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REVIEW

Genomics enabled breeding approaches for improving cadmium stress tolerance in plants

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Abstract Heavy metal (HM) toxicity is a considerable challenge that the current agricultural production systems and human population face worldwide. Among the HMs with pronounced toxic effects, cadmium (Cd) potentially contaminates a range of vital agricultural resources including soil and water together with severely impacting crop performance. Besides, gradual accumulation of Cd in food chain poses a global threat to food safety and environmental sustainability. Plants are equipped with meticulously orchestrated physiological and molecular mechanisms to respond and acclimatize to Cd-challenged scenarios. However, limited understanding about the HM toxicity mechanism involving metal uptake/transport, associated candidate gene (s) or QTLs and signaling crosstalk has greatly constrained breeding capacities to improve plants for HM tolerance. In the context, quantifying genetic variation for Cd tolerance accompanied by appropriate breeding schemes allowing the most efficient utilization of the estimated variation should be essentially undertaken. Concurrently, efforts are needed to facilitate fast-track introgression of genomic segments harboring candidate gene(s)/QTL for Cd tolerance to high yielding yet Cd-susceptible backgrounds. Advances in plant molecular biology have introduced refined techniques and methods to pinpoint genetic factors describing plant Cd tolerance. Ancillary to conventional breeding and marker assisted selection methods are modern transgenic technologies that offer attractive means to precisely interrogate the relevant molecular networks and manipulate the key Cd-related genes in plants.

Keywords Heavy metal · Cadmium · Tolerance · Genomics · QTL · Genetic engineering · MAS

Introduction

HM toxicity is an important crop production constraint that substantially impacts the twenty-first century agriculture along with presenting a global threat to human health (Sanitá di Toppi and Gabbrielli 1999; Benavides et al. 2005; Nawrot et al. 2006; Satarug et al. 2010; Hossain et al. 2012a; Hasanuzzaman and Fujita 2012; Hasanuzzaman et al. 2012, 2013; Gill et al. 2013). Key contributors to growing HM toxicity include rapid industrialization, indiscriminate mining, heavy discharge of wastewater/effluents and geological activity (Foy et al. 1978; Mishima et al. 2004; Nagajyoti et al. 2010; Arao et al. 2010). From the human health perspective, Cd toxicity has received

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considerable attention in recent years (Alloway1995) with Cd ranking seventh among the top 20 toxins (Yang et al. 2004; Gill and Tuteja 2011). Equally important in this context is the Cd toxicity caused by the excessive use of phosphate/nitrogenous fertilizers, atmospheric deposition, contaminated irrigation/rain water and application of sludge (Saito 2004; Arduini et al. 2006; Singh et al. 2006; Kikuchi et al. 2007; Arao et al. 2010; Li et al. 2011). This in turn results in a dramatic accumulation of Cd in human food chain (Grant et al. 2008). The first instance of 'Itai-itai' (a human disease caused by Cd toxicity) was recorded in Japan from the inhabitants of the area surrounding Jinzu river basin (Ishihara et al. 2001; Kobayashi et al. 2008). Since then, Cd toxicity is reported to cause various disorders like renal dysfunction, osteoporosis and cancer (Nordberg et al. 1997; Nowrot et al. 2006; Honda et al. 2010; Satarug et al. 2010).

HMs gain entry to the human food chain through contaminated irrigation water and food crops such as rice (Watanabe et al. 1996, 2004; Grant et al. 2008). For example, 9.5 % of the paddy fields in Japan were known to be Cd-contaminated (Asami 1984). Similarly, nearly 13,000 ha agricultural land covering various provinces in China is reported to be Cd-contaminated (Zhang and Huang 2000; Liu et al. 2009). Limei et al. (2008) reported two highly Cd toxic prone areas in Chenzhou region in China covering approximately 320,000 km^2. Similarly, a total of 1,700,000 ha land accounting for 7.3 % of the cultivated area in Guangdong Province in China was found to be severely impacted by Cd-toxicity (Shu 1997; Yang et al. 2006). As reported from various parts of the world including Japan, the USA and South East China, rice predominantly serves to incorporate Cd into human food chain given the fact that it constitutes the major staple worldwide (Watanabe et al. 1996, 2000, 2004; Shimbo et al. 2001; Tsukahara et al. 2003; Jarup 2003; Cheng et al. 2006; Egan et al. 2007; Ueno et al. 2009a, b).

Notably, people from South and South East Asian countries remain immensely vulnerable to chronic Cd toxicity which as mentioned above is largely ascribed to their greater reliance on rice-based diets (Watanabe et al. 2004; Cheng et al. 2006; Meharg et al. 2013). With regard to the permissible level of Cd for human consumption, the Codex Alimentarius Commission/World Health Organization has standardized the maximum allowable concentration of Cd to be 0.4, 1, 0.2 and 0.2 mg kg^{-1} in case of polished rice grain, unpolished rice, wheat and soybean, respectively (Codex 2006; WHO 2001; Codex Alimentarius Commission 2001; Commission of the European Communities 2008; CODEX STAN 193-1995 2009). However, in Japan, the concentrations of Cd in polished rice grains and flour were found to be 50 and 19 ng g^{-1}, respectively (Shimbo et al. 2001). By analyzing rice grains sampled from nearly 500 Cd-contaminated fields in Western Thailand, Simmon et al. (2005) have reported grain Cd concentrations enhancing up to 7.7 mg kg^{-1}. Additionally, the authors also found that the Cd content ranged from 0.5 to 284 mg kg^{-1} Cd contaminated soil of the given zone. In view of the worldwide occurrence of Cd toxicity, a comprehensive list of crops and countries influenced by Cd toxicity is presented in Table 1.

Taking note of the escalating impact of Cd toxicity on human health and crop productivity, here we offer an overview on breeding important crops against Cd toxicity. An emphasis is laid to capture the underlying physiological and molecular mechanisms in plants (under the Cd-toxic scenario) and the potential of genomics-aided breeding strategies to incorporate Cd tolerance in plants. Finally, we underscore wide-ranging applications of modern omics technologies enabling fast-track recovery of Cd-tolerant cultivars.

Impact of Cd accumulation on plants

Cd exerts negative impacts on plants when it accumulates beyond the range i.e. 5–10 μg Cd g^{-1} leaf dry weight, thus causing cell death (White and Brown 2010). Several biological and physiological pathways in plants are reported to be impaired by Cd toxicity which include photosynthesis (Greger et al. 1994; Alcantara et al. 1994; Mobin and Khan 2007; Gill et al. 2012), metabolism of carbohydrate, nitrogen, phosphorus, and sulphur (Sanitá di Toppi and Gabbrielli 1999; Gill et al. 2012; Balestrasse et al. 2003; Gill and Tuteja 2011), chlorophyll biosynthesis (Stobart et al. 1985), Calvin cycle (Sandalio et al.2001), Co_2 fixation (Perfus-Barbeoch et al. 2002). Besides, Cd-toxicity substantially alters the function of plasma membrane due to lipid peroxidation (Fodor et al. 1995), induces oxidative stress (Balestrasse et al. 2004; Mohanpuria et al. 2007; Gill and Tuteja 2010) and ultimately results in cell death (Sanitá di Toppi and Gabbrielli 1999; Garnier et al. 2006; Michele et al. 2009).

Table 1 List of important food crop and countries affected by cadmium toxicity

Crop	Country	Area/province/city affected by Cd toxicity	Remarks	References
Potato	Japan	–	10 % of Cd utake in human occur via potato in year 2004	UNEP (2008)
Potato	European	–	Cd concentration in potato was 0.14 mg kg^{-1}, 10 times higher permissible limit	EFSA (2009)
Rice	Korea	Sambo mine area	Cd concentration in rice remained 121 μg/d	Jung and Thornton (1997)
Rice	Korea	–	–	Watanabe et al. (1989)
Rice	Tiwan	–	Cd concentration in rice remained > 50 ng g^{-1}	Watanabe et al. (1989)
Rice	Japan	–	Cd concentration in rice remained > 50 ng g^{-1} Cd concentration in rice remained 5.70 ng g^{-1}	Watanabe et al. (1989, 1996)
Rice	Japan	–	–	Izuno et al. (2000)
Rice	Japan	–	Cd concentration in rice 50 ng/g and	Shimbo et al. (2001)
Rice	China	–	–	Nordberg et al. (2002)
Rice	Japan	Jinzu river basin	Cd concentration ranged 0.02–1.06 mg kg^{-1} in rice	Watanabe et al. (2002), Matsuda et al. (2003)
Rice	Japan	Northern- and southern-most Hokkaido and Okinawa Prefecture	–	Tsukahara et al. (2003), Chiyoda et al. (2003)
Rice	Japan	Kakehashi river basin and Jinzu river basin	Cd con. 0.02–1.06 μg/g and 0.11–0.67 ng g − 1	Nogawa et al. (2004)
Rice	China	Wu Jiang River basin Guangdong Province, southern China	1,700,000 ha area is highly contaminated by heavy metal including Cd	Yang et al. (2006)
Rice	Japan	Kakehashi river basin and Jinzu river basin	–	Uetani et al. (2006), Kobayashi et al. (2008)
Rice	Japan	–	44 % of Cd utake in human occur via rice in year 2004	UNEP (2008)
Rice	China	Chenzhou City (Shizhuyuan, Jinshiling, Yaogangxian, Baoshan and Huangshaping mine sites)	Cd concentration in soil ranged 2.72–4.83 mg kg^{-1}	Limei et al. (2008)
Rice	China	–	–	Wu et al. (2008)
Rice	China	Chenzhou City	Cd con. in soil was 2.72 and 4.83 mg kg^{-1} and in rice 0.01–4.43 mg kg^{-1}	Zhai et al. (2008)
Rice	China	–	–	Zhen et al. (2008)
Rice	China	Zhejiang (Taizhou)	31 % of sampled rice contains Cd above permissible limit	Fu et al. (2008)
Rice	China	Fujian	11 % of sampled rice contains Cd above permissible limit	Xie et al. (2008)
Rice	Italy	Rosate, near Milan	Cd concentration in soil remained 0.96 mg kg^{-1}	Cattani et al. (2008)
Rice	China	Hunan Province	65 % of rice were polluted due to Cd toxicity	William et al. (2009), Kong (2014)
Rice	South China	–	70 % of sampled rice contains Cd above permissible limit	Zhang et al. (2009)
Rice	Japan	–	Data from 2000 to 2009 suggested Cd enter into human body 3.0 μg kg^{-1} body weight per week via mostly rice intake	http://www.maff.go.jp/j/syouan/nouan/kome/k_cd/cyosa/pdf/-cdtds.pdf

