Genetic and Functional -Omics Studies in Cells, Animals, and Humans

Scope of the Guidelines

These guidelines were developed to support our commitment for increasing transparency in research, and to clarify the data sharing policy and increase author compliance. These guidelines are provided for studies investigating the relation of variants in parts or all of the genome in relation to phenotypes related to musculoskeletal tissues and mineral metabolism. These guidelines may be applicable to other forms of –omic studies focusing on the transcriptome, epigenome, metabolome, and/or proteome. Further, research comprising genetic and functional -omics studies should also be within the scope described in the new publication policies of the journals (see "Focusing on the Science" Editorial). These guidelines are reviewed annually by an Editorial task group.

Human Genetic Studies

With the advent of high-throughput technologies like micro-array genotyping and next-generation sequencing, large-scale collaborative efforts like the Human Genome, HapMap, 1000 Genomes, and ENCODE projects have been enabled. These projects have facilitated genetic investigations in humans with the potential of revolutionizing research in the field of bone, muscle, and mineral metabolism.

While publication of those discoveries is a central element for disseminating knowledge, the ASBMR Journals' responsibility is to ensure that the design, analysis, and interpretation of the results of human genetic studies published in the Journals meet key aspects of scientific rigor similar to those stipulated by the STrengthening the REporting of Genetic Associations (STREGA) statement.

The Journals' editors and reviewers will place particular emphasis on the evaluation of the following aspects of design, analysis, and biological/clinical significance of -omic studies submitted for publication:

Clear Description of the Approach

Studies should clearly state whether they followed a hypothesis-driven or a hypothesis-free approach. Hypothesis-driven studies mostly include (but are not limited to) candidate gene association studies, replication studies of established associations, and evaluation of discoveries using experimental procedures in cells and/or other organisms. Hypothesis-free approaches do not rely on existing knowledge and are carried out without pre-specification of the variants to be tested. These include genome-wide association, epigenome-wide, whole-exome, and whole-genome sequencing approaches. Additional designs like gene x environment and gene x gene interaction studies should also specify the type of approach pursued.

Validation of Findings in Humans

All discoveries need to show evidence for "replication," defined as observing consistency of the reported finding in at least one or more additional independent studies. Single studies drawn in one human population where highly relevant functional

data with strong biological evidence is presented and/or for extremely rare conditions where no other samples can be collected, will be considered on a case-by-case basis.

The study should clearly state the threshold that was used to declare statistical significance of the findings, which should be consistent with the study design, and consider aspects of multiple hypothesis testing (e.g., multiple variants, subgroup analyses, genetic models, and phenotypes tested). These thresholds will be specific to the approach and as such, need to be consistently reported and justified.

Sample Size and Power Considerations
Studies should perform power calculations in the design phase justifying that the sample sizes used in the study are sufficient to achieve the statistical power needed to detect an effect.

Power calculations for a given genetic effect are particularly important for studies reporting negative findings to ensure that the negative findings are robust when reporting the effect size that the study design (power) is able to detect. These types of studies will be considered particularly relevant when refuting findings from prior published association studies or when the genetic determinants in question are of established significance to disease pathogenesis.

Population Stratification and Design Biases
Studies should describe their attempts to control for population stratification bias in concordance with the level of admixture in their populations. Methods include, but are not confined to, outlier exclusion, genomic control, and use of principal components. Similarly, those strategies seeking the control of other biases (e.g., genotyping artefacts, sample selection, selective reporting, or cryptic relatedness) should be presented.

Family-based studies
Family-based and genealogy studies should apply appropriate methodology that considers familial relations. Pedigree-based studies (usually of rare diseases) and studies of rare variants supported by association, segregation, and similar analyses, should refer to Online Mendelian Inheritance in Man (OMIM) for potential posting of their results.

Functional Validation
Functional data strengthening the genetic findings in humans that are relevant to the reported phenotypes are highly encouraged, although not compulsory. Beyond the statistical evidence, these data serve to support the biological and clinical significance of the reported findings. Specifically, detail regarding the source, authentication, derivation, and contamination status for the cell lines (such as mycoplasma and/or other cell lines) are required.

Animal Model Studies using Genetics and -omics approaches

Rodents have been widely used for the genetic analysis of complex musculoskeletal traits. Common experimental designs include F2 intercrosses, panels of recombinant inbred strains, panels of inbred strains, and, more recently, genome-wide association in outbred populations.

Independently of the experimental design, the Journals require all the applicable considerations described above for human genetic studies (e.g., clear description of the approach, sample size and power considerations, and controlling for population stratification) be adhered to for rodent genetic mapping studies. Further specific details are required, which include the generation at which the animals were genotyped and phenotyped. The source (i.e., vendor) and exact strains names for all animals used must be reported; for transgenic animals (e.g., zebrafish or mouse), the genetic background of the transgenes must be reported.

Authors submitting research on animal studies are required to complete an adapted Animals in Research: Reporting In Vivo Experiments (ARRIVE) checklist with their submission.

Additionally, the Journals expect that all data (genotypic, phenotypic, and/or molecular) be deposited in appropriate public repositories. The Journals encourage the use of repositories specific for rodent genetic data such as GeneNetwork (http://www.genenetwork.org/webqtl/main.py) and the "QTL Archive" (https://phenome.jax.org/centers/QTLA).

Public Release of Results

Authors are expected to deposit datasets including loci (genes, fragile sites, DNA segments), probes, cell lines, DNA clones, and organisms that are described in the paper, with a community-recognized data repository where available. Authors of manuscripts are expected to deposit their data at the time of publication and provide a Data Availability Statement on the availability of results after publication.

Similarly, the Journals require that summary results of other "-omic" data such as gene expression, proteomic, or other high-throughput data be posted on an accessible website such as Gene Expression Omnibus (GEO) or equivalent publicly accessible database. Deposition in dbGaP is expected.

Authors should note in the manuscript the database(s) to which they have submitted their variants, repository accession numbers (and version numbers, if appropriate) and provide the URL or a DOI. The Journals reserve the right to consider the willingness to abide by these principles in decisions regarding publication.

Examples of repositories can be found here:

- **https://osp.od.nih.gov/scientific-sharing/data-repositories-and-trusted-partners**
- **https://nlm.nih.gov/NIHbmic/nih_data_sharing_repositories.html**
- Mouse Genome Informatics (MGI)

- Rat Genome Database (RGD)
- Zebrafish Model Organism Database (ZFIN)

The list is neither representative nor exhaustive of the suitable repositories available to authors.

If you have any questions, please email us at asbmr@asbmr.org