Searching Online Mendelian Inheritance in Man (OMIM): A Knowledgebase of Human Genes and Genetic Phenotypes

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Online Mendelian Inheritance in Man (OMIM) at OMIM.org is the primary repository of comprehensive, curated information on genes and genetic phenotypes and the relationships between them. This unit provides an overview of the types of information in OMIM and optimal strategies for searching and retrieving the information. OMIM.org has links to many related and complementary databases, providing easy access to more information on a topic. The relationship between genes and genetic disorders is highlighted in this unit. The basic protocol explains searching OMIM both from a gene perspective and a clinical features perspective. Two alternate protocols provide strategies for viewing gene-phenotype relationships: a gene map table and Quick View or Side-by-Side format for clinical features. OMIM.org is updated nightly, and the MIMmatch service, described in the support protocol, provides a convenient way to follow updates to entries, gene-phenotype relationships, and collaborate with other researchers.

Keywords: disease gene discovery • human genetic disorders • molecular genetics • OMIM

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INTRODUCTION

Online Mendelian Inheritance in Man (OMIM) is a continuation of Dr. Victor McKusick's *Mendelian Inheritance in Man* (MIM; McKusick, 1998), a seminal medical genetics resource used primarily by physicians and other professionals interested in genetic disorders, by genetics researchers, and by advanced students in science and medicine. It provides concise textual information based on the peer-reviewed biomedical literature on over 15,500 genes, 26,200 allelic variants, and 7,800 genetic phenotypes. In addition, OMIM.org provides tabular views of phenotype-gene relationships (gene map), overviews of clinical features of phenotypes (clinical synopses), phenotypic series, and a convenient way to follow updates and collaborate (MIMmatch). All entries in OMIM contain extensive targeted links to external data resources. The overall structure of OMIM is shown in Figure 1.2.1 and illustrates the intersection of gene and phenotype information.

The Basic Protocol describes a basic text search and overview of the layout of search results. Alternate Protocol 1 explains searching the Gene Map to reveal unique displays of the intersection between gene and phenotype. Alternate Protocol 2 explains searching clinical information to display the Quick View and Side-by-Side views of the Clinical Synopses. The Support Protocol describes how to register for MIMmatch alerts.

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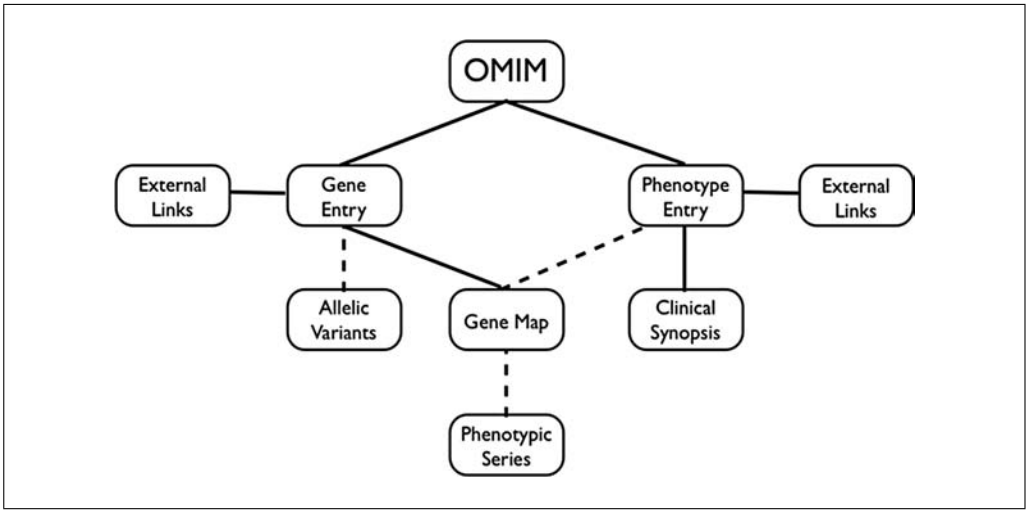


Figure 1.2.1 Diagram of OMIM content. Dashed lines indicate that not all genes have allelic variants, not all phenotypes are mapped, and mapped phenotypes are not necessarily part of a Phenotypic Series.

BASIC PROTOCOL

SEARCHING OMIM

OMIM.org is the official Web site for OMIM information. It has been optimized to retrieve and display information from OMIM in a straightforward and clear manner. OMIM.org supports free-text and field-directed searches. Detailed help, example searches, and tips are available from every screen. The top of the **OMIM home page** (*https://omim.org*) shows the black menu bar that is common across all OMIM.org Web pages. From this menu, a user can always access Statistics, Download/API registration, Contact Us, or obtain MIMmatch access, Help/FAQ, and Tips specific for the page (see the '?' icon). Statistics include the Update List of new and added entries, number of entries in OMIM, and number of phenotype-gene relationships cataloged by OMIM. Below the search box is access to advanced search pages, example searches, search help, and a tutorial.