Table 1 continued

Crop	Country	Area/province/city affected by Cd toxicity	Remarks	References
Rice	China	Zhejiang Province (Jiaoweibao, Nanbaixiang Yantou)	–	Liang et al. (2012)
Rice	China	Taizhou and Hangzhou, Lechang		Cheng et al. (2006), Yang et al. (2006)
Rice	Western Thailand	–	Cd concentraion in rice grain was 0.05–7.7 mg kg^{-1}	Simmon et al. (2005)
Rice	Sri Lanka	Anuradhapura district North Central Province	–	Bandara et al. (2007), Meharg et al. (2013)
Rice	Thailand	Mae Sot District, Tak Province	–	Teeyakasem et al. (2007), Honda et al. (2010)
Rice	Thiland	Mae Sot District, Tak Province	Cd concentration in rice remained 0.12–1.27 mg Cd kg^{-1}	Sriprachote et al. (2012)
Rice	(Sri Lanka)	Anuradhapura and Polonnaruwa	Cd concentration in agricultural soil was 1.8–2.4 mg kg^{-1}	Bandara et al. (2010)
Rice	Bangladesh	–	Cd concentration in raw rice grain remained 33.1 µg kg^{-1}	Khan et al. (2010)
Rice	Japan	Hokuriku region	–	Osada et al. (2011)
Rice	China	Guangdong Province	Cd concen. in soil remained from zero to 3.94 mg kg^{-1}	Zhang et al. (2011)
Rice	Bangladesh	–	Cd concentration in rice grain remained 1.31 mg kg^{-1}	Meharg et al. (2013)
Rice	China	Zhejiang Province (Jiaoweibao, Nanbaixiang and Yantou)	–	Liang et al. (2012)
Rice	Ghana		Cd concentration in rice grain remained 0.27 mg kg^{-1}	Meharg et al. (2013)
Rice	Sri Lanka	–	Cd concentration in rice grain remained 0.80 mg kg^{-1}	Meharg et al. (2013)
Rice	China	–	–	Lam et al. (2013)
Rice	China	Nanjing City	Cd concentration was more 3.3 % than permissible amount	Fang et al. (2014)
Rice	China	Dabaoshan Mine	Cd concentration in soil sample was 4.42 mg kg^{-1}	Wang et al. (2014c)
Rice	China	Wanshan mining area in Guizhou Province	–	Li et al. (2014)
Rice	Australia	–	Cd concentration in rice was 7.5 µg kg^{-1}	Rahman et al. (2014)
Rice	China	Guangdong Province	Lives of 100 million inhabitants are under threat owing to contamination of soil by heavy metal including Cd	Wang and Bjorn (2014b)
Soybean	Canada	–	Cd concentrain remained 3–4 time above the permissible limit	Shute and Macfie (2006)
Soybean	Thailand	Mae Sot District, Tak Province	Cd concentration remained 0.07–0.80 mg kg^{-1}	Sriprachote et al. (2012)
Soybean	Japan	–	Concentration of Cd remains 0.2 mg kg^{-1} in one-sixth of soybean seed	Haque et al. (2014)

Table 1 continued

Crop	Country	Area/province/city affected by Cd toxicity	Remarks	References
Wheat	Japan	Central and Southern	–	Kubo et al. (2008
Wheat	Japan	–	Cd concentration in flour 19 ng g^{-1} surveyed from year 1998–2000	Shimbo et al. (2001)
Wheat	Canada	–	Cd concentration remained 0.060–0.145 mg kg^{-1} in durum wheat	Gao et al. (2013)

Cd signaling, uptake, transport and detoxification in plants

Plants are endowed with exquisite abilities to cope HM toxicity via meticulously coordinated physiological and molecular mechanisms involving activities like regulation of HM uptake and transport, chelation, compartmentalization and storage (Briat and Lebrun 1999; Clemens 2001, 2006; Hall 2002; Pollard et al. 2002).

Roots constitute the key sensing site in plants through which Cd enters into plant, and Cd stress is perceived by signaling molecules in the root cell wall (Blinda et al. 1997; Hall 2002; Polle and Schuetzenduebel 2003; Dalcorso et al. 2010; Chmielowska-Bąk and Deckert 2012). Cd mediates generation of reactive oxygen species (ROS) subsequent to its entry into the plant root cells (Chmielowska-Bak et al. 2014 and references therein) which in turn induces mitogen-activated protein kinase (MAPK) cascade (Jonak et al. 2004; Yeh et al. 2007; Liu et al. 2010a; Ye et al. 2013; Chmielowska-Bak et al. 2014) along with impacting calcium (Ca)-cadmodulin system (Suzuki et al. 2001; Yeh et al. 2007) and a range of stress-related hormones like jasmonic acid, ethylene, abscisic acid and salicylic acid (Dalcorso et al. 2008; Rodríguez-Serrano et al. 2009; Stroinski et al. 2013; Chmielowska-Bak et al. 2013, for details see Chmielowska-Bak et al. 2014). Accompanying this, the activated transcription factors (TFs) trigger a set of metal detoxification genes (reviewed by Dalcorso et al. 2010; Verbruggen et al. 2009; Gallego et al. 2012; Chmielowska-Bak et al. 2014). In some cases, the activated genes encode various transporters located in plasma membrane (Thomine et al. 2000) which successively guide removal of excessive Cd from the cell (Dalcorso et al. 2010). Alternatively, the activated genes might produce phytochelatin synthase (PCS) enzyme (Clemens et al. 1999; Ha et al. 1999) which uses glutathione as substrate to generate sulphur containing phytochelatins (PCs) (Grill et al. 1987, 1989; Steffens 1990; Rauser 1995; Salt and Rauser 1995; Clemens et al. 1999; Cobbett 2000; Cobbett and Goldsbrough 2002; Hall 2002; Gill and Tuteja 2011). Ultimately, these PCs compartmentalize the toxic Cd into vacuoles from cytoplasm through creating Cd-phytocheletin sulphide complex (Salt and Rauser 1995; Dalcorso et al. 2010). Also, metal binding Cys-rich peptides i.e. metallothioneins (MTs) encoded by MT genes are reported to be involved in protecting plants from toxicity under Cd stress (Zhou and Goldsbrough 1994; Prasad 1999; Hall 2002) by facilitating Cd sequestration to vacuoles (Hall 2002; Clemens 2006; Dalcorso et al. 2010).

The pathways that explain Cd uptake and transport in plants involve (i) Cd-uptake from soil, an event regulated by various transporters located in root plasma membrane, for example *OsIRT1*, *OsIRT2* (Nakanishi et al. 2006), *OsNramp1* (Takahashi et al. 2011), *OsHMA3* (Ueno et al. 2010; Ishikawa et al. 2011; Miyadate et al. 2011) in rice (ii) sequestration of Cd from cytoplasm into root vacuole via ABC type transporter or through Cd^{2+}/H^{+} antiport activity such as observed in oat (Salt and Rauser 1995; Salt and Wanger 1993) (iii) xylem loading of Cd through “symplastic (intracellular)” or “apoplastic (extracellular)” pathway (Salt et al. 1995) under the influence of transporters like *OsNramp5* (Sasaki et al. 2012), *OsHMA2* (P1B-type ATPases) in rice (Nocito et al. 2011; Takahashi et al. 2012a, b; Satoh-Nagasawa et al. 2012) and *AtHMA4* in *Arabidopsis* (Mills et al. 2005; Verret et al. 2004; Wong and Cobbett 2009) (iv) transportation of Cd from xylem to phloem i.e. root to shoot (Riesen and Feller 2005; Fujimaki et al. 2010) and finally (v) translocation of Cd to grain which is regulated by transporters like *OsLCT1* in rice (Uraguchi et al. 2011) (for details see Uraguchi and Fujiwara 2012, 2013; Clemens et al. 2013; Gallego

Table 2 List of transporter gene involved in Cd transport in various plant species

