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In silico analysis of functional linkage among arsenic induced MATE genes in rice

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ABSTRACT

MATE genes play an important role in cellular detoxification processes. Nine MATE genes were identified by a transcriptomics study previously. Candidate gene prioritization was done where 29 new genes were found to interact with 09 guide genes. Therefore, a total of 38 genes were analyzed here to predict a concise model by gene prioritization study. Those genes were analyzed further in Rice Interactions Viewer programme, and based on high ICV, 10 new genes were found to interact among themselves at protein level. Surprisingly, only 05 genes were found to play a key role at protein level. These 15 genes were analyzed for their interaction with soil available inorganic arsenic species. Maximum expression levels were found mostly at young inflorescence and seed development stage for those genes. So, these genes may have a direct role in arsenic sequestration from cells and thereby providing safety to the developing embryo within the seed.

1. Introduction

According to the WHO, Arsenic (As) toxicity has been a well-known phenomenon and a matter of great concern for the world where at least 140 million people in 50 countries have been exposed to it. Arsenic, a toxic metalloid commonly present in subsoil has been reported to be a carcinogenic for human [1]. Many a times this carcinogenic metalloid is coming to human and ruminants through a number of agricultural produces being grown in the arsenic contaminated areas but the biological availability, transport, accumulation and toxicity of arsenic are principally decided by its speciation forms (methylated or inorganic) whereas inorganic arsenic species are known to be more toxic than organic arsenic species. Although, As (III) is graded to be more toxic than As (V) but the degree of toxicity can be reduced with the increase in methylation. Very often the symptoms of reduced root and shoot growth are observed in various plant species which are exposed to arsenate [2,3]. Inorganic arsenic species stimulates the production of reactive oxygen species (ROS) such as superoxide radical (O^{2-}), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2) in the plant cellular system whenever exposed with arsenic [4,5]. This reactive oxygen species chemically disrupt different proteins, amino acids and nucleic acids at cellular level and can damage membrane lipids by causing peroxidation [6].

Rice is known to accumulate higher quantity of arsenic than any other cereals [7]. So, there is every chance of entry of arsenic into the food chain through rice where it is the major staple crop. Like other plants, rice also permits the entry of different arsenic species such as arsenate (phosphate analogue) entering through root phosphate transporters and arsenite enters through silicic acid transporter [8]. There are reports of arsenic sequestration as well as uploading in different organs including grain of rice plant following several pathways [9]. It is evident that, neither arsenic contaminated soil nor contaminated irrigation water can be withdrawn from the reported contaminated zones; thereby it becomes compulsory either to breed low arsenic accumulating genotypes or inventing management technologies to ameliorate the physical sources of arsenic in the environment. In order to breed low arsenic accumulating genotypes, understanding the detoxification mechanism as well as revealing the genetic network induced by arsenic is necessary. Various mechanisms of detoxification have been found in plants like sequestration and binding of toxicants, enzyme induction, biotransformation of absorbed compounds, co-substrates and MATE (multidrug and toxic compound extrusion) genes [10]. Multidrug and toxic compound extrusion gene is one of the major detoxifying gene-families present in bacteria, fungi, plants and mammals [11]. Previously MATE genes were reported to detoxify secondary metabolites but presently they are known to extrude organic compound, transport a wide range of organic acids, plant hormones etc. [12]. In 2008, a study was done by Norton *et al.*, to reveal Rice-arsenate interaction in hydroponics. In that study, a whole genome transcriptional

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analysis was conducted through micro-array where a large number of transcription factors, stress related proteins and several other classes of genes were found to show differential expression pattern. Strikingly, nine MATE transporters were also documented by them. Those nine MATE genes were taken into consideration as candidate genes in this present study to find out whether any functional linkage was there among them or with other cellular proteins. Exploring functional linkage would help to understand how these MATE genes are getting influenced by other genes. This would strongly help in defining all the relevant associated genes related to arsenic detoxification. Because targeting only a few key genes may become a futile exercise to create any desired phenotype in routine plant breeding experiments [13,14]. Advancement of molecular genetics suggests that, ultimate phenotype is determined by the genetic network rather than the mere activity of a single or few genes. In this back drop, the present experiments were designed and performed by in silico platforms.

2. Materials and methods

2.1. Mate genes

Norton et al., conducted whole genome transcriptional analysis to know rice-arsenate interaction in hydroponics and the work was published in journal of experimental botany in 2008. This group of researchers conducted the Affymetrix (52 K) Gene Chip Rice Genome array of two rice varieties which were arsenic tolerant and sensitive respectively. After analysis of the genome wide gene expression pattern, several transporter genes were found to be differentially expressed where there were nine identified MATE transporters also. Apropos to that report, those MATE transporters were found to be up and down regulated in rice genotypes were induced by the presence of arsenic. In this present study, these MATE genes were considered as candidate genes of interest for finding the genetic network behind arsenic detoxification. So, these Nine MATE genes happened to be used as guide gene for this study. The guide genes were subjected for analysis through computational biology for the evaluation of the information on functional linkage among the arsenic induced MATE genes (Table 1).

2.1.1. Candidate gene prioritization by Rice netV2

Prioritization of genes helps to predict new candidate gene networks for different phenotypes and biological pathways. In a genetic network, genes which are connected to one another are hypothesized to be functionally associated as candidate genes of the pathway. There are two complementary network prioritization algorithms which are provided by the RiceNet v2 (https://www.inetbio.org/ricenet/) based on network direct neighbourhood and context-associated hubs.

