Improving understanding and outcomes: Linking genomic, clinical and epidemiological data for meningococcal disease.

Authors

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Introduction

Whole genome sequencing (WGS) of *Neisseria meningitidis* (Nme) isolates brings powerful new insights. We are unlocking further knowledge by linking genomic profiles for eight calendar years (2009-2016) to comprehensive clinical and epidemiological data for individual patients. This will enable genomic differences occurring in association with case clustering, patient clinical presentation, underlying risk factors, vaccine history, age, sequelae and death, to be determined, ultimately improving diagnosis, treatment and prevention.

Methods

Genomic information has been linked to clinical and epidemiological data, giving a comprehensive host-pathogen dataset for each individual meningococcal episode. This includes enhanced meningococcal surveillance, hospitalisation, prescribing, death and WGS data, analysed according to the MRF-Meningococcus Genome Library approach. Linkage of this information and in-depth bespoke analysis is required to release their full potential. Statistical associations of particular clinical or epidemiological characteristics with different genetic strains or elements will be investigated. WGS data were obtained using the Illumina sequencing platform and assembled de novo using Velvet combined with Velvet optimiser. Resultant assemblies were deposited in the pubmlst.org/neisseria database (MRF-MGL project). Isolate records were linked to short read accession numbers deposited in the European Nucleotide Archive (ENA). WGS data were annotated with strain typing designations including genogroup, PorA, FetA sequence type (ST) and clonal complex(cc). Data were then compared using ribosomal MLST (rMLST) loci as well as genes core to the meningococcus (cgMLST). Pan-genome analyses have been undertaken using Roary.

Results

337 Nme isolates were sequenced. The majority belonged to: cc269 (63, 19%); cc41/44 (59, 18%); cc11 (48, 14%); and cc23 (35, 10%) with serogroup B isolates most predominant (233, 69%) followed by serogroups W and Y (both 44, 13%) and serogroup C (14, 4%) (Figures 1 and 2). There was a very noticeable increase in ST-11 cc from 2014 onwards due to serogroup W. There has been a general increase in serogroup Y over time, with a marked increase in serogroup C disease in 2016.

Preliminary WGS comparisons revealed a diverse meningococcal population with clustering by clonal complex (Figure 3). Data suggest that the meningococcal population in Scotland was, for the most part, the same as the rest of the UK.

More detailed analysis of Bexsero® Antigen Sequence Typing (BASTs) reveals clustering by clonal complex (Figure 4). No isolate in the dataset was an exact match, but BAST-1 analysis does not take into account cross-reactivity, which can represent over 50% samples.

Conclusions

The study will enable us to elucidate genomic associations with case clustering, and patient clinical presentation, vaccine history, age, long term complications and death, all of which will then be available for improved diagnosis, treatment and prevention. Statistical associations of particular clinical or epidemiological characteristics with different genetic strains or elements will be investigated. Further work is underway to establish presence of accessory genomic components unique to each genomic cluster which, in turn, may be linked to distinct clinical phenotypes observed.

Figure 1: Clonal Complex distribution of invasive *N. meningitidis* isolates in Scotland

