REVIEW

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Progress of pharmacogenomic research related to minerals and trace elements

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Pharmacogenomics explores the variations in both the benefits and the adverse effects of a drug among patients in a target population by analyzing genomic profiles of individual patients. Minerals and trace elements, which can be found in human tissues and maintain normal physiological functions, are also in the focus of pharmacogenomic research. Single-nucleotide polymorphisms (SNPs) affect the metabolism, disposition and efficacy of minerals and trace elements in humans, resulting in changes of body function. This review describes some of the recent progress in pharmacogenomic research related to minerals and trace elements.

1. Introduction

Over the past decades, advanced technology of studying genomes has led to considerable improvement of personalized medicine. Information about a person's genes, proteins, enzyme activities, and cellular environment was utilized to diagnose and treat diseases. As an important part in the development of personalized medicine, pharmacogenomics is the study of variations in DNA sequence related to drug response. Pharmacogenomics studies genetic variations in drug metabolizing enzymes, receptors, transporters, and targets, and how these variations interact to exert an effect on response or toxicity of drugs and nutrients (Vaiopoulou et al. 2013). Current research mainly focuses on studying the interactions between human gene polymorphisms and drugs, such as *CYP2C19* (**2, *3 and *17*), *VKORC1* (rs9923231) and warfarin (Ross and Pare 2013), *SLC22A1* (rs628031 and rs36056065) and metformin (Semiz et al. 2013), and *SLCO1B 1*5* and statins (Johnson and Cavallari 2013). However, pharmacogenomic studies on nutrients including carbohydrates, proteins, fat, vitamins, minerals and water are inadequate. In this review, we will summarize recent pharmacogenomic research related to minerals and trace elements.

Minerals are essential nutrients for the human body and have important functions in the human physiology. On one hand, minerals are the staples that make up the organs and tissues. For example, calcium, phosphorus and magnesium are the main ingredients of bones and teeth; iron and iodine are required for the synthesis of hemoglobin and thyroid hormone. On the other hand, minerals have important physiological functions and their metabolic abnormalities lead to many diseases. For example, selenium is an essential trace element that may prevent prostate carcinogenesis (Geybels et al. 2013); abnormity of plasma magnesium concentration is related to a variety of chronic diseases such as diabetes, hypertension, and osteoporosis (Meyer et al. 2010).

Carbon, oxygen, hydrogen, nitrogen and other elements are mainly present in the form of organics in the human body, and the remaining 60 + elements are often referred to as minerals (also called inorganics). Calcium, magnesium, potassium, sodium, phosphorus, sulfur, and chlorine account for approximately 60% to 80% of total minerals in the body. Therefore, these seven elements are called macroelements. Iron, copper, iodine, zinc, selenium, manganese, molybdenum, cobalt, chromium, tin, vanadium, silicon, nickel, and fluorine account for less than 0.005% of total minerals in the body; hence, these 14 elements are called microelements or trace elements.

Minerals and trace elements exert their functions in the body through a variety of enzymes, transporters, receptors and binding proteins. These proteins are involved in the disposition and response of minerals/trace elements. Therefore, the *in vivo* processing and the corresponding function of minerals can be abnormal when polymorphisms of these genes occur. Recently, some studies have shown the relationship between pharmacogenomics and minerals/trace elements: the A allele of vitamin D receptor (VDR) gene in the intestine results in an increased bone mineral density (BMD) through a better intestinal absorption of calcium (Khan et al. 2014); mutations in the *ATP7B* gene can cause an copper-overload disorder, known as Wilson disease (Yamaguchi et al. 1993; Tanzi et al. 1993; Bull et al. 1993); carriers of the haplotype *SCNN1B* (ENaC β subunit) excreted comparably higher volumes of sodium and chloride in response to loop diuretics (Vormfelde et al. 2007). These findings suggest that the interactions between human gene polymorphisms and minerals/trace elements may affect the normal physiological functions of the human body and the occurrence of diseases.

2. Calcium

Calcium is an essential mineral nutrient for humans and the trigger for many biochemical and physiological processes, such as muscle contraction, hormone release, spike transmission, blood clotting, heart rate regulation, and milk secretion (Chung et al. 2009). It is closely associated with functions of the immune, nervous, endocrine, digestive, circulatory, motor, and reproductive systems in human body.

