Journal of Plant Development
Vol. **31**, Dec **2024**: 215-227
DOI: 10.47743/jpd.2024.31.1.943
Research Article

ISSN 2065-3158 print / e-ISSN 2066-9917
Available online: www.plant-journal.uaic.ro

COMPUTATIONAL SCREENING TO IDENTIFY GENES INVOLVED IN DNA REPAIR IN *ARABIDOPSIS THALIANA*

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Abstract: The repair of damaged DNA is an essential function for living organisms. While great strides have been made in understanding this process in animal and yeast models, our knowledge in plant DNA repair is not as developed. Plants face many sources of DNA damage which they cannot so easily avoid: UV radiation from sunlight, reactive oxygen species produced endogenously by their mitochondria and chloroplasts, reactive oxygen species accumulated while under conditions of cold, heat, or salt stress. Understanding plant DNA repair is particularly relevant as the accumulation of DNA damage can negatively impact the growth and yield of agronomically important species. In this study, a broad classification of genes related to DNA repair in the model dicot *Arabidopsis thaliana* was conducted using gene ontology and gene enrichment analysis. The results of this broad classification serve to elucidate pathways for further study in plant DNA damage response and repair.

Keywords: cell death, DNA repair, gene enrichment analysis, gene ontology, stress response.

Introduction

DNA encodes the necessary instructions for life [CHATTERJEE & WALKER, 2017]. Yet organisms inevitably encounter various sources of damage to their DNA from their environment and their metabolism [EKER & al. 2009], which threaten the genomic integrity of their cells. Damaged DNA, if not repaired, can lead to the impairment of important cellular processes and ultimately cell death [SZURMAN-ZUBRZYCKA & al. 2023]. Thus, the evolution of mechanisms to detect and repair damaged DNA are essential for the survival and perpetuation of living organisms [CHATTERJEE & WALKER, 2017; MANOVA & GRUSZKA, 2015]. This process is believed to be highly conserved across animals, fungi, plants and yeast, although key distinctions remain [GRIN & al. 2023; SZURMAN-ZUBRZYCKA & al. 2023; YOSHIYAMA & al. 2013].

Much of our understanding of the DNA damage response (DDR) pathway comes from models of mammalian cells due to its pertinence in understanding the development of cancer, the cellular aging process, and the development of certain diseases [GIMENEZ & MANZANO-AGUGLIARO, 2017; GRIN & al. 2023] as well as from work with single celled yeast, but our knowledge in plant DDR lags behind [GIMENEZ & MANZANO-AGUGLIARO, 2017; SINGH & al. 2010]. Nonetheless, important work in the past a few decades, primarily in the model plant *Arabidopsis thaliana*, has significantly enhanced our understanding of plant DDR [SZURMAN-ZUBRZYCKA & al. 2023].

As the accumulation of DNA damage in plants can negatively impact their growth and yield [MANOVA & GRUSZKA, 2015; SZURMAN-ZUBRZYCKA & al. 2023], gaining a comprehensive understanding of the plant DDR network has many key applications for the improvement of agronomically important species. Additionally, understanding the plant DDR

Received: 17 June 2024 / ***Revised***: 22 November 2024 / ***Accepted***: 26 November 2024

network has important applications for precise and efficient gene targeting, insertion, and incorporation of *Agrobacterium*-mediated T-DNA for genome editing and modification [SHEN & LI, 2022].

In contrast to animals, plants are challenged with many additional sources of DNA damage due to their unique life history [GRIN & al. 2023]. As organisms anchored to their environment by their root systems, they are unable to move away from many environmental sources of DNA damage [SPAMPINATO, 2017]. Reliant on photosynthesis, plants are also constantly exposed to the DNA-damaging UV radiation of the sun [YOSHIYAMA & al. 2013]. ROS can accumulate and lead to DNA damage while plants experience various forms of abiotic stress: salt stress, conditions of drought, cold or heat stress, or acidic soils [SZURMAN-ZUBRZYCKA & al. 2023]. Biotic stress from the pathogen attack by fungal, bacterial, or viral pathogens, as well as insect herbivores can also lead to the accumulation of DNA damage for plants [MANOVA & GRUSZKA, 2015; TUTEJA & al. 2008]. Additionally, exposure to genotoxic pollutants or heavy metals in the soil can contribute to the damage of plant DNA [GRIN & al. 2023; SZURMAN-ZUBRZYCKA & al. 2023, WATERWORTH & al. 2011]. Plants can also produce a wide variety of genotoxic secondary metabolites, of which psoralens, topoisomerase inhibitors (camptothecins, podophyllotoxins), and aristolochic acid are probably the best-studied examples [see GRIN & al. 2023]. And some widespread plant protein toxins, such as ribosome-inactivating proteins, also damage DNA [STIRPE & al. 2006].

