

Deciphering the impact of genomic variation on function

<https://doi.org/10.1038/s41586-024-07510-0>

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Received: 11 April 2023

Accepted: 2 May 2024

Published online: 4 September 2024

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Our genomes influence nearly every aspect of human biology—from molecular and cellular functions to phenotypes in health and disease. Studying the differences in DNA sequence between individuals (genomic variation) could reveal previously unknown mechanisms of human biology, uncover the basis of genetic predispositions to diseases, and guide the development of new diagnostic tools and therapeutic agents. Yet, understanding how genomic variation alters genome function to influence phenotype has proved challenging. To unlock these insights, we need a systematic and comprehensive catalogue of genome function and the molecular and cellular effects of genomic variants. Towards this goal, the Impact of Genomic Variation on Function (IGVF) Consortium will combine approaches in single-cell mapping, genomic perturbations and predictive modelling to investigate the relationships among genomic variation, genome function and phenotypes. IGVF will create maps across hundreds of cell types and states describing how coding variants alter protein activity, how noncoding variants change the regulation of gene expression, and how such effects connect through gene-regulatory and protein-interaction networks. These experimental data, computational predictions and accompanying standards and pipelines will be integrated into an open resource that will catalyse community efforts to explore how our genomes influence biology and disease across populations.

Since the initial sequencing of the human genome, genetic studies have been immensely productive^{1–3}. Exome and genome sequencing studies have identified hundreds of millions of genomic variants, including single-nucleotide variants (SNVs), small insertions and deletions (indels) and larger structural variants^{4,5} (Fig. 1). Comparisons within families, case–control cohorts and population-scale biobanks have revealed hundreds of thousands of associations between such variants and phenotypes in both health and disease^{6–12}.

Our next challenge is to understand how genomic variation affects molecular and cellular processes to influence organismal phenotype (Fig. 1). At a molecular level, genomic variation can affect the temporal-spatial and quantitative expression of genes or the activity and localization of proteins. Altered gene expression or protein activity can, in turn, affect other genes and proteins, for example via gene-regulatory and protein–protein interaction networks. Changes in such molecular networks affect the properties of cells and tissues, and in doing so can influence organismal phenotypes. Here we use ‘genome function’ to refer to these processes encoded by the genome, and note that this does not necessarily imply ‘function’ in terms of evolutionary selection^{13,14}.

Previous and ongoing efforts have produced breakthroughs in mapping various aspects of genome function, including locating and annotating millions of noncoding regulatory elements in the human genome^{15,16}; mapping associations between genomic variants and effects on gene or protein expression across dozens of human tissues^{17–19}; profiling hundreds of cell types and states through

single-cell measurements of gene expression^{20,21}; applying saturation mutagenesis to analyse coding variants in selected disease genes^{22–24}; and characterizing how genes and proteins interact genetically or physically in molecular networks^{25–27}. These efforts, as well as disease-specific consortia and other studies, have also demonstrated how mapping the effects of genomic variation on genome function can reveal molecular mechanisms in human biology and disease, guide genetic diagnosis and clinical management, and facilitate the development of novel therapies (Fig. 1 and Box 1; reviewed in refs. 1, 28, 29).

Yet, connecting genomic variants to functions and phenotypes continues to prove challenging and slow. The molecular mechanisms that underlie most genetic associations for common diseases remain to be established^{2,29}, genetic diagnosis for rare diseases continues to be hindered by the preponderance of variants of uncertain significance^{7,30} (VUSs), and the effects of genomic variation across diverse groups and populations remains poorly studied^{31,32}. New approaches are needed to accelerate research throughout the community and thereby unlock the vast unrealized potential for understanding human biology and improving human health^{33,34}.

Advances in experimental and computational genomics now promise to overcome some of the key challenges:

(1) Regulatory elements and genes can have cell-type or context-dependent activities, which have been challenging to analyse comprehensively. Emerging single-cell technologies now enable the generation of comprehensive maps of chromatin state and gene expression in nearly any cell type in the body^{20,21}, and computational

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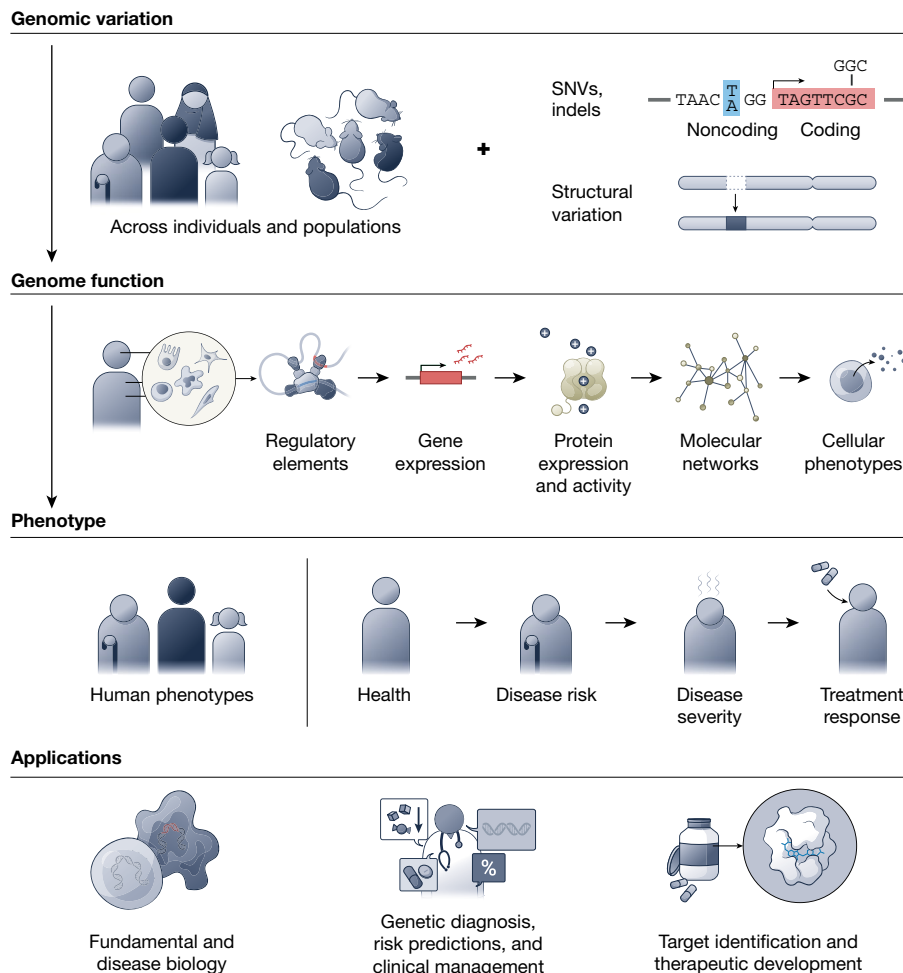


Fig. 1 | Genomic variation influences genome function and phenotype.

Genomic variation includes SNVs, indels and structural variants, which can alter protein-coding sequences or noncoding sequences. Genome function encompasses the cell-type-specific activities and interactions among regulatory

elements, genes and proteins within molecular networks that underlie cellular phenotypes. Organismal phenotypes include quantitative and binary traits in health and disease.

- analysis of these datasets can help to locate candidate regulatory elements, identify transcription factor binding regions and footprints, and delineate gene-regulatory networks^{35–38}.
- (2) Previously it has been difficult to uncover the causal relationships between genomic variation and genome function, including owing to challenges of linkage disequilibrium between common variants. New approaches in statistical fine-mapping now enable improved interpretation of genome-wide association studies (GWAS) and quantitative trait loci (QTL) studies^{39–42}, and high-throughput technologies for designed genomic perturbations, such as with CRISPR screens^{43–50} and massively parallel reporter assays^{51–57} (MPRAs), provide a powerful means to systematically characterize the effects of variants, elements and genes.
 - (3) The scale of the problem is immense. With billions of possible single-nucleotide genomic variants, 20,000 genes, and thousands of cell types, we cannot expect to experimentally map the effects of all possible variants on all aspects of genome function in all possible contexts. To address this, recent studies have highlighted the possibility of training computational models that can generalize to make predictions about genome function for untested variants, cell types and/or contexts^{58–64}.
 - (4) Previous efforts have largely focused on particular types of genome variation or individual diseases. Integrative analysis of coding and noncoding variation in molecular networks and comparisons across

- diverse cellular contexts and diseases could greatly accelerate progress^{28,65–67}.
- (5) Finally, recent successes by CASP⁶⁸ (critical assessment of protein structure prediction), ENCODE¹⁵ (Encyclopedia of DNA Elements) and others^{17,21,69} have highlighted how uniting a diverse community of investigators under a common framework can catalyse advances throughout the global scientific community by developing uniform standards and analysis pipelines, creating uniformly processed, artificial intelligence-readable datasets that are amenable to predictive modelling, and enabling the comparison and synthesis of alternative strategies.

With these challenges and opportunities in mind, the National Human Genome Research Institute (NHGRI) launched the IGVF Consortium in 2021, with the goal of developing a systematic understanding of the effects of genomic variation on genome function and how these effects shape phenotypes. The Consortium consists of more than 120 laboratories that are collaborating on five key activities to address the above challenges: (1) Mapping Centres: to analyse regulatory element and gene activity at single-cell resolution across hundreds of cell types; (2) Functional Characterization Centres: to systematically characterize the molecular and cellular effects of introducing variants or perturbing elements and genes; (3) Predictive Modelling Projects: to develop and apply computational approaches to comprehensively

Box 1

Mapping the effect of genomic variation on genome function can reveal biological mechanisms and advance precision health

Selected examples are discussed below (see also refs. 1,28,29).