RiceNet maintained by the National Research Foundation of Korea grant (2010-0017649, 2012M3A9B4028641, 2012M3A9C7050151) is supported as a part by the Joint Bioenergy Institute, Office of Biological and Environmental Research, U. S. Department of Energy Under Contract No. DE-aC02-05CH11231, and the Department of Energy Systems Biology Knowledgebase (KBase) is an advanced platform for inventing network prioritization of rice genes. The rice interactome is predicted on the basis of conserved interactions among the proteins across species over the course of evolution where a confidence value (CV) as an internal quality control is assigned. The improved quality of the network and prediction power is given by RiceNet V2 (p-value = 1.11e-6, specified by Wilcoxon signed rank sum test). It is useful for the prediction of both major subspecies of rice, japonica and Indica.

2.2. Rice interaction viewer (bar)

It is well evidenced that protein-protein interactions (PPI) were found to play an important roles in the cellular environment where Co-immunoprecipitation, co-sedimentation and two-hybrid systems were convetionally used to characterize interactions at single protein complex level [15]. Nowadays, high-throughput methods are available for large-scale detection of pairwise interactions (two-hybrid systems, the split-ubiquitin method) [16–18] or multi-protein complexes (TAP-TAG, HMS-PCI) [19–21] and [22]. The Bio-Analytic Resource for Plant Biology (BAR) is a web platform (http://bar.utoronto.ca/interactions/cgi-bin/rice_interactions_viewer.cgi) to access enormous data sets from about 15 different plant species to successfully analyze transcriptomics, protein-protein interaction and promoter data.

2.3. Stitch V5.0

The knowledge about the interactions among the proteins and small molecules is crucial for a better understanding of the molecular and cellular functions like metabolism, signaling, drug treatments as the cases may be. However, information of such interactions is widely available crossways a number of databases and the literatures. STITCH (search tool for interactions of chemicals) has been so developed to integrate information regarding the interactions from metabolic pathways, crystal structures, binding protein experiments and drug–target relationships [23]. This is an integrated platform (http://stitch.embl.de/) for the discovery of interactions which is connected over 300,000 chemicals and 2.6 million proteins from 1133 organisms. [24]

Table 1
List of the nine guide MATE genes and their functions.

Locus Name	Function	Reference
LOC_Os03g37490.1 (MATE efflux family protein)	Transport, membrane, vacuole, cellular process, transporter activity	UniProtKB - Q10HY1
LOC_Os05g48040.1 (MATE efflux family protein)	Transport, membrane, vacuole, cellular process, transporter activity	Rice Genome annotation project
LOC_Os08g37432.1 (MATE efflux family protein)	Transport, membrane, ripening, cellular process, transporter activity	UniProtKB - Q6ZB84
LOC_Os10g20450.1 (MATE efflux family protein)	Transport, membrane, ripening, cellular process, transporter activity, response to biotic stimulus	UniProtKB - Q7XFI4
LOC_Os10g20470.1 (MATE efflux family protein)	Transport, membrane, ripening, cellular process, transporter activity, response to biotic stimulus	UniProtKB - Q7XFI3
LOC_Os12g03260.1 (MATE efflux family protein)	Transport, membrane, cellular process, transporter activity	UniProtKB-Q2QYB0
LOC_Os04g48290.1 (MATE efflux family protein)	Transport, membrane, cellular process, transporter activity	UniProtKB - Q7XU48
LOC_Os09g29284.1 (MATE efflux family protein)	Transport, membrane, ripening, cellular process, transporter activity	UniProtKB - Q6K5E6

Information regarding LOC_Os08g37430 could not be retrieved.
Among these different MATE genes, LOC_Os05g48040 was reported to have some function in arsenic sequestration in stem and in lowering the level of arsenic in grain. LOC_Os10g20470 and LOC_Os12g03260 were reported to have some role in arsenic resistance in rice (Debnath et. al., 2016).

2.4. Rice eFP browser

The electronic fluorescent pictograph (eFP) software is a famous tool for visual display of the transcriptome data and is extensively used for different model organisms. [25] It was developed at the University of Toronto to aid visual examination of gene expression. The function of this software (http://bar.utoronto.ca/transcriptomics/efp_rice/cgi-bin/efpWeb.cgi?dataSource=rice_leaf_gradient) is to exhibit cartoon images for illustrating various tissue types where each tissue is represented with distinguished colors indicating the level of expression for a targeted gene. [25]

3. Results and discussion

3.1. Functional linkage of the mate genes

Finding functionally related genes help in determining the presence of epistasis at molecular level. Such gene interaction models have already been exploited for drug target discovery. In rice, system level gene interaction model may open up the ways for prediction and discovery of genes as well as associated pathways related to environmental stress tolerance and resistance [13,14]. In this present study, novel genetic interaction were predicted from gene prioritization based on context associated hub analysed at RiceNet V2 platform. The nine MATE genes were subjected to gene prioritization study based on context associated hub before network direct neighbourhood study because we assumed them (MATE genes) as differentially expressed genes. According to the protocol of RiceNet V2 prioritization based on context associated hub should be the option for abiotic and biotic stress response gene. Here, 29 new genes were found to interact rather functionally associated with the nine candidate MATE genes which were put as guide genes (Table 2)

The p-value <0.01 indicated that, the model was statistically highly significant. Therefore all these 29 genes were taken into consideration as target genes for designing gene based molecular markers for utilization in marker assisted breeding for further studies.

LOC_Os03g16920 gene encoding the heat shock cognate 70 kDa protein was located in cytoplasm. It is involved in ATP binding, misfolded protein binding and unfolds protein binding. It was also found to show cellular response to heat (UniProtKB - Q10NA1). Protein encoded by the gene LOC_Os03g60620 was also belong to heat shock 70 family and involved in ATP binding activity. It was found to show response to heat stress, cadmium ion (UniProtKB - A0A0E0D8U9). LOC_Os03g16860 gene represents 70 kDa heat shock protein. It give response towards heat stress, cadmium ion stress, response to high

Table 2
List of 29 new candidate genes interacting with 9 MATE gene.

