transgenic flies fed increasing doses of either AK-1 or AGK2 had a striking dose-dependent rescue of dorosomedial neurons (Fig. 4, H and I). No change occurred in steady-state levels of α-Syn after administration of the SIRT2 inhibitors (fig. S5).

Rescue via inclusion enlargement, and the concomitant reduction in total surface area of inclusions, agrees with a cytotoxic role of aggregates (19) and suggests a mechanistic basis for the effect of SIRT2 inhibition—that it reduces aberrant interactions of aggregates with cellular proteins. Conceivably, coalescence of misfolded proteins into larger inclusions may lower the concentration of toxic, submicroscopic α-Syn oligomers, thereby leading to the rescue of proteasome dysfunction. Indeed, the formation of large β-amyloid aggregates is protective against proteotoxicity in Caenorhabditis elegans (20).

The exact mechanism whereby SIRT2 inhibition affects α-Syn aggregation remains uncertain. Increased α-tubulin acetylation is associated with microtubule stabilization, and α-Syn has been reported to interact with α-tubulin as well as the microtubule-binding proteins MAPB1 and tau (21, 22). One possibility is that the increase in acetylated α-tubulin resulting from SIRT2 inhibition may stimulate aggregation of α-Syn through its affinity to microtubules. Moreover, microtubule stabilization itself could be an important factor contributing to neuroprotection. A neuroprotective role for another microtubule deacetylase, HDAC6, was recently proposed, although the protective mechanism is unclear (23–25). Our data are consistent with the recent observation that α-Syn–dependent inhibition of histone acetylation is associated with increased neurotoxicity (4). Thus, SIRT2 targeting may be therapeutically beneficial in other diseases where aggregation of misfolded proteins is central to disease pathogenesis.

The exact mechanism whereby SIRT2 inhibition affects α-Syn aggregation remains uncertain. Increased α-tubulin acetylation is associated with microtubule stabilization, and α-Syn has been reported to interact with α-tubulin as well as the microtubule-binding proteins MAPB1 and tau (21, 22). One possibility is that the increase in acetylated α-tubulin resulting from SIRT2 inhibition may stimulate aggregation of α-Syn through its affinity to microtubules. Moreover, microtubule stabilization itself could be an important factor contributing to neuroprotection. A neuroprotective role for another microtubule deacetylase, HDAC6, was recently proposed, although the protective mechanism is unclear (23–25). Our data are consistent with the recent observation that α-Syn–dependent inhibition of histone acetylation is associated with increased neurotoxicity (4). Thus, SIRT2 targeting may be therapeutically beneficial in other diseases where aggregation of misfolded proteins is central to disease pathogenesis.

The near eastern origin of cat domestication

Carlos A. Driscoll,1,2*, Marilyn Menotti-Raymond,1 Alfred L. Roca,3 Karsten Hupe,4 Warren E. Johnson,1 Eli Geffen,5 Eric H. Harley,6 Miguel Delibes,7 Dominique Pontier,8 Andrew C. Kitchener,9,10 Nobuyuki Yamaguchi,2 Stephen J. O’Brien,2* David W. Macdonald2*

The world’s domestic cats carry patterns of sequence variation in their genome that reflect a history of domestication and breed development. A genetic assessment of 979 domestic cats and their wild progenitors—Felis silvestris silvestris (European wildcat), F. s. lybica (Near Eastern wildcat), F. s. ornata (central Asian wildcat), F. s. cafa (southern African wildcat), and F. s. bieti (Chinese desert cat)—indicated that each wild group represents a distinctive subspecies of Felis silvestris. Further analysis revealed that cats were domesticated in the Near East, probably coincident with agricultural village development in the Fertile Crescent. Domestic cats derive from at least five founders from across this region, whose descendants were transported across the world by human assistance.

The domestic cat may be the world’s most numerous pet, yet little is certain of the cat’s origin (1–9). Archaeological remains and anthropological clues suggest that, unlike species domesticated for agriculture (e.g., cow, pig, and sheep) or transport (horse and donkey), the cat probably began its association with humans as a commensal, feeding on the rodent pests that infested the grain stores of the first farmers (1). The earliest evidence of cat-human association involves their co-occurrence in Cyprus deposits determined to be 9500 years old (6). Domestic cats are generally considered to have descended from the Old World wildcats, but they differ from these hypothesized progenitors in behavior, tameness, and coat color diversity (9, 10). Further, domestic cats appear to lack neotenic characteristics typical of other domesticated species (11).