Necessary Resources

Hardware

Any Internet-connected computer, tablet, or mobile device

Software

Up-to-date Web browser such as Chrome, FireFox, Safari, Microsoft Internet Explorer, or Microsoft Edge

Performing an OMIM search for genes

1. If, for example, you are interested in potassium channel genes, you can enter your search in a number of ways. For example, `+potassium +channel` (352 entries retrieved), `KCN*` (333 entries retrieved), or `''potassium channel''` (with quotes; `potassium` and `channel` must appear as a phrase, 276 entries retrieved). Of note, entering `potassium channel` without qualifiers applies both Boolean `AND` and `OR` to the search. Entries satisfying the `AND` operator are given higher relevance (1,334 entries retrieved). OMIM searches are vocabulary enhanced to accommodate synonyms, British spelling, and user-selected thesaurus terms. Figure 1.2.2 shows an **entry retrieval page** for a search on `+potassium +channel` and is described below.

   a. The blue buttons Gene Map Table and Clinical Synopsis to the right of the search box navigate the search results to the Gene Map display and Clinical Synopsis

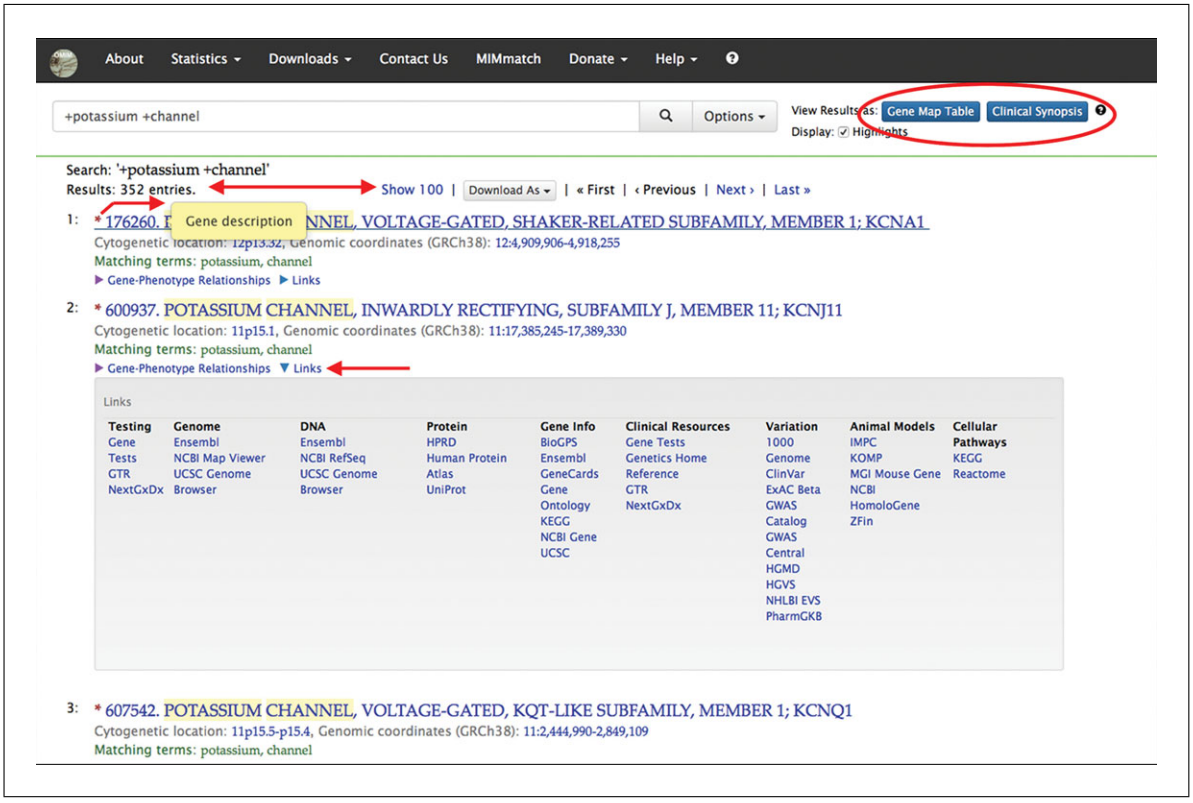


Figure 1.2.2 Search results page from a search of `+potassium +channel` at OMIM.org. Targeted links for entry 600937 are displayed by clicking the Links button below the entry title. The mouse-over explanation of the MIM number prefix (in this case "Gene description") is also displayed.

(see Alternate Protocols 1 and 2). If thesaurus terms are available for the search, they will be displayed below the search box.

b. The text below the green line shows the total number of entries retrieved with that search; an option to expand the number of titles displayed; an option to download the search results; and retrieval navigation buttons.

c. Each entry in OMIM has a unique and stable *MIM number*. The MIM number has a *prefix* denoting whether the entry represents a gene or phenotype; a mouse-over reminds the user which of these it is. The number is followed by the preferred *MIM title* and *symbol*. Clicking on the title brings up the full display of that entry. Below the title is the *cytogenetic location* and *genomic coordinates*; clicking on either of them takes the user to that gene/locus in OMIM's gene map or in UCSCs Genome Browser.

d. Colored triangles precede links to reveal on-page information and access to *Gene-phenotype/Phenotype-gene Relationships*, *ICD+* codes, *Phenotypic series*, and *Links* (opened for entry 600937). ICD+ and Phenotypic series links will not appear in gene entries. Access to this information is also present on the entry full view.

2. Clicking on the title for 176260 opens the **entry full view** for this gene (Fig. 1.2.3). Note that the search terms are highlighted, and there is a green bar next to the Description paragraph denoting information that has been changed or added in the last 3 months. Highlights and change bars can be toggled off by selecting the option to the right of the search box.

a. Following the number and preferred title are alternative names that may have been given to the entry. The HGNC-approved gene symbol display and link are above the mapping information links and Gene-Phenotype relationship table.

