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Proposal for assignment of allele numbers for mobile colistin resistance (*mcr*) genes

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The initial report of the *mcr-1* (mobile colistin resistance) gene has led to many reports of *mcr-1* variants and other *mcr* genes from different bacterial species originating from human, animal and environmental samples in different geographical locations. Resistance gene nomenclature is complex and unfortunately problems such as different names being used for the same gene/protein or the same name being used for different genes/proteins are not uncommon. Registries exist for some families, such as *bla* (β-lactamase) genes, but there is as yet no agreed nomenclature scheme for *mcr* genes. The National Center for Biotechnology Information (NCBI) recently took over assigning *bla* allele numbers from the longstanding Lahey β-lactamase website and has agreed to do the same for *mcr* genes. Here, we propose a nomenclature scheme that we hope will be acceptable to researchers in this area and that will reduce future confusion.

A plasmid-borne gene encoding a phosphoethanolamine transferase conferring resistance to colistin was reported in 2015 in China and named *mcr-1* (mobile colistin resistance).[1] An identical gene has now been reported in several different bacterial species isolated from as far back as the 1980s, from different hosts and in at least 30 countries in six continents.[2–5] This gene is associated with one copy, two copies or no copies of IS*Apl1* on different plasmids, including I2-, X4- and HI-type plasmids.[6] Several publications have now reported minor variants of the original *mcr-1*, as well as more divergent genes also predicted to encode phosphoethanolamine transferases.[7]

Various registries have been responsible for keeping track of and assigning names to some families of resistance genes, e.g. http://www.lahey.org/Studies/ for β-lactamases, now managed by the National Center for Biotechnology Information (NCBI); https://www.ncbi.nlm.nih.gov/pathogens/submit_beta_lactamase/.[8] Other resistance gene families have remained relatively neglected and it has not been uncommon for the same gene/protein to be assigned multiple names or for different genes/proteins to be given the same name. One contributing factor is that many researchers prefer that the sequences they deposit in International Nucleotide Sequence Database Collaboration (INSDC) databases are given 'hold-until-publication' (HUP) status until any associated manuscripts are accepted. This means that researchers who find a potential new allele may not be aware of all the other alleles that have been identified but which are not yet publicly available. When there is no clearing house to 'reserve' and keep track of allele numbers this leads to nomenclature collisions and a system similar to the one in place for β-lactamases is needed to avoid confusion. NCBI has agreed to assign allele numbers to and keep track of *mcr* genes, in consultation with the antibiotic resistance research community.

The first variant of *mcr-1* with a single non-synonymous nucleotide change was reported in a *Klebsiella pneumoniae* ST512 clinical isolate from Italy, on an X4-type plasmid in a genetic

context also seen for *mcr-1*, and was named *mcr-1.2*.[9] Following on from this, we propose that *mcr* gene and allele numbers are assigned in the same manner as for β-lactamases, i.e. based on amino acid sequence identity rather than on nucleotide sequence identity, and that the original allele is effectively *mcr-#.1*, with subsequent alleles then assigned *mcr-#.2*, *mcr-#.3*, *mcr-#.4* etc. (e.g. *mcr-1.2*, *mcr-1.3*, *mcr-1.4* etc.). The terms '*mcr-1*-family/MCR-1-family' etc. can then be used to refer more generally to genes/proteins within each group and for related genes/proteins where a specific allele number has not been requested. Each full-length MCR protein will also be assigned a WP_ number, a non-redundant protein accession number used to annotate the same protein sequence in different RefSeq entries from one or more species. In response to requests from researchers, allele numbers have already been assigned by NCBI to additional MCR-1 variants (Table 1), all of which have one or two amino acid changes from MCR-1 (Table 2).

