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Genus level analysis of secondary metabolism reveals the origin of *Aspergillus* hybrid NRPS-PKS gene clusters

Sebastian Theobald (1), Tammi C. Vesth (1), Jane L. Nybo (1), Inge Kjærboelling (1), Jens C. Frisvad (1), Kristian F. Nielsen (1), Thomas O. Larsen (1), Igor V. Grigoriev (3), Asaf Salamov (3), Uffe H. Mortensen (1), Scott E. Baker (2), Mikael R. Andersen (1)

1. Department of Systems Biology, Technical University of Denmark, Kgs. Lyngby, Denmark
2. Joint Bioenergy Institute, Berkeley, CA, USA
3. Joint Genome Institute, Walnut Creek, CA, USA

The World Health Organization is reporting a rising number of multiple drug resistant pathogens every year, increasing the need for new drug development. However, current methods for natural product discovery rely on time consuming experimental work, making them unable to keep up with this demand.

In the *Aspergillus* genus sequencing project, we are sequencing and analyzing over 300 species of *Aspergilli*, a group of filamentous fungi rich in natural compounds. Natural products are encoded by genes located in close proximity, called secondary metabolic gene clusters (SMGC), which makes them interesting targets for genomic analysis. Important classes of SMGC include non ribosomal peptide synthetases (NRPS), polyketide synthases (PKS) and hybrids thereof.

We use a modified version of the Secondary Metabolite Unique Regions Finder (SMURF) algorithm, combined with InterPro annotations, network analysis and approximate maximum likelihood (ML) trees of conserved domains, giving insights into the secondary metabolism gene diversity and evolution. In this study we describe the diversity of hybrid SMGC among *Aspergilli*, horizontal gene transfers within and outside *Aspergilli* and identify possible ancestors of hybrids. ML analysis indicated PKS-NRPS hybrids being of bacterial origin and having an ancestor cluster in the *Streptomyces* and *Achromobacter* genus. NRPS-PKS hybrids showed a wide diversity with orthologs being found in different Ascomycete classes like Dothideomycetes, Eurotiomycetes, Sordariomycetes and others. Here, our genus level study enables us to determine which hybrids might have been horizontally transferred to the precursor of a whole section, driving speciation of this section by a selective advantage. Examining these events helps us to identify the origin of secondary metabolites in *Aspergilli* and also provides us with new variants of compounds for industrial applications.