ROLE OF GENETIC FACTORS IN REGULATING CADMIUM UPTAKE, TRANSPORT AND ACCUMULATION MECHANISMS AND QUANTITATIVE TRAIT LOCI MAPPING IN RICE. A REVIEW

RASHEED, A.[1] – FAHAD, S.[2] – AAMER, M.[3] – HASSAN, M. U.[3] – TAHIR, M. M.[4] – WU, Z. M.[1*]

[1]Key Laboratory of Crop Physiology, Ecology and Genetic Breeding, Ministry of Education/Collage of Agronomy, Jiangxi Agriculture University, Nanchang 330045, PR. China

[2]Department of Agriculture, University of Swabi, Khyber Pakhtunkhwa, Pakistan

[3]Research Center on Ecological Sciences, Jiangxi Agricultural University, Nanchang 330045, PR. China

[4]Department of Soil and Environmental Sciences, Faculty of Agriculture, University of Poonch, Rawalaot, Azad Jammu and Kashmir, Pakistan

*[*]Corresponding author
e-mail: wuzm@jxau.edu.cn*

Abstract. Rice is an imperative staple food globally; however, it is a major source of cadmium (Cd) intake for humans. Cd is a heavy metal and it has no biological functions in plant and, thus it causes adverse effects in plant and humans. Thus, it is of the utmost importance to minimize the Cd content in rice to protect humans from its drastic effects. In this review, we discussed the mechanisms related to the uptake and translocation of Cd in rice. *OsNramp*5, *OsHMA3 OsHMA2* are the genes responsible for Cd uptake, translocation, and sequestration in the vacuole, so modification of these genes function result in no uptake of Cd, and leading to reduction in risk of Cd toxicity in rice. The different genetic factors involved in Cd stress and accumulation are shown here and put into several categories according to their function. The identification of novel QTLs (*qSH6*, *qSH7* and *qLR3*) detected for morphological traits could be cloned and transferred to develop Cd resistant rice lines. Use of mapping population and some putative quantitative traits loci related to uptake and transport could provide strong base to develop the Cd tolerant genotypes. In addition, use of different agronomic practices may be more fruitful to minimize Cd in rice.
Keywords: *cd, master assisted selection, QTLs, agronomic practices, toxicity*

Background

Cd is heavy metal and has no biological role in plants, therefore, it has a high rate of mobility in living things, especially in humans (Song et al., 2015). Heavy metals and mineral oil are the major pollutants causing the soil contamination globally. Globally, it has been reported that about 820 metric tons per year Cd released into the environment through the weathering of soils, volcanic eruptions (Cook and Morrow, 1995; Hayat et al., 2019). Additionally, human activities also responsible for the addition of more than 8000-10,000 mt Cd per year in our environment (WHO, 1992). The chief sources of Cd entry into our environment includes, chemical fertilizers, sewage sludge and effluents, Cd manufacturing, and run-offs of agriculture (Xue et al., 2014). Cadmium is of great concern, because it enters in the plant leaves in higher quantity and therefore can easy enter in the food chains is (Zu et al., 2005). The excess of Cd cause severe implications in humans, including the dys-functing of kidneys and lungs. Additionally, Cd also cause

kidney cancer, breast cancer, failure of heart, hypertensions, proteinuria, eyes cataract, emphysema and renalin sufficiency (Nawrao et al., 2006; Godt et al., 2016). The WHO, has suggested the tolerable weekly intake for the Cd is 7 µg/kg of body weight. This tolerable weekly intake accounts for 60 µg and 70 µg for an average 60 kg and 70 kg man and woman per day (WHO, 1992). Additionally, the concentration of cd in different food stuff has been given in the *Table 1*.

**Table 1.** *Concentration of Cd in different food stuff*

Food stuff	Cd concentration (µg/kg)
Sunflower	375
Spinach	117
Potato chips	93
French fries	44
Roasted peanuts	45
Wheat Cereal	51
Peanut butter	53
Leaf lettuce	62

Spungen, 2019

In China about 2.786×109 m^2 of agricultural land is contaminated by Cd (Liu et al., 2014). Third major pollutant of supreme hazard to the environment after mercury and lead is Cd and is considered as the only metal that has health threats to humans and animals at the concentration that is usually not phytotoxic (Ismael et al., 2019). Cd due to its non-essential nature and it causes several deleterious changes in, physiology, biochemistry and morphology of plants even at low concentrations (Song et al., 2015). Reduction in plant growth, development, chlorosis and finally plants death are the most critical symptoms observed under Cd toxicity (Ashraf et al., 2015).

In China, heavy doses of nitrogen resulted in more acidic and Cd contaminated soils. Cadmium is released from industrial wastes, and sewage irrigation (John et al., 2007; Pandey et al., 2007). Globally, more than 50% world's population consumes rice as a daily diet (Li et al., 2012b; Song et al., 2015). Therefore, Cd simply moved from soil to rice grains and entered into the human body (Aziz et al., 2015; Xie et al., 2015) and causing several deadly diseases including cancer, heart failure, hypertension and eye cataract formation. Cadmium was responsible for the occurrence of Itai-Itai disease in Japan in 1950s, via consumption of Cd contaminated rice (Horiguchi et al., 1994). Moreover, from 1990-2015, the normal consumption of Cd in diet in the Chinese population was more than double (Song et al., 2017; Chen et al., 2018). Schematic display of Cd uptake in soil is shown below in *Figure 1*.

