Question 11

An investigator has identified and cloned a human gene, but no corresponding mouse ortholog has yet been identified. How can a mouse genomic sequence with similarity to the human gene sequence be retrieved?

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For purposes of this example, assume that the user does not already have the human sequence of interest to hand. The first step will be to locate the human gene of interest using the UCSC Genome Browser. Begin by pointing to the UCSC Genome Browser home page, at <http://genome.ucsc.edu>. Select *Human* from the *Organism* pull-down menu and then click on *Browser*; both are located on the blue navigation bar at the left side of the page. This will take the user to the Human Genome Browser Gateway. Select the *Dec. 2001* version of the UCSC genome assembly, type the gene symbol 'AGPS' into the *position* box, and then click *Submit*. On the resulting page, follow the link for AGPS in the *Known Genes* section.

The result of the search on AGPS is shown in Fig. 11.1. In the main figure are a series of 'tracks', which are labeled along the left-hand side. The *Known Gene* track is for AGPS, corresponding to the query. Clicking on AGPS returns a summary of information on that gene, including the full name of the protein product (alkylglycerone phosphate synthase precursor), a link to the GeneCards database at the Weizmann Institute²⁰ and links to the translated protein, mRNA and genomic sequences. Focus now on the track labeled *Mouse Translated Blat Alignments*. What is shown in this track are the results of aligning the November 2001 version of the mouse genome assembly with the human genome using the program BLAT⁸ in its translated protein mode. More details about the BLAT algorithm and about how the mouse BLAT track is automatically generated can be found by clicking on the *Mouse Blat* hyperlink found below the main graphical display.

Click anywhere within the *Mouse Blat* track to expand the single BLAT track so that it now shows each individual mouse sequence that aligns with human sequence in the region of inter-

est (Fig. 11.2). Especially in a translated mode, mouse and human gene sequences are usually more similar in exons than in introns. Look carefully at the two alignments that derive from a mouse sequence called *chr3 81178k* (Fig. 11.2, arrow). On the *Mouse Blat* track, the brown vertical lines represent alignments and the horizontal lines are gaps. These alignments correspond to the blue vertical lines indicating the exons of AGPS on the *Known Genes* track.

To see the kind of information available for a translated BLAT alignment, click on the mouse genomic sequence labeled *chr3 81178k*. The resulting page (Fig. 11.3) provides the details of the alignment of the trace with the human genome assembly. This mouse genomic sequence is 607 nt in length and aligns with the human sequence in eight blocks. Within the blocks, the mouse and human sequences are 78% identical. To view the alignment itself, click on the *View details of parts of alignment*. . . link. On the resulting page (Fig. 11.4), the mouse sequence is shown on top, with the region of alignment in blue. The human genomic sequence is shown next, and a side-by-side alignment of the human and mouse sequences is at the bottom of the web page (not shown).

The NCBI's UniGene_Mouse map shows alignments of mouse mRNA and EST sequences with the human genome. Add this map using *Maps & Options* (Fig. 3.9). The easiest way to find the mouse ortholog of a human gene is probably to use Ensembl's precomputed *Homology Matches*. These matches, where available, link directly from a human gene to a putative mouse homolog (Fig. 1.9).

Figure 11.1

Figure 11.2

Figure 11.3

Mouse Translated Blat Alignments

Mouse position: chr3:81178397-81179004
 Mouse size: 607
 Human position: chr2:176950263-176988838
 Human size: 38575
 Bases in aligning blocks: 481
 Number of Aligning Blocks: 9
 Percent identity within aligning blocks: 78.1%
 Browser window position: chr2:176843392-176988896
 Browser window size: 145504
[View details of parts of alignment within browser window](#)

Description

This track displays alignments of the mouse genome vs. the human genome.

Methods

The alignments were done with BLAT in translated protein mode using the parameters `-q=dmx -t=dmx` and otherwise the default settings. Both genomes were masked with RepeatMasker and Tandem Repeat Finder before running BLAT. Places where more than 250 alignments happened over the same place were filtered out. Beware of alignments of greater than 97% identity: these may reflect mouse contamination in the human genome or human contamination in the mouse genome.

Data Release Policy

This data is made available before scientific publication with the following understanding:

1. The data may be freely downloaded, used in analyses, and repackaged in databases.
2. Users are free to use the data in scientific papers analyzing particular genes and regions if the providers of this data (the Mouse Sequencing Consortium) are properly acknowledged.
3. The Centers producing the data reserve the right to publish the initial large-scale analyses of the dataset including large-scale identification of regions of evolutionary conservation and large-scale genomic assembly. Large-scale refers to regions with size on the order of a chromosome (that is, 30 Mb or more).
4. Any redistribution of the data should carry this notice.

