Contrasting demographic histories revealed in two invasive populations of the dry rot fungus *Serpula lacrymans*

Inger Skrede[1], Claude Murat[2], Jaqueline Hess[3], sundy Maurice[1], Jørn Henrik Sønstebø[1], Annegret Kohler[4], Dominique Barry-Etienne[5], Dan Eastwood[6], Nils Högberg[7], Francis Martin[8], and Håvard Kauserud[9]

[1]University of Oslo
[2]Institut National de la Recherche Agronomique
[3]Universitat Wien Fakultat fur Lebenswissenschaften
[4]Institut National de la Recherche Agronomique
[5]Societe Mycea
[6]University of Swansea
[7]Sveriges lantbruksuniversitet
[8]INRA, UMR1136 INRA-Université de Lorrain
[9]University in Oslo

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Abstract

Globalization and international trade have impacted organisms around the world leading to a considerable number of species establishing in new geographic areas. Many organisms have taken advantage of human-made environments, including buildings. One such species is the dry rot fungus *Serpula lacrymans*, which is the most aggressive wood-decay fungus in indoor environments in temperate regions. By using population genomic analyses of 36 full genome sequenced isolates, we revealed that isolates from Europe and Japan are highly divergent and that these populations split 3,000 - 19,000 generations ago, probably predating human influence. Approximately 250 generations ago, the European population went through a tight bottleneck, likely corresponding to the time it colonized the built environment. Moreover, evidence of admixture between European and Japanese populations was shown in an isolate from New Zealand. Genomic analyses revealed that low differentiation appeared in genes with functions related to of growth and intracellular transport, possibly important to its ability to effectively decay large substrates. These functions may have enabled both populations to independently establish in the human-made environment. Further, selective sweep analyses identified rapid changes in genes possibly related to decay of various substrates in Japan and in genes involved DNA replication and protein modification in Europe. These two fungal populations were preadapted to the built environment, but have more recently and independently adapted to their local environment.

INTRODUCTION

Due to globalization and climate change an increasing number of fungal species are colonizing new areas worldwide. Numerous plant pathogenic fungi have benefited from modern agriculture practices and trade, and are recognized as growing threats to food security, conservation of biodiversity and global economy (Rosenblum *et al.* 2010; Fisher*et al.* 2012; Islam *et al.* 2016). These fungi often show complex population genetic structure due to multiple dispersal and back-dispersal events, varying demographic histories and hybridization events (Brasier & Kirk, 2010; Gladieux *et al* . 2018, 2014; Stukenbrock *et al* . 2007). Modern agricultural practices involve large-scale monocultures where well-adapted fungal pathogens can colonize and spread rapidly (Stukenbrock & McDonald 2008; Croll & McDonald 2017).

It is less known to what degree fungi adapt to other dimensions of human-made habitats. A few fungi have colonized buildings where the environment is dry. Such species may cause a reduction in indoor air quality or the decomposition of wooden structures with substantial economic losses (Schmidt 2007). In this study, we focus on the dry rot fungus *Serpula lacrymans* (Serpulaceae, Boletales, Agaricomycetes, Basidiomycota). *Serpula lacrymans* is known to be a primary decomposer of large substrates both in nature and in buildings (Harmsen 1960; Kauserud *et al.* 2012). It has a natural distribution in conifer woodlands in high altitude and/or latitude in Asia, from which it has invaded human-made constructions in temperate regions all over the world (Kauserud *et al* . 2007).

Previous population genetic studies based on microsatellites showed that the genetic diversity of the European population is very low (Kauserud*et al.* 2007; Engh *et al.* 2010b; Maurice *et al.*2014), suggesting that a few individuals established through a founder event. Further evidence for a narrow population bottleneck in Europe stems from the observations of a limited number of mating type (MAT) and self-recognition vegetative incompatibility (*vic*) alleles present in European isolates (Kauserud 2004; Kauserud *et al.* 2006; Engh*et al.* 2010b; Skrede *et al.* 2013; Maurice *et al.*2014). Observation of natural Agaricomycete populations indicates high numbers of MAT and *vic* alleles are expected due to frequency-dependent selection acting on both loci (Raper 1996; Engh*et al.* 2010b; Coelho *et al.* 2017).

The European population of *S. lacrymans* has most likely dispersed via human vectors to North and South America, Australia and New Zealand (Kauserud *et al.* 2007). Population genetic analyses indicate that the Japanese dry rot population represents a separate transition from the natural habitat in mainland Asia to the built environment. In addition, the Japanese population possesses significantly higher genetic diversity compared to the European population (Kauserud *et al.*2007), also manifested in the presence of a higher number of MAT and*vic* alleles (Engh *et al.* 2010b). Evidence of admixture between Asian and European populations was identified in isolates from New Zealand (Kauserud *et al* . 2007), suggesting multiple introduction events from different source populations. However, which populations and genetic material have contributed to the variation in the New Zealand population is unknown.