DNA damage can be classified into two primary categories: damage, breaks, or errors that occur on a single strand of DNA, single stranded breaks (SSB), or damage or breaks to both strands of DNA, double stranded breaks (DSB) [SZURMAN-ZUBRZYCKA & al. 2023]. The latter carries more severe consequences for the cell due to chromosomal fragmentation and the loss of considerable amounts of genetic information [MANOVA & GRUSZKA, 2015]. In response to this damage, plants initiate the DDR pathway. First, DNA damage must be detected. Two sensor kinases of the phosphoinositide-3-kinase-related protein kinase (PIKKs) family, ATM (Ataxia Telangiectasia Mutated) and ATR (ATM and Rad3-related) are involved in this process [SHEN & LI, 2022; WATERWORTH & al. 2011]. With ATM being recruited to the sites of DSBs while ATR being recruited to the sites of SSBs or general replication stress [NIMETH & al. 2020; HIRAKAWA & al. 2017]. Both of these proteins then phosphorylate suppressor of gamma 1 (SOG1) which serves as a key regulator of the DDR process in plants and a functional homolog of the animal p53 tumor suppressor protein [YOSHIYAMA, 2015]. From the sensing of DNA damage and the activation of SOG1, an important checkpoint is reached. The cell cycle is arrested to prevent serious genetic errors from being passed forward to daughter cells and to provide the cell with time to repair [GIMENEZ & MANZANO-AGUGLIARO, 2017; LAZZARO & al. 2009].

The main regulator of the DDR pathway in plants, SOG1, activates not only many genes related to DNA repair, but also those related to cell cycle regulation [SZURMAN-ZUBRZYCKA & al. 2023]. Cell cycle arrest is the first effect of DDR activation and is crucial to allow time to repair to avoid transmission of lesions to daughter cells . If an extreme number of DNA lesions occur and DNA repair machinery is not able to fix them, the endoreduplication could be activated [SZURMAN-ZUBRZYCKA & al. 2023]. In this case DNA replication is not followed by mitotic division. This could cause an increase in ploidy level and usually leads to enlargement and differentiation of the cell [LANG & SCHNITTGER, 2020]. Endoreduplication is known to be implicated in various stres responses in plants [LANG & SCHNITTGER, 2020]. If the DNA damage is sensed to be repairable, a variety of DNA repair mechanisms are available to address the specific kind of DNA damage or lesion that has occurred. Or the severity of the

DNA damage may be sensed to be sufficient to warrant progression to programmed cell death [SZURMAN-ZUBRZYCKA & al. 2023].

SSBs may be addressed by nucleotide excision repair (NER), base excision repair (BER), or mismatch repair (MMR) [NIMETH & al. 2020]. Base excision repair addresses modified, damaged, or missing bases [GRIN & al. 2023]. Nucleotide excision repair addresses UV induced lesions and bulky adducts that distort the conformation of the DNA helix [MANOVA & GRUSZKA, 2015]. Mismatch repair addresses various errors that occur during DNA replication, mismatched, wrongly inserted, or deleted bases [SPAMPINATO, 2017]. For SSB repair by NER, BER, or MMR the complementary strand serves as a template for the accurate recovery of sequence information [SZURMAN-ZUBRZYCKA & al. 2023].

DSBs may be addressed through homologous recombination (HR) or through non-homologous end joining (NHEJ). In the case of homologous recombination, the availability of sister chromatids or homologous chromosomes is required for accurate repair without the loss of sequence information. In the case of non-homologous end joining, fragmented DNA stranded are repaired without the availability of a template and are the prone to errors or loss of sequence information [SHEN & LI, 2022].

With the progress in our understanding of the genetic and biochemical details of these repair processes in plants, the molecular checkpoints and decision between repair, endoreduplication, and programmed cell death in response to DNA damage have yet to be fully understood. Towards this, a more comprehensive network analysis or systems biology view will certainly be a plausible approach as indicated in our previous work in various plant species [ARMAS & XING, 2022; CONROY & al. 2013; YOUNG & al. 2018].

