Genetic Background of Variable Fumonisin Production in the *Fusarium fujikuroi* Species Complex

Sharmin Sultana¹ and Haruhisa Suga²*

¹ The United Graduate School of Agricultural Science, Gifu University, 1-1 Yanagido, Gifu, 501-1193, Japan
² Life Science Research Center, Gifu University, 1-1 Yanagido, Gifu, 501-1193, Japan

**ABSTRACT**

Fumonisin is a worldwide mycotoxin that has devastating implications for human and animal health and food security. The principal source of fumonisin contamination is the members of the *Fusarium fujikuroi* species complex (FFSC). A cluster (*FUM* gene cluster) of 16 co-expressed genes (*FUM*) responsible for fumonisin biosynthesis has been identified and characterized in *Fusarium verticillioides*. The *FUM* gene cluster has been detected from other members of the FFSC. In this review, the fumonisin production ability and the status of the *FUM* gene cluster in 3 clades (African, American, and Asian) of the FFSC have been presented. The comprehensive studies revealed that intraspecific variation is caused by several types of mutations in the *FUM* gene cluster. In addition, we summarized the regulatory genes involving fumonisin biosynthesis. A comparative study of fumonisin production ability and regulatory mechanism of fumonisin biosynthesis provides valuable insight for control of the mycotoxin contamination.

**Keywords**

Fumonisin, *FUM* gene cluster, inter- and intra-species diversity, regulatory genes

1. Introduction

The *Fusarium fujikuroi* species complex (FFSC) includes important pathogens to various crops. This species complex corresponds to mostly *Fusarium moniliforme* Sheild. or section *Liseola* defined by Wollenweber and Reinking. Fifty phylogenetically different species and 12 mating populations (MP-A to MP-L) are comprised in the FFSC at least [1, 2]. The FFSC members can be divided into three phylogenetic clades; the American, African, and Asian clades [1] and are known to produce a broad spectrum of secondary metabolites including fumonisin.

Fumonisin is a carcinogenic polyketide mycotoxin, chemically, a diester of propane-1, 2, 3-tricarboxylic acid and pentahydroxyicosane containing primary amino acid [3]. There are several types of fumonisin. Fumonisin B₁ (FB₁), B₂ (FB₂) and B₃ (FB₃) are the major forms found in varieties of crops and foods. In the world, fumonisin contamination has an impact on the quality of maize products such as cornflakes, Portuguese maize bread, chips, corn starch, grits, flour, popcorn and so on [4,5] because fumonisin is heat stable. The maximum tolerable daily intake of FB₁, FB₂ and FB₃ alone or together, is 2 µg/kg body weight per day [6].

Fumonisin has adverse effects on humans and animals [7]. Fumonisin intake causes leukoencephalomalacia in horses [8], pulmonary edema, liver and pancreatic lesions in swine [9], neural tube defect in the fetus of the pregnant woman [10], skin lesions [11], liver and kidney disease in mammals [12, 13]. Consume of high concentration of FB₁ causes esophageal cancer in China and South Africa and upper gastrointestinal tract cancer in Northern Italy [7, 14]. Furthermore, fumonisin contamination in breast milk has been also reported [15]. FB₁ causes damages to the cell...
membranes, disruption of chlorophyll and sphingolipid biosynthesis in maize [16]. Doehlert et al. [17] suggested that high concentration fumonisin might have a deleterious effect on maize seedling emergence.

Twenty four members of the FFSC were identified as fumonisin producers. All over the world, FFSC members that produce FB₁ were detected from maize, rice, wheat, barley, oat, hops, sorghum, millet, soybean, asparagus, garlic, ginger, oil palm, mango, banana, strawberry and so on [18, 19, 20, 21]. Fusarium verticillioides, the pathogen of maize ear rot, has been known as the predominant contaminant source of fumonisin worldwide. The whole-genome sequence of F. verticillioides was revealed by Ma et al. [22]. The presence of inter and intra-specific variation in fumonisin production has been notified in the FFSC. However, fumonisin producibility in the FFSC is confused and the information of the cause of fumonisin production variability is limited so far.

2. Fumonisin biosynthetic pathway and the gene cluster

The fumonisin biosynthesis starts with the formation of linear dimethylated polyketide (20-carbon linear polyketide) as well as the condensation of the polyketide with alanine, followed by a carbonyl reduction, oxygenations and esterification with two propane-1, 2, 3-tricarboxylic acids (tricarboxylic acid-coA) [23] (Fig. 1). The 16 FUM genes involved in the fumonisin biosynthesis are clustered in the 42 kbp-stretch of the F. verticillioides genome (FUM gene cluster) (Fig. 2, Table 1). The order and orientation of FUM genes were the same in F. verticillioides and Fusarium proliferatum [24, 25]. The cluster contains a Zn(II)-2Cys6 DNA binding transcription factor (FUM21) [26], a polyketide synthase (FUM1) [24], an aminotransferase (FUM8) catalyzes the condensation of polyketide and alanine to form the 20-carbon-long fumonisin backbone [25], a cytochrome p450 monoxygenase (FUM6) catalyze hydroxylation at C-14 and C-15 [27], a C-3 carbonyl reductase (FUM13) [28], another cytochrome p450 monoxygenase (FUM12) catalyzes the hydroxylation of C-10 [29], 2-ketoglutarate deoxygenase (FUM3) catalyzes the hydroxylation of C-5 [30]. Tricarboxylic acid esterification is conducted by four genes FUM7, FUM10, FUM11 and FUM14 [31, 32]. Two genes are longevity assurance factors (FUM17 and FUM18) and the terminal one is ABC transporter (FUM19) [24]. However, each gene disruption of FUM15 (cytochrome p450 monoxygenase gene), FUM16, FUM17, FUM18 and FUM19 did not affect fumonisin production in F. verticillioides [23, 31].

![Figure 1: Fumonisin biosynthetic pathway in Fusarium verticillioides. The pathway shows genes and products. The final products were indicated by gray ellipses. The chemical structure of fumonisin B₁ (FB₁) was indicated at the bottom.](image-url)
Figure 2: Fumonisin biosynthesis gene cluster in FFSC members. The presence of genes is indicated by black arrows whereas the absence of genes is indicated by white arrows. Gray box indicates insertional sequence.

