1	Genetic variability and limited clonality of Mycoplasma hyorhinis in pig herds						
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21 Abstract

22 Mycoplasma hyorhinis is a common inhabitant of the upper respiratory tract and tonsils of pigs. Its role as a possible pathogen remains controversial. In order to gain more insight into the 23 epidemiology and population structure of Mycoplasma hyorhinis we genetically characterized 60 24 isolates by multi locus sequence typing (MLST). The M. hyorhinis strains originated from Swiss 25 and German pig herds with knowledge on the clinical background. The MLST scheme of 26 Tocqueville et al. (J.Clin.Microbiol. 2014) was optimized, primers for the six MLST gene 27 fragments were newly designed to allow amplification and sequencing with a single protocol. A 28 total of 27 ST were observed with the 60 strains, 26 of those were previously unknown types. 29 30 Generally identical genotypes were observed within a farm but they differed between farms. The identical genotype was also observed in three different Swiss farms. On the other hand different 31 genotypes within a farm were found with three German farms. The Swiss isolates formed a distinct 32 33 cluster but otherwise there was no geographical nor a clinical association with specific clusters observed. Data shows a high variability of *M. hyorhinis* comparable to what is observed for 34 35 Mycoplasma hyopneumoniae. Similar to this pathogen the population structure of M. hyorhinis also shows some limited clonality with predominant genotypes within an animal and a single farm but 36 different ones between farms. The comparable population structure of *M. hyopneumoniae* and *M.* 37 38 *hyorhinis* could indicate a similar evolution of the two species in the common pig host.

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40 Keywords: MLST, genotyping, pig disease, enzootic pneumonia, coughing

42 1. Introduction

43 Mycoplasma hyorhinis, a common inhabitant of the upper respiratory tract and tonsils of pigs, was first described in the fifties by Switzer (1955). It is generally regarded as a commensal, however, a 44 role of *M. hyorhinis* as a potential pathogen has also been discussed. Infections with this organism 45 are subclinical, even though arthritis, polyserositis, conjunctivitis and otitis as well as abortions are 46 clinical disorders that may be observed in an infected pig (Friis and Feenstra, 1994; Kobisch and 47 Friis, 1996; Shin et al., 2003). Mycoplasma hyorhinis has also been found associated with 48 pneumonia, however, rather as a secondary pathogen (Falk et al., 1991; Kawashima et al., 1996; 49 Kobayashi et al., 1996; Lin et al., 2006). Nevertheless, an increase in the detection of M. hyorhinis 50 51 in recent years has been observed and the relevance of this pathogen as an emerging issue causing 52 significant economic losses is suspected (Dos Santos et al., 2015).

Genotyping allows epidemiological investigation and population studies. This can help to clarify 53 54 the role of a possible pathogen, identify specifically involved strains and their transmission. Multilocus sequence typing (MLST) is a highly selective and specific method which has been 55 utilized for the characterization of many bacterial species including Mycoplasma hyopneumoniae 56 and *M. hyorhinis* (Mayor et al., 2008; Tocqueville et al., 2014). Genotyping of *M. hyorhinis* using 57 MLST is based on sequences of internal fragments from six housekeeping genes, i.e. the 58 59 chromosomal replication initiation protein (*dnaA*), the RNA polymerase β subunit (*rpoB*), the DNA gyrase subunit B (gyrB), the glutamyl-tRNA synthetase (gltX), the adenylate kinase (adk) and the 60 guanylate kinase (*gmk*). 61

In this study, we optimized the MLST scheme of six loci by defining completely new primer sets. They were used to genetically characterize 60 *M. hyorhinis* isolates belonging to twenty-five Swiss and German herds. Information about the herd health status, i.e. clinical respiratory disease, of the fattening units from where strains came from were gathered as well. The MLST data of the *M. hyorhinis* isolates was used to elucidate genetic variability of the species and was related to the clinical presentation of the pig in order to define possible virulent strains.