Parathyroid hormone (PTH) and vitamin D are two major calcium regulation endogenous hormones *in vivo*. A primary hyperparathyroidism (PHPT) can generate excessive PTH and accelerate bone turnover, thus resulting in hypercalcemia and low bone density. Research has found that vitamin D receptor (VDR) gene rs7975232 locus is associated with lumbar spine bone density. Carriers of AA/CA genotype had significantly lower bone density than those of CC genotype (1.01-1.04 g/cm^2 vs 1.21 g/cm^2, $P = 0.003$), indicating that rs7975232 locus CC genotype is more conducive to the lumbar spine bone calcium deposition (Christensen et al. 2013). Lambrinoudaki et al. have proven that comparing to those with VDR BB genotype male and premenopausal female, subjects carrying VDR B allele had higher Z score for cervical spine bone density, and higher lumbar spine bone density as well, with 3% higher plasma calcium concentration (9.5 mg/dl vs 9.23 mg/dl, $P = 0.008$) (Suh et al. 2010; Lambrinoudaki et al. 2013; Valdivielso and Fernandez 2006). Research on pigs also found that the 1963A > G mutation in complement factor 2 (C2) gene, which plays an important role in humoral immune response, showed a strong correlation with plasma calcium levels ($P = 5.9 \times 10^{-5}$). This result provides a useful reference for human subject research (Lee et al. 2012).

3. Magnesium

As the second most abundant intracellular cation (Weisinger and Bellorin-Font 1998), magnesium acts as a cofactor in many vital physiological processes, such as nucleic acids synthesis and enzymatic reactions (Swaminathan 2003). Magnesium plays important physiological roles, including regulation of blood glucose levels, maintenance of normal cardiac rhythm and blood pressure and involvement in energy metabolism and protein synthesis (Dennehy and Tsourounis 2010).

In a human genome-wide association study (GWAS) involving 15,336 European CHARGE syndrome samples, researchers studied the effect of 2.5 million gene polymorphisms on plasma magnesium levels. Using microarrays, at $P < 5 \times 10^{-8}$ or $P < 4 \times 10^{-7}$ (related) sites, researchers found in 8463 subjects that six gene regions were correlated with plasma magnesium concentrations at GWAS level: *MUC1*, *ATP2B1*, *DCDC5*, *TRPM6*, *SHROOM3* and *MDS1*. Multiple SNPs on these genes were associated with hypomagnesemia. Magnesium ion transporters CNNM2, CNNM3, and CNNM4 were significantly correlated with magnesium concentration *in vivo*. This large-scale research provided important targets for further studies on human blood magnesium homeostasis and its regulation mechanism (Meyer et al. 2010).

4. Sodium and potassium

The key cations in extracellular and intracellular fluids are sodium (Na) and potassium (K), respectively. Na and K are necessary in the regulation of fluid balance, muscle contraction and membrane potential. They have been widely linked to health effects, such as blood pressure (BP), cardiovascular disease (CVD), osteoporosis, gastric cancer, asthma, cardiac arrhythmias, kidney stones, muscle weakness and glucose intolerance (Whelton and He 2014).

Three renal sodium reuptake transporters, namely the sodium-potassium dichloride cotransporter NKCC2 (encoded by the gene *SLC12A1*), the sodium-chloride cotransporter NCC (encoded by the gene *SLC12A3*), and the epithelial sodium channel ENaC, are the primary targets of the loop, thiazide- and potassium-sparing diuretics. There are three subunits: α, β, and γ, encoded by SCNN1A, SCNN1B, and SCNN1G, in ENaC. Rare loss of function mutations in these genes cause Bartter's syndrome, Gitelman's syndrome, and pseudohypoaldosteronism, respectively, but functional or medical effects of other common polymorphisms have rarely been reported (Vormfelde et al. 2003).

In NCC, Gly264Ala variant accompanies with a 50% lower sodium translocation and the increment of chloride and thiazide affinity in Xenopus oocytes (Moreno et al. 2004). Moreover, *SLC12A3* polymorphism Gly264Ala was significantly associated with the 24-h excretion of chloride and potassium. Carriers of the alanine allele excreted more chloride and potassium upon intake of the loop diuretics, comparable among the three loop diuretic drugs bumetanide, frusemide and torsemide (Vormfelde et al. 2007). Another amino-acid substitution, Arg913Gln, has been associated with primary hypertension, diabetic nephropathy, and renal albumin loss (Tanaka et al. 2003; Matsuo et al. 2004; Nishiyama et al. 2005; Kim et al. 2006). The association of a $C > T$ polymorphism in intron 1 of *SLC12A3 (rs13306673)* with the response to thiazide diuretics has been reported (Matayoshi et al. 2004). Weaker capacity in sodium chloride transportation infers lower counterregulatory capacity in the context of loop diuretic blockade of the more proximally located NKCC2. Weaker counterregulation could thereby cause higher excretion of sodium and chloride (Vormfelde et al. 2007). In the ENaC β subunit, Gly442Val has been associated with hypertension, greater sodium retention, and lower levels of plasma aldosterone (Ambrosius et al. 1999).