Crop	Transporter gene	Gene product/transporter	Probable function	References
Arabidopsis	*AtNramps*	AtNramps	Transport of Cd	Thomine et al. (2000)
Arabidopsis	*AtHMA4*	AtHMA4	Regulates Cd loading in xylem	Verret et al. (2004), Mills et al. (2005), Mills et al. (2010)
Arabidopsis	*HMA4*	HMA4	Involved in Cd transport	Courbot et al. (2007)
Arabidopsis	*AtPDR8*	AtPDR8	Involved in pumping out Cd	Kim et al. (2007)
Arabidopsis	*AtMRP6/AtABCC6*	AtMRP6/ AtABCC6	Regulation of Cd transport	Gaillard et al. (2008)
Arabidopsis	*AtHMA3*	AtHMA3	Vacuolar storage of Cd	Morel et al. (2009)
Arabidopsis	*ATPases*, *HMA2* and *HMA4*	HMA2 and HMA4	Root to shoot translocation of Cd	Wong and Cobbett (2009)
Arabidopsis	*AtNRAMP6*	AtNRAMP6	Regulate Cd transport	Cailliatte et al. (2009)
Arabidopsis	*Heavy Metal ATPase 3 (HMA3)*	HMA3	Leaf Cd accumulation	Chao et al. (2012)
Arabidopsis	*AtABCC1 and AtABCC2*	AtABCC1 and AtABCC2	Sequestration of Cd	Park et al. (2012)
Barley	*HvHMA2*	HvHMA2	Involved in Cd transport	Mills et al. (2012)
Noccaea caerulescens	*NcNramp1*	NcNramp1	Controls transport of Cd from root to shoot	Milner et al. (2014)
Populus	*HMA5*	HMA5	Cd transport	Migeon et al. (2010)
Rice	*OsZIP1*	OsZIP1	Transport Cd	Ramesh et al. (2003)
Rice	Mutant of *OsHMA2*	OsHMA2	Restrict transport of Cd	Satoh-Nagasawa et al. (2012)
Rice	*OsLCT1*	OsLCT1	Transport Cd into grain	Uraguchi et al. (2011)
Rice	*OsHMA1*, *OsHMA2*	OsHMA1, OsHMA2	Transports Cd from root to shoot	Takahashi et al. (2012a, b)
Rice	*OsHMA3*	OsHMA3	Controls transport of Cd from root to shoot and overexpression causes reduction in Cd accumulation	Ueno et al. (2010), Miyadate et al. (2011), Takahasi et al. (2012b), Sasaki et al. (2014)
Rice	*OsNRAMP5*	OsNRAMP5	Transport Cd	Ishimaru et al. (2012)
Rice	*Nramp5*	Nramp5	Uptake of Cd	Sasaki et al. (2012)
Rice	*OsMTP1*	OsMTP1	Translocation of Cd	Yuan et al. (2012)
Rice	*OsNRAMP1*	OsNRAMP1	Involved in transport of Cd from root to shoot	Tiwari et al. (2014)
Thlaspi caerulescens	*TcHMA4*	TcHMA4	Involved in Cd transport	Bernard et al. (2004)

et al. 2012). A variety of transporters with their roles in Cd transportation are presented in Table 2. In recent years, several research groups have successfully untangled important pathways and mechanisms vital to Cd accumulation and transportation in plants. However, a comprehensive examination of contributions of TFs, miRNAs, and epigenetic changes in imparting Cd tolerance in plants remains to be undertaken (Chmielowska-Bak et al. 2014).

Harnessing genotypic variation for Cd toxicity tolerance

The workable strategies applied so far to address Cd toxicity in plants have focused on selecting potential genotypes that (i) demonstrate low metal uptake (Ueno et al. 2009a, b) (ii) capable of phytoremediation whereby HM is extracted from contaminated soils and accumulated in plant shoot (Lasat 2002; Tripathi et al.

2007; Murakami et al. 2007, 2009; Ibaraki et al. 2009; Takahashi et al. 2014).

Hence, identification of low Cd accumulating genotypes from a wider germplasm collection including wild types and landraces sets the initial step while progressing towards developing Cd-tolerant cultivars. Promising accessions with enhanced capacity of low Cd accumulation have been identified in various crops including rice (Liu et al. 2003a, b; He et al. 2006; Grant et al. 2008), wheat (Cakmak et al. 2000; Zhang et al. 2002), flax (Li et al. 1997, 2002), non oil seed sunflower (Li et al. 1997, 2002), barley (Chen et al. 2007) and soybean (Vollmann et al. 2014). A brief update on the studies that measured variation for Cd accumulation/tolerance in different crops is presented below in a crop-wise manner:

Rice

A 23-fold difference was observed for Cd concentration among 49 rice cultivars (Arao and Ae 2003). Additionally, the authors found LAC23 (An African upland cultivar) as a promising genotype with lesser grain Cd accumulation. Similarly, Liu et al. (2007) also noted Cd concentration in polish rice varying from 0.14 to 1.43 mg kg^{-1}. Variable Cd concentration ranging from 0.06 to 0.99 mg kg^{-1} was evident in a set of 38 brown rice cultivars, with authors concluding that the 'indica' type cultivars have greater ability to accumulate Cd than the 'japonica' types (He et al. 2006). A similar observation was made by Ueno et al. (2009a). Genetic variation (0.004–0.057 mg kg^{-1}) was observed for grain Cd across 110 rice hybrids (Shi et al. 2009). Concentrations varying from 0.14 to 1.43 mg kg^{-1} were also noted in grain of polished rice by Liu et al. (2005). Subjecting 43 rice cultivars under Cd exposure ranging between 1.75 and 1.85 mg kg^{-1} resulted in the selection of 30 pollution safe genotypes (Yu et al. 2006).

Based on the variable response of rice genotypes to Cd toxicity as assessed in terms of yield loss, two genotypes viz. Shanyou 63 and Yangjing 9538 were found to exhibit significant reduction in yield loss (up to ~9 %) in comparison to Yangdao 6 and Wuyunjing 7 that witnessed almost 50 % yield loss (Huang et al. 2008). An analysis conducted under two different rice growing soils unearthed notable genotypic differences for Cd uptake and grain partitioning between hybrid rice and super rice along with presence of significant differences between the two soils and soil × cultivar interactions (Gong et al. 2007). By analyzing trials of 152 genotypes grown across 12 different locations in China, Cao et al. (2014a) indentified three genotypes Xiushui817, Jiayou08-1 and Chunyou689 accumulating low grain Cd.

The difference reported for Cd accumulation in rice genotypes is credited to the accumulation of Cd in grain than in any other organ of the plant (Liu et al. 2007). However, genotypic variations evident in 146 rice accessions accounted this variability to shoot Cd accumulation (Kojima et al. 2005; Ebana et al. 2008; Ueno et al. 2009a). In a similar fashion, Ueno et al. (2009a) reported a 13-fold difference in shoot Cd concentrations between the highest and lowest Cd accumulating rice genotypes. Besides, genotypic variations were also measured based on 'root to shoot' translocation of Cd in rice (Ueno et al. 2009b, 2011; Uraguchi et al. 2009). Sub cellular distribution of Cd was recorded to vary among rice genotypes (Liu et al. 2014). Similarly, better root growth under Cd-challanged hydroponic condition as exhibited by the genotypes 'Subhadra' and 'Sankar' furnished clues to understand the tolerance mechanism (Rout et al. 2000). Cao et al. (2015) compared effects of varying Cd levels (up to 100 mg kg^{-1}) and soil added GSH on different growth stages (seedling and elongation) of two cultivars (Bing97252: tolerant and Xiushui63: susceptible). On GSH application to Cd-treated soil, the authors found that only Bing97252 could show enhanced yield at seedling stage while grain Cd-accumulation was significantly hampered in both cultivars. These findings advocated augmenting the Cd-tolerant cultivars with externally supplied GSH to adequately address Cd-toxicity in plants. Owing to their ability to show remarkable phytoextraction, some genotypes enable removal of adequate quantities of Cd from the contaminated soils. For instance, a rice cultivar 'Chokoukoku' was found to extract 883 g Cd from one hectare of Cd-affected soil (Murakami et al. 2009).

Wheat

Grain Cd content was reported to differ significantly in both durum wheat (Meyers et al. 1982; Penner et al. 1995; Clarke et al. 1997) and bread wheat (Greger and Löfstedt 2004), and according to Gao et al. (2013) durum wheat grains accumulate greater Cd than the hexaploid. Based on the screening, Clarke et al. (2002) identified a durum line '8982-TL-L' as low Cd accumulating type. With regard to the accumulation of Cd in root and shoot, durum wheat genotypes 'Kyle' and 'Arcola' showed differential Cd accumulation at flowering and ripening stages under hydroponic condition (Chan and Hale 2004). Variability was also observed with respect to translocation of Cd from root to shoot in durum wheat (Clarke et al. 1997; Cakmak et al. 2000; Harris and Taylor 2013) and bread wheat (Cakmak et al. 2000). Isogenic lines of durum wheat had notable differences for Cd uptake and translocation (Harris and Taylor 2001, 2004; Hart et al. 2006). Significant genotypic variation exists in Japanese wheat for Cd tolerance as was reported by Kubo et al. (2008) while analyzing a set of 237 accessions. Five accessions AS623321, AS623402, AS623194, AS623186, and AS623173 of *Aegilops tauschii* were reported to be tolerant to Cd stress (Qin et al. 2015). Apart from phenotypic screening, marker assisted selection (MAS) using 'usw47' (a co-dominant DNA marker) helped categorize 314 durum lines into low Cd accumulators (165 lines), high Cd accumulators (144 lines) and heterogeneous (five lines) (Zimmerl et al. 2014). The potential of these accessions which possess greater tolerance to Cd stress could be thoroughly realized during introgression breeding that intends to develop Cd tolerant wheat cultivars.