In order to prevent human health from Cd toxicity, reliable steps should be taken to reduce Cd from rice gains, including agronomic practices, like water management, tillage management and fertilizer management. One of the most powerful techniques to decrease the bioavailable Cd in rice is in situ immobilization of Cd (Homa et al., 2016). Absorption, cation exchange and surface complexation are primary mechanisms of Cd immobilization mediated by agronomic practices (Shaheen and Rinklebe, 2016). Efforts have been made to introduce a novel and cost-effective approaches. In recent studies conducted by Shaheen and Rinklebe (2016) and Li et al. (2017) revealed that lime stone and sugar beet industry meaningfully reduced the cadmium solubility because of higher contents of total calcium carbonate and alkalinity.
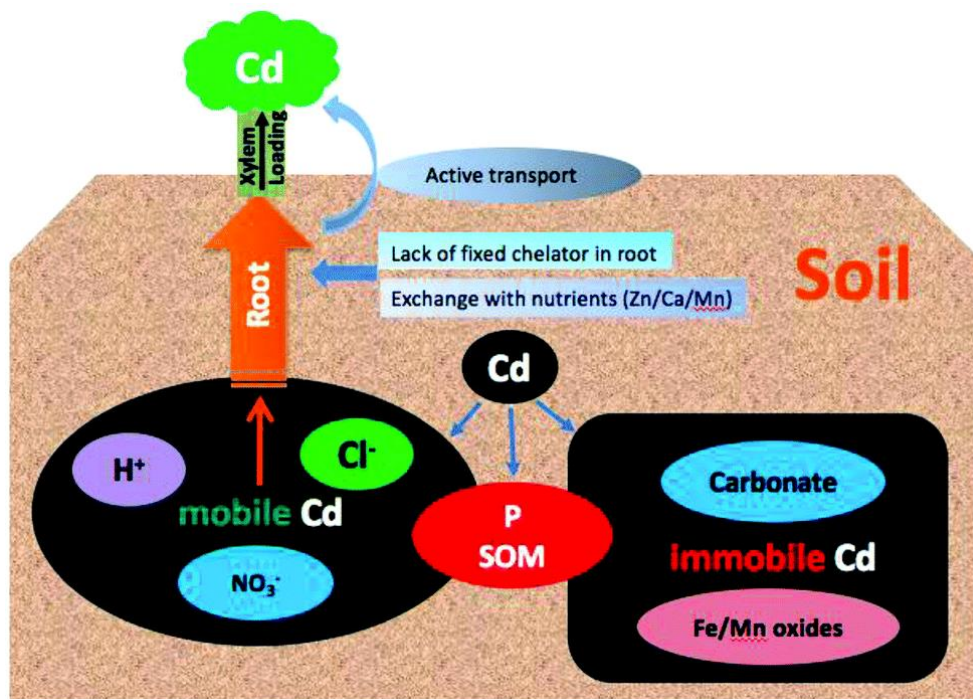
Figure 1. Factors affecting the Cd uptake from the soil (adopted from Huang et al., 2017)

Biochar application decreased the concentration of Cd as studied by Rinklebe et al. (2016). Use of fertilizers can also alter the soil characteristics like, surface charge, pH, but sometime it directly interacts with soils Cd. Use of fertilizers of phosphate, MPP (potassium phosphate monobasic), TCP (calcium phosphate tribasic), DAP (diammonium phosphate) and SSP (calcium super phosphate on) decreased the bioavailable Cd in soil as evidenced by Yan et al. (2015) and Li et al. (2017). Thirdly, water management had a key part in reducing the Cd availability in soil by changing (redox potential) and pH of soil (Li et al., 2015; Homa et al., 2016). Some of the recent findings of experiments (pot and field) presented that use of flooding before & after the heading significantly decreased cadmium concentration in rice, while Cd concentration enhanced under aerobic condition (Hu et al., 2015). Hence, stage of heading in rice stage is a crucial time for lowering Cd entrance. Use of water managing technique would be a cheapest & cost-effective plan to reduce Cd assimilation in rice. Crops rotations, inter-cropping and tillage managing changed the soil, physical, chemical, and biological properties and therefore can reduce Cd uptake in rice as reported by Liu et al. (2016), Li et al. (2017) and Chen et al. (2019). High concentration of organic matter in reduced tillage soil, produced due to deposit of previously grown crops, could increase the adsorption & complexation of Cd. Guo et al. (2010) reported a decrease in Cd in rice by application of reduced tillage management practice because of the decrease of microbial activity. Bioremediation is environmental friendly and cost-effective technique to eliminate the heavy metals from a contaminated environment, which involve the use of certain microorganisms to treat the contaminated soils to retain to its healthy state (Gaur et al., 2014). Phyto-extraction is most cost effective and novel technique for elimination of heavy metals and metalloids from polluted oils and water. Cd tolerant plant species that can absorb high concentration of Cd can be used for this strategy (He et al., 2015). Some of the indica rice cultivars have the capability to accumulate the Cd up to the

concentration of 3.9 mg kg^{-1} in grains by using phyto extraction technique. Indica rice variety, Chokoukoku tested for two years and showed a reduction of 883 g Cd ha^{-1}, and reduced Cd in japonica rice grown later with reduced yield (Murakami et al., 2009). It is therefore more viable strategy to use rice cultivars with high contents of cadmium for remediation of contaminated paddy fields. Soil microorganism have strong interaction with plants and can influence plant growth and nutrients mobility, therefore understanding the complex interaction between soil microorganisms and plant is necessary for best results of phyto-remediation (Muehe et al., 2015; Li e al., 2017). Liu et al. (2015) showed that use of plant growth promoting rhizobacteria (PGPR) can improve plant tolerance to heavy metals. They used roots of cadmium accumulating plants, and isolated 9 strains of cadmium tolerant plant growth promoting rhizobacteria and discovered that cadmium hyper-accumulator (S. plumbizincicola) treated with Rhodococcus erythropolis *NSX2* and Cedecea davisae *LCR1* showed better growth and more cadmium accumulation in shoots. Together all of these agronomic practices are highly recommended to reduce Cd in rice for decreasing human health risk and to sustain rice production on Cd effected soils.