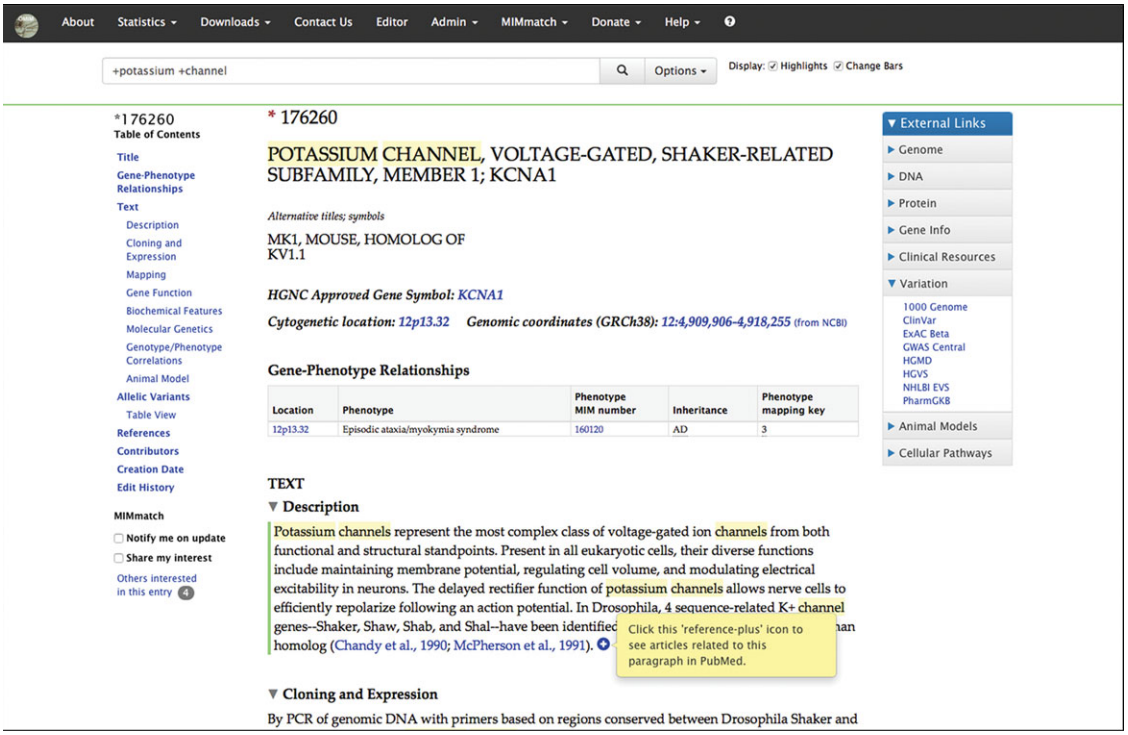


Figure 1.2.3 Entry full view for 176260 displaying highlighted search terms, green entry change bar (left of description paragraph), and Reference Plus link.

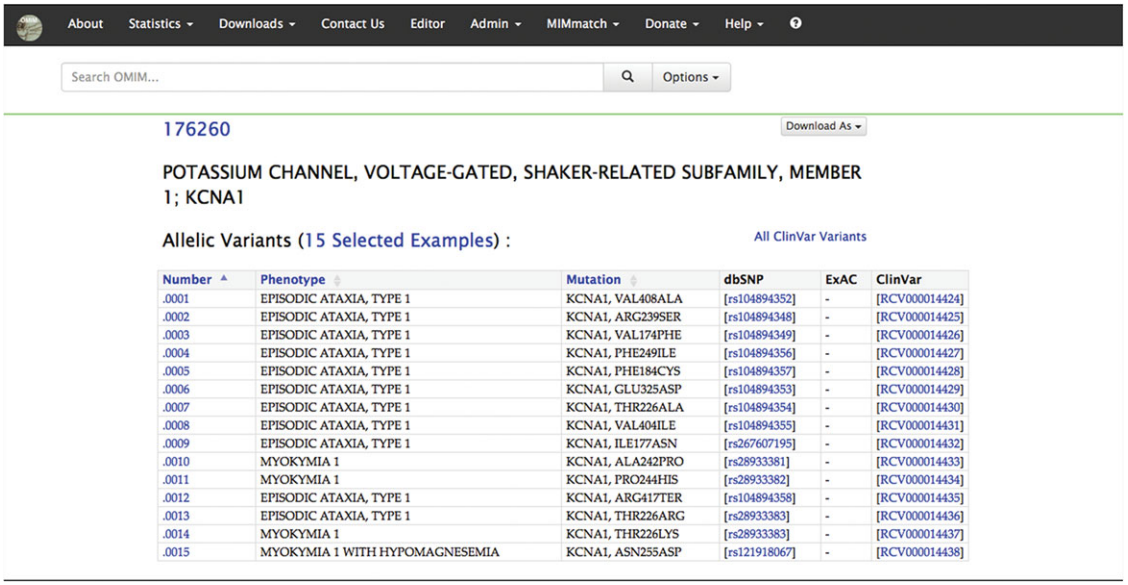


Figure 1.2.4 Allelic variant table view showing dbSNP, ExAC, and ClinVar links.

b. To the left of the title is the entry navigation *Table of Contents*. Selecting the heading takes the user directly to that section in the entry. Note that *Allelic Variants* are listed in a gene entry and can be viewed as descriptive text or in a **Table View** (Fig. 1.2.4). Both versions have links, when available, to dbSNP, ExAC, and ClinVar.

c. To the right of the title are *External Links*. The topically organized pull-down menus in this stack contain links to over 55 resources including genome browsers, DNA