The indoor habitat exploited by *S. lacrymans* resembles its natural habitat in terms of relatively dry conditions during most of the year and scattered presence of large resource units that it colonizes. Nevertheless, the transition to the indoor environment probably imposed a series of novel selective regimes. Based on analyses of allelic variation in a few neutral microsatellite loci, European and Japanese indoor populations appear to be genetically highly differentiated (Kauserud *et al* . 2007). Recent gene expression analyses suggested a wider niche related to competitive ability and substrate breath for a Japanese strain compared to a European strain (Hess *et al* . 2021). However, it is not known whether the two indoor populations possess different adaptations or physiological characteristics as a consequence of their independent evolutionary histories. Adaptive similarities between the two independent founder populations (Europe versus Japan) could indicate which characteristics are crucial for long-term survival in the built environment. Isolates of *S. lacrymans* possess significantly more efficient wood decay on spruce compared to the sister species *S . himantioides* (Balasundaram *et al* . 2018; Hess *et al* . 2021). Further, genomic analyses of these three isolates suggested that the extremely effective brown rot decay mechanism of *S. lacrymans* was due to increased capacity of a chelator mediated Fenton reaction (CMF). The evolution of specifically efficient CMF may be linked to the reduced enzymatic machinery compared to other brown rot fungi (Eastwood *et al.* 2011; Presley & Schilling 2017; Balasundaram *et al.* 2018), including its sister species *S. himantioides* (Balasundaram *et al.* 2018). These genomic analyses suggested that the selection of genes related to intracellular transport and growth were important for the colonization of large substrates.

In this study, we confirmed the presence of two divergent populations of*S. lacrymans* in Europe and Japan. We aimed to estimate the time since establishment in the built environment and the number of haplotypes founding each of these two populations using demographic inference. Previous analyses indidcated that isolates from New Zealand possessed admixed genotypes between European and Japanese isolates. We aimed to investigate whether this is due to a recent admixture event. Finally, we aimed to test whether the European and Japanese populations are locally adapted to the built environment, and whether growth and

wood decay are important during local adaptation. Thus, we searched for genomic islands of differentiation and selective sweeps as signals of selection. We also investigated the wood decay ability of some isolates as a measure of fitness differences across the populations.

MATERIAL AND METHODS

Isolates included

A total of 36 dikaryotic isolates were included in the analyses, 18 from Japan, 16 from Europe (France, Germany, Norway, Poland, UK) and 2 from New Zealand (Table 1). Southern France isolates M1 and M2 were collected from different parts of the same building. French and Japanese isolates were kindly provided by Dr. G. Le Floch, University of Brest, France and Dr. Sakae Horisawa, Kochi University of Technology, Japan, respectively.

DNA extraction and sequencing procedures

DNA of the isolates from Japan and New Zealand, and the non-French European isolates was extracted using a phenol-chloroform protocol available at the JGI webpage (Isolation of genomic DNA from*Phytophthora* : http://jgi.doe.gov/collaborate-with-jgi/pmo-overview/protocols-sample-preparation-information/) combined with the Qiagen Genomic tip protocol (Qiagen, Hilden, Germany). Briefly, about 500 mg fresh mycelium, from isolates grown on Serpula Capex Dox medium (see (Eastwood *et al.* 2011)), was flash frozen in liquid N_2 and ground to powder in a mortar. Sixty mL extraction buffer (0.2 M Tris pH 8.5, 0.25 M NaCl, 25 mM EDTA, 0.5% SDS) was added to the mortar before the sample was distributed into four 50 mL tubes. 15 mL 7:3 phenol:chloroform was added to each sample, before they were mixed and incubated for 90 min at room temperature. The samples were centrifuged at 6000 G for 15 min. The aqueous phase was added to equal volume (V) of chloroform. After mixing, the samples were centrifuged for another 5 min on 6000 G. The aqueous phase was transferred to a clean tube and 0.6 V isopropanol added. The samples were incubated on ice for 30 min before centrifugation at 4 °C at 6000 G for 15 min. The pellet was washed with 20 mL 70% EtOH and dried for five min at RT. The DNA was then dissolved in 500 µL of milli-Q H_2O. The four samples were pooled, 2 mg RNase A (Invitrogen) was added, and incubated for 90 min at 37 °C. Eight mL Qiagen QBT buffer was added, and the mix transferred to Genomic-tip columns and processed following the Qiagen Genomic-tip protocol. The three samples SL200, SL198 and SL265 were extracted without using the Genomic-tip protocol, according to Balasundaram *et al* . (2018). DNA of the French isolates was extracted using a CTAB – Qiagen genomic tip protocol as described in Payen *et al* . (2015).

Genomic DNA was used to construct paired-end (2 x 125 bp) libraries using SBS v4 Sample Prep Kit. Libraries were sequenced using the Illumina HiSeq 2500 platform (Illumina, Inc., San Diego, CA, USA) at the GeT-PlaGe sequencing facility (Toulouse, France). For the isolates SL200, SL198 and SL265 (2 x 108 bp) libraries were sequenced on the Illumina GAII at the SNP&SEQ Technology Platform (Uppsala, Sweden).

Sequence alignment and variant calling

Genomic sequences were analyzed in parallel using two pipelines: (1) the first pipeline trimmed the data using TrimGalore version 0.3.3, aligned using Bowtie2 (Langmead & Salzberg), and SAMtools (Li *et al.* 2009) to include only reads that mapped concordantly and only once to remove PCR duplicates. Variants were called for each alignment using HaplotypeCaller, combined into a common variant file with GenotypeGVCFs and further quality filtered with VariantFiltration (QD<2.0||FS>60.0||MQ<40.0||MQRankSum< -12.5||ReadPosRankSum< -8.0) in Genome Analysis Tool Kit (GATK) (McKenna *et al.* 2010; Van der Auwera*et al.* 2013). (2) The second pipeline trimmed the sequences using Trimmomatic (Bolger *et al.* 2014), mapped the reads using BWAmem (Li 2013), filtered using SAMtools, called variants using BCFtools call and filtered with BCFtools view. For both pipelines, the sequence data were mapped to the monokaryotic *Serpula lacrymans* isolate S7.3, version 2 (Eastwood *et al.* 2011). Repetitive regions of the*S. lacrymans* v. 2 genome were annotated using the REPET package v.2.5 (Flutre *et al.* 2011), following the procedure outlined in (Sipos *et al.* 2017). Regions annotated as transposable element-derived were filtered from the SNP data set using BEDtools (Quinlan & Hall 2010). A combined data set using only SNPs called by both pipelines

resulted in 419,196 high quality SNPs for the 36 isolates included in this analysis.