Soybean

Soybean genotypes differing in their capacities to accumulate Cd were described by various researchers (Arao et al. 2003; Sugiyama et al. 2011; Salazar et al. 2012; Vollmann et al. 2014). For example, pot and field experiments by Arao et al. (2003) led to the discovery of low Cd accumulating soybean cultivar 'En-b0-1-2'. Recently, Wang et al. (2014a) reported difference in the extent of root Cd accumulation between two soybean cultivars i.e. Westag97 and AC Hime. Likewise, SSR marker assayed over 48 soybean genotypes has helped establish discrimination between low and high Cd accumulating lines (Vollmann et al. 2014).

Other crops

In potato, a 3-fold less storage of Cd in cultivar Kennebec than Wilwash was attributable to the difference in partitioning of Cd (Dunbar et al. 2003). An emphasis on lesser accumulation of Cd helped Liu et al. (2009) to declare 'Lvxing 70' cultivar of Chinese cabbage as tolerant of the total 40 genotypes screened. Likewise, cultivars of *Brassica rapa* L. ssp. *chinensis* including New Beijing 3 and Fengyuanxin 3 (Liu et al. 2010b), Hangzhouyoudonger, Aijiaoheiye 333, and Zaoshenghuajing (Chen et al. 2012) were reported to manifest tolerance against Cd toxicity. Low Cd accumulating genotypes were discovered in other crops such as Beitalys and Shang 98-128 in barley (Chen et al. 2007) and AC Sterling in safflower (Pourghasemian et al. 2013). Under Cd-stressed hydroponic condition, mungbean genotypes 'K-851', 'LGG-407' and 'PDM-116' showed better root growth, thereby these can be presumed to possess tolerance mechanism for the Cd toxicity (Rout et al. 2000). As described here, the existing genetic variation that explains variable extent of Cd accumulation within a crop species opens an exciting avenue for crop breeders to increasingly breed low Cd accumulating or Cd tolerant cultivars.

Understanding the genetic make-up of Cd tolerance and genomics assisted improvement for Cd tolerance

Recent advancements in plant genomics including high throughput DNA marker assays have allowed the construction of genetic linkage maps, thereby offering a high-resolution genetic framework to precisely locating gene/QTL(s) that confer HM tolerance in crops (Ueno et al. 2009a, b; Ishikawa et al. 2005, 2010; Sato et al. 2011; Benitez et al. 2012).

In rice, a set of putative QTLs on chromosomes 3, 6 and 8 was identified from the chromosome segment substitution lines (CSSL) constructed in the genetic background of Koshihikari and particularly, the DNA markers on chromosome 3 viz. S1513 and R663 enabled differentiating low Cd accumulating CSSLs viz. SL-207 and SL-208 (Ishikawa et al. 2005). Similarly, Xue et al. (2009) mapped 22 QTLs for Cd tolerance and accumulation at seedling stage in rice. Shoot and root traits were found to be directly linked with these QTLs (Table 3). A major QTL governing transport of Cd from root to shoot was mapped on chromosome 11 using F_2 population (Badari Dhan × Shwe War) in rice (Ueno et al. 2009a).

Table 3 List of QTLs attributing Cd tolerance in plant

Crop	Mapping population	QTL/loci	Marker	PV %	Linkage group/ chromosome	References
Arabidopsis	BC, *A. halleri* × *A. lyrata* sp. *petraea*	*Cdtol-1*, *Cdtol-2*, *Cdtol-3*	AFLP	82.5	LG3, LG4, and LG6	Courbot et al. (2007)
Arabidopsis	BC, *A. halleri* × *A. l. petraea*	3 QTLs, major QTL *Cdtol-1*	–	16–43	3	Courbot et al. (2007)
Arabidopsis	*Landsberg erecta* × Columbia	3 QTLs	–	26	2, 4 and 5	Tazib et al. (2009)
Barley	–	One common QTL for shoot Cd and root to shoot and 2 major grain Cd QTLs	–	–	2H and 5H	Wu et al. (2015)
Maize	RIL, B73 × Mo17	One major QTL	–	20	2	Zdunić et al. (2014)
Populus trichocarpa	BC	*16 QTLs*		8.2	–	Induri et al. (2012)
Raphanus sativus L	F2,*NAU-Dysx* × *NAU-Yh*	6 QTLs and major QTL *qRCd9*	SRAP, RAPD,SSR,ISSR, RAMP and RGA	9.86–48.64	1, 4, 6, 9	Xu et al. (2012)
Rice	BC, Koshihikari/Kasalath/ Koshihikari	Putative QTLs for grain Cd	RFLP	–	3, 6, 8	Ishikawa et al. (2005)
Rice	F2, *Anjana Dhan* × *Nipponbare*	*1 QTL*	SSR	85.6	7	Ueno et al. (2009b)
Rice	F2, *Badari Dhan* × *Shwe War*	*1QTL*	SSR	16.1	2, 5, and 11	Ueno et al. (2009a)
Rice	RIL, Bala × Azucena	*qCd1*, *qCd3*, *qCd6*(leaf*)*	–	9.7–22.7	1, 3, 6	Norton et al. (2009)
Rice	RIL, Bala × Azucena	*qCd1,qCd2,qCd3,qCd7,qCd9,qCd10*		8.7–20.2	1, 2, 3, 7, 9, 10	Norton et al. (2009)
Rice	BC, Kasalath × Nipponbare	*qcd4-1* and *qcd4-2*	–	–	–	Kashiwagi et al. (2009)
Rice	DH, JX 17 × ZYQ8	22 QTLs	RFLP, SSR	–	1, 3, 5, 6 7, 8 and 10	Xue et al. (2009)
Rice	BIL, Sasanishiki × Habataki	*qGCd2* and *qGCd7,qSCd12*	SSR	7.24–35.5	2, 7 and 12	Ishikawa et al. (2010)
Rice	F2, Anjana Dhan × Nipponbare	*OsHMA3*	SSR	–	7	Ueno et al. (2010)
Rice	F2, Cho-Ko-Koku × Akita 63	Single recessive gene, and QTL *qCdT7*	–	–	7	Tezuka et al. (2010)
Rice	RIL, Fukuhibiki × ‘LAC23’	*qLCdG11*, *qLCdG3*	SSR, CAPS	8.3–13.9	11 and 3	Sato et al. (2011)
Rice	BIL, Koshihikari × Jarjan	*qCdp7*	SSR	31–54	7	Abe et al. (2011)
Rice	*DH*, *JX17* × *ZYQ8*	3 putative *QTLs qCdc3*, *qCdc4,qCdc6*	RFLP and SSR	10.83–41.66	3, 4, 6	Zhang et al. (2011)
Rice	F2, Cho-Ko-Koku × Akita 63	*qCDT7*	CAPS,dCAPS	–	7	Miyadate et al. (2011)
Rice	–	*LCD*	–	–	–	Shimo et al. (2011)
Rice	F_2, Kasalath × Koshihikari(mutant)	*OsNRAMP5* and *OsNRAMP1*	SSR	–	7	Ishikawa et al. (2012)
Rice	RIL, Suwon490’ × ‘SNU-SG1’	5 QTLs,(scc10,gcc3, gcc9, gcc11, srg5)	–	16.1–24.9	10, 3, 9, 11, and 5	Yan et al. (2013)
Rice	BC, LAC23 × Koshihikari	*qlGCd3*	SSR, CAPS, SNP		–	Abe et al. (2013)

Table 3 continued

Crop	Mapping population	QTL/loci	Marker	PV %	Linkage group/ chromosome	References
Thlaspi caerulescens	F_2	2 QTLs	AFLP,ESTs	23.8–60.4	3	Deniau et al. (2006)
Soybean	RIL, AC Hime × Westag-97	One major QTL, *Cda1*	SSR	57.3	LG-K	Jegadeesan et al. (2010)
Soybean	RIL, Harosoy × Fukuyutaka	One major QTL *cd1*	SSR, dCAPS	–	9	Benitez et al. (2010), Benitez et al. (2012)
Wheat	DH, W9262-260D3 × Kofa	*Cdu1*	SSR	–	5B	Knox et al. (2009)
Wheat	DH, W9262-260D3 × Kofa	*Cdu1* and one minor QTL	STS, ESMs	80	5B	Wiebe et al. (2010)
Wheat	RIL, Ch × Sh	26 QTLs	–	7.97–60.16	–	Ci et al. (2012)
Wheat	–	pdil5-1, Acc-1,DME-5A,TaAP2-D, TaAP2-B,Vrn-B1, and FtsH-like protein	SNP	–	–	Qin et al. (2015)

DH double haploid, *BIL* back cross inbred line

Likewise, a large effect QTL explaining 85.6 % phenotypic variance (PV) was detected from an F_2 population in rice derived from Anjana Dhan × Nipponbare, and the QTL accounting for higher Cd accumulation was mapped on short arm of chromosome 7 (Ueno et al. 2009b). Importantly, for the given QTL the authors also pinpointed a candidate genomic region residing within the interval RM21238–RM7153. Xue et al. (2009) also located a QTL on the chromosome 7 for Cd accumulation in rice, however, this QTL was different from the one identified earlier by Ueno et al. (2009b) on the same chromosome. A novel QTL *qGCd7* explaining up to 35.5 % PV for grain Cd content was also mapped on short arm of chromosome 7 in rice (Ishikawa et al. 2010). Recently, a major QTL for Cd accumulation detected on chromosome 7 from Anjana Dhan × Nipponbare population was found to lie in close association with markers RM21260 and RM21268 (Ueno et al. 2010). More imporatnly, the authors have eventuallycloned the causative gene *OsHMA3* responsible for low Cd accumulation.

