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Comment on: Resistance gene naming and numbering: is it a new gene or not?

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Sir,

Recently, Hall and Schwarz[1] have suggested the need for a universally consistent antibiotic resistance gene nomenclature system in order to replace the current multiple and incompatible systems which exist. They arbitrarily proposed a threshold value of ≥2% difference of either the nucleotide or amino acid sequence, or both, as the cut-off for assigning a new gene in order to stimulate debate within the field.

We welcome this suggestion and subsequent discussions, and agree that resistance gene nomenclature systems need updating and aligning in order to address the increasing availability of genetic data and our understanding of the molecular evolution of resistance genes. We would, however, like to add a note of caution that the arbitrary ≥2% cut-off may not be universally appropriate.

In the case of the tetracycline resistance genes, covering the three known mechanistic classes of protein (ATP-dependant efflux, ribosomal protection and enzymatic inactivation), the nomenclature system is based on amino acid identity. A new determinant must show <80% amino acid identity to known determinants to be designated a new class.[2]

While Hall and Schwartz[3] suggest a cut-off of ≥2% will reduce the number of gene designations for those encoding OXA ß-lactamases, the opposite will in fact be true for the tetracycline resistance genes, as indicated by Jacoby *et al*.[4] Taking *tet*(M) as an example, there are well over 100 sequences within the NCBI database under this gene class. To implement a ≥2% cut-off for new gene designations would dramatically increase the number of tetracycline resistance genes which once

belonged to the *tet*(M) class. Additionally this increase in new gene designations would be compounded by the fact that there are at least 59 other tetracycline resistance gene classes currently assigned,[5] many with multiple examples showing ≥2% sequence divergence.

Furthermore, such a cut-off would also cause confusion and complications in the identification of a subclass of the ribosomal protection protein encoding genes known as the mosaic tetracycline resistance genes, which have an atypical evolutionary path involving naturally occurring recombination between two or more progenitor genes.[6] These currently have their own version of a nomenclature system indicating their mosaic ancestry and this would disappear if a ≥2% divergence rule was implemented.

We propose here to contact all investigators involved in the historical and current discovery, annotation, naming and curation of tetracycline resistance genes, and will facilitate a discussion in order to determine if there is a consensus on any proposed change to the current nomenclature system. We urge stakeholders to contact the authors of this comment in order to indicate their interest in participation. Following this process, we will report any agreement or hurdles perceived within the field. We suggest other investigators involved in the nomenclature of other resistance genes do the same and it is possible that these subgroups could form the basis of a larger committee as proposed by Evans.[7]

Transparency declarations

None to declare.

References

1. Hall RM, Schwarz S. Resistance gene naming and numbering: is it a new gene or not? *J Antimicrob Chemother* 2016; **71**(3):569-71

2. Levy SB, McMurry LM, Barbosa TM *et al*. Nomenclature for new tetracycline resistance determinants. *Antimicrob Agents Chemother* 1999; **43**: 1523-1524.

3. Hall RM, Schwarz S. Resistance gene naming and numbering: is it a new gene or not?—authors' response. *J Antimicrob Chemother* 2016;**71**(6):1743

4. Jacoby GA, Bonomo RA, Bradford PA, *et al*. Comment on: Resistance gene naming and numbering: is it a new gene or not? *J Antimicrob Chemother* 2016; Jun 3. pii: dkw204

5. Roberts MC. Mechanism of resistance for characterized *tet* and *otr* genes. http://faculty.washington.edu/marilynr/tetweb1.pdf (Correct as of 13th July 2016).

6. Warburton PJ, Amodeo N, Roberts AP. Mosaic tetracycline resistance genes encoding ribosomal protection proteins. *J Antimicrob Chemother* 2016; in press.

7. Evans BA. Comment on: Resistance gene naming and numbering: is it a new gene or not? *J Antimicrob Chemother* 2016; **71**: 1742-1745.