QTLs mapping is one of the most powerful technique to locate the gene of interest on chromosomes. Use of different mapping population is an economically sustainable approach to enhance rice production under cadmium stress conditions (Xue et al., 2009). To screen cadmium tolerant genotypes at seedling stage by using different levels of Cd stress in hydroponic condition is more viable way. Cd toxicity tolerance in rice at morphological, physiological and biochemical has been widely investigated. Use of agronomic practices is an important strategy to minimize Cd in rice (Li et al., 2017). Genetic factors regulating cadmium uptake and transport should need to understand to minimize cadmium contents in grains (Chen et al., 2019). The present review focused on understanding the genetic basis of Cd stress, uptake, accumulation and transportation in rice and to suggest the ways to improve rice tolerance against the Cd toxicity. There are several QTLs reported being responsible for Cd accumulation and for breeding Cd free rice cultivars. We need to transfer these QTLs via markers-assisted selection (MAS selection) along with the alleles with novel functions to accumulate low Cd in rice. The development of Cd resistant rice lines and identification of unknown transporters would be more useful to grow rice on Cd affected soils to maintain production to ensure the food security.

Survey methodology

The papers reviewed in this review paper were obtained from the diverse databases and the professional websites. We conducted a survey in the Google scholar, web of science, science direct, PubMed, CAB abstracts, Springer, Taylor and Francis using different keywords including rice, cadmium, genes, QTLs, Cd transport, Cd accumulation, mass selection, Cd stress, Putative QTLs, efflux protein and molecular mechanism to obtain any relevant information regarding, toxic effects of Cd, and genetic factors in regulating the cadmium uptake, transport and accumulation mechanisms in rice.

Rice growth under Cd stress

Cd toxicity is worldwide problem for crop growth and environmental safety (Aamer et al., 2018). Rice germination and growth is badly affected by Cd stress (He et al., 2006; Liu et al., 2014, 2019a), and exposure of rice seeds to Cd for a long time resulted in lower

germination (Ahsan et al., 2007), and it also leads to chlorosis and necrosis in rice (Ishimaru et al., 2006). Moreover, Cd stress also caused different physiological as well as physical changes in rice including the reduction in seedling length, number of roots and shoots (Kanu et al., 2017). Cadmium stress affects the stomatal conductance in rice (Li et al., 2012b), absorption and transport of important nutrients in rice crop (Li et al., 2012a, 2012b), and thereby results in severe reduction in final production and grain nutrient contents (Mahmood et al., 2006; Abin and Prasad, 2014; Kanu et al., 2017). Rice cope with Cd toxicity by possessing numerous strategies at molecular and physiological levels (Zhang et al., 2018; Islam et al., 2019).

Plants have mechanisms including the accumulation of Cd in cell wall and vacuole of root cell, which enable them to stop the transportation of Cd from root to shoots and thus leads to reduction in the corresponding effects of Cd on other cells (Fu et al., 2011; Qiu et al., 2011). Many ATP binding-cassette (ABC) protein facilitates the vacuolar spreading of Cd-glutathione in Arabidopsis thaliana (Kim et al., 2007). Rice genes (*OsPDR5/ABCG43*) are responsible to hold ABC-type proteins, which favors the Cd extrusion from the cell cytoplasm (Oda et al., 2011). Cadmium transporter (*OsHMA3*) in membranes of the vacuole in rice roots can enhance rice tolerance to Cd and lessen the accumulation of Cd in rice grains (Ueno et al., 2010a; Ke et al., 2015). The vacuoles inside the plants are targeted by detoxification of metal due to chelated toxic metals (Hall, 2002; Haydon and Cobbett, 2007). Organic acids including malate and citrate are accountable for uptake and long-distance transportation of metals into plant vacuoles (Verbruggen et al., 2009; Revathi and Venugopal, 2013). Chelators played a key role in forming a barrier against Cd accumulation (Nocito et al., 2011). Plants boost the antioxidant defense system to improve tolerance against Cd stress (Hassan et al., 2005; Zhao et al., 2013). The concentration of various substances including, glutathione, salicylic acid, jasmonic acids and nitric oxide considerably increased on exposure to Cd stress (Wang et al., 2011; Asgher et al., 2015). Mitogen-activated protein kinase *OsWJUMK*1, *OsMSRMK2* regulates auxin signal fluctuations which result in disruption of rice root growth exposed to Cd stress (Agrawal et al., 2003; Zhao et al., 2013). Cadmium stress response and root development are associated with auxin transporter *OsAUX1* in rice (Yu et al., 2015). Cadmium accumulation and uptake are reduced by the application of iron, zinc and silicon (Hermans et al., 2013; Chen et al., 2018). Cadmium pathway from roots towards shoots shown in *Figure 2*.
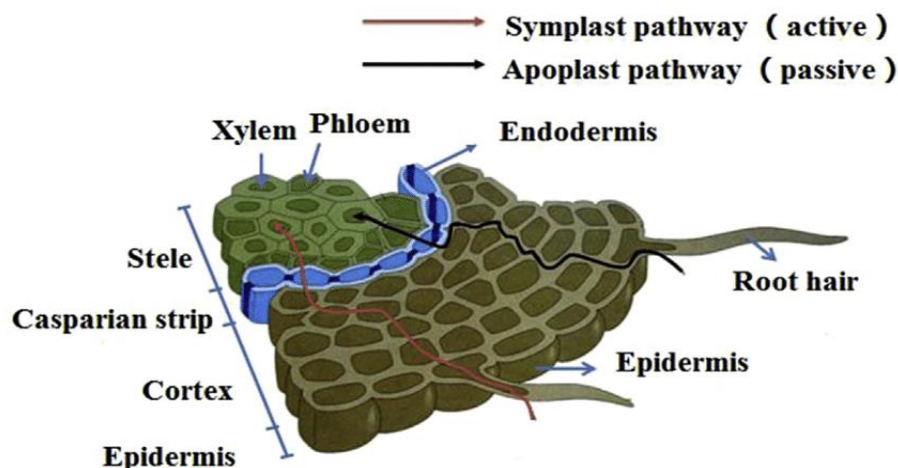

