Methods

Strains were cultivated on agar plates seeded with *E. coli* strain OP50 at 22°C.

The LSJ2 strain is a sister strain to the standard N2 laboratory strain. Both LSJ2 and N2 are descended from a single animal isolated by W. Nicholas from a mushroom compost culture provided by L. Staniland in Bristol, England. The strain was transferred to E. Dougherty's lab at the Kaiser Foundation Research Institute in the 1950s, and in the late 1950s it separated into two substrains. One of these substrains was mistakenly believed to be *C. briggsae* and represents the LSJ2 lineage. S. Brenner received a cultivar of the second substrain from E. Dougherty in 1964; this cultivar became N2. The LSJ2 lineage was continuously cultivated in liquid axenic media at the University of California - Berkeley and at San Jose State University thereafter. In 1995 a cultivar of the strain was sent to the *Caenorhabditis* genetics center, and frozen to become LSJ1. In 2009, N. Lu from San Jose State University provided a second cultivar of the strain that had been grown for an additional 14 years in axenic media; this strain is designated LSJ2.

Other strains used in this study are:
N2
CC1
LSJ1
MY14
AF16
DR1690
CX12311 *kyIR1(V, CB4856>N2); qgIR1(X,CB4856>N2)*
CX13249 *kyIR88(X, LSJ2>N2)*
CX13330 *kyIR88(X, LSJ2>N2); kyEx3927 [srg-36/srg-37 genomic region + P_{elt-2}::gfp]*
CX13331 *kyIR88(X, LSJ2>N2); kyEx3928 [srg-36/srg-37 genomic region + P_{elt-2}::gfp]*
CX13332 *kyIR88(X, LSJ2>N2); kyEx3929 [srg-37 genomic region + P_{elt-2}::gfp]*
CX13333 *kyIR88(X, LSJ2>N2); kyEx3930 [srg-37 genomic region + P_{elt-2}::gfp]*
CX13334 *kyIR88(X, LSJ2>N2); kyEx3931 [srg-37 genomic region + P_{elt-2}::gfp]*
CX13335 *kyIR88(X, LSJ2>N2); kyEx3932 [P_{srg-36}::srg-36:sl2:gfp + P_{elt-2}::gfp]*
CX13336 *kyIR88(X, LSJ2>N2); kyEx3933 [P_{srg-36}::srg-36:sl2:gfp + P_{elt-2}::gfp]*
CX13337 *kyIR88(X, LSJ2>N2); kyEx3934 [P_{srg-36}::srg-36:sl2:gfp + P_{elt-2}::gfp]*

CX13338 *kyIR88(X, LSJ2>N2); kyEx3935 [P_{srg-37}::srg-37:sl2:gfp + P_{elt-2}::gfp]*

CX13339 *kyIR88(X, LSJ2>N2); kyEx3936 [P_{srg-37}::srg-37:sl2:gfp + P_{elt-2}::gfp]*

CX13340 *kyIR88(X, LSJ2>N2); kyEx3937 [P_{srg-37}::srg-37:sl2:gfp + P_{elt-2}::gfp]*

CX13431 *kyIR94(X, DR1690>AF16)*

CX13591 *kyIR95(X, CC1>N2)*

CX13592 *kyIR95(X, CC1>N2); kyEx4118 [srg-36/srg-37 genomic region + P_{elt-2}::gfp]*

CX13593 *kyIR95(X, CC1>N2); kyEx4119 [srg-36/srg-37 genomic region + P_{elt-2}::gfp]*

CX13594 *kyIR95(X, CC1>N2); kyEx4120 [srg-36/srg-37 genomic region + P_{elt-2}::gfp]*

CX13685 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4171 [P_{sra-6}::srg-36 + P_{ofm-1}::rfp]*

CX13686 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4172 [P_{sra-6}::srg-36 + P_{ofm-1}::rfp]*

CX13687 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4173 [P_{sra-6}::srg-36 + P_{ofm-1}::rfp]*

