Published in final edited form as:

Pharmacogenet Genomics. 2013 August ; 23(8): 449–453. doi:10.1097/FPC.0b013e3283636822.

PharmGKB summary: diuretics pathway, pharmacodynamics

Caroline F. Thorn^a, David H. Ellison^d, Stephen T. Turner^c, Russ B. Altman^{a,b}, and Teri E. Klein^a

^aDepartment of Genetics, Stanford University Medical Center, Stanford, California, USA

^bDepartment of Bioengineering, Stanford University Medical Center, Stanford, California, USA

^cDepartment of Internal Medicine, Division of Nephrology & Hypertension, Mayo Clinic, Rochester, Minnesota

^dDepartment of Medicine, Division of Nephrology & Hypertension, Oregon Health & Science University, Portland, Oregon, USA

Keywords

diuretics; hypertension; pathway; pharmacogenetic; pharmacogenomic

Introduction

Diuretics are the most commonly prescribed drugs for hypertension in the USA [1]. Diuretics modulate the reabsorption of sodium in the kidney and affect the homeostasis of water and sodium and thus the volume of blood and blood pressure. From a pharmacogenomics perspective, the most well studied drug in this class is the thiazide diuretic hydrochlorothiazide (HCT). HCT is excreted primarily by renal elimination with greater than 95% of the drug recovered unchanged in the urine [2]. Therefore, pharmacodynamic genes have been the focus for studies of the variation in response to thiazide diuretics. Thiazide diuretics act by inhibiting the sodium chloride cotransporter, NCC, coded for by *SLC12A3* [3]. Also acting on sodium regulation in the kidney, loop diuretics such as furosemide, target the sodium potassium chloride cotransporter (NKCC2, *SLC12A1*). In addition, another subclass of diuretics, potassium-sparing diuretics like amiloride, act on the sodium channel ENaC, coded for by *SCNN1* family of genes. Table 1 shows the common names and their corresponding HGNC gene symbols for the key transporters.

This brief summary introduces the candidate genes in the pharmacodynamic pathway of diuretics (Fig. 1) and discusses the pharmacogenomic studies.

Copyright © Lippincott Williams & Wilkins.

Correspondence to Teri E. Klein, PhD, Department of Genetics, Stanford University Medical Center, 300 Pasteur D. Lane L301, Mail Code 5120, Stanford, CA 94305-5120, USA, Tel: +1 650 725 0659; fax: +1 650 725 3863; feedback@pharmgkb.org.

Conflicts of interest

There are no conflicts of interest.

Thiazide diuretics

The sodium chloride cotransporter SLC12A3 is also known as the thiazide-sensitive transporter. It controls uptake of sodium accompanied by a chloride ion from the lumen into the kidney epithelial cell in the distal convoluted tubule (DCT) [4]. Sodium is then returned to the bloodstream through the ATP-dependent sodium-potassium pump, Na,K-ATPase [5] (Fig. 1). The Na,K-ATPase is coded for by several genes of the ATPase family, which show tissue specific expression [5].

The uptake of sodium by SLC12A3 can be blocked by thiazide diuretics, or by rare, hereditary loss of function mutations in the *SLC12A3* gene that result in Gitelman's syndrome [3,4]. Thiazides inhibit the binding of chloride to SLC12A3, which then prevents the cotransport of sodium [6]. In order to have its pharmacological effect the thiazide must first be excreted into the lumen by transporters OCT1 and OCT3, coded for by *SLC22A6* and *SLC22A8* [PMID: 18216144].

