BRIEF COMMUNICATION

Tracking human genes along the translational continuum

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Understanding the drivers of research on human genes is a critical component to success of translation efforts of genomics into medicine and public health. Using publicly available curated online databases we sought to identify specific genes that are featured in translational genetic research in comparison to all genomics research publications. Articles in the CDC’s Public Health Genomics and Precision Health Knowledge Base were stratified into studies that have moved beyond basic research to population and clinical epidemiologic studies (T1: clinical and population human genome epidemiology research), and studies that evaluate, implement, and assess impact of genes in clinical and public health areas (T2+: beyond bench to bedside). We examined gene counts and numbers of publications within these phases of translation in comparison to all genes from Medline. We are able to highlight those genes that are moving from basic research to clinical and public health translational research, namely in cancer and a few genetic diseases with high penetrance and clinical actionability. Identifying human genes of translational value is an important step towards determining an evidence-based trajectory of the human genome in clinical and public health practice over time.

results

We used the Public Health Genomics and Precision Health Knowledge Base (PHGKB), a curated suite of genomics databases maintained by the CDC Office of Public Health Genomics which tracks the impact and translation of genome discoveries on clinical practice and public health. We included two databases from PHGKB in this exercise: (1) the Human Genome Epidemiology Navigator (HuGE, https://phgkb.cdc.gov/PHGKB/hNHome.action) which is a collection of publications on population and clinical epidemiologic studies of human genes in relation to health outcomes, corresponding with T1 translation and (2) the Genomics & Precision Health Database (GPH, https://phgkb.cdc.gov/PHGKB/translationalStartPage.action) which is a collection of publications reflecting the T2-T4 stages of translation. These two databases were compared to all gene-associated Medline/PubMed publications. The details of the stages T1–T4 are explained in Supplementary Fig. 1 and Supplementary Note 1.

The PubMed articles with associated genes ascertained through the gene2pubmed file contained 609,633 PMIDs. The HuGE database and the subset from GPH of original research studies,
studies on evidence synthesis, and/or guidelines publications contained 143,417 and 8526 PMIDs, respectively.

NUMBER OF GENES REPRESENTED IN PUBLICATIONS FROM HUGE AND GPH

While PubMed and GPH articles were associated with 24,656 human genes, HuGE and GPH only identified 11,081 and 1846 genes, respectively (Table 1), representing 44.94% and 7.49% relative to the genes that appeared in PubMed (Supplementary Fig. 2). Most of the genes mentioned in GPH are also in HuGE (n = 1682). However, 164 genes (8.88%) in GPH were not mentioned in HuGE. Over 96% of these were associated with a publication count of one (n = 158).

The most common genes based on publication count in PubMed, HuGE and GPH are listed in Table 2. The top 10 most common genes are represented in 3.50% of all PubMed publications. The top 10 common genes represented in HuGE and GPH are 12.13% and 28.31%, respectively (Table 1).

Some genes are significantly more or less popular in HuGE and GPH than PubMed. Table 2 shows the top 20 most significant genes in HuGE and GPH compared to PubMed.

Nine of the top 10 genes in GPH are cancer-related genes. These genes are associated with hereditary breast and ovarian cancer (BRCA1, BRCA2), Lynch syndrome (MLH1, MSH2, MSH6, PMS2), and her2/neu mutations in breast cancer (ERBB2). LDLR is one gene associated with familial hypercholesterolemia. Nine of the 10 top genes are hereditary single gene disorders.

In contrast, the top 10 genes studied in HuGE include genes relevant to many disease conditions. The top gene is MTHFR, a gene associated with defects in folic acid metabolism extensively studied in relation to birth defects, cancer, cardiovascular disease, and other conditions, but has yet to be “translated” into implementation in practice. Similarly, the APOE gene has been popularized resulting from the strong association of APOE4 alleles with Alzheimer’s disease. APOE variation has been studied in relation to cardiovascular diseases and other outcomes.