CX13603 *kyIR88(X, LSJ2>N2); kyEx4125 [P_{str-3}::srg-36::gfp + P_{elt-2}::gfp]*

CX13739 *kyIR94(X, DR1690>AF16); kyEx4201 [CBG24690 genomic region + P_{myo-2}::mcherry]*

CX13740 *kyIR94(X, DR1690>AF16); kyEx4202 [CBG24690 genomic region + P_{myo-2}::mcherry]*

CX13741 *kyIR94(X, DR1690>AF16); kyEx4203 [CBG24690 genomic region + P_{myo-2}::mcherry]*

CX13977 *kyIR88(X, LSJ2>N2); kyEx4316 [P_{srg-47}::srg-36::sl2::gfp + P_{ofm-1}::rfp]*

CX13978 *kyIR88(X, LSJ2>N2); kyEx4317 [P_{srg-47}::srg-36::sl2::gfp + P_{ofm-1}::rfp]*

CX13979 *kyIR88(X, LSJ2>N2); kyEx4318 [P_{srg-47}::srg-36::sl2::gfp + P_{ofm-1}::rfp]*

CX13980 *kyIR88(X, LSJ2>N2); kyEx4319 [P_{gcy-8}::srg-36::sl2::gfp + P_{ofm-1}::rfp]*

CX13981 *kyIR88(X, LSJ2>N2); kyEx4320 [P_{gcy-8}::srg-36::sl2::gfp + P_{ofm-1}::rfp]*

CX13982 *kyIR88(X, LSJ2>N2); kyEx4321 [P_{gcy-8}::srg-36::sl2::gfp + P_{ofm-1}::rfp]*

CX13983 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4322 [P_{sra-6}::srg-37.c + P_{ofm-1}::rfp]*

CX13984 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4323 [P_{sra-6}::srg-37.c + P_{ofm-1}::rfp]*

CX13985 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4324 [P_{sra-6}::srg-37.c + P_{ofm-1}::rfp]*

CX13986 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4325 [P_{sra-6}::CBG24690 + P_{ofm-1}::rfp]*

CX13987 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4326 [P_{sra-6}::CBG24690 + P_{ofm-1}::rfp]*

CX13988 *kyEx2865 [P_{sra-6}::GCaMP3.0 + P_{ofm-1}::gfp]; kyEx4327 [P_{sra-6}::CBG24690 + P_{ofm-1}::rfp]*

CX14023 *kyIR88(X, LSJ2>N2); kyEx4342 [P_{flp-6}::srg-36::sl2::gfp + P_{ofm-1}::rfp]*
CX14024 *kyIR88(X, LSJ2>N2); kyEx4343 [P_{flp-6}::srg-36::sl2::gfp + P_{ofm-1}::rfp]*

Dauer formation assays

Dauer plates contained 1 μl (for *C. elegans)* or 25 μl (for *C. briggsae)* crude *C. elegans* dauer pheromone, or 80 nM-2 μM ascarosides (synthesized as described[11, 31, 32]), in NGM agar without peptone (2.2% Noble Agar, 5 μg/ml cholesterol, 15 mM NaCl, 1 mM $CaCl_2$, 1 mM $MgSO_4$, and 25 mM KPO_4). For *C. elegans,* 20 μl of heat-killed *E. coli* OP50 bacteria (10 μg/ml) were added to each plate, and then five adult animals were picked onto the plate, allowed to lay eggs for 4 h and then removed. Plates were incubated at 25°C for 72 h before being scored for dauers, identified by a thin body morphology and non-pumping pharynx. At least five plates were assayed for each strain/condition. For *C. briggsae,* OP50 lawns killed with 50 mg/ml streptomycin were used, because otherwise animals crawled off the heat-killed bacterial lawn and died. Higher levels of pheromone were required to induce dauer formation on the streptomycin-killed bacteria.

