## Discussion

We introduced PlantFUNCO, a database to allow the community further inspection of the crosstalk between evolution and phenotypic plasticity in terms of epigenomics/functional-genomics. This database is derived from two resources presented and analysed in this work for three well-established plant models. On one hand, we generated inter-species CS using hiHMM (**fig. 1**). While this flexible framework provides a consistent definition of CS across multiple genomes, making easier direct comparison between them, the stack approach allows the understanding of the potential epigenomic regulation over several tissues/conditions such as differentiating constitutively active/repressive regions (Vu & Ernst, 2022). CS link with different types of evolutionary information setted a foundation for the epigenomics inter-species perspective (**fig. 2**; **fig. 3**). It should be noted that all the approaches have trade-offs so this resource should be considered complementary to and not a replacement to other single-species/condition annotations. On the other hand, we obtained functional genomics conservation scores using LECIF. In accordance to the abovementioned framework, LECIF can handle very diverse datasets and take advantage of it to quantify functional conservation. Plants LECIF-score elucidated functional-genomics cross-species agreement without being correlated with other comparative-genomics sources (**fig. 5**). Hence, probably reflecting a complementary side of the evolution. Despite the greater divergence between plants models compared to metazoans (Ho et al., 2014; Kwon & Ernst, 2021), both resources results are coungruent with a higher plant epigenomic/functional complexity probed by more states with species-specific features and lower values of LECIF-scores.

A major focus of this study was to illustrate an application of the generated resources. Due to the holistic approach adopted and exploiting that our inter-species CS could differ between constituvely active/repressive regions, we replicated two previously published models predicting paralogous functional divergence in Arabidopsis (Cusack et al., 2021; Ezoe, Shirai, & Hanada, 2021) including our CS information. We evaluted if CS simmilarity could be a determinant of duplicates degree of functional divergence under the initial hypothesis that two paralogs covered by different state profiles are more likely to present distinct functions. Although models are far from being perfect, useful information about gene features can be extrapolated. These models independently reported CS information as relevant and including this type of data improved general redundancy predictions (**fig. 4**). Thus, showing an example of how PlantFUNCO integrative resources could be effectively employed to genomic elements prediction.

An important goal of a database is to functionally translate applications into solutions for explaining complex biological mechanisms, so we decided to check redundancy predictions of AOX genes. DFD values were high enough to be considered and AOX earlier research made their context of high biological interest. Very briefly, past reports were mainly focused in the dominant isoform *AOX1A* (cita) which have a redundancy relation described with *AOX1D* (cita), but current literature is not congruent with the use of single *aox1a* or double *aox1a-aox1d* mutants (citas) to discover retrograde-signalling/metabolism/stress-response (cita) causal drivers. Additionally, more AOX isoforms exists but their relationships were still not addressed. To test our redundancy predictions we monitorized seedlings phenotypes in root-expressed AOX single knockout mutants (*aox1a*, *aox1d* and *aox1c*) under drought-heat and oxidative stresses (**fig. 6**). The abnormal seedling growth observed for all the single mutants in control and mock conditions validated our high functional divergent predictions because in case of redundancy other duplicates could rescue these phenotypes (Ezoe, Shirai, & Hanada, 2021). Our findings suggested that the dominant *AOX1A* could retain the ancestral AOX function because it was marked as functionally conserved with the distant-related *O. sativa* and was the only one covered by an active CS, so all the redundancy relations could be pontentially compared to this gene*.* Taking into account that oxidative stress was more severe than drought-heat conditions, we found putative evidence of a probable stress-dependent partial non-mutual redundacy of *AOX1D* to *AOX1A*. While *AOX1D* could partially alleviate *aox1a* raw hydrogen peroxide content in drought-heat (no significant), during more severe oxidative conditions *AOX1D* would not be enough to supply *AOX1A* function (significant). It is defined as a potential non-mutual relation because in all the cases *aox1d* phenotypes remained significant. Finally, nonmeaningful differences in raw hydrogen peroxide content for both stresses and WT-like root length under drought-heat in *aox1c* would probably propose *AOX1C* as a non-stress-responsive gene. This could agree to the already described *AOX1C* oxidative-stress expression insensitivity (cita), but we still found root length significant differences in our severe oxidative assay. That said and compared to other genotypes, p-value was close to significance absence so *AOX1C* may only be related to stress under severe conditions and could be probably defined as almost non-stress-responsive. In summary, stress seems to be a crucial evolutionary force driving neosubfunctionalization (cita) in AOX genes and we characterized the unknown *AOX1C* asalmost stress-insensitive in seedling stages. Furthermore, extra attention should be taken when using double AOX mutants to interrogate causal determinants of biological processes because all AOX genes evaluated appeared to be functionally divergent during early development.

PlantFUNCO resource; genomic diversity and unification. Hypothesis paralog evolution, e utility of LECIF will continue to grow for identifying regions conserved at the functional genomics level and transferring findings from mouse and other model organism research to human biology.

We further developed a functional application revealing

Con el increment de track Genome Era etc.

The resources and tools which constitute PlantFUNCO

Integrative features needed for genomic elements and patterns discovery.

Therefore, simplifying genome annotation across tissues/species through a single segmentation.

Paralog ancestral function hypothesis

Diversidad de datos perdida de oportunidad para entender conservacion. DB and future of evolutionary epigenomics. Hypotehsiis unificar conclusions y ver como fascinanemente ha evolucionar la diversidad molecular. Further expansion to other well know models.

wide range of genomic prediction properties for the community.. Deep and narrow vs shallow and broad

--- last intro parragraph

Previous research analyzing inter-species functional-genomics has mostly been focused on compare same assay matched experiments. These works have been crucial for in-depth study of molecular machinery, but missed the power of diverse datasets for conservation inference. In contrat to this narrow but deep knowledge bottleneck, we adopted a broad but shallow approach using heterogeneous functional-genomics to directly search simple large-scale answers that we would never have contemplated asking based on our understanding of single-assay/species information (cita). In the current Earth Biogenome era there are more and more genomes and functional tracks becoming available (cita), thus, highlighting the urge of using integrative tools that consider the vast diversity of biological strategies and enable broad genomic elements prediction. In the present study, taking into account the abovementioned knowledge trade-off, we introduced PlantFUN(ctional)CO(nservation) database constituted by several tools and two main resources, inter-species chromatin states and functional genomics conservation scores, for the well-known plant models *Arabidopsis thaliana*, *Oryza sativa* and *Zea mays*. Overall, both resources can elucidate evolutionary information in terms of cross-species functional agreement, therefore PlantFUNCO can complement other comparative-genomics sources to asses conservation and diversity. To illustrate how results derived from the resources generated could be functionally relevant, we developed an application of the database and found that chromatin state information improved paralogous degree of functional divergence predictions. Lastly, we validated the redundancy predictions based on phenotypic effects of AOX genes knockout mutants under several stres conditions.