Besides, the secretion of potassium ions in the kidney is subjected to aldosterone, and in turn the body potassium storage capacity is regulated. An excess of aldosterone will cause a huge loss of potassium and magnesium ions through the urine, resulting in lower plasma potassium and higher plasma sodium, which lead to hypertension; whereas higher potassium and lower sodium, hypotension may occur. CYP17A1 is a member of the cytochrome P450 superfamily and plays an important role in the synthesis of cortisol and mineralocorticoid. In the GWAS in European populations, researchers found that the rs11191548 SNP locus, close to *CYP17A1,* was associated with hypertension and systolic blood pressure. In a research involving 1101 primary hypertension patients and 1109 healthy controls, Li et al. (2013) found that rs11191548 SNP was associated with hypertension onset, and the C allele was significantly correlated with reduced potassium levels in the hypertensive patients who used non-renin-angiotensin-aldosterone system (RAAS) antagonists (-0.093 *vs* -0.067, $P = 0.003$), indicating that the *CYP17A1* gene polymorphism may reduce renin activity and plasma potassium levels by changing CYP17A1 activity.

5. Selenium

Selenium presents as selenocysteine (Sec) at the active site of a wide range of proteins and exerts important biological functions (Papp et al. 2007; Rayman 2012). Twenty five human selenoproteins containing Sec as part of their polypeptide chains have been characterized recently. The GPXs *(GPX1*, *GPX2*, *GPX3*, and *GPX4*), iodothyroninedeiodinases (three genes), selenoprotein P (*SEPP1*), thioredoxinreductases (TXRs) (three genes), and selenophosphatesynthetase2 are the well characterized selenoproteins (Lobanov et al. 2009). They can catalyze

redox reactions, and the presence of Sec instead of cysteine in their active center hugely improves their catalytic power (Arner 2010).

Selenium has antioxidative activity, which protects the human body from free radicals and carcinogens. Selenium may also relieve inflammation, enhance immunity, promote heart health, and enhance the role of vitamin E. Selenium is essential for the male reproductive system, deficiency in the metabolism and intake of selenium may be associated with cancer, premature aging, cataracts, hypertension, recurrent infections and so on.

5.1. Alzheimer's disease

Alzheimer's disease (AD) is a complex genetic disease characterized by a variety of cognitive disorders. Oxidative stress may play a key role in its pathogenesis. Cytosolic glutathione peroxidase (GPx1) widely exists in many tissues that have high oxidative stress. The GPx1 gene Pro198Leu is associated with reduced enzyme activity. In a research involving elderly AD patients and healthy controls, researchers found that GPx1 Pro198Leu polymorphism itself had nothing to do with the pathogenesis of AD, but Pro198Pro homozygous patients' plasma and erythrocyte selenium level was significantly lower than those in healthy people with Pro198Pro genotype (31.44 μg/l *vs*. 54.87 μg/l, $P = 0.002$; 40.25 μg/l *vs*. 87.75 μg/l, $P = 0.0004$). It was also found that the selenium level in erythrocytes is positively correlated with GPx1 activity in Pro198Pro genotype AD patients and healthy controls ($r = 0.59$, $P < 0.005$; $r = 0.72$, $P < 0.0001$), while the correlation in GPx1 mutant population was not observed (Cardoso et al. 2012). These results indicate that GPx1 Pro198Leu polymorphism is correlated to some extent with the selenium level in the AD patients, suggesting that the effect of selenium, as a health supplement, can be affected by GPx1 genotype.

