Assessing Sequence Variants

Sequencing technologies have developed rapidly in the last few years. It is possible to sequence an entire genome or a larger panel within just a few days. At the MLL, data from the sequencing machine is loaded to our private cloud in real time and automatically preprocessed using the very latest algorithms. These algorithms compare the sequence of four bases (the nucleotides A, C, G, and T) obtained for individual patients to a reference sequence. It quickly becomes apparent that no one patient is identical to any other. An individualized sequence assessment is a prerequisite for personalized diagnostics and therapy.

In the past, sequence alterations were typically assigned to two categories: “Mutations” and “Polymorphisms”. Most of the sequence differences – the ones we see on a daily basis – are polymorphisms. These occur in the population with varying frequencies, are transmitted, and, according to what we know today, usually have nothing to do with any subsequent diseases. They explain blood type features or hair and eye color, for example. Acquired mutations are different. These are caused by errors introduced whilst copying the double stranded DNA during cell division. Targeted therapies as well as cell-based and/or animal models that extensively characterize the function of the more frequently occurring acquired mutations such as JAK2 V617F or BRAF V600E already exist.

However, the rapid increase in sequencing data from healthy and a wide variety of diseased tissues has made it clear that there is a broad spectrum between mutations that are clearly associated with diseases and non-pathogenic polymorphisms. Just because a change has occurred during the course of disease does not automatically make it the cause (or the “driver”) of the disease. Some changes are merely byproducts of rapid cell division or of a defective DNA repair mechanism and are referred to as “passenger” alterations. In addition, a patient may have been born with a change that favors the development of the disease or influences the response to medications. Making it even more difficult is the fact that individual genes (e.g. TET2) exhibit such a diverse mutational landscape that functional characterization of each individual mutation is often not feasible.

For this reason, scientists prefer to use the term “variant” instead of mutation or polymorphism. Every day we face the challenge of interpreting each patient's variants in the overall clinical context. To do this, we employ the most advanced technical resources. Thanks to artificial intelligence, we are better able to predict the function of a variant (see Hutter et al. ASH 2019). Moreover, the GnomAD database project enables us to compare each change with data from more than 100,000 individuals with just one click of the mouse.

Even so, it still happens that we are the first in the world to detect a variant or that the data is contradictory. A comparison with germ line material can be helpful in these cases. To do this we collect a buccal swab and a sample of fingernail. If no evidence of the variant can be found in these samples, we then assume that the variant has been acquired and is therefore only present in the leukemic cell and its precursors. This type of variant serves as a marker of outcome, as it should no longer be present following successful therapy.

Once such a variant becomes better described, we can use this information to help subsequent patients. That is the reason why we have been collecting all mutations, variants, and polymorphisms for more than 14 years. We have access to this expanding wealth of information for each new case and this contributes to improve the diagnostics for each individual patient every day.

More information can be found here.

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Questions & Information

Do you have questions regarding this article or do you need further information? Please send an e-mail to our author.

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