Rank	RGAP locus ID	paralog	gene description	p- value
1	LOC_Os03g16920		response to stress;response to virus;response to heat;response to bacterium; response to cadmium ion	8.16E-10
2	LOC_Os03g60620		response to stress;response to virus;response to heat;response to cadmium ion	9.16E-10
3	LOC_Os03g16860	LOC_Os05g38530	response to stress;response to virus;response to hydrogen peroxide;response to heat;response to bacterium;response to temperature stimulus;response to high light intensity;response to cadmium ion;protein ubiquitination	1.00E-09
4	LOC_Os05g38530		DnaK family protein, putative, expressed	1.19E-09
5	LOC_Os01g62290	LOC_Os05g38530	response to stress	1.23E-09
6	LOC_Os11g47760	LOC_Os12g38180	response to stress;response to heat;response to cadmium ion	1.37E-09
7	LOC_Os05g33240		RNA splicing, via endonucleolytic cleavage and ligation;transcription, DNA-dependent;transcription from RNA polymerase II promoter	0.000137
8	LOC_Os07g10840		metabolic process	0.000151
9	LOC_Os09g19560		protein amino acid methylation;methylation;peptidyl-arginine N-methylation	0.000353
10	LOC_Os03g45370	LOC_Os12g42910	transmembrane transport	0.000407
11	LOC_Os09g30130		cellulose biosynthetic process	0.000482
12	LOC_Os09g30120		cellulose biosynthetic process	0.000489
13	LOC_Os07g22720		pyruvate metabolic process;metabolic process	0.00054
14	LOC_Os07g44410		proteolysis;toxin catabolic process;response to ethylene stimulus;abscisic acid mediated signaling pathway;response to cyclopentenone;methylglyoxal catabolic process to D-lactate	0.000547
15	LOC_Os06g45480		purine base metabolic process;proteolysis;metabolic process;ureide catabolic process;chlorophyll catabolic process	0.000593
16	LOC_Os02g01500	LOC_Os06g01630	pyruvate metabolic process;metabolic process	0.000605
17	LOC_Os06g08600		metabolic process;oxidation reduction	0.000804
18	LOC_Os08g05910		transport;oligopeptide transport;response to water deprivation;response to nitrate;nitrate transport	0.000831
19	LOC_Os07g20150		translation;methylation	0.000975
20	LOC_Os02g02110		Alg9-like mannosyltransferase protein, putative, expressed	0.001015
21	LOC_Os02g36870	LOC_Os08g33680	YGL010w, putative, expressed	0.001025
22	LOC_Os01g14440		OsWRKY1v2 - Superfamily of TFs having WRKY and zinc finger domains, expressed	0.00113
23	LOC_Os01g40070	LOC_Os05g51520	expressed protein	0.001388
24	LOC_Os01g31610		tRNA aminoacylation for protein translation;tyrosyl-tRNA aminoacylation; phosphatidylglycerol biosynthetic process;chloroplast organization;embryonic development ending in seed dormancy;thylakoid membrane organization; vegetative to reproductive phase transition of meristem;iron-sulfur cluster assembly;ovule development	0.002289
25	LOC_Os06g49120		translational initiation	0.002504
26	LOC_Os02g07160		aromatic amino acid family metabolic process;vitamin E biosynthetic process; plastoquinone biosynthetic process;carotenoid biosynthetic process;oxidation reduction	0.004493
27	LOC_Os03g55240		oxidation reduction	0.00496
28	LOC_Os01g55740		proteolysis	0.006715
29	LOC_Os10g40570		glucosinolate biosynthetic process;glucosinolate biosynthetic process from homomethionine;oxidation reduction;defense response to fungus	0.006968

light intensity, protein ubiquitination (UniProtKB - A0A0D3FGU6). LOC_Os05g38530 gene encode the Os05g0460000 protein and it was found to play roles in molecular activities like DNA binding, DNA directed 5′-3′ RNA polymerase activity, protein dimeritization. It was also involved in transcription and DNA templating (UniProtKB - Q6L509). LOC_Os01g62290 gene was reported to show response to stress and played role in ATP binding (UniProtKB - Q943K7). LOC_Os11g47760 gene represents HSP 70 kDa protein which involving in ATP binding activity and give response to heat, stress and cadmium ion (UniProtKB - Q2QZ41). Gene belonging to HSP 70 family were reported to show highly additive gene expression at the m RNA and protein level on high exposure to As and heat stress [26]. Heat shock proteins were found to be responding during abiotic stresses [27]. The K-exchanger protein encoded by the gene LOC_Os03g45370 was an integral component of membrane. It was a putative and expressed protein (UniProtKB - Q7Y0B2). LOC_Os08g05910 gene was involved in transport activities like oligopeptide transport, transport of nitrate. It was also found to show response towards water depriviation in the cell (UniProtKB-A2YRC4). LOC_Os10g40570 gene encodes flavin containing monooxygenase protein. This protein was reported to play major role in NADP binding, flavin adenine dinucleotide binding, N,*N*-dimethylaniline monooxygenase activity. It was also involved in biosynthesis of glucosinolate from homomethionine, oxidation reduction process. This gene was found to show defensive response towards fungal infection in the plant. So, it may be concluded that triggering MATE gene expression is associated with a numbers of transporter/defence/ATP binding activities and these findings corroborated with the findings of [28].

A set of 38 genes (29 newly found genes with 09 guide genes) were analyzed further by putting them as guide genes in Rice Net V2 to predict a concise model by gene prioritization based on network direct neighbourhood where LOC_Os08g37430 was found to be invalid as guide gene by the programme itself. Hence, the model was prepared for a total of 37 genes that were identified by RGAP7.0 as well as in RiceNet having AUC value of 0.9712 and p = 6.684656e- 100 (Fig. 1). The model was found to show AUC (area under the ROC curve) >0.7 i.e. 0.9. As the value of AUC was >0.9, it indicated perfect prediction rather than random [13,14].