68 **2. Materials and methods**

69 *2.1. Strains and template preparation*

A total of 60 *M. hyorhinis* isolates with 47 from Germany and 13 from Switzerland previously included in a transnational cross sectional study determining the prevalence of *M. hyorhinis* were analyzed (Luehrs, 2015). For every source of strains, relevant pathological conditions in the corresponding animals were available from databases. This includes presence of (enzootic) pneumonia varying from mild, moderate to severe assessed during lung scoring after dissection, as well as arthritis and/or polyserositis. Moreover, the simultaneous infection with *M. hyopneumoniae* was examined in every sample using real-time PCR (Dubosson et al., 2004).

Strains of *M. hyorhinis* were kept at -80°C and cultured fresh in 1 ml liquid medium (Mycoplasma
Experience, Bletchingley, Great Britain) for 1-2 days at 37°C. Once medium color change from red
to yellow occurred the culture was centrifuged for 10 min. at 5000xg. The pellet was dissolved in
70µl ddH₂O and boiled for 15 min. at 95°C. This crude lysate was then kept at -20°C until being
used for PCR.

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83 2.2. Optimization of MLST

The MLST scheme of Tocqueville et al. (2014) using the six housekeeping genes dnaA, rpoB, gyrB, 84 gltX, adk and gmk served as a basis to optimize the protocol. Primers with identical annealing 85 temperatures were defined, allowing amplification of all targets with a single PCR protocol instead 86 of 3 different ones as described by Tocqueville et al. (2014). For this purpose target genes were 87 extracted from available genome sequences of M. hyorhinis strains DBS 1050, HUB-1, GDL-1, 88 MCLD, SK76 as well as the type strain $\text{ATCC17981}^{\text{T}}$ (=BTS7^T) and sequences were aligned. 89 Consensus sequence stretches as close as possible to the starting sequence used for typing were 90 defined and primers with similar annealing temperature selected (Table 1). Each PCR was 91 92 performed in a 30-µl total volume containing 12 pmol of each primer, 1 x FIREPol® Master Mix Ready to Load (Solis BioDyne, Tartu, Estonia) and 1 µl lysate at the following cycling conditions: 93

3 min denaturation at 95°C, followed by 35 cycles at 95°C for 30 s, 55°C for 30 s and 72°C for 45 94 s. A final extension step for 7 min at 72°C was included. Subsequently, the amplification products 95 of the six genes from one strain were pooled and then purified using the "High pure PCR 96 97 purification Kit" (Roche Diagnostics, Rotkreuz, Switzerland). Finally the purified pooled PCR products was used for sequencing with the BigDye® Terminator v3.1 Cycle Sequencing Kit 98 (Thermo Fisher, Reinach, Switzerland), using the same primers as for PCR (Table 1). For this 99 purpose 96-well plates (Thermo Fisher) were prepared with corresponding primers (5 pmol/well) 100 using a multichannel pipette. The plates allowed batch-wise analysis of 8 strains and could be kept 101 at -20°C until being used for sequencing (Korczak et al., 2009). 102

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104 *2.3. Data analysis*

Sequences were edited using the Sequencher program v5.1 (GeneCodes, Ann Arbor, MI, USA) and 105 106 imported into Bionumerics v7.5 (AppliedMaths, Sint Marten, Belgium). Sequence types (ST) were determined using the MLST plugin allowing direct query of the PubMLST database 107 108 (www.pubmlst.org). New alleles and allele combinations were submitted to the curator of the database to assign allele and ST numbers. The MLST sequences of the 33 strains from the study of 109 Tocqueville et al. (2014) as well as the ones of the type strain BTS7^T (GenBank accession 110 111 ARTL00000000) were also imported to the database and included in the analyses. The resulting 94 entries were used for creating a minimal spanning tree based on allele numbers and a UPGMA tree 112 based on allele sequences in Bionumerics. 113

The START2 program (pubmlst.org) was used to calculate the ratio of synonymous and 114 nonsynonymous substitutions as well as the index of association (I_A) . The index of discrimination 115 using formula of Hunter 116 (D)was calculated the and Gaston (1988). LIAN (guanine.evolbio.mpg.de/cgi-bin/lian/lian.cgi.pl) was used to calculate the genetic diversity (*H*). 117