Felis silvestris, from which domestic cats were derived, is classified as a polytypic wild species composed of three or more distinct interfertile subspecies: F. s. silvestris in Europe, F. s. lybica in Africa and the Near East, F. s. ornata in the Middle East and central Asia (1, 2, 12–15), and possibly the Chinese desert cat, F. s. bieti (Fig. 1A, inset). The domestic cat is sometimes considered an additional subspecies, F. s. catus, possibly derived from wildcats in the Middle East or Egypt (1, 12, 14, 15). The imprecise subspecific status of F. silvestris populations and of the relationship of the domestic cat within this assemblage stems from morphological similarities among these groups (1, 13). A feral domestic cat with a “wild-type” mackerel tabby pattern is difficult to distinguish visually from a “true” wildcat (15, 16), which is further confounded by ongoing admixture (16–19). Moreover, the relationship between F. silvestris and the Chinese desert cat—which may be a

1Laboratory of Genomic Diversity, National Cancer Institute, Frederick, MD 21702, USA. 2Wildlife Conservation Research Unit, Department of Zoology, University of Oxford, Oxford OX1 3PS, UK. 3Laboratory of Genomic Diversity, SAIC-Frederick Inc., NCI-Frederick, Frederick, MD 21702, USA. 4JagdEinrichtungBüro, Am Sahibach 9a, 37170 Fürstenhagen, Germany. 5Department of Zoology, Tel Aviv University, Tel Aviv 69978, Israel. 6Division of Chemical Pathology, University of Cape Town, Observatory 7925, Cape Town, South Africa. 7Department of Applied Biology, Estación Biológica de Doñana, CSIC, Avda María Luisa s/n Pabellón del Perú, 41013 Sevilla, Spain. 8UMR-CNRS 5538 Biomatére et Biologie Evolutive, Université Claude Bernard Lyon 1, 43 boulevard du 11 novembre 1918, 69622 Villeurbanne, France. 9Department of Natural Sciences, National Museums Scotland, Chambers Street, Edinburgh EH1 1JF, UK. 10Institute of Geography, School of Geosciences, University of Edinburgh, Drummond Street, Edinburgh EH8 9XP, UK.

To whom correspondence should be addressed. E-mail: obrien@ncifcrf.gov; driscoll@ncifcrf.gov; david.macadonald@zoolgy.oxford.ac.uk

References and Notes

www.sciencemag.org/cgi/content/full/1143780/DC1
Materials and Methods
Figs. 51 to 55
References
13 April 2007; accepted 8 June 2007
Published online 21 June 2007; 10.1126/science.1143780
Include this information when citing this paper.

www.sciencemag.org
**Fig. 1.** (A) Current range of *F. silvestris* and areas of sample collection. Colored regions reflect the location of capture of individuals carrying different STR clade genotypes (defined at lower left). mtDNA haplotype frequencies are indicated in pie charts specifying the number of specimens carrying mtDNA haplotypes for each clade. Central Asian denotes Asian cats east of the Caspian Sea. Near Eastern denotes cats in Israel, Saudi Arabia, Bahrain, and the United Arab Emirates. European denotes specimens collected west of the Caspian Sea. Domestic cats (*F. s. catus*) are distributed worldwide and overwhelmingly carry clade IV mtDNA haplotypes (beige). Inset: Current and historical range of *F. silvestris* subspecies on the basis of traditional morphology-based taxonomy (2,12,13). The Chinese desert cat is referred to throughout as a wildcat subspecies, *F. silvestris bieti* (9,12), as supported by data presented here. (B) Phenogram of 851 domestic and wild specimens created on the basis of STRs, Dps genetic distance, and minimum evolution (neighbor-joining) algorithm. Color groups correspond to geographic locales specified in (A). Symbols indicate cytonuclear-discordant individuals that contain a STR composite clade of the indicated cluster but carry mtDNA of an alternative locale (see text); in parentheses are the numbers of cats in each STR clade that carry various mtDNA clade haplotypes.
separate Felis species, Felis bieti, or a wildcard subspecies, F. silvestris bieti (9, 12)—is uncertain. The sand cat F. margarita, a distinct species of Felis that ranges across North Africa and the Middle East, is the closest outgroup of the F. silvestris/bieti complex on the basis of morphological and molecular data (12, 13, 20).

