
exomiser Documentation

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Jules Jacobsen, Damian Smedley, Peter Robinson

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CHAPTER 1

Introduction

The Exomiser is a Java program, developed as a collaboration between members of the Monarch Initiative for finding potential disease-causing variants in whole-exome or whole-genome sequencing data. It is available for use by all as an offline command-line tool, or on the web as a demo application/teaching tool.

It requires a VCF file and a set of phenotypes encoded using the Human Phenotype Ontology (HPO) from which it will annotate, filter and prioritise likely causative variants. The program does this based on user-defined criteria such as a variant's predicted pathogenicity, frequency of occurrence in a population and also how closely the given phenotype matches the known phenotype of diseased genes from human and model organism data.

The functional annotation of variants is handled by the Jannovar library and uses any of UCSC, RefSeq or Ensembl KnownGene transcript definitions and hg19 or hg38 genomic coordinates.

Variants are prioritised according to user-defined criteria on variant frequency, pathogenicity, quality, inheritance pattern, and model organism phenotype data. Predicted pathogenicity data is extracted from the dbNSFP resource. Variant frequency data is taken from the 1000 Genomes, ESP, TOPMed, UK10K, ExAC and gnomAD datasets. Subsets of these frequency and pathogenicity data can be defined to further tune the analysis. Cross-species phenotype comparisons come from our PhenoDigm tool powered by the OWLTools OWLSim algorithm.

1.1 Installation

1.1.1 Pre-built Binaries

Note: This is the recommended way of installing for normal users.

Pre-built binaries are available from [The Monarch Initiative](#). Download `exomiser-cli-distribution.zip` from [here](#).

1.2 Getting Started

1.3 Interpreting the Results

1.4 Publications

A Whole-Genome Analysis Framework for Effective Identification of Pathogenic Regulatory Variants in Mendelian Disease.

Smedley D, Schubach M, Jacobsen JOB, Köhler S, Zemojtel T, Spielmann M, Jäger M, Hochheiser H, Washington NL, McMurry JA, Haendel MA, Mungall CJ, Lewis SE, Groza T, Valentini G, Robinson PN.

The American Journal of Human Genetics 2016;99;3;595-606

PMID:27569544 DOI:[10.1016/j.ajhg.2016.07.005](https://doi.org/10.1016/j.ajhg.2016.07.005)

Phenotype-driven strategies for exome prioritization of human Mendelian disease genes.

Smedley D, Robinson PN.

Genome Medicine 2015, 7(1):81

PMID:26229552 DOI:[10.1186/s13073-015-0199-2](https://doi.org/10.1186/s13073-015-0199-2)

Next-generation diagnostics and disease-gene discovery with the Exomiser.

Smedley D, Jacobsen JO, Jäger M, Köhler S, Holtgrewe M et al.

Nature protocols 2015;10;12;2004-15

PMID:26562621 DOI:[10.1038/nprot.2015.124](https://doi.org/10.1038/nprot.2015.124)

Computational evaluation of exome sequence data using human and model organism phenotypes improves diagnostic efficiency.

Bone WP, Washington NL, Buske OJ, Adams DR, Davis J et al.

Genetics in medicine : official journal of the American College of Medical Genetics 2015

PMID:26562225 DOI:[10.1038/gim.2015.137](https://doi.org/10.1038/gim.2015.137)

Walking the interactome for candidate prioritization in exome sequencing studies of Mendelian diseases.

Smedley D, Köhler S, Czeschik JC, Amberger J, Bocchini C et al.

Bioinformatics (Oxford, England) 2014;30;22;3215-22

PMID:25078397 DOI:[10.1093/bioinformatics/btu508](https://doi.org/10.1093/bioinformatics/btu508)

Effective diagnosis of genetic disease by computational phenotype analysis of the disease-associated genome.

Zemojtel T, Köhler S, Mackenroth L, Jäger M, Hecht J et al.

Science translational medicine 2014;6;252;252ra123

PMID:25186178 DOI:[10.1126/scitranslmed.3009262](https://doi.org/10.1126/scitranslmed.3009262)

Improved exome prioritization of disease genes through cross-species phenotype comparison.

Robinson PN, Köhler S, Oellrich A, Sanger Mouse Genetics Project, Wang K et al.

Genome research 2014;24;2;340-8

PMID:24162188 DOI:[10.1101/gr.160325.113](https://doi.org/10.1101/gr.160325.113)

1.4.1 Collaborations

Publications for other projects and resources in which the Exomiser is used as a component:

Defining Disease, Diagnosis, and Translational Medicine within a Homeostatic Perturbation Paradigm: The National Institutes of Health Undiagnosed Diseases Program Experience.

Gall T, Valkanas E, Bello C, Markello T, Adams C, Bone WP, Brandt AJ, Brazill JM, Carmichael L, Davids M, Davis J, Diaz-Perez Z, Draper D, Elson J, Flynn ED, Godfrey R, Groden C, Hsieh CK, Fischer R, Golas GA, Guzman J, Huang Y, Kane MS, Lee E, Li C, Links AE, Maduro V, Malicdan MCV, Malik FS, Nehrebecky M, Park J, Pemberton P, Schaffer K, Simeonov D, Sincan M, Smedley D, Valivullah Z, Wahl C, Washington N, Wolfe LA, Xu K, Zhu Y, Gahl WA, Tiffet CJ, Toro C, Adams DR, He M, Robinson PN, Haendel MA, Zhai RG, Boerkoel CF.

Front Med (Lausanne). 2017;4:62

PMID: 28603714 DOI:[10.3389/fmed.2017.00062](https://doi.org/10.3389/fmed.2017.00062)

PhenomeCentral: A Portal for Phenotypic and Genotypic Matchmaking of Patients with Rare Genetic Diseases.

Orion J. Buske, Marta Girdea, Sergiu Dumitriu, Bailey Gallinger, Taila Hartley, Heather Trang, Andriy Misyura, Tal Friedman, Chandree Beaulieu, William P. Bone, Amanda E. Links, Nicole L. Washington, Melissa A. Haendel, Peter N. Robinson, Cornelius F. Boerkoel, David Adams, William A. Gahl, Kym M. Boycott, Michael Brudno.

Human Mutation 2015, 36(10):931-940

PMID: 26251998 DOI:[10.1002/humu.22851](https://doi.org/10.1002/humu.22851)

Phenopolis: an open platform for harmonization and analysis of genetic and phenotypic data.

Nikolas Pontikos, Jing Yu, Ismail Moghul, Lucy Withington, Fiona Blanco-Kelly, Tom Vulliamy, Tsz Lun, Ernest Wong, Cian Murphy, Valentina Cipriani, Alessia Fiorentino, Gavin Arno, Daniel Greene, Julius OB Jacobsen, Tristan Clark, David S. Gregory, Andrea M. Nemeth, Stephanie Halford, Chris F. Inglehearn, Susan Downes, Graeme C. Black, Andrew R. Webster, Alison J. Hardcastle, UKIRDC, Vincent Plagnol.

Bioinformatics 2017,33(15):2421-2423

PMID: 28334266 DOI:[10.1093/bioinformatics/btx147](https://doi.org/10.1093/bioinformatics/btx147)