By using back cross inbred lines (BILs: Koshihikari × Jargan) in brown rice, a new QTL *qCdp7* controlling Cd accumulation was reported on chromosome 7 placed within the marker interval RM21160–RM3635 (Abe et al. 2011). Further, a QTL *qCdT7* governing Cd translocation was identified on chromosome 7 in a rice population derived from the cross Cho-Ko-Koku × Akita 63 (Tezuka et al. 2010). Notably, the causative gene that concerns the QTL on chromosome 7 was found to be recessive in nature. Recently, Abe et al. (2013) reported a *qlGCd3* gene responsible for Cd reduction flanked by QTL-*Hd6* (Takahashi et al. 2001) and marker RM16153 on chromosome 3 in BC_4F_3 lines derived from CSSL (LAC23 × Koshihikari). Apart from the QTLs detected on chromosome 7 and 3, a QTL *qLCdG11* (linked with the markers NBLAC61 and NBLAC63) for reduced Cd content was mapped on chromosome 11 in a recombinant inbred line (RIL) population (Fukuhibiki × LAC23) (Sato et al. 2011). Recently, five main effect QTLs on chromosomes 3, 5, 9, 10 and 11 were identified in rice which governed Cd accumulation in shoot and grain (Yan et al. 2013). Likewise, SSR markers were employed in durum wheat for mapping *Cdu1* gene that is responsible for Cd uptake (Knox et al. 2009). Wiebe et al. (2010) also found a major locus (*Cdu1*) on 5B chromosome in durum wheat that governed grain Cd concentration. In case of soybean, SSR markers based genetic linkage analysis facilitated mapping of low Cd accumulating QTL on LG-K (Jegadeesan et al. 2010), and this QTL exerted substantially higher effect on phenotype i.e. up to 57.3 %. Of the seven SSR markers reported as linked with locus (*Cda1*), the three SSR markers i.e. SatK147, SacK149 and SattK152 were found to be very tightly associated with the low Cd accumulating locus (*Cda1*). Recently, four QTLs were detected in *Raphanus sativus* on different chromosomes viz. 1, 4, 6, and 9 affecting Cd accumulation in roots whereas shoot Cd accumulation was reported to be controlled by two QTLs (Xu et al. 2012). Furthermore, a major effect QTL *qRCd9* was mapped in *Raphanus sativus* in the vicinity of DNA markers NAUrp011_754 and EM5me6_286 (Xu et al. 2012). An updated list of QTLs contributing tolerance to toxic metals is available at PLANTSTRESS site (http://www.plantstress.com/biotech/index.asp?Flag=1).

In recent years, predictive DNA markers have gained wider acceptanceto allow speedy selection of desirable phenotypes (He et al. 2014). The modern genomic tools especially the trait-linked functional DNA markers hold tremendous relevance to crop breeding schemes including the development of high-yielding genotypes with improved stress resilience. Notable instances illustrating the marker assisted transfer of Cd tolerance are reported in rice (Ishikawa et al. 2005, 2010, 2012; Abe et al. 2013). For example, CSSLs viz. SL-207 and SL-208 showing low Cd accumulation were developed by placing QTLs from Kasalath in the background of Koshihikari. Conversely, the other CSSLs viz. SL-215, SL-217 and SL-218 derived from the same cross exhibited greater Cd accumulation (Ishikawa et al. 2005). A major effect QTL *qGCd7* explaining higher grain Cd accumulation (flanked by SSRs RM6728 and RM7273) was validated in the background of Sasanishiki (Ishikawa et al. 2010). Recently, Ishikawa et al. (2012) have reported rice cultivars containing mutant gene '*osnramp5*' linked with the markers RM8007 and RM3635, can facilitate in distinguishing rice cultivars containing low grain Cd.

The paramount importance of rice chromosomes 7 and 11 is evident from multiple QTL studies that intended to illuminate the genetic landscape of Cd tolerance in rice. The exceptionally high PVs accounted to these QTLs [QTLs on chromosome 7: 35.5 % PV (Ishikawa et al. 2010) and 85.6 % PV (Ueno et al. 2009a)] provide evidence for their robust candidature for downstream analyses. A causative gene *OsHMA3* from the candidate genomic region on chromosome 7 was successfully cloned in rice through analyzing F_2 (Anjana Dhan × Nipponbare: Ueno et al. 2010) and $F_{2:3}$ (Cho-Ko-Koku × Akita 63: Miyadate et al. 2011) using a map-based cloning approach. On the other hand, the discrepancies observed across different QTL studies regarding the number and genomic locations of the detected QTLs can be credited to several factors like experimental design, number of mapping individuals, genetic map saturation, trait-variation (between parental genotypes), plant's growth stage and parts/tissues chosen for phenotyping assay (grain and shoot in case of Cd accumulation) etc. (Erickson et al. 2004; Xue et al. 2009; Ishikawa et al. 2009; Ueno et al. 2009b).

In durum wheat, a random amplified polymorphic DNA (RAPD) marker OPC20 (Penner et al. 1995) remains crucial for practicing MAS, which led to the development of several Canadian cultivars including Strongfield (Clarke et al. 2005), Eurostar (Clarke et al. 2009a), Brigade (Clarke et al. 2009b) and CDC Verona (Pozniak et al. 2009). Likewise, low Cd containing cultivar CDC Vivid was developed in durum wheat using a sequence characterized amplified region (SCAR) marker ScOPC20 (Pozniak 2013). Also, suitability of the two sequence-specific DNA markers i.e. CAPS (usw47) and SCAR (ScOPC20) in distinguishing low and high Cd genotypes was successfully demonstrated in durum wheat (Zimmerl et al. 2014).

In soybean, derived CAPS (dCAPS: Gm-dCAPS-HMA1) marker linked with the *cd1* QTL controlling seed Cd concentration, can play important role in distinguishing high seed Cd accumulating genotypes (Benitez et al. 2012). The candidate gene '*GmHMA1*' underlying this QTL has been also cloned (Benitez et al. 2012). Similarly, implications of *Cda1* locus and SSR (Sack149) marker for distinguishing low seed Cd in soybean has been discussed by Vollmann et al. (2014).

Molecular breeding to improve Cd stress tolerance in plants is in infancy stage; however it is gradually gaining momentum with the availability of the high-throughput methods which expand the array of breeder-friendly DNA markers or candidate gene(s)/QTLs. To this end, as was reported recently in

Aegilops tauschii (Qin et al. 2015) increasing implementation of genome scale techniques like genome-wide association studies (GWAS) dramatically improves scope for genomics assisted breeding.

Emerging genomics technologies for discovering candidate markers/genes for Cd tolerance

Advances in next generation sequencing (NGS) techniques have heralded a technological shift from microarray to high-throughput transcriptome or RNA Sequencing (RNA-Seq) enabling genome wide candidate gene(s) and their expression patterns accessible to the research community (Verbruggen et al. 2013; Halimaa et al. 2014). Employing cDNA-AFLP analysis, Fusco et al. (2005) reported 52 genes in *Brassica juncea* associated with cellular metabolism, photosynthetic activity, TFs and stress response under Cd stress. In response to Cd stress, a global expression analysis revealed up-regulated expression of 65 genes, whereas 338 genes showed down-regulation in plants (Kovalchuk et al. 2005). Similarly, transcriptome analysis in rice unearthed a set of 1172 Cd-responsive regulatory genes (Lin et al. 2013). In barley, microarray-based transcript profiling of a Cd-tolerant genotype (Weisuobuzhi) and a Cd-sensitive genotype (Dong17) uncovered a set of 91 Cd-responsive genes showing up and down regulation (Cao et al. 2014b). These genes were found to be associated with Cd detoxification through producing catalase against ROS and sequestering Cd into vacuoles. Occurrence of some common genes has been suggested which encode proteins to negate the detrimental effects associated with inflated levels of ROS and chaperons in plants (Suzuki et al. 2001; Sharma and Dietz 2009; Hossain et al. 2012a; Lin et al. 2013). Transcriptome profiling of bark tissue of *Populus* × *canescens* with Affymetrix poplar genome array revealed significantly altered expression of transcripts involved in microstructural and physiological processes conditioning Cd toxicity (He et al. 2013). Further, this study showed active roles of 43 hub genes in regulating Cd response in bark tissue. Likewise, whole genome-microarray analysis facilitated the identification of nine Cd responsive genes corresponding to putative QTL regions in *Populus* (Induri et al. 2012). Importantly, the genes encoding metal transporter and glutathione-S-transferase were also recovered from the given QTL interval. In chickpea, a large-scale set of 1579 ESTs was produced from Cd treated roots of genotype ‘Pusa1105’ and subsequently, 914 unigenes were obtained by analyzing the EST assembly (Gaur et al. 2014). A genome wide transcriptome profiling was performed in *Arabidopsis* in order to yield greater insights into plant’s response to Cd toxicity (Herbette et al. 2006; Mendoza-Cózatl et al. 2011). Recently, RNA-Seq analysis of Cd-treated and non treated rice seedling revealed various transcripts associated with heavy metal detoxification, signal transduction and metal transport causing Cd tolerance (Oono et al. 2014). Similarly, transcriptome analysis of *Sedum alfredii* Hance (belonging to the Crassulaceae family) hyperaccumulating ecotype with Roche 454 and Illumina/Solexa suggested up- and down-regulation of 110 and 123 contigs, respectively (Gao et al. 2013).

