Letters to the Editor

Neisseria meningitidis Subtype Nomenclature

We believe the novel subtyping nomenclature proposed for Neisseria meningitidis (7) is flawed and, if adopted, will create chaos for meningococcal epidemiology with serious implications for public health monitoring and vaccine development. The meningococcal subtype is determined by amino acid sequence variation in the cell-surface-exposed loops I and IV of the porA gene, respectively. Although this variation was first recognized by the use of murine monoclonal antibodies (MAbs) (1), it is more reliably deduced from the nucleotide sequence of the porA gene, considering the deficiencies inherent in the serological approach: the panel of MAb subtyping reagents is not comprehensive (4, 7, 9); it is becoming increasingly obse- late, as the antigenic composition of PorA continually evolves under the immune selection imposed by the host (6); murine MAbs have limited relevance to vaccine design, when epitopes recognized in the human immune response are required (3, 9); and the early use of antibiotic therapy in meningococcal disease has increased the dependence on PCR-based diagnoses and subtyping (2).

Sacchi et al. (7) propose a nomenclature that attempts to encompass both genotypic, or DNA-based, subtyping data and phenotypic subtyping data which is based on the reactions of PorA with a panel of MAbs. The proposal is unsound for a number of important reasons: (i) it is unnecessary, and potentially confusing, to attempt to convey different types of information in a single nomenclature; (ii) the proposed nomenclature ignores the fundamental relationship between genotype and phenotype, naming genetically related antigens disparately contingent upon the availability of MAb reagents; (iii) their assignment of VRs to families on the basis of our 80% amino acid identity cutoff using a denominator that makes no allow- ance for genetic insertions, duplications, and deletions results in genetically related PorA proteins having unrelated names; and (iv) such radical changes to the previously published names of meningococcal PorA epitopes will create unnecessary confusion in meningococcal epidemiology. Finally, the combined use of uppercaser, lowercase, and underlined letters for the nomenclature is excessively complicated and difficult to understand, even for those familiar with meningococci.

We maintain that the meningococcal subtype nomenclature should be based primarily on the amino acid sequence deduced from the nucleotide sequence of porA but should accommodate existing names assigned originally from serological data (8). This scheme has several advantages: closely related VR sequences have similar names regardless of their reactivity with a specific MAb; the potential for a nontypeable result is eliminated; it can be readily expanded to include novel sequences; and, since porA is under immune selection in humans, it provides more reliable information for the design of candidate vaccines based on PorA than analyses based on murine MAbs. The genetic relationships between the porA genes of the meningococci are best conveyed by using the conventional genetic designation porA followed by a number representing each unique allele. We have made a comprehensive collection of these data available on a website, http://mlst.zoo.ox.ac.uk/Meningococcus, that is regularly updated to accommodate novel sequences. New VR and allele numbers can be obtained on request.

REFERENCES

1. Abdillahi, H., and J. T. Poolman. 1988. Definition of meningococcal class 1 OMP subtyping antigens by monoclonal antibodies. FEMS Microbiol. Immunol. 1:139–144.
2. Borrow, R., H. Claus, M. Guiver, L. Smart, D. M. Jones, E. B. Kaczmarski, M. Frosch, and A. J. Fox. 1997. Non-culture diagnosis and serogroup deter- mination of meningococcal B and C infection by a sialyltransferase (siaD) PCR ELISA. Epidemiol. Infect. 118:111–117.
3. Delvg, A., S. Jahn, B. Kuscecc, J. E. Heckels, E. Rosensvist, E. A. Hoiby, T. E. Michaelaen, and M. Achtman. 1994. A comparison of human and murine monoclonal IgGs specific for the P1.7 PorA protein of Neisseria meningitidis. Mol. Immunol. 31:1257–1267.
4. Feavers, I. M., A. J. Fox, S. Gray, D. M. Jones, and M. C. J. Maiden. 1996. Antigenic diversity of meningococcal outer membrane protein PorA has implications for epidemiological analysis and vaccine design. Clin. Diag. Lab. Immunol. 3:444–450.
5. Maiden, M. C. J., J. Suker, A. J. McKenna, J. A. Bygraves, and I. M. Feavers. 1991. Comparison of the class 1 outer membrane proteins of eight sero- logical reference strains of Neisseria meningitidis. Mol. Microbiol. 5:727–736.
6. Russell, J. E., M. C. J. Maiden, and I. M. Feavers. 1998. Molecular analysis of antigenic variation within the porA gene of disease causing Neisseria meningitidis isolated in the United Kingdom. p. 281. In X. Nassif, M.-J. Quentin-Millet, and M. K. Taha (ed.), Eleventh International Pathogenic Neisseria Conference. EDK, Paris, France.
7. Sacchi, C. T., A. P. S. Lemos, M. E. Brandt, A. M. Whitney, C. E. A. Melles, C. A. Solari, C. E. Frasch, and L. W. Mayer. 1996. Proposed standardisation of Neisseria meningitidis PorA variable region typing nomenclature. Clin. Diag. Lab. Immunol. 3:844–855.
8. Suker, J., I. M. Feavers, M. Achtman, G. Morelli, J.-F. Wang, and M. C. J. Maiden. 1994. The porA gene in serogroup A meningococci: evolutionary stability and mechanism of genetic variation. Mol. Microbiol. 12:253–265.
9. Suker, J., I. M. Feavers, and M. C. J. Maiden. 1996. Monoclonal antibody recognition of members of the P1.10 variable region family: implications for serological typing and vaccine design. Microbiology 142:63–69.
10. van der Ley, P., J. E. Heckels, M. Virji, P. Hoogerhout, and J. T. Poolman. 1991. Topology of outer membrane proteins in pathogenic Neisseria species. Infect. Immun. 59:2963–2971.