Population structure and demographic history

To investigate the structure of the dataset, we used a model-based clustering approach as implemented in Admixture (Alexander*et al.* 2009). For the Admixture analyses the number of populations was inferred by analyzing different number of populations (K) and the cross-validation (CV) error for each K. The CV error is used to find which K has the best predictive accuracy, but does not try to determine the absolute K. The full data set including all isolates and SNPs were analyzed, in addition to reduced data sets of only European and only Japanese isolates (SNP data set reduced by minor allele count [?] 1 in VCFtools (Danecek *et al.* 2011)). All datasets were transformed from vcf format to plink format in VCFtools. Furthermore, the variation and genetic distance between and within populations were visualized by a PCA plot analyzed in Eigensoft (Price *et al.* 2006). The PCA analyses were run on the full SNP data set, and also on the split data sets (European and the Japanese isolates) as in the Admixture analyses. Three PC axes were produced for each of the three PCA analyses.

Coalescent simulations were used to infer the demographic history of*S. lacrymans* in Europe and Japan using the model-based approach implemented in Fastsimcoal2 (Excoffier & Foll 2011; Excoffier*et al.* 2013). In Fastsimcoal2 the likelihood of predefined evolutionary models can be compared. In addition, demographic parameters, such as the effective population size, population growth rate, as well as timing of evolutionary events, can be estimated for the different evolutionary models. To test the divergence of *S. lacrymans* , we defined three realistic evolutionary models, supported by what is known from the literature. The first model represents a scenario, where *S. lacrymans* moved to an indoor environment in Japan, before migrating to the built environment in Europe. The second model represents a scenario where *S. lacrymans* has moved into the built environment, independently in Japan and Europe, from two natural populations that diverged prior to the colonization into houses. In addition to the divergence between Europe and Japan, the change in population size is important for understanding current patterns of genetic variation. The European population has been shown to be highly reduced in genetic diversity, likely resulting from a founder event when the population was established. To account for that, we included a population growth rate in Europe for both models. In the third model, we also implemented a growth rate for the Japanese population.

The likelihood of each model was inferred from the simulated site frequency spectrum (SFS) fitted to the observed minor allele frequency spectrum with the composite likelihood calculated in Fastsimcoal2. For each model 50 independent Fastsimcoal2 runs of 1000000 coalescence simulations and 40 cycles were analyzed. Confidence intervals for the point estimates were calculated using the parametric bootstrap approach used in Excoffier*et al* . (2013). We analyzed the data with both 10^{-7} and 10^{-8} as the mutation rate per site per year. The number of generations rather than years was calculated, as commonly used for such analyses. The generation time for*S. lacrymans* is probably highly context-dependent. For instance, under optimal growth conditions, the fungus can colonize, grow and expand extremely quickly and fruit after one year, and probably fruit successively for several years. Alternatively, under sub-optimal conditions the fruiting frequency will vary extensively. It is highly plausible that fruiting in the human-made habitat will lead to a reaction from the home owner and often the death of the fungus. Compared to other taxa, all somatic mutations in a fungal individual have a chance to contribute to the next generation, explaining the different scales of mutation rates across organisms. There are also few available estimates of mutation rates for wood decay basidiomycetes. Recently, a mutation rate of 10^{-10} was estimated for a single diploid individual of the fungal pathogen and wood decay fungus*Armillaria gallica* (Anderson *et al.* 2018). This relatively slow mutation rate is probably not representative of a sexually reproductive and flexible population. Regarding other fungal phyla, higher mutations rates have been estimated, e.g. 7.29 x 10^{-7} for the chytrid *B. dendrobatidis* (O'Hanlon*et al.* 2018), 2.4 x 10^{-6} to 2.6 x 10^{-6} for ascomycete yeast *Saccharomyces cerevisiae* (Gallone *et al.* 2016) and on average 1.98 x 10^{-8} in *Magnaporthe oryzae* (Ascomycota) using tip dating of temporally separated samples (Gladieux *et al.*2018). Thus, using both mutation rates of 10^{-7} and 10^{-8} in our demographic analyses allows us to explore the effect of mutation rates on the analyses.

Admixture in New Zealand isolates

In founder events involving a few initial founders, the small effective population size will result in strong effect of genetic drift and increased linkage disequilibrium, often resulting in large changes in allele and haplotype frequencies. Thus, founder events complicate estimates of the relationship between populations using allele frequency-based methods, such as Admixture. However, the haplotype structure contains information that may be used to identify the relationship between populations. To utilize the haplotype structure to infer the relationship between the New Zealand population and the European and Japanese populations we performed a local ancestry assignment using PCAdmix (Brisbin *et al.* 2012) with both Europe and Japan as ancestral groups and the New Zealand isolates as an admixed population. PCAdmix uses phased haplotypes derived from both reference panels and the admixed isolates to infer the ancestry of genomic windows. We used Beagle 4.0 (Browning & Browning 2007) to phase the data for each population, without imputation, using default settings. The local ancestry was inferred with PCAdmix, which uses principal components analysis in windows of 10 SNPs along the genome to identify ancestry from a set of predefined potential ancestral populations. Thus, in the case of the two individuals from New Zealand, the populations from Europe and Japan were defined as the ancestral populations.

