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Nematode Gene Sequences: Update for December 2003

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The molecular characterization of parasitic nematodes and development of novel control strategies can benefit from genomic approaches. The high-throughput generation of expressed sequence tags (ESTs) from numerous nematode cDNA libraries is now providing thousands of new gene sequences, and their availability in public databases will facilitate broad characterization of their function. A project at Washington University's Genome Sequencing Center is nearing the completion of 235,000 5′ ESTs from 28 nematode species (227,272 ESTs as of October 2003). Another 32,078 ESTs from seven species have been contributed by a sister project at the Sanger Institute and Edinburgh University. Sequences are immediately submitted to the database of expressed sequence tags (dbEST) at GenBank and are also available from specialized Web sites (Table 1A). Nematode ESTs have diverse applications (e.g., Blaxter et al., 2002; Jasmer et al., 2001; Murray et al., 2001; Pleasance et al., 2003; Scholl et al., 2003; Srinivasan et al., 2002), and strategies for their use have been reviewed (Blaxter et al., 1999; Grant and Viney, 2001; Marra et al., 1998; McCarter et al., 2000; Parkinson et al., 2001; Parkinson et al., 2003).

Here we provide an update on the availability of nematode ESTs and genomes. Since our June 2002 report (McCarter et al., 2002) 153,750 new nematode ESTs have been submitted to dbEST including 129,818 from parasites. A review by Parkinson et al. (2003), focusing on NEMBASE and NemaGene clustering also provides EST totals from November 2002. *Caenorhabditis elegans* has long been a focus of genome studies (The *C. elegans* Sequencing Consortium, 1998), and 42% of all nematode ESTs are from *C. elegans* (Kohara, 1996; McCombie et al., 1992; Waterston et al., 1992). The 300,497 ESTs from 34 nematode species beyond *Caenorhabditis* include sequences from 22 mammalian parasites, 10 plant parasites, and two free-living bacteriovores (Table 2). For most species, ESTs dominate the conventionally submitted nucleotide and protein sequences in GenBank. ESTs are redundant, with common mRNAs being highly represented. Extrapolating from initial clustering of ESTs in 12 species, the 300,497 ESTs likely represent no more than 100,000 genes. For example, clustering of 12,269 ESTs from *Onchocerca volvulus* formed 4,208 groups (Williams et al., 2002), and 5,713 ESTs from *Meloidogyne incognita* formed 1,625 clusters (McCarter et al., 2003). New gene discovery can be maximized by sampling multiple cDNA libraries produced from different stages and tissues. In *Strongyloides stercoralis,* for example, several thousand ESTs were generated from both first (L1) and third (L3) larva stages. Despite redundancy within each library, only 12% of clusters contained ESTs from both stages (Mitreva et al., 2003). Generating two distinct libraries per source can also substantially increase the pool of identified transcripts. For example, *Ancylostoma caninum* L3 libraries produced by an SL1 splice leader PCR protocol vs. a modified SMART™ protocol and sequenced to a depth of ~800 and ~2,800, respectively, found only 3.5% overlap (Mitreva, unpubl.). *Ancylostoma caninum* clusters, along with those from seven other species, are searchable on www.nematode.net, a Web-accessible resource for investigating nematode gene sequences (Fig. 1). Among its features, the site provides NemaGene EST cluster consensus sequences, enhanced online BLAST search tools, functional classifications of cluster sequences, and instructions for clone requests (Wylie et al., 2003). Hundreds of cDNA clones have been provided to 37 nematologists in 12 countries.

Plant-parasitic nematode ESTs have been generated from root-knot nematodes (five species, 54,483 ESTs) (Dautova et al., 2001; McCarter et al., 2003), cyst nematodes (four species, 30,698 ESTs) (Popeijus et al., 2000), and one migratory endoparasite, *Pratylenchus penetrans* (1,928 ESTs, in preparation). Representation of multiple life-stages is improving with 20,114 ESTs now available from five life stages for *Heterodera glycines* (egg, J2, J3, J4, virgin female) and sequencing from five life stages of *Meloidogyne* species in progress. However, plant-parasitic nematode genomics is still a nascent field. Within clade IVB (Blaxter et al., 1998), sampling has yet to occur from most migratory *Tylenchida* species. Virtually no sequence information is available from the distant clade II nematodes including the *Dorylaimida* and *Triplonchida* parasites. Perhaps the most visible gap hindering the field is the lack of a draft or complete plant-parasitic nematode genome. The recent announced opening of the National Science Foundation/

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TABLE 1. Web sites for nematode genomics

1A. Nematode ESTs Resources	
GenBank dbEST	www.ncbi.nlm.nih.gov/dbEST
Genome Sequencing Center ESTs and NemaGene Clusters	www.nematode.net
Blaxter Lab ESTs and Clusters, Nembase	www.nematodes.org
EMBL Parasite Genome Server	www.ebi.ac.uk/parasites/parasite-genome.html
The Filarial Genome Network	http://circuit.neb.com/fgn/ests.html
1B. *Caenorhabditis* Genome Resources	
Wormbase	www.wormbase.org
C. elegans WWW Server	http://elegans.swmed.edu
Sanger Centre—Wormpep, *C. elegans* and *C. briggsae* Projects	www.sanger.ac.uk
Genome Sequencing Center—*C. elegans* and *C. briggsae* Projects	http://genome.wustl.edu

TABLE 2. Nematode species with more than 50 ESTs registered in the GenBank dbEST database, October 2003.