The regulatory micro RNA (miRNAs) engaged in molecular mechanism underlying HM tolerance in various plants is worth mentioning (Ding and Zhu 2009; Mendoza-Soto et al. 2012; Fang et al. 2013; Srivastava et al. 2013). To this end, NGS technology has helped greatly to elucidate the HM toxicity related regulatory miRNAs, their expression patterns and concerned mRNA targets in plants (Zhou et al. 2012; Yu et al. 2012; Xu et al. 2013). Microarray based profiling of Cd-stressed rice resulted in the detection of 19 miRNAs. Importantly, the target genes of the given miRNAs were found to encode TFs and stress responsive proteins (Ding et al. 2011). Similarly, microarray analysis of soybean genotypes ‘Huaxia3’ (Cd-tolerant) and ‘Zhonghuang 24’ (Cd sensitive) uncovered a set of 26 Cd responsive miRNA (Fang et al. 2013). Differential expression of 13 conserved miRNAs was investigated under Cd-stressed conditions in *Brassica napus* (Huang et al. 2010). In a similar way, application of deep sequencing in *B. napus* following Cd treatment profiled a total of 84 conserved and non conserved miRNAs expressed in root and shoot (Zhou et al. 2012). In *Raphanus sativus*, known (15) as well as novel (8) Cd stress responsive regulatory miRNA families were discovered through transcriptome analysis (Xu et al. 2013).

Concerning proteome dynamics in response to Cd stress, considerable changes in proteins participating in mitochondrial protein import and maturation, and those contributing to nitrogen metabolism were noticed in *Populus tremula* L (Sergeant et al. 2014). Further, differential expressions of both stress and primary metabolism related proteins were noted in relation to Cd toxicity in poplar (Kieffer et al. 2008, 2009; Durand et al. 2010). Based on root proteomic analysis using MALDI-TOF/TOF MS, Wu et al. (2013) reported enhancement of proteins involved in anti-oxidant defenses and anti-stress protection under Cd exposure in *Solanum torvum.* Similarly, 36 leaf and root proteins were found to be both up and down regulated following Cd stress in rice as demonstrated by Lee et al. (2010) using MALDI-TOF MS analysis. Proteomic analysis of rice root treated with Cd showed higher accumulation of GSH and phytochelatins, leading to Cd tolerance (Aina et al. 2007). While investigating the *Arabidopsis* leaf proteome under Cd-stressed situation, up regulation was observed for proteins associated with oxidative stress, protein metabolism, photosynthesis and energy production (Semane et al. 2010). In soybean, a combined proteomic and metabolomic analysis of cultivar 'Enrie' showed a set of proteins playing significant role in Cd-chelating pathway and lignin biosynthesis (Ahsan et al. 2012). Likewise, leaf proteomic analysis in soybean under Cd stress using cultivars Harosoy (high Cd accumulator), Fukuyutaka (low Cd accumulator) and their RILs indicated higher accumulation of photosynthesis related proteins, glutamine synthetase facilitating Cd detoxification and an increase in antioxidant enzymes (Hossain et al. 2012b). Changes in expression levels of 14 proteins were reported from flax (tolerant versus susceptible genotypes) as a response to Cd toxicity (Hradilová et al. 2010) and a proposition was established that the tolerance to Cd might be due to up-regulation of ferritin and glutamine synthetase enzyme under Cd stress. Up regulation of proteins associated with sulfur assimilation, redox homeostasis and xenobiotic detoxification was also predicted as a plant's response to counter Cd toxicity in *B. junceae* by applying fluorescence two-dimensional difference gel electrophoresis (2-D DIGE) and quantitative proteomic assay (iTRAQ) (Alvarez et al. 2009).

It is evident from the above discussion that there exist some common genes across different plant species which are regulated under HM stress (Zhao et al. 2009; Lin et al. 2013). Some of these candidate genes involved in manifestation of Cd tolerance are listed in Table 4. Evolving cutting-edge functional genomic tools including digital expression analysis (DGA) are likely to enrich researchers in comprehending the molecular mechanism describing plant's response to Cd stress, thereby broadening the range of candidate genes or functional genetic variants for incorporating Cd tolerance in plants.

Engineering Cd tolerance in plants using transgenic technologies

Genetic engineering (GE) permits overcoming the restrictions posed by the sexual incompatibility in plants, and noteworthy achievements were made towards developing commercially viable transgenics against biotic and abiotic stress across a range of crops (Daniell et al. 2002; Ashraf 2010; Ahmad et al. 2012). To impart tolerance against metal toxicity, transgenic technology has been applied to manipulate specific genes including cation exchanger genes (Guo-ming et al. 2012 and references therein) which encode tonoplast-localized Cd transporters (Koren'kov et al. 2007a, b), plasma membrane based HM transporter (Ishimaru et al. 2012; Ovecka and Takac 2014; Sasaki et al. 2014), PCS genes and the genes encoding HM binding peptides participating in sequestration of HM into vacuoles or chelating them in cytoplasm (Zhu et al. 1999; Picault et al. 2006; Shukla et al. 2012). Further, development of genetically engineered hyperaccumulating plants capable of extracting HMs from the metal contaminated soils stands to be one of the most attractive and environmental-friendly approaches (Zhu et al. 1999; Doucleff and Terry 2002; Krämer 2005; Tripathi et al. 2007; Krämer 2010; Maestri et al. 2010; Rascio and Navari-Izzo 2011; Chen et al. 2013). Table 5 provides a list of transgenes that are known to confer tolerance to Cd toxicity in different plants. In addition to the transgenes related to Cd tolerance, a comprehensive list of transgenes relating to the other metals is available at PLANTSTRESS site (http://www.plantstress.com/biotech/index.asp?Flag=1).

Utilizing the root vacuolar sequestration of Cd^{2+} by Arabidopsis CAtion eXchangers (CAXs) genes, transgenic tobacco was developed with the CAX4 and CAX2 genes driven by CaMV35S promoter, and the resultant transgenics exhibited substantially higher transport and selectivity of Cd^{+2} into root tonoplast (Koren'kov et al. 2007a). Similar results of *AtCAX4* and *AtCAX2* genes encoding divalent cation/proton antiporters causing higher accumulation of Cd into

Table 4 Selective list of candidate genes (only contributing Cd tolerance) in response of cadmium stress under transcriptome and proteome analysis in various plant species

Crop	Candidate gene	Putative function	References
Arabidopsis	*At5g44070*	Phytochelatins synthesis	Herbette et al. (2006)
	At5g44070	PCS synthesis	
	At1g17190 and others	GSH S-transferase	
Arabidopsis	*At2g30860*	Glutathione S-transferase phi 9	Semane et al. (2010)
Barley	*Contig15264_at*, *Contig20831_at*	Glutathione S-transferase (GST)	Cao et al. (2014b)
	HV_CEb0004O15r2_s_at	Glutathione S-transferase (GST)	
	Contig9764_at	Glutathione S-transferase (GST)	
	Phytochelatin synthetase-like protein		
Brassica	*FG567250*	ABC transporter	Zhou et al. (2012)
	CD826328	Metal transporter Nramp1	
	GT073274	Metal transporter Nramp1	
Radish	*Glutathione S-transferase 5 (GST5)*	Phytochiletins synthesis	Xu et al. (2013)
	Phytochelatin synthase 1		
Rice	*OsGSTU22*[a] and *OsGSTU19*[a]	Glutathione-*S*-transferase (GST)	Lin et al. (2013)
	Os02t0585200-01[a]	Metal ion transporter (HMA family)	Oono et al. (2014)
	Os04t0571600-01[a]	Metal ion transporter (MatE family)	
	Os01t0972200-00[a]	Metal ion transporter (Zip family)	
Populus	*fgenesh4_pg.C_LG_III001134*	Multidrug resistance-associated protein; ATP-type transporter	Induri et al. (2012)
Sedum alfredii	*Sa_Contig14529*	Metal transporter Nramp4	Gao et al. (2013)
	Sa_Contig03765	Metal transporter Nramp2	
	Sa_Contig30461	Metal transporter Nramp3	
Soybean	*Glyma03g40280.2*	Copper/zinc superoxide dismutase 1	Fang et al. (2013)
	Glyma03g40280.3	Copper/zinc superoxide dismutase 1	

[a] Only candidate gene showing fold changes greater than 5 are taken

root tonoplast were demonstrated in tobacco (Korenkov et al. 2007b), whereas engineering of *AtCAX4* and *AtCAX2* genes with root-selective promoters resulted in lower Cd accumulation in tobacco leaves which in turn caused lowering in upload of Cd into shoots (Korenkov et al. 2009). Overexpression of yeast protein *YCF1* gene into *Arabidopsis* resulted in the manifestation of Cd tolerance by means of sequestering Cd into vacuoles (Song et al. 2003). Given the active role of transporters in imparting HM tolerance (Table 2), overexpression of *OsHMA3* gene (a member of the heavy metal ATPase: HMA) family conferred tolerance to rice against Cd via compartmentalizing Cd into roots (Sasaki et al. 2014). Exploring the potentiality of phytoremediation, *Stylosanthes hamata SHST1* gene encoding for a high-affinity sulfate transporter was transferred into *B. juncea*, thus leading to greater Cd accumulation in roots (Lindblom et al. 2006). Likewise, overexpression of ATP sulfurylase in *B. juncea* caused enhanced Cd tolerance at seedling stage (Wangeline et al. 2004).