Both the trafficking of SLC12A3 to the membrane and phosphorylation and activation of SLC12A3 is controlled by the with-no-lysine kinases (WNKs) [7]. As seen in Fig. 1, the WNKs are central to a complex regulatory network that balances the relative roles of the different transporters and ion channels in the different parts of the kidney (for a full review of the detailed signaling see Hoorn and Ellison [7]). In the DCT, WNK3 activates SLC12A3 both directly and through STK39 (also known as SPAK, or Ste20/SPS1-related kinase) [8,9]. WNK1 may also activate STK39 [7]. STK39 phosphorylates SLC12A3 in the DCT leading to its activation. STK39 can be differently spliced, with the short form or kinase defective form (KS-SPAK), which does not phosphorylate SLC12A3 or OXSR1, being expressed in the thick ascending limb of the kidney [8]. SLC12A3 is inhibited by WNK4 by promotion of its degradation via the lysosomal pathway [7], however angiotensin II (AngII) may act to counteract this by switching WNK4 to stimulate STK39 and so stimulate SLC12A3 [10]. Also a kidney specific splice variant of WNK1 inhibits SLC12A3 by inhibition of WNK1, which in turn inhibits WNK3 [7]. WNK1 can also inhibit the WNK4 effects on SLC12A3 [7]. Mutations in the *WNK1* or *WNK4* genes cause FHHt, familial hyperkalemic hypertension or Gordon syndrome or pseudohypoaldosteronism type II, whereby SLC12A3 is overactive and results in hypertension [11]. Patients with FHHt can have six to seven times the average response to HCT [12].

There is also regulation of SLC12A3 by aldosterone [13]. Aldosterone increases SLC12A3 protein expression by activation of SGK1, which phosphorylates NEDD4L and prevents NEDD4L binding to and inhibiting SLC12A3 [13].

Other hormones may also influence the activity of SLC12A3. Male patients with mutations in *SLC12A3* tend to have more severe symptoms of Gitelman syndrome than female patients [14]. Estrogens have been shown to increase SLC12A3 density at the membrane in rats [15].

The Na,K-ATPase is formed from three subunits α , β , and γ . Several genes encode the catalytic α subunit with different tissue expression patterns. *ATP1A1* is the predominant form expressed in the kidney [5]. There are also several genes for the β subunit (*ATP1B1*, *ATP1B2*, *ATP1B3*) [16]. The γ subunit is coded for by *FXYD2* [17]. Mutations in *FXYD2*

result in hypomagnesemia and hypocalciuria [17]. In-vitro studies have shown that the Na,K-ATPase is regulated by phosphorylation on the α subunit by protein kinase A (PKA) and protein kinase C (PKC) [18–20]. Phosphorylation can also affect the transporters trafficking to the membrane with G-protein coupled receptor kinases (GRKs) and arrestins promoting phosphorylation and phosphatase PP2AC reversing this process [18]. The FXRD2 subunit expression is alternatively spliced and the ratios of these may be affected by the transcription factor HIF1B [21]. Variants in the *ARNT* gene that codes for HIF1B may therefore result in hypomagnesemia [21]. Experiments in mice showed that the epithelial Mg^{2+} channel transient receptor potential channel subfamily M member 6, *TRPM6*, is downregulated in *SLC12A3* knock-out animals treated chronically with HCT [PMID: 15902302]. In addition, hypomagnesemia has been reported in patients receiving both diuretics and protonpump inhibitors, which interact with *TPRM6* [PMID: 23538697].

The DCT is responsible for only around 5% of the sodium reabsorbed within the nephron therefore thiazide diuretics have only a limited capacity to change sodium balance [4]. However, these drugs are often sufficient in patients with uncomplicated hypertension and no concurrent renal disease [4]. One of the side effects of thiazides is hypokalemia, reduced serum potassium. This results from thiazides inhibiting NaCl transport along the DCT, thus increasing sodium delivery into the connecting tubule and collecting duct. These segments express the epithelial sodium channel, ENaC, and the potassium channel, ROMK, at their apical membranes, so that potassium secretion is a consequence of enhanced sodium reabsorption through ENaC [22]. Thiazide-related potassium loss is dose dependent and at high doses can lead to arrhythmia and sudden cardiac death [22]. Therefore, rather than increase the dose, if low doses of thiazides are insufficient to reduce blood pressure a second antihypertensive drug is added, such as an ACE inhibitor or AngII receptor blocker which often reduces the renal potassium excretion as well as synergistically reducing blood pressure [22]. The mechanism for this counter-balancing is likely through AngII on WNK4 (as discussed above) [10].

