

Whole genome sequencing, a novel and powerful tool against tuberculosis

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The whole genome sequencing by next generation sequencing technologies (WGS-NGS) applied to the diagnosis of tuberculosis (TB) has been located as a powerful tool for the generation of new knowledge, and help in the analysis and characterization of polymorphisms associated with drug resistance, as well as in the development of clinical and epidemiological studies (1-3).

Most researches related with WGS are based on the analysis of TB genome, leaving aside the characteristics of the individual or the affected population. However, the article recently presented by Dr. Yang's (4) team shows us how valuable the combination of information generated by WGS and the epidemiological data of the population that can be affected.

The study was conducted in Shanghai, China, a city with about 24 million inhabitants and one of the highest population densities in the world. The study start with an important number of individuals, close to 8,000, from the period Jan 2009 to December 2012 and with a confirmed diagnosis of TB and drug-susceptibility profile determined phenotypically. Clinical, demographic and epidemiological data were provided by the local surveillance system. Of the total number of individuals included, only 367 (5%) had multidrug resistance (MDR), and the WGS analysis was performed on 324 isolates.

WGS analysis showed that a large proportion of the isolates could be grouped into clusters, which showed that most individuals (73%) had acquired the infection through the transmission of an MDR isolate, and showed that only 25% of MDR isolates were derived from poor adherence to treatment by the patient.

They also identified risk factors that showed a significant association for an individual to be infected by a multidrug-resistant strain. These factors were: being between 45 and 64 years of age have a 2.15 times risk, while being over 65 years increases this risk to 3.15 times, confirming that the most susceptible population is that which exceeds 45 years. On the other hand, being diagnosed 2 months or more, after the occurrence of the first symptoms, increased 2.20 times the risk of having an infection by a MDR strain. These two factors demonstrate the importance of early detection of TB, with emphasis on the population older than 45 years, because unidentified MDR strains will have the opportunity to continue the transmission of infection, increasing the number of MDR -TB cases in the population.

The article mentions that the incorrect treatment of TB is a major problem in China (5,6) that favors the emergence of new cases of MDR-TB. Unfortunately, this problem is not unique to that country. However, through the application of diagnostic procedures and characterization

of these isolates by WGS individually or collectively, could be possible to help in the identification and prevention of such damage since the beginning of the infection in the individual and the potential dispersion of the strain in the population. Although this establishes important costs for its implementation, there is no doubt that the information generated, as well as the prevention and containment measures that can be derived, would justify this expense. And they would undoubtedly support WHO's intention to eradicate TB as an important epidemiological problem in 2030 (7).

Attention was drawn to the fact that contagion of MDR-TB isolates identified in the study population occurred predominantly among individuals living in close proximity rather than in members of a family. This raises important questions about endogenous (biological) or exogenous (social) factors that may be involved in TB transmission. Perhaps a more detailed description of the identified clusters would help to describe in a broader way the identified clusters and with this information try to answer these questions.

Regarding compensatory mutations and their possible influence on the transmission of MDR strains, we agree with the authors' conclusions that a greater number of prospective studies are required in different places, in order to verify their degree of influence in the transmission of disease in a population, although there are reports that such mutations confer advantages, such as higher growth rates, and are mostly present in isolates of MDR patients (8).

One point that caught the attention was that the majority of the individuals showed an infection by the Beijing strain, this lineage is characterized by being highly virulent and of an important tendency to develop resistance against drugs (9). The predominant presence of this lineage allowed to characterize in detail its phylogenetic development in the population, as well as its evolution. However, this aspect could be a significant weakness of the study, since it will not allow an extrapolation of these results in regions where the presence of several circulating lineages is described. This would then force similar studies to be carried out in various settings, in order to evaluate the behavior of MDR-TB transmission under these conditions.

In conclusion, we consider that this study provides important information about how the recent transmission of MDR-TB is the main element related to the generation of TB resistance in Shanghai. And place to the WGS

as a useful tool to determine transmission patterns, and undoubtedly, this procedure will have an important impact on the biological, clinical, and epidemiological characterization of TB in the near future, helping to establish measures of containment and prevention, considering the characteristics of the circulating isolates in the different settings, increasing the success of its implementation.

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Footnote

Conflicts of Interest: The authors have no conflict of interest to declare.

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