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120 **3. Results**

121 *3.1. Genetic diversity of* M. hyorhinis

All 60 isolates could be analyzed with the optimized MLST scheme. There were two new alleles 122 observed for *dnaA* (totaling 12) and *gyrB* (totaling 8), as well as three new alleles for the targets 123 rpoB (totaling 10), gltX (totaling 10), adk (totaling 7) and gmk (totaling 8). With the additional new 124 alleles the genetic diversity (H) of the six loci varies from 0.4155 (gltX) to 0.7596 (gyrB). The ratios 125 126 of nonsynonymous and synonymous substitutions varied from 0.1303 (dnaA) to 0.6785 (gmk). The index of association (I_A) was 0.026, indication no linkage disequilibrium. A total of 27 ST were 127 defined, 26 of them were new resulting in a total of 55 different *M. hyorhinis* genotypes based on 128 129 MLST. Including all strains, i.e. also those from the same herd and same animals, the index of 130 discrimination (D) was 0.982. When only single representatives of such repetitive isolations were included in the analysis the index of discrimination (D) was 0.995. 131 All the isolates from our study belong to the clonal complex 1 as defined by at least 4 common 132 alleles (Tocqueville et al., 2014). The clonal relationship of STs is graphically shown by the 133 minimal spanning tree in Fig. 1. Six of the seven previously observed singletons remained while 134

135 ST-28 was integrated into complex 1 (Tocqueville et al., 2014). There is only one common ST (ST-

136 13) between our study and the latter one as shown in Fig.2.

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138 *3.2. Limited clonality of* M. hyorhinis

There are no clear and discrete geographic clusters present, even though some grouping can be observed. The type strain BTS7^T originating from the USA was determined as ST-16 based on *in silico* analysis of its genome sequence. This ST was also observed in France. The Chinese isolate represents an out-group while most of the branches consist of isolates from more than one country. Noteworthy, all Swiss isolates can be found on a single cluster containing only isolates from one German farm where polyserositis was diagnosed in piglets. Another discernable cluster is formed by only German isolates. This cluster contains isolates from farm DE_03 where two slightly

different strains based on a single base-pair change in *gmk* could be detected. Clearly different 146 147 strains were observed in farm DE 16. In all other cases isolates from a single farm had the same genotype, while isolates from different farms were also of different genotype. Identical genotypes 148 were also found when multiple isolates from single animals were analyzed (indicated by C2, C3). 149 Identical genotypes were observed in three Swiss farms. In German farms, M. hyorhinis was 150 isolated from animals that were in most cases (32 of 44) affected by *M. hyopneumoniae* as was 151 152 diagnosed by real-time PCR indicated by ABC/REP in Fig. 2. In one case with a clear clinical status of enzootic pneumonia (strain numbers 10003) a follow up was done a few months later (strain 153 numbers. 10025). While at both stages *M. hyorhinis* could be isolated from broncho-alveolar lavage 154 155 fluid (BALF) and showed identical genotypes in different animals, the isolates from the two 156 different time points differed in genotypes, indicating a switch of *M. hyorhinis* population over 157 time.

158 There were no clusters or genotypes associated with certain clinical manifestations.

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161 **4. Discussion**

This study analyzed the genetic variability of *M. hyorhinis* from pig farms in Germany and 162 163 Switzerland. Genotypes were put in relation to available clinical data and were also compared to isolates contained in the PubMLST database. For this purpose the MLST scheme of Tocqueville et 164 al. (2014) was optimized to allow a uniform PCR amplification and sequencing protocol. The new 165 protocol, based on a completely new set of primers for the six target genes, proved to be robust. All 166 60 isolates could be genotyped. The genetic diversity of *M. hyorhinis* increased by 26 genotypes to 167 168 a total of 55 different STs based on MLST. While in the previous study by Tocqueville et al. (2014) mainly isolates from France were genotyped, we analyzed strains from Germany and Switzerland. 169 Except from one farm, where the previously identified ST-13 was found, all other were new STs. 170 171 Generally the same ST was observed within a farm and also within a single animal. The same ST