The *mcr-2* gene, identified in *Escherichia coli* isolated from food animals in Belgium, is 77% identical to *mcr-1*. It encodes a phosphoethanolamine transferase significantly different from MCR-1 (81% amino acid identity, 89% similarity) that confers colistin resistance and is carried on an X4-type plasmid,[4] but in a different genetic context from *mcr-1*.[10] The initial reports of MCR-1[1] and MCR-2,[1,4] and subsequent identification of genes encoding proteins with ∼60% identity to both MCR-1 and MCR-2 in various *Moraxella* species,[11] suggested that this genus may be the original source of genes related to *mcr-1* and *mcr-2*. These genes were apparently mobilized by different ISs, IS*Apl1*[6,12] in the case of *mcr-1* and IS*Ec69* in the case of *mcr-2*,[10] and transferred to other bacterial species relevant to human and veterinary medicine.

A gene from *Moraxella* spp. that is 97.6% identical to *mcr-1*, encoding a protein with seven amino acid changes from the original MCR-1, was then identified as a closer ancestor by AbuOun *et al.*[13] and named *mcr-1.10*. This group also reported a gene from *Moraxella pluranimalium* that is 96.1% identical to the original *mcr-2*, encoding a protein with only eight amino acid differences from MCR-2 that was named MCR-2.1.[13] Our suggested scheme would assign 'MCR-2.1' to the original MCR-2 protein and as the name MCR-2.2 has already been used for an identical protein (MG545606),[14] we propose referring to this protein as MCR-2.2 and the gene as *mcr-2.2* (Table 1). The name MCR-2.2 has also been used for a third gene from *Moraxella* spp. reported by AbuOun *et al.*,[13] which encodes a protein 87.9% identical to the original MCR-2. As this protein is also 82.8% identical to MCR-1 (Figure 1) we suggest that it becomes part of a new group and is assigned the name MCR-6.1. Both of these changes have been agreed by AbuOun *et al.*[13] and updated in the respective GenBank entries. We have not proposed *mcr-#* numbers for the genes encoding proteins designated MCR-POR (from *Moraxella porci*; MF432696) MCR-LIN (*Moraxella lincolnii*; MF432697), *mcr*-OSL (*Moraxella osloensis*, MF432698) or MCR-CAT (*Moraxella catarrhalis*, e.g. CP000205) by Kieffer *et al.*[11] at this time, as closely related, mobilized versions are yet to be identified outside *Moraxella*.

The name *mcr-3* was given to a gene reported as 45% identical to *mcr-1* and 47% identical to *mcr-2*, encoding a protein that is ∼32% identical to MCR-1 and MCR-2, found on an HI2-type plasmid in *E. coli* isolated from a pig in China in 2015.[15] Genes encoding proteins identical to or with one amino acid change from MCR-3 were also identified in contigs from *E. coli*, *K. pneumoniae*, *Salmonella enterica* subsp. *enterica* serovar Typhimurium available in the INSDC database.[15] Genes encoding proteins up to 94% identical to MCR-3 were also identified in various *Aeromonas* spp., leading to the suggestion that members of this genus may be the source of *mcr-3*-family genes.[15]

Multiple examples of MCR-3 and a number of MCR-3 variants have now been identified from both *Aeromonas* and other species [Table 3 and Figure S1 (available as Supplementary data at *JAC* Online)] and have been assigned MCR-3.# numbers by NCBI (Tables 1 and 3). These *mcr-3*-family variant genes and the corresponding MCR-3-family proteins all show >93% nucleotide and >94% amino acid identity to one another, but the relationships between members of this group appear to be complex. The publication reporting *mcr-3.3* in *Aeromonas veronii* also identified a downstream gene encoding another phosphoethanolamine transferase 84.8% identical to MCR-3.1.[16] As it was found not to confer colistin resistance the encoded protein was designated 'MCR-3.3-like' by the authors.[16] Examination of nucleotide alignments of *mcr-3.1*, *mcr-3.3* and this *mcr-3*-like gene suggest that *mcr-3.1* could be a hybrid made up of the start of *mcr-3.3* and the end of the *mcr-3*-like gene, perhaps generated by homologous recombination (Figure S1). Proteins designated MCR-3.2, MCR-3.4, MCR-3.5 and MCR-3.11, all found in species other than *Aeromonas*, are minor variants of MCR-3.1 (Table 3).