Loop diuretics

The main target of loop diuretic is the sodium potassium chloride cotransporter, NKCC2, *SLC12A1*, which is found predominantly in the thick ascending limb of the loop of Henle (i.e. earlier in the resorption process than the DCT where thiazides act). Thirty percent of the filtered sodium chloride is reabsorbed in the thick ascending limb [23]. *SLC12A1* transports sodium, potassium, and two chloride ions across the apical membrane. Potassium is recycled out across the apical membrane by the potassium channel ROMK, coded for by *KCNJ1* [23]. At the basolateral membrane, sodium is exported from the cell through the Na,K-ATPase, whereas chloride diffuses through the channels ClC-Ka and ClC-Kb, coded for by *CLCNKA* and *CLCNKB* [24]. The membrane location of the chloride channels is regulated by barttin, *BSND*. Inactivating mutations in any of these genes (*SLC12A1*, *KCNJ1*, *CLCNKA*, *CLCNKB*, and *BSND*) can result in Bartter syndrome, where sodium, water, potassium, chloride, and calcium homeostasis is disrupted [24].

As with the thiazide-sensitive transporter, the phosphorylation and location of *SLC12A1* at the membrane can be modulated by WNK signaling [7]. An undefined WNK phosphorylates

OSR1 which in turn phosphorylates SLC12A1 and increases function [25]. OSR1 is inhibited by the kinase-deficient splice variant of STK39 [8].

Potassium-sparing diuretics

Around 1–2% of sodium resorption occurs in the collecting duct [26]. This region is the main site of action of the potassium-sparing diuretics, amiloride, and triamterene, which target the epithelial sodium channel, ENaC. ENaC is coded for by the *SCNN* family of genes, *SCNN1A*, *SCNN1B*, *SCNN1G*, *SCNN1D* whose products combine to form a heterotrimeric protein, although *SCNN1D* may not be a relevant candidate gene for efficacy as it is more prominently expressed in tissues other than kidney [27]. Mutations in *SCNN1B* or *SCNN1G* that interfere with ubiquitylation of the channel by NEDD4-2 cause increased channel activity and Liddle syndrome, characterized by early onset hypertension and hypokalemia [28].

The WNKs are also involved in regulation of SCNN1 at the membrane [7]. WNK1 and WNK4 can increase the amount of SCNN1 at the membrane [7]. Aldosterone, acting through SGK1 and NEDD4L can also lead to increased SCNN1 at the membrane [13]. Increased intracellular sodium leads to down regulation of SCNN1, and this mechanism is defective in Liddle syndrome [28].

Pharmacogenomics

There have been a considerable number of PGx studies of thiazide diuretics (Table 2). A few studies have also looked at other diuretics or grouped drugs by class [29–31] (Table 3). The majority of these have taken candidate gene approaches, confirming genes already known to be involved in hypertension and blood pressure control, with two GWAS studies involving diuretics published to date [32,33].

The results of these associations can be roughly grouped into six intersecting sets, (the first three are depicted in Fig. 1): (a) variants that act at the SLC12A3 transporter (in *SLC12A3*, *NEDD4L*, *WNK1*), (b) variants that act at the Na,K-ATPase (in *ADD1*, *NEDD4L*), (c) variants that act at the SCNN1 transporter (in *SCNN1G*, *NEDD4L*, *WNK1*), (d) variants that act in the RAAS pathway (in *ACE*, *AGT*, *AGTR1*, *CYP11B*, *REN*, *KNG1*, *NOS3*), (e) variants that act in the β -adrenergic pathway (in *ADRB2*, *ADRB3*, *GNB3*), (f) variants with other or unknown pathway effects (in *SLC22A6* and *SLC22A8*, which are genes involved in the PK of thiazides and loop diuretics; *YEATS4*, a transcription factor; *NT5C2*; *GRK5*).

