

<https://doi.org/10.1038/s42003-024-07068-7>

Acquisition and evolution of the neurotoxin domoic acid biosynthesis gene cluster in *Pseudo-nitzschia* species

Check for updates

Ziyan He^{1,2,3,4,7}, Qing Xu^{1,2,4,5,7}, Yang Chen^{1,2,3,4}, Shuya Liu^{1,2,4}, Huiyin Song^{1,2,4}, Hui Wang^{1,2,4}, Chui Pin Leaw⁶ & Nansheng Chen^{1,2,4}

Of the hitherto over 60 taxonomically identified species in the genus of *Pseudo-nitzschia*, 26 have been confirmed to be toxigenic. Nevertheless, the acquisition and evolution of the toxin biosynthesis (*dab*) genes by this extensive group of *Pseudo-nitzschia* species remains unclear. Through constructing chromosome-level genomes of three *Pseudo-nitzschia* species and draft genomes of ten additional *Pseudo-nitzschia* species, putative genomic integration sites for the *dab* genes in *Pseudo-nitzschia* species were explored. A putative breakpoint was observed in syntenic regions in the *dab* gene cluster-lacking *Pseudo-nitzschia* species, suggesting potential independent losses of *dab* genes. The breakpoints between this pair of conserved genes were also identified in some *dab* genes-possessing *Pseudo-nitzschia* species, suggesting that the *dab* gene clusters transposed to other loci after the initial integration. A “single acquisition, multiple independent losses (SAMIL)” model is proposed to explain the acquisition and evolution of the *dab* gene cluster in *Pseudo-nitzschia* species.

Species of the diatom genus *Pseudo-nitzschia* have attracted worldwide attention since the first reported *Pseudo-nitzschia* poisoning incident in 1987 at Prince Edward Island, Canada, which resulted in at least three deaths and 107 cases of illness, and the identification of the neurotoxic glutamate receptor agonist domoic acid (DA) as the toxin synthesized by *P. multiseriata*^{1,2}. DA synthesized by *Pseudo-nitzschia* species has been found to be transferred in the marine food web during bloom events, which may cause illness or death for marine organisms and humans, leading to what is called amnesic shellfish poisoning (ASP)². An unprecedented bloom of another toxigenic *P. australis* in the spring of 2015 resulted in the largest recorded outbreak of DA along the North American west coast, ranging from the Aleutian Islands of Alaska, USA, to the Baja peninsula, Mexico, and resulted in prolonged closures of razor clam, rock crab, and Dungeness crab fisheries³. Similar neurotoxic symptoms have also been observed in animals, including birds and marine mammals⁴. In addition, numerous harmful algal bloom (HAB) events caused by *Pseudo-nitzschia* species have continued to erupt globally, exerting severe impacts on fisheries and the aquaculture industry^{5–7}.

Pseudo-nitzschia blooms have motivated intensive research on the identification and geographical distribution of new *Pseudo-nitzschia* species,

and on the elucidation of mechanisms of DA biosynthesis in *Pseudo-nitzschia* species, which resulted in the identification of key genes of the DA biosynthetic pathway in *P. multiseriata* through comparative gene expression analysis⁸. This study successfully identified a gene cluster, *dab*, with four protein-coding genes: *dabA* (terpene cyclase), *dabB* (hypothetical protein), *dabC* (α -dependent dioxygenase), and *dabD* (CYP450), which encode key enzymes catalyzing reactions extending from the substrate glutamate and geranyl pyrophosphate (GPP) to isodomoic acid A in the genome of *P. multiseriata*⁸. Following this success, *dab* genes were readily identified in *P. multistriata* through genomic analysis and the search for homologous genes⁹, and in *P. australis* and *P. seriata* through transcriptomic analyses^{8–10}. The characterization of the *dab* gene clusters has also facilitated research on the impact of ocean warming and acidification on DA biosynthesis¹¹.

Pseudo-nitzschia is a genus with over 60 cosmopolitan species, up to 50% of which are capable of synthesizing DA^{8,12,13}. This may explain the wide distribution of DA from the Pacific subarctic (58°N) to the Southern Ocean (66°S)¹⁴. Notably, *Pseudo-nitzschia* species that are capable of producing DA are not necessarily phylogenetically closer. Furthermore, of the 26 DA-producing *Pseudo-nitzschia* species, 24 were found to produce DA in some

¹CAS Key Laboratory of Marine Ecology and Environmental Sciences, Institute of Oceanology, Chinese Academy of Sciences, Qingdao, 266071, China.

²Laboratory of Marine Ecology and Environmental Science, Qingdao National Laboratory for Marine Science and Technology, Qingdao, 266200, China. ³College of Marine Science, University of Chinese Academy of Sciences, 10039 Beijing, China. ⁴Center for Ocean Mega-Science, Chinese Academy of Sciences, Qingdao, 266071, China. ⁵Hubei Key Laboratory of Tumor Microenvironment and Immunotherapy, College of Basic Medical Sciences, China Three Gorges University, Yichang, 443002, China. ⁶Bachok Marine Research Station, Institute of Ocean and Earth Sciences, University of Malaya, 16310 Bachok, Kelantan, Malaysia.

⁷These authors contributed equally: Ziyan He, Qing Xu. e-mail: chenn@qdio.ac.cn