To investigate the relationships among domestic cats, their indigenous wild progenitors, and related species of the genus Felis, we collected tissue from 979 individuals (fig. S1; see table S1 for breakdown of number of cats tested for different genetic markers) including putative wildcats and feral domestic cats on three continents (N = 629), fancy-bred domestic cats (N = 112), sand cats (F. margarita, N = 11), and Chinese desert cats (F. s. bieti, N = 5). We extracted DNA and genotyped 851 cats for 36 short tandem repeat (STR) or microsatellite domestic cat loci (21) variable in F. silvestris, F. s. bieti, F. margarita, and domestic cats, and sequenced 2604 base pairs (bp) of mitochondrial DNA (mtDNA) genes ND5 and ND6 from 742 cats.

Neighbor-joining phylogenetic analyses for STR genotypes with kinship coefficient (DKf) and proportion of shared alleles (Dps) genetic distance estimators provided concordant topologies that specified six clusters (Fig. 1B; referred to here as “clades” as also specified by mtDNA phylogenetic analyses; see below) corresponding to the following subspecies designations: (i) F. s. silvestris, wildcats from Europe (STR clade I, green in Fig. 1); (ii) F. s. ornata, wildcats from central Asia east of the Caspian Sea (STR clade III, purple); (iii) F. s. lybica, wildcats from the Near East (STR clade IV, beige); (iv) F. s. cahra, wildcats from southern Africa (STR clade II, blue); (v) F. s. bieti, Chinese desert cats (STR clade V, red); and (vi) F. s. margarita, sand cat (STR clade VI, black). Felis cahra was first named in 1822 and renamed as F. lybica cahra subspecies in 1944 on the basis of a description of a wildcat specimen captured in “Kaffariya” (9), an area from whence our southern African wildcat samples derive.

The composite STR genotypes of all known domestic house cats, fancy-bred cats, and feral domestic cats occurring in the wild populations all fell within a large monophyletic group (clade IV) that also included wildcats from the Near East. The phylogenetic tree suggests that domestication occurred in the Near East, where STR clade IV wildcats live today. This inference was further explored by examining mtDNA variation, STR variation, and ongoing admixture hybridization in the study areas (17–19).

Phylogenetic analysis of ND5 and ND6 sequence reveals 245 parsimony-informative sites specifying 176 distinct mtDNA genotypes (Fig. 2A, fig. S2, and table S2). The mtDNA haplotypes were analyzed with Bayesian Markov chain Monte Carlo (MCMC), maximum parsimony, maximum likelihood, and distance-based methods (22, 23). All methods resulted in identical topologies for the principal groupings corresponding to both geographic origins and STR clade designations. The consensus mtDNA gene tree (Fig. 2A), rooted with F. margarita, shows F. s. bieti basal to F. silvestris, as inferred from morphology. However, the short branch lengths and relatively weak bootstrap support for the node separating F. s. bieti from F. silvestris (27 to 68% bootstrap) indicates a close genetic relationship between these two taxa, which supports the grouping of F. s. bieti and F. silvestris as a single species, F. silvestris.

The F. silvestris mtDNA haplotypes fall into specific geographic locales (Fig. 2A). A basal lineage (clade I, F. s. silvestris (European wildcat), green) is found in European populations from Scotland and Portugal in the west to Hungary and Serbia in the east and is sister to F. silvestris from Asia and Africa and to domestic cats. An early/basal European versus Africa-Asia divergence supported by recent morphological studies of fossil specimens of wildcats (15, 24) may reflect a postglacial repopulation of Europe from Iberian founders, as previously suggested (9, 15, 24). The basal position of an Iberian wildcat, Fsi-257, within mtDNA clade I also supports an Iberian refugium (Fig. 2A).