Learning basic and disease biology:

- Expression QTL (eQTL) and gene-knockdown studies of a GWAS locus for coronary artery disease identified sortilin (*SORT1*) as a regulator of low-density lipoprotein (LDL) cholesterol levels and elucidated its molecular function in LDL uptake^{158,159}.
- Epigenomic maps and variant-to-function studies revealed a role for the transcription factor genes *IRX3* and *IRX5* in regulating adipocyte browning to influence obesity^{160,161}.
- Characterization of risk variants for inflammatory bowel disease has identified multiple genes involved in autophagy, including *ATG16L1* and *LRRK2*, revealing new roles for these genes in myeloid and intestinal epithelial cells^{162,163}.

Guiding genetic diagnosis:

- Saturation genome editing of *BRCA1* led to improved diagnosis of inherited risk for breast and ovarian cancer²³.
- Functional variant annotations improve the applicability of polygenic risk scores across populations¹¹⁷.

Guiding therapeutic development:

- Designed mutagenesis of *SMN2* identified an intronic splice-enhancing sequence that guided development of antisense oligonucleotides to treat spinal muscular atrophy^{164,165}.
- Dissection of a GWAS locus led to identification of *BCL11A* as a repressor of fetal haemoglobin and development of CRISPR editors for sickle-cell disease^{50,166,167}.

model the impact of genomic variation on genome function and guide experimental design; (4) Regulatory Network Projects: to advance network-level understanding of the influence of genetic variation and genome function on cellular and organismal phenotypes; and (5) a Data and Administrative Coordinating Centre: to lead development of resources and infrastructure to share IGVF data, standards and pipelines with the scientific community. IGVF membership and activities are expanding further via affiliate membership, a process by which any researcher or research project can apply to join IGVF to drive its vision and execution. Through these activities, the IGVF Consortium aims to generate a catalogue that can be broadly deployed for exploring genome function and the effect of genetic variation on human biology and diseases in diverse populations. Below we describe the goals, strategies and anticipated deliverables of the IGVF (Box 2).

Map-perturb-predict framework

To create a comprehensive catalogue of the effects of genomic variation, IGVF has developed a strategy that integrates three complementary components (Fig. 2). One component will be to quantify the activity of regulatory elements and the expression of genes via single-cell mapping. Another will conduct systematic perturbations of variants, regulatory elements and genes. A third will seek to generalize results to new, unstudied genomic variants and cellular contexts via predictive modelling. Integration of these three components in

Box 2

IGVF goals and approaches

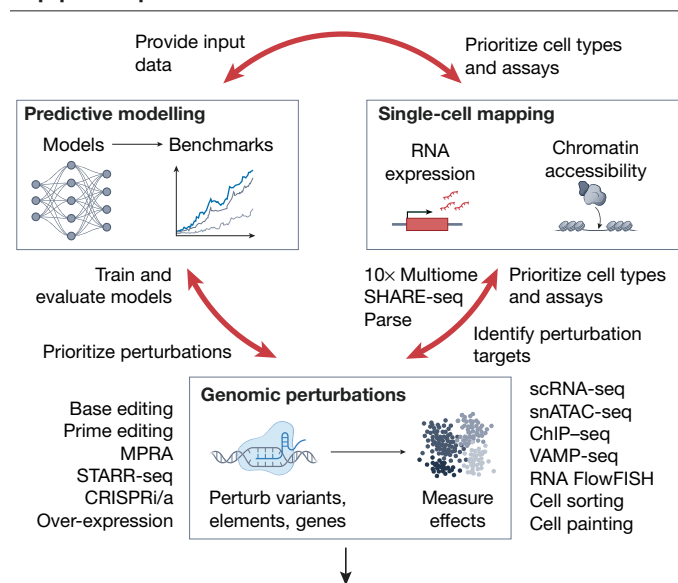
- Characterize the effects of genomic variants, regulatory elements and genes on molecular and cellular phenotypes—by analysing naturally occurring or designed genomic perturbations across dozens of cellular models.
- Identify where and when regulatory elements and genes are active, with resolution for individual cell types and states—by applying single-cell mapping technologies across hundreds of biological samples including cellular models, tissues and environmental contexts.
- Predict the consequences of genomic variation on genome function and phenotype for previously unstudied variants and/or cellular contexts—by developing predictive computational models that can generalize across contexts and establishing benchmarking pipelines to evaluate and calibrate their accuracy.
- Study diverse cellular and disease systems, types of genomic variation and aspects of genome function—by developing and applying a ‘map-perturb-predict’ framework in which single-cell mapping, genomic perturbations and predictive modelling are synergistically combined.
- Create an initial map that annotates the predicted effects of every possible SNV in the human genome on key aspects of genome function—by integrating models for how coding variants might alter protein function, how noncoding variants might affect gene expression and how noncoding and coding variants might connect within molecular networks.
- Advance our understanding of the effects of genomic variation on disease—by exploring how best to apply IGVF resources to inform genetic diagnosis and to identify biological mechanisms of disease risk.
- Ensure that these advances are applicable to and inclusive of people of diverse sexes, ancestries and populations—by studying individuals with different genetic backgrounds, assaying and predicting effects of variants observed in diverse populations, and studying diseases that disproportionately affect disadvantaged or under-represented populations.
- Catalyse research by others towards the long-term goal of understanding the effects of genomic variation—by partnering with the broader research community and developing resources and infrastructure to share IGVF data, methods, standards and pipelines.

a map-perturb-predict framework will create substantial synergy across the consortium.

Single-cell mapping

Identifying noncoding regulatory elements and genes and mapping their activities across cell types and states is foundational for understanding where, when and how genomic variation might affect genome function. Yet, many previous efforts have lacked this level of resolution. We will collect single-cell data across hundreds of cell types and states (see below for biological systems and contexts). We will apply primarily single-nucleus assay for transposase-accessible chromatin with sequencing (snATAC-seq) and single-nucleus RNA sequencing (snRNA-seq), including in multiomic formats, to enable integration of IGVF data with other emerging datasets (Fig. 2). Individual projects will explore additional single-cell approaches including transcription factor binding, histone modifications, chromatin interactions, protein levels and activity, and clonal tracing. Key assays (including 10x Multiome,

Map-perturb-predict framework



Biological questions

Focus areas:	Example prediction problems:
Coding variation	Which missense VUS are likely to be pathogenic?
Non-coding variation	Which variants affect the expression of which genes?
Molecular networks	What are the direct target genes of transcription factors?
Disease	Which variants, cell types, genes and pathways influence disease risk?

Fig. 2 | A map-perturb-predict framework to connect genome variation to genome function and phenotype. Top, IGVF projects will apply single-cell mapping, genomic perturbations and predictive modelling, which will interact in a synergistic and iterative manner (arrows). Examples of experimental approaches are shown, including 10x Multiome, SHARE-seq⁷⁰ and Parse Evercode⁷¹, MPRA^{52,56,57}, self-transcribing assay of RNA reporters⁵¹ (STARR-seq), CRISPR interference and activation¹⁴⁹ (CRISPRi/a), variant abundance by massively parallel sequencing²² (VAMP-seq), RNA FlowFISH⁸⁵ and Cell Painting⁸⁴. Bottom, IGVF projects will address a wide variety of biological questions and utilize diverse biological systems, models and samples using the model systems and samples shown in Table 1. ChIP-seq, chromatin immunoprecipitation with sequencing; scRNA-seq, single-cell RNA sequencing.

simultaneous high-throughput assay for transposase-accessible chromatin and RNA expression with sequencing⁷⁰ (SHARE-seq) and split-pool combinatorial indexing single-cell RNA sequencing⁷¹ (Parse Evercode)) will be directly compared and calibrated on the same samples, and the performance of computational analyses and predictive models will be assessed as a function of sequencing depth. These data will provide a foundation for interpreting the effects of functional characterization experiments and building cell-type-specific maps of variant effects.

Genomic perturbations

Perturbation experiments will be crucial for understanding the causal relationships among variants, regulatory elements, genes and phenotypes, but until recently have been challenging to apply at sufficient scale. New enabling technologies include high-throughput screens using CRISPR genetic or epigenetic perturbations or over-expression strategies^{22,23,43–50}, reporter assays for enhancer or promoter activities^{51–57}, and fine-mapping of different types of QTLs^{17,42,72} including single-cell eQTLs^{73–75}. IGVF plans to conduct more than two million experimental perturbations, including to directly study the effects of naturally occurring or designed DNA variants, and to perturb regulatory elements and genes to build maps of genome function (Fig. 2). We will characterize the effects of these perturbations using diverse

assays, including measurements of chromatin accessibility⁷⁶, gene expression^{77–79}, protein expression and activity^{25,80–83}, and molecular and cellular phenotypes⁸⁴. These data will enable direct characterization of variants of interest, such as those associated with disease, and provide data to train or evaluate predictive models of variant effects.

