Mosaic-like gene deletion and duplication pattern shaping the immune system discovered

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The field of genetic sequencing has undergone a dramatic revolution over the past 20 years. In 2001 the first copy of the three billion base pairs that assemble the human genome was published. Since then, the price of genetic sequencing has dramatically declined, and sequencing of

DNA fragments has become routine in biology and medical laboratories. Many studies focus on identification of genetic patterns and genes related to normal functions and disease. However, certain genomic regions are still poorly characterized.

In a study published today in the journal *Nature Communications*, a team of researchers, led by Prof. Gur Yaari, of the Alexander Kofkin Faculty of Engineering at Bar-Ilan University, reveals a novel computational tool it has developed to study variations in genes that determine the immune system's dynamics and used to analyze genetic variation among 100 individuals.

Current knowledge of the regions which determine the immune system's function is very limited. The reason for this is the repetitive structure of those regions, which hinders mapping of short DNA reads to their exact location within these regions. "Despite limited knowledge about those regions, they are critically important for a deeper understanding of the immune system, as well as for prediction of diseases and development of novel tools for personalized medicine in cancer, inflammation, autoimmune diseases, allergies and infectious diseases," says Prof. Yaari.

Our immune system can adapt itself to countless threats (pathogens), even ones that continuously evolve. "Among other mechanisms, this is done through a huge repertoire of receptors expressed by B and T white blood cells," explains Moriah Gidoni, a doctoral student who participated in the study. "The human body contains tens of billions of B cells, each of which expresses a different antibody receptor that can bind a different pathogen. How can such a huge diversity of antibodies be achieved, when the genomic regions encoding for antibodies are relatively short? Diversity is achieved by each B cell expressing only a small number of DNA fragments that are randomly chosen from the entire region, which together encode for a complete antibody."

Similar to other human characteristics, the genomic region encoding the immune receptors changes between people, and each person has two such regions that are inherited from the mother and the father. The fragments encoding each antibody are selected in each B cell from only one chromosome, and therefore it is highly valuable to map the fragments that are found on each chromosome, which are the pool from which that person is able to encode antibodies. For example, a person who is missing certain fragments is unable to produce certain antibodies, which can hinder his ability to fight a certain pathogen, making him more susceptible to the disease caused by the pathogen.

According to the researchers an indirect way to learn about the genetic variations in these regions is to read genetic sequences of mature B cells after they have already chosen which fragments they express, and from these data to infer the genetic variety within each person.

The analysis showed a much richer than expected pattern of deletions and duplications of many genomic regions. Prof. Yaari, who led the study, says: "Despite the critical importance of these genomic regions for our understanding of the immune system and a wide variety of diseases, our knowledge so far has been limited to what was under the standard sequencing lamppost. Computational tools like the one recently developed by our group enable a completely different point of view on this very important genomic region that contains a large wealth of valuable biological and medical information."

The study was conducted in collaboration with research groups from the United States, Norway, and Australia.

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