Gene ontology (GO) allows for the classification of genes and gene products into functional categories, i.e. at the level of molecular function, which describes the biochemical activity; at the level of cellular component, which describes the location within the cell; and at the level of biological process, which describes the wider pathway and biological operation [ASHBURNER & al. 2000]. A variety of tools are available for the sorting of gene lists into functional categories in accordance with gene ontology [GE & al. 2020]. In this study we aim to investigate plant DDR using a broad computational screening approach including the widely available and abundant genomic data for *Arabidopsis thaliana,* gene enrichment analysis, and gene ontology. It is the hope that the identification of genes related to DDR in *Arabidopsis thaliana* and their classification into functional categories in accordance with gene ontology will aid in mapping out the DDR process in plants.

Methods

Literature search

A literature search was preformed to obtain a reference list (n=30) of known DNA repair genes in *Arabidopsis thaliana* from reputable journal publications by querying the search terms '*Arabidopsis thaliana* anti-cell death genes', '*Arabidopsis thaliana* DNA repair genes', and '*Arabidopsis thaliana* pro-survival genes' into Web of Science and Google Scholar. This list was then used to obtain protein-protein interaction data, gene co-expression data, and genetic interaction data for each reference gene.

Protein-protein interactions

Protein-protein interactions for each of the reference genes were obtained through the use of STRING database (https://string-db.org) [SZKLARCZYK & al. 2023] with a default cutoff score of (score >= 0.400).

Gene co-expressions

Gene co-expression data were obtained using the Bio-Analytic Resource for Plant Biology (https://bar.utoronto.ca) [WAESE & al. 2017] and ePlant expression angler tool therein with a cutoff of the top 25 results for each reference gene.

Genetic interactions

Genetic interactions were obtained using BioGRID Database of Protein, Genetic, and Chemical Interactions (https://thebiogrid.org) [OUGHTRED & al. 2021] with all unique interactions collected for each reference gene.

Gene enrichment analysis and categorization (GO and KEGG)

The protein-protein interaction data, gene co-expression data, and genetic interaction data were compiled together. Genes were ranked according to how many approaches they were found in. Those found in all three approaches were assigned 1st priority, those found in two approaches were assigned 2nd priority, and those found in only one approach were assigned 3rd priority. The compiled data were then entered into the ShinyGO gene enrichment tool (http://bioinformatics.sdstate.edu/go) [GE & al. 2020] with an FDR cutoff of 0.05 for gene ontology enrichment and classification. KEGG (Kyoto Encyclopedia of Genes and Genomes, https://www.genome.jp/kegg) analysis is integrated and describes how genes and proteins interact in specific pathways and systems.

Results and discussions

DDR-related gene identification

Through the use of STRING database examining protein-protein interactions, BAR ePlant expression angler examining gene co-expression, and BioGRID database examining genetic interactions, a gene list of potential DDR or DDR related genes within the DDR network in *Arabidopsis thaliana* (n=852) were identified from an original list of known DDR genes through literature extraction (n=30 and see Supplementary data Table 1). In the rest of this work, all the related genes in this network will be call DDR-related genes or DDR for simplicity.

The potential *Arabidopsis* DDR genes were ranked by priority in accordance with the number of approaches they were identified in (see Methods section) (Supplementary data Table 2). Of these, an insufficient amount (n=4) fell into 1st priority, being identified in all three approaches, to proceed to gene enrichment analysis. As a result, 1st and 2nd priority (n = 58) were combined for the purposes of enrichment analysis.

The potential *Arabidopsis* DDR genes with the strongest evidence (combined 1st and 2nd priority) were compared to all identified potential *Arabidopsis* DDR genes (1st, 2nd, and 3rd priority) during the following enrichment analysis.

GO Enrichment Analysis

Enrichment analysis and classification into functional GO terminology of our *Arabidopsis* DDR genes provided an interesting mixture of results with some seeming to provide support to previous knowledge in plant DDR while others indicating potential areas for further analysis (Supplementary data Table 2, Figures 1, 2, 3, and 4).