A gene encoding a protein 34%, 35% and 49% identical to MCR-1, MCR-2 and MCR-3, respectively, and 82%–99% identical to genes encoded by *Shewanella* spp. was named *mcr-4*[17] and several variants have now been identified (Table 4). A gene identified in a *d*-tartrate fermenting *S. enterica* subsp. *enterica* serovar Paratyphi B isolate from chicken meat in Germany was named *mcr-5*.[18] The *mcr-5* gene is part of the Tn*21*-family transposon Tn*6452*, located on a non-conjugative plasmid. The MCR-5 protein shows low identities (33%–36%) to MCR-1, MCR-2, MCR-3 and MCR-4.[18] The minor variant MCR-5.2 differs by deletion of Glu234 (698–700AAGΔ).[19] A gene designated *mcr-7.1* encoding a protein ∼70% identical to MCR-3.1, also possibly originating from *Aeromonas* and ∼30%–45% identical to other MCR types, has now been reported.[20]

Other subgroups of MCR-type enzymes encoded by mobilized genes are likely to be identified in the future and deciding when an *mcr* gene/MCR protein should be assigned a new 'family' number is potentially more problematic than numbering alleles with minor variations. Existing family numbers were mostly assigned to newly identified MCR proteins by the authors that discovered them. We suggest generally retaining these numbers (apart from redesignating 'MCR-2.2' as MCR-6.1, above) as there are clear distinctions between current groups (Figure 1). While various percentage identities have been put forward to define resistance gene subgroups (summarized in Hall and Schwarz[21]), avoiding fixed numerical cut-offs has also been suggested.[22] Current MCR groupings suggest a cut-off between ∼88% and ∼96%, but we think it is better not to define a precise cut-off, to enable re-evaluation of boundaries between families as new data become available. Such flexibility would allow discussions between authors, reviewers, editors, other representatives from the antibiotic resistance community and NCBI to arrive at the best solution if members of potential new subgroups are identified, while assignment of a number by NCBI, if required, avoids possible nomenclature clashes.

Information in Tables 1–4 and Figure 1 represents the current situation (May 2018) for unambiguous *mcr-#* family and allele