could be observed even within three different Swiss farms. On the other side different ST were 172 173 observed in three German farms (DE 16, DE 03 and DE 05). From farm DE 05 one sample resulted in an ambiguous base call at two positions what made a genotyping impossible but showed 174 175 that it contained a mix of at least two different strains (data not shown). This was an indirect 176 indication that indeed more than one strain can be present in a single animal, even though it might not be the rule. Nevertheless, the observation that within a farm and individual animal the same 177 178 genotype is generally found is a fact that would allow for direct genotyping of clinical material. This approach is successfully used with *M. hyopneumoniae* (Kuhnert and Overesch, 2014; Kuhnert 179 et al., 2011; Mayor et al., 2008) and could therefore also be applied for M. hyorhinis. This allows a 180 181 rapid straight forward genotyping eliminating the culture step.

The high variability but still limited clonality of *M. hyorhinis* is very similar to what can be observed with *M. hyopneumoniae* (Kuhnert and Overesch, 2014; Mayor et al., 2008; Mayor et al., 2007; Nathues et al., 2011). Given this observation and fact that *M. hyorhinis* is mainly a commensal inhabiting the same niche as the more pathogenic *M. hyopneumoniae* could point to a similar selection pressure if not co-evolution of the two species. Nevertheless, while whole genome comparisons between these two species showed that rearrangements are common, clear differences in gene composition indicate that a direct interaction and dependency of the two is rather unlikely.

189 Clinical information was gathered from all cases including diagnostic results on enzootic pneumonia (EP) caused by M. hyopneumoniae. While M. hyopneumoniae was detected in more 190 than 70% of German cases, all Swiss cases were negative for this pathogen (Fig.2). This reflects the 191 192 different situation in these two countries. While in Switzerland only a few sporadic cases of EP are observed per year due to a successful eradication program, EP is still endemic in Germany (Nathues 193 et al., 2014; Stark et al., 2007). Furthermore, clinical data is also available for strains contained in 194 195 the PubMLST database (Tocqueville et al., 2014). No correlation or association of specific genotypes or clusters with clinical manifestations could be discerned. Similar observations were 196 made by Dos Santos et al. (2015) using a multi-locus variable-number tandem-repeat analysis 197

(MLVA) that is based on more variable genes than the house-keeping genes used for MLST. These 198 199 authors also could not find an association between isolates and clinical manifestations. The MLVA approach was less discriminating than MLST with a diversity index of 0.814 compared to 0.982, 200 respectively. However, the MLVA is based on only 2 genes compared to the six genes used for 201 MLST and is therefore less work intensive and less expensive than the MLST. Nevertheless, the 202 MLST is highly reproducible with all six targets successfully analyzable in all strains whereas with 203 MLVA one of the targets could not be amplified in about 2% of strains and more than 40% of 204 clinical specimens (Dos Santos et al., 2015). Moreover, we could improve the MLST by designing 205 new primers that allow a single PCR amplification and sequencing protocol. The PCR purification 206 207 step using pooled samples as well as the pre-preparing of 96-well microtiter plates containing all sequencing primers for 8 strains further reduce hands on time and costs. This makes MLST the 208 209 method of choice if comparing efforts and outcome.

In conclusion the MLST scheme for *M. hyorhinis* was optimized and the number of isolates analyzed by this method was extended. Thereby the variability of *M. hyorhinis* in farms and related clinical data of the host to genetic data of the potential pathogen was systematically investigated. A limited clonality of *M. hyorhinis* was observed, i.e. a high variability of genotypes was accompanied by identical genotypes within a farm and individual animal. No specifically virulent genotypes could be discerned, indicating the commensal nature of *M. hyorhinis* in the pig lung.