Predictive modelling

Genome function is complex, and we cannot expect to experimentally map the effects of all possible variants on all possible activities in all possible cellular contexts. Predictive models will be needed to make predictions that generalize across contexts—for example, to link genetic variants to effects on transcription factor binding and chromatin accessibility^{57,61–64}, connect regulatory elements to their target genes^{64,85,86}, or identify causal genes and cell types enriched for heritability for complex diseases or traits^{87–92}. We will leverage advances in machine learning and artificial intelligence to tackle key prediction problems, such as mapping aspects of genome function, interpreting the impact of genomic variation and guiding the design of future experimental assays such that the data produced will be maximally informative for subsequent predictive modelling. To systematically evaluate and calibrate such models, we will build benchmarking pipelines that compare predictions to perturbation data, including from IGVF functional characterization experiments as well as external sources such as QTLs, GWAS and genome sequencing studies^{87,88,93,94}. In areas where data collection is already advanced, we will engage the external community by designing prediction challenges with held-out assessment datasets produced by IGVF.

Application areas

Together, these three activities will form an iterative map-perturb-predict framework that IGVF will apply to explore a wide array of cell types, cellular phenotypes and diseases (Table 1). Projects will apply distinct but overlapping sets of experimental assays and computational models, enabling a broad exploration of possible strategies and integration of insights across biological systems.

IGVF projects have flexibility to study diverse biological models, prioritized on the basis of relevance to human disease, expertise of consortium members, tractability and other considerations. Current models include human embryonic and iPS cells differentiated into lineages spanning all germ layers in 2D and 3D (for example, gastruloids, cardiomyocytes and neurons); primary cell types relevant to disease areas of interest (for example, smooth muscle cells for coronary artery disease); and human and mouse tissues in vivo to inform how cell–cell interactions and environment alter genome function (for example, liver and lung in the presence of bacterial lipopolysaccharide) (Table 1). Selected models include dynamic biological processes that will provide insights into how regulatory networks change over time, such as B cell activation and differentiation or fibroblast-to-iPS cell reprogramming.

Although the primary objective of IGVF is to characterize variation and function of the human genome, IGVF studies will also study and create resources for mouse models, such as for comparing the effects of variants, elements and genes across different genetic backgrounds, and for in vivo genomic perturbation experiments to understand how variants or genes affect cellular phenotypes in a tissue environment. IGVF will leverage the genetic diversity found in the Collaborative Cross⁹⁵, which includes more than 15 million SNVs between the 8 founder strains. These strains include the reference C57BL/6J strain, mouse disease models such as NOD, and recombinant inbred Collaborative Cross strains. Current efforts include collecting single-cell mapping data across eight tissues in adult male and female mice to identify cell-type-specific cellular programmes and QTLs and compare to matching human samples.

The map-perturb-predict framework will enable integration across biological systems and models. For example, to enable integrative analysis across all projects studying gene regulation, we will generate and harmonize multiomic snRNA-seq and snATAC-seq data as a reference

map in each cellular model. To compare genomic perturbation datasets across projects, we will deploy consistent data processing pipelines, quantify reproducibility and assess power. To integrate information across experimental assays and cellular models, we will train predictive models that learn from diverse data types and can generalize to new, unstudied cell types.

Throughout, a unifying analysis framework will be to consider and evaluate which cellular models and assays provide the best ability to distinguish or enrich for genomic variants associated with disease. For example, studies of coding variation in known Mendelian disease genes will validate the relevance of their cellular assays by comparison to known pathogenic and benign variants. Studies of noncoding variants associated with a common, complex disease might select a cellular model whose regulatory elements are globally enriched for containing risk variants. Such comparisons to human genomic variation will provide an external benchmark applicable to evaluating many methods and design decisions throughout IGVF (see below).

A map of genome function and variant effects

IGVF will deliver a preliminary variant effect map that integrates three key aspects of genome function: gene expression, protein function and molecular networks (Fig. 3). This draft map would enable querying—for any possible SNV in the genome, is this variant measured or predicted to: (1) affect transcription factor binding, regulatory element activity and target gene expression in particular cell contexts, for non-coding variants; (2) affect protein function, for coding variants; and (3) connect to other genes or proteins via gene-regulatory networks and/or protein-interaction networks, for both coding and noncoding variants?

For each of these aspects of genome function, computational models have shown promise but much work is needed to improve their accuracy. Towards this goal, this preliminary map will integrate annotations of the different aspects of genome function and establish benchmarking pipelines to quantify the accuracy of all predictions against perturbation data and external human genetics datasets. We will encode this map of genome function, along with benchmarks and external data, in a multi-relational knowledge graph^{96–99} as part of the IGVF Catalog. The IGVF Catalog will provide a foundation for an iterative and ongoing effort extending beyond IGVF to improve the accuracy of this map over time (Fig. 3).

Effects on gene regulation

In the 99% of our genome that does not encode for proteins, noncoding variants can affect genome function by altering gene expression, splicing, chromatin state or other aspects of gene regulation. Despite advances by ENCODE, GTEx and other projects, we still lack models that can make accurate causal inferences about how genomic variation affects gene regulation^{94,100,101}. We will seek to build genome-wide annotations of key components of this *cis*-regulatory code: which SNVs affect transcription factor binding sites, regulatory element activity and gene expression in *cis*, in which cell types or states, with what magnitude and direction of effect?

To do so, IGVF plans to: (1) generate multiomic snRNA-seq and snATAC-seq data at a depth needed to identify candidate *cis*-regulatory elements, detect probable transcription factor binding sites^{35,102} and predict enhancer–gene relationships^{36,37,64,86,88,93}; (2) test more than a million noncoding variants in enhancer activity reporter assays^{51,52,56,57,103}; (3) test thousands of noncoding variants for effects on expression through fine-mapping of eQTLs or direct CRISPR-based genome editing^{17,42–45,47}; (4) measure more than 100,000 putative regulatory interactions between candidate regulatory elements and nearby genes, for example using dCas9-based epigenome editing^{85,104–107}; and (5) perturb transcription factors to read out effects on gene expression using Perturb-seq^{77–79}. These experiments will be conducted in multiple

Table 1 | Systems and diseases studied and types of samples used in IGVF projects

Systems and diseases			
Cardiometabolic	Immune and haematopoietic	Neurological and neurodevelopmental	Developmental and syndromic
• Coronary artery disease • Type 2 diabetes • Lipid traits • Blood pressure • Congenital heart defects	• Systemic lupus erythematosus • Rheumatoid arthritis • Red blood cell traits	• Parkinson's disease • Alzheimer's disease • Neurodevelopmental delay	• Williams syndrome • DiGeorge syndrome • Hereditary cancers
Samples			
Cell lines and primary cells	hPS cell differentiation and reprogramming	Organoids	Tissues
• K562 • GM12878 • HUDEP-2 • HAP1 • ENCODE cell lines • B cells • Smooth muscle cells	• Cardiomyocytes • Endothelial cells • Fibroblast to iPS cells • Macrophages • Neurons • Pancreatic cells • Trophoblasts	• Cardioids • Cerebral organoids • Gastruloids	• Aorta • Blood • Bone marrow • Brain • Heart • Liver

hPS cells, human pluripotent stem cells; iPS cells, induced pluripotent stem cells.

cellular models, so that the data can be used to develop predictive models that generalize across many cell types. These cellular models will include several that have been studied previously in ENCODE¹⁵ and GTEx¹⁷, to enrich and benefit from rich existing datasets.

Effects on protein function

For protein-coding sequences, our ability to interpret the functions of genomic variation is based on our knowledge of the genetic code for protein synthesis—which has enabled identification of open reading frames that encode novel proteins and understanding of nonsense or frameshift variants. However, most coding variants, including missense variants and in-frame indels, remain difficult to interpret, and we still lack a comprehensive understanding of how changes in protein sequence might affect different aspects of protein structure, expression, dynamics and activity.

We will improve the annotation of protein-coding missense variants by applying high-throughput technologies^{25,80–83} to experimentally characterize the effects of more than 200,000 missense variants on protein and cellular properties, including protein stability, subcellular localization, cell viability, cell morphology and protein–protein interactions. These experiments will directly characterize thousands of variants in clinically relevant genes, such as those associated with Mendelian diseases, and provide data to refine or develop new models to predict the probable effects of coding variants in other genes across the genome.

Molecular networks and cellular phenotypes

Upon linking a variant to effects on gene expression or protein activity in *cis*, we will seek to annotate the sets of other genes and proteins linked to the variant in *trans* through molecular networks in a given cell type or state. Specifically, we will focus on defining three types of molecular networks: (1) gene expression programmes, described by sets of genes whose expression levels are correlated across single cells; (2) gene-regulatory networks that identify transcription factors that regulate specific target genes via specific noncoding regulatory sequences; and (3) sets of interacting proteins or protein complexes. We will also examine dynamic changes to these molecular networks