Table 1. *mcr* names assigned by NCBI and/or available in GenBank

Allele	INSDC accession of prototype	GenBank protein accession of prototype/RefSeq WP_	Reference
mcr-1.1	KP347127.1	AKF16168.1/WP_049589868.1	1
mcr-1.2	KX236309.1	ANR95875.1/WP_065274078.1	9
mcr-1.3	KU934208.1	ANJ15621.1/WP_077064885.1	23
mcr-1.4	KY041856.1	APM87143.1/WP_076611062.1	24
mcr-1.5	KY283125.1	APM84488.1/WP_076611061.1	25[a]
mcr-1.6	KY352406.1	AQK48217.1/WP_077248208.1	26
mcr-1.7	KY488488.1	AQQ11622.1/WP_085562392.1	24
mcr-1.8	KY683842.1	AQY61516.1/WP_085562407.1	
mcr-1.9	KY964067.1	ASK38392.2/WP_099982800.1	
mcr-1.10	MF176238.1	ASK49940.1/WP_096807442.1	13
mcr-1.11	KY853650.1	ATM29809.1/WP_099982815.1	
mcr-1.12	LC337668.1	BBB21811.1/WP_104009850.1	27
mcr-1.13	MG384739.1	AVM85874.1/WP_109545056.1	
mcr-2.1	LT598652.1	SBV31106.1/WP_065419574.1	4
mcr-2.2[b]	MF176239.1	ASK49941.1/WP_078254299.1	13
mcr-3.1	KY924928.1	ASF81896.1/WP_039026394.1	15
mcr-3.2	NMWW01000143.1	OYN70668.1/WP_094315354.1	28[c]
mcr-3.3	MF495680.1	ASU10319.1/WP_099982814.1	16
mcr-3.4	FLXA01000011.1	SBZ31568.1/WP_065804663.1	
mcr-3.5	MF489760.1	ASU04896.1/WP_089613755.1	29
mcr-3.6	MF598076.1	AST36140.1/WP_042649074.1	30
mcr-3.7	MF598077.1	AST36141.1/WP_099156047.1	30
mcr-3.8	MF598078.1	AST36143.1/WP_099156048.1	30
mcr-3.9	MF598080.1	AST36144.1/WP_099156049.1	30
mcr-3.10	MG214531.1	ATQ63376.1/WP_099982820.1	31
mcr-3.11	MG489958.1	AUN87920.1/WP_102607465.1	32
mcr-3.12	MG564491.1	AVZ47168.1/WP_109545070.1	33
mcr-4.1	MF543359.1	ASR73329.1/WP_099156046.1	17
mcr-4.2	MG822663.1[d]	AVK94777/WP_109545058.1[d]	34, 35
mcr-4.3[e]	MG026621.1	AUI38915.1/WP_011638903.1	36
mcr-4.4	MG822665.1	AVK94779.1/WP_109545055.1	35
mcr-4.5	MG822664.1	AVK94778.1/WP_109545054.1	35
mcr-4.6[f]			37
mcr-5.1	KY807921.1	ASK40551.1/WP_053821788.1	18
mcr-5.2	MG384740.1	AVM85875.1/WP_109545057.1	19
mcr-6.1[b]	MF176240.1	ASK49942.1/WP_099982813.1	13
mcr-7.1	MG267386.1	AUR80098.1/WP_104009851.1	20

[a]This citation does not correspond to the first report in GenBank.
[b]Originally called MCR-2.1, but renamed here with the agreement of the authors (AbuOun *et al.*[13]). An identical protein was also published as MCR-2.2.[14] A protein originally called MCR-2.2[13] almost as closely related to MCR-1, has been renamed MCR-6.1.
[c]Also reported by Roer *et al.*,[38] but no GenBank entry.
[d]The original *mcr-4.2* sequence (MG581979.1/AUE22029[34]) is missing the last three nucleotides and stop codon, so details of the first complete version published are given.
[e]Originally also named *mcr-4.2*.
[f]Originally named *mcr-4.3*, but initially published without an INSDC entry.[37]

numbers designated according to the principles described here. All definitive numbers will be available in the continually updated resistance gene database under BioProject PRJNA313047. MCR variants identified by NCBI staff for which allele numbers have not been requested have been assigned WP_ numbers and are identified as 'MCR-# family phosphoethanolamine–lipid A transferase' (and could be assigned allele numbers if requested by submitting authors).

Table 2. Nucleotide/amino acid changes in *mcr-1*/MCR-1 alleles from species other than *Moraxella*[a]

Allele[b]	Identified in[c]	Nucleotide differences from *mcr-1.1*	Amino acid differences from MCR-1.1
1.1	*E. coli*, *Escherichia fergusonii*, *S. enterica*, *Shigella*, *Klebsiella*, *Citrobacter*, *Enterobacter*, *Kluyvera ascorbata*, *Cronobacter sakazakii*, *Providencia alcalifaciens*	—	—
1.2	*E. coli*, *K. pneumoniae*	A8T	Gln3Leu
1.3	*E. coli*	AA111-2GG	Ile38Val
1.4	*E. coli*	G1318A	Asp440Asn
1.5	*E. coli*	C1354T	His452Tyr
1.6	*S. enterica*	G1263A, G1607A	Arg536His
1.7	*E. coli*	G643A	Ala215Thr
1.8	*E. coli*	A8G	Gln3Arg
1.9[d]	*E. coli*	T1238C	Val413Ala
1.11[e]	*E. coli*	GTG19-21dup	Val7dup
1.12	*E. coli*	G9C	Gln3His
1.13	*E. coli*	G465A	Met155Ile

[a]*mcr-1.10* is found in *Moraxella* spp. and has 36 nucleotide differences from *mcr-1.1* and MCR-1.10 has 7 amino acid differences from MCR-1.1.
[b]Allele numbers assigned by NCBI are in bold.
[c]Species/genera in which each allele has been detected to date.
[d]Using start codon that matches other *mcr-1* genes rather than the one in the original INSDC entry.
[e]dup, duplication of nucleotides/amino acids at positions indicated.