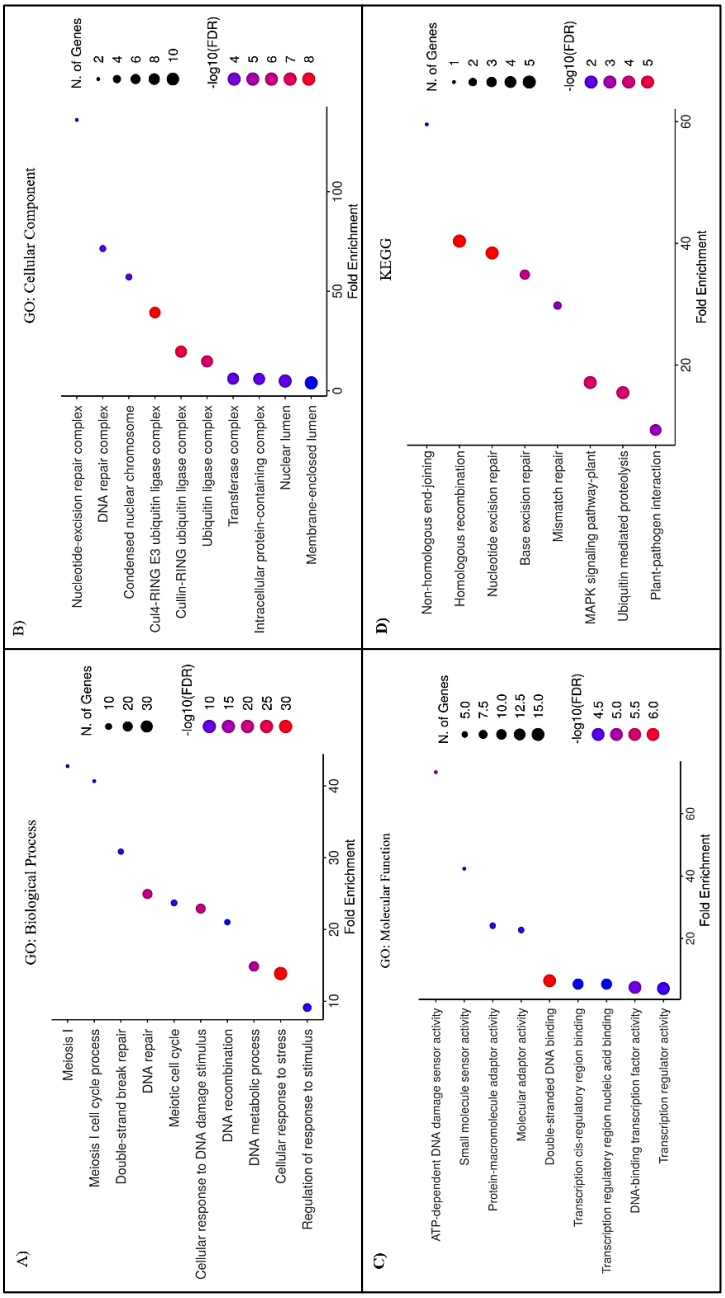

Figure 1. Gene ontology analysis for genes ranked 1st and 2nd priority. Dot plot illustrating the top ten categories by fold enrichment with an FDR cutoff of 0.05 for the following classification systems: A) biological process, B) cellular component, C) molecular component, and D) KEGG (Kyoto Encyclopedia of Genes and Genomes).