Beyond Europe, mtDNA clades II, III, and IV correspond with geography and STR analysis (Fig. 2A). Within mtDNA clade IV, we identified five principal lineages of mtDNA haplotypes (A to E, Fig. 2A) with no obvious phylo-geographic association among these lineages. Domestication appears to have occurred within the Near Eastern region where clade IV wildcats are currently extant (beige, Fig. 2A), because clade IV wildcats and domestic cats are monophyletic.

Because of hybridization between wildcats and feral domestic cats, domestic cat mtDNA haplotypes (clade IV in Fig. 2A) are commonly found in European, African, and central Asian populations along with indigenous wildcat haplotypes (Fig. 1A). The observed genetic admixture may be explained by the presence of feral domestic cats or by hybridization between wildcats and domestic cats. Hybrid individuals carrying one mtDNA-clade genotype but a different STR-clade genotype can be identified. Such cytonuclear-discordant individuals were common in our data set (Figs. 1B and 2A). Of cats sampled for both STR and mtDNA genotypes, seven of the 472 cats in STR clade IV were discordant, with a wildcat mtDNA type (Fig. 1B). However, among 108 putative European wildcats (on the basis of STR genotype; Fig. 1B), 28 carried the clade IV (domestic) mtDNA type, as did 3 of 13 southern African (STR clade II) wildcats. The wildcats in central Asia (STR clade III) included the highest frequency of discordant individuals (mtDNA clades III and IV; Fig. 1B), perhaps as a result of incomplete lineage sorting or recent gene flow between adjacent populations (Fig. 2A).

We implemented the Bayesian population genetic analysis program STRUCTURE, which assesses population subdivision (25) and characterizes genomic evidence of recent hybridization. STRUCTURE analyses of the 851 STR genotypes placed cats into discrete population clusters corresponding to European, African, and central Asian wildcats and identified a subdivision of domestic cats from different regions (Fig. 2B). Interestingly, we identified a discrete population of wild and domestic cats from the Near East (brown group in Fig. 2B) distinct from the other F. silvestris subspecies, as well as three subgroups of domestic cats. These 15 individuals had concordant mtDNA and STR phylogenies identical to those of domestic cats and were collected in remote deserts of Israel, United Arab Emirates, Bahrain, or Saudi Arabia. These data suggest that these Near Eastern wildcats may represent the ancestral founder population of domestic cats, supporting a domestication origin in the Near East.

Identification of hybrids (STRUCTURE Q < 0.8) revealed that some (~22%) of the identified cytonuclear-discordant cats in Figs. 1B and 2A showed evidence of recent hybridization. For this reason, we removed 81 hybrid cats defined by STRUCTURE and generated new phylogenies combining the STR genotypes of cats grouped within the distinct populations (Fig. 2C). This analysis reaffirms the recognition of the major F. silvestris subspecies groups illustrated in Fig. 1A and the distinctiveness of Near Eastern wildcats as the closest group to all domestic cats. The results also suggest a close affinity between F. s. bieti (Chinese desert cat) and the Asian wildcats, plus paraphyly of other F. silvestris subspecies with respect to F. s. bieti, in support of the recognition of F. s. bieti as a subspecies of F. silvestris (Fig. 2C).