*Figure 2. Cd pathway from roots towards shoots (adopted from Li et al., 2017)*

Some important Cd tolerance genes are shown below (*Table 2, Figure 3*). *OsHMA*9 is an important copper (Cu) efflux protein, present in the plant plasma membranes; this protein favors the efflux of Cd from the plant roots, therefore, leads to a substantial reduction in the Cd accumulation in rice grains (Lee et al., 2007). Knockout of a low Cd gene (LCD) decreased Cd accumulation and therefore improves the rice growth in Cd stressed conditions, and low Cd gene is a protein linked with Cd equilibrium (Shimo et al., 2011). Arabidopsis thaliana plant growth under Cd stress enhanced by *OsCDT1* owing to fact; cysteine rice rich peptide encoded by *OsCDT1* improved the rice tolerance against the Cd stress (Kuramata et al., 2008). *OsCLT1* probably responsible for normalizing the transfer of glutamylcysteine and glutaione plastids to cytoplasm, which therefore, effects Cd reclamation in rice (Islam et al., 2019). A schematic display of cadmium transport from soil towards rice grains is shown in *Figure 4*.

Table 2. *Putative genes expressed in rice in response to Cd stress*

Gene	Chr	Location	Genotype	Screening	Gene name	Role	References
OsIRT2	3	26276301–26277206	Rice	Hydroponic	Iron-regulated transporter	Cd and Fe transporter	(Nakanishi et al., 2006)
OsIRT1	3	26286156–26292023	Rice	Hydroponic	Iron-regulated transporter	Cd and Fe transporter	(Lee and An, 2009)
OsNramp5	7	8871436–8878905	Rice	Hydroponic	Natural Resistance associated Macrophage protein	Cd, Mn and Fe Transporters	(Ishimaru et al., 2012)
OsNramp1	7	8966025–8970882	Rice	Hydroponic	Natural resistance-associated macrophage protein	Cd and Fe transporters	(Takahashi et al., 2011)
OsZIP1	1	42905566–42907474	Rice	Hydroponic	Zinc- and iron-regulated transporter	Cd and Zn transporter	(Ramesh et al., 2003)
OsHMA3	7	7405745–7409553	Rice		P-Type Heavy Metal ATPase	Sequestrate Cd in the plant roots	(Ueno et al., 2010b)
OsHMA2	6	29477949–29480905	Rice	Hydroponic	P-Type Heavy Metal ATPase	Cd and Zn translocations	(Takahashi et al., 2012)