3.2. Validation of the paralogi based functional linkage at protein level in rice interaction viewer (BAR)

The previous model (Fig no.03) was prepared on the basis of paralogous relationship which means that these genes are having homology as they may have been evolved by the course of evolution indicating their belongings to a common ancestral gene. For a further validation of this network model at protein level, same set of genes were analyzed in Rice Interaction Viewer (BAR) at http://bar.utoronto.ca/interactions/cgi-bin/rice_interactions_-viewer.cgi, and based on high confidence value (as set by the programme itself) we found a total of 178 interactions at the protein level among those 37 genes with having low, medium and high interolog confidence value. Apart from the aforesaid 37 genes, 10 other genes were found to interact among themselves at protein level (Fig. 2). Surprisingly, only 05 genes (Os05g33240, Os05g38530, Os09g19560, Os02g01500 and Os03g16920) from the initial 37 genes were found to play a key role at protein level.

3.3. Interaction of identified genes with different species of arsenic at protein level at stitch v5.0 platform

These 15 genes were subjected to analysis for their interaction at STITCH Version 5.0 with soil available inorganic species of arsenic viz., arsenate [As (V)] and arsenite [As (III)] and organic arsenic species viz., monomethylarsonic acid (MMA) and dimethylarsinic acid (DMAA). Finally, among those 15 candidate genes, 03 genes (LOC_Os05g38530, LOC_Os03g16920, LOC_Os08g39140) were found to interact directly both with arsenate and arsenite whereas 03 genes (LOC_Os01g23610,

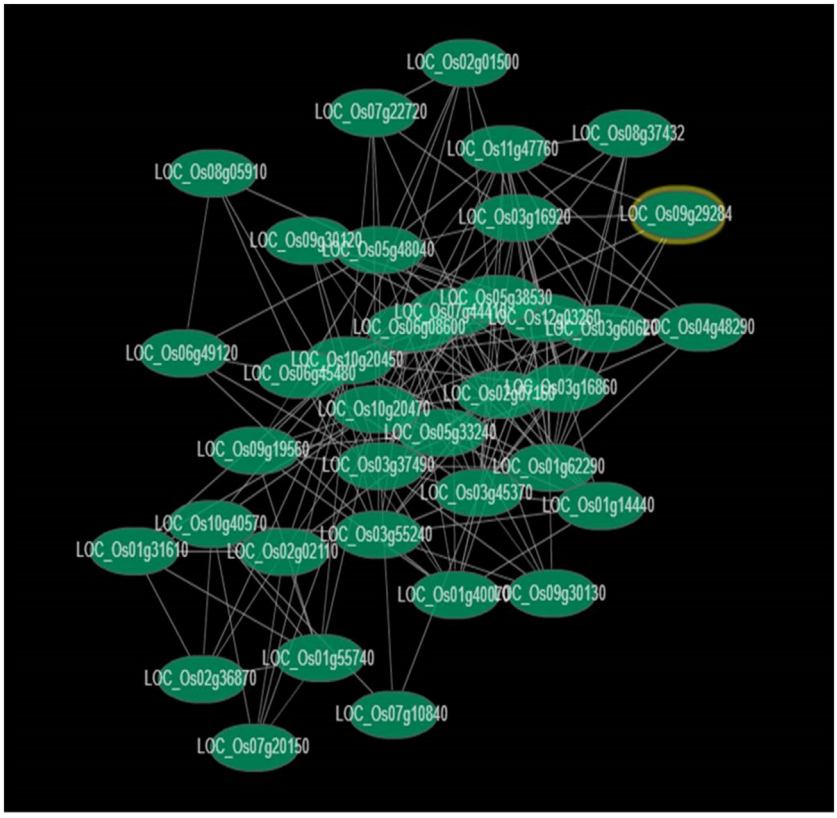

Fig. 1. genetic network of 37 guide genes.