5.2. Prostate cancer

The risk of prostate cancer is associated with low selenium levels. Selenoprotein P (SEPP1) is the most abundant plasma selenoprotein and is responsible for the transportation of dozens of selenocysteine residues. SEPP1 gene polymorphism may affect selenium function and prostate cancer pathogenesis. In a study including 1,352 prostate cancer patients and 1382 healthy controls, SEPP1 gene rs13168440 polymorphism loci were significantly correlated with plasma selenium levels. The study also showed that the patients with minor allele and high plasma selenium levels had lower prostate cancer risk ($P_{interaction} = 0.01$). This correlation was not observed in the population with the main allele (Penney et al. 2013). In another study targeting selenoprotein P gene 1 (*SEP15*), which is highly expressed in the prostate, researchers compared four common polymorphisms of *SEP15* in 1,286 prostate cancer patients and 1,267 controls, and found that these polymorphisms were not associated with the prostate cancer. However, rs561104 locus and plasma selenium levels had significant interaction with the prostate cancer mortality ($P_{interaction} = 0.02$), i.e., the patient who did not carry risky rs561104 genotype had lower prostate cancer mortality if they had higher plasma selenium levels (Penney et al. 2010). These studies illustrate that prostate cancer patients with specific genotype may have a reduced risk of death by supplementing selenium.

In another research involving 567 prostate cancer patients and 764 healthy controls, it was found that manganese superoxide dismutase (MnSOD) gene codon 16 V > A polymorphism was significantly associated with the *in vivo* antioxidant levels ($P_{interaction} \leq 0.05$): AA genotype patients with high plasma selenium level had lower risk of prostate cancer [Odd ratio (OR) = 0.3], and this AA-type plus high selenium level also showed protective effect on progressive prostate cancer (OR = 0.2). However, selenium alone had less protective effect on VA and VV-type patients (OR = 0.6 and 0.7, respectively); for AA-type patients, selenium, lycopene and vitamin E had 10-fold protective effect comparing with other genotype patients (Li et al. 2005).

6. Iron

Iron is the most abundant trace element in the human body. It is essential for normal body functions such as oxygen transportation, energy production, and cellular proliferation through associating with proteins, binding to oxygen, and mediating catalytic reactions (Stathopoulou et al. 2012). The most important chemical moieties containing iron are iron–sulfur clusters (ISC) and heme. Normal iron level is critical to human health, whereas excessive level leads to Fenton reaction characterized by excess hydroxyl radicals and tissue damage (Hentze et al. 2004). A deficiency of iron can result in anemia. The absorption and storage of iron are critical in maintaining normal iron levels.

Baeza-Richer et al. (2013) studied SNPs sites of 10 candidate genes and their relationship with iron status in human. They found that the rs1375515 located in calcium channel gene *CACNA2D3* was significantly associated with mean corpuscular volume, hemoglobin and ferritin level. The G allele was related to the reduction of the above levels and might be a risk factor for iron deficiency anemia. Rs1375515 or its linked loci may regulate body iron storage by influencing the function of calcium channels, it may also affect the therapeutic effect of iron supplementation.

Non-alcoholic fatty liver disease (NAFLD) can alter hepatic iron transportation, causing iron accumulation in the liver, and leading to hepatocellular carcinoma and severe liver injury. Transmembrane protease serine 6 (TMPRSS6) genes can affect iron metabolism by regulating the transcription of hepatic hepcidin. In 216 NAFLD patients, a study found that Val homozygotes of TMPRSS6 gene p.Ala736Val polymorphic loci were not only associated with hepatic iron accumulation and decreased ferritin levels (223 vs 308 ng/ml, $P = 0.01$), but also associated with oxidative stress-induced hepatocyte ballooning degeneration. In the iron overload HFE-negative population, TMPRSS6 gene p.Ala736Val polymorphism has more influence on the hepatic iron accumulation, and 736Val genotype and hepatic iron accumulation are negatively correlated (OR = 0.59), indicating that the locus can significantly affect the secondary iron accumulation in the liver of NAFLD patients (Valenti et al. 2012).

7. Chromium

Chromium is an essential trace element for the body's glucose and lipid metabolism (Jiajun et al. 2011). Trivalent chromium ions are beneficial to humans, but hexavalent chromium ions are toxic (Kuo et al. 2003; Steinbrecher et al. 2010; Patlolla et al. 2009; Chiu et al. 2010). Chromium and other metabolism-control substances, such as hormones, insulin, a variety of enzymes and cell genetic materials (DNA and RNA), play a role in physiological functions. The physiological functions of chromium include regulation of glucose and lipid metabolism, and stabilization of nucleic acids (DNA and RNA), etc. Constantly exposing to chromium can cause lung cancer and other occupational diseases (Davies et al. 1991; De Flora 2000).

Zheng et al. studied the relationship between hexavalent chromium ions and nine major DNA repair gene mutations.