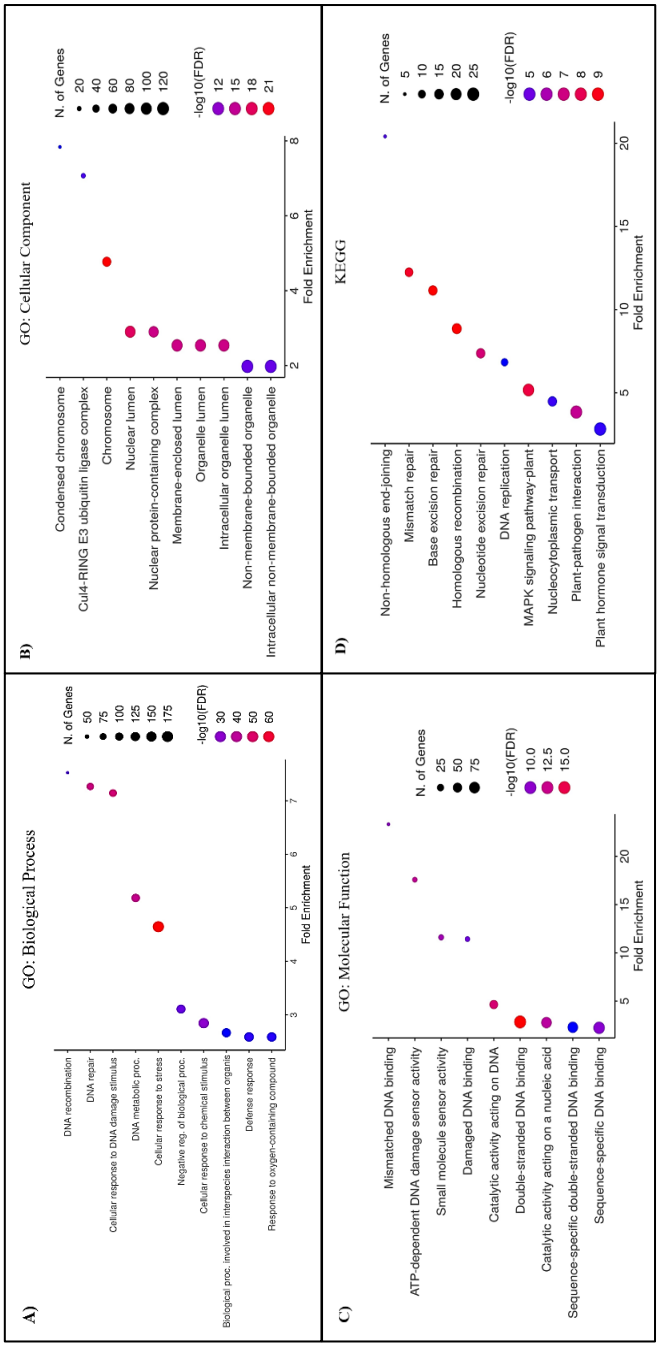

Figure 2. Gene ontology analysis for genes of all priorities. Dot plot illustrating the top ten categories by fold enrichment with an FDR cutoff of 0.05 for the following classification systems: A) biological process, B) cellular component, C) molecular component, and D) KEGG.