OsZIP7	5	6090801–6094068	Rice	HS/field screening	Zinc- and iron-regulated transporter	Cd and Zn accumulation	(Tan et al., 2019)
OsLCT1	6	22566775–22571982	Rice		Low affinity cation transporter	Cd transporter in phloem	(Uraguchi et al., 2011)
OsMTP1	5	1675488–1679056	Rice		Metal tolerance protein gen	Cd translocation	(Yuan et al., 2012)
OsZIP6	5	3807974–3810752	Rice	Hydroponic	Zinc- and iron-regulated transporter	Cd transport	(Kavitha et al., 2015)
PEZ1	3	20793053–20799805	Rice		Phenol efflux protein	Cd accumulation	(Ishimaru et al., 2011)
OsCDT4	2	6078179–6079111	Rice	Hydroponic	Encoding a Cys-rich peptide	Cd uptake inhibitor	(Kuramata et al., 2008)
OsMSRMK3	6	29398191–29402466	Rice	Invitro/vivo	Mitogen-activated protein kinase	Cd signal	(Agrawal et al., 2003)
OsABCG43	7	20214025–20218702	Rice		ATP-binding cassette transporter	Cd compartmentalization	(Oda et al., 2011)
OsCLT1	1	42086484–42095424	Rice	Hydroponic	CRT-like transporter 1	Cd tolerance	(Yang et al., 2016b)
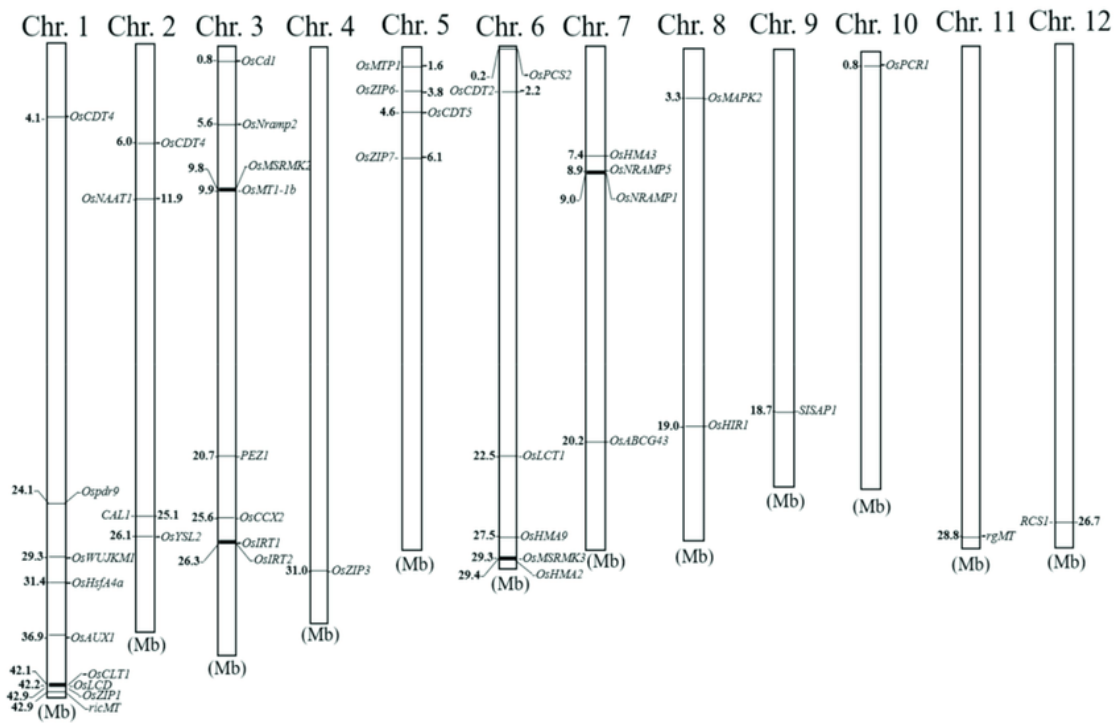
Figure 3. Physical location of genes related to Cd toxicity tolerance in rice (adopted from Chen et al., 2019)
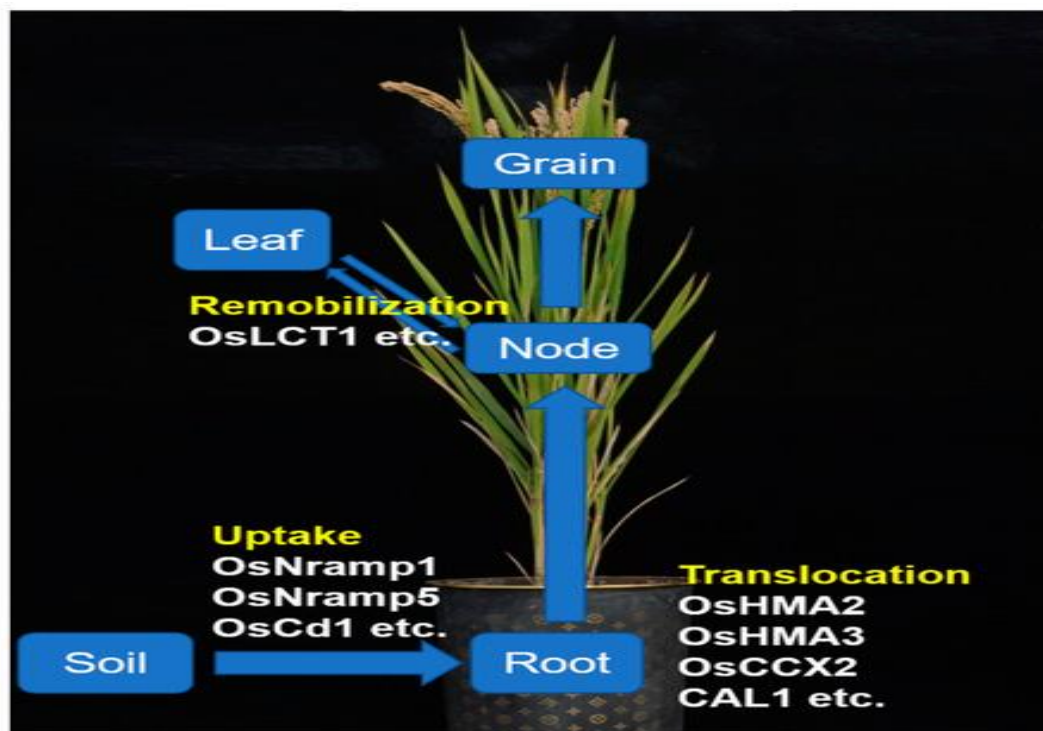
Figure 4. Shows how Cd moves from soil to roots. First cadmium moves from soil to root and grains and this process is mediated by the genes (OsNramp1, OsNramp5, and OsCd1) (adopted from Chen et al., 2019)

Rasheed et al.: Role of genetic factors in regulating cadmium uptake, transport and accumulation mechanisms and quantitative trait
loci mapping in rice. A review
- 4012 -

Cd uptake and transport mechanism in rice

Cd uptake and transport pathway in rice plant include these four steps: (i) uptake via roots; (ii) transportation to shoots via xylem tissues (iii) circulation and transport by the plant nodes (iv) Cd passage to grains from leaf blades by the phloem as shown in *Figure 4* (Chen et al., 2019). The *Figure 4* shows, how Cd moves from soil to roots. First cadmium moves from soil to root and grains and this process is mediated by the genes (*OsNramp1*, *OsNramp5*, and *OsCd1*) as shown in *Figure 4* (Chen et al., 2019).