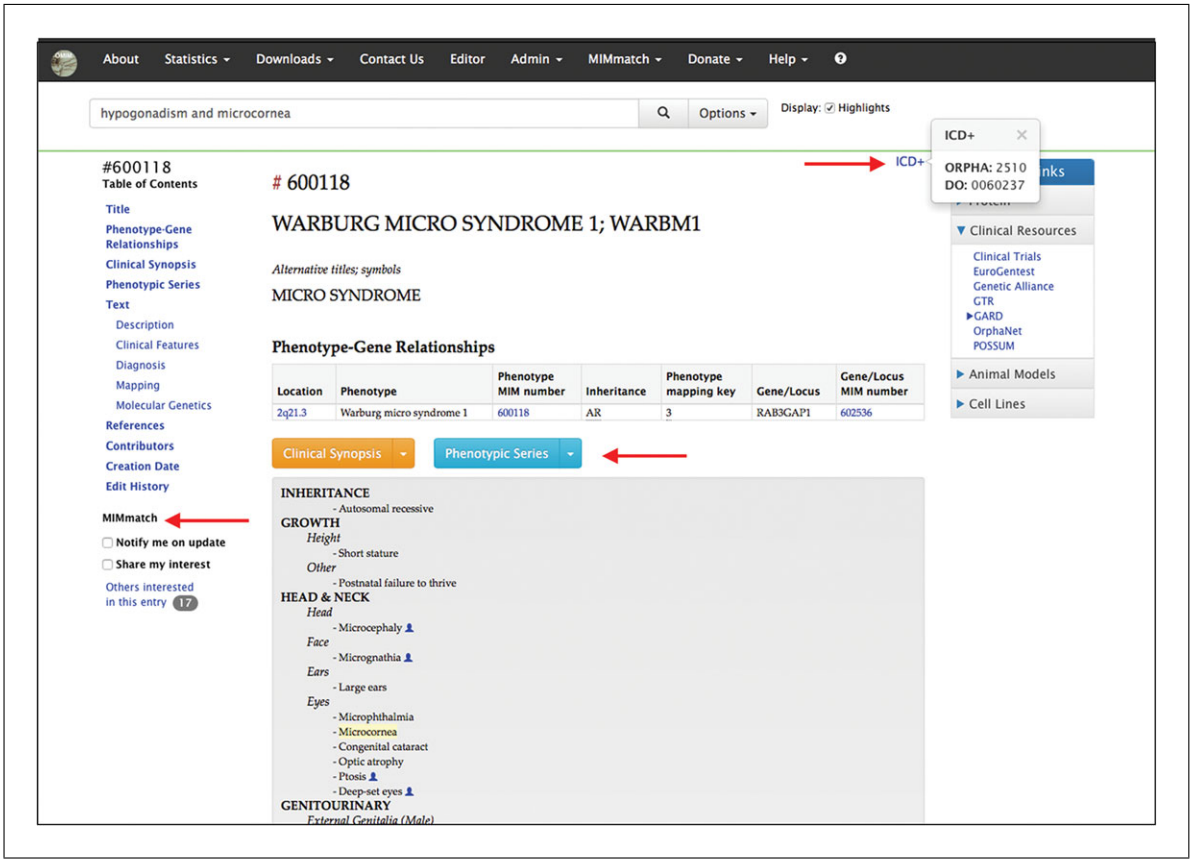


Figure 1.2.5 Full view of entry 600118 showing the ICD+ coding numbers, in-page view of the *clinical synopsis*, and MIMmatch information.

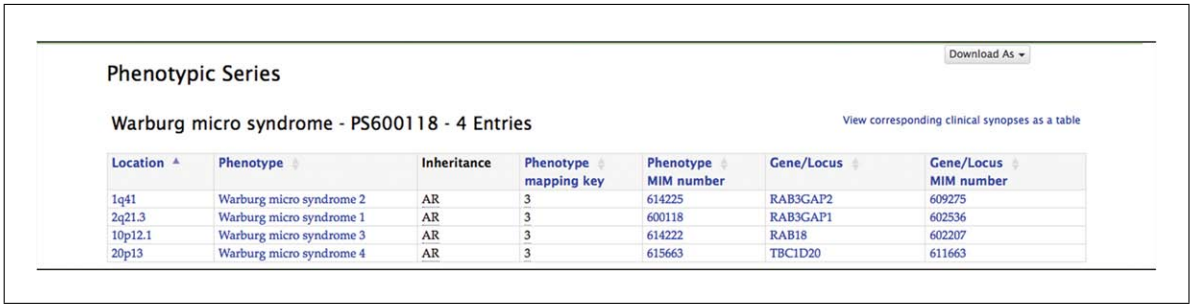
and protein sequence databases, model organism databases, pathway databases, etc. Each link takes the user directly to the relevant information in that resource.

d. The *plus sign* at the end of text paragraphs takes the user to articles in PubMed that are related to the citation(s) in the MIM entry paragraph. This is an easy way to find additional articles that may be available on a specific topic.

Performing an OMIM search for phenotypes (including disorders) or clinical features

3. Information in a phenotype entry is different from that in a gene entry. Organizationally, each phenotype in a unique phenotype-gene relationship has its own OMIM entry and number. Clinical features in an entry are specific to that phenotype-gene relationship. To show how a class of related phenotypes lies across the genome, OMIM has *Phenotypic Series*. Users can search by disorder name or clinical features. For example, starting at the OMIM.org home page, search on `hypogonadism` and `microcornea`. Optional thesaurus terms related to hypogonadism (e.g., hypogenitalism, micropenis, small testis, etc.) are displayed under the search box, which can be selected to further broaden a search. For the purposes of this protocol, select 600118 by clicking on the title, Warburg Micro syndrome 1 (Fig. 1.2.5).

   a. The ICD+ link shows the available disease identifiers. The External Links have robust *Clinical Resources* (shown), *Animal Model*, and *Cell Lines* sections. These links appear only if there is information in the external resource that is relevant to the MIM entry.
   b. The *Clinical Synopsis* (a feature-based list) and *Phenotypic Series* links can display contents in-page (down triangle, shown here) or in a new page (main button).