To date there have been few attempts to replicate associations identified in either candidate studies or GWAS. Some candidates have been replicated but further replication has failed in other cohorts, for example *ACE*, *ADD1*. This appears to be a common problem with pharmacodynamic PGx, given that the clearest examples where PGx has been sufficiently replicated to be applied to practice in dosing recommendations (warfarin, codeine, mercaptopurines) are all PK. Many believe that some kind of complex network prediction for PD PGx will be necessary because of the ways in which alterations in one candidate gene may induce compensatory mechanisms in other parts of the pathway or other blood pressure pathways [34]. Some of the difficulty may be because of the different phenotypes

measured (ambulatory vs. office blood pressure), treatment regimen (treatment naive vs. long-term treatment, or polytherapy) and heterogeneity of the patients (sex, race, age, dietary salt intake). Although some suggest that the effects of common drug response variants may be larger than the effects of common variants influencing blood pressure and hypertension etiology, and therefore may be detectable in GWAS, if the effect sizes are as small, both the candidate gene and GWA studies so far are likely severely underpowered. This suggests that many of the reported associations may be false positives, and underscores the importance of replication studies.

Conclusion

Hypertension is a complex disease. If looked at from a molecular perspective it is a phenotype (elevated blood pressure) that results from alterations in the multiple pathways of blood pressure regulation. As such, determining the likely efficacy of different therapies for hypertension is challenging. However, a large number of candidate genes and single-nucleotide polymorphisms for both disease etiology and response to therapies have already been identified. There is a great need for these to be replicated in studies with sufficient size and power. Using current knowledge to better define molecular subtypes of hypertension in order to select more homogeneous patient populations during study design may enable the pharmacogenomics to be predicted.

Acknowledgments

The authors thank Fen Liu for assistance with the graphics. This work is supported by the NIH/NIGMS R24 GM61374 and U01 GM074492.

References

1. Duarte JD, Turner ST, Tran B, Chapman AB, Bailey KR, Gong Y, et al. Association of chromosome 12 locus with antihypertensive response to hydrochlorothiazide may involve differential YEATS4 expression. *Pharmacogenomics J.* 2013; 13:257–263. [PubMed: 22350108]
2. Beermann B, Groschinsky-Grind M, Rosen A. Absorption, metabolism, and excretion of hydrochlorothiazide. *Clin Pharmacol Ther.* 1976; 19(Pt 1):531–537. [PubMed: 1277708]
3. Reissinger A, Ludwig M, Utsch B, Promse A, Baulmann J, Weisser B, et al. Novel NCCT gene mutations as a cause of Gitelman–s syndrome and a systematic review of mutant and polymorphic NCCT alleles. *Kidney Blood Press Res.* 2002; 25:354–362. [PubMed: 12590198]
4. Brater DC. Pharmacology of diuretics. *Am J Med Sci.* 2000; 319:38–50. [PubMed: 10653443]
5. Lingrel JB. Na,K-ATPase: isoform structure, function, and expression. *J Bioenerg Biomembr.* 1992; 24:263–270. [PubMed: 1328175]
6. Morrison RT. Edema and principles of diuretic use. *Med Clin North Am.* 1997; 81:689–704. [PubMed: 9167652]
7. Hoorn EJ, Ellison DH. WNK kinases and the kidney. *Exp Cell Res.* 2012; 318:1020–1026. [PubMed: 22405999]
8. McCormick JA, Mutig K, Nelson JH, Saritas T, Hoorn EJ, Yang CL, et al. A SPAK isoform switch modulates renal salt transport and blood pressure. *Cell Metab.* 2011; 14:352–364. [PubMed: 21907141]
9. Mercier-Zuber A, O'Shaughnessy KM. Role of SPAK and OSR1 signalling in the regulation of NaCl cotransporters. *Curr Opin Nephrol Hypertens.* 2011; 20:534–540. [PubMed: 21610494]
10. Castaneda-Bueno M, Gamba G. Mechanisms of sodium-chloride cotransporter modulation by angiotensin II. *Curr Opin Nephrol Hypertens.* 2012; 21:516–522. [PubMed: 22820370]

