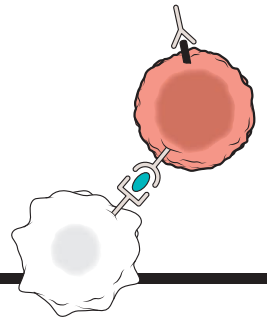
Microbiome affects immunotherapy *p. 1031* ▸

Pushing the boundaries of optical nonlinearity *p. 1033*



PERSPECTIVES

HUMAN GENOME

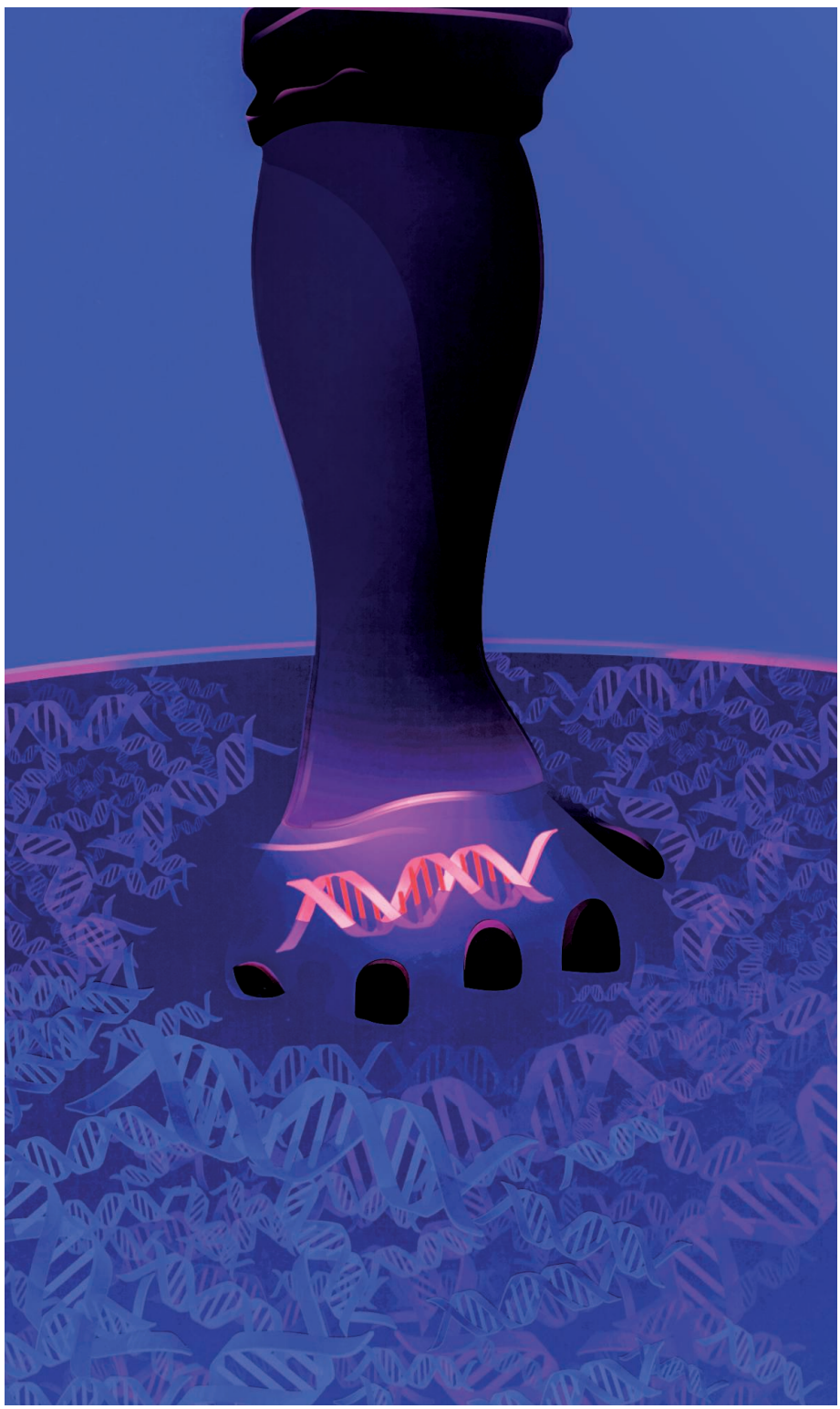
The indispensable genome

The core genes essential for life in human cells are defined

By **Charles Boone** *and* **Brenda J. Andrews**

Game-changing moments in functional genomics often reflect the development and application of powerful new reagents and methods to provide new phenotypic insight on a global scale. Three independent studies describe systematic, genome-scale approaches to defining human genes that are indispensable for viability, which collectively form the essential gene set. On pages 1092 and 1096 of this issue, Blomen *et al.* (*1*) and Wang *et al.* (*2*), respectively, report a consistent set of ~2000 genes that are indispensable for viability in human cells. Moreover, very similar results were obtained by Hart *et al.* (*3*). For the first time, we now have a firm handle on the core set of essential genes that are required for human cell division. This opens the door to studying the roles of essential genes, how gene essentiality depends on genetic and tissue contexts, and how essential genes evolve.

Scientists could anticipate identifying a core set of human cell essential genes since the first description of the essential gene set in yeast, a model organism that has been a reliable test bed for functional genomics studies. In yeast, defining the essential gene set was relatively straightforward because it has a compact genome and efficient homologous recombination, which enables precise



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gene deletions within their normal chromosomal context.