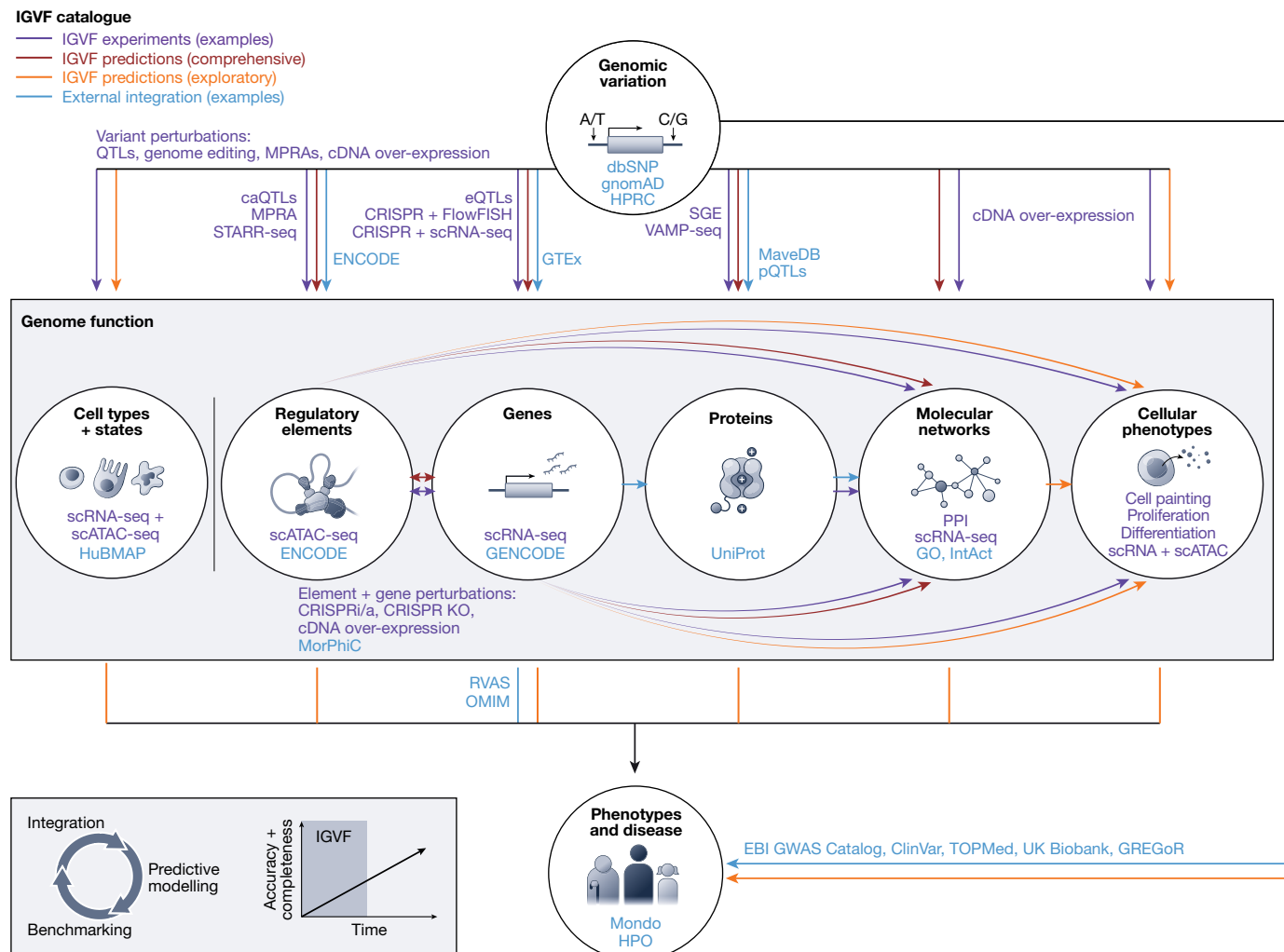


Fig. 3 | The IGVF Catalogue of genome function and the effects of genomic variation. IGVF will create a catalogue that links genomic variation (top) to genome function (middle box) and phenotype (bottom). Examples of experimental methods applied by IGVF are shown in purple. Relationships where IGVF plans to develop and apply computational models to comprehensively annotate all possible SNVs across many cell types are in red. Relationships where IGVF plans to develop and apply computational methods in a more targeted fashion, for example in the context of certain cellular phenotypes or diseases are in orange. Examples of external resources or ontologies that could interact with and/or be incorporated into this catalogue are shown in blue. The listed set of edges represent current plans and are not exhaustive with respect to topics relevant

to interpreting genomic variation. Citations: dbSNP¹⁵⁰, ENCODE¹⁵, GENCODE¹⁵¹, Gene Ontology¹⁵² (GO), gnomAD⁴, GTEx¹⁷, HuBMAP²⁰, Human Pangenome Reference Consortium¹⁴⁷ (HPRC), Human Phenotype Ontology¹⁵³ (HPO), IntAct Molecular Interaction Database¹⁵⁴, MaveDB²⁴, Mondo Disease Ontology¹⁵⁵, Online Mendelian Inheritance in Man¹⁵⁶ (OMIM), saturation genome editing²³ (SGE), UniProt¹⁵⁷ and VAMP-seq²². caQTLs, chromatin accessibility QTLs; CRISPR KO, CRISPR-mediated knockout; MorPhiC, NHGRI Molecular Phenotypes of Null Alleles in Cells Consortium; PPIs, protein–protein interactions; pQTLs, protein QTLs; RVAS, rare variant association studies; scATAC-seq (or scATAC), single-cell assay for transposase-accessible chromatin with sequencing; scRNA-seq (or scRNA), single-cell RNA sequencing.

across cell-fate or cell-state transitions and, to a more limited extent, explore links to downstream cellular phenotypes.

To build these maps, we will collect longitudinal multiomic data across dynamic cellular processes including differentiation and reprogramming^{70,108–110}, study how genes and proteins interact in molecular networks, including by mapping protein–protein interactions²⁵ and conducting large-scale Perturb-seq^{77–79}, and assess how CRISPR-based perturbations or natural genetic variation across individuals affects cellular phenotypes including differentiation, gene expression programmes and cellular states. Such time-resolved datasets will be used to build dynamical regulatory models that incorporate feedback and feed forward loops and account for cell fate or state transitions.

We anticipate that many aspects of this map will be cell-type-specific, with annotations for each of the hundreds of cell types, states and contexts studied by IGVF. For example, predictive models that use

snRNA-seq and snATAC-seq as inputs could be developed using data from cellular models, in which predictions can be directly evaluated with matching perturbation data, and applied to make cell-type-specific predictions in cell types from primary tissues^{36,37,86,111}.

Exploring the effects of variation on disease

The map–perturb–predict framework and IGVF variant effect map will provide new resources for the community to study the impact of genomic variation on human diseases and phenotypes, but this goal presents additional challenges. For many diseases, an individual's risk is likely to be determined by a combination of thousands of independently acting variants^{112,113}—including for diseases presumed to follow Mendelian inheritance patterns, where penetrance and expressivity may include a polygenic component¹¹⁴. A single variant may have pleiotropic effects on multiple genes and pathways, only one or several of which

may be important for disease^{1,17,88,89}. Disease susceptibility can involve many different cell types, possibly at specific timepoints, with effects accumulating over decades or in specific environmental contexts¹¹⁵. The effects of genomic variation on genome function and phenotype can also differ across age, sex, populations and ancestry—for example, owing to differences in allele frequencies¹¹⁶ or possible genetic or environment interactions^{117–121}.

Towards addressing some of these challenges, we will focus on assessing how IGVF maps and methods can be best applied to: (1) inform clinical variant interpretation, particularly for rare diseases; (2) learn about molecular and cellular mechanisms underlying risk for common and rare diseases; and (3) ensure that lessons about the impact of genomic variation on genome function are applicable across diverse populations. Notably, each of these questions represents a major research area involving many strategies beyond those pursued in IGVF^{7–9,28,122–124}, and these exploratory efforts will seek to integrate with other efforts in the field.

Informing genetic diagnosis

IGVF will apply variant effect maps of coding variation to inform the clinical interpretation of VUSs in genes with known and suspected links to Mendelian genetic diseases. Data from multiplexed assays of variant effect can be translated into powerful evidence for clinical variant interpretation—for example, moving 50% of VUSs in *BRCA1*, 70% in *TP53*, 74% in *MSH2* and 90% in *DDX3X* into more definitive pathogenic or benign classifications^{81,125,126}. These studies have improved genetic test results for cancer risk and ended diagnostic odysseys for families with neurodevelopmental disease.

To expand this approach, IGVF laboratories will experimentally measure the effects of hundreds of thousands of variants in known disease genes, with a particular focus on those where identification of loss-of-function variants is clinically actionable^{127,128}. We will assess the extent to which experimental data or computational predictions correctly identify variants previously classified as either pathogenic or benign, and calibrate these analyses for clinical applications^{129,130}. Clinicians routinely use experimental and predictive data to interpret the effects of coding variants, but do not yet do so for noncoding variants. Thus we will explore whether IGVF data and predictions could also improve the clinical interpretation of noncoding variants. IGVF will deliver variant effect maps and calibrated predictions that will ultimately substantially reduce the VUS burden in aetiological diagnosis of rare disease¹²⁴. Integration of maps for both coding and noncoding variants could also aid in the development of next-generation polygenic risk score methodologies for better risk characterization in complex phenotypes¹¹⁷.

Molecular mechanisms of disease risk

Improved variant effect maps could be transformative for identifying new biological mechanisms that influence genetic risk for disease. In particular, we will seek to understand how best to combine the map–perturb–predict framework and variant effect maps with human genetic data to nominate variants, genes, cell types and cellular programmes that influence disease risk.

We will study a variety of diseases and traits guided by the expertise of consortium members, including highly powered quantitative traits with simpler biological architectures, such as lipid and haematological traits, as well as complex diseases involving many cell types such as systemic lupus erythematosus, coronary artery disease and Alzheimer's disease. Comparison of strategies between these systems will be informative. For example, IGVF investigators are studying variants associated with lipid traits, where GWAS and whole-exome sequencing studies have already identified hundreds of associated noncoding and coding variants, and where certain key genetic pathways involved in lipid handling are already known^{11,131–133}. By conducting CRISPR screens to identify variants and regulatory elements that affect lipid uptake in

cellular models enriched for trait heritability, testing variant effects on enhancer activity in massively parallel reporter assays, and applying state-of-the-art predictive models, we will evaluate which combinations of experiments and/or predictive models provide the best ability to predict disease-associated variation and known causal genes. To complement these high-throughput maps, certain projects will conduct detailed studies of mechanisms of particular GWAS loci or known disease genes, including in animal models. These combined efforts will reveal mechanisms of genetic risk for selected diseases, inform the molecular genetic architecture of complex traits and help to develop strategies to identify causal variants, genes and pathways for any complex disease.