CORRELATION BETWEEN THE PUBLICATIONS IN PUBMED, HUGE, AND GPH DATABASES

Supplementary Figure 3a shows the correlation between all the publications in PubMed and the publications in HuGE. The publication count in HuGE is closely and positively related to the publication count in PubMed (Pearson correlation coefficient is 0.76). We found that all top 20 most published genes in HuGE are included in the top 0.5% of the most published genes in PubMed.

As shown in Supplementary Fig. 3b, the publication count in GPH is also positively correlated to that of PubMed. However, this correlation is weaker than the correlation between HuGE and PubMed results (Pearson correlation coefficient is 0.40). We also observe that BRCA1, BRCA2, or HER2 have significantly more publications in GPH compared to PubMed which are far from the fitted linear regression line. Supplementary Figure 3b also shows that GPH focuses on only a few selected genes. Only 9 out of the top 20 genes in GPH are in the top 0.5% of the most published genes in PubMed. The change by year in the number of publications in each database for BRCA1, APOE, LDLR, GJB2, and EGFR are shown in Supplementary Fig. 4. Most of the HuGE and GPH publications on BRCA1 and EGFR genes are cancer-related. The figure also shows that GJB2 and LDLR publications are mostly describing rare diseases and heart, lung, blood, and sleep (HLBS) disorders, respectively.

| Rank | Publication count | Statistical significance of the publications compared to PubMed |
|------|------------------|----------------------------------------------------------|
|      | PubMed | HuGE | GPH | HuGE | GPH |
| 1    | TP53   | APOE | BRCA1 | MTHFR | BRCA1 |
| 2    | TNF    | MTHFR| BRCA2 | APOE | BRCA2 |
| 3    | EGFR   | TFN  | EGFR  | HLA-DRB1 | PMS2 |
| 4    | VEGFA  | EGFR | ERBB2 | GSTM1 | MSH6 |
| 5    | IL6    | HLA-DRB1 | KRAS | KRAS | MSH2 |
| 6    | APOE   | TP53 | TP53  | ACE  | LDLR |
| 7    | TGFB1  | ACE  | BRAF  | GSTT1 | MLH1 |
| 8    | MTHFR  | IL6  | MLH1  | COMT | ERBB2 |
| 9    | ESR1   | KRAS | MSH2  | BRF  | KRAS |
| 10   | AKT1   | GSTM1| LDLR  | IL10 | PALB2 |
| 11   | HIF1A  | IL10 | MSH6  | CYP2C19 | BRAF |
| 12   | NFKB1  | GSTT1| PMS2  | VDR  | EGFR |
| 13   | IL10   | COMT | CYP2C19| SLC6A4 | NAR5 |
| 14   | BRCA1  | BRAF | PIK3CA| CYP3A5 | CYP2C19 |
| 15   | ERBB2  | SLC6A4| CYP2D6| ABCB1| CYP2D6 |
| 16   | MMP9   | BRCA1| NAR5  | EGFR | PCSK9 |
| 17   | HLA-DRB1| ABCB1| ALK  | CYP2C9 | CHEK2 |
| 18   | IL1B   | VDR  | CFTR  | GSTP1 | ALK |
| 19   | ACE    | BRCA2 | CHEK2 | CYP2D6 | PIK3CA |
| 20   | APP    | BDNF | PCSK9 | TNF  | VKORC1 |

The ranking of “Publication count” column is simply sorted by the number of appearances in each database, and the other column is calculated and ranked using the z-score of each gene representing the significance of the publication count difference compared with PubMed.

DISCUSSION

Using well established and curated publically available publication databases, we have extended the analysis of Stoeger et al. on the
overall publications on human genes to publications in translational phases. Our overall goal is to describe which genes have been more likely to be studied epidemiologically (T1) or evaluated and implemented in clinical and public health practice (T2–T4). We observed that translational studies focus on only a small number of human genes, and the farther along the continuum, the smaller the number.