Yeast gene deletion can be performed in a diploid cell, which then can be induced to undergo meiosis, producing pure haploid cells carrying a precise deletion of a single gene. The failure of a haploid deletion mutant strain to grow after such manipulations identifies genes that are essential for cell division. Genome-scale application of this deletion mutant analysis revealed that ~1000 of yeast's 6000 genes are essential for viability in standard growth conditions (*4*, *5*). The yeast essential genes encode proteins that drive basic cellular functions such as transcription, translation, DNA replication, cell division cycle control, and fundamental metabolism. Moreover, the yeast essential genes share several attributes that reflect their critical role in cellular life. For example, they are often conserved and evolutionarily constrained, are highly expressed, and encode abundant proteins that tend to form stable complexes and thus are rich in protein-protein interactions (*6*–*8*).

The landscape of essential genes in human cells can now be explored using the conceptual framework established in yeast. Blomen *et al.* surveyed the essential genes in a near-haploid chronic myelogenous leukemia (CML) cell line, KBM7, and its nonhematopoietic cell derivative HAP1, which is haploid for all chromosomes. These haploid cell lines enable essential genes to be identified using the gene-trap insertional mutagenesis methodology. Wang *et al.* also surveyed KBM7 cells using gene-trap analysis, but they further used a gene-editing strategy based on clustered regularly interspaced short palindromic repeats (CRISPR) that enabled exploration for essential genes in diploid cell lines, including another CML cell line (K562) and two Burkitt's lymphoma cell lines (Raji and Jiyoye). Similarly, Hart *et al.* used a CRISPR-Cas9 gene-editing strategy to explore essential genes, but they did so across a diverse series of adherent cell types including colorectal cancer cell lines, cervical cancer cells, primary patient-derived glioblastoma cells, and immortalized retinal epithelial cells. All three groups found that human essential genes are highly conserved, and much like yeast, they encode abundant proteins that engage in protein-protein interactions. The core set of human cell essential genes also tend not to be duplicated and appear to have increased evolutionary constraints, as they evolve slowly and are associated with fewer deleterious single-nucleotide polymorphisms. Although many essential genes are involved in fundamental biological processes including transcription, translation, and DNA replication, a substantial fraction remains functionally uncharacterized. Indeed, each analysis prioritized a wealth of uncharacterized genes whose essential roles are waiting to be explored.

Blomen *et al.* and Wang *et al.* identified a coherent and overlapping set of essential genes in two related haploid cell lines, which emphasizes the potential to characterize the core set of human cell essential genes that drives life in all cell types. Nonetheless, the essentiality of some genes, as demonstrated previously by large-scale RNA interference–based screens (*9*, *10*) as well as the Hart *et al.* analysis, is context-dependent and affects viability in a cell type–specific manner. Indeed, by screening additional CML or Burkitt's lymphoma diploid cell lines, Wang *et al.* discovered 48 genes that exhibited cell type–specific essentiality. These results highlight the potential of genome-scale genetic screens to reveal the biology underlying cell differentiation and the potential to identify specific cancer cell vulnerabilities that can be exploited as targets for personalized therapeutic strategies. Large-scale genetic screens will have to be implemented in a number of different cell lines to generate a complete picture of the human cell essential gene set.

"...the essentiality of some genes... is context dependent..."

All three studies (*1*–*3*) conclude that ~10% of the ~20,000 genes in human cells are essential for cell survival. Although this frequency may change somewhat with screening of other cell lines, it is clear that most human genes are nonessential under laboratory culture conditions. This finding is consistent with the results of large-scale screens from various model organisms that have established a comparable ratio of essential to nonessential genes, highlighting the buffering against genetic and environmental insults inherent in eukaryotic genomes (*11*). Many nonessential genes impinge on essential functions, but they do so in the context of a sophisticated biological machine that has been wired with backup pathways (*12*).

The essential functions of pairs of nonessential genes can be examined in synthetic lethal double-mutant screens. Synthetic lethality occurs when two mutations, neither of which is lethal on its own, combine to generate a lethal double mutant—a genetic interaction that has been explored in yeast. Global genetic interaction screens have identified hundreds of thousands of synthetic lethal genetic interactions, revealing contextual lethality that is at least an order of magnitude more prevalent than the lethality caused by single gene perturbation (*12*). Blomen *et al.* begin to address the extent of synthetic lethal interactions in human cells by screening a set of five nonessential genes with roles in secretion for synthetic lethal negative genetic interactions. They discovered an average of ~20 synthetic lethal double-mutant interactions for a given nonessential gene, and these interactions tend to occur with functionally related genes. Even this relatively small genetic network suggests that the properties of the extensive genetic networks mapped for yeast are conserved and can now be mapped efficiently in human cells. The genetic network described by Blomen *et al.* ought to catalyze large-scale, collaborative efforts to map genetic interactions in human cells. Such an effort promises to enable functional annotation of the human genome, because genetic interaction profiles are rich in functional information and provide a quantitative measure of gene function.

The ability to systematically assess all genes within a genome for a particular phenotype greatly accelerated the functional analysis of yeast genes (*13*). The yeast deletion mutant collection also opened the door to the field of chemical genetics, enabling new approaches for linking bioactive compounds to their cellular targets (*14*). Genome-wide mutant collections can be analyzed in pools, but there is also the potential to generate arrays of mutants, providing a new resource for high-content screening approaches to address cell biology phenotypes. The studies of Blomen *et al.*, Wang *et al.*, and Hart *et al.* reveal the core essential gene set for human cells, setting the stage for the next wave of new genetic and chemical-genetic science that will take place directly in human cells. A future challenge will be to develop genetic tools, such as conditional alleles of essential genes, for exploring the terminal phenotypes and the various molecular mechanisms underlying the lethality associated with perturbation of different essential functions. ■

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