Table 1: Genes involving fumonisin biosynthesis

| Gene   | Gene ID  | Function                                      | Reference |
|--------|----------|-----------------------------------------------|-----------|
| FUM21  | FVEG_14633 | Fumonisin biosynthesis gene cluster           | [26]      |
| FUM1   | FVEG_00316 | Polyketide synthase                           | [24]      |
| FUM6   | FVEG_00317 | Fumonisin oxygenase                           | [27]      |
| FUM7   | FVEG_00319 | Alcohol dehydrogenase                         | [27]      |
| FUM8   | FVEG_00318 | Aminotransferase                              | [25]      |
| FUM3   | FVEG_00320 | Fumonisin 5-oxygenase                         | [30]      |
| FUM10  | FVEG_00321 | Tricarballylic esterification                 | [31]      |
| FUM11  | FVEG_00322 | Tricarballylic esterification                 | [31]      |
| FUM12  | FVEG_00323 | Fumonisin 10-oxygenase                        | [29]      |
| FUM13  | FVEG_00324 | C3 carbonyl reductase                         | [24]      |
| FUM14  | FVEG_00325 | Tricarballylic esterification                 | [32]      |
| FUM15  | FVEG_00326 | Cytochromosome P450 monoxygenase              | [24]      |
| FUM16  | FVEG_00327 | Similarity to tomato longevity assurance factor | [24]      |
| FUM17  | FVEG_00328 | Similarity to tomato longevity assurance factor | [24]      |
| FUM18  | FVEG_00329 | Similarity to ATP-binding cassette (ABC)      | [24]      |
| AMY1   | FVEG_12951 | a-Amylase                                     | [36]      |
| ARE4   | FVEG_02033 | Regulator of nitrogen metabolism              | [47]      |
| ART1   | FVEG_02083 | Starch-responsive transcription factor         | [93]      |
| CPP1   | FVEG_09543 | Protein phosphatase 2A catalytic subunit      | [94]      |
| FCC1   | FVEG_11306 | FCK1 cyclin                                   | [95]      |
| FCK1   | FVEG_11159 | Cyclin-dependent kinase                       | [95]      |
3. Regulation of fumonisin production

Most research on the factors that affect fumonisin production has been conducted with *F. verticillioides*. The environmental factors impacting the fungal growth and fumonisin production are temperature, light wavelength, and humidity [33, 34, 35]. Nitrogen availability, surrounding pH, carbon nutrients also affect fumonisin production in *F. verticillioides* [36, 37]. Regulatory mechanisms of fumonisin production have been revealed (Fig. 3, Table 1) though these are considered as a part of complex mechanisms of fumonisin production regulation.

| Gene ID (Fusarium verticillioides) | Gene ID (Fusarium fujikuroi) | Function Description |
|----------------------------------|-------------------------------|----------------------|
| FLBA1 FVEG_08855                |                                | Regulator of G-protein signaling [96] |
| FLBA2 FVEG_06912                |                                | Regulator of G-protein signaling [96] |
| FST1 FVEG_08441                 |                                | Hoxose transporter [97] |
| FUG1 FVEG_04008                 |                                | Unknown, likely transcriptional regulator [42] |
| FvBCK1 FVEG_05000               |                                | Mitogen-activated protein kinase (MAPK) kinase [98] |
| FvMK1 FVEG_05063                |                                | MAPK [44] |
| FvSET1 FVEG_07811               |                                | H3K4 methyltransferase [49] |
| FvSO FVEG_08055                 |                                | WW domain protein, signaling component [45] |
| FvVE1 FVEG_09521                |                                | Velvet-domain-containing protein [99] |
| FvVELB FVEG_01498               |                                | Velvet-domain-containing protein [100] |
| GBB1 FVEG_10291                 |                                | Heterotrimeric G-protein B subunit [101] |
| GBP1 FVEG_05543                 |                                | Monomeric G-protein [102] |
| LAE1 FVEG_05214                 |                                | Global regulator of secondary metabolism [40] |
| MADS1 FVEG_01965                |                                | MADS-box transcription factor [41] |
| MADS2 FVEG_03759                |                                | MADS-box transcription factor [41] |
| PAC1 FVEG_05393                 |                                | pH regulatory component [103] |
| SGE1 FVEG_01950                 |                                | Transcriptional regulator [39] |
| ZFR1 FVEG_09648                 |                                | FCC1-dependent transcription factor [104] |
| GCN5 FUJ_00382                  |                                | Histone 3 lysines (H3K4, H3K9) acetylase [50] |

a) Gene ID of whole genome sequence of *Fusarium verticillioides* strain 7600 [22]
b) Gene ID of whole genome sequence of *Fusarium fujikuroi* strain IMI 58289 [105]
Figure 3: Regulatory mechanism model of expression of fumonisin biosynthesis gene cluster. The ellipses show characteristic categories. The genes with “∗” are negative regulator and the genes with “†” are included in multiple characteristic categories. The histone modification is shown by dot ball. The white arrow in the ‘eu chromatin’ means expression of the FUM gene cluster.

### 3.1 Pathway specific activator

FUM21, a Zn(II)2Cys6 transcription factor with alternative splice forms, plays a key role in fumonisin production in *F. verticillioides* [26]. Sultana et al. [38] identified the stop codon causing 11 amino acids deletion in the terminal region of FUM21 resulted in fumonisin non-production in a *F. fujikuroi* strain. The global regulators LAE1 and SGE1 are also involved in fumonisin production [39, 40]. Disruption of MADS1 (a conserved transcription factor) exhibits a reduction of polyketide synthase gene transcription and fumonisin biosynthesis [41]. Recently, FUG1 was identified as a transcriptional regulator integral to fumonisin production in *F. verticillioides* [42].

### 3.2 Signaling components

The signaling pathway has adapted and diverged within *F. verticillioides* and *Fusarium graminearum* to regulate species-specific secondary metabolite production [43]. Disruption of MAPK (FvMk1) causes a decrease of fumonisin production in *F. verticillioides* [44]. Similarly, disruption of FvSo that is the homologue of *Neurospora crassa* SO gene involving hyphal fusion exhibited pleiotropic symptoms and reduced FB1 production [45]. The HOG-type MAP kinase pathway was shown to be decisive for the fumonisin production in *F. proliferatum* [46]. Disruption of AREA that is a global regulator and involved in nitrogen utilization lost fumonisin production in *F. verticillioides* although its direct regulation of FUM genes remains to be unknown [47].