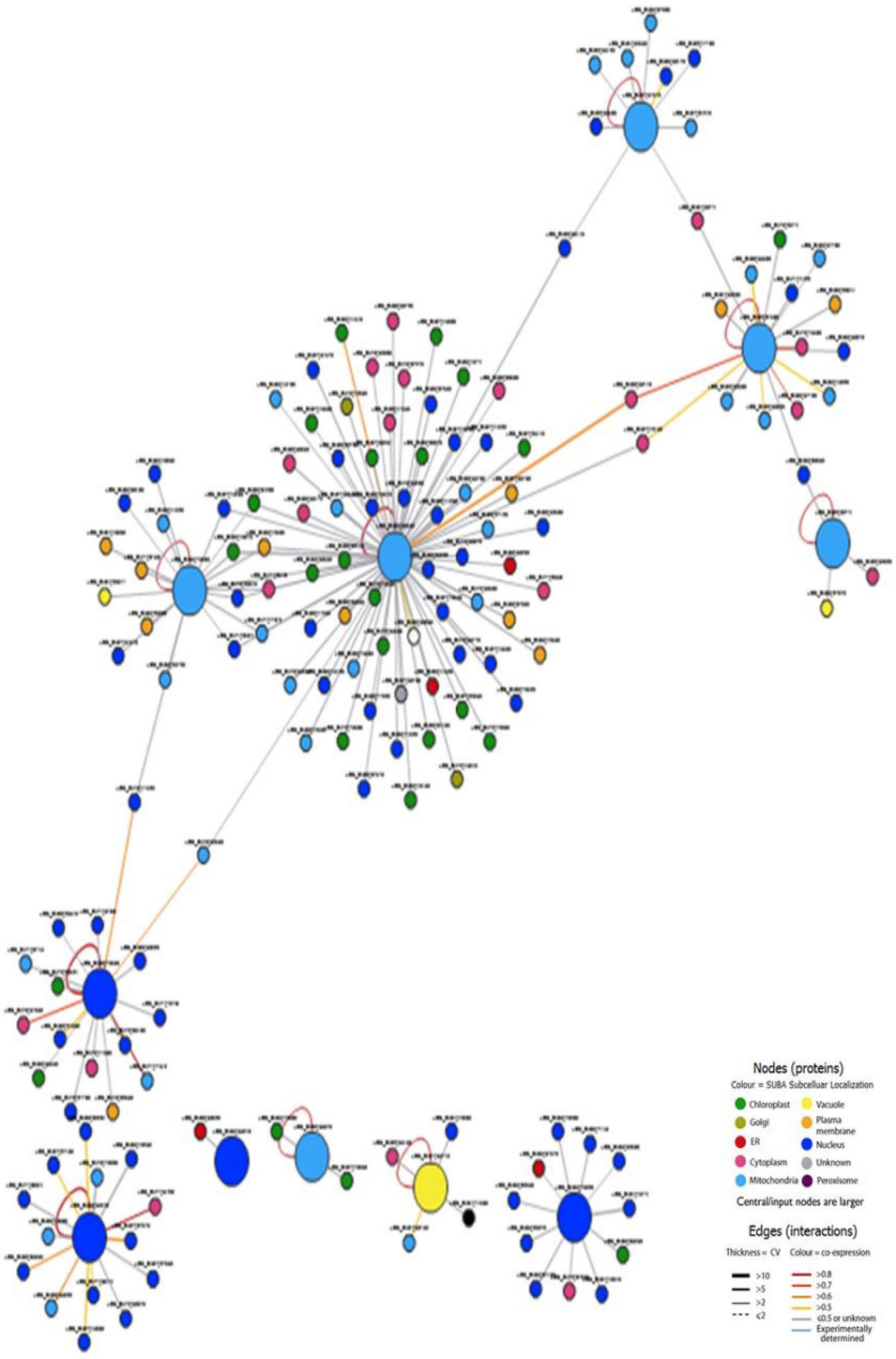

Fig. 2. Interactions at the protein level.

Table 3
Interaction of arsenate with the identified genes at protein level.

Node1	node2	node1 annotation	score
4326849 (LOC_Os01g23610.1)	Arsenate (233) sodium arsenate	dihydrolipoyl dehydrogenase, putative, expressed	0.514
4326980 (LOC_Os01g22520.1)	Arsenate (233) sodium arsenate	dihydrolipoyl dehydrogenase 1, mitochondrial precursor, putative, expressed	0.455
4331335 (LOC_Os03g01770.1)	Arsenate (233) sodium arsenate	rhodanese, putative, expressed; Possesses arsenate reductase activity in vitro. Catalyzes the reduction of arsenate [As(V)] to arsenite [As(III)]. May play a role in arsenic retention in roots	0.606

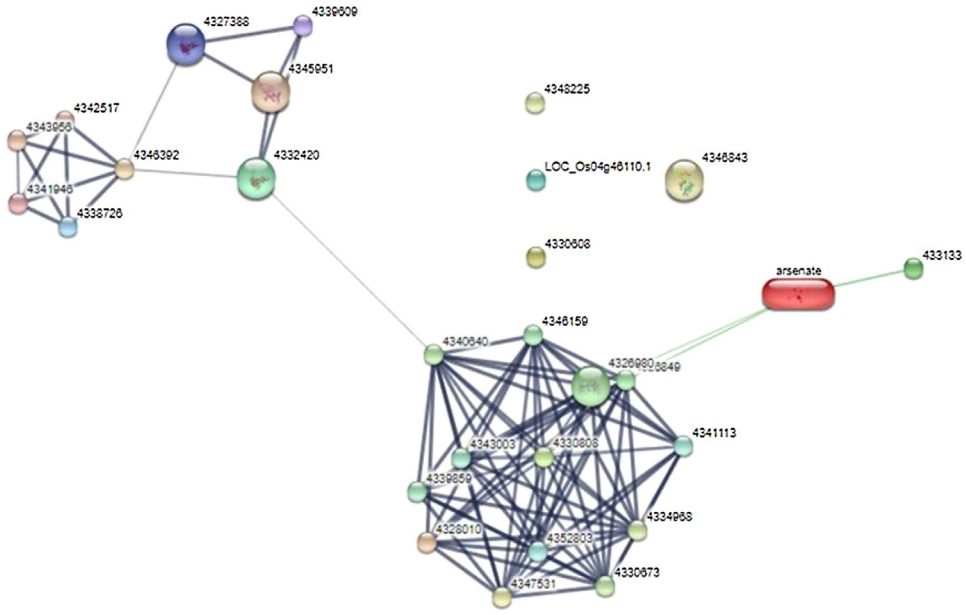

Fig. 3. Direct interaction with arsenate.