Population diversity

The two isolates composing the New Zealand population were omitted from further population genetic analyses. As linkage disequilibrium (LD) is expected to decay rapidly with large effective population size and high recombination rate, here we calculated LD within 5 kb non-overlapping windows for the European and the Japanese populations separately using the –geno-r2 command in VCFtools (Danecek *et al.*2011). The mean r^2 values for each distance between loci were plotted in R to visualize LD decay. Given that the LD decay decreased rapidly for the Japanese population, a genomic window of 10 kb was chosen as a compromise between LD decay and SNP density for the analyses of genome-wide diversity within and between Japan and Europe. Nucleotide diversity π (Nei & Li 1979) was calculated for both populations using VCFtools. Levels of genetic differentiation between populations was estimated by calculating F_{ST} (Hudson*et al* . 1992) and nucleotide substitution per site (D_{XY}) using the python script from Simon Martin (https://github.com/simonhmartin). VCFtools was used to estimate Tajima´s D statistics (Tajima 1989) across the 10 kb windows, in order to detect departure from the standard neutral model. Tajima's D was estimated on a genome wide level and for specific genomic windows of interest. Estimated on a single locus, positive values of Tajima´s D indicate balancing selection, while negative values indicate directional selection. Whereas genome-wide distribution of Tajima´s D values can give insights into demographic population events, with negative value as an indicator of population expansion while positive values indicate population contraction. Manhattan plots were created using the R package qqman to visualize the F_{ST}, D_{XY}, π and Tajima's D along the whole genome and for scaffolds of interest (Turner 2014).

Selection pressure

We used a Bayesian approach, as incorporated in BayeScan (Foll & Gaggiotti 2008) to estimate candidate loci (island of differentiation) under natural selection between the Japanese and European populations. The approach estimates a posterior probability for each locus being under selection based on the allele frequencies of the two populations being significantly more or less divergent than the total shared allele frequencies of all loci in the dataset. The method incorporates uncertainties of small population sizes and varying effective population size, thus appropriate for our study. We analyzed the combined SNP set of Japanese and European isolates where the two populations were compared, using default settings. The resulting files were analyzed in R, after formatting with PGDSpider (Lischer & Excoffier 2011).

Signatures of selective sweeps can be investigated both within population using the integrated haplotype homozygosity (IHH) or between populations applying the population extended haplotype homozygosity (XP-EHH) (Voight *et al.* 2006). Considering that IHH is dependent on knowledge of the ancestral state, we focused on the XP-EHH approach to detect selective sweeps in which the selected allele has approached fixation within one population. The analysis was done using the R program rehh (Gautier & Vitalis 2012). Since calculation of XP-EHH is dependent on knowledge of haplotypes, the data was first phased using fastPHASE v.1.4 with default settings (Scheet & Stephens 2006).

All significant loci in predicted genes were further analyzed for function by InterProScan, using version InterPro 83.0 (www.ebi.ac.uk/interpro/). InterPro and PFAM domains were used for evaluation of gene function.

Wood decay experiments

The decay ability of five isolates from Japan, four isolates from Europe and one isolate from New Zealand was investigated by measuring wood mass loss after 60 days of growth on three different substrates, *Abies lasiocarpa* (fir), *Pinus sylvestris* (pine) and *Picea abies*(spruce) according to Balasundaram *et al* . (2018). The included isolates are indicated in Table 1. Three to ten replicates were included for each isolate.

Data availability.

The raw sequence reads of SL200 are available on NCBI SRA at Bioproject PRJNA412961. The raw sequence reads of SL198 are available on NCBI SRA at Bioproject PRJNA655420. All other raw sequence reads are available on NCBI SRA at Bioproject PRJNA685018. The final SNP data set (vcf file) was deposited in the Dryad repository under accession: doi:XXXXXX.

RESULTS

For the 36 isolates of *Serpula lacrymans* from Europe, Japan and New Zealand, between 55.9% and 98.9% of the reads mapped to the reference genome of *S. lacrymans* S7.3 (Table 1). After quality control and filtering, 419,196 SNPs were called from the full dataset and used for the subsequent analyses.

Population divergence and demography

The admixture analyses of the population genomics data revealed that the isolates of *S. lacrymans* were divided into geographically structured groups and sub-groups (Figure 1). When enforcing a two-group structure (K = 2), isolates from Europe and New Zealand were clearly separated from Japanese isolates (the cross-validation error was clearly lowest for K = 2; Supplementary Figure S1). The Principal Component Analysis (PCA, Figure 2a) likewise divided the isolates into the same two main groups (Europe/New Zealand vs Japan) along the first axis, explaining 49.8% of the variation. F_{ST} and D_{XY} estimates confirmed that the Japanese and European populations were strongly differentiated, both based on average F_{ST} of 0.572, D_{XY} of 0.524 and the genome-wide plots (Figure 3).

When the number of groups in the admixture analysis was raised to four (K = 4), both the Japanese population and the European/New Zealand group split into two (Figure 1d). Four French individuals were separated from the rest of the European/New Zealand isolates and five Japanese isolates were separated from the rest of the Japanese isolates. One individual from New Zealand (ICMP18202) was separated from the European samples along axis 1 in the PCA plot and from the European population in the admixture analyses at K = 7 (Figure 1d).