Nematode species	ESTs 3/97	ESTs 12/00	ESTs 6/02	ESTs 10/03	Other GenBank entries 10/03	Major EST sources
Caenorhabditis elegans	30,196	109,215	191,268	215,200	96,850	1, 2, 11
Ascaris suum	0	588	24,492	39,242	426	2, 3, 6
Brugia malayi	7,496	22,392	22,439	26,215	18,449	3, 4, 5
Haemonchus contortus	0	2,399	4,906	21,967	552	3, 6, 9, 10
Heterodera glycines	0	1,506	4,327	20,114	366	2
Meloidogyne hapla	0	0	6,157	16,305	38	2
Onchocerca volvulus	310	13,802	14,922	14,974	791	5, 2
Strongyloides ratti	0	0	8,645	14,761	23	2
Meloidogyne incognita	0	6,626	10,899	14,081	239	2, 7
Meloidogyne chitwoodi	0	0	0	12,218	38	2
Strongyloides stercoralis	57	10,922	11,392	11,392	55	2
Trichinella spiralis	0	0	4,247	10,767	162	2
Ancylostoma ceylanicum	0	0	2,690	10,651	73	2
Ancylostoma caninum	0	5,546	7,656	9,331	112	2
Pristionchus pacificus	703	4,989	8,818	8,818	15	2
Parastrongyloides trichosuri	0	0	7,963	7,963	3	2
Ostertagia ostertagi	0	0	5,591	7,009	189	2, 3, 6
Meloidogyne javanica	22	1,208	5,600	6,861	55	2
Globodera rostochiensis	0	894	5,934	5,934	152	2, 7, 8
Meloidogyne arenaria	0	0	3,334	5,018	49	2
Toxocara canis	8	519	3,920	4,889	85	2, 3
Necator americanus	0	211	961	4,766	168	3, 6
Teladorsagia circumcincta	0	0	315	4,313	125	3, 6
Dirofilaria immitis	0	0	0	4,005	170	2
Trichuris vulpis	0	0	0	3,063	1	2
Trichuris muris	0	301	2,125	2,716	315	3, 6
Heterodera schachtii	0	0	0	2,818	26	2
Caenorhabditis briggsae	2,424	2,424	2,424	2,424	1,151	2
Wuchereria bancrofti	119	131	131	2,166	77	5
Pratylenchus penetrans	0	0	0	1,928	21	2
Globodera pallida	0	94	1,832	1,832	66	12
Ascaris lumbricoides	0	0	0	1,822	138	3
Nippostrongylus brasiliensis	0	0	734	1,234	37	3
Litomosoides sigmodontis	0	198	198	873	33	3
Zeldia punctata	0	378	391	391	5	2
Onchocerca ochengi	0	60	60	60	13	5
Meloidogyne paranaensis	0	0	0	Pending	0	2
Total sequences	41,335	184,403	364,371	518,121	121,068	
Total non-*Caenorhabditis*	8,715	72,764	170,679	300,497	23,067	

