MedSeq Project Yields Algorithm for Extensive Blood Typing

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NEW YORK (GenomeWeb) – Having access to whole-genome sequences can provide detailed blood typing insights that can be critical for some individuals receiving frequent blood transfusions, according to research published online yesterday in *The Lancet Haematology*.

"Blood transfusion complications are common in patients needing chronic transfusion, but with current technology it is not cost effective to do blood typing for all antigens," co-first author William Lane, director of the Brigham and Women's Hospital Department of Pathology's clinical laboratory informatics program and assistant director of the center's tissue typing lab, said in a statement.

Lane and his colleagues documented the red blood cell alterations and platelet antigen patterns present in whole-genome sequence data for 110 participants in the MedSeq Project, a randomized controlled trial to study the clinical utility of whole-genome sequencing. Based on this burgeoning database, they established an aptly named "bloodTyper" algorithm to predict an individual's red blood cell antigen patterns, blood groups, and platelet antigen types from their genome sequence data — a tool they improved using MedSeq participant data and validated in 200 individuals sequenced for another trial.

Lane explained that the bloodTyper algorithm "can be applied to type everyone for all relevant blood groups at a low cost once sequencing is obtained."

Most blood transfusions are uneventful, the team explained. But serious complications can arise when individuals become sensitized or react to the diverse antigens present on red blood cells and platelets — a collection that dramatically surpasses the antigens represented in the well-known ABO and Rh blood group systems. And those immune reactions can be particularly problematic for patients who need blood transfusions frequently.

"Although transfusion-related deaths are rare, about [15 percent] of deaths associated with blood transfusions each year are the result of hemolytic transfusion reactions due to blood-group antibodies," Lane and co-authors wrote, noting that "sensitization to foreign [red blood cell] antigens results in a lifetime risk of delayed or acute hemolytic transfusion reactions, fetal anemia, and complications in pregnancy."

Nevertheless, they explained, more extensive antigen typing is typically time-consuming and cost-prohibitive in most situations, in part owing to the availability of antibodies or SNP markers that span the full suite of antigens and variations underlying them.

In contrast, the researchers reasoned that whole-genome sequence data, which are becoming ever more available to individuals, could provide a window into these vast collections of red blood cell and platelet antigens.

For their proof-of-principle analysis, they tapped into data for 110 individuals sequenced to 30-fold average depth for MedSeq between late 2012 and early 2017, including 89 individuals of European ancestry, 13 individuals of African ancestry, four Asians, and four Hispanics.

After identifying blood type-related variants across the full genome set, the team came up with and applied its algorithm to a subset of 20 MedSeq genomes, identifying typing errors that arose with either the genome sequence-based approach, SNP typing, or serological tests. At that stage of the study, the algorithm correctly identified 1,194 of 1,200 possible antigen types from the whole-genome sequence data.

The investigators further tweaked the algorithm and incorporated blood type-related copy number analyses before applying it to genome sequence data for the remaining 90 MedSeq participants. Across 38 red blood cell antigens and 22 platelet antigens, the improved algorithm correctly made 5,390 of 5,400 possible antigen typing calls, coming in at 99.8 percent concordance.

Incorporating still more iterative improvements to the algorithm, the team applied bloodTyper to genome sequence data for 200 Interval study participants sequenced to an average depth of 15-fold at the Wellcome Trust Sanger Institute. In that dataset, the method was 99.2 percent concordant with typing results from serological blood typing at 21 red blood cell antigens.

"This approach has the potential to be one of the first routine clinical uses of genomics for medical care for patients needing blood transfusion," co-first author Connie Westhoff, head of blood group genomics at the New York Blood Center and executive scientific director of its National Center for Blood Group Genomics, said in a statement, adding that it could "prevent serious or even fatal complications."

"[O]nce patients are sensitized, they have a life-long risk of hemolytic transfusion reactions if blood transfusion is needed in an emergency," Westhoff explained.

The bloodTyper algorithm is available online at www.bloodantigens.com/bloodTyper.

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