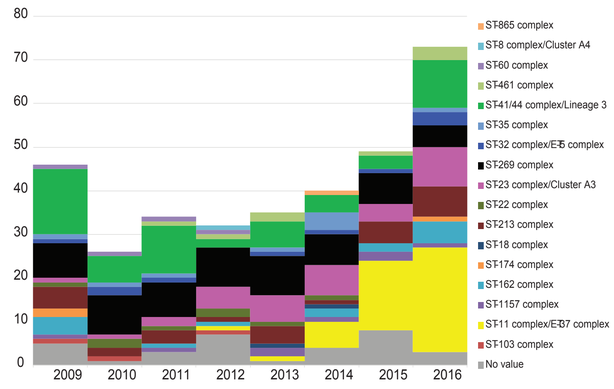


Figure 2: Serogroups associated with IMD in Scotland

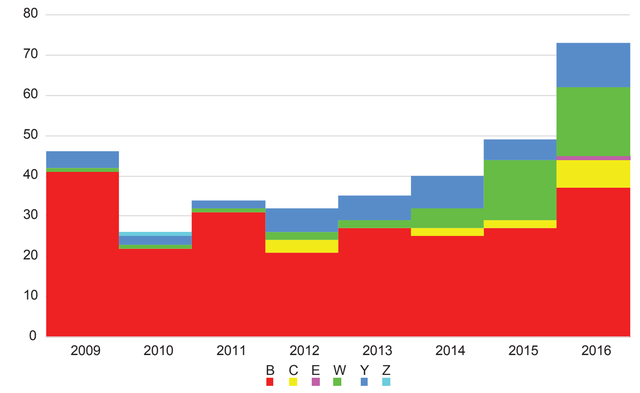


Figure 3: cgMLST phylogenetic analysis of all Scottish IMD isolates cgMLST

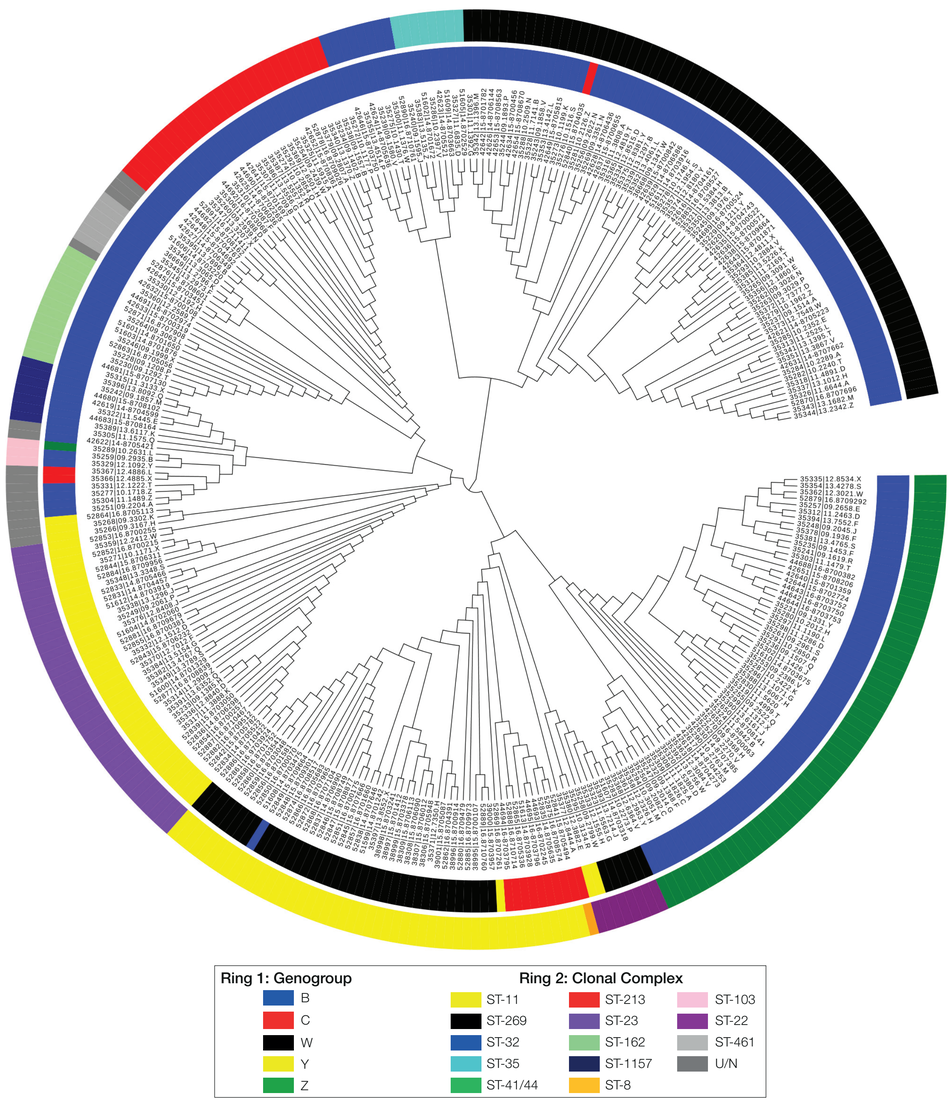


Figure 4: Bexsero® Antigen Sequence Typing (BASTs) by clonal complex

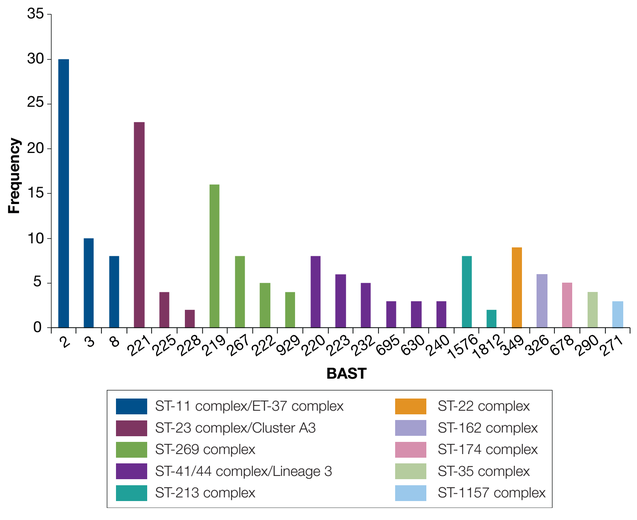
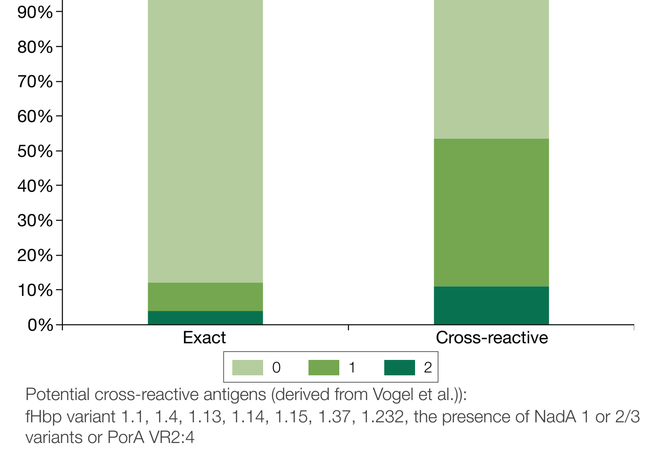


Figure 5: Genomic coverages estimates



Potential cross-reactive antigens (derived from Vogel et al.)):
fHbp variant 1.1, 1.4, 1.13, 1.14, 1.15, 1.37, 1.232, the presence of NadA 1 or 2/3 variants or PorA VR2:4

Vogel et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. Lancet Infectious Diseases 2013;13:416–25.

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