Impact of variation across populations

IGVF aims to ensure that insights about the impact of genomic variation are applicable to and inclusive of people of diverse groups. To do so, we will promote diversity in functional genomics studies, experimentally study and computationally annotate variants observed in diverse populations, study diseases disproportionately affecting disadvantaged or under-represented populations, and explore the extent to which particular variants might exert the same or different effects due to interactions with genetic background or environment^{134–136}.

We will use both experimental and computational strategies. In the current design phase, we have incorporated variants from diverse populations, including from the 1000 Genomes Project¹³⁷, Millions Veterans Program¹³⁸, and cross-ancestry GWAS meta-analyses^{131,139–142}. Biological models include iPS cells derived from individuals from different populations (including European, East Asian and African), and genetically diverse mouse lines from the Collaborative Cross¹⁴³. Saturation mutagenesis will be employed to measure variant effects in clinically relevant protein-coding sequences to enable interpretation of variants observed in any individual¹⁴⁴. We will deploy computational models to make context-specific predictions for SNVs across the genome, including methods to predict individual-specific effects of noncoding variants on chromatin state and gene expression^{61,63,64}. These data and analyses will provide insights into variant effects across groups and provide a valuable resource for investigating the effects of variants discovered in diverse populations.

Data release and resources

A major goal of IGVF is to catalyse future research to understand the relationships between genome function, genomic variation and phenotype. To do so, we will build the IGVF Data Resource to enable biomedical researchers across diverse disciplines to access and apply IGVF datasets, predictions and methods (<https://igvf.org>).

For researchers who want to explore data and predictions, we will create the IGVF Catalog. The IGVF Catalog will consist of one or more web portals that enable searching for information about specific variants, genomic loci or genes, and will draw from processed data, analysis products and computational predictions generated by IGVF as well as external data sources (Fig. 3). To support users who want programmatic access to perform integrative analyses or to develop web applications, we will also provide an application programming interface to the underlying knowledge graph.

For researchers who want to access raw or processed data, we will develop the IGVF Data Portal. The Data Portal will provide web-browser and programmatic access to uniformly processed datasets, analysis products and rich metadata, enabling users to develop new computational methods, analyse IGVF data in new ways, or compare their data to IGVF standards. The IGVF Data Portal will follow principles of making data FAIR¹⁴⁵ (findable, accessible, interoperable and reusable). Data will be stored in cloud file buckets to facilitate computing on the data in place. Some IGVF data may not have consent for public sharing—such data will be deposited in the NHGRI Analysis, Visualization and

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Informatics Lab (AnVIL) platform to provide access control in adherence to National Institutes of Health (NIH) policy¹⁴⁶.

For researchers who want to apply IGVF methods and strategies to additional systems, the Data Portal will also share documentation on IGVF standards, protocols and best practices for experimental design, data analysis and predictive modelling. These resources will include computational methods, data formats and consensus data processing pipelines for key assays and analysis products, such as for snRNA-seq and snATAC-seq, CRISPR experiments, MPRA, eQTL studies, and others. Data analysis tools will include approaches to assess replicates, quantify experimental noise and assess power. All data processing code will be released with open-source licenses to enable others to analyse similar data in an identical fashion, and we will strive to make sure that it can be run on computer resources that are accessible to researchers throughout the global research community.

For all researchers, we will provide training and support on how to access these IGVF resources. Up-to-date information on where to find instructional streaming videos, online notebooks and tutorials, and schedules for seminars and webinars are available at www.igvf.org. Altogether, we expect that these resources will enable a wide range of scientific activities, expanding far beyond the specific studies undertaken by the IGVF Consortium.

Finally, IGVF is committed to rapid release of data and results. Data and predictions will be released upon quality control and no later than manuscript submission, and manuscripts will be posted on preprint servers prior to manuscript submission.

Collaborations and community

Understanding genomic variation and genome function is a grand challenge that demands global and interdisciplinary collaboration. IGVF welcomes collaboration with and input from the broader scientific community. Researchers interested in joining IGVF can apply for affiliate membership. Affiliate members can participate fully in working groups and other IGVF collaborations, and thereby drive the vision, goals, and execution of consortium activities. Further information is available at <https://igvf.org/affiliate-membership/>.

IGVF is actively coordinating with other consortia, including ClinGen⁸, the Genomics Research to Elucidate the Genetics of Rare diseases (GREGoR) consortium, and the Atlas of Variant Effects (AVE) Alliance¹⁴⁴. These collaborations will facilitate the open exchange and interoperability of genomic data and resources, for example to use common variant naming schema, genome and transcriptome builds, and analysis pipelines.

Similarly, IGVF activities will benefit from close interactions with efforts to characterize human genomic variation and assemblies, such as the Human Pangenome Reference Consortium¹⁴⁷ (HPRC), with efforts to catalogue disease-associated variation across ancestries, including All of Us¹⁴⁸ and TOPMed¹⁰ (Trans-Omics for Precision Medicine), with efforts to build atlases using single-cell tools, such as the Human Cell Atlas²¹ and HuBMAP²⁰ (Human Biomolecular Atlas Program), and with efforts to compare and evaluate strategies for interpreting genetic variation associated with disease, such as the International Common Disease Alliance²⁸.

Outlook

With the rapid expansion of human genetics studies linking variation to disease, the interpretation of the impact of genomic variation on function is currently a rate-limiting step for delivering on the promise of precision medicine. The IGVF Consortium will pursue a unique, coordinated strategy for accelerating progress (Box 2).

Success for IGVF will involve creating resources and generating scientific advances not possible through individual efforts. Key outcomes include: (1) insights into genome biology and advances in genetic

diagnosis enabled by the map–perturb–predict framework and variant effect maps; (2) an interoperable ecosystem of data, predictions, and models that will be used by IGVF and the broader scientific community to derive insights into genome function, genomic variation, and phenotype; (3) massive, uniformly processed datasets spanning single-cell and functional characterization assays that directly assay large swaths of the genome and serve as an enduring, foundational resource for developing predictive models; (4) a catalogue that provides web and programmatic access to look up integrative predictions and experimental data regarding variants, genomic elements and genes across many cell types and contexts; and (5) new methods and strategies for studying genome variation and function, derived through systematic comparisons of methods. Altogether, these activities will set in motion community efforts to expand on this framework by collecting additional datasets, training improved models, generating more accurate maps and expanding the approach to additional cell types and aspects of genome function.

Although ambitious, IGVF activities do have limitations in scope. IGVF aims for systematic analysis of certain aspects of genome function, but others—including effects on nuclear organization, RNA splicing, localization and translation, protein signalling and metabolism, and cellular phenotypes, cell–cell interactions and tissue organization—are of great interest but will require efforts beyond the current membership of the consortium. IGVF projects span a great breadth of cellular models and disease areas, but are not necessarily designed for comprehensive analysis of any single disease. IGVF will use cellular models to develop predictive models that are applicable to understanding variants in many systems, but systematic analysis to map epistatic interactions among variants, environment, time and other variables will require deeper studies and alternative approaches. IGVF welcomes interactions with or membership of projects that aim to explore or systematically address these areas of interest.

Many challenges lie ahead. Genomic technologies, both experimental and computational, are developing rapidly, and balancing the implementation of the newest scalable tools with continuing standards to ensure data interoperability will require attention. Although data generation technologies have increased throughput exponentially over the last 15 years, the amount of data needed to build accurate models of genome function is unknown, and fully realizing the goal of mapping the impact of genomic variation on function will require additional advances in both experimental and computational methods. For all of these challenges, the framework developed by the IGVF Consortium to develop and benchmark methods, refine best practices and standards, and share data and methods will drive scientific discoveries in human health and disease for years to come.

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Acknowledgements This work was supported by the NIH NHGRI IGVF Program (UM1HG011966, UM1HG011969, UM1HG011972, UM1HG011989, UM1HG011996, UM1HG012003, UM1HG012010, UM1HG012053, UM1HG011986, UM1HG012076, UM1HG012077, U01HG011952, U01HG011967, U01HG012009, U01HG012022, U01HG012039, U01HG012064, U01HG012069, U01HG012041,

U01HG012047, U01HG012051, U01HG012059, U01HG012079, U01HG012103, U24HG012012, U24HG012070), NIH NCI (R01CA197774), and the Novo Nordisk Foundation (NNF21SA0072102). Artwork in Figs. 1–3 were created by SciStories and V. Yeaung. We thank members of the IGVF External Consultants Panel (G. Bourque, P. Mali, J. Cho, B. Engelhardt and O. Troyanskaya) for critical feedback on the manuscript.

Author contributions J.M.E., H.A.L. and H. Singh co-led the Writing Group. J.M.E., H.A.L., H. Singh, L. M. Starita, G.C.H., H. Carter, N. Sahni, T.E.R., X. Lin, Y. Li, N.V.M., M.H.C., B.C.H. and A.M. wrote initial text based on input from principal investigators, the Writing Group, and Working Group and Focus Group co-chairs. J.M.E., A.P.B. and J. Ryu developed figures. All authors contributed to developing the vision and goals of the IGVF Consortium, outlining the project, and editing the manuscript. The role of the NHGRI Program Management in the preparation of this paper was limited to coordination and scientific management of the IGVF Consortium.