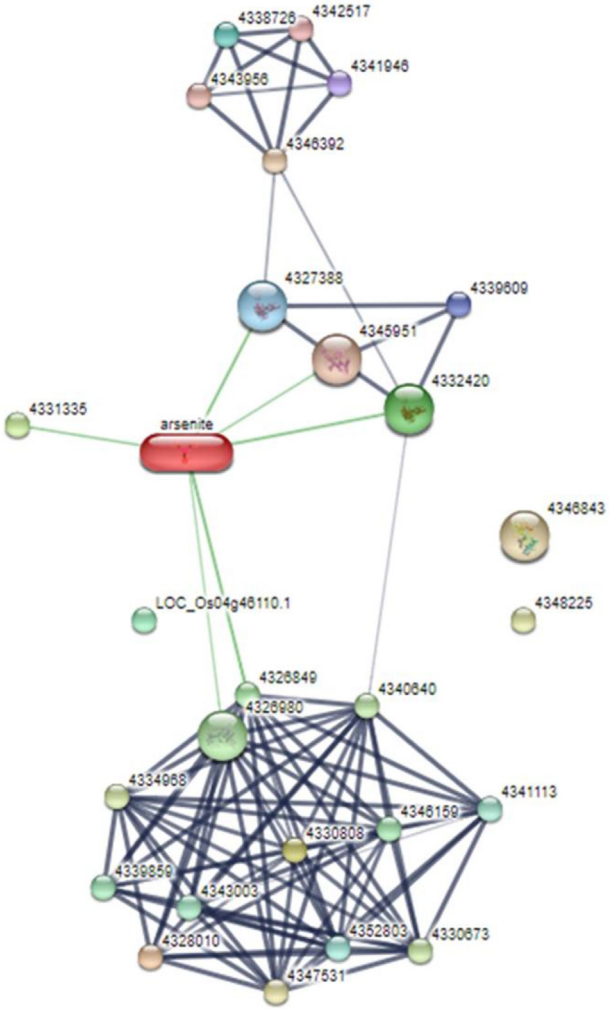

Fig. 4. Direct interaction with arsenite.

Table 4
Interaction of arsenite with identified genes at protein level.

Node 1	Node 2	Function of Node 1 genes	Score
4326849 LOC_Os01g23610.1	Arsenite	Dihydrolipoyl dehydrogenase	0.652
4326980 LOC_Os01g22520.1	Arsenite (544)	Dihydrolipoyl dehydrogenase 1, mitochondrial precursor	0.454
4327388 LOC_Os05g38530.1	Arsenite (544)	DnaK family protein	0.627
4331335 LOC_Os03g01770.1	Arsenite (544)	Rhodanese, arsenate reductase activity	0.54
4332420 LOC_Os03g16920.1	Arsenite (544)	DnaK family protein	0.627
4345951 LOC_Os08g39140.1	Arsenite (544)	Heat shoch protein, molecular chaperon	0.5

LOC_Os1g22520, LOC_Os03g01770) were found to show direct interaction exclusively with arsenite only (Table 3 and 4; Fig. 3 and 4).

Arsenate reductase 2.2 (ARC 2.2) protein encoded by the gene LOC_Os03g01770 located in both nucleus and cytoplasm have tyrosine protein phosphatase activity. It was also involved in arsenate reductase activity and act as a catalyst for reduction of arsenate [As (V)] to arsenite [As (III)]. (UniProtKB - B8ALE5).This indicated that it may play some roles in controlling the entry of arsenic to the seed and other plant parts by retaining it in the roots and help in reducing the accumulation of more arsenic in grains. Accumulation of arsenic in grain was less than ten percent of the arsenic accumulated in stem [29].

3.4. Expression potential of the genes which were found to interact with different species of arsenic

All the six genes were subjected to analyze individually to know their expression potential. The level of expression potential of LOC_Os01g22520 was high at seedling root and low in the shoot

Table 5
Expression potential of the LOC_Os01g22520 gene.

Group #	Tissue	Expression Level	Standard Deviation	Samples	Links
1	Seedling Root	16899.39	513.75	Seedling_Root_Rep1,Seedling_Root_Rep2, Seedling_Root_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Mature Leaf	9060.44	922.76	MatureLeaf_Rep1,MatureLeaf_Rep2,MatureLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Young Leaf	6867.62	946.85	YoungLeaf_Rep1,YoungLeaf_Rep2,YoungLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
3	SAM	4997.96	484.6	SAM_Rep1,SAM_Rep2,SAM_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Young Inflorescence	6490.03	681.19	YoungInflorescence_Rep1,YoungInflorescence_Rep2, YoungInflorescence_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P2	6995.48	1017.12	InflorescenceP2_Rep1,InflorescenceP2_Rep2, InflorescenceP2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P3	6499.46	317.02	InflorescenceP3_Rep1,InflorescenceP3_Rep2, InflorescenceP3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P4	7178.98	594.35	InflorescenceP4_Rep1,InflorescenceP4_Rep2, InflorescenceP4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P5	8500.99	310.84	InflorescenceP5_Rep1,InflorescenceP5_Rep2, InflorescenceP5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P6	9305.58	676.05	InflorescenceP6_Rep1,InflorescenceP6_Rep2, InflorescenceP6_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S1	10128.84	867.01	Seed_S1_Rep1,Seed_S1_Rep2,Seed_S1_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S2	9486.12	808.74	Seed_S2_Rep1,Seed_S2_Rep2,Seed_S2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S3	7764.57	502.79	Seed_S3_Rep1,Seed_S3_Rep2,Seed_S3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S4	5933.47	187.33	Seed_S4_Rep1,Seed_S4_Rep2,Seed_S4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S5	6086.38	530.49	Seed_S5_Rep1,Seed_S5_Rep2,Seed_S5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893

Table 6
Expression potential of the LOC_Os01g23610 gene.