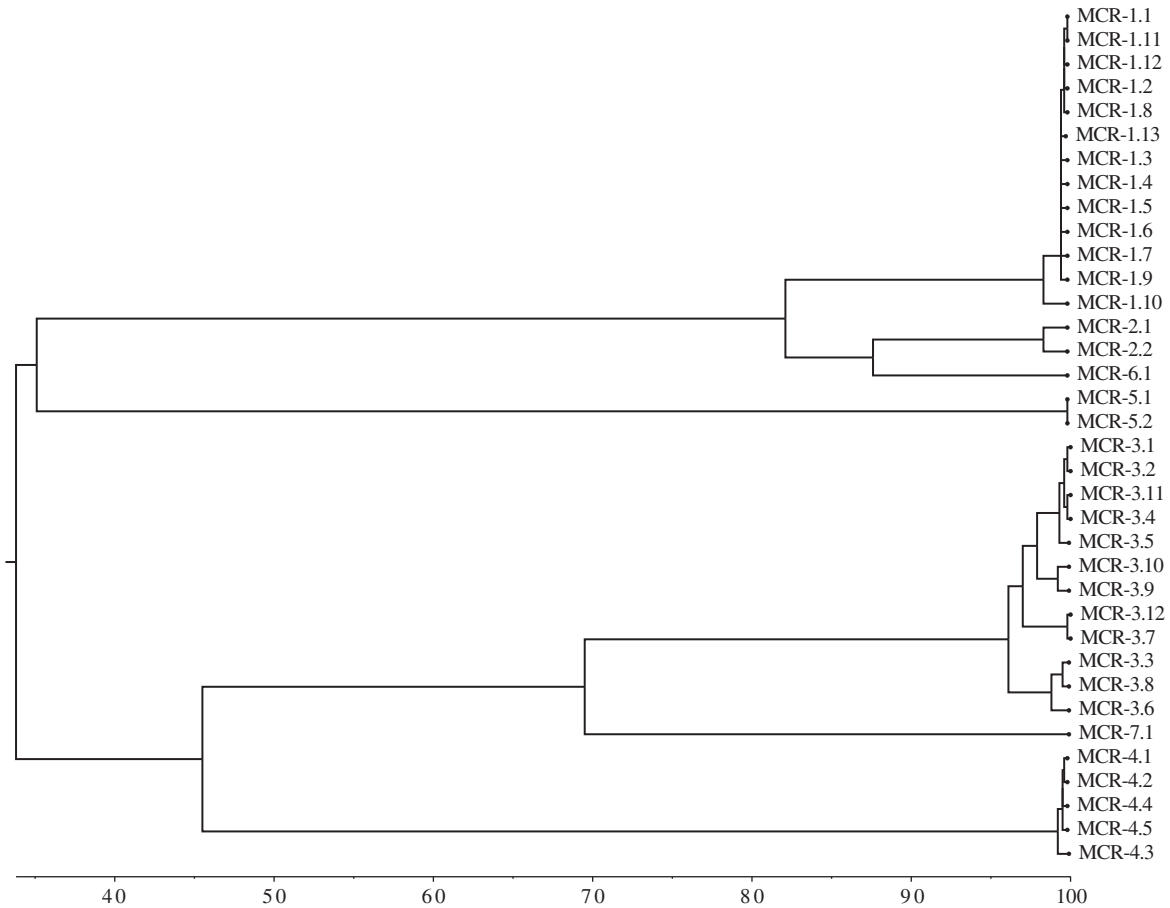

Figure 1. Relationships between proposed MCR subgroups and alleles. UPGMA tree constructed from a MUSCLE alignment of protein sequences obtained from accession numbers listed in Table 1. Numbers on the bottom axis represent percentage identity among aligning amino acids, but do not reflect differences due to insertions and/or deletions.