Phenotypic Series

Download As

Warburg micro syndrome - PS600118 - 4 Entries

View corresponding clinical synopses as a table

Location	Phenotype	Inheritance	Phenotype mapping key	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
1q41	Warburg micro syndrome 2	AR	3	614225	RAB3GAP2	609275
2q21.3	Warburg micro syndrome 1	AR	3	600118	RAB3GAP1	602536
10p12.1	Warburg micro syndrome 3	AR	3	614222	RAB18	602207
20p13	Warburg micro syndrome 4	AR	3	615663	TBC1D20	611663

Figure 1.2.6 Phenotype Series for Warburg micro syndrome. The sort can be changed by clicking on the triangle links in the table headers. Explanation of the Inheritance and Phenotype mapping keys are available through a mouse-over pop-up.

c. If the user is a *MIMmatch* member, MIMmatch options will be displayed below the Table of Contents to the left of the entry. The user has options to follow updates to the entry or share interest. This entry has 15 individuals sharing their interest. The link provides details and a way to share contact information.
d. The *Phenotypic Series* shows the genetic heterogeneity of Warburg Micro syndrome (Fig. 1.2.6).

Guidelines for understanding entry structure and content

Number. Each OMIM entry is given a unique and stable six-digit number based on the chromosomal location. Autosomal entries start with a 1, 2, or 6; X-linked entries start with a 3, Y-linked entries start with a 4, and mitochondrial entries start with a 5. Numbers that start with a 1 or 2 do not refer to a mode of inheritance.

MIM numbers are preceded by a prefix:

An **asterisk (*)** before an entry number indicates a gene.

A **number symbol (#)** before an entry number indicates that it is a descriptive entry, usually of a phenotype, and does not represent a unique locus. The reason for the use of the number symbol is given in the first paragraph of the entry. Discussion of any gene(s) related to the phenotype resides in another entry or entries) as described in the first paragraph.

A **plus sign (+)** before an entry number indicates that the entry contains the description of a gene of known sequence and a phenotype.

A **percent sign (%)** before an entry number indicates that the entry describes a confirmed Mendelian phenotype or phenotypic locus for which the underlying molecular basis is not known.

No symbol before an entry number generally indicates a description of a phenotype for which the Mendelian basis, although suspected, has not been clearly established, or that the separateness of this phenotype from that in another entry is unclear.

A **caret (^)** before an entry number means the entry was removed from the database or moved to another entry as indicated.

Title. Each entry has a "Preferred title" with symbol. Synonymous names and symbols that have been used in the literature are included as "Alternative title(s)." "Included titles" mark placement of information on a topic that does not warrant a separate entry (e.g., fusion genes).

Text. Information in the main text of an OMIM entry is put under standard headings (e.g., Description, Clinical Features, Cloning and Expression,

etc.) that can be targeted in fielded searches (see online search help 1.5; *https://omim.org/help/search#1_5*).

Allelic Variants. This section reports mutations and variations in the gene that are found to underlie a phenotype. OMIM includes only select variants. Criteria for inclusion include the first mutation to be discovered, high population frequency, distinctive phenotype, historic significance, unusual mechanism of mutation, unusual pathogenetic mechanism, and distinctive inheritance (e.g., dominant with some mutations, recessive with other mutations in the same gene). Most of the allelic variants represent disease-causing mutations. A few polymorphisms are included, many of which show a positive correlation with particular common disorders. Effective January 2013, based on a rigorous assessment of published reports, OMIM created phenotype-gene relationships that are "established," "provisional," or of "unknown significance." An established relationship may be based on (1) the existence of multiple, unrelated individuals with pathogenic variants in the same gene; (2) variants that segregate with the phenotype in multiplex families; and/or (3) variants that occur de novo in a statistically significant number of individuals. Functional data and/or animal models support the causality but are not required. A provisional relationship may be based on (1) only one multiplex family reported to have variants in a single gene and the variants segregating with the phenotype in the family, and (2) supportive functional data such as in vitro enzyme activity, a comparable phenotype in a model organism experiment, or an animal model. In this case, the gene-phenotype relationship is qualified by noting that the variant has been identified in only one family. In rare instances, a similar gene-phenotype relationship may be established on the basis of a single patient if there is robust supporting phenotype and functional data. A variant of unknown significance may be created if a report identifies only one patient or family and provides no supporting functional data.

References. All information in an OMIM entry is cited. The references are listed in alphabetical order in this section. There are links to PubMed and to the full text of the article, when available.

SEARCHING OMIM'S GENE MAP

ALTERNATE PROTOCOL 1

OMIM's Gene Map is a table of the genes and loci in OMIM organized by chromosome. OMIM currently has entries for over 15,500 genes and focuses on gene-phenotype relationships. The tabular format provides easy access to multiple gene-phenotype relationships in a single view. The table includes the cytogenetic location, genomic coordinates, gene/locus symbol and title, gene/locus MIM#, comments, and homologous mouse gene. If there is a phenotype or phenotypes associated with a gene/locus, there is a column for phenotype, the phenotype MIM#, the inheritance mode, and the phenotype mapping key. Mousing over the number will display the definition of the key. A summary of the definitions is as follows: (1) the disorder was positioned by mapping of the wild-type gene; (2) the disease phenotype itself was mapped; (3) the molecular basis of the disorder is known; (4) the disorder is a chromosome deletion or duplication syndrome. This protocol describes accessing the gene map table view of a standard search of OMIM, then restricting the view to genes with phenotypes, and finally performing a direct search of the gene map by genomic coordinates to show the phenotypes within a region.