Admixture and PCA analyses performed on the European and Japanese populations separately revealed further geographic sub-structuring within both populations (Figure 1 and 2). For K = 4, the European population was divided into a northern European group, two groups in eastern France, and a southern French group, also visible in the PCA plot (Figure 2). When splitting the Japanese population into K = 7, a distinct northern group was identified, three additional admixed groups and three southern groups. These groups were also partially recognized in the PCA (Figure 2). Demographic analyses based on a mutation rate of 10^{-7}, indicated that the historic population that gave rise to the current European population split from the Japanese population around 3,000 generations ago (confidence interval 2012-6157; Figure 4). The estimated divergence time (i.e. generations) was highly sensitive to the selected mutation rate, which increased to 18,770 generations with a mutation rate of 10^{-8}. The modelled demographic scenario where both the European and the Japanese population experienced a change in population size was more likely than the scenario with only a population size change in Europe (the difference in likelihood between the two models, ΔAIC = 58,899). The European population went through a strong bottleneck about 250 generations ago (confidence interval 198-650), and Fastsimcoal2 analyses indicated that only six haplotypes were involved (confidence interval:

4.18-19.40). This could be a slight underestimate, since some of the European isolates were sampled at earlier time points (i.e. from 1935 to 2014; Table 1), which may affect the models. Nevertheless, based on our model, the Japanese population experienced a reduction in population size considerably earlier and in the same time period as the ancestral population diverged (around 3,500 generations). The reduction in the ancestral Japanese population was less severe, with an estimated effective population size of 1,337. The current effective population sizes were estimated to 1,273 individuals in Europe and 12,500 individuals in Japan (Figure 4).

Admixture in one New Zealand isolate

The two isolates from New Zealand showed varied ancestry patterns when the level of admixture was analyzed with PCAdmix (Figure 5). Isolate 950 shared 100% common ancestry with European isolates along the whole genome. The majority of the genome of isolate ICMP18202 showed common ancestry with the European population, but a large portion of scaffolds 1 and 3, together with other smaller regions scattered throughout the genome, showed shared ancestry with the Japanese population.

Population diversity

There were marked differences between the European and Japanese populations in their levels of linkage disequilibria. The European population possessed strong linkage disequilibrium, with slow LD decay, while the Japanese population demonstrated a more rapid LD decay (Figure 6). The European population possessed a lower genetic diversity (π = 0.00028, number of SNPs = 18,982) compared to the Japanese population (π = 0.00235, number of SNPs = 231,952; Table 2). The higher level of genetic diversity in the Japanese population was observed throughout the entire genome (Figure 7). Nevertheless, the Japanese population possessed some genomic regions of lower genetic diversity, specifically in scaffolds 1 and 3 (which are the same genomic regions as where the isolate ICMP18202 from New Zealand shared ancestry to the Japanese population; Figure 5). In contrast, the European population had more narrow genomic regions of high genetic diversity (Figure 7). Both populations showed high inbreeding coefficients, with an average F_{IS} of 0.978 for the European and 0.520 for the Japanese population (Table 1).

The average Tajima's D values calculated using 10 kb genomic windows along the genome were higher in the Japanese population than in the European population (0.724 versus -0.079, Table 2).

Genomic islands of differentiation and selective sweeps

BayeScan analyses were used to detect genetic loci with signatures of selection. When comparing the European and Japanese populations using a false discovery rate of $\alpha < 0.05$, two loci were detected (Supplementary Figure S2; *S. lacrymans* S7.3 v. 2: scaffold 27, position 4,748 and *S. lacrymans* S7.3 v. 2: scaffold 8, position 2,440,344). Both loci had significantly lower F_{ST} than expected from the BayeScan analyses, with F_{ST} of 0.45 and 0.36 for the loci at scaffold 27 and 8, respectively, indicating purifying or balancing selection (See Supplementary Figure S3 for F_{ST} and D_{XY} along these scaffolds).

The locus at scaffold 8 is in a predicted gene (protein ID 139103) with a SNF1 protein kinase subunit beta-2/beta-3 Interpro domain (Table 3). The D_{XY} of a 10 kb genomic window surrounding this locus was intermediate (0.525). The European population had low π (0.00025) and negative Tajima's D (-2.388), and the opposite was recorded for the Japanese population (π = 0.00560 and Tajima's D = 2.042) (Table 2, see Supplementary Figure S3 and S4 for detailed plots of D_{XY}, F_{ST}, π and Tajima's D along scaffold 8). The locus at scaffold 27, was located in a predicted gene (protein ID 79357/190659) with an oxysterol-binding Interpro domain (Table 3). As opposed to the locus at scaffold 8, the locus at scaffold 27 had a less than average D_{XY} (0.450). Further, the π for the European population was high compared to the average for this population (0.00184), while the Japanese population had an average π = 0.00245. Tajima's D estimate for the Japanese populations was negative (-0.648) and opposite of what was described for the European population (0.829) (Table 2, Supplementary Figure S3 and S5).

Extended haplotype homozygosity (EHH) indicates selective sweeps, and more recent selection than the F_{ST} outliers detected by BayeScan (Gautier & Vitalis 2012; Vitti *et al.* 2013). EHH identified two selective

sweeps in the European population, located in a gene in scaffold 8 (protein ID 79617) and a gene in scaffold 13 (protein ID 77115; Supplementary Table 1), annotated with DNA helicase Pif1-like and a GDP-fucose protein O-fucosyltransferase Interpro domains, respectively (Table 3). For the Japanese population, the EEH analyses detected a selective sweep in a locus between predicted genes on scaffold 32. Within a 10 kb window surrounding this sweep there are three predicted genes, one with a Cytochrome P450 Interpro domain (protein ID 79618), one with a WW Interpro domain (protein ID 79617), and one without any conserved domains.