Competing interests R.D.S. has been a consultant for Leadiant Biosciences, Mirum Pharmaceuticals, PTC Therapeutics and Traverre. He has received honoraria from Medscape and is an employee and shareholder of PreventionGenetics, part of Exact Sciences. B.P.K. is a co-inventor on patents and patent applications that describe genome engineering technologies, and is on the scientific advisory board of Acrigen Biosciences, Life Edit Therapeutics and Prime Medicine. The other authors declare no competing interests.

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Peer review information *Nature* thanks Tiffany Amariuta and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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UM1HG012053

Charles A. Gersbach^{69,118}, Gregory E. Crawford^{69,119}, Timothy E. Reddy¹⁵, Andrew S. Allen¹⁵, William H. Majors¹⁵, Nahid Iglesias^{69,118}, Alejandro Barrera^{15,69}, Ruhi Rai⁶⁹, Revathy Venukuttan⁶⁹, Boxun Li^{69,118}, Taylor Anglen^{69,120}, Lexi R. Bounds^{69,118}, Marisa C. Hamilton⁶⁹, Siyan Liu⁶⁹, Sean R. McCutcheon^{69,118}, Christian D. McRoberts Amado^{69,121}, Samuel J. Reisman^{69,120}, Maria A. ter Weele^{69,118}, Josephine C. Bodle^{69,118}, Helen L. Stref^{69,118}, Keith Siklenka¹⁵ & Kari Strouse¹⁵

⁷⁶Howard Hughes Medical Institute, Seattle, WA, USA. ⁷⁷Systems Immunology, Benaroya Research Institute, Seattle, WA, USA. ⁷⁸Allen Discovery Center for Cell Lineage Tracing, Seattle, WA, USA. ⁷⁹mRNA Center of Excellence, Sanofi Pasteur Inc, Waltham, MA, USA. ⁸⁰Center of immunotherapy and Immunity, Seattle Children's Research Institute, Seattle, WA, USA. ⁸¹Bioinformatics Division, WEHI, Parkville, Victoria, Australia. ⁸²Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA. ⁸³Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA. ⁸⁴Department of Bioengineering, Stanford University School of Engineering, Stanford, CA, USA. ⁸⁵Institute for Computational and Mathematical Engineering, Stanford University, Stanford, CA, USA. ⁸⁶Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA. ⁸⁷Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA. ⁸⁸Department of Applied Physics, Stanford University, Stanford, CA, USA. ⁸⁹Division of Pediatric Cardiology and Cardiovascular Institute, Stanford University School of Medicine, Stanford University, Stanford, CA, USA. ⁹⁰Altos Labs, Redwood City, CA, USA. ⁹¹Cancer Biology Program, Stanford University School of Medicine, Stanford, CA, USA. ⁹²Immunology Graduate Program and Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA. ⁹³European Molecular Biology Laboratory (EMBL), Genome Biology Unit, Heidelberg, Germany. ⁹⁴Department of Biology, Stanford University, Stanford, CA, USA. ⁹⁵Department of Plant Biology, Carnegie Institution for Science, Stanford, CA, USA. ⁹⁶Stanford Genome Technology Center, Palo Alto, CA, USA. ⁹⁷Department of Biomedical Informatics, Stanford University School of Medicine, Stanford, CA, USA. ⁹⁸Laboratory of Viral Interactomes, GIGA Institute, University of Liège, Liège, Belgium. ⁹⁹Donnelly Centre for Cellular and Biomolecular Research (CCBR), University of Toronto, Toronto, Ontario, Canada. ¹⁰⁰Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada. ¹⁰¹Lunenfeld-Tanenbaum Research Institute (LTRI), Sinai Health System, Toronto, Ontario, Canada. ¹⁰²TERRA Teaching and Research Center, University of Liège, Gembloux, Belgium. ¹⁰³Department of Computer Science, University of Toronto, Toronto, Ontario, Canada. ¹⁰⁴Computational Biology and Bioinformatics, Université Libre de Bruxelles, Brussels, Belgium. ¹⁰⁵Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX, USA. ¹⁰⁶Quantitative Biomedical Research Center, Peter O'Donnell Jr School of Public Health, University of Texas Southwestern Medical Center, Dallas, TX, USA. ¹⁰⁷Department of Pediatrics, Division of Hematology/Oncology, University of Texas Southwestern Medical Center, Dallas, TX, USA. ¹⁰⁸Children's Medical Center Research Institute, University of Texas Southwestern Medical Center, Dallas, TX, USA. ¹⁰⁹Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ¹¹⁰Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ¹¹¹Department of Pediatrics, Harvard Medical School, Boston, MA, USA. ¹¹²Montreal Heart Institute, Montreal, Quebec, Canada. ¹¹³Département de Médecine, Université de Montréal, Montréal, Quebec, Canada. ¹¹⁴Department of Pathology, Massachusetts General Hospital, Boston, MA, USA. ¹¹⁵Center for Genomic Medicine and Department of Pathology, Massachusetts General Hospital, Boston, MA, USA. ¹¹⁶PhD Program in Biological and Biomedical Sciences, Harvard University, Boston, MA, USA. ¹¹⁷Broad Institute of MIT and Harvard, Boston, MA, USA. ¹¹⁸Department of Biomedical Engineering, Duke University, Durham, NC, USA. ¹¹⁹Department of Pediatrics, Duke University, Durham, NC, USA. ¹²⁰Department of Cell Biology, Duke University Medical Center, Durham, NC, USA. ¹²¹Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, USA.

Mapping Awards (contact PI, MPIs (alphabetical by last name), other members (alphabetical by last name))

UM1HG011986

Jason D. Buenrostro^{4,66}, Bradley E. Bernstein^{4,53}, Juliana Babu^{4,66}, Guillermo Barreto Corona⁴, Kevin Dong⁴, Fabiana M. Duarte^{4,66}, Neva C. Durand⁴, Charles B. Epstein⁴, Kaili Fan^{4,66,70}, Nina P. Farrell⁴, Elizabeth Gaskell⁴, Amelia W. Hall⁴, Alexandra M. Ham⁴, Mei K. Knudson⁴, Eugenio Mattei⁴, Rachel E. Savage^{4,66}, Noam Shores⁴, Siddarth Wekhande⁴, Cassandra M. White⁴ & Wang Xi^{4,66}

UM1HG012076

Ansuman T. Satpathy^{122,123,124}, M. Ryan Corces^{125,126,127}, Serena H. Chang^{125,126,127}, Iris M. Chin^{125,126,127}, James M. Gardner^{128,129}, Zachary A. Gardell^{125,126,127}, Jacob C. Gutierrez^{122,124}, Alia W. Johnson^{125,126,127}, Lucas Kampman^{125,126,127}, Maya Kasowski^{122,130}, Caleb A. Lareau^{122,123,124}, Vincent Liu^{122,124}, Leif S. Ludwig^{131,132}, Christopher S. McGinnis^{122,123,124}, Shreya Menon^{125,126,127}, Anita Qualls^{128,129}, Katalin Sandor^{122,123,124}, Adam W. Turner^{125,126,127}, Chun J. Ye^{123,133,134}, Yajie Yin^{122,124} & Wenxi Zhang¹²²

UM1HG012077

Ali Mortazavi^{29,30}, Barbara J. Wold^{47,135}, Sina Boeshaghi⁴⁷, Maria Carilli¹³⁶, Dayeon Cheong²⁹, Ghassan Filibam²⁹, Kim Green^{29,137}, Ingileif Hallgrimsdottir⁴⁷, Shimako Kawauchi³⁰, Charlene Kim⁴⁷, Heidi Liang³⁰, Rebekah Loving⁴⁷, Laura Luebbert⁴⁷, Grant MacGregor²⁹, Angel G. Merchan⁴⁷, Lior Pachter^{47,75}, Elisabeth Rebboah²⁹, Fairlie Reese^{29,30}, Narges Rezaie^{29,30}, Jasmine Sak^{30,138}, Delaney K. Sullivan⁴⁷, Nikki Swarna¹³⁹, Diane Trout⁴⁷, Sean Upchurch⁴⁷, Ryan Weber²⁹ & Brian A. Williams⁴⁷

Perspective

¹²²Department of Pathology, Stanford University, Stanford, CA, USA. ¹²³Parker Institute for Cancer Immunotherapy, San Francisco, CA, USA. ¹²⁴Gladstone-UCSF Institute of Genomic Immunology, San Francisco, CA, USA. ¹²⁵Gladstone Institute of Neurological Disease, San Francisco, CA, USA. ¹²⁶Department of Neurology, University of California San Francisco, San Francisco, CA, USA. ¹²⁷Gladstone Institute of Data Science and Biotechnology, Gladstone Institutes, San Francisco, CA, USA. ¹²⁸Department of Surgery, University of California San Francisco, San Francisco, CA, USA. ¹²⁹Diabetes Center, University of California San Francisco, San Francisco, CA, USA. ¹³⁰Sean N Parker Center for Allergy and Asthma Research, Stanford University, Stanford, CA, USA. ¹³¹Berlin Institute of Health at Charité—Universitätsmedizin Berlin, Berlin, Germany. ¹³²Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin Institute for Medical Systems Biology (BIMSB), Berlin, Germany. ¹³³Institute for Human Genetics, Department of Medicine, Division of Rheumatology, University of California, San Francisco, CA, USA. ¹³⁴Chan Zuckerberg Biohub, San Francisco, CA, USA. ¹³⁵Richard N. Merkin Institute for Translational Research, California Institute of Technology, Pasadena, CA, USA. ¹³⁶Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA, USA. ¹³⁷Department of Neurobiology and Behavior, UC Irvine, Irvine, CA, USA. ¹³⁸Department of Pharmaceutical Sciences, UC Irvine, Irvine, CA, USA.