### 3.3 Epigenetic regulation

Chromatin-based regulation through histone modifications, such as acetylation or methylation affects the expression of the secondary metabolite gene cluster. The epigenetic analysis demonstrated that histone acetylation...
has a significant effect on FUM gene expressions and fumonisin biosynthesis [48]. Disruption of FvSET1 encoding H3K4-specific histone methyltransferase caused the loss of FB1 production in F. verticillioides [49]. GCN5, the components of the SAGA complex, is known to be essential for acetylation of histone 3 lysines (H3K4, H3K9, H3K18, and H3K27) in F. fujikuroi. Disruption of GCN5 caused downregulation of H3K9ac and FUM1 expression [50].

4. Fumonisin production diversity

The frequency and the amount of fumonisin production in the members of FFSC have been varied in the preceding publications [51, 52]. Direct comparisons of fumonisin production among publications are difficult due to different assay methods taken in individual investigations. Consequently, the fumonisin amount indicated in this review needs to be evaluated in consideration of these difficulties.

4.1 African clade
4.1.1 F. verticillioides

Almost all F. verticillioides strains from maize have been reported to produce a high amount of fumonisin. Detected fumonisin concentration and the frequency of fumonisin producing strain were 10.6 to 4,749 µg/g and 94%, respectively, in Choi et al. [53] and 5.6 to 25, 846.4 µg/g and 97.1% in Acuna et al. [54]. The highest amount (32,756 µg/g) of fumonisin was detected in F. verticillioides from maize in Indonesia [55]. Fumonisin production has also been detected in F. verticillioides from wheat (2,050 to 14,400 µg/g) [56], rice [51], banana, and so on. F. verticillioides strains from banana in Central America and the Canary Islands were unable to produce fumonisin [57] due to the absence of the FUM gene cluster except for portions of FUM21 and FUM19 [58] (Fig. 2). It was revealed that FB2 or FB3, not FB1 production attributed to the defect of FUM12 and FUM3 [61].

4.1.2 Fusarium nygamai

Nelson et al. [62] detected fumonisin production in F. nygamai from millet and sorghum (3148 µg/g, 37% of the strains investigated). Theil et al. [63] identified one strain of F. nygamai that produced 605 µg/g fumonisin. All F. nygamai strains from poultry feeds of Argentina were found to be fumonisin producers (11.0 to 487 µg/g) [64]. The FUM gene cluster was detected from F. nygamai [65].

4.1.3 Other species

The FUM gene cluster was detected in Fusarium ramigenum and Fusarium phyllophilum (2.5 µg/g) that were reported to produce fumonisin (Fig. 2) [65, 66]. Besides, Fusarium thapsinum (30 µg/g), Fusarium napiforme (16 to 479 µg/g, 16%), Fusarium dialni (42 to 82 µg/g, 55%), Fusarium acutatum (0.14 µg/g), Fusarium brevicatenulatum (0.15 µg/g), Fusarium pseudocircinatum (0.28 µg/g) and Fusarium pseudonygamai (trace amount) were found to produce a low amount of fumonisin [62, 66, 67, 68].
4.2 American clade
4.2.1 Fusarium subglutinans

*F. subglutinans* from maize produced 186 to 426 µg/g fumonisin [51, 69]. Kim *et al.* [70] detected fumonisin production in 7.1% in 141 strains of *F. subglutinans* from rice and corn grains. Reyneso *et al.* [71] observed 95 *F. subglutinans* strains from maize in Argentina produced fumonisin. Whereas, Leslie *et al.* [72] identified only one *F. subglutinans* from prairie grasses produced a trace amount of fumonisin.

4.2.2 Fusarium temperatum

*F. temperatum* has been recognized as a maize pathogen in Poland for three decades [73]. Waskiewicz and Stepien [74] detected 2.25 µg/g fumonisin in *F. temperatum* from pineapple. Wang *et al.* [75] reported that *F. temperatum* from maize in China produced fumonisin under field conditions and Fumero *et al.* [76] detected fumonisin production in 25% of *F. temperatum* strains from maize in Argentina. Recently, Fumero *et al.* [77] obtained the whole genome sequence of a *F. subglutinans* strain and a *F. temperatum* strain from Argentina and that suggested absence of *FUM* genes and fumonisin production in these strains.

4.2.3 Other species

*Fusarium bulbicola* and *Fusarium anthophilum* were found to carry the *FUM* gene cluster and produced fumonisin (58 to 613 µg/g, 18%) (Fig. 2) [62, 65]. These two species were fumonisin C (FC) producers. Two amino acid substitutions in *FUM8* were detected between FB (*F. verticillioides*) and FC-producing species [65]. Darnetty and Saleh [55] found only one strain of *Fusarium konzum* produced 30.1 µg/g fumonisin as Leslie *et al.* [72] detected 120 µg/g fumonisin in this species. *Fusarium begonia* produced 0.07 µg/g fumonisin [66].

4.3 Asian clade
4.3.1 Fusarium proliferatum

The predominant fumonisin producing species in the Asian clade is *F. proliferatum*. *F. proliferatum* is considered the most hazardous because of the wide variety of host plants. Laday *et al.* [78] showed high genetic variability and host preferences in *F. proliferatum*. Significant intraspecific variability of growth rate was observed in *F. proliferatum* from garlic [79]. The highest amount (30,949 µg/g) of fumonisin production in *F. proliferatum* was reported as the strain from maize [80]. The frequency of fumonisin production in *F. proliferatum* was 38 to 100% [55, 62]. FB1 production was detected at 156 to 21,423 µg/g of 100% [55] in *F. proliferatum* from maize, 6 to 7,969 µg/g of 96% from rice, maize, barley and soybean [53], 7.0 to 3,299 µg/g of 100% from pineapple [81], 5 to 922 µg/g of 100% from wheat [56], 663 to 3,503 µg/g of 99% from wine grapes [51], 155 to 2,936 µg/g of 38% from peanuts, pearl millet, sorghum, wheat and corn [62]. The *FUM* gene cluster was detected in *F. proliferatum* [65] (Fig. 2).