Using Olive Tail Moments (OTM), they evaluated the extent of DNA damage and found that at XRCC1 gene Arg399Gin (G/A) allele, GG genotype was associated with significantly higher OTM, comparing with GA and AA genotype (0.93 vs 0.73 or 0.5, $P = 0.048$), suggesting that A allele carriers were less susceptible to the damaging effect of hexavalent chromium compared with the G allele carriers (OR = 0.39). Therefore, *XRCC1* gene Arg399Gln (G/A) mutations may become protective biomarkers for hexavalent chromium induced DNA damage (Zhang et al. 2012; Schou 2001).

8. Lithium

Lithium was the first pharmacological agent that was proven to be effective as a mood stabilizer in the treatment of bipolar disorder to prevent relapse of mania and depression (Schou 2001). However, in addition to its multifaceted antidepressant therapeutic uses, lithium has a particularly problematic clinical side effect profile. It has a very narrow therapeutic window, which makes overdosing a risk, such as severe consequences ranging from weight gain, diabetes insipidus, renal failure, thyroid enlargement (goiter) and hypothyroidism (Werneke et al. 2012; Lazarus 2009; Rej et al. 2012; Adityanjee et al. 2005). Various SNPs can affect the therapeutic effects of lithium in treating mood disorders. Therefore, it is important to develop individualized treatment based on the genotype of patients, in order to have the beneficial and unique efficacy of lithium but not the side effects and slow onset of action.

Chen et al. (2014) performed a discovery genomewide association study and replication studies on selected subgroups from a sample of 1761 patients of Han Chinese descent with bipolar I disorder who were consecutively recruited by the Taiwan Bipolar Consortium. They found that two SNPs in high linkage disequilibrium, rs17026688 and rs17026651, located approximately 7.2 kb apart in the introns of the gene encoding glutamate decarboxylase-like protein 1 (*GADL1*) showed the strongest associations in the GWAS on samples from one subgroup of 294 patients with bipolar I disorder who were receiving lithium treatment ($P = 5.50 \times 10^{-37}$ and $P = 2.52 \times 10^{-37}$, respectively). In the first replication sample of 100 patients ($P = 9.19 \times 10^{-15}$ for each SNP) and in the second replication cohort among the 24 patients, the two top SNPs were also in complete linkage disequilibrium. These two SNPs had a sensitivity of 93% for predicting a response to lithium and differentiated between patients with a good response and those with a poor response in the follow up cohort. Resequencing of *GADL1* showed a novel variant, a 1-base deletion in intron 8 of the gene (IVS8 + 48delG), is in complete linkage disequilibrium with rs17026688 and is predicted to alter splicing. Their study suggests that rs17026651, *GADL1* IVS8 + 48delG, and rs17026688 are useful biomarkers in predicting the response to lithium maintenance treatment in patients of Asian ancestry who have bipolar I disorder.

9. Conclusion

A description of the current knowledge on selected minerals/trace elements and their associations with genetics and diseases has been presented (briefly shown in Tables 1 and 2). Although in a preliminary stage, the study of minerals/trace elements and their interaction with genetic variants is expected to increase our knowledge of human physiology and lead to the realization of the personalized nutrition concept. In addition, the pharmacogenomic approach has broadened the range of research tools for the study of minerals/trace elements metabolism and its involvement in human health and diseases. Future studies need to be improved in experimental design, sufficient certainty,

Table 1: Macroelements and gene polymorphisms

Macroelements	Gene	Polymorphisms	Effects	Disease	Refs
Calcium	VDR gene	Rs7975232	rs7975232 CC genotype is more conducive to the lumbar spine bone calcium deposition	PHPT	(Christensen et al. 2013)
	CASR	A986S and R990G	Patients with either the RR or RG genotype had lower blood calcium levels than the GG genotype.		(Han et al. 2013)
	VDR gene	Bsm1 polymorphism	Carriers of the B allele exhibited higher levels of calcium	Bone disease and MS	(Lambrinoudaki et al. 2013)
	C2	1963A < G	Showed a strong correlation with plasma calcium levels	Humoral immune abnormalities	(Lee et al. 2012)
	VDR gene	*Fok*I polymorphism	The positive association between 1,25OHD and eGFR was steeper in Fok*I*CT and CC polymorphisms than Fok*I*TT polymorphism.	CKD in Patients with Type 2 Diabetes	(Yokoyama et al. 2012)
Magnesium	*MUC1, ATP2B1*,.	Multiple SNPs	These genes were associated with serum magnesium levels	Hypomagnesemia	(Meyer et al. 2010)
Potassium	*CYP17A1*	Rs11191548	Reducing renin activity and plasma potassium levels	Hypertension	(Li et al. 2013)
	SLC12A3	Gly264Ala	Carriers of the alanine allele excreted more potassium		(Vormfelde et al. 2007)
Phosphorus	VDR *FokI*	Rs10735810	1,25OHD were negatively associated with P levels	CKD in Type 2 Diabetes	(Yokoyama et al. 2012)
Sodium	*ADD1*	Rs4961	Rs4961 is related to systolic blood pressure and blood sodium concentration.	hypertension	(Tu et al. 2011)
	SCNN1B	Gly442Val	Greater sodium retention		(Ambrosius et al. 1999)