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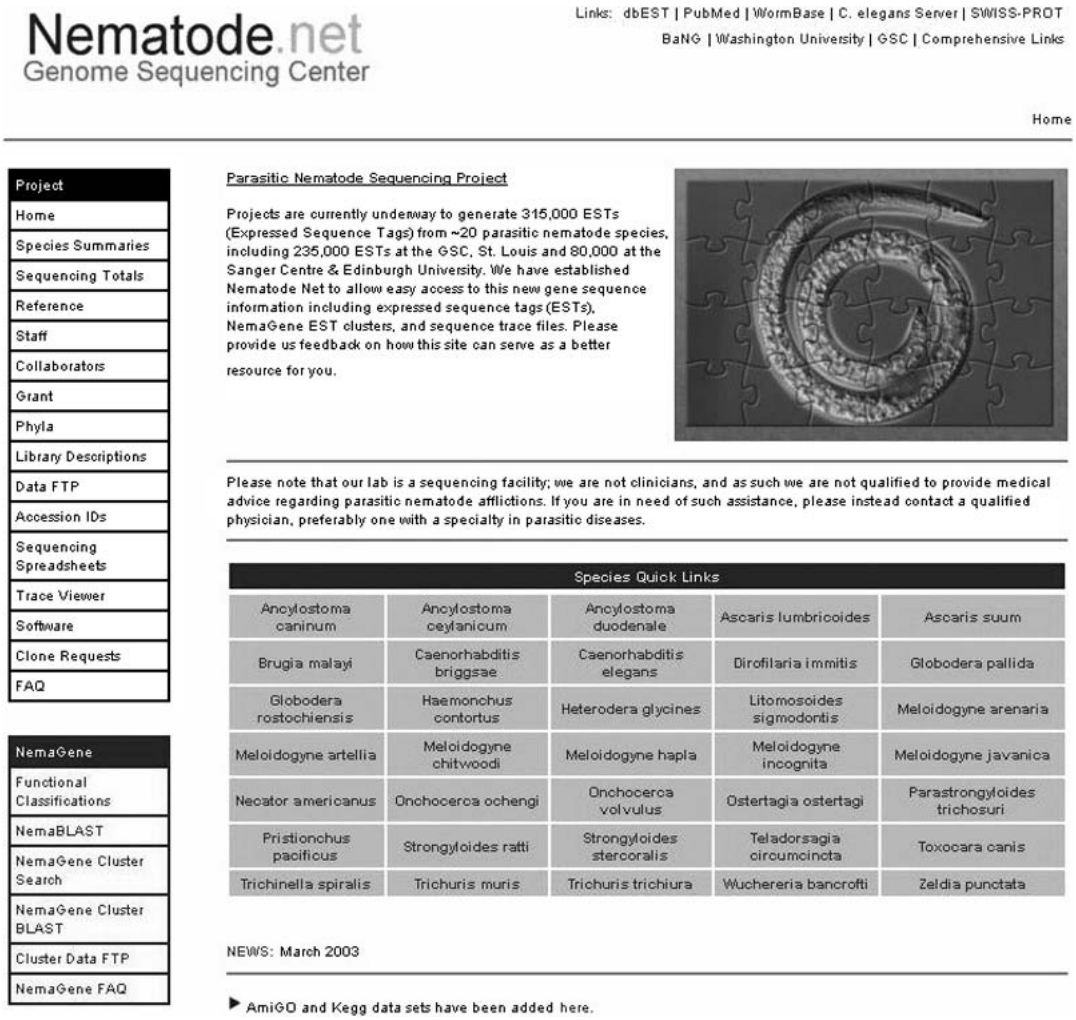

FIG. 1. Nematode.net Homepage.

U.S. Department of Agriculture Microbial Genome Sequencing Program to proposals for nematode genomes may mark a significant step toward this goal (www.nsf.gov/pubsys/ods/getpub.cfm?ods_key=nsf03603).

There are 204,179 ESTs available from human- and animal-parasitic nematodes, and analyses of many species have been completed (Allen et al., 2000; Blaxter 2000; Blaxter et al., 1996, 2002; Daub et al., 2000; Hoekstra et al., 2000; Lizotte-Waniewski et al., 2000; Maizels et al., 2000; Moore et al., 1996; Tetteh et al., 1999; Unnasch and Williams, 2000). Marking the first generation of a draft genome sequence from a parasitic nematode, the human-filarial parasite *Brugia malayi* has now been sequenced to 8X draft coverage by the Institute for Genomic Research with funding from the National Institute of Allergy and Infectious Diseases (www.tigr.org/tdb/e2k1/bma1/). Publication and data release are expected in 2004.

For most parasitic nematodes, comparison to the complete *C. elegans* genome is more informative than comparison to any species' sequence (Bird et al., 1999; The *C. elegans* Sequencing Consortium, 1998). Analysis of the 2,826 *S. stercoralis* clusters with significant BLAST homologies in other species ($<10^{-5}$) (Altschul et al., 1990), for example, found *C. elegans* homologs for 90%, and these homologs were typically the top-ranking match available (Mitreva et al., 2003). Among the 1,280 *M. incognita* clusters with homologs in other species, 85% had matches in *C. elegans* (McCarter et al., 2003). *Caenorhabditis elegans* information is easily accessible from several sources (Table 1B) and includes the complete cell lineage, a map of its neuroanatomy, an extensive genetic map, predicted exon/intron structure and translation products for all of its genes, and expression information for most genes. Mapped genetic mutations and publications on various aspects of *C. elegans* molecular biology number in the thousands. The discovery of RNA interference in *C. elegans* (Fire et al., 1998) has allowed systematic knockout of most of the worm's genes, defining mutant phenotypes for more than 1,700 genes (Fraser et al., 2000; Gonczy et al., 2000; Kamath et al., 2003; Maeda et al., 2001; Piano et al., 2002). RNA interference is also effective in some parasitic nematodes (Aboobaker and Blaxter, 2003; Hussein et al., 2002; Urwin et al., 2002). The *C. briggsae* genome was sequenced to 10X draft coverage and

made available in July 2002 by the groups at Washington University and the Wellcome Trust Sanger Institute that completed the *C. elegans* genome (ftp://ftp.sanger.ac.uk/pub/wormbase/cbriggsae/). Whole genome comparisons between *C. elegans* and *C. briggsae* (Kent and Zahler, 2000; Le et al., 2003; Webb et al., 2002; Witherspoon and Robertson, 2003) as well as *C. elegans* and *B. malayi* (Guiliano et al., 2002) have begun.

DNA sequence information, along with the tools of comparative and functional genomics, has the potential to further accelerate discovery in molecular nematology and parasitology in the years ahead. We will continue to provide periodic updates on the status of nematode genomics as the sequence data sets continue their rapid expansion.

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