Predictive Modeling Awards (contact PI, MPIs (alphabetical by last name), other members (alphabetical by last name))

U01HG011952

Alan P. Boyle^{27,28}, Christopher P. Castro²⁷, Elysia Chou²⁷, Fan Feng²⁷, Andre Guerra¹³⁹, Yuanhao Huang²⁷, Linghua Jiang²⁷, Jie Liu²⁷, Ryan E. Mills^{27,28}, Weizhou Qian²⁷, Tingting Qin²⁷, Maureen A. Sartor^{27,39}, Rintsen N. Sierpa²⁷, Jinhao Wang²⁷, Yiqun Wang²⁷, Joshua D. Welch²⁷, Zhenghao Zhang²⁷ & Nanxiang Zhao²⁷

U01HG011967

Andrew S. Allen¹⁵, William H. Majoros¹⁵, Sayan Mukherjee^{140,141,142}, C. David Page¹⁵, Shannon Clarke¹⁵, Richard W. Doty¹⁵, Yuncheng Duan¹⁴³, Raluca Gordan^{15,142}, Kuei-Yueh Ko¹⁵, Shengyu Li¹⁵, Boyao Li¹⁵, Timothy E. Reddy¹⁵ & Alexander Thomson¹⁵

U01HG012009

Soumya Raychaudhuri^{54,74}, Alkes Price^{16,39,74}, Shamil Sunyaev^{54,64}, Tahmina A. Ali³⁸, Kushal K. Dey³⁸, Arun Durvasula^{39,144}, Manolis Kellis^{177,145}, Evan Koch⁵⁴ & Saori Sakaue^{64,74}

U01HG012022

Predrag Radivojac⁴³, Lilia M. Iakoucheva¹⁴⁶, Tulika Kakati¹⁴⁶, Sean D. Mooney⁵⁶, Yile Chen⁵⁶, Mariam Benazouze⁵⁶, Vikas Pejaver^{57,58}, Shantanu Jain⁴³, Daniel Zeilberg⁴³, M. Clara De Paolis Kaluza⁴³ & Michelle Velyunskiy⁴³

U01HG012039

Mark Craven³¹, Audrey Gasch¹⁴⁷, Kunting Huang¹⁴⁸, Yiyang Jin³¹, Qiongshi Lu³¹, Jiacheng Miao³¹, Michael Ohtake¹⁴⁹, Eduardo Scovel¹⁴⁷, Robert D. Steiner^{150,151,152} & Yuriy Sverchkov³¹

U01HG012064

Zhiping Weng⁷⁰, Manuel Garber⁷⁰, Xihong Lin^{6,17}, Yu Fu⁷⁰, Natalie Haas⁷⁰, Xihao Li^{6,18,19}, Nishigandha Phalke⁷⁰, Shuo C. Shan⁷⁰, Nicole Shedd⁷⁰, Eric Van Buren¹⁶, Tianxiong Yu⁷⁰, Yi Zhang⁵³ & Hufeng Zhou¹⁶

U01HG012069

Anshul Kundaje¹³⁴, Alexis Battle^{154,155,156,157}, Ziwei Chen³⁴, Salil Deshpande⁸⁵, Jesse M. Engreitz^{12,3,4}, Livnat Jerby¹, Eran Kotler¹, Soumya Kundu¹³⁴, Andrew R. Marderstein¹²², Georgi K. Marinov¹, Stephen B. Montgomery^{1122,158}, Surag Nair³⁴, AkshatKumar Nigam¹³⁴, Evin M. Padhi¹²², Anusri Pampari³⁴, Aman Patel³⁴, Jonathan Pritchard¹, Ivy Raine¹, Vivekanandan Ramalingam¹, Kameron B. Rodrigues¹²², Jacob M. Schreiber¹, Arpita Singhal³⁴, Riya Sinha⁹⁷, Valeh Valiollah Pour Amiri¹ & Austin T. Wang³⁴

¹³⁹Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA. ¹⁴⁰Department of Statistical Science, Duke University, Durham, NC, USA. ¹⁴¹Department of Mathematics, Duke University, Durham, NC, USA. ¹⁴²Department of Computer Science, Duke University, Durham, NC, USA. ¹⁴³Department of Biology, Duke University, Durham, NC, USA. ¹⁴⁴Department of Genetics, Harvard Medical School, Boston, MA, USA. ¹⁴⁵MIT Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA. ¹⁴⁶Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. ¹⁴⁷Department of Genetics, University of Wisconsin, Madison, WI, USA. ¹⁴⁸Department of Statistics, University of Wisconsin, Madison, WI, USA. ¹⁴⁹Department of Computer Sciences, University of Wisconsin, Madison, WI, USA. ¹⁵⁰Department of Pediatrics, University of Wisconsin, Madison, WI, USA. ¹⁵¹PreventionGenetics Inc., Part of Exact Sciences, Marshfield, WI, USA. ¹⁵²Marshfield Clinic Health System, Marshfield, WI, USA. ¹⁵³Department of Data Science, Dana-Farber Cancer Institute, Boston, MA, USA. ¹⁵⁴Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA. ¹⁵⁵Malone Center for Engineering in Healthcare, Johns Hopkins University, Baltimore, MD, USA. ¹⁵⁶Department of Computer Science, Johns Hopkins University, Baltimore, MD, USA. ¹⁵⁷Department of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA. ¹⁵⁸Department of Biomedical Data Science, Stanford University, Stanford, CA, USA.

Network Projects (contact PI, MPIs (alphabetical by last name), other members (alphabetical by last name))

U01HG012041

Harinder Singh⁶, Jishnu Das⁶, Nidhi Sahni^{13,14}, Marisa Abundis⁶, Deepa Bish¹³, Trirupa Chakraborty⁶, Jingyu Fan⁶, David R. Hall⁶, Zarifeh H. Rarani⁶, Abhinav K. Jain¹³,

Babita Kaundat¹³, Swapnil Keshari⁶, Daniel McGrail¹⁵⁹, Nicholas A. Pease⁶, Vivian F. Yi⁶ & S. Stephen Yi^{71,72}

U01HG012047

Hao Wu¹⁶⁰, Sreeram Kannan¹⁶¹, Hongjun Song¹⁶², Jingli Cai¹⁶³, Ziyue Gao¹⁶⁰, Ronni Kurzion¹⁶², Julia I. Leu¹⁶⁰, Fan Li¹⁶⁰, Dongming Liang¹⁶⁰, Guo-li Ming¹⁶², Kiran Musunuru¹⁶³, Qi Qiu¹⁶⁰, Junwei Shi¹⁶⁴, Yijiang Su¹⁶², Sarah Tishkoff¹⁶⁰, Ning Xie¹⁶⁰, Qian Yang¹⁶², Wenli Yang¹⁶³, Hongjie Zhang¹⁶⁰ & Zhijian Zhang¹⁶²

U01HG012051

Danwei Huangfu^{48,49}, Michael A. Beer¹⁶⁵, Anna-Katerina Hadjantonakis^{48,49}, Sharon Adeniyi^{48,49}, Hyein Cho^{48,49}, Ronald Cutler¹⁶⁶, Rachel A. Glenn^{48,49,167}, David Godovich^{48,49}, Nan Hu^{48,49}, Svetlana Jovanic^{48,49}, Renhe Luo^{48,49}, Jin Woo Oh¹⁶⁵, Milad Razavi-Mohseni¹⁶⁵, Dustin Shigaki¹⁶⁵, Simone Sidoli¹⁶⁶, Thomas Vierbuchen^{48,49}, Xianming Wang^{48,49}, Breanna Williams^{48,49}, Jielin Yan^{48,49}, Dapeng Yang^{48,49} & Yunxiao Yang¹⁶⁵

U01HG012059

Maïke Sander⁷³, Hannah Carter¹², Kyle J. Gaulton⁷³, Bing Ren^{168,169}, Weronika Bartosik¹⁶⁸, Hannah S. Indralingam¹⁶⁸, Adam Klie¹⁷⁰, Hannah Mumme¹⁷⁰, Mei-Lin Okishio¹⁷¹, Gaowei Wang⁷³, Nathan R. Zemke¹⁶⁸, Kai Zhang¹⁶⁸ & Han Zhu⁷³

U01HG012079

Chongyuan Luo⁶⁷, Kathrin Plath⁶⁸, Noah Zaitlen¹⁷², Brunilda Balliu^{44,45,46}, Jason Ernst^{45,68}, Justin Langerman⁶⁸, Terence Li⁶⁷ & Yu Sun⁶⁸

U01HG012103

Christina S. Leslie³⁸, Alexander Y. Rudensky^{173,174}, Preethi K. Periyakoil³⁸, Vianne R. Gao³⁸, Melanie H. Smith¹⁷⁵, Norman M. Thomas³⁸, Laura T. Donlin^{175,176}, Amit Lakhnpal¹⁷⁵, Kaden M. Southard³⁸ & Rico C. Ardy³⁸