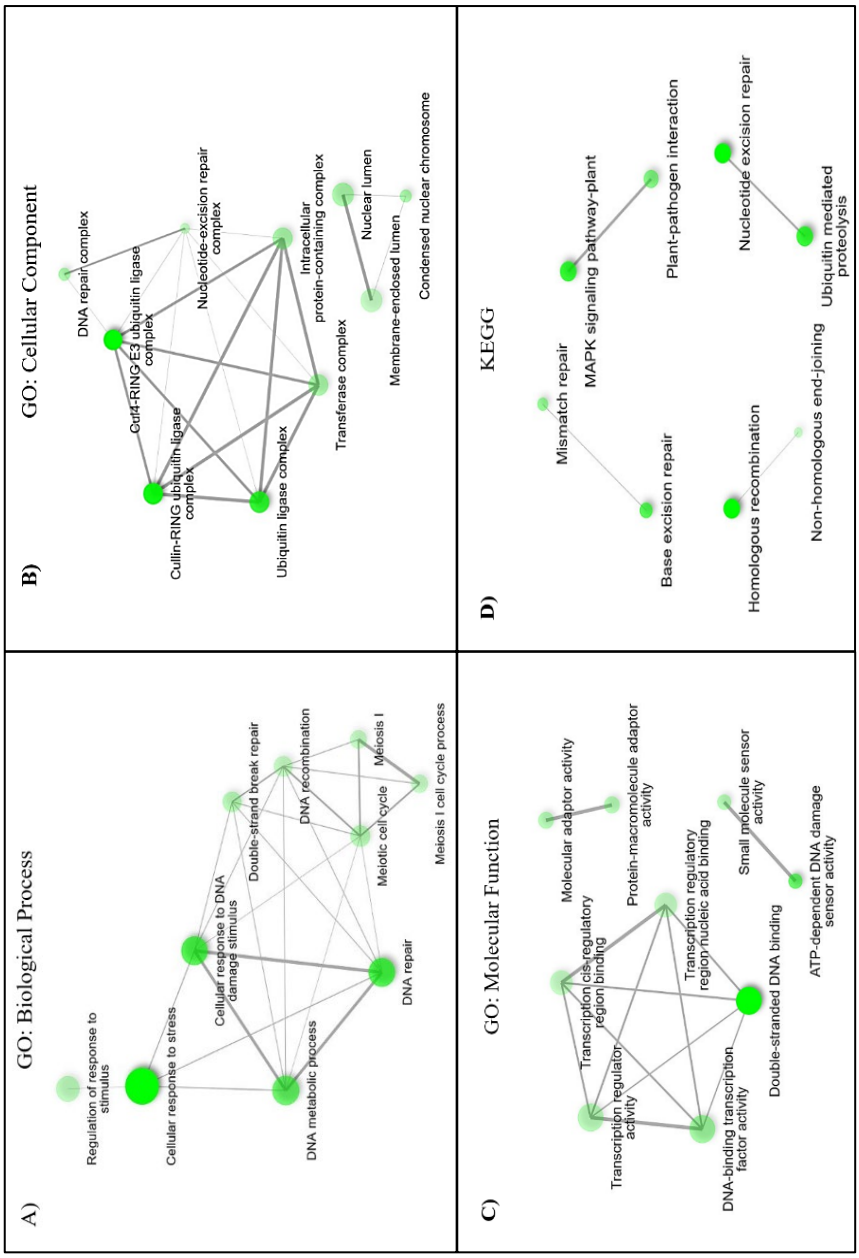

Figure 3. Gene ontology analysis with network plot for genes ranked 1st and 2nd priority. Network plot illustrating the connections between the top ten categories by fold enrichment with an FDR cutoff of 0.05 and an edge cutoff of 0.3 for the following classification systems: A) biological process, B) cellular component, C) molecular component, D) KEGG. Edge thickness indicates greater shared genes between pathways. Darker nodes indicate higher enrichment. Node size indicates the number of genes.

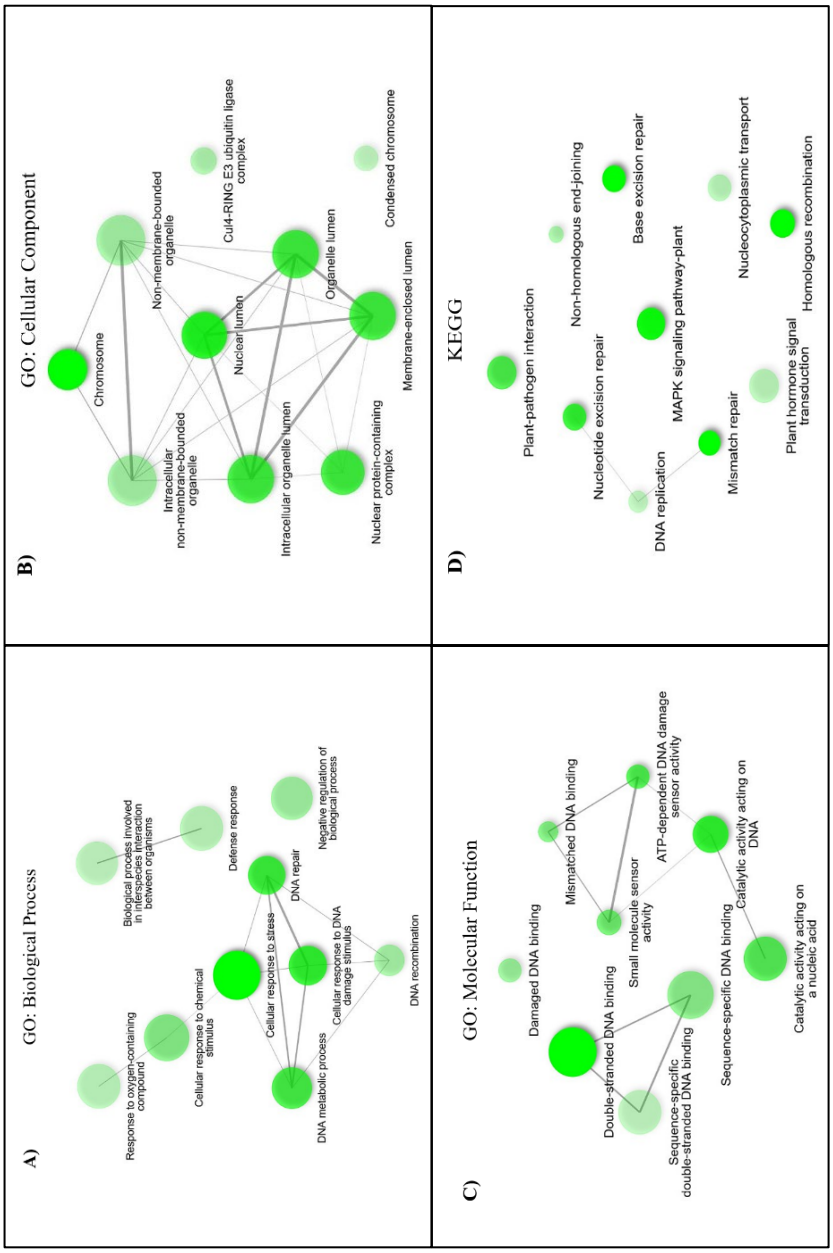

Figure 4. Gene ontology analysis with network plot for genes of all priorities. Network plot illustrating the connections between the top ten categories by fold enrichment with an FDR cutoff of 0.05 and an edge cutoff of 0.3 for the following classification systems: A) biological process, B) cellular component, C) molecular component, D) KEGG. Edge thickness indicates greater shared genes between pathways. Darker nodes indicate higher enrichment. Node size indicates the number of genes.