Figure 11.4

Alignment of Mouse.chr3

Mouse.chr3 genomic block1 block2 block3 block4 block5 block6 block7 block8 together

Mouse.chr3

AGcATAGCCA CACTACTGTT cGAGGGaGAc GGTGAGAAGG TTCTTCAGCA caAAAA aca 81178457
 agcagatgac atcaacagaa agtttggt G cctGGGCACTT GGAGAACTTA AgGACACAG 81178517
 cGCTGATG CACACATGTC CACTGACAA CAGGcGAc TTGGGTTTG ANATATATAC 81178577
 AATAGGAGAA TCCTTTTGA GA CTTCGCTCC TTGGGcCAG GTtTAGATTC TgtTAGAAAT 81178637
 TGTAAAGAG AGATTAAGhA GGAATcGhA AGAAAGcAA GcTgAGTTTG CcCTcAcATC 81178697
 TAChA cAGG GTtATGChA tGTtATGATC AGGcGcATG ANTCGCTCT ATTTTCCTCT 81178757
 TAACACAGG GGAATAGTG ACCCACTGAC gaacagact gag CAGCTG CTAAGAGAG 81178817
 AATCTCTTSC AATGAGGGA GCCTGcCACE TCACCATGGT AGhCAGAT TACGAAAGCA 81178877
 GTGCTTAGAG GAGATGCTCT CTGATCTCCT CTCTGGGATG CTAAAGCTCT TCAGhAGhTA 81178937
 TTGAGACCC AGTtACATCT TTGGAACAG AAACCTTTTA TAAGcCATT AATtACATTA 81178997
 tgAAAA

Human.chr2:

cGtTAGCCA CACTACTGTT tGAGGGGAT cGTGAGAAGG TTCTTCAGCA tgAAAA aca 176950323
 tGttagatga ttgtgcaaaa atttgggtat ggttccaagt tcataatgac aagagaaga 176950383
 gtcaaaagct aagatctcaa tctcccaag caattatcaa agtactagag abtaagtct 176950443
 ccaaacagac tgcagtctc aaagttagta ttaatttcag tttagtgta aatttgggt 176950503
 aatttatgat agtaaaccta aaatattgtt ttgttttaca tccagaatt ttgagaagt 176950563
 aagatgatat gttgctctgt tcataatcaa tatattatat tattaacact tgtatttct 176950623
 ctgatttttt acattaatgt caatttcacg atatttgctc tactagatga aatagagaa 176950683
 ttcaattgct tcattactgt ttgtgataat agttagtga taagcgtgc tactagtgt 176950743
 tttttaaaag gaatttggt tttaactgaag gtatttgata aatttatcat actgcaccc 176950803
 ctgtacatta ttgtttgtgt ctgttataaa gaacagaaa acatttcaa tctataaca 176950863
 actgaataat ggtaggggtg ttctctctgt ttcttttgat ggtattataa actgattgat 176950923
 gagaactata gtgaaaagc cattatcac gactagtgt ttctcttccc tttaaaagt 176950983
 catabaacaa cagttctag acactaacct ttcttttttt gatttcaggt abtaaaat 176951043
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 ttgtttttta agaaacaaa tgaacanta atttgaccc atgtgtttta gaatgoccca 176951163
 ctlttatgta tttttttcca tctataaat tagccttca tctctaggtt tgtctpaatt 176951223
 tagtgttaac gtgcagatt cttaaaaggg aaatagctct aactctagac ttaatttita 176951283
 ttcttttttt gactatttt taagtattga aaagtctca cttttaccct attctgaat 176951343
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 ctgcataagt gttttggaaa ttgtgtat tttaactaaa tcaatataa atatttgtg 176951463
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 agactgaagc tttaaaaaat tgtcattgt gtatttaaat attacttgtt atttcataat 176951763
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 gtatatagag tttaatttgc ttagtctac ctagctgtc tctctgtca caaacact 176951883
 cacatgtga caaacacca caacagagg aatttcagtt tttaggatct attcttata 176951943
 tttaacttaa ttatgtctag taactatata ctagttagta atgtgtcaac ttctctgta 176952003
 gaabgggtta ggtgtgtgt ataatgtgt ttgttgtgga ctaataatt tttagggga 176952063
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 tataatgaa ttctttttaa aatatgcat ccaagtgcct tcaagatcgt caacttagc 176952723
 ccaagacta ttgtgtact tctagagtt ttgtctact aaacaaaact tgaataaat 176952783
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 tgaagacac