase 2	0.65	0.53-0.80	2.02E-02
O75882	ATRN	Attractin	0.65	0.52-0.80	2.19E-02
K7EPZ6	MBD1	Methyl-CpG binding domain protein 1	1.53	1.24-1.88	2.46E-02
Q96RW7	HMCN1	Hemicentin-1	0.67	0.54-0.81	2.52E-02
P21266	GSTM3	Glutathione S-transferase Mu 3	0.65	0.52-0.80	2.54E-02
P00738	HP	Haptoglobin	1.52	1.23-1.87	2.62E-02
P55017	SLC12A3	Solute carrier family 12 member 3	0.68	0.56-0.82	2.90E-02
J3KPF9	KIF3A	Kinesin-like protein	1.44	1.20-1.73	3.32E-02
Q9BQ51	PDCD1LG2	Programmed cell death 1 ligand 2	0.66	0.54-0.81	3.39E-02
F8WE86	TCN2	Transcobalamin 2	0.67	0.54-0.82	3.47E-02
P43358	MAGE4A	Melanoma-associated antigen 4	1.45	1.20-1.75	3.57E-02
A0A075B6N7	IGHA2	Immunoglobulin heavy constant alpha 2	1.46	1.12-1.77	4.60E-02

SE = standard error, CI = confidence interval, eGFR = estimated glomerular filtration rate

Table S5. Urinary biomarkers associated with DHFA adjusting for randomization arm.

Urinary proteins significantly associated with the outcome when adjusting for spironolactone (placebo versus spironolactone arm) include 38 proteins, all of which were present in the primary analysis.

Uniprot ID	Short name	Full name	HR	95%CI	P value
P24855	DNASE1	Deoxyribonuclease-1	0.57	0.46-0.69	6.03E-06
P04746	AMY2A	Pancreatic alpha-amylase	0.56	0.46-0.69	1.13E-05
Q9UKU9	ANGPTL2	Angiotensin-converting enzyme 2	0.58	0.48-0.71	2.51E-05
P01133	EGF	Pro-epidermal growth factor	0.58	0.47-0.71	4.25E-05
A0A0C4DGN4	ZG16B	Zymogen granule protein 16 homolog B	0.60	0.49-0.73	8.71E-05
P00352	ALDH1A1	Aldehyde dehydrogenase 1A1	0.59	0.48-0.72	8.97E-05
P19961	AMY2B	Alpha-amylase 2B	0.60	0.49-0.73	0.0001948
P00749	PLAU	Urokinase-type plasminogen activator	0.60	0.49-0.73	0.0002170
K4DIA0	ICOSLG	ICOS ligand	0.61	0.50-0.74	0.00022086
P10809	HSP60	60 kDa heat shock protein, mitochondrial	0.60	0.49-0.74	0.00027407
P15291	B4GALT1	Beta-1,4-galactosyltransferase 1	0.60	0.49-0.74	0.0002886
P22732	SLC2A5	Solute carrier family 2, facilitated glucose transporter member 5	0.61	0.50-0.75	0.0004492
A0A087X0K0	COL15A1	Collagen alpha-1(XV) chain	0.64	0.53-0.77	0.001404
X6R868	X6R868	X6R868	0.64	0.52-0.77	0.001890

P05026	ATP1B1	Sodium/potassium-transporting ATPase subunit beta-1	0.64	0.52-0.78	0.002986
Q16651	Prostasin	Prostasin	0.64	0.52-0.78	0.003200
A0A087X0S5	COL6A1	Collagen alpha-1(VI) chain	0.64	0.53-0.78	0.003225
Q16769	QPCT	Glutaminyl-peptide cyclotransferase	0.65	0.53-0.78	0.003453
P00558	PGKA	Phosphoglycerate kinase 1	0.66	0.54-0.79	0.004354
P25705	ATP5F1A	ATP synthase subunit alpha, mitochondrial	0.64	0.52-0.78	0.004836
P33908	MAN1A1	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA	0.65	0.53-0.79	0.004878
P02743	APCS	Serum amyloid P-component	1.54	1.26-1.87	0.0054568
P01717	IGLV3-25	Immunoglobulin lamda variable 3-25	1.58	1.28-1.95	0.006024
P08582	MELTF	Melanotransferrin	0.66	0.54-0.80	0.01121
Q9H756	LRRC19	Leucine-rich repeat-containing protein 19	0.66	0.55-0.81	0.01531
P22891	PROZ	Vitamin K-dependent protein Z	0.67	0.55-0.81	0.01643
P16870	CPE	Carboxypeptidase E	0.67	0.55-0.82	0.02165
P02768	Albumin	Albumin	1.49	1.22-1.81	0.02346
P35858	IGFALS	Insulin-like growth factor-binding protein complex acid labile subunit	0.66	0.54-0.81	0.02386
Q96RW7	HMCN1	Hemicentin-1	0.67	0.55-0.82	0.02933

Q9H0W9	C11orf54	Ester hydrolase C11orf54	0.67	0.55-0.82	0.03138
P55017	SLC12A3	Solute carrier family 12 member 3	0.68	0.56-0.82	0.03205
O43895	XPNPEP2	Xaa-Pro aminopeptidase 2	0.67	0.55-0.82	0.03594
K7EPZ6	MBD1	Methyl-CpG-binding domain protein 1	1.51	1.23-1.87	0.03597
P00738	Haptoglobin	Haptoglobin	1.50	1.22-1.84	0.03698
P05154	SERPINA5	Plasma serine protease inhibitor	0.67	0.55-0.82	0.03874
P43358	MAGEA4	Melanoma-associated antigen 4	1.46	1.20-1.77	0.03929
A0A075B6N7	IGHA2	Immunoglobulin heavy constant alpha 2 (IGHA2)	1.46	1.20-1.77	0.04635

HR = Hazard ratio, CI = confidence interval