Biological process

At the level of biological process, when analysing genes with the greatest support (1st and 2nd priority), the top 10 GO terms by fold enrichment were: meiosis I, meiosis I cell cycle process, double strand break repair, DNA repair, meiotic cell cycle, cellular response to DNA damage stimulus, DNA recombination, DNA metabolic process, cellular response to stress, and regulation of response to stimulus.

When analyzing genes from all priorities, the top 10 GO terms by fold enrichment were: DNA recombination, DNA repair, cellular response to DNA damage stimulus, DNA metabolic process, cellular response to stress, negative regulation of a biological process, cellular response to chemical stimulus, biological process involved in interspecies interaction between organisms, defense response, and response to oxygen containing compound.

The return of GO terms such as 'DNA repair', 'DNA recombination', 'double strand break repair' and 'cellular response to DNA damage stimulus' among others, provide support that our identified genes fall within the realm of DDR network at the biological process level.

The return of GO terms 'meiosis I', 'meiosis I cell cycle process', and 'meiotic cell cycle' in combination with 'DNA recombination' and 'double strand break repair' when analysing genes with the greatest support (1st and 2nd priority), seems to be suggestive of the homologous recombination DNA repair network. As during meiosis, sister chromatids become available as a template for homologous recombination repair of double strand breaks [LUI & al. 2022]. This pathway is even more clear when observing the bubble figure (Figure 3A).

Cellular Component

At the level of cellular component, when analysing genes with the greatest support (1st and 2nd priority) the top 10 GO terms by fold enrichment were: nucleotide excision repair complex, DNA repair complex, condensed nuclear chromosome, cul4-RING E3 ubiquitin ligase complex, cullin-RING ubiquitin ligase complex, ubiquitin ligase complex, transferase complex, intracellular protein-containing complex, nuclear lumen, and membrane enclosed lumen.

When analyzing genes from all priorities, the top 10 GO terms by fold enrichment were: condensed chromosome, cul4-RING E3 ubiquitin ligase complex, chromosome, nuclear lumen, nuclear protein-containing complex, membrane enclosed lumen, organelle lumen, intracellular organelle lumen, non-membrane-bounded organelle, and intracellular non-membrane-bounded organelle.

The return of the GO terms 'condensed nuclear chromosome', 'chromosome', 'nuclear lumen', 'organelle lumen' among others provides support that our genes and gene products are active at the sites of DNA within the cell - the nucleus, chloroplasts, and mitochondria.

The appearance of the GO terms 'cul4-RING E3 ubiquitin ligase complex', 'cullin-RING ubiquitin ligase complex', and 'ubiquitin ligase complex' presents an interesting opportunity for further study and may be related to cell cycle regulation through ubiquitination [SZURMAN-ZUBRZYCKA & al. 2023]. This process also appears to have a relation with nucleotide excision repair (Figure 3B).

Molecular Function

At the level of molecular function, when analysing genes with the greatest support (1st & 2nd priority), the top 10 GO terms by fold enrichment were: ATP-dependant DNA damage sensor activity, small molecule sensor activity, protein-macromolecule adaptor activity, molecular adaptor activity, double stranded DNA binding, transcription cis-regulatory region

binding, transcription regulatory region nucleic acid binding, DNA-binding transcription factor activity, and transcription regulator activity.

When analysing genes from all priorities, the top 10 GO terms by fold enrichment were: mis-matched DNA binding, ATP-dependant DNA damage sensor activity, small molecule sensor activity, damaged DNA binding, catalytic activity acting on DNA, double stranded DNA binding, catalytic activity acting on a nucleic acid, sequence specific double stranded DNA binding, sequence specific DNA binding.

The return of the GO terms 'ATP-dependant DNA damage sensor activity', 'double stranded DNA binding', and 'catalytic activity acting on a nucleic acid' among others provides further support that our identified genes are within the realm of DDR and their potential action via DNA. The network seen in (Figure 4C) for all gene priorities appears to show a pathway-like relationship for mismatch repair.