4.3.2 Fusarium fujikuroi

*F. fujikuroi* is well known as the rice pathogen. Desjardins [82] reported that 58% of *F. fujikuroi* strains from rice produced 5 to 1,000 µg/g fumonisin in maize culture. Subsequently, fumonisin production has been detected in *F. fujikuroi* from maize [53], wheat [56], strawberries [83], grapes [51] and soybeans [53]. A high amount of fumonisin production has been observed in *F. fujikuroi* from soybeans (5,065 µg/g) [53], rice (14,002 µg/g) [34], maize (3,149 µg/g) [53] and grapes (3,503 µg/g) [51], although different assay methods were used in these studies. The frequencies of fumonisin production in *F. fujikuroi* strains were 40 to 100% [51, 52, 84]. It was found that the
presence of the FUM gene cluster in the genome does not certify the ability of fumonisin production as causative mutations of fumonisin non-production were detected in FUM21 and FUM7 in a F. fujikuroi strain [38]. Rosler et al. [85] detected the low expression of FUM21 in strain IMI 58289 resulted fumonisin low producibility. Recently, the causative mutations of fumonisin non-production were characterized in 44 F. fujikuroi strains: 1) pretermination of FUM21, 2) lack of a part of the FUM gene cluster, 3) the presence of insertional sequences in FUM6 [86] (Fig. 2).

4.3.3 Other species

Fusarium globosum carries the FUM cluster and produced 325 µg/g fumonisin [65, 87]. Fusarium concentricum from pineapple produced fumonisin at 10 µg/g [81]. Kim et al. [70] reported the frequency of fumonisin production in F. concentricum strains from the rice and cornfield was 6% and 3%, respectively.

4.3.4 Clade-unspecified species

Several FFSC members that have not been classified into three clades such as Fusarium polyphialidicum (3 to 19 µg/g), Fusarium ananatum (0.2 to 10 µg/g), Fusarium andiyazi (trace amount) from pineapple, maize, and other crops were reported to produce fumonisin at the low level [68, 81].

5. Overview

The level of fumonisin production depends on genetic variation, environment, and substrate [88]. In the FFSC, the ability of fumonisin production is correlated with the presence of FUM genes but not correlated with phylogenetic relationships [59, 87]. Lack of FUM genes was indicated in the species that had been reported as fumonisin producer (F. napiforme, F. dlamni, F. subglutinans, F. temperatum) [67, 77, 89, 90]. The possible reason for these irrationalis is an intraspecific variation of fumonisin producibility. Strain dependent analyses should help to resolve this issue. Proctor et al. [87] suggested that FUM genes are discontinuously distributed in the FFSC. In addition, even if FUM genes are present, a mutation causing the genes non-functional results in fumonisin non-production. Genetic variations associated with fumonisin producibility have been mainly investigated in F. verticillioides, F. proliferatum and F. fujikuroi [79, 86, 91, 92] and that in other members have not been elucidated so far.

Sexual reproduction might increase the adaptation ability in an adverse environment with the creation of intraspecific genetic variations. Genetical differences responsible for secondary metabolite producibility can be identified by molecular genetic and biochemical analyses. Inter and intraspecific natural variation of fumonisin production in the FFSC has received attention because this variation has an impact on agriculture and human health. Research on genetic variation associated with fumonisin producibility in the FFSC is valuable for the welfare of mankind in the future.

REFERENCES

[1] O’Donnell K, Cigelnik E and Nirenberg HI (1998) Molecular systematics and phylogeography of the Gibberella fujikuroi species complex. Mycologia, 90: 465–493.
[2] Lima CS, Pfennig LH, Costa SS, Abreu LM and Leslie JF (2012) Fusarium tupiense sp. nov., a member of the Gibberella fujikuroi complex that causes mango malformation in Brazil. Mycologia, 104: 1408–1419.
[3] Gurung NK, Rankens DI and Shelby RA (1999) In vitro ruminal disappearance of fumonisin B1 and its effects on in vitro dry matter disappearance. Vet. Hum. Toxicol., 41: 196–199.
[4] Scudamore K, Scriven F and Patel S (2009) Fusarium mycotoxins in the food chain: Maize-based snack foods. World Mycotoxin J., 2: 441–450.

[5] Castells M, Marin S, Sanchis V and Ramos AJ (2008) Distribution of fumonisin and aflatoxins in corn fractions during industrial cornflake processing. Int. J. Food Microbiol., 123: 81–87.

[6] World Health Organization (2002) Evaluation of certain mycotoxins in food. WHO Tech. Rep., 906: 16–27.

[7] Marasas WFO (2001) Discovery and occurrence of the fumonisins: a historical perspective. Environ. Health Perspect., 109: 239–243.

[8] Marasas WFO, Kellerman TS, Gelderblom WCA, Coetzer JAW, Theil PG and van der Lugt JJ (1988) Leucoencephalomalacia in a horse induced by fumonisin B1 isolated from Fusarium moniliforme. Onderstepoort J. Vet. Res., 55: 197–203.

[9] Harrison LR, Colvin BM, Greene JT, Newman LE and Cole JR (1990) Pulmonary edema and hydrothorax in swine produced by fumonisin B1 a toxic metabolite of Fusarium moniliforme. J. Vet. Diagn. Invest., 2: 217–221.

[10] Missmer SA, Suarez M, Felkner M, Wang E, Jr, Merrill AH, Rothman J and Hendricks KA (2006) Exposure to fumonisins and the occurrence of neural tube defects along the Texas-Mexico border. Environ. Health Perspect., 114: 237–241.

[11] Ajello L, Padhye AA, Chandler FW and Girmis MR (1985) Fusarium verticillioides (SAAC.) Nirenberg (CABI-IMI 392668) isolated from rice in Nigeria. Agric. Biol. J. N. Am., 1: 103–112.