Crude dauer pheromone was purified from 2L of N2 cultured in S basal with HB101 bacteria for 11 days. Supernatants were clarified by centrifugation, further filtered through a Buchner filter funnel (medium frit, Chemglass) under vacuum, then filtered through 0.2 μm PES membranes (Nalgene), concentrated using a rotary evaporator, and lyophilized. Solids were extracted three times with 100% ethanol (100 ml each), and the eluents were combined and concentrated using a rotary evaporator to yield 5 ml of crude dauer pheromone (stored at -20°C).

LSJ2 and N2 sequencing and analysis

Genomic DNA was isolated from 7 strains: LSJ2, LSJ1 (a sample from the LSJ2 lineage frozen in 1995), MY14 (a wild strain used as an outgroup), and four EMS-mutagenized N2-derived strains. 10 micrograms of genomic DNA was provided to the Rockefeller Genomics Resource Center for sequencing. DNA samples were processed using the

gDNA Paired-end Sample Preparation kit from Illumina, and sequencing was performed using a GAII instrument.

SNP analysis

Sequencing reads with an average quality score above 27 (Sanger format) were aligned to the WS195 *C. elegans* reference sequence and used to identify SNPs using the MAQ software suite (version 0.7.1 easyrun command, using default settings)[33]. The final filtered SNPs (the cns.final.snp file) for each strain were further analyzed using custom software that analyzed the number of reference and mutant reads that were present for the polymorphisms in all the sequenced strains. Many of the predicted SNPs both in LSJ2 and in N2 were supported by reads that matched both the reference N2 nucleotide and a mutant nucleotide. These "heterozygous" SNPs could represent heterozygous alleles maintained by balancing selection, but different levels of coverage of the two reads suggests that these apparent SNPs are actually alignment errors.

To be considered a true polymorphism between the LSJ2 and the N2 strains, we required at least 90% of the reads from the LSJ2 sequencing to be mutant and fewer than 10% of the reads from the N2-derived strains to be mutant. A total of 223 SNPs passed these criteria. Using MY14 as an outgroup, the SNPs were then classified into the LSJ2 branch if fewer than 10% of the reads from the MY14 sequencing were mutant and classified in the N2 branch if more than 75% of the reads from the MY14 sequencing were mutant. Eight SNPs could not be classified, because there were no reads from the MY14 sequencing. We further broke down the LSJ2 lineage into mutations occurring before and after 1995 using sequence from the LSJ1 strain. If more than 90% of the reads from LSJ1 supported the mutant read, then the SNP was classified as occurring before 1995. If fewer than 25% of the reads from LSJ1 supported the mutant read, then the SNP was classified as occurring after 1995. One SNP could not be classified.

A recent whole-genome sequencing report indicated a substantially higher level of mutation between N2 and LSJ1, with 877 SNPs instead of 171[34]. 14 SNPs predicted by that analysis, but not by this one, were examined by PCR and Sanger sequencing of N2 and LSJ1; 13/14 were not confirmed and 1/14 was ambiguous. If these SNPs are

representative, ~80% of the SNPs in the previous report are either miscalled bases or SNPs specific to that laboratory's strains.

Indel analysis

We created a custom algorithm to identify insertions and deletions (indels) in LSJ2 with respect to the N2 reference. Because MAQ does not use gapped alignment for aligning single end reads to the reference sequence, we reasoned that most reads covering an insertion or deletion would be unaligned by the MAQ software. We identified regions of low coverage (defined as < 12 reads) using custom software and identified any reads unaligned by MAQ with partial matches (defined as reads with 18 contiguous matches) in these regions. We then realigned the partial reads considering all possible one base pair insertions and deletions within the low coverage region. If the one base pair indel region with the best alignments to the partial matches resulted in an average match of 35 out of 36 bp in all the sequence reads, then we considered this evidence of a real difference from the reference N2 sequence. For each of these 1 bp indels, we searched the unaligned reads from N2 for evidence of an identical polymorphism (again using an average match of 35 out of 36 bp as evidence for the polymorphism), as these 1 bp indels that are found in both LSJ2 and N2 sequencing are likely reference errors. We considered the remaining 41 one bp indels as genuine differences between LSJ2 and N2 and classified them into the LSJ2 or N2 lineage using the unaligned MY14 sequencing reads as an outgroup.