The coalescence-based age of mtDNA ancestral nodes for domestic cats (clade IV) and all F. silvestris mtDNA lineages was estimated with the linearized tree method (26). After fulfilling the requirement for molecular clock rate homogeneity across all lineages (table S4), we constructed a neighbor-joining algorithm on the basis of the linearized tree with Kimura two-parameter distances. We adopted a sequence divergence rate specific for ND5 and ND6 genes of 2.24 bp per million years (27). This rate would predict one new variant, on average (range: 0 to 2), in the most recent 17,000-year period of domestic cat ancestry (28). Indeed, 90% of the domestic cats within the five lineages (A to E in Fig. 2A) share haplotypes that are 0 to 3 bp apart, reflecting modest mutation accumulation within lineages. By contrast, the estimated coalescent date on the basis of the mtDNA data for all F. silvestris (including F. s. bieti) subspecies is 230,000 years ago, whereas the estimated age for the ancestor of F. s. lybica and domestic cats is 131,000 years. Other methods of date estimation suggested a range from 107,000 to 155,000 years (28). These estimates are all greater by an order of magnitude than the age implied by archaeological evidence for cat domestication (6). The persistence of five well-supported mtDNA lineages dating back 100,000 years before any
archaeological record of domestication would suggest that domestic cats originated from at least five matrilineal mtDNA haplotypes. The variation described here is important for the conservation and management of free-ranging wildcat populations (16, 29). In table S6 we present a full list of population-specific (private) STR alleles as well as mtDNA population-specific site genotypes suitable for assessment of a wildcat’s population, subspecies of origin, and distinction from domestic cats. The domestication of wild species to complement human civilization stands as one of the more successful “biological experiments” ever undertaken. For cats, the process began more than 9000 years ago when the earliest domestic cat, European wildcat, Near Eastern wildcat, central Asian wildcat, southern African wildcat, Chinese desert cat, and sand cat. Trees created from Bayesian, maximum likelihood, and maximum parsimony methods result in identical topologies for principal clade groupings. Confidence/bootstrap values (from left to right: Bayes/maximum parsimony/maximum likelihood/minimum evolution) are based on 1000 iterations and are adjacent to nodes. The number of single-nucleotide differences is indicated in red below the corresponding branch. Clade designations and numbers of individuals are indicated in parentheses after the corresponding common name and taxonomic trinomial. A through E designate lineages within mtDNA clade IV. Confidence/bootstrap values for these nodes are as follows: A, 1.00/87/71/54; B, 1.00/82/80/80; C, 0.97/63/59/42; D, 1.00/98/99/88; E, 1.00/100/100/82. Purple and brown tree limbs within mtDNA clade IV reflect individuals from two locales that bear cytonuclear-discordant mtDNA versus STR genotypes (see text). Clade IV individuals bearing mtDNA haplotypes are found among domestic cats; in wild potentially admixed populations in Europe, Asia, or Africa (see Fig. 1A); and in Near Eastern wildcats (see text). (B) STRUCTURE-based populations resolved 851 cats into several wildcat groups, three domestic cat groups, and one group (brown) that included both domestic cats and Near Eastern wildcats. The y axis represents Q-value, the percent representation of resolved populations (colors) within each individual (listed on x axis). (C) Phylogenetic relationships among "F. silvestris" groups as defined by composite STR genotypes based on 36 STR loci. Tree is rooted at sand cat. Bootstrap values at corresponding nodes are based on 1000 iterations with the following measures (from left to right): Dps = 1 - (ps)/Dkf = 1 - (kf); Dps = -ln(ps)/Dkf = -ln(kf). All methods resulted in identical topologies. Individuals were clustered into representative populations based on STRUCTURE Q-value of 0.80 or greater with the same loci (see text). All known domestic cats cluster into domestic-Asia, domestic-Europe, or Near Eastern wildcats, regardless of provenance, and these groups also cluster together.

Fig. 2. (A) Phylogenetic tree of mitochondrial DNA sequence [minimum evolution (neighbor-joining) phylogram of 2604 bp of the ND5 and ND6 genes] of 176 haplotypes discerned from 742 cats sampled across the range of the domestic cat, European wildcat, Near Eastern wildcat, central Asian wildcat, southern African wildcat, Chinese desert cat, and sand cat. Trees created from Bayesian, maximum likelihood, and maximum parsimony methods result in identical topologies for principal clade groupings. Confidence/bootstrap values (from left to right: Bayes/maximum parsimony/maximum likelihood/minimum evolution) are based on 1000 iterations and are adjacent to nodes. The number of single-nucleotide differences is indicated in red below the corresponding branch. Clade designations and numbers of individuals are indicated in parentheses after the corresponding common name and taxonomic trinomial. A through E designate lineages within mtDNA clade IV. Confidence/bootstrap values for these nodes are as follows: A, 1.00/87/71/54; B, 1.00/82/80/80; C, 0.97/63/59/42; D, 1.00/98/99/88; E, 1.00/100/100/82. Purple and brown tree limbs within mtDNA clade IV reflect individuals from two locales that bear cytonuclear-discordant mtDNA versus STR genotypes (see text). Clade IV individuals bearing mtDNA haplotypes are found among domestic cats; in wild potentially admixed populations in Europe, Asia, or Africa (see Fig. 1A); and in Near Eastern wildcats (see text). (B) STRUCTURE-based populations resolved 851 cats into several wildcat groups, three domestic cat groups, and one group (brown) that included both domestic cats and Near Eastern wildcats. The y axis represents Q-value, the percent representation of resolved populations (colors) within each individual (listed on x axis). (C) Phylogenetic relationships among "F. silvestris" groups as defined by composite STR genotypes based on 36 STR loci. Tree is rooted at sand cat. Bootstrap values at corresponding nodes are based on 1000 iterations with the following measures (from left to right): Dps = 1 - (ps)/Dkf = 1 - (kf); Dps = -ln(ps)/Dkf = -ln(kf). All methods resulted in identical topologies. Individuals were clustered into representative populations based on STRUCTURE Q-value of 0.80 or greater with the same loci (see text). All known domestic cats cluster into domestic-Asia, domestic-Europe, or Near Eastern wildcats, regardless of provenance, and these groups also cluster together.