11. Yang CL, Zhu X, Ellison DH. The thiazide-sensitive Na-Cl cotransporter is regulated by a WNK kinase signaling complex. *J Clin Invest*. 2007; 117:3403–3411. [PubMed: 17975670]
12. Mayan H, Vered I, Mouallem M, Tzadok-Witkon M, Pauzner R, Farfel Z. Pseudohypoaldosteronism type II: marked sensitivity to thiazides, hypercalciuria, normomagnesemia, and low bone mineral density. *J Clin Endocrinol Metab*. 2002; 87:3248–3254. [PubMed: 12107233]
13. Arroyo JP, Lagnaz D, Ronzaud C, Vazquez N, Ko BS, Moddes L, et al. Nedd4-2 modulates renal $\text{Na}^+\text{-Cl}^-$ cotransporter via the aldosterone- SGK1-Nedd4-2 pathway. *J Am Soc Nephrol*. 2011; 22:1707–1719. [PubMed: 21852580]
14. Riveira-Munoz E, Chang Q, Godefroid N, Hoenderop JG, Bindels RJ, Dahan K, et al. Transcriptional and functional analyses of SLC12A3 mutations: new clues for the pathogenesis of Gitelman syndrome. *J Am Soc Nephrol*. 2007; 18:1271–1283. [PubMed: 17329572]
15. Verlander JW, Tran TM, Zhang L, Kaplan MR, Hebert SC. Estradiol enhances thiazide-sensitive NaCl cotransporter density in the apical plasma membrane of the distal convoluted tubule in ovariectomized rats. *J Clin Invest*. 1998; 101:1661–1669. [PubMed: 9541496]
16. Malik N, Canfield V, Sanchez-Watts G, Watts AG, Scherer S, Beatty BG, et al. Structural organization and chromosomal localization of the human Na,K-ATPase beta 3 subunit gene and pseudogene. *Mamm Genome*. 1998; 9:136–143. [PubMed: 9457675]
17. Cairo ER, Swarts HG, Wilmer MJ, Willems PH, Levchenko EN, De Pont JJ, et al. FXYD2 and Na,K-ATPase expression in isolated human proximal tubular cells: disturbed upregulation on renal hypomagnesemia? *J Membr Biol*. 2009; 231:117–124. [PubMed: 19865785]
18. Kimura T, Han W, Pagel P, Nairn AC, Caplan MJ. Protein phosphatase 2A interacts with the Na,K-ATPase and modulates its trafficking by inhibition of its association with arrestin. *PLoS One*. 2011; 6:e29269. [PubMed: 22242112]
19. Galuska D, Pirkmajer S, Barres R, Ekberg K, Wahren J, Chibalin AV. C-peptide increases Na,K-ATPase expression via PKC- and MAP kinase-dependent activation of transcription factor ZEB in human renal tubular cells. *PLoS One*. 2011; 6:e28294. [PubMed: 22162761]
20. Poulsen H, Nissen P, Mouritsen OG, Khandelia H. Protein kinase A (PKA) phosphorylation of Na^+/K^+ -ATPase opens intracellular C-terminal water pathway leading to third Na^+ -binding site in molecular dynamics simulations. *J Biol Chem*. 2012; 287:15959–15965. [PubMed: 22433860]
21. Ferrè S, Veenstra GJ, Bouwmeester R, Hoenderop JG, Bindels RJ. HNF-1B specifically regulates the transcription of the γ -subunit of the Na^+/K^+ -ATPase. *Biochem Biophys Res Commun*. 2011; 404:284–290. [PubMed: 21130072]
22. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part II: electrolyte and acid-base disorders complicating diuretic therapy. *Expert Opin Drug Saf*. 2010; 9:259–273. [PubMed: 20095916]
23. Bichet DG, Fujiwara TM. Reabsorption of sodium chloride – lessons from the chloride channels. *N Engl J Med*. 2004; 350:1281–1283. [PubMed: 15044637]
24. Seyberth HW, Schlingmann KP. Bartter- and Gitelman-like syndromes: saltlosing tubulopathies with loop or DCT defects. *Pediatr Nephrol*. 2011; 26:1789–1802. [PubMed: 21503667]
25. Lin SH, Yu IS, Jiang ST, Lin SW, Chu P, Chen A, et al. Impaired phosphorylation of $\text{Na}(+)\text{-K}(+)\text{-2Cl}(-)$ cotransporter by oxidative stressresponsive kinase-1 deficiency manifests hypotension and Bartter-like syndrome. *Proc Natl Acad Sci USA*. 2011; 108:17538–17543. [PubMed: 21972418]
26. Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med*. 2009; 361:2153–2164. [PubMed: 19940300]
27. Giraldez T, Rojas P, Jou J, Flores C, Alvarez de la Rosa D. The epithelial sodium channel delta-subunit: new notes for an old song. *Am J Physiol Renal Physiol*. 2012; 303:F328–F338. [PubMed: 22573384]
28. Kellenberger S, Gautschi I, Rossier BC, Schild L. Mutations causing Liddle syndrome reduce sodium-dependent downregulation of the epithelial sodium channel in the *Xenopus* oocyte expression system. *J Clin Invest*. 1998; 101:2741–2750. [PubMed: 9637708]
29. Vormfelde SV, Brockmoller J. The genetics of loop diuretic effects. *Pharmacogenomics J*. 2012; 12:45–53. [PubMed: 20877298]