Wood decay assessment

We also assessed differences in wood decay efficiency as a measure of fitness by conducting decomposition experiments of isolates from Europe, Japan and New Zealand. Spruce was decayed fastest by all strains, followed by fir and then pine. For pine there were higher variation in the decay rate among the strains, however the differences among the populations were not significant (Figure 8).

DISCUSSION

We confirmed that the two populations of *Serpula lacrymans* var.*lacrymans* from the built environment in Japan and Europe are highly divergent, as previously revealed by Kauserud *et al.*(2007), and that the divergence between the two populations predated human influence. The results from the demographic modelling analyses strongly support this hypothesis, indicating that the ancestral population split more than 3,000 generations ago and led to the current divergent populations in Japan and Europe. Based on genomic similarity of the wild *Serpula lacrymans* var. *shastensis* and the building occupant *Serpula lacrymans* var. *lacrymans* , we have previously suggested that this species is one of few wood-decay fungi that was highly pre-adapted to the built environment (Balasundaram*et al.* 2018). As a result, it established extensive populations in temperate regions worldwide vectored by human translocation (Kauserud*et al* . 2007).

The split between the two invasive populations predates human influence. The natural habitat of *S. lacrymans* is high alpine regions with scattered large conifer logs (Kauserud *et al.* 2012). From there, *Serpula lacrymans* has established independently at least twice in the indoor habitat (Kauserud *et al* . 2007). However, our dating of this split is influenced by the implemented mutation rate, illustrated by an increase in number of generations from 3,067 to 18,770 when using 10^{-8} as alternative mutation rate (to 10^{-7}). Assuming a split approximately 3,000 generations ago and a generation time of one year under optimal fungal growth conditions, human-made habitats will have existed, i.e. 3,000 years before present. Indeed, there are dated wooden constructions circa 7,000 years ago from Europe (Tegel *et al.*2012). However, a longer generation time than one year (for establishment, vegetative growth and fruiting) is plausible and the mutation rate is uncertain, which suggest that the split of the ancestral population probably predated the availability of the built environment. Central and eastern Asia, where *S. lacrymans* can be found in nature, were not covered by ice sheets during the last glaciation 115 – 11 K BP (Tian & Jiang 2016). The dry and cold areas may have driven *S. lacrymans* into refugia, thus splitting*S. lacrymans* into several sub-populations. Although speculative, such a scenario also fits well with the estimated reduction in population size at almost the same time as the split. Consequently, the Himalayas, where the fungus has it westernmost natural distribution (Kauserud *et al.* 2012), and another north Eastern Asian population, might have functioned as separate source populations of the current indoor populations in Europe and Japan. From previous population studies of *S* . *lacrymans* , it is known that the European population shares genetic material with specimens from the Himalayas, and that the Japanese population is geographically and genetically closer to the natural population in East Asia (Kauserud *et al* . 2012, 2007).

The genome-wide SNP data confirmed that the Japanese population is genetically more variable than the European population and that more genetic variation was retained during its founder event(s). This is mirrored by the higher number of vegetative incompatibility (*vic*) alleles and diversity of mating types present in the Japanese population (Engh *et al.* 2010a). The two genetic regions in scaffold 1 and 3 with lower genetic diversity, cover two large genomic regions containing many genes with various functions. One

possible interpretation is that these two genomic regions harbor inversions and therefore show lower rates of recombination in the Japanese population (and in one New Zealand isolate). However, better genome assemblies, which can be achieved with long read sequence data is required to test this. Currently, the function and effect of these possible genome rearrangements are unknown.

The European population invaded the built environment about 250 generations ago. As noted above, genetic similarity between Himalayan specimens collected in forests and the European indoor population has previously been observed (Singh *et al.* 1993; Kauserud *et al.* 2007). Our demographic modelling suggests that the colonization of Europe happened between 200 and 400 generations ago. Assuming a generation time of one year, this estimate of 200-400 generations fits well with the species description of *S. lacrymans* in 1781 (Wulfen 1781), based on a collection from Europe (Austria). During this period, and also somewhat earlier, there were considerable trade activities between Europe and Asia which could easily have vectored the colonization of *S. lacrymans* to Europe, e.g. through the trade and transport of timber. Human activity might have further spread*S. lacrymans* , from Europe to North America and Australia (Kauserud *et al.* 2007) and is also considered the main agent for dispersal of several plant pathogens, such as *Microbotryum lychnidis-dioicae* and *Ophiostoma ulmi* (Brasier 1991; Fontaine*et al.* 2013). To better understand the colonization event of*S . lacrymans* in Europe, the relatedness of European isolates to isolates from the natural range in the Himalayas should be further investigated.

The European population of *S. lacrymans* holds low genetic diversity, and the founding members were estimated to consist of only four or five haplotypes (depending on mutation rate). Hence, it is possible that only two or three heterokaryotic isolates colonized and founded the entire European population. This assumption is strongly supported by few mating (MAT) and vegetative incompatibility (*vic*) alleles detected in the European population where three heterokaryotic isolates may account for the entire allelic diversity (Kauserud *et al.* 2006; Engh *et al.* 2010b; Skrede *et al.* 2013). Similar to *S. lacrymans* , the European population of the invasive ash dieback fungus *H. fraxineus* is genetically extremely homogenous and was established by only two haploid individuals (McMullan *et al.* 2018). Two different subspecies of the Dutch Elm disease parasite *Ophiostoma novo-ulmi* established as clonal parasites in Europe. Later, sexual reproduction between these populations produced a hybrid with high pathogenicity (Brasier & Kirk 2010). Hence, there are now multiple lines of evidence that invasive fungi may establish on other continents through very tight founder events followed by extensive population growth.