Cd tolerance genes in rice

Mechanisms of uptake of some important elements (Mn, Zn, and Fe) which are responsible for Cd entrance into rice plants is described by (Abin and Prasad, 2014; Islam et al., 2019). Cadmium efflux activity in yeast is shown by iron transporters (*OsIRT1 and OsIRT2*) which shows that *OsIRT*1 and *OsIRT2* may have a role in the uptake of Cd in the root system (Nakanishi et al., 2006; Abin and Prasad, 2014). Expression of *OsIRT1* considerably improved the Cd in roots and shoots in MS medium presented by Murashige and Skoog with surplus Cd but no noticeable phenotype was detected under field conditions, proposing that *OsIRT1* may be responsible for Cd uptake in rice but environment had enormous effects on its contribution (Lee et al., 2007; Lee and An, 2009). Cadmium uptake in rice roots owing to natural resistance associated with macrophage protein *5 OsNramp5* which is accountable for the transport of Cd from soil solution to root cells (Ishimaru et al., 2012; Sasaki et al., 2012). A researcher recently identified the main quantitative traits loci (*qGMN7.1*) for Cd tolerance (Liu et al., 2017). New most effective lines of rice with less Cd accumulation have been developed by bumping out the metal transporters (*OsNramp5*). Using (CRISPR/CAS9) system, a chain of *indica* rice lines having the capability of accumulating low Cd were developed. *OsNRAMP1* genes located on the plasma membrane participated in Cd transport activity in roots cells (Takahashi et al., 2011; Islam et al., 2019). Yeast sensitivity to Cd is increased by the function of *OsZIP1*; a zinc-regulated/iron-regulated transporter-like protein (Ramesh et al., 2003), and Cd uptake in Xenopus leaves oocytes could be enhanced by *OsZIP6* overexpression (Kavitha et al., 2015).

The key factor defining the Cd accumulation in shoots is xylem-mediated Cd translocation (Uraguchi and Fujiwara, 2012), and *OsHMA2* and *OsHMA3* (Yamaji et al., 2013; Kavitha et al., 2015). Transport of Cd from roots to shoots is controlled by *OsHMA2* and it has important role in regulating the spread of Cd via phloem to developing tissues (Takahashi et al., 2012). *OsHMA3* has the main part in vacuolar requisition of Cd in cells of the root, the over-expression of *OsHMA3* decreases the Cd burden in the xylem and Cd accretion in the plant shoot. Moreover, the *OsHMA3* deficiency leads to higher Cd concentration both in plant roots and shoots (Ueno et al., 2010a). *OsZIP7* has substantial role in the xylem loadings in the roots, and to bring the Cd and Zn in the upper parts of rice (Tan et al., 2019). Cadmium transfer from xylem to phloem by the plant nodes has imperative part in the Cd transportation to grains (Fujimaki et al., 2010). *OsLCT1* is a Cd efflux carrier located on plasma membrane and accountable for phloem Cd transportation (Uraguchi et al., 2011). *OsLCT1* expression was found to be higher in nodes and leaf blades during the propagative period, particularly in node I. The Cd concentration in the rice grains, as well as the exudates of phloem in RNAi plants were appreciably decreased compared with wild plants, however, the Cd concentration in the xylem sap remained same in both plants. The current outcomes indicated that *OsLCT1*

genes in the leaf blade of plants help in re-mobilization of Cd by the phloem. Moreover, in node I, *OsLCT1* has an important part in the intra-vascular Cd translocation, which involves in translocation of Cd from a larger vascular bundle to diffused ones attached with the panicle (Uraguchi et al., 2011). *Figure 3* and *Table 2* showed positions of cloned cadmium stress-related genes in rice chromosomes.

Molecular mechanism behind Cd accumulation

The major transporter for Cd in rice roots is *OsNramp5* family (Sasaki et al., 2012), which is the transporter of divalent cations like, Fe and Cd (Supek et al., 1996), while one *OsNrat1* transfer toxic aluminum in rice (Xia et al., 2010). *OsNramp5* is also controlled Mn uptake in rice (Sasaki et al., 2012). The knockout of this gene results in complete loss of Cd uptake which showed that this gene is responsible for Cd uptake. *OsIRT1* and *OsIRT1* are also responsible for Cd uptake in rice (Nakanishi et al., 2006). Ample NO_3 enriched Cd efflux in the elongation zone of rice roots by enhancing *OsIRT1* expression causes more uptake and accumulation of Cd in rice grains (Yang et al., 2016a). The second important step is vacuolar sequestration of Cd in rice roots. *OsHMA3* a major member of heavy metals family involved in this process. This gene was isolated from large QTLs located on the short arm of chromosome 7 resulting from the cross a cross among *indica* cultivar (Anjana Dhan) which contains more Cd contents in grain, and second japonica cultivar (Nipponbare) with lower contents of cadmium (Ueno et al., 2009). *OsHMA3* is mostly expressed in the roots, and its expression is not affected by Cd exposure. A recent study showed that the novel function of *OsHMA3* named as zinc carrier (Sasaki et al., 2014).

The third step is root to shoot translocation of Cd. *OsHMA3* was studied to be accountable for translocation from root to shoot in rice (Yamaji et al., 2013). This gene is localized in the plasma membrane and pericycle of roots. The knockout in the activity of this gene caused a decrease in Cd accumulation in yeast. The final stage of this mechanism is Cd accumulation in rice grains. *OsHMA2* is responsible for Cd distribution in rice grains, more importantly, its functions appeared to be stronger at the reproductive stage in node 1; *OsHMA2* is present at the phloem of enlarged and diffuse vascular bundles in node 1 (Yamaji et al., 2013). The knockout of *OsHMA2* resulted in the reduction in the concentration of Zn and Cd in upper nodes and reproductive organs compared with wild-type rice. *OsLCT1* (*Oryza sativa*) low-affinity cation transporter 1 involved in the intravascular transfer of Cd. *OsLCT1* is localized in the plasma membrane and represents efflux carrying activity for Cd and K, and not for the Fe and Na (Uraguchi et al., 2011). The knockdown of *OsLCT1* resulted in a reduction in Cd concentration in phloem and grains (Uraguchi et al., 2011). Expression of *OsLCT1* in the nodes was only observed at the ripening stage as compared to *OsHMA2* which expressed in nodes throughout the reproductive stage.