30. Yang YY, Lin HC, Lin MW, Chu CJ, Lee FY, Hou MC, et al. Identification of diuretic non-responders with poor long-term clinical outcomes: a 1-year follow-up of 176 non-azotaemic cirrhotic patients with moderate ascites. *Clin Sci (Lond)*. 2011; 121:509–521. [PubMed: 21692745]
31. Vormfelde SV, Sehrt D, Toliat MR, Schirmer M, Meineke I, Tzvetkov M, et al. Genetic variation in the renal sodium transporters NKCC2, NCC, and ENaC in relation to the effects of loop diuretic drugs. *Clin Pharmacol Ther*. 2007; 82:300–309. [PubMed: 17460608]
32. Turner ST, Bailey KR, Fridley BL, Chapman AB, Schwartz GL, Chai HS, et al. Genomic association analysis suggests chromosome 12 locus influencing antihypertensive response to thiazide diuretic. *Hypertension*. 2008; 52:359–365. [PubMed: 18591461]
33. Turner ST, Bailey KR, Schwartz GL, Chapman AB, Chai HS, Boerwinkle E. Genomic association analysis identifies multiple loci influencing antihypertensive response to an angiotensin II receptor blocker. *Hypertension*. 2012; 59:1204–1211. [PubMed: 22566498]
34. Ritchie MD. The success of pharmacogenomics in moving genetic association studies from bench to bedside: study design and implementation of precision medicine in the post-GWAS era. *Hum Genet*. 2012; 131:1615–1626. [PubMed: 22923055]

Fig. 1.

Graphic representation of the candidate genes involved in the pharmacodynamics of diuretics. A fully interactive version of this pathway is available online at PharmGKB (<http://www.pharmgkb.org/pathway/PA165984799>).

Table 1

Transporters and accessory proteins involved in diuretic pharmacodynamics and the genes that encode them

Transporters and accessory proteins, common names, and symbols	HGNC gene symbols
Barttin	<i>BSND</i>
Chloride channel Ka	<i>CLCNKA</i>
Chloride channel Kb	<i>CLCNKB</i>
ENaC	<i>SCNN1A</i> , <i>SCNN1B</i> , and <i>SCNN1G</i>
NCC	<i>SLC12A3</i>
NKCC2	<i>SLC12A1</i>
Sodium Potassium ATPase, Na,K-ATPase	<i>ATP1A1</i> , <i>ATP1B1-4</i> , <i>FXD2</i>
ROMK	<i>KCNJ1</i>