The small founder event establishing the European population is also reflected in the slow LD decay and high levels of Fis observed in the European population. A high degree of selfing or clonal dispersal may cause such abnormal linkage decay curves (Nieuwenhuis & James 2016). Similar patterns of linkage disequilibrium were observed for isolated and highly biparentally inbred wolf populations in Italy and the Iberian peninsula (Pilot *et al.* 2014). The very low number of isolates founding the European population of *S. lacrymans* has probably also led to high levels of biparental inbreeding. The limited number of mating alleles available will necessarily lead to a reduction in mating opportunities between individuals, and the tetrapolar mating system of *S. lacrymans* still allows 25% of the spores from the same fruit body to mate. No putative clonal isolates were found in our or previous studies (Kauserud *et al.* 2007; Engh *et al.*2010b; Maurice *et al.* 2014), supporting that selfing or clonal dispersal is not the main explanation of the slow linkage decay.

Signatures of selection in the built environment. In both populations, we observed signals indicative of balancing or purifying selection acting on two loci. For these two loci we observed significantly lower F_{ST} values than expected (D_{XY} was not different from the expectations). Genomic regions of low differentiation could be caused by pleiotropic effects (one locus having an effect on two or more phenotypes), where these phenotypes have different selection pressure in the two populations. The differences in Tajima's D and π between the populations at these two loci indicate that pleiotropic effects may be involved, i.e., the SNF1 complex at scaffold 8 show signals of purifying selection in the European populations, but balancing selection in the Japanese populations. The SNF1 complex is involved in gene expression regulation as a response to starvation in yeast (Sanz 2003), but is also shown to be involved in responses to several different environmental stressors (summarized in Shashkova *et al* . 2015). The homolog of the main SNF1 kinase was differentially

expressed in response to varying substrate composition during wood decay in *S. lacrymans,*supporting a role in substrate-dependent gene regulation (Hess *et al* . 2021).

Another gene with an oxysterol-binding domain (as was found in the locus at scaffold 27 in our analyses) evolved at a specifically rapid pace (significantly higher dN/dS) in *S. lacrymans* compared to the sister taxon *S. himantioides* (Balasundaram *et al.* 2018). Oxysterol-binding proteins are involved in transportation of lipids in eukaryotic cells (revised in Qui & Zeng 2019), and have shown to be important to polarized hyphal formation and growth in *Candida* and*Aspergillus* (Ghugtyal *et al* . 2015; Bühler *et al* . 2015). Maintaining diversity for both the oxysterol-binding and the SNF1 complex could therefore be important for *S. lacrymans'* unique ability for rapid growth and decay of large substrates.

In the European population, selective sweeps were found in genes related to DNA replication (a DNA helicase with a Pif1 domain) and protein modification (O-Fuct domain involved in glycosylation). In parallel to this, associations between helicases and the environment have been found in several landscape genomic studies, i.e. the wood decay fungus*Phellopilus nigrolimitatus* (Sønstebø *et al* . in prep.), the ectomycorrhizal *Suillus brevipes* (Branco *et al.* 2017) and the red bread mold *Neurospora crassa* (Ellison *et al* . 2011). Suggesting that modification of DNA replication may be the first signals of local adaptation for recently founded populations. Thus, in the European population we may be observing recent events, which corresponds well with the demographic history of the European population, with its small effective population size and the recent bottleneck.

The selective sweep in the Japanese population was in a non-coding region. Thus, we cannot conclude about the function of this sweep. However, within a 10 kb window of this sweep there are three predicted genes, of which one is a Cytochrome P450. Cytochrome P450s are monooxygenase enzymes known to be involved in the detoxification of polyphenols and other defense molecules secreted by other organisms or encountered during wood decay (Cresnar and Petric 2011; Ichinose 2013; Xu *et al* . 2015). For fungi, cytochrome P450s were recently suggested to be involved in heavy metal tolerance in *Suillus luteus* (Bazzicalupo *et al.* 2019) and during pathogenic interactions between *Heterobasidion annum* and conifer trees (Karlsson *et al.* 2008). Wood type dependent difference in gene expression of cytochrome P450s have previously been found for two wood decay species (Wymelenberg *et al* . 2011). Further, in our recent study of *S. lacrymans* (Hess *et al* . 2021), a larger repertoire of differentially expressed cytochrome P450s was associated with significantly faster decay of recalcitrant pine wood in a Japanese isolate compared to an isolate from the European population. However, in the experiments in the current study we did not detect systematic differences in the ability to decay different substrates between the Japanese and the European populations, rather that there is high strain to strain variation in this trait. More detailed functional studies are therefore required to better understand the functions of individual cytochrome P450s.

The New Zealand population is admixed between European and Asian populations. Inclusion of two isolates from New Zealand enabled us to test whether this population has an admixed ancestry, as hypothesized in Kauserud *et al* . (2007). Indeed, isolate ICMP18202 possessed a combination of European and Japanese alleles, in support of this hypothesis. Similarly, in other invasive fungi, like *B. dendrobatidis* , *O. ulmi/novo-ulmi, H. fraxineus* and the oomycete pathogen *Phytophthora alni* , secondary admixture between independently evolved lineages have been observed (Ioos *et al.*2006; Brasier & Kirk 2010; McMullan *et al.* 2018; O'Hanlon*et al.* 2018). The merging of genetic lineages in founder areas may lead to novel and more aggressive genotypes, as shown for most of these species (Ioos *et al.* 2006; Stukenbrock & McDonald 2008; Brasier & Kirk 2010; McMullan *et al.* 2018; O'Hanlon *et al.* 2018). In our wood decay experiment, the New Zealand isolate ICMP18202 decayed pine wood rapidly (Figure 8), though more isolates are needed to confirm this pattern. Since only one of the two isolates showed signals of admixture, the admixture could be a recent event. Further, the admixture was heterogeneously distributed in the genome (mainly scaffolds 1 and 3), indicating limited cycles of recombination. It could also be that PCAdmix assigned genomic windows more readily to homogenous genomic regions with low diversity, and hence, more readily detects admixture in scaffolds 1 and 3 with lower diversity as compared to the rest of the genomes of the Japanese isolates. The reasons for reduced diversity and admixture in large genomic regions in the admixed isolate from