Abbreviations: VDR, vitamin D receptor; CASR, calcium-sensing receptor; PHPT, hyperparathyroidism; MS, multiple sclerosis; C2, complement factor 2; eGFR, estimated glomerular filtrationrate; CKD, chronic kidney disease; MUC1, mucin 1; ATP2B1, ATPase, Ca++ transporting, plasma membrane 1; CYP17A1, cytochrome P450, family 17, subfamily A, polypeptide 1.; SLC12A3, solute carrier family 12, member 3; ADD1, alpha-adducin; SCNN1B, sodium channel, non-voltage-gated 1, beta subunit.

Table 2: Trace elements and gene polymorphisms

Trace elements	Gene	Polymorphisms	Effects	Disease	Refs
Selenium	GPx1 gene	Pro198Leu	Pro198Leu is correlated to the selenium level	AD	(Cardoso et al. 2012)
	SEPP1	Rs13168440	Selenium levels were negatively associated with PCa risk among men with the minor allele	PCa	(Penney et al. 2013b)
	SEP15	Rs561104	Rs561104 and plasma selenium levels had significant interaction with the PCa mortality		(Penney et al. 2010)
	MnSOD gene	Valine to Alanine	AA genotype patients who had high plasma selenium level had lower risk of prostate cancer		(Li et al. 2005)
Iron	*CACNA2D3*	Rs1375515	The G allele is related to the reduction of the levels of hemoglobin and ferritin	Iron deficiency anemia	(Baeza-Richer et al. 2013)
	TMPRSS6 gene	Ala736Val	Homozygosity for the p.736Val allele was associated with lower hepatic iron stores, and ferritin levels	Severe liver damage and hepatocellular carcinoma	(Valenti et al. 2012)
	HFE gene	H67D (homologous to human H63D)	Brain iron management protein expression was altered in the H67D mice	Neurodegenerat-ive diseases	(Nandar et al. 2013)
	A1AT gene	Glu 342 Lys Glu 264 Val	Plasma concentration of A1AT was negatively related to ferritin	Iron balance disorders	(Ghio et al. 2013)
Chromium	XRCC1 gene	Arg399Gln	XRCC1 gene Arg399Gln mutations may become protective biomarkers for hexavalent chromium induced DNA damage	Occupational chromium exposure disease	(Zhang et al. 2012)
Fluorine	CTR gene	Taq polymorphisms	The interactive effect of F burden and CTR genotype was significant	The F bone injury	(Tu et al. 2011)
Copper	*ATP7B*	Rs2147363	The ATP7B gene plays a key role in controlling body copper balance.	AD	(Bucossi et al. 2013)
Lithium	*GADL1*	Rs17026688 and rs17026651	Associated with the response to lithium	Bipolar disorder	(Chen et al. 2014)
	GSK-3	Rs334558	C allele carriers showed more improvement after lithium treatment		(Benedetti et al. 2005)
	NTRK2	Rs2769605	G/G carriers manifested worse response to lithium.		(Wang et al. 2013)

Abbreviations: GPx1, glutathione peroxidase 1; AD, Alzheimer's disease; SEPP1, selenoprotein P, plasma, 1; SEP15, 15 kDa selenoprotein; PCa, prostate cancer; MnSOD, manganese superoxide dismutase; CACNA2D3, calcium channel, voltage-dependent, alpha 2/delta subunit.

randomized samples, longer observation period and stricter inclusion criteria based on the past results. We hope in the coming years, more solid, repeatable and higher quality results can be achieved in the pharmacogenetics and pharmacogenomics of minerals/trace elements, thus accelerating the individualized medicine of minerals and trace elements.

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