Stoeger et al. reported that most of the research focuses on only around 2000 genes in PubMed. In our analysis, we found that epidemiology and translational studies focus on an even much smaller number of genes. First, the number of genes and the number of publications represented in HuGE and GPH are a significantly small proportion of all PubMed articles, and only a limited number of genes are the main focus in epidemiology and translational studies.

It is evident from this analysis through the observation of top genes that the “action” in translation beyond bench to bedside is in the field of cancer, including genes associated with hereditary breast and ovarian cancer and Lynch syndrome. These two hereditary cancers have emerged as conditions with important numbers of early discovery research articles and later translational research publications. It is entirely possible the more genes are studied, the more the likelihood at establishing clinical validity and utility for later translational and implementation studies. It is also unclear what classes of mediating and confounding factors (funding, popular interest, etc.) influence publication rates for individual genes at each translational phase. Although our work establishes a baseline approach for tracking the translational trajectory of human genes into clinical and population health impact, future analyses will have to develop models of translation trajectories for specific genes and their associated diseases.

METHODS
Collecting overall publications on human genes
To obtain the publication count specific to each gene, we collected Gene-PubMed identifier (PMID) data separately from the three databases. For publications on genes indexed in PubMed, we used the “gene2pubmed” file obtained from the NCBI gene website, as similarly done in the study of Stoeger et al. Human data (Taxonomy ID is 9606) from the “gene2-pubmed” file was used here, providing gene-PMID crosslinking information, which is either manually curated by indexers from the National Library of Medicine or integrated from other public databases.

The publications in translational research T1 and T2–T4 phases were downloaded from HuGE and GPH databases, respectively. The selected articles downloaded from the GPH were previously identified as original research studies, studies on evidence synthesis, and/or guidelines publications. Excluded from GPH for this analysis were reviews, comments, and methods articles. The gene-PMID data from HuGE and GPH were ascertained using an automated literature annotation tool, PubTator. PubTator provides gene-PMID information collected using automated named-entity recognition tools and third-party resources. We found genes mentioned in each abstract of the publication in HuGE and GPH, and used them to count publications for each gene.

Gene ranking based upon number of publications
To compare the publication count on genes in HuGE and GPH to the entire literature in PubMed, we ranked the genes for those with the most publications with resulting top most common genes. Additionally, results were calculated using the number of results representing the significance of the publication count difference between two datasets. The statistical significance of the resulting z-scores were calculated for all genes having equal or greater than five publications. Longitudinal publication count data (from 2000 to 2017 for PubMed and HuGE and 2011 to 2017 for GPH) for a few selected top genes was also performed. To understand disease association of these publication changes, we also added the numbers of HLBS disorders, cancer, and rare disease related publications obtained from our former research.

Correlation analysis
To explore the correlation in publication count for genes between PubMed, HuGE, and GPH, we obtained Pearson correlation coefficients and Spearman’s rank correlation coefficients. We drew a linear regression line in correlation figures. Correlation coefficients, and linear regression line was performed using SciPy python library.

Reporting Summary
Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY
All data generated or analyzed during this study are publicly available at Public Health Genomics and Precision Health Knowledge Base website, PubMed FTP (ftp://ftp.ncbi.nlm.nih.gov/gene/DATA/gene2pubmed.gz) and PubTator FTP (ftp://ftp.ncbi.nlm.nih.gov/pub/lu/PubTator/). The organized data are also available as Supplementary data file.
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AUTHOR CONTRIBUTIONS

M.J.K., Z.L. and M.C. conceived the idea. K.L., M.C. and M.J.K. drafted the manuscript. W.Y. and K.L. collected the data. K.L. and Z.L. designed and performed the data analysis. M.C. and M.J.K. interpreted results. Z.L. and M.J.K. supervised the study. All authors reviewed and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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