Group #	Tissue	Expression Level	Standard Deviation	Samples	Links
1	Seedling Root	1246.59	39.47	Seedling_Root_Rep1,Seedling_Root_Rep2, Seedling_Root_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Mature Leaf	1567.78	222.41	MatureLeaf_Rep1,MatureLeaf_Rep2,MatureLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Young Leaf	1649.46	53.54	YoungLeaf_Rep1,YoungLeaf_Rep2,YoungLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
3	SAM	1149.82	206.98	SAM_Rep1,SAM_Rep2,SAM_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Young Inflorescence	1617.58	148.65	YoungInflorescence_Rep1,YoungInflorescence_Rep2, YoungInflorescence_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P2	2784.01	201.14	InflorescenceP2_Rep1,InflorescenceP2_Rep2, InflorescenceP2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P3	1557.54	182.34	InflorescenceP3_Rep1,InflorescenceP3_Rep2, InflorescenceP3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P4	1435.78	153.26	InflorescenceP4_Rep1,InflorescenceP4_Rep2, InflorescenceP4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P5	1006.91	104.72	InflorescenceP5_Rep1,InflorescenceP5_Rep2, InflorescenceP5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P6	1088.79	26.81	InflorescenceP6_Rep1,InflorescenceP6_Rep2, InflorescenceP6_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S1	918.56	55.62	Seed_S1_Rep1,Seed_S1_Rep2,Seed_S1_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S2	1035.12	140.05	Seed_S2_Rep1,Seed_S2_Rep2,Seed_S2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S3	1202.26	190.18	Seed_S3_Rep1,Seed_S3_Rep2,Seed_S3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S4	869.77	116.99	Seed_S4_Rep1,Seed_S4_Rep2,Seed_S4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S5	1876.85	538.6	Seed_S5_Rep1,Seed_S5_Rep2,Seed_S5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893

Table 7
Expression potential of the LOC_Os03g01770 gene.

Group #	Tissue	Expression Level	Standard Deviation	Samples	Links
1	Seedling Root	2905.35	244.75	Seedling_Root_Rep1,Seedling_Root_Rep2, Seedling_Root_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Mature Leaf	1042.59	76.24	MatureLeaf_Rep1,MatureLeaf_Rep2,MatureLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Young Leaf	4050.5	359.89	YoungLeaf_Rep1,YoungLeaf_Rep2,YoungLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
3	SAM	5097.81	576.57	SAM_Rep1,SAM_Rep2,SAM_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Young Inflorescence	2415.9	480.4	YoungInflorescence_Rep1,YoungInflorescence_Rep2, YoungInflorescence_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P2	2680.78	417.52	InflorescenceP2_Rep1,InflorescenceP2_Rep2, InflorescenceP2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P3	2703.51	84.16	InflorescenceP3_Rep1,InflorescenceP3_Rep2, InflorescenceP3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P4	2599.58	198.27	InflorescenceP4_Rep1,InflorescenceP4_Rep2, InflorescenceP4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P5	3689.42	439.91	InflorescenceP5_Rep1,InflorescenceP5_Rep2, InflorescenceP5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P6	2750.63	218.28	InflorescenceP6_Rep1,InflorescenceP6_Rep2, InflorescenceP6_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S1	3200.68	418.02	Seed_S1_Rep1,Seed_S1_Rep2,Seed_S1_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S2	2134.29	160.11	Seed_S2_Rep1,Seed_S2_Rep2,Seed_S2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S3	1363.85	175.65	Seed_S3_Rep1,Seed_S3_Rep2,Seed_S3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S4	1041.95	390.84	Seed_S4_Rep1,Seed_S4_Rep2,Seed_S4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S5	902.81	47.52	Seed_S5_Rep1,Seed_S5_Rep2,Seed_S5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893

Table 8
Expression potential of the LOC_Os03g16920 gene.

Group #	Tissue	Expression Level	Standard Deviation	Samples	Links
1	Seedling Root	42.25	5.03	Seedling_Root_Rep1,Seedling_Root_Rep2, Seedling_Root_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Mature Leaf	29.72	22.09	MatureLeaf_Rep1,MatureLeaf_Rep2,MatureLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Young Leaf	81.82	83.51	YoungLeaf_Rep1,YoungLeaf_Rep2,YoungLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
3	SAM	19.12	14.71	SAM_Rep1,SAM_Rep2,SAM_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Young Inflorescence	26.37	30.23	YoungInflorescence_Rep1,YoungInflorescence_Rep2, YoungInflorescence_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P2	53.12	8.05	InflorescenceP2_Rep1,InflorescenceP2_Rep2, InflorescenceP2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P3	21.46	12.11	InflorescenceP3_Rep1,InflorescenceP3_Rep2, InflorescenceP3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P4	23.36	12.09	InflorescenceP4_Rep1,InflorescenceP4_Rep2, InflorescenceP4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P5	40.15	5.63	InflorescenceP5_Rep1,InflorescenceP5_Rep2, InflorescenceP5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P6	58.81	13.82	InflorescenceP6_Rep1,InflorescenceP6_Rep2, InflorescenceP6_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S1	3903.05	758.55	Seed_S1_Rep1,Seed_S1_Rep2,Seed_S1_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S2	1446.98	593.3	Seed_S2_Rep1,Seed_S2_Rep2,Seed_S2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S3	6426.1	1243.72	Seed_S3_Rep1,Seed_S3_Rep2,Seed_S3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S4	9732.32	2173.79	Seed_S4_Rep1,Seed_S4_Rep2,Seed_S4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S5	9529.92	300.4	Seed_S5_Rep1,Seed_S5_Rep2,Seed_S5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893

apical meristem (Table 5) indicating its involvement in some activity of controlling the entry of arsenic to the root at seedling stage (UniProtKB - A0A0E0HNB8). Besides, the expression potential was observed to be high for LOC_Os01g23610 in the inflorescence P2 (meiotic stage) and low in the embryo maturation stage. (Table 6). Strikingly, LOC_Os03g01770 gene encoding arsenate reductase 2.2 protein which was reported to be observed only in roots and found to be responsible for reduction of arsenate

Table 9
Expression potential of the LOC_Os05g38530 gene.