Necessary Resources

Hardware

Any Internet-connected computer, tablet, or mobile device

Software

Up-to-date Web browser such as Chrome, FireFox, Safari, Microsoft Internet Explorer, or Microsoft Edge

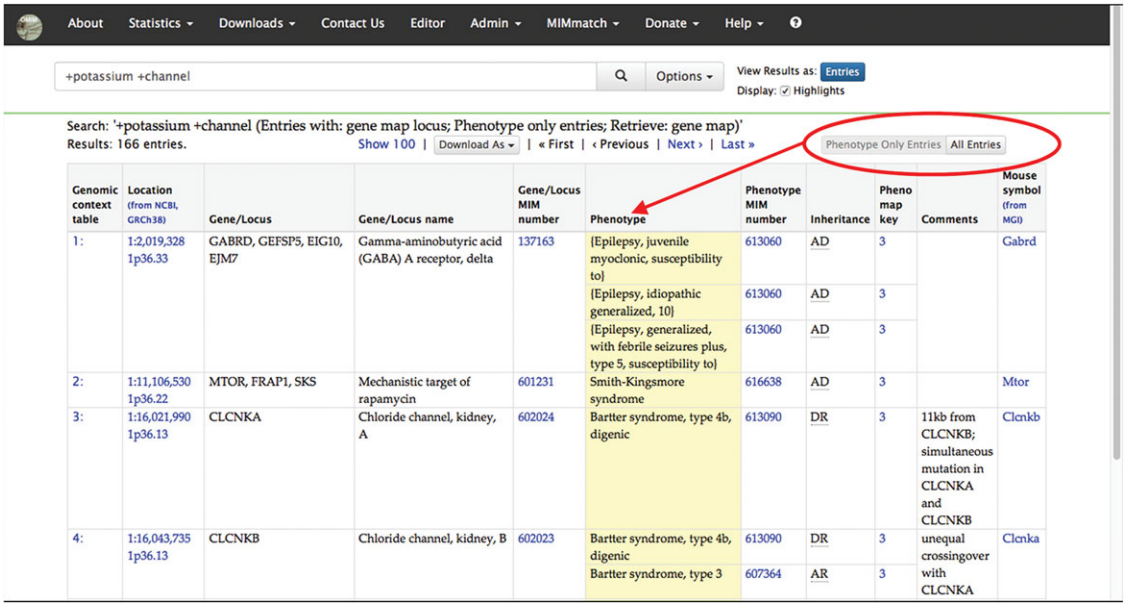


Figure 1.2.7 OMIM Gene map with phenotype only view selected.

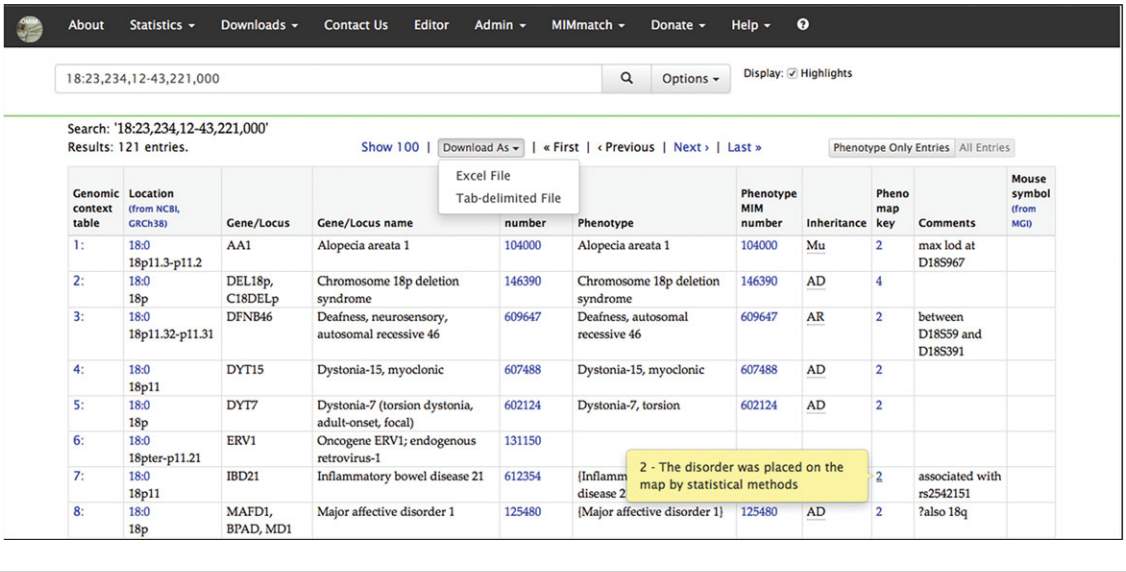


Figure 1.2.8 OMIM Gene map results from a genomic coordinate search: `18:23,234,12-43,221,000.`

View phenotypes associated with a gene-based search

1a. Go to *https://omim.org* and type a gene symbol or words like `''potassium channel''` (with quotes) in the search box. Click the magnifying glass icon to activate the search.

2a. From the retrieval entry page, select the Gene Map Table button to the right of the search box (Fig. 1.2.2). This will display the search retrieval in table form in the Gene Map viewer.

3a. Select the Phenotype Only Entries toggle to display only those entries from the search that have phenotypes (Fig. 1.2.7).

Perform a genomic coordinate search

1b. Go to *https://omim.org* and select Gene Map from the advanced search options below the search box.

2. Type in a chromosome number followed by a genomic region (e.g., `18:23,234,12-43,221,000`) or cytogenetic location (e.g., `18p11.3`). The display will include all genes and loci in OMIM that are in or that overlap the search region (Fig. 1.2.8). The explanation of the phenotype mapping key and download options are displayed.