archaeological record of domestication would suggest that domestic cats originated from at least five matrilineal mtDNA haplotypes. The variation described here is important for the conservation and management of free-ranging wildcat populations (16, 29). In table S6 we present a full list of population-specific (private) STR alleles as well as mtDNA population-specific site genotypes suitable for assessment of a wildcat’s population, subspecies of origin, and distinction from domestic cats. The domestication of wild species to complement human civilization stands as one of the more successful “biological experiments” ever undertaken. For cats, the process began more than 9000 years ago when the earliest
farms and grain stores and abandoning their aggressive behavior. The archaeological imprints left in the genomes of living cats here weigh into our understanding of domestication—a dynamic exercise depicted in art, history, and in human cultural development since recorded evidence began.

References and Notes
7. M. D. Donalson, The Domestic Cat in Roman Civilization (Mellen, New York, 1999).
28. We thank M. W. Smith, A. Schmidt-Kuntzel, C. O’Hugain, and B. Gold for discussions and J. Brukhis, A. Brandt, S. Rosendal, and F. Hussain for technical assistance. We appreciate the efforts of all of our collaborators listed in fig. S1 who provided biological specimens used in this study. All tissues were collected in full compliance with federal fish and wildlife permits (Convention on International Trade in Endangered Species of Wild Fauna and Flora [CITES] issued to the National Cancer Institute [NCI; principal officer, S.J.O.] by the Fish and Wildlife Service, U.S. Department of the Interior. Supported by NCI grant N01-CO-12400 and the Intramural Research Program of the NCI Center for Cancer Research. Sequences have been deposited in GenBank with accession numbers EF587016 to EF587179.

Candidatus Chloracidobacterium thermophilum: An Aerobic Phototrophic Acidobacterium

Donald A. Bryant,1* Amaya M. Garcia Costas,2 Julia A. Maresca,1† Aline Gomez Maqueo Chew,1‡ Christian G. Klatt,2 Mary M. Bateson,2 Luke J. Tallon,3 Jessica Hostetler,3 William C. Nelson,4 John F. Heidelberg,3,4 David M. Ward2

Only five bacterial phyla with members capable of chlorophyll (Chl)–based phototrophy are presently known. Metagenomic data from the phototrophic microbial mats of alkaline siliceous hot springs in Yellowstone National Park revealed the existence of a distinctive bacteriochlorophyll (BChl)–synthesizing, phototrophic bacterium. A highly enriched culture of this bacterium grew phototrophically, synthesized BChls a and c under oxic conditions, and had chlorosomes and type 1 reaction centers. Candidatus Chloracidobacterium thermophilum is a BChl-producing member of the poorly characterized phylum Acidobacteria. Sequencing environmental DNA is a powerful approach for predicting the physiological and metabolic potential of microbial ecosystems. Metagenomic analyses have provided insights into the properties of uncultured microorganisms that have escaped detection in field studies (1–6). We used metagenomic data from the microbial mat communities

Supporting Online Material
www.sciencemag.org/cgi/content/full/1139518/DC1

SOM Text
Tables S1 to S6
Figs. S1 and S2
References
4 January 2007; accepted 18 June 2007
Published online 28 June 2007; 10.1126/science.1139518
Include this information when citing this paper.