Table 2

Summary of the candidate genes and SNPs associated with PGx of thiazides

SNP(s)	Gene	Phenotype	References (PMID)
rs1799752	<i>ACE</i>	Replicated association of del/del with increased reduction in SBP but opposite association in women	12371972 and 21269061
rs4961	<i>ADD1</i>	Replicated association of GT and TT with increased reduction in BP. Inconsistent with association of GG with reduced risk of MI, although this was in treatment comparison of thiazides vs. other antihypertensives. Genotype GG associated with increased risk of DM	9149697, 10523341, 11882573, 18591455, 19145769, and 19247266
rs2400707	<i>ADRB2</i>	Genotypes AA + AG associated with increased reduction in SBP	16172412
rs4994	<i>ADRB3</i>	Genotype AA associated with increased reduction	15824464
rs5051	<i>AGT</i>	Allele T associated with increased reduction in BP in African-American women	14735111
rs5186	<i>AGTR1</i>	Allele A associated with increased reduction in BP in African-American women. Allele A associated with increased risk of DM	14735111 and 19247266
rs5443	<i>GNB3</i>	Genotype TT associated with increased reduction in BP. Genotype CC associated with increased risk of DM	11230366 and 19247266
rs17098707	<i>GRK5</i>	Genotypes TT + AT associated with decreased risk of adverse cardiovascular outcomes	21127457
rs4686799, rs5030062, and rs698078	<i>KNG1</i>	Alleles T, A, G, respectively, associated with response to aldosterone	19584173
rs4149601	<i>NEDD4L</i>	Allele A associated with increased reduction in BP	19635985
rs1799983	<i>NOS3</i>	Genotype GG associated with increased reduction in DBP	14553962
rs11191548	<i>NT5C2</i>	Allele A associated with decreased reduction in DBP	22525200
rs11240688	<i>REN</i>	Genotype GG associated with increased reduction in SBP	21261619
rs5723 and rs5729	<i>SCNN1G</i>	Genotypes CC and TT, respectively, associated with decreased reduction in DBP	16172412
rs13306673	<i>SLC12A3</i>	Genotype CC associated with increased reduction in BP	15824464
rs10792367	<i>SLC22A6</i> and <i>SLC22A8</i>	Allele G associated with decreased reduction in BP	21164499
rs2277869, rs2107614, and rs1159744	<i>WNK1</i>	Genotypes CC, CC + CT, and GG, respectively, associated with increased reduction in BP	16172412
rs7297610	<i>YEATS4</i>	Allele C associated with increased reduction in BP	18591461

See <http://www.pharmgkb.org/drug/PA449899> under the PGx Research tab for an interactive table with more details.

BP, blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; MI, myocardial infarction; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism.

Table 3

Summary of the candidate genes and SNPs associated with PGx of other diuretics

SNP(s)	Gene	Drug(s)	Phenotype	References (PMID)
rs4341	<i>ACE</i>	Spironolactone and furosemide	Genotypes CG + GG associated with increased likelihood of diuretic unresponsiveness	21692745
rs4961	<i>ADD1</i>	Diuretics including both loop and thiazide diuretics. Spironolactone and furosemide	Genotypes GT + TT associated with decreased likelihood of MI. Genotypes GT + TT associated with increased likelihood of diuretic unresponsiveness	11926892 and 21692745
rs1799998	<i>CYP11B2</i>	Spironolactone and furosemide	Genotypes AA + AG associated with increased likelihood of diuretic unresponsiveness	21692745
rs2070744	<i>NOS3</i>	At least three antihypertensive drugs including a diuretic	Genotype CC is associated with increased risk of resistant hypertension	19650939
rs5723 and rs5729	<i>SCNN1G</i>	Bumetanide, furosemide, and torasemide	Alleles G and A, respectively, associated with decreased response	17460608
rs1529927	<i>SLC12A3</i>	Bumetanide, furosemide, and torasemide	Allele C associated with increased response	17460608

SNP, single-nucleotide polymorphism.