[12] Makun HA, Gbodi TA, Akanya HO, Salako EA, Ogbadu GH and Umar T (2010) Acute toxicity and total fumonisin content of the culture material of Fusarium verticillioides (SAAC.) Nirenberg (CABI-IMI 392668) isolated from rice in Nigeria. Agric. Biol. J. N. Am., 1: 103–112.

[13] Prelusky DB and Rotter R (1994) Toxicology of mycotoxins. In: Mycotoxins in grains: Compounds other Than Aflatoxins (Miller JD and Trenholm HL eds.) pp.359–403. Eagan press, MN, US.

[14] Wang Y and Zhu T (2002) Mycoflora analysis in staple corn from Linxian Jinggtoucun with high incidence of esophageal cancer. Journal of China Agricultural University, 7: 5–8.

[15] Magoha H, Kimanya M, De Meulenaer B, Roberfroid D, Lachat C and Kolsteren P (2014) Association between aflatoxin M1 exposure through breast milk and growth impairment in infants from Northern Tanzania. World Mycotoxin J., 7: 277–284.

[16] World Health Organization (2000) Environmental health criteria on fumonisin B1 monograph WHO Tech. Rep., 219: 1–87.

[17] Doehlert DC, Knutson CA and Vesonder RF (1994) Phytotoxic effects of fumonisin B1 on maize seedling growth. Mycopathologia, 127: 117–121.

[18] Abbas HK, Cartwright RD, Shier WT, Abouzied MM, Bird CB, Rice LG, Ross PF, Sciumbato GL and Meredith FI (1998) Natural occurrence of fumonisins in rice with Fusarium sheaf rot disease. Plant Dis., 82: 22–25.

[19] Azliza NI, Mohd MH, Nor NMIM and Zakaria L (2017) Fumonisin B1-producing Fusarium species from agricultural crops in Malaysia. Crop Prot., 98: 70–75.

[20] Liu C, Xu W, Liu F and Jiang S (2007) Fumonisins production by Fusarium proliferatum strains isolated from asparagus crown. Mycopathologia, 164: 127–134.

[21] Shetty PH (2011) Natural occurrence and management of fumonisin mycotoxins. Pudicherry University India, Ph.D. Thesis.

[22] Ma LJ, van der Does HC, Borkovich KA, Coleman JJ, Daboussi MJ, Di Pietro A, Dufresne M, Freitag M, Grabherr M, Hentissat B, Houterman PM, Kang S, Shim WB, Woloshuk C, Xie X, Xu JR, Antoniw J, Baker SE, Bluhm BH, Breakspear A, Brown DW, Butchko RA, Chapman S, Coulson R, Coutinho PM, Danchin EG, Diener A, Gale LR, Gardiner DM, Goff S, Hammond-Kosack KE, Hilburn K, Hua-Van A, Jonkers W, Kazan K, Kodira CD, Koehrsen M, Kumar L, Lee YH, Li L, Manners JM, Miranda-Saavedra D, Mukherjee M, Park G, Park J, Park SY, Proctor RH, Regev A, Ruiz-Roldan MC, Sain D, Sathikumar S, Sykes S, Schwartz DC, Turgeon BG, Wapinski I, Yoder O, Young S, Zeng Q, Zhou S, Galagan J, Cuomo CA, Kistler HC and Rep M (2010) Comparative genomics reveals mobile pathogenicity chromosomes in Fusarium. Nature, 464: 367–373.

[23] Desjardins AE (2006) Fumonisins. In: Fusarium mycotoxins chemistry, genetics, and biology (Desjardins AE, ed.): 79–108. The American Phytopathology Society Press.

[24] Proctor RH, Brown DW, Plattner RD and Desjardins AE (2003) Co-expression of 15 contiguous genes delineates a fumonisin biosynthetic gene cluster in Gibberella moniliformis. Fungal Genet. Biol., 38: 237–249.

[25] Proctor RH, Busman M, Seo J-A, Lee Y-W and Plattner RD (2008) A fumonisin gene cluster in Fusarium oxysporum strain O-1890 and the genetic basis for B versus C fumonisin production. Fungal Genet. Biol., 45: 1016–1026.

[26] Brown DW, Butchko RA, Busman M and Proctor RH (2007) The Fusarium verticillioides fum gene cluster encodes a Zn(II)2Cys6 protein that affects FUM gene expression and fumonisin production. Eukaryot. Cell, 6: 1210–1218.
[27] Seo J-A, Proctor RH and Plattner RD (2001) Characterization of four clustered and coregulated genes associated with fumonisin biosynthesis in *Fusarium verticillioides*. Fungal Genet. Biol., 34: 155–165.

[28] Butchko RAE, Plattner RD and Proctor RH (2003a) *FUM13* encodes a short-chain dehydrogenase/reductase for C3 carbonyl reduction during fumonisin biosynthesis in *Gibberella moniliformis*. J. Agric. Food Chem., 51: 3000–3006.

[29] Proctor RH, Plattner RD, Desjardins AE, Busman M and Butchko RAE (2006) Fumonisin production in the maize pathogen *Fusarium verticillioides*: genetic basis of naturally occurring chemical variation. J. of Agric. Food Chem., 54: 2424–2430.

[30] Butchko RAE, Plattner RD and Proctor RH (2003b) *FUM9* is required for C-5 hydroxylation of fumonisins and complements the meiotically defined *fum3* locus in *Gibberella moniliformis*. Appl. Environ. Microbiol., 69: 6935–6937.

[31] Butchko RAE, Plattner RD and Proctor RH (2006) Deletion analysis of *FUM* genes involved in tricarballylic ester formation during fumonisin during biosynthesis. J. Agric. Food Chem., 54: 9398–9404.

[32] Zaleta-Rivera K, Xu C, Yu F, Butchko RAE, Proctor RH, Hidalgo-Lara ME, Raza A, Dussault PH and Du L (2006) Bidomain non-ribosomal peptide synthetase encoded by *FUM14*, catalyzes the formation of tricarballylic esters in the biosynthesis of fumonisins. Biochemistry, 45: 2561–2569.

[33] Magan N (2007) Fungi in extreme environments. In: Environmental and Microbial Relationships. The Mycota, vol.4. (Kubicek CP and Druzhinina IS eds.). pp.85–103. Springer, Berlin, Heidelberg.