Table 3. Nucleotide/amino acid changes in selected *mcr-3*/MCR-3 alleles[a]

Allele[b]	Identified in[c]	Nucleotide differences from *mcr-3.1* or *mcr-3.7*	Amino acid differences from MCR-3.1 or MCR-3.7
3.1	*E. coli*, *K. pneumoniae*, *Salmonella* Typhimurium, *Shigella sonnei*	—	—
3.2	*E. coli*, *Shigella*	C1463T	Thr488Ile
3.4	*K. pneumoniae*, *S. sonnei*	G1118T	Gly373Val
3.5	*E. coli*, *Shigella*	A67G, C1370A, C1463T	Met23Val, Ala457Glu, Thr488Ile
3.11	*E. coli*	G1118T, CA1402-3AC	Gly373Val, Gln468Thr
3.7	*Aeromonas media*	—	—
3.12	*E. coli*	T380C + 9 other differences	Val127Ala

[a]*mcr-3.3* and *mcr-3.6*–*mcr-3.9* have been found in various *Aeromonas* spp. (see Figure S1a) and have 34–100 nucleotide changes from *mcr-3.1*, while the MCR-3.3 and MCR-3.6–MCR-3.9 proteins have 11–27 amino acid differences from MCR-3.1. *mcr-3.10* has been found in *Aeromonas caviae*, *E. coli* and *Proteus mirabilis* and has 19 nucleotide changes from *mcr-3.1* and MCR-3.10 has 7 amino acid changes from MCR-3.1.
[b]Allele numbers assigned by NCBI are in bold.
[c]Species/genera in which each allele has been detected to date.

Table 4. Nucleotide/amino acid changes in *mcr-4*/MCR-4 alleles from species other than *Shewanella*

Allele[a]	Identified in[b]	Nucleotide differences from *mcr-4.1*	Amino acid differences from MCR-4.1
4.1	*E. coli*, *Salmonella* spp.	—	—
4.2	*E. coli*, *Salmonella* Typhimurium	A992G	Gln331Arg
4.3[c]	*Enterobacter cloacae*	T536G, G706T	Val179Gly, Val236Phe
4.4	*E. coli*	C613A, A992G	His205Asn, Gln331Arg
4.5	*E. coli*	C329T, A992G	Pro110Leu, Gln331Arg
4.6[d]	*Salmonella* Kedougou	not available	Val236Phe

[a]Allele numbers assigned by NCBI are in bold.
[b]Species/genera in which each allele has been detected to date.
[c]Originally named *mcr-4.2*.
[d]Originally named *mcr-4.3*, but initially published without an INSDC entry,[37] so not included in Figure 1.

Analysis of currently available sequences indicates that no synonymous nucleotide changes are present in genes encoding MCR-1.2–MCR-1.13 and all alleles of MCR-2–MCR-7 (May 2018). In the case of MCR-1.1 a few different synonymous nucleotide variants, some affecting the first of two ATG codons at the start of the gene and only two found in more than one to two sequences (Table S1), are found amongst the >600 examples in INSDC databases. If such nucleotide differences do become important for epidemiological tracking of *mcr* genes then the use of automated allele assignments based on nucleotide sequences can be explored.

We hope that the suggestions presented here are acceptable to researchers working in this area. To avoid confusion, we would encourage authors to submit all new allele sequences to INSDC and to approach NCBI (pd-help@ncbi.nlm.nih.gov) for assignment and registration of *mcr* allele numbers prior to submitting sequences and/or manuscripts, and journals to recommend this and initiate discussions if manuscripts describing related genes that may fall into new subgroups are received.

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Transparency declarations

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Supplementary data

Figure S1 and Table S1 are available as Supplementary data at *JAC* Online.

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