SEARCHING OMIM CLINICAL SYNOPSES

ALTERNATE PROTOCOL 2

Each OMIM phenotype entry has a clinical synopsis that contains a list of the salient clinical features described for the phenotype. These features are curated from the biomedical literature and are specific to unique gene-phenotype combinations. This protocol describes accessing the Clinical Synopsis Quick View format and the Side-by-Side viewer.

Necessary Resources

Hardware

Any Internet-connected computer, tablet, or mobile device

Software

Up-to-date Web browser such as Chrome, FireFox, Safari, Microsoft Internet Explorer or Microsoft Edge

Accessing the OMIM Clinical Synopsis Quick View and Side-by-Side view

1. Go to *https://omim.org* and type `microcornea` AND `hypogonadism` in the search box. Click the magnifying glass icon to activate the search.

2. From the entry retrieval page, select the Clinical Synopsis button to the right of the search box (see Fig. 1.2.2).

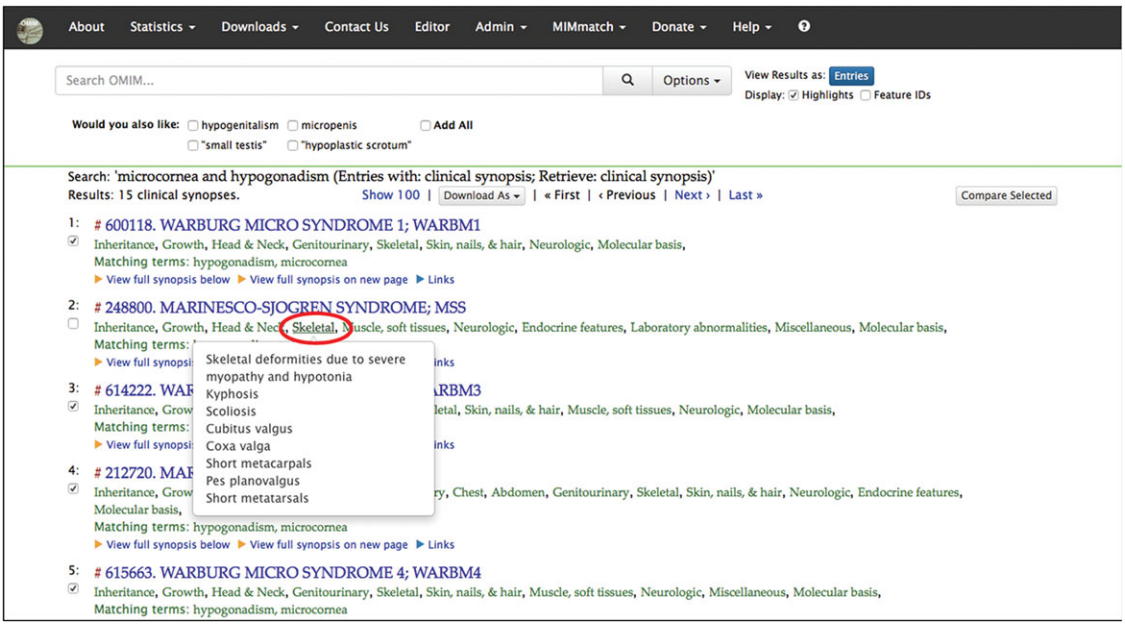


Figure 1.2.9 Clinical Synopsis Quick View with mouse-over of the anatomical headings to pop-up the features.

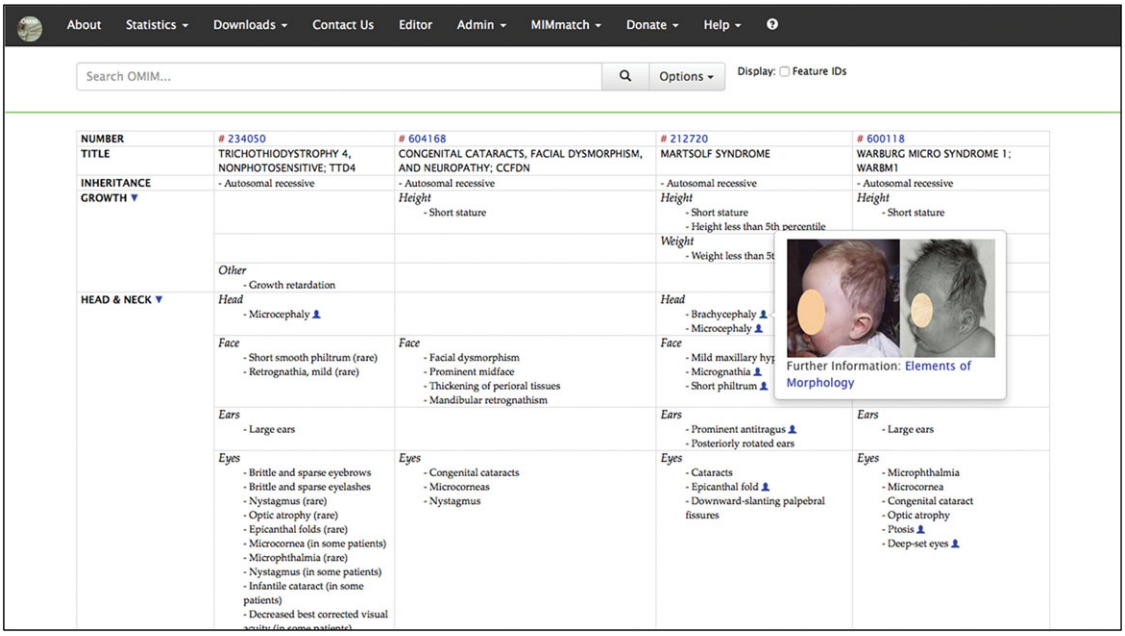


Figure 1.2.10 Clinical Synopsis Side-by-Side view with Elements of Morphology brachycephaly feature photo pop-up open.