[34] Matic S, Spadaro D, Preluț A, Gullino ML and Garibaldi A (2013) Light affects fumonisin production in strains of *Fusarium fujikuroi*, *Fusarium proliferatum* and *Fusarium verticillioides* isolated from rice. Int. J. Food Microbiol., 166: 515–523.

[35] Fanelli F, Schmidt-Heydlt M, Haidukowski M, Geisen R, Logrieco A and Mule G (2012) Influence of light on growth, fumonisin biosynthesis and *FUM1* gene expression by *Fusarium proliferatum*. Int. J. Food. Microbiol., 153: 148–153.

[36] Bluhm BH and Woloshuk CP (2005) Amylopectin induces fumonisin B1 production by *Fusarium verticillioides* during colonization of maize kernels. Mol. Plant. Microbe. Interact., 18: 1333–1339.

[37] Shim WB and Woloshuk CP (1999) Nitrogen repression of fumonisin B1 biosynthesis in *Fusarium verticillioides*. J. Agric. Food Chem., 47: 109–116.

[38] Sultana S, Kitajima M, Kobayashi H, Nakagawa H, Shimizu M, Kageyama K and Suga H (2019) A Natural variation of fumonisin in *Gibberella fujikuroi*. FEMS. Microbiol. Lett., 177: 109–116.

[39] Sultana S, Kitajima M, Kobayashi H, Nakagawa H, Shimizu M, Kageyama K and Suga H (2019) A Natural variation of fumonisin gene cluster associated with fumonisin production difference in *Fusarium fujikuroi*. Toxins, 11: 200.

[40] Butchko RA, Brown DW, Busman M, Tudzynski B and Wiemann P (2012) *Lae1* regulates expression of multiple secondary metabolite gene cluster in *Fusarium verticillioides*. Fungal Genet. Biol., 49: 602–612.

[41] Ortiz CS and Shim WB (2013) The role of MADS-box transcription factors in secondary metabolism and sexual development in the mize pathogen *Fusarium verticillioides*. Microbiology, 159: 2259–2268.

[42] Ridenour JB and Bluhm BH (2017) The novel fungal-specific gene *FUG1* has a role in pathogenicity and fumonisin biosynthesis in *Fusarium verticillioides*. Mol. Plant Pathol., 18: 513–528.

[43] Guo L, Breakspear A, Zhao G, Gao L, Kistler H, Xu J-R and Ma L-J (2016) Conservation and divergence of the cyclic adenosine monophosphate protein kinase A (cAMP-PKA) pathway in two plant pathogenic fungi *Fusarium graminearum* and *Fusarium verticillioides*. Mol. Plant Pathol., 17: 196–209.

[44] Zhang Y, Choi Y-E, Zou X and Xu J-R (2011) The *FvMK1* mitogen activated protein kinase gene regulates conidiation, pathogenesis, and fumonisin production in *Fusarium verticillioides*. Fungal Genet. Biol., 48: 71–79.

[45] Guo L, Wenner N and Kuldau GA (2015) *FvSO* regulates vegetative hyphal fusion, asexual growth, fumonisin biosynthesis, and virulence in *Fusarium verticillioides*. Fungal Genet. Biol., 119: 1158–1169.

[46] Kohut G, Adam AL, Fazekas B and Hornok L (2009) N-starvation stress induced *FUM13* expression by *Gibberella moniliformis*. Appl. Environ. Microbiol., 69: 6935–6937.

[47] Guo L, Breakspear A, Zhao G, Gao L, Kistler H, Xu J-R and Ma L-J (2016) Conservation and divergence of the cyclic adenosine monophosphate protein kinase A (cAMP-PKA) pathway in two plant pathogenic fungi *Fusarium graminearum* and *Fusarium verticillioides*. Mol. Plant Pathol., 17: 196–209.

[48] Guo L, Breakspear A, Zhao G, Gao L, Kistler H, Xu J-R and Ma L-J (2016) Conservation and divergence of the cyclic adenosine monophosphate protein kinase A (cAMP-PKA) pathway in two plant pathogenic fungi *Fusarium graminearum* and *Fusarium verticillioides*. Mol. Plant Pathol., 17: 196–209.

[49] Guo L, Breakspear A, Zhao G, Gao L, Kistler H, Xu J-R and Ma L-J (2016) Conservation and divergence of the cyclic adenosine monophosphate protein kinase A (cAMP-PKA) pathway in two plant pathogenic fungi *Fusarium graminearum* and *Fusarium verticillioides*. Mol. Plant Pathol., 17: 196–209.
[50] Rosler SM, Kramer K, Finkemeier I, Humpf H-U and Tuzynski B (2016a) The SAGA complex in the rice pathogen *Fusarium fujikuroi*: structure and functional characterization. Mol. Microbiol., 102: 951–974.

[51] Bolton SL, Brannen PM and Glenn AE (2016) A novel population of *Fusarium fujikuroi* isolated from southeastern U.S. winegrapes reveals the need to re-evaluate the species' fumonisin production. Toxins, 8: 1–14.

[52] Lee S-H, Kim J-H, Son S-W, Lee T and Yun S-H (2012) Fumonisin production by field isolates of the *Gibberella fujikuroi* species complex from rice and corn in Korea. Plant Dis., 18: 310–316. (In Korean with English abstract)

[53] Choi J-H, Lee S, Nah J-Y, Kim H-K, Paek J-S, Lee S, Ham H, Hong SK, Yun S-H and Lee T (2018) Species composition of and fumonisin production by the *Fusarium fujikuroi* species complex isolated from Korean cereals. Int. J. Food. Microbiol., 267: 62–69.

[54] Accuna A, Lozano MC, de Garcia MC and Diaz GJ (2005) Prevalence of *Fusarium* Species of the Liseola section on selected Colombian animal feedstuffs and their ability to produce fumonisins. Mycopathologia, 160: 63–67.

[55] Darnetty T and Saleh B (2013) Toxigenicity of *Fusarium* species in *Gibberella fujikuroi* species complex associated with stalk and ear rot disease in corn. ESci. J. Plant Pathol., 2: 147–154.