Phytochelatins, sulphur rich metal binding peptides, play significant role in achieving tolerance against Cd mentioned earlier. Introduction of *AtPCS1* gene into plastid of *Arabidopsis* under the control of CaMV35S promoter enhanced PCs in transgenic lines under Cd stress. By contrast, overexpression of this gene in cytosol resulted in lower Cd tolerance (Picault et al. 2006). Similarly, Cd tolerance was manifested in plants (harboring *AtPCS gene)* transformed using an *in planta* protocol. Examples include crops like rice (Venkataramaiah et al. 2011), *B. juncea* (Gasic and Korban 2007a) and tobacco (Pomponi et al. 2006). Likewise, transgenic of tall fescue containing Phragmites australis Phytochelatin Synthase (PaPCS) gene showed higher synthesis of PCs, thereby offering Cd

Table 5 Genetic manipulation of Cd tolerance gene deploying transgenic technology

Source of gene	Transformed plant sp. (accession)	Concentration of Cd used	Name of gene	Name of the protein	Promoter used	Outcome	Comments	Reference
Arabidopsis	*Arabidopsis* (cv Columbia)	85 and 75 µM $CdCl_2$	*AtPCS1*	Phytochelatin synthase	CaMV35S	−	Toxic effect of excess PC causes sensitivity for Cd	Lee et al. (2003a)
Arabidopsis	*Arabidopsis*	50 or 85 µM $CdCl_2$	*AtPCS1*	Phytochelatin synthase	–	−	Hypersensitivity for Cd due to PC toxicity	Lee et al. (2003b)
Arabidopsis	*Vicia faba*	–	*MT2a*, *MT3*	Metallothionein	–	+	Higher production of MTs causes Cd detoxification	Lee et al. (2004)
Arabidopsis (*cad1-3*)	–	50 µM $CdCl_2$	*AtPCS1*, *AtPCS2*	Phytochelatin synthase	CaMV35S	−	Mutation in AtPCS1gene causes Cd stress suceptibilty	Lee and Kang (2005)
Arabidopsis	*Nicotiana tabacum* (cv Petit Havana)	60, 100 or 200 µM $CaSO_4$	*AtPCS1*	Phytochelatin synthase	CaMV35S	+	Produces excess PCs and causes Cd tolerance	Pomponi et al. (2006)
Arabidopsis (ecotype Wassilewskija)	–	50 or 75 µM $CdCl_2$	*AtPCS1*	Phytochelatin synthase	CaMV35S	−	Overexpression of cytosolic AtPCS1 causes lower Cd tolerance	Picault et al. (2006)
Arabidopsis	–	40 µM$CdCl_2$	*AtPDR8*	ATP-binding cassette(ABC) transporter	CaMV35S	+	Efflux pump of Cd from plasma membrane	Kim et al. (2007)
Arabidopsis	*Brassica juncea* L (accession no. 426308)	0.1–0.2 mM $CdCl_2$	*AtPCS1*	Phytochelatin synthase	CaMV35S	+	Produces excess PCs and helps in Cd tolerance	Gassic and Korban (2007a)
Arabidopsis	*Brassica juncea* L (accession no. 426308)	100 µM $CdCl_2$	*AtPCS1*	Phytochelatin synthase	CaMV35S	+	Produces excess PCs and helps in Cd tolerance	Gassic and Korban (2007b)
Arabidopsis	*Nicotiana tabacum* (cv. KY14)	3 µM Cd and 0.005 µM Cd	*AtCAX2* and *AtCAX4*	Divalent cation/H antiporters	CaMV35S and FS3	+	Sequestration of excess Cd into root vacuole enhances Cd transport into root tonoplst vesicle	Korenkov et al. (2007a, b, 2009)
Arabidopsis	Barley	–	*HvAPX1*	Ascorbate peroxidase	–	+	Produces ascorbate peroxidase thereby helps in Cd tolerance	Xu et al. (2008)
Arabidopsis	*Nicotiana tabacum* (var. Xanthi)	5 and 25 µM $CdCl_2$	*AtPCS1* and *CePCS*	Phytochelatin synthase	CaMV35S	−	Overexpression of AtPCS causes hypersensitivity to Cd	Wojas et al. (2008)
Arabidopsis	–	–	*GSH1* and *AsPCS1*	Phytochelatin synthase	–	+	Higher accumulation of Cd	Guo et al. (2008)
Arabidopsis	Tomato	300 µM $CdCl_2$	*AtTSB1*	Tryptophan synthase beta 1	CaMV35S	+	Trytophan may involved in Cd tolerance	Sanjaya et al. (2008)
Arabidopsis	*Arabidopsis thaliana* (Columbia type)	300 µM $CdCl_2$	*AtTSB1*	Tryptophan synthase beta 1	CaMV35S		Cd tolerance by tryptophan	Sanjaya et al. (2008)

Table 5 continued

Source of gene	Transformed plant sp. (accession)	Concentration of Cd used	Name of gene	Name of the protein	Promoter used	Outcome	Comments	Reference
Arabidopsis	*Nicotiana tabacum* (var Xanthi)	–	*MRP7*	AtMRP7	–	+	Detoxification of Cd by storing it in vacuole	Wojas et al. (2009)
Arabidopsis	–	10 µM $CdCl_2$	*AHA1*	H^+-ATPase	CaMV35S	+	Increase of root to shoot Cd translocation and its detoxification by citrate secretion	Hou et al. (2011)
Arabidopsis	*Nicotiana tabacum*	–	*AtPCS1*	Phytochelatin synthase	–	–	Lowering of cytosolic and vacuolar PC	Wojas et al. (2010)
Arabidopsis	*Oryza sativa*	125 µM	*AtPCS*	Phytochelatin synthase	–	+	Produces excess PCs and causes Cd tolerance	Venkataramaiah et al. (2011)
Arabidopsis	*Petunia*	–	*Ca^{2+}/H^+ CAX variant*		–	+	Enhance Cd tolerance and accumulation	Wu et al. (2011)
Arabidopsis	Tobacco	–	*AtHMA4*	AtHMA4 metal transporter	–	+	Increases Cd tolerance	Siemianowski et al. (2011)
Arabidopsis	Arabidopsis	30 µM $CaSO_4$	*AtPCS1*	Phytochelatin synthase	CaMV35S	–	Cd sensitive AtPCS1 over-expressing seedling showed damage in root	Brunetti et al. (2011)
Arabidopsis	*Arabidopsis thaliana* (ecotype Columbia)	–	*AtbHLH39 and FIT/ AtbHLH38* and *FIT/ AtbHLH39*	FIT, AtbHLH38, and AtbHLH39 Transcription factor	–	+	Enhances Cd sequestration	Wu et al. (2012)
Arabidopsis	–	50 µM Cd	*HY1*	Heme oxygenase 1	CaMV35S	+	Lowers nitric oxide production thereby causing Cd tolerance	Han et al. (2013)
Arabidopsis	Arabidopsis mutant (Col-0 and Ws-0 type)	0.5 or 5 µM $CdCl_2$	*AtPCS2*	Phytochelatin synthase	CaMV35S	+	Produce excess PC and rescue the Cd hypersensitive mutant	Kühnlenz et al. (2014)
Arabidopsis	*Nicotiana tabacum* (v. Xanthi)	0.25 µM $CdCl_2$	*AtHMA4*	HMA4	CaMV35S	+	Lowering in Cd uptake and accumulation	Siemianowski et al. (2014)
Bacteria	*Arabidopsis*	–	*Gamma-ECS*	Glutamyl cysteine synthase	Actin regulatory sequence (A2)	–	Increased level of γ-EC-related peptides causes sensitivity to Cd	Li et al. (2005)
Brassica juncea	Arabidopsis (ecotype Columbia)	50 µM $Cd(NO_3)_2$	*BjMT2*	Metallothionein	CaMV35S	+	Produces type-2 MT and detoxify Cd	Zhigang et al. (2006)
Brassica juncea	*Arabidopsis* and Tobacco	10 µM $Cd(NO_3)_2$	*BjCdR15*	bZIP transcription factor	CaMV35S	+	Regulation of Cd uptake and transport in root	Farinati et al. (2010)

Table 5 continued

Source of gene	Transformed plant sp. (accession)	Concentration of Cd used	Name of gene	Name of the protein	Promoter used	Outcome	Comments	Reference
Bacteria	Eastern cottonwood	–	*ECS*	Gamma-glutamylcysteine synthetase	–	+	Accumulates excess Cd/phytoremediation of Cd	LeBlanc et al. (2011)
Ceratophyllum demersum L.	Tobacco (cv. Petit Havana)	50, 100, 200, 300 µM $CdCl_2$ and 300 µM $CdCl_2$	*CdPCS1*	Phytochelatin synthase	CaMV35S	+	Increase in PCs production caused higher accumulation of Cd	Shukla et al. (2012)
Escherichia coli	*Brassica juncea* (accession no. 173874)	0.05, 0.075, or 0.10 mM $CdSO_4$	*gshI*	Gamma-glutamylcysteine synthetase	CaMV35S	+	Sequestration of excess Cd	Zhu et al. (1999)
–	*Brassica juncea*	–	*(ECS)* and *(GS)*	Gamma-glutamylcysteine synthetase glutathione synthase	CaMV35S	+	PCs and glutathione assisted in high Cd accumulation thereby helping in Cd phytoremediation	Bennette et al. (2003)
–	*Brassica juncea* (accession no. 173874)	–	*ATP sulfurylase*	ATP sulfurylase	CaMV35S	+	Detoxification of Cd by sulfur-rich compounds	Wangeline et al. (2004)
–	*Nicotiana tabacum* L. (Wisconsin 38)	0.6 mg Cd l^{-1}	(HisCUP)	Polyhistidine cluster and metallothionein	CaMV35S	+	Higher accumulation of Cd and resistance for Cd	Pavlikova et al. (2004)
Glycine max	–	0.3–0.4 mM $CdCl_2$	*GmOASTL4*	*O*-Acetylserine (thiol) lyase	CaMV35S	+	Higher accumulation of thiol compounds causes Cd tolerance	Ning et al. (2010)
Human	*Brassica napus*	100 µM $CdCl_2$	*MT-II*	Metallothionein-II	CaMV35S	+	Sequestration of excess Cd	Misra and Gedamu (1989)
Lycium chinense	*Nicotiana tabaccum*	–	*LchERF*	ERF	CaMV35S	+	Increase in higher GSH gene expression cause Cd tolerance	Guan et al. (2015c)
Lycium chinense	*Arabidopsis thaliana*	–	*LcGSHS*	Glutathione synthase	–	+	Cd tolerance due to excess accumulation of glutathione	Guan et al. (2015b)
Nicotiana tabaccum	*Nicotiana tabaccum*	300 µM $CdSO_4$	*NtUBQ2*	Ub-extension protein	–	+	Cd tolerance due to increased activity of 20S proteasome	Lee and Hwang (2015a)
Nicotiana tabaccum	*Nicotiana tabaccum*	50 µM $CdSO_4$	*NtHb1*	Non-symbiotic class 1 hemoglob	Phospho glycerate kinase (PGK)	+	Increase Cd tolerance reducing NO	Lee and Hwang (2015b)