New Zealand are currently unknown. This could be a consequence of genomic areas of low recombination, resulting from chromosomal rearrangements. In the future, more thorough analyses of genomic synteny, based on assembled genomes, among these three populations may shed light on their effect on population divergence. Furthermore, the isolate(s) that contributed to the admixture were not necessarily of Japanese origin, but could originate from other locations in Asia. Thus, including more isolates from the full geographic distribution of *S. lacrymans* may contribute to better understand the admixture event in New Zealand.

Concluding remarks. By using full genome data in combination with growth experiments, we revealed genomic differences among isolates of *S. lacrymans* from Europe, Japan and New Zealand. We estimated that the source population of the European population split from the Japanese population 3,000 to 19,000 generations ago, and that the European population established about 200 – 400 generations ago through a tight bottleneck event. Two genes related to mycelial growth seemed particularly important for survival of both indoor populations and probably evolved before the species became invasive in the built environment. However, population specific selective sweeps identified more recent events, which show that decay of various substrates in Japan and rapid adaptation of DNA replication and protein modification in Europe influence population survival. We were able to confirm that one isolate from New Zealand held genomic signatures of admixed ancestry. However, more samples from New Zealand and the native Asian populations are needed to infer, with better certainty the source populations of*S. lacrymans* and for in-depth analyses of the evolutionary history of the populations in the built environment.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

IS, CM, JH, SM, JHS, NH, DE, FMM and HK designed the study. IS cultured and extracted DNA from all non-French samples. IS, CM, JH, AK and JHS organized sequencing and analyzed data. IS, SM, DB-E contributed samples. IS, JH, SM, JHS, DE and HK interpreted results and wrote the manuscript. All authors read, commented and approved the final version of the manuscript.

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FIGURE LEGENDS

Figure 1. Geographic distribution of the included isolates of*Serpula lacrymans* from the built environment in Europe, Japan and New Zealand. a-c show genetic assignment groups using the software Admixture. Large pie charts indicate results from the full data set (Admixture K = 2), the smaller pie charts indicate genetic structuring when each population was analyzed separately. As only two isolates were included from New Zealand, they were not analyzed separately and the small pie charts are derived from the full data set. d) demonstrate the assignment for all 36 isolates (each bar shows the assignment for one individual) to K = 2, K = 4, K = 5, and K = 7 (i.e. those with the lowest cross validation error; see Supplementary Figure S1).

Figure 2 . Principal Component Analyses of 419,196 SNPs from 36 isolates of the dry rot fungus *Serpula lacrymans* . a) analyses of the full dataset, colored by geographic origin b) analyses of a separate data set of only European strains, colored by the two groups from Europe when the full data set was separated by K = 4 (Fig 1d), c) analyses of a separate data set of only Japanese strains, colored by geographic origin from S (Honsu) or N (Hokkaido).

Figure 3. Manhattan plot of D_{XY} and F_{ST} between the European and Japanese populations of*Serpula lacrymans* using 10 kb genomic windows along the 30 largest scaffolds of the European *S. lacrymans* S7.3 genome. Black and grey dots separate the adjacent scaffolds. a) D_{XY}, b) F_{ST}.

Figure 4. The three different models used in Fastsimcoal2 when modelling the demographic history of the Japanese and European populations. Two different mutation rates were used, 10^{-7} and 10^{-8}. The model with a population split followed by a bottleneck is the most probable with a lower AIC. The current effective population size is annotated with N, while Bot indicates the effective population size of the bottleneck. TBot indicates time since bottleneck, TDIV indicates time since populations diverged.

Figure 5 . The genomic assignment of the two isolates of*Serpula lacrymans* from New Zealand (sl 950 and ICMP18202) to the European and Japanese populations estimated with PCAdmix. Strain ID-a and -b indicate the two different haplotypes after phasing the SNPs from the dikaryotic strains using Beagle. Blue indicates parts of the genome assigned to the European population, while yellow indicates parts of the genome assigned to the Japanese population. The x-axis represents the scaffolds.

Figure 6 : Linkage decay of the European and the Japanese population of *Serpula lacrymans* . Blue indicates the European linkage decay while yellow indicate Japanese linkage decay. Distance in x axis indicate number of base pairs, while R_2 indicates linkage disequilibrium.

Figure 7 . Manhattan plots of nucleotide diversity, π, and Tajima's D along the genome of *Serpula lacrymans* for 10 kb genomic windows. a) π of European isolates, b) π of isolates from Japan, c) Tajima's D of European isolates and d) Tajima's D of isolates from Japan.

Figure 8 . The wood decay rates of *Serpula lacrymans* on spruce, fir and pine for isolates from Europe, Japan and New Zealand. Five, four and one isolate included in the mass loss experiments from Japan (yellow), Europe (blue) and New Zealand (green), respectively. The y axis indicates the percent mass loss of the wood blocks after 60 days of decay.

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