[56] Busman M, Desjardins AE and Proctor RH (2012) Analysis of fumonisin contamination and the presence of *Fusarium* in wheat with kernel black point disease in the United States. Food Addit. Contam., 29: 1092–1100.

[57] Mirete S, Vasquez C, Mule C, Jurado M and Gonzales-Jaen MT (2004) Differentiation of *Fusarium verticillioides* from banana fruits by IGS and EF-1α sequence analysis. Eur. J. Pathol., 110: 515–523.

[58] Glenn AE, Zitomer NC, Zimeri AM, Williams LD, Riley RT and Proctor RH (2008) Transformation-mediated complementation of a *FUM* gene cluster deletion in *Fusarium verticillioides* restores both fumonisin and pathogenicity on maize seedlings. Mol. Plant Microbe Interact., 21: 87–97.

[59] Van Hove F, Waalwijk C, Logrieco A, Munaut F and Moretti A (2011) Survey of fumonisin species complex associated with rice and corn in Korea. Int. J. Food. Microbiol., 267: 62–69.

[60] Plattner RD, Desjardins AE, Leslie JF and Nelson PE (1996) Identification and Characterization of Strains of *Gibberella fujikuroi* mating population A with rare fumonisin production phenotypes. Mycologia, 88: 416–424.

[61] Desjardins AE, Plattner RD and Proctor RH (1996) Linkage among genes responsible for fumonisin biosynthesis in *Gibberella fujikuroi* mating population A. Appl. Environ. Microbiol., 62: 2571–2576.

[62] Nelson PE, Plattner RD, Shackelford DD and Desjardins AE (1992) Fumonisin B1 production by *Fusarium* species other than *F. moniliforme* in section Liseola and by some related species. Appl. Environ. Microbiol., 58: 984–989.

[63] Theil PG, Marasas WFO, Sydenham EW, Shepherd GS Gelderblom WCA and Nieuwenhuis JJ (1991) Survey of fumonisin production by *Fusarium* species. Appl. Environ. Microbiol., 57: 1089–1093.

[64] Magnoli CE, Saenz MA, Chiачchiera SM and Dalcero AM (1999) Natural occurrence of *Fusarium* species and fumonisin production by toxigenic strains isolated from poultry feeds in Argentina. Mycopathologia, 145: 35–41.

[65] Proctor RH, Hove FY, Susca A, Stea G, Busman M, van der Lee T, Waalwijk C, Moretti A, Ward TJ and (2013) Birth, death and horizontal transfer of the fumonisin biosynthetic gene cluster during the evolutionary diversification of *Fusarium*. Mol. Microbiol., 90: 290–306.

[66] Fotso J, Leslie JF and Smith JS (2002) Production of beauvericin, moniliform, fusaproliferin and fumonisin B1, B2 and B3 by fifteen ex-type strains of *Fusarium* species. Appl. Environ. Microbiol., 68: 5195–5197.

[67] Leslie JF, Marasas WFO, Shepherd GS, Sydenham EW, Stockenstrom S and Theil PG (1996) Duckling toxicity and the production of fumonisin and moniliformin by isolates in the A and F mating populations of *Gibberella fujikuroi* (*Fusarium moniliforme*). Appl. Environ. Microbiol., 62: 1182–1187.

[68] MacKenzie SE, Savard ME, Blackwell JD and Apsimon JW (1998) Isolation of a new fumonisin from *Fusarium moniliforme* grown in liquid culture. J. Nat. Prod., 61: 367–369.

[69] Zhang L, Wang J, Zhang C and Wang Q (2012) Analysis of potential fumonisin-producing *Fusarium* species in corn products from three main maize-producing areas in eastern China. J. Sci. Food Agric., 93: 693–701.

[70] Kim J-H, Kang M-R, Kim H-k, Lee S-H, Lee T and Yun S-H (2012) Population structure of the *Gibberella fujikuroi* species complex associated with rice and corn in Korea. Plant Pathol. J., 28: 357–363.

[71] Reynoso MM, Torres AM, and Chulze SN (2004) Fusaproliferin, beauvericin and fumonisin production by different mating population among the *Gibberella fujikuroi* complex isolated from maize. Mycol. Res., 108: 154–160.
Please cite this article as
Sultana and Suga. Reviews in Agricultural Science, 9: 43–55, 2021
https://dx.doi.org/10.7831/ras.9.0_43

[72] Leslie JF, Zeller KA, Wohler M and Summerell BA (2004) Interfertility of two mating populations in the Gibberella fujikuroi species complex. Eur. J. Plant Pathol., 110: 611–618.

[73] Stepień L, Gromadzka K, Ciełkowskii J, Basiańska-Barczak A and Lalak-Kańczugowska J (2019) Diversity and mycotoxin production by Fusarium temperatum and Fusarium subglutinans as causal agents of pre-harvest Fusarium maize ear rot in Poland. J. Appl. Genetics, 60: 113–121.

[74] Waskiewicz A and Stepień L (2012) Mycotoxins biosynthesized by plant-derived Fusarium isolates. Arh. Hig. Rada. Toksikol., 63: 437–446.

[75] Wang ZH, Zhang JB, Li HP, Gong AD, Xue S, Agboola RS and Liao YC (2014) Molecular identification, mycotoxin production and comparative pathogenicity of Fusarium temperatum isolated from maize in China. J. Phytopathol., 162: 147–157.

[76] Fumero MV, Reynoso M, and Chulze S (2015) Fusarium temperatum and F. subglutinans isolated from maize in Argentina. Int. J. Food Microbiol., 199: 86–92.

[77] Fumero MV, Villani A, Susca A, Haidukowski M, Cinmarusti MT, Toomajian C, Leslie JF, Chulze SN and Moretti A (2020) Fumonisin and Beauvericin Chemotypes and Genotypes of the sister species Fusarium subglutinans and F. temperatum. Appl. Environ. Microbiol., 86: e00133–20.

[78] Laday M, Mule G, Moretti A, Hamari Z, Juhasz A, Szecsi A and Logrieco A (2004) Mitochondrial DNA variability in Fusarium species. Mycol. Res., 108: 563–571.

[79] Galvez L, Urbaniak M, Waskiewicz A and Stepień L (2017) Fusarium proliferaturn (Gibberella intermedia). Eur. J. Plant Pathol., 110: 563–571.

