whom 86% had received prior treatment with a BTK inhibitor, with 33% discontinuing the prior BTK inhibitor due to reasons other than progressive CLL. Furthermore, LOXO-305 had promising efficacy in this heavily pretreated population with an overall response rate of 62% in 121 efficacy-evaluable patients with CLL/small lymphocytic leukemia who had previously been treated with a BTK inhibitor.

Taken together, these studies challenge the traditional sequencing paradigm of switching drug classes in the setting of CLL therapy discontinuation for intolerance. In Figure 1, we propose a sequencing algorithm incorporating the new data from Rogers et al. While venetoclax is an acceptable option in the setting of intolerance to BTK inhibitors, CLL remains an incurable, chronic disease and there is a strong scientific rationale for maximizing clinical benefit from each drug class prior to exposing patients to the selective pressures of another therapeutic class. In the case of the common problem of intolerance to ibrutinib it is best to keep the solution “all in the (BTK inhibitor) family.”

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Contributions
MCT and ARM drafted the manuscript. MCT, LER and ARM provided feedback and edited the manuscript.

References
1. Rogers KA, Thompson PA, Allan JN, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. Haematologica. 2021;106(9):2364-2373.
2. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica. 2018;103(5):874-879.
3. UK CLL Forum. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. Haematologica. 2016;101(12):1563-1572.
4. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia. 2020;34(6):787-798.
5. Coutre SE, Byrd JC, Hillmen P, et al. Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. Blood Adv. 2019;3(12):1799-1807.
6. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. Blood Adv. 2019;3(9):1553-1562.
7. Mato AR, Ghosh N, Schuster SJ, et al. Phase 2 study of the safety and efficacy of umbralisib in patients with CLL who are intolerant to BTK or PI3Kδ inhibitor therapy. Blood. 2021;137(20):2817-2826.
8. Mato AR, Shah NN, Jurczak W. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;397(10277):892-901.
9. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol. 2018;19(1):65-75.

Do we need more genome wide association studies?

Stephan Menzel
Red Cell Research Unit, King’s College London, London, UK
E-mail: STEPHAN MENZEL - stephan.menzel@kcl.ac.uk
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Much of the individual biological traits we have, of what we look like, of our physical and mental abilities, of our risk to suffer from the non-communicable diseases that will ultimately end our lives, is encoded in the genetic ‘background’, consisting of millions of single-nucleotide polymorphisms (SNP) and other common sequence variants that each have minute functional effects on regulatory sequences within our genome.

Genome-wide association studies (GWAS) are the tool of choice to make the connection between common-variant genotype data, collected either through genome sequencing or with genotyping arrays (‘chips’), and human phenotype. In its simplest form, GWAS compare the frequency for each of of thousands or millions of common genetic variants between groups of patients and controls, thus identifying genetic risk factors for the diseases studied this way.

There are limits to what the traditional GWAS approach can achieve. Suffocating type-I error rates arising from the analysis of millions of genetic variants make it necessary to assemble very large groups of patients and controls, but even then, only the strongest genetic risk factors can be identified with meaningful certainty. Even so, finding this initial set of genetic factors has significantly enhanced our understanding of pathways leading to common disease or shaping health-relevant physiological traits. With the majority of disease risk factors still hidden, however, it is presently impossible to assemble enough genetic information to...
make clinically relevant predictions for any given person. The gambit for detecting additional disease-relevant genetic factors has been to the assemble ever larger subject cohorts, reaching hundreds of thousands of participants for some conditions. Still the majority of the disease-relevant genetic background remains untouchable, trapped in what is termed the ‘missing heritability’. General frustration with the GWAS approach is prevalent among researchers.

Corre et al., on page 2499 of this issue, report a study of the type that offers a way out of this trap. The authors present a quantitative-trait association study, comparing circulating levels of the hormone erythropoietin with the genotype of a genome-wide SNP set. In contrast to the original case-control setup, such quantitative-trait GWAS offer crucial advantages. They allow ‘drilling down’ into the pathways underlying biological characters and disease pathogenesis, thereby reducing complexity and increasing the signal-to-noise ratio of genetic analysis. Quantitative-trait GWAS can utilise various large subject cohorts assembled for other studies, such as groups of patients or population samples, if the parameter of interest or related biological traits have been recorded. Loci and variants discovered in quantitative-trait studies can subsequently be evaluated with more complex traits, such as disease risk.

Several large GWAS with red blood cell traits have been conducted and the genes identified have contributed to our understanding of anemia. This has been complemented with GWAS investigation of circulating erythropoietin levels, the main hormonal regulator of the system. Unsurprisingly, the set of genes detected overlap between the two approaches, e.g., HBS1L-MYB, which is a quantitative-trait locus (QTL) for various red-blood cell traits (HbF%, MCV, MCH, RBC), has also shown strong association with erythropoietin levels in a 2018 Dutch population study with 6,777 participants (Grote Beverborg et al.). The present study of Corre et al., while smaller, has provided confirmation of HBS1L-MYB as an erythropoietin locus and the joint analysis of both cohorts has yielded a significance level of $P<10^{-7}$. Heritability of erythropoietin levels was found to be higher than in another previous study (by Wang et al.) and the set of genes detected is also somewhat different.

In quantitative-trait studies, heritability estimates and the spectrum of loci detected is fluid, and specific outcomes depend on peculiarities of subject recruitment, trait assay method, and measurement routines. However, with multiple cohorts available to study a given parameter and its related traits, a network of quantitative-trait studies can be built that, together with knowledge gained from laboratory-experimental studies, paints a picture of functional and genetic architecture of the investigated tissue system and any disease risk connected with it.

The most intriguing outcome of the present paper is the detection of a putative new QTL for erythropoietin levels on chromosome 15, with evidence for trait association ($P=1.05\times10^{-7}$) just short of the acknowledged level of genome-wide statistical significance. Corre et al. have started to harness data from GWAS performed with blood cell parameters in an attempt to confirm the validity of this preliminary result: in the UK Biobank study variants at this locus were found associated with erythroid traits, e.g., with hemoglobin concentration and reticulocyte count at $P<10^{-5}$, but it is not clear why Corre and colleagues have not presented a ‘look up’ of their new locus in the erythropoietin GWAS dataset of Grote Beverborg et al. Confirmation of initial, ‘suggestive’, findings in a set of related studies must be integral part to any QTL GWAS, thus harnessing the full power of this approach. Obtaining data for that from colleagues in the field is usually straightforward.

It will be fascinating to see how this story develops following publication in Haematologica. The possibility of uncovering a new mechanism regulating oxygen transport capacity through erythropoietin is tantalising. In general, present efforts to build large population cohorts of extensively phenotyped individuals with complementary genotype data (genome array or sequence) will generate increasingly powerful datasets allowing to decipher our genetic blueprint and help to fulfil the promise of genetics for the improvement of human health.

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References
1. Goldstein DB. Common genetic variation and human traits. N Engl J Med. 2009;360(17):1696-1698.
2. Corre T, Ponte B, Pivin E, et al. Heritability and association with distinct genetic loci of erythropoietin levels in the general population. Haematologica. 2021;106(8):2499-2501.
3. Grote Beverborg N, Verweij N, Klip IT, et al. Erythropoietin in the general population: reference ranges and clinical, biochemical and genetic correlates. PLoS One. 2015;10(4):e0125215.
4. Wang Y, Nudel R, Benros ME, et al. Genome-wide association study identifies 16 genomic regions associated with circulating cytokines at birth. PLoS Genet. 2020;16(11):e1009165.