Putative QTLs in response to Cd stress in rice

Rice genotypes have significant genetic diversity regarding their ability to Cd accumulation and tolerance which stated the scope of selection (Liu et al., 2003; He et al., 2006). Genetic factors controlling Cd assimilation in rice have scanty described. *OsHMA3* encodes a Cd transporter found in the membrane of vacuoles, which favors the Cd segregation in the vacuole (Liu et al., 2019a). The reduction in *OsHMA3* functioning frequently enhanced Cd transfer in shoots and grains of rice (Abe et al., 2013; Liu et al., 2019a). *OsHMA*3 improves Cd tolerance in the rice plant and reduces the Cd accretion in

the rice kernels (Ueno et al., 2010a; Sasaki et al., 2014). A gene *OsCd1* from major facilitator superfamily was identified by Yan et al. (2019) through genome-wide association analysis (GAWS) which has an association with the variation for Cd assimilation in rice. Two quantitative traits loci governing the Cd application in brown rice stated by Sato et al. (2011) *qLCdG11* contributed to 9.4–12.9% phenotypic variance and *qLCdG3* contributed 8.3–14% phenotypic alterations. Yan et al. (2013) made a RIL population of F₇ to recognize Cd cadmium assimilation and dispersal. Abe et al. (2013) studied population containing 46 CSSL (chromosome segment substitution lines) and detected 8 quantitative traits loci correlated with Cd contents in grain by single-label analysis of variance). Additional different genes QTLs expressed in the rice exposed to Cd stress are given in *Table 3*.

Table 3. *Putative QTLs express during the rice exposure to the Cd stress*

Parents	Population	Stage	Traits	QTLs	Marker	Chr	Ref
Nipponbare/Anjana Dhan	965 F2	Seedling stage	Cd concentration in shoot	*OsHMA3*	SSR	7	(Ueno et al., 2010b)
SNU-SG1/Suwon490	91 RIL	Seedling stage	Cd concentration in shoot	*scc10*	124 SSR	10	(Yan et al., 2013)
Koshihikari/LAC23 46 CSSLs	46 CSSLs	Seedling stage	Cd concentration in shoots	*glGCd3*	345 SNP	3	(Abe et al., 2013)
Anjana Dhan/Nipponbare	177 F2	Seedling stage	Root-to-shoot Cd translocation	*qCdT7*	SSR	7	(Ueno et al., 2009)
Tainan1/Chunjiang06	119DH,3651 BC3F3	Seedling stage	Cd accumulation in leaves	*CAL1*	RFLP	1	(Luo et al., 2018)
JX17/ZYQ8	127 rice cultivars	Maturing stage	Cd accumulation in grains	*OsCd1*	GWAS	3	(Yan et al., 2019)
Sasanishiki/Habataki	85 BIL	Maturing stage	Cd accumulation in grains	*qGCd7*	SSR	2,7	(Ishikawa et al., 2009)
Fukuhibiki/LAC23	126 RIL	Maturing stage	Cd accumulation in grains	*gLCdG3, gLCdG1*	454 SNP	3,11	(Sato et al., 2011)
SNU-SG1/Suwon490 91 RIL	91 RIL	Maturing stage	Cd accumulation in grains	*gcc3, sgr5*	124 SSR	3,5	(Yan et al., 2013)
Xiang 743/Katy	115 RIL,	Maturing Stage	Cd accumulation in grains	*qCd-2, qCd-7*	SSR GWA	2,7	(Liu et al., 2019b)
JX17/ZYQ8	378 rice cultivars	Maturing Stage	Cd accumulation in grains	*qCd3, qCd5.*	GWAS (Statistical approach)	3,5	(Hosseini et al., 2012)

Chr: chromosomes, Ref: references, RIL: recombinant inbred lines, DH: double haploid, BIL: backcross inbred lines population, CSSL: chromosomal segment substitution lines, SSR: single sequence repeat, RFLP: restriction fragment length polymorphism, SNP: single nucleotide polymorphism, GWAS: genome wide association study

Identification of QTLs is response to Cd toxicity in rice at seedling stage

Use of mapping population in to identify the putative QTLs in rice regarding Cd toxicity tolerance, has been a fruitful way to screen resistant rice genotypes. Significant difference among the rice genotypes in Cd tolerance at seedling stage has been widely studied (Cheng et al., 2006; Yu et al., 2006; Xue et al., 2009; Ding et al., 2018). Recently lots of genetic factors have been identified controlling Cd tolerance in rice at seedling stage. Evaluation of rice genotypes in hydroponic condition using different levels of Cd

stress is an economically sustainable approach to increase rice production (Ding et al., 2018).