Table 5 continued

Source of gene	Transformed plant sp. (accession)	Concentration of Cd used	Name of gene	Name of the protein	Promoter used	Outcome	Comments	Reference
Oryza sativa	*Nicotiana tabacum* (cv Xanthi)	0.1 mmol/L $CdCl_2 \cdot 2.5H_2O$	*RCS1*	A cytosolic cysteine synthase	CaMV35S	+	Detoxification of Cd by excess sulphur compounds	Harada et al. (2001)
–	*Oryza sativa*	10 mg kg^{-1} Cd	*OsPCS1*	Phytochelatin synthase	ZMM1	+	Lower accumulation of Cd in grain	Li et al. (2007)
Oryza sativa	–	–	*OsNRAMP5*	OsNRAMP5 transporter	–	+	Increases high translocation of Cd into shoot	Ishimaru et al. (2012)
Oryza sativa L.	*Arabidopsis thaliana* (Col-0)	75 µM $CdCl_2$	*OsDEP1*	Cysteine rich G protein γ subunit	–	+	Produces cysteine rich compound causing removal of Cd ions	Kunihiro et al. (2013)
Oryza sativa	Tall Fescue	150 µM $CdCl_2$	*PaPCS and PaGCS*	Phytochelatin synthase Glutamyl cysteine synthetase	CaMV35S	+	Produces excess PCs thereby helping in Cd tolerance	Zhao et al. (2014)
Oryza sativa (Anjana Dhan)	–	–	*OsNRAMP5*	OsNRAMP5 transporter	–	+	High translocation of Cd	Takahashi et al. (2014)
Phragmites australis	*Agrostis palustris*	0.15 mM $CdCl_2$	*PaGCS*	Glutamyl cysteine synthetase	CaMV35S		Produces excess PCs	Zhao et al. (2010)
Phragmites australis	–	–	*OsHMA3*	OsHMA3 transporter	–		Vacuolar sequestration of Cd	Sasaki et al. (2014)
Stylosanthes hamata	*Brassica juncea* (accession no. 173874)	10 mg/l Cd as $CdSO_4$	*SHST1*	Sulphate transporter	CaMV35S	–	Higher accumulation of Cd/help in phytoremediation	Lindblom et al. (2006)
Trichoderma virens	*Nicotiana tabacum* (cv. Havana 425)	10, 50, 100 and 200 µM Cd	*TvGST*	Glutathione transferases	CaMV35S	+	Glutathione transferases helps in reducing oxidative stress induced by Cd	Dixit et al. (2011)
Triticum aestivum	*Oryza sativa* (Dongjin)	100–300 µM $CdCl_2$	*Ta HsfA4a*	Heat shock transcription factor	–	+	Up regulation of MT genes causes tolerance for Cd	Shim et al. (2009)
Triticum aestivum	*Oryza sativa* L. (cv. Zhonghua11)	250 and 500 mM $CdCl_2$	*TaPCS1*	Phytochelatin synthase	CaMV35S	–	Overexpression of the given gene causes sensitivity to Cd	Wang et al. (2012)
Triticum aestivum	Tobacco	0.05 mM $Cd(NO_3)_2$	*LCT1*	–	CaMV35S	+	Protective actionof Ca + 2 causes low accumulation of Cd	Antosiewicz and Henning (2004)
Yeast	*Arabidopsis* (Columbia ecotype)	70 µM $CdCl_2$	*YCF1*	Yeast protein	CaMV35S	+	Higher accumulation of Cd	Song et al. (2003)

+ Improvement in Cd tolerance due to outcome of transformation event

– Negative effect on plant due to outcome of transformation event tolerance (Zhao et al. 2014). Conversely, expression of wheat *TaPCS1* gene caused sensitivity in rice for Cd toxicity due to higher accumulation of Cd in shoots (Wang et al. 2012).

Transformation of *Agrostis palustris* with *Phragmites australis* gamma-glutamylcysteine synthetase (*PaGCS*) gene showed higher accumulation of Cd in transgenics than the wild types (Zhao et al. 2010). Higher PC accumulation was reported in transgenic *B. juncea* caused by the overexpression of gamma-glutamylcysteine synthetase (ECS) and glutathione synthetase (GS) enzymes (Bennett et al. 2003). Similarly, tobacco plants engineered with rice gene *RCS1* (a cytosolic cysteine synthase gene) were found to accumulate PCs to a greater extent as a means to counter Cd toxicity (Harada et al. 2001).

Given the role of MT (metal binding peptides), early reports on transgenic *B. napus* and *Nicotiana tabacum harboring* human metallothionein-II (MT-II) gene provided evidences about unaffected root and shoot growth under Cd stress (Misra and Gedamu 1989). Tobacco plants engineered with a yeast MT (combined with a polyhistidine tail) also showed enhanced level of tolerance to Cd toxicity (PavlÍková et al. 2004). Tolerance against Cd was noticed in *Arabidopsis* seedlings that contained transgenic *B. juncea* 2 metallothionein (*BjMT2*) gene under the control of 35S promoter (Zhigang et al. 2006). Similarly, overexpression of barley peroxisomal ascorbate peroxidase gene (*HvAPX1*) in *Arabidopsis* also provided Cd tolerance (Xu et al. 2008). Sanjaya et al. (2008) also reported that overexpression of *Arabidopsis thaliana* tryptophan synthase beta 1 *(AtTSB1)* gene in *Arabidopsis* and tomato offered Cd tolerance in both, highlighting the involvement of tryptophan in case of Cd toxicity.

In regards to the role of TFs in HM toxicity, transformation of tobacco and *Arabidopsis* with *B. juncea* (BjCdR15) bZIP TF garnered a higher tolerance level against Cd (Farinati et al. 2010). More recently, RNAi-led suppression of *OsNRAMP5* gene in rice cultivar Anjandhan increased the accumulation of Cd in the shoots (Takahashi et al. 2014). Thus, the RNAi technology can serve as a potential genetic means for the removal of toxic Cd from the Cd-polluted paddy fields. To reduce Cd toxicity in future, HM accumulating genes could also be harnessed from a range of plant species such as *Pteris vittata* (Ma et al. 2001; Meharg 2002), *Pityrogramma calomelano* (Visoottiviseth et al. 2002), *Arabidopsis halleri* and *Thlaspi caerulescens* (Bert et al. 2002; Baker and Whiting, 2002; Lombi et al. 2001; Zhao et al. 2002; Roosens et al. 2003), *Sedum alfredii* (Lu et al. 2008) which intrinsically accumulate greater quantities of metals (Rascio and Navari-Izzo 2011). Transgenic research aiming to decipher the genetic control of Cd tolerance thus far has been confined to model plant species like *Arabidopsis* and some non edible plant species. Nevertheless, transgenic technology needs to be rapidly extended to field crops to expedite the development of Cd tolerant crop cultivars.

Conclusion and future prospects

In the face of indiscriminate industrialization, HM toxicity becomes one of the most important abiotic stresses that the plants and human beings encounter alike. Several researchers have underlined the alarming consequences of this toxic element being increasingly accumulated in the agricultural resources viz. soil, irrigation water and crop as an outcome of anthropogenic activities (Mishima et al. 2004; Nagajyoti et al. 2010; Arao et al. 2010). Besides manifesting detrimental impacts on plant yield, Cd accumulated in food crops enters into human food chain, thus posing a great challenge to food safety and human health (Ueno et al. 2009a, b). To mitigate the risk of Cd toxicity, measurement of genotypic variation is warranted which eventually enables discovery of low Cd accumulating or the tolerant genotypes from the large germplam pool. Further, modern plant omics technologies combined with genetic improvement schemes will facilitate the identification of crucially-important QTLs/candidate genes contributing to Cd tolerance and also, the transfer of desirable QTL alleles or causative genes into agronomically superior yet Cd susceptible cultivars. Additionally, GE techniques will greatly aid in precisely improving the Cd tolerance related genes across the plant kingdom. Besides, the GE can potentially be applied as a phytoremediation tool to effectively remove Cd from the contaminated soil (Takahashi et al. 2014). We hope that the novel plant breeding methods strengthed by modern technological interventions will help address the enormity of global Cd toxicity in soil and crops, thereby protecting human lives from Cd related disorders worldwide.

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Compliance with ethical standards

Conflicts of interest The authors declare that there is no conflict of interest.

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