Group #	Tissue	Expression Level	Standard Deviation	Samples	Links
1	Seedling Root	512.95	96.75	Seedling_Root_Rep1,Seedling_Root_Rep2, Seedling_Root_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Mature Leaf	703.76	77.61	MatureLeaf_Rep1,MatureLeaf_Rep2,MatureLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Young Leaf	349.1	114.65	YoungLeaf_Rep1,YoungLeaf_Rep2,YoungLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
3	SAM	126.48	26.84	SAM_Rep1,SAM_Rep2,SAM_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Young Inflorescence	829.22	427.86	YoungInflorescence_Rep1,YoungInflorescence_Rep2, YoungInflorescence_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P2	1277.77	135.91	InflorescenceP2_Rep1,InflorescenceP2_Rep2, InflorescenceP2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P3	1428.59	368.4	InflorescenceP3_Rep1,InflorescenceP3_Rep2, InflorescenceP3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P4	871.31	186.87	InflorescenceP4_Rep1,InflorescenceP4_Rep2, InflorescenceP4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P5	330.06	63.87	InflorescenceP5_Rep1,InflorescenceP5_Rep2, InflorescenceP5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P6	1331.87	85.09	InflorescenceP6_Rep1,InflorescenceP6_Rep2, InflorescenceP6_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S1	8756.77	2270.0	Seed_S1_Rep1,Seed_S1_Rep2,Seed_S1_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S2	3925.47	1657.18	Seed_S2_Rep1,Seed_S2_Rep2,Seed_S2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S3	10169.83	2145.6	Seed_S3_Rep1,Seed_S3_Rep2,Seed_S3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S4	8080.99	1916.94	Seed_S4_Rep1,Seed_S4_Rep2,Seed_S4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S5	3980.54	511.99	Seed_S5_Rep1,Seed_S5_Rep2,Seed_S5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893

Table 10
Expression potential of the LOC_Os08g39140 gene.

Group #	Tissue	Expression Level	Standard Deviation	Samples	Links
1	Seedling Root	17879.66	978.71	Seedling_Root_Rep1,Seedling_Root_Rep2, Seedling_Root_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Mature Leaf	5995.85	402.62	MatureLeaf_Rep1,MatureLeaf_Rep2,MatureLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
2	Young Leaf	6824.24	913.83	YoungLeaf_Rep1,YoungLeaf_Rep2,YoungLeaf_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
3	SAM	9195.96	1203.2	SAM_Rep1,SAM_Rep2,SAM_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Young Inflorescence	8947.63	2032.27	YoungInflorescence_Rep1,YoungInflorescence_Rep2, YoungInflorescence_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P2	9974.24	1067.34	InflorescenceP2_Rep1,InflorescenceP2_Rep2, InflorescenceP2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P3	10031.8	1646.06	InflorescenceP3_Rep1,InflorescenceP3_Rep2, InflorescenceP3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P4	8748.31	1388.24	InflorescenceP4_Rep1,InflorescenceP4_Rep2, InflorescenceP4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P5	10849.74	1535.85	InflorescenceP5_Rep1,InflorescenceP5_Rep2, InflorescenceP5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
4	Inflorescence P6	10471.43	592.63	InflorescenceP6_Rep1,InflorescenceP6_Rep2, InflorescenceP6_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S1	16985.9	2014.02	Seed_S1_Rep1,Seed_S1_Rep2,Seed_S1_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S2	8728.46	2571.56	Seed_S2_Rep1,Seed_S2_Rep2,Seed_S2_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S3	22379.66	1486.43	Seed_S3_Rep1,Seed_S3_Rep2,Seed_S3_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S4	20331.83	4730.64	Seed_S4_Rep1,Seed_S4_Rep2,Seed_S4_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893
5	Seed S5	14113.16	2492.14	Seed_S5_Rep1,Seed_S5_Rep2,Seed_S5_Rep3,	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6893

to arsenite. In the present study, (Table 7) the observed expression potential for the said gene was found to be high in the matured seedling as well as vacuolated pollen stage (inflorescence P5). LOC_Os03g16920 (Table 8) was shown to have high expression potential during matured embryo stage which indicated that, it may restrict the entry of arsenic to the embryo while in the shoot apical meristem, it was found to show less expression. In some other studies it was found that arsenic accumulation is significantly higher in shoot as compared to the root [7]. The accumulation of arsenic in grain is usually less than ten percent of the stem accumulation and majority of the grain arsenic is uploaded by phloem [30,29]. The maximum expression potential of the gene LOC_Os05g38530 was shown in the embryo morphogenesis stage and minimum in the shoot apical meristem (Table 9). This indicated that, LOC_Os05g38530 may have some role in reduction in arsenic content in grain as less grain accumulation is evident from other studies. This gene was also involved in the activity of DNA binding and protein dimerization (UniProtKB - Q6L509). The expression of LOC_Os08g39140 was high both at embryo morphogenesis and maturity stage (Table 10) indicating it involvement in some activity of restricting the entry of the arsenic to the embryo of the seed. LOC_Os08g39140 is known to encode a heat shock protein (HSP81-1) located in cytoplasm and act as molecular chaperon which promotes the structural maintenance, maturity and regulating several target proteins (UniProtKB - A2YWQ1). Additionally, the expression was found to be low at matured leaf stage. Therefore, maximum expression levels (expression potential) of these 06 genes were found mostly at young inflorescence and seed development stage after the analysis at Rice eFP Browser (BAR) which was developed at the University of Toronto. So, these six genes may have a direct role in arsenic sequestration from cells and thereby providing safety to the developing embryo within the seed.

4. Conclusion

This result which was found from this current investigation concluded that, these six genes may have a direct role in arsenic sequestration from cells and thereby providing safety to the developing embryo as well as the seed. So, those genes can be used to breed rice genotypes having low arsenic in grain using them as target for finding and designing gene based molecular markers. Additionally, the results would focus towards the successful use of computational biology in the field of plant breeding by reducing cost, labour and time of biological experiments.

Declaration of Competing Interest

The authors declare that, they have no potential conflict of interest in the publication of this manuscript

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.btre.2019.e00390.

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