¹⁵⁹Center for Immunotherapy and Precision Immuno-Oncology, Cleveland Clinic, Cleveland, OH, USA. ¹⁶⁰Department of Genetics, University of Pennsylvania, Philadelphia, PA, USA. ¹⁶¹Department of Electrical and Computer Engineering, University of Washington, Seattle, WA, USA. ¹⁶²Department of Neuroscience, University of Pennsylvania, Philadelphia, PA, USA. ¹⁶³Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ¹⁶⁴Department of Cancer Biology, University of Pennsylvania, Philadelphia, PA, USA. ¹⁶⁵Department of Biomedical Engineering and McKusick-Nathans Department of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA. ¹⁶⁶Department of Biochemistry, Albert Einstein College of Medicine, Bronx, NY, USA. ¹⁶⁷Weill Cornell Graduate School of Medical Sciences, Weill Cornell Medicine, New York, NY, USA. ¹⁶⁸Department of Cellular and Molecular Medicine, University of California, San Diego, CA, USA. ¹⁶⁹Center for Epigenomics, University of California, San Diego, CA, USA. ¹⁷⁰Bioinformatics and Systems Biology Program, University of California, San Diego, CA, USA. ¹⁷¹Biomedical Sciences Program, University of California, San Diego, CA, USA. ¹⁷²Department of Neurology, University of California Los Angeles, Los Angeles, CA, USA. ¹⁷³Howard Hughes Medical Institute and Immunology Program at Sloan Kettering Institute, New York, NY, USA. ¹⁷⁴Ludwig Center for Cancer Immunotherapy, Memorial Sloan Kettering Cancer Center, New York, NY, USA. ¹⁷⁵Division of Rheumatology, Department of Medicine, Hospital for Special Surgery, New York, NY, USA. ¹⁷⁶Weill Cornell Medical College and Graduate School, New York, NY, USA.

Data and Administrative Coordinating Center Awards (contact PI, MPIs (alphabetical by last name), other members (alphabetical by last name))

U24HG012012

J. Michael Cherry¹, Mark B. Gerstein^{177,178,179,180,181}, Kalina Andreeva¹, Pedro R. Assis¹, Beatrice Borsari^{177,178}, Eric Douglass¹, Shengcheng Dong¹, Idan Gabdank¹, Keenan Graham¹, Benjamin C. Hitz¹, Otto Jolanki¹, Jennifer Jou¹, Meenakshi S. Kagda¹, Jin-Wook Lee¹, Mingjie Li¹, Khine Lin¹, Stuart R. Miyasato¹, Joel Rozowsky^{177,178}, Corinn Small¹, Emma Spragins¹, Forrest Y. Tanaka¹, Ian M. Whaling¹, Ingrid A. Youngworth¹ & Cricket A. Sloan¹

U24HG012070

Ting Wang^{5,33}, Feng Yue^{35,36}, Eddie Belter³³, Xintong Chen³⁵, Rex L. Chisholm¹⁸², Sarah Cody³³, Patricia Dickson¹⁸³, Changxu Fan⁵, Lucinda Fulton³³, Heather A. Lawson⁵, Daofeng Li⁵, Tina Lindsay³³, Yu Luan³⁵, Yuan Luo¹⁸⁴, Huijue Lyu³⁵, Xiaowen Ma⁵, Jian Ma⁴², Juan Macias-Velasco⁵, Karen H. Miga¹⁸⁵, Kara Quaid⁵, Nathan Stitzziel¹⁸⁶, Barbara E. Stranger¹⁸⁷, Chad Tomlinson³³, Juan Wang³⁵, Wenjin Zhang⁵, Bo Zhang¹⁸⁸, Guoyan Zhao^{5,189,190} & Xiaoyu Zhuo⁵

¹⁷⁷Program in Computational Biology and Bioinformatics, Yale University, New Haven, CT, USA. ¹⁷⁸Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT, USA. ¹⁷⁹Department of Computer Science, Yale University, New Haven, CT, USA. ¹⁸⁰Department of Statistics and Data Science, Yale University, New Haven, CT, USA. ¹⁸¹Department of Biomedical Informatics and Data Science, Yale University, New Haven, CT, USA. ¹⁸²Center for Genetic Medicine and Department of Cell and Developmental Biology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA. ¹⁸³Department of Pediatrics, Washington University, St Louis, MO, USA. ¹⁸⁴Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Evanston, IL, USA. ¹⁸⁵UC Santa Cruz Genomics Institute, University of California Santa Cruz, Santa Cruz, CA, USA. ¹⁸⁶Department of Medicine, Washington University, St Louis, MO, USA. ¹⁸⁷Center for Genetic Medicine, Department of Pharmacology, Northwestern University, Chicago, IL, USA. ¹⁸⁸Department of Developmental Biology, Washington University, St Louis, MO, USA. ¹⁸⁹Department of Pathology and Immunology, Washington University, St Louis, MO, USA. ¹⁹⁰Department of Neurology, Washington University, St Louis, MO, USA.

IGVF Affiliate Member Projects (contact PIs, other members (alphabetical by last name))

Brennand lab

Kristen Brennand¹⁹¹

Ciccia lab

Alberto Ciccia¹⁹², Samuel B. Hayward¹⁹², Jen-Wei Huang¹⁹², Giuseppe Leuzzi¹⁹², Angelo Taglialatela¹⁹², Tanay Thakar¹⁹² & Alina Vaitsiankova¹⁹²

Dey lab

Kushal K. Dey³⁸ & Thahmina A. Ali³⁸

Gazal lab

Steven Gazal^{60,61,62} & Artem Kim⁶⁰

Grimes lab

H. Leighton Grimes¹⁹³ & Nathan Salomonis¹⁹³

Gupta lab

Rajat Gupta⁵⁰, Shi Fang⁵⁰ & Vivian Lee-Kim⁵⁰

Heinig lab

Matthias Heinig^{194,195,196} & Corinna Losert^{194,195}

Jones lab

Thouis R. Jones³, Elisa Donnard³, Maddie Murphy³, Elizabeth Roberts³ & Susie Song³

Moore lab

Jill E. Moore⁷⁰

Mostafavi lab

Sara Mostafavi^{197,198}, Alexander Sasse¹⁹⁷ & Anna Spiro¹⁹⁷

Pennacchio and Visel lab

Len A. Pennacchio^{199,200}, Momoe Kato¹⁹⁹, Michael Kosicki¹⁹⁹, Brandon Mannion¹⁹⁹, Neil Slaven¹⁹⁹ & Axel Visel^{199,200}

Pollard lab

Katherine S. Pollard^{134,201,202}, Shiron Drusinsky^{201,202} & Sean Whalen²⁰¹

Ray lab

John Ray^{77,203}, Ingrid A. Harten⁷⁷ & Ching-Huang Ho⁷⁷

Reilly lab

Steven K. Reilly⁶³

Sanjana lab

Neville E. Sanjana^{204,205}, Christina Caragine^{204,205} & John A. Morris^{204,205}

Seruggia lab

Davide Seruggia^{206,207}, Ana Patricia Kutschat^{206,207} & Sandra Wittibschlager^{206,207}

Xu lab

Han Xu¹³, Rongjie Fu¹³, Wei He¹³ & Liang Zhang¹³

Yi lab

S. Stephen Yi^{71,72} & Daniel Osorio^{71,72}

¹⁹¹Departments of Psychiatry and Genetics, Division of Molecular Psychiatry, Department of Genetics, Wu Tsai Institute, Yale University School of Medicine, New Haven, CT, USA. ¹⁹²Department of Genetics and Development, Institute for Cancer Genetics, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY, USA. ¹⁹³Cincinnati Children's Hospital, Cincinnati, OH, USA. ¹⁹⁴Institute of Computational Biology, Helmholtz Zentrum Munich, Neuherberg, Germany. ¹⁹⁵Department of Computer Science, School of Computation, Information and Technology, Technical University Munich, Munich, Germany. ¹⁹⁶Munich Heart Alliance, DZHK (German Center for Cardiovascular Research), Munich, Germany. ¹⁹⁷Paul G. Allen School of Computer Science and Engineering, University of Washington, Seattle, WA, USA. ¹⁹⁸Canadian Institute for Advanced Research, Toronto, Ontario, Canada. ¹⁹⁹Lawrence Berkeley National Laboratory, Berkeley, CA, USA. ²⁰⁰DOE Joint Genome Institute, Berkeley, CA, USA. ²⁰¹Gladstone Institutes, San Francisco, CA, USA. ²⁰²University of California, San Francisco, CA, USA. ²⁰³Department of Immunology, University of Washington, Seattle, WA, USA. ²⁰⁴New York Genome Center, New York, NY, USA. ²⁰⁵Department of Biology, New York University, New York, NY, USA. ²⁰⁶St Anna Children's Cancer Research Institute (CCRI), Vienna, Austria. ²⁰⁷CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria.

NHGRI Program Management (alphabetical by last name)

Zo Bly²⁰⁸, Stephanie Calluori^{37,209}, Daniel A. Gilchrist³⁷, Carolyn M. Hutter³⁷, Stephanie A. Morris³⁷, Michael J. Pazin³⁷ & Ella K. Samer^{37,210}

²⁰⁸Division of Genomic Medicine, National Human Genome Research Institute (NHGRI), National Institutes of Health (NIH), Bethesda, MD, USA. ²⁰⁹Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, NY, USA. ²¹⁰Masters of Physician Assistant Studies Program, Colorado Mesa University, Grand Junction, CO, USA.