KEGG (Kyoto Encyclopedia of Genes and Genomes)

Enrichment analysis using KEGG terminology, when analysing genes with the greatest support (1st & 2nd priority) the top ten GO terms by fold enrichment were: non-homologous end joining, homologous recombination, nucleotide excision repair, base excision repair, mismatch repair, MAPK signaling pathway, ubiquitin mediated proteolysis, and plant-pathogen interaction.

In the enrichment analysis of genes of all priorities using KEGG terminology, the top 10 GO terms by fold enrichment were: non-homologous end joining, mismatch repair, base excision repair, homologous recombination, nucleotide excision repair, DNA replication, MAPK signaling pathway, nucleocytoplasmic transport, plant pathogen interaction, and plant hormone signal transduction.

The return of the KEGG terms 'non homologous end joining' and 'homologous recombination' for our high priority genes (1st and 2nd priority) provides support for the importance of addressing DSBs in plant DDR. The return of the KEGG terms 'MAPK signaling pathway' and 'plant pathogen interaction' suggests a possible involvement of MAP kinase pathway in cell death and DDR in *Arabidopsis* biotic stress response and offers an interesting area for further study.

NHEJ was observed as the KEGG term with the greatest fold enrichment for both data sets, which appears indicative of the importance of NHEJ in plant DDR. DSBs are the most serious form of DNA damage [MANOVA & GRUSZKA, 2015], and our results appear supportive of NHEJ as the dominant repair mechanism in addressing them over HR in *Arabidopsis thaliana.* This is supportive of previous knowledge of plant DDR in which plants share the predominance of NHEJ in addressing DSBs over HR with animals and in contrast with yeast, *Saccharomyces cerevisiae* [SHEN & LI, 2022].

In Figure 3 D, for genes with the greatest support (1st and 2nd priority), the nodes for NHEJ and HR were connected, which indicates >20% of shared genes between the two pathways. This may be due to both addressing the repair of DSBs [SHEN & LI, 2022]. Relations were also shown between mismatch repair and base excision repair, both of which act on SSBs and damaged or mismatched bases [GRIN & al. 2023; NIMETH & al. 2020]. Relations were shown between NER and ubiquitin mediated proteolysis, which was also observed previously at the level of cellular component. In addition, the return of the KEGG terms 'non-homologous end joining', 'homologous recombination', 'nucleotide excision repair', 'base excision repair', and 'mismatch repair' for both gene lists provide further support that our identified genes fall within the realm of the DDR network.

Conclusions

The appearance in multiple approaches (protein-protein interactions, gene co-expressions, and genetic interactions) as well as the results of GO gene enrichment analysis at the levels of biological process, cellular component, molecular function, and KEGG provide compounding support that our identified genes in *Arabidopsis thaliana* fall within the realm of the DDR network.

Results from GO enrichment analysis such as the relation between NER and ubiquitin mediated proteolysis or the appearance of MAPK signaling pathway provide interesting areas for future study. We have identified a select number of genes (n = 20, Supplementary data Table 3) of high priority (1st and 2nd priority) related to DDR that fall into the GO categories of 'cell cycle process' or 'meiotic cell cycle' or are MAP kinases that may be of interest for immediate future study in relation to the DDR network in *Arabidopsis thaliana*.

With the wide availability of genomic data on *Arabidopsis thaliana* as well as programs for GO enrichment analysis the results of this brief study only begin to scratch the surface of investigation into the plant DDR network through computational means. It is the hope that the results of this broad scale screening and classification of DNA repair related genes in *Arabidopsis thaliana* will serve as an important basis for future studies in plant DNA repair.

Understanding the DNA repair network is critical in improving the resistance of plants to a wide variety of abiotic and biotic stresses [GAO & al. 2022; SZURMAN-ZUBRZYCKA & al. 2023] as well as for providing a means of efficient genome modification [MANOVA & GRUSZKA, 2015; SHEN & LI, 2022]. By gaining a strong understanding of the plant DDR network in *Arabidopsis thaliana,* we set the stage to progress to applying this knowledge for the improvement of agriculturally important crop species [GRIN & al. 2023].

Acknowledgements

This work was supported by a research grant to Tim XING from Bayer Crop Science Inc. and Carleton University, Canada.

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How to cite this article:
MORAN J. & XING T. 2024. Computational screening to identify genes involved in DNA repair in *Arabidopsis thaliana*. *J. Plant Develop*. **31**: 215-227. https://doi.org/10.47743/jpd.2024.31.1.943