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218 **5. Acknowledgements**

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222 6. References

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285	Figure legends
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287	Fig. 1 Minimal spanning tree of <i>M. hyorhinis</i> sequence types (ST) based on allele numbers built in
288	Bionumerics v7.6. A clonal complex relation is defined as a minimum of 4 identical alleles out of
289	the six. Branch length and intensity reflects number of different alleles. The circle size represents
290	the number of isolates belonging to the specific ST which is indicated by the corresponding number.
291	
292	Fig. 2 Cluster analysis and strain information of <i>M. hyorhinis</i> isolates. A UPGMA tree was built in
293	Bionumerics v7.6 based on the six partial gene sequences used for MLST. The isolate name,
294	sequence type (ST), country and year of isolation, clinic and source are indicated. For the strains
295	analyzed in this study the real-time PCR results for M. hyopneumoniae (ABC/REP) are included as
	well. The bar indicates the genetic distance.

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Gene	Primer	Sequence	seq. (bp) ^a
dnaA	dnaA-F2	CAGAAGTCTTAGGTGGTTTTG	459
	dnaA-R2	TGTGGAATGATCCTTGCCTC	
rpoB	rpoB-F2	TCAAGCTGTTCCATTAATTACTAC	509
	rpoB-R2	GCACTAACTTCTGATCCAATAC	
gyrB	gyrB-F2	GATTCTGATGGTTCACATATTAG	358
	gyrB-R2	GTCTAGGTTTTTTGCATATTTTGC	
gltX	gltX-F2	CTGAAAGACTCTCAAAATCACC	448
	gltX-R2	TTACAAGCCTTTTTGAAATTAGTTC	
adk	adk-F2	CGATGGCATCTAATTCTTTTAAAG	437
	adk-R2	TACTCAGGCAAAGTTTTTAGAAC	
gmk	gmk-F2	GCGCCTGTTTCTGTTAATATTG	452
	gmk-R2	AAGAGACAAAAGACCTAATGAAG	

299 Table 1. Primers used for uniform MLST of *Mycoplasma hyorhinis*

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^a length of the informative sequence, i.e. of the PCR product without primer sequences

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Gene	Primer	Sequence	seq. (bp) ^a
dnaA	dnaA-F2	CAGAAGTCTTAGGTGGTTTTG	459
	dnaA-R2	TGTGGAATGATCCTTGCCTC	
rpoB	rpoB-F2	TCAAGCTGTTCCATTAATTACTAC	509
	rpoB-R2	GCACTAACTTCTGATCCAATAC	
gyr B	gyrB-F2	GATTCTGATGGTTCACATATTAG	358
	gyrB-R2	GTCTAGGTTTTTTGCATATTTTGC	
gltX	gltX-F2	CTGAAAGACTCTCAAAATCACC	448
	gltX-R2	TTACAAGCCTTTTTGAAATTAGTTC	
adk	adk-F2	CGATGGCATCTAATTCTTTTAAAG	437
	adk-R2	TACTCAGGCAAAGTTTTTAGAAC	
gmk	gmk-F2	GCGCCTGTTTCTGTTAATATTG	452
	gmk-R2	AAGAGACAAAAGACCTAATGAAG	

Table 1. Primers used for uniform MLST of Mycoplasma hyorhinis

^a length of the informative sequence, i.e. of the PCR product without primer sequences

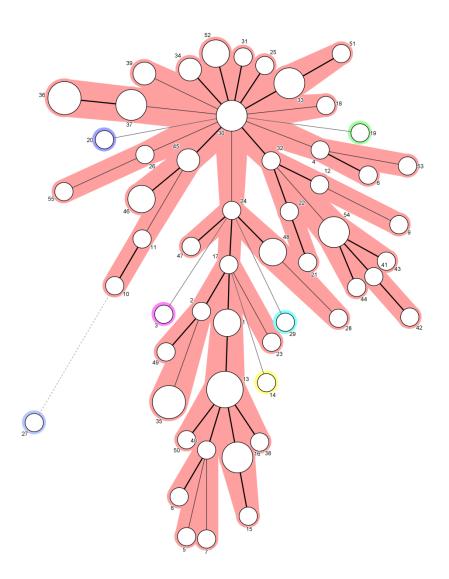


Fig. 1 Minimal spanning tree.

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