[80] Castella G, Bragulat MR and CabanesFJ (1999) Fumonisin production by different Fusarium species isolated from cereals and feeds in Spain. J. Food Prot., 62: 811–813.

[81] Stepień L, Koczyk G and Waskiewicz A (2013) Diversity of Fusarium species and mycotoxins contaminating pineapple. J. Appl. Genet., 54: 367–380.

[82] Desjardins AE, Plattner RD and Nelson PE (1997) Production of fumonisin B1 and moniliformin by Gibberella fujikuroi rice from various geographic areas. Appl. Environ. Microbiol., 63: 1838–1842.

[83] Suga H, Kitajima M, Nagumo R, Tsukiboshi T, Uegaki R, Nakajima T, Kuroshi M, Nakagawa H, Shimizu M and Kageyama K (2014) A single nucleotide polymorphism in the translation elongation factor 1α gene correlates with the ability to produce fumonisin in Japanese Fusarium fujikuroi. Fungal Biol., 118: 402–412.

[84] Desjardins AE, Plattner RD, Shackelford DD, Leslie JF and Nelson PE (1992) Heritability of fumonisin B1 production in Gibberella fujikuroi mating population A. Appl. Environ. Microbiol., 58: 2799–2805.

[85] Sultana S, Bao W, Shimizu M, Kageyama K and Suga H (2021) Frequency of three mutations in the fumonisin biosynthetic gene cluster of Fusarium fujikuroi that are predicted to block fumonisin production. World Mycotoxin J., 14: 49–59.

[86] Proctor RH, Plattner RD, Brown DW, Seo J-Ah and Lee Y-W (2004) Discontinuous distribution of fumonisin biosynthetic genes in the Gibberella fujikuroi species complex. Mycol. Res., 108: 815–822.

[87] Bacon CW and Nelson PE (1994) Fumonisin production in corn by toxigenic strains of Fusarium moniliforme and Fusarium proliferatum. J. Food Protect., 57: 514–521.

[88] Desjardins AE, Plattner RD, Shackelford DD, Leslie JF and Nelson PE (1992) Heritability of fumonisin B1 production in Gibberella fujikuroi mating population A. Appl. Environ. Microbiol., 58: 2799–2805.

[89] Sultana S, Bao W, Shimizu M, Kageyama K and Suga H (2021) Frequency of three mutations in the fumonisin biosynthetic gene cluster of Fusarium fujikuroi that are predicted to block fumonisin production. World Mycotoxin J., 14: 49–59.

[90] Proctor RH, Plattner RD, Brown DW, Seo J-Ah and Lee Y-W (2004) Discontinuous distribution of fumonisin biosynthetic genes in the Gibberella fujikuroi species complex. Mycol. Res., 108: 815–822.
[95] Bluhm BH and Woloshuk CP (2006) FcK1, a C-type cyclin dependent kinase, interacts with Fcc1 to regulate development and secondary metabolism in Fusarium verticillioides. Fungal Genet. Biol., 43: 146–154.

[96] Mukherjee M, Kim J-E, Park Y-S, Kolomiets MV and Shim W-B (2011) Regulators of G-protein signaling in Fusarium verticillioides mediate differential host-pathogen responses on nonviable versus viable maize kernels. Mol. Plant Pathol., 12: 479–491.

[97] Niu C, Payne GA and Woloshuk CP (2015) Transcriptome changes in Fusarium verticillioides caused by mutation in the transporter-like gene FST1. BMC Microbiol., 15: 90.

[98] Zhang C, Wang J, Tao H, Dang X, Wang Y, Chen M, Zhai Z, Yu W, Xu L, Shim W-B and Lu G (2015) FvBck1, a component of cell wall integrity MAP kinase pathway, is required for virulence and oxidative stress response in sugarcane Pokkah Boeng pathogen. Front. Microbiol., 6: 109.

[99] Li S, Myung K, Guse D, Donkin B, Proctor RH, Grayburn WS and Calvo AM (2006) FvVE1 regulates filamentous growth, the ratio of microconidia to macroconidia and cell wall formation in Fusarium verticillioides. Mol. Microbiol., 62: 1418–1432.

[100] Lan N, Zhang H, Hu C, Wang W, Calvo AM, Harris SD, Chen S and Li S (2014) Coordinated and distinct functions of velvet proteins in Fusarium verticillioides. Eukaryot. Cell, 13: 909–918.

[101] Sargaram US and Shim W-B (2007) Fusarium verticillioides GBB1, a gene encoding heterotrimeric G protein ß subunit, is associated with fumonisin B1 biosynthesis and hyphal development but not with fungal virulence. Mol. Plant Pathol., 8: 375–384.

[102] Sargaram US, Butchko RAE and Shim W-B (2006) The putative monomeric G-protein GBP1 is negatively associated with fumonisin B1 production in Fusarium verticillioides. Mol. Plant Pathol., 7: 381–389.

[103] Flaherty JE, Pirrtilla AM, Bluhm BH and Woloshuk CP (2003) PAC1, a pH regulatory gene from Fusarium verticillioides. Appl. Environ. Microbiol., 69: 5222–5227.

[104] Bluhm BH, Kim H, Butchko RA and Woloshuk CP (2008) Involvement of ZFR1 of Fusarium verticillioides in kernel colonization and the regulation of FST1, a putative sugar transporter gene required for fumonisin biosynthesis on maize kernels. Mol. Plant Pathol., 9: 203–211.

[105] Wiemann P, Sieber CMK, von Bargen KW, Studt L, Niehaus E-M, Espino JJ, Huff K, Michielse CB, Albermann S, Wagner D, Bergner SV, Connolly LR, Fischer A, Reuter G, Kleigrewe K, Bald T, Wingfield BD, Ophir R, Freeman S, Hippler M, Smith KM, Brown DW, Proctor RH, Münnstercötter M, Freitag M, Humphre H-U, Guldener U and Tudzynski B (2013) Deciphering the cryptic genome: genome-wide analyses of the rice pathogen Fusarium fujikuroi reveal complex regulation of secondary metabolism and novel metabolites. PLOS. Pathog., 9: e1003475.