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Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

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Citation (APA):

Kjærboelling, I., Vesth, T. C., Frisvad, J. C., Rasmussen, J. L. N., Theobald, S., Grigoriev, I. V., ... Andersen, M. R. (2017). *Identifying more than 300 Biosynthetic Gene Clusters with Potential Resistance Genes in over 75 Aspergillus species using Resistance Gene-Guided Genome Mining*. Poster session presented at 29th Fungal Genetics Conference, Pacific Grove, United States.

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Identifying more than 300 Biosynthetic Gene Clusters with Potential Resistance Genes in over 75 *Aspergillus* species using Resistance Gene-Guided Genome Mining

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With the increasing number of genome sequences, an increasing number of orphan /cryptic secondary metabolite biosynthetic gene clusters (BCGs) has followed. These clusters potentially encode pathways for bioactives, however linking genes to compound and elucidating bioactivity requires extensive work. Thus, the question remains how to select the most interesting clusters in a rational manner and find their bioactivity. By using Resistance Gene-Guided Genome mining, it is possible to identify novel bioactive compounds and their clusters.

The hypothesis for this approach is that some BGCs include a gene which is a resistant form of the enzyme targeted by the compound produced by the cluster. In filamentous fungi, this mechanism has been seen for mycophenolic acid as well as Fellutamide B. By using this knowledge and a large number of fungal genomes, we have set up a pipeline, which extracts predicted clusters with potential resistance genes.

A total of over 300 clusters were found to exhibit this specific pattern by running our algorithm on more than 75 species and 5000 (SMURF) predicted gene clusters. With further filtering and analysis, we ended up with a manageable number of potential resistance genes and clusters. The filters used in this algorithm will return clusters where one gene in the cluster has a homolog conserved in 98% of the examined species. Although we use a conservative approach it ensures that the identified clusters are most likely of interest. Selected clusters and resistance genes are now being validated experimentally both to confirm the resistance mechanism and to identify the compounds produced.