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Author’s Reply

We view the letter to the editor concerning our article as a healthy sign of a continuation of a long-standing tradition in the scientific community for open discussions and disagreement on the Neisseria nomenclature (1, 2, 4).

Several points raised in the letter highlight the problematic nature of Neisseria meningitidis nomenclature, which we believe are well-addressed in our approach. Most importantly, we
must disagree with the statement that it is “unnecessary, and potentially confusing, to attempt to convey different types of information in a single nomenclature . . .” From the public health point of view, it is quite necessary to relate serosubtyping and VR typing by using the same nomenclature. Indeed, sequence-based approaches, such as VR typing will most likely be a method of choice in the future. However, in light of our extensive hands-on experience with the laboratory activities of developing countries, we believe that, for economic and other reasons, serotyping will continue to be their main method of subtyping N. meningitidis for many years to come. After all, the great majority of the meningococcal disease cases are occurring in the developing world, and the scientific community would be at a loss without the ability to correlate these two systems. With that in mind, our nomenclature was designed to allow one to instantly correlate serosubtyping and VR typing. Since our approach does not mandate the use of monoclonal antibodies (MAbs), our proposed nomenclature will not need to be changed when serotyping is no longer used.

The comment on the use of 80% amino acid identity is somewhat unexpected, as this cutoff was used directly from the article by Suker et al. (3), who reported that “the 80% cutoff distinguished the two most closely related VR sequences that contained epitopes identified by different MAbs.” The authors of the letter are correct in saying that our system “. . . makes no allowance for genetic insertions, duplications, and deletions.” Perhaps the rule about 80% amino acid identity for the PorA VR family will have to be modified to include variants which may have been created by one or a limited number of genetic events. We agree that, as with all other rules, exceptions may well be found.

The public availability of the data is crucially important for global communications and exchange of data. The web site mentioned in the letter remains a significant and important resource; however, more than half of the sequences found there are not available at GenBank. Furthermore, naming of novel variants is under their discretion, and no precise description of the criteria or guidelines used is provided. Our use of GenBank allows everyone the benefit of cross-checking their sequences with those already released. Therefore, researchers are allowed to name their novel variants at the time of submission.

REFERENCES

1. Hitchcock, P. J. 1989. Unified nomenclature for pathogenic Neisseria species. Clin. Microbiol. Rev. 2(Suppl.):S64–S65.
2. Kellogg, D. S., H. Smith, and J. Swanson. 1978. Summary of discussion about need for a modified colonial morphology classification of Neisseria gonorrhoeae, p. 180. In G. F. Brooks, E. C. Gotschlich, K. K. Holmes, W. D. Sawyer, and F. E. Young (ed.), Immunobiology of Neisseria gonorrhoeae. American Society for Microbiology, Washington, D.C.
3. Sukar, J., I. M. Fevers, M. Achtman, G. Morelli, J.-F. Wang, and M. C. J. Maiden. 1994. The porA gene in serogroup A meningococci: evolutionary stability and mechanism of genetic variation. Mol. Microbiol. 12:253–265.
4. Swanson, J., and J. Heckels. 1980. Nomenclature of gonococcal outer membrane proteins, p. xxi–xxiii. In D. Danielson and S. Normark (ed.), Genetics and immunobiology of pathogenic Neisseria. University of Umea, Umea, Sweden.