3. Entries from the search with Clinical Synopses are displayed in the Quick View format. Mouse over the anatomical headings to view the features (Fig. 1.2.9).
4. Check the box under the entry retrieval number to select the entries to compare side-by-side.
5. Click the Compare Selected button to reveal the selected synopses side-by-side (Fig. 1.2.10). An Elements of Morphology feature definition photo for brachycephaly is displayed.

SUPPORT PROTOCOL

REGISTERING FOR AND USING MIMmatch

MIMmatch is a service available through OMIM.org that provides easy ways to stay up to date and collaborate. MIMmatch users can (1) designate entries that they wish to follow and receive e-mail alerts when the entries are updated; (2) find other researchers who may share their interest in certain entries; (3) receive a daily update on any new gene-phenotype relationships established in OMIM; and/or (4) save search queries. Your name will appear only to other MIMmatch users and only on those entries that you designate. All MIMmatch alerts for a user are collected in a single e-mail, and a user's information is not shared without the user's consent.

Necessary Resources

Hardware

Any Internet-connected computer, tablet, or mobile device

Software

Up-to-date Web browsers such as Chrome, FireFox, Safari, Microsoft Internet Explorer, or Microsoft Edge

1. Go to *https://omim.org* and select *MIMmatch* from the menu items on the black bar at the top of the page. Enter the required information on the entry form and click

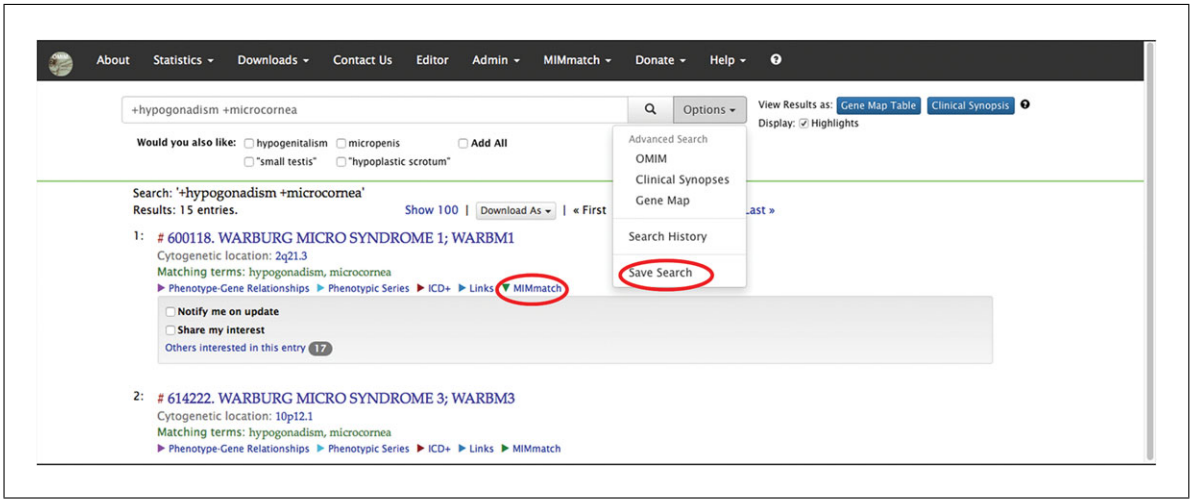


Figure 1.2.11 MIMmatch options.

"create account." An e-mail will be sent to you requiring you to activate the newly created account.

The MIMmatch options described below will not appear on the Web site unless you are logged into MIMmatch.

2. When you sign into MIMmatch from the MIMmatch option on the black bar at the top of every OMIM.org page, you will be taken to your MIMmatch dashboard page. From this page, you can check the box to be notified of new gene-phenotype relationships and will see three tabs: (1) MIM Entries Flagged for following or sharing interest; (2) Phenotypic Series Flagged for following updates to phenotypic series; and (3) Saved Searches.

3. Once you have established a MIMmatch account and are logged in, you can populate your MIM Entries Flagged when you search OMIM. For example, from a search of `+hypogonadism +microcornea`, you can select "Notify me on update" or "Share my interest" by clicking on the MIMmatch link below the desired entry. You can view others who have chosen to share their interest on this entry from the "Others interested in this entry" link below the MIM titles on a search retrieval page (Fig. 1.2.11). The MIMmatch options also appear below the Table of Contents in the full entry (Fig. 1.2.3).

4. The "Save search" option supports an easy way to perform the same query of OMIM on a regular basis. A query can be saved by selecting "Save search" from the *Options* link to the right of the search box.

COMMENTARY

Background Information

OMIM entries are based on the peer-reviewed biomedical literature and are expertly curated into structured entries. These executive summaries are a great place to learn about genes and phenotypes, and users are encouraged to explore the copious links both within OMIM entries and to the many linked external resources. Should a user have additional questions about specific information in an OMIM entry, there are links directly to the source reference for further investigation and clarification. The knowledgebase is updated nightly, and the Web site is designed to display on desktop, tablet, and mobile devices.

Alternative Data Access Options: Download and API

From the Downloads link on the black bar, users can access `mim2gene.txt`, a tab-delimited file linking MIM numbers with NCBI Gene IDs, Ensembl Gene IDs, and HGNC Approved Gene Symbols. Access to additional OMIM data and the API are available after registration. The API is robust and includes the functionality of the Web site.

Online help that is specific for API use is available under the Help menu option on the black menu bar at the top of the page.

Acknowledgement

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Description of phenotype nosology and gene-phenotype ascertainment.

Internet Resources

http://omim.org
The OMIM Web site.

http://omim.org/help/faq
Frequently asked questions (FAQ) about OMIM.