Xue et al., (2009) conducted a hydroponic experiment and reported some of the functional QTLs (*qSH6, qSH7, qRL1, qCDS7*) in rice explaining 9.11%, 14.36%, 8.11% and 0.12% of the phenotypic variance. Positive additive effect was shown by the QTLs for shoot height and allele was contributed by donor parent. These results suggested their novel role in increasing cadmium tolerance at seedling stage. A QTL *qCD7* was involved in reducing CD concentration in rice. Wang et al. (2018) identified a cadmium tolerance QTL *qGLR3* for leaf rolling in rice and concluded that this region had novel contribution in response to cadmium stress n rice. Additionally, another major QTL *qLR1* was responsible for controlling leaf rolling in DH population of rice at seedling stage. Defection of QTLs for cadmium toxicity tolerance for morphological traits are rarely reported in rice, however use of high-resolution mapping population, and use of different levels of Cd in hydroponic condition would be an effective method to identify the putative QTLs controlling Cd tolerance at seedling stage. Hence Cd tolerance could be increased using an effecting nutrient solution and secondly genetically divergent parents to construct progeny to be evaluated in cultural solution *Table 4*.

Table 4. *Some of the novel QTLs identified in rice for morphological traits in hydroponic environment*

Parents	Progeny	Indexes	QTLs	Stage	Markers	Chr	Ref
ZYQ8/JY17	127DH	SH	qSH6	seedling	160RFLP	6	Xue et al., 2009
ZYQ8/JY17	127DH	SH	qSH7	seedling	160RFLP	7	Xue et al., 2009
ZYQ8/JY17	127DH	RL	qRL1	seedling	160RFLP	1	Xue et al., 2009
ZYQ8/JY17	127DH	CDS	qCDS7	seedling	160RFLP	7	Xue et al., 2009
ZYQ8/JY17	27DH	LR	qGLR3	seedling	83SSR/160RFLP	3	Wang et al., 2018
ZYQ8/JY17	27DH	LR	qLR1	seedling	83SSR/160RFLP	1	Wang et al., 2018
ZYQ8/JY17	27DH	GLR	qLR9	seedling	83SSR/160RFLP	9	Wang et al., 2018

DH: double haploid, QTLs: quantitative traits loci, Chr: chromosomes, Ref: references, RFLP: restriction fragment length polymorphism, SSR: single nucleotide polymorphism, SH: shoot height, LR: leaf rolling, GLR: green leaf ratio, CDS: cadmium concentration

Conclusion and future research direction

Globally, Cd toxicity is a serious threat to living organisms especially humans (Aziz et al., 2015). The different agronomic practices like tillage, nutrients management, water management, use of fertilizers could be adopted to minimize Cd uptake in rice (Li et al., 2012b; Kanu et al., 2019). Many genetic factors involved in Cd uptake and accumulation have been identified and fruitful progress has been made in this aspect. The factors affecting uptake and accumulation of Cd needs to be understand to make strategies for reducing Cd toxicity. The identification of more unknown transporter and molecules is an urgent need to understand the way through which Cd is accumulated in rice grains. The use of biotechnological tools is important for this and genes (*OsNramp5*) mutation (*OsNramp5*) result in a noticeable reduction in the accumulation of Cd in rice grains (Ishimaru et al., 2012). Many transporters need to be recognized in future studies by using different techniques. Cd efflux transporters in rice roots exodermis and endodermis cells are accountable for xylem unloading and phloem loading of Cd, however, these was not still studied. There is no specific transporter involved in Cd accumulation but these are the transporters belong to other metals, like Mn (*OsNramp5*) and Fe (*OsHMA2*). We

cannot use these genes for developing new rice varieties but there is a need to screen new alleles with new functions to develop resistant varieties to Cd toxicity.

A hybrid cultivar of rice was developed which has low contents of Cd in rice grain (Tang et al., 2017). The accumulation and translocation of Cd were reduced by overexpression of functional *OsHMA3* (Ueno et al., 2009). Three rice mutants were made by (Ishikawa et al., 2012) using carbon ion-beam irradiation and in these mutants, Cd was not recognized when grown on the Cd stress conditions, additionally, and there was no pronounced difference among the wild and mutants. The use of markers assisted selection is one of the best strategies to identify the locus governing Cd accumulation in rice. Transfer of QTLs from a low Cd cultivar to a cultivar with higher contents of Cd could be a significant approach (Uraguchi and Fujiwara, 2012). Few genetic factors regarding Cd accumulation have been recognized and cloned (Ueno et al., 2010a) but natural variation in alleles of Cd grain accumulation among the varieties has not fully understood.

The present review suggested to do more investigation on the identification of QTLs controlling Cd accumulation in grain essential to clone further QTLs governing grain Cd accumulation and use of the theoretical base for MAS (markers assisted selection) to develop rice varieties with low Cd contents. Secondly, identification of unknown transporters is a fruitful approach to find the novel function and built a barricade against Cd uptake and accumulation in rice grains. Some of the novel QTLs (*qSH6, qSH7 and qLR3*) reported for morphological traits should be transferred to develop Cd resistant lines in rice. Hence use of mapping population and screening of genotypes at seedling stage in hydroponic environment would be a powerful way to reduce Cd toxicity in rice. There are a lot of QTLs reported being responsible for Cd accumulation and for breeding Cd free rice cultivars we need to transfer these QTLs via MAS selection. For instance, Identification of quantitative traits loci from a low cadmium accumulating cultivar and then transfer this QTL to high Cd cultivar may be a more feasible way to decrease Cd accumulation in rice. Additionally, specific farms practices should be adopted to prevent the entry of Cd in soils. Futuristic studies should be aimed to understand the Cd uptake and translocation in diverse soils and its interference with Fe and Zn pathways. Moreover, develop the scrutiny system Cd in crops and reduce the allowable Cd in the fertilizers. Moreover, understand the bio-available fractions of Cd from the different food stuffs and factors influencing the Cd absorption in human body.

Competing Interests. All authors declare that there are no competing interests.

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Rasheed et al.: Role of genetic factors in regulating cadmium uptake, transport and accumulation mechanisms and quantitative trait
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