The remaining low coverage regions with partial matches were then visually inspected for the presence of larger deletions or insertions. The exact breakpoints for each deletion or insertion were defined using unambiguous regions, with MY14 as an outgroup to classify the insertion/deletion into the N2 or LSJ2 lineage. A total of 26 indels larger than one bp were identified by this analysis.

A total of 331 indels were identified between LSJ1 and N2 in the previous whole-genome sequencing report[34], a significantly higher number than the 67 indels identified here. Unlike the SNPs, we have not assessed the differences in indel predictions by PCR and Sanger sequencing.

Deletion information

Large deletions were verified using Sanger sequencing. The *srg-36/srg-37* region in LSJ2 contained a deletion of 4906 bp replaced with an AT nucleotide pair. The first 50 bp of the deleted region are:

gtgagagcggagtgatttcaaacacgggaatggccaaatacaacatcttc

The last 50bp of the deleted region are:
tagtatgaacgattgaaaaaaatcaggccggctggaatcattggatatac

In CC1, 6795 bp were deleted. The first 200 bp of the deleted region are:

gtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgt
gtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgt
gtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgt
gtgtgtgatgtgatcaccctgtgattgtaggtgctccaaatggacgaaca

The last 50 bp of the deleted region are:
acgaagacgaggcgtgaataatgtacaccacgcccgccccatccccccat

We were unable to locate the exact endpoints of the deletion in DR1690 due to the presence of a large microduplication of undetermined size. However, we used a series of PCR amplifications in AF16 and DR1690 to approximate its size around 33,000bp. We narrowed down the left breakpoint using the primers 5'-attgctgtctctgcggatct-3' and 5'-tctcagaatctcagaatctcagga-3', which readily amplified a PCR product from both AF16 and DR1690, and the primers 5'-tggtcacaaggaagaatcca-3' and 5'-tctcagaatctcagaatctcagaa-3', which readily amplified a PCR product from AF16 but not DR1690. The right breakpoint was narrowed down using the primers 5'-actttcgaaggcgagagtga-3' and 5'-tgagagtaggggccagaaaa-3', which readily amplified a PCR product from AF16 but not DR1690, and the primers 5'-ttcggggctaaacctcctat-3' and 5'-cgggaattctaaaaatcgca-3', which readily amplified a PCR product from both AF16 and DR1690.

RIL construction and genotyping

The starting strains for generating recombinant inbred lines were LSJ2 and CX12311, a strain with a small region surrounding *glb-5* and a small region surrounding *npr-1* introgressed from the wild Hawaiian strain CB4856 into an N2 background. The use of CX12311 eliminated two laboratory-derived N2 polymorphisms in the *glb-5* and *npr-1* genes that affect many *C. elegans* behaviours[7,27]. The *npr-1* introgression was created in Matt Rockman's laboratory at NYU and the *glb-5* introgression was created in the Bargmann laboratory; the N2 background is therefore a mixture of two laboratory substrains of N2. Reciprocal crosses between LSJ2 and CX12311 animals were conducted, and 108 F2 progeny (54 from each of the initial reciprocal crosses) were cloned to individual plates and allowed to self-fertilize for ten generations to create inbred lines. 94 clones were selected for further genotyping.

A custom Illumina GoldenGate genotyping assay for VeraCode was used to genotype 192 SNPs that differed between the LSJ2 and N2 strains. Potential SNPs were identified from whole-genome sequencing of LSJ2 or N2-derived strains from the Bargmann lab, and 192 candidates were chosen using a combination of Illumina design criteria and uniform spacing. Because some regions did not have any true N2/LSJ2 SNPs suitable for genotyping, a few SNPs are specific to the Bargmann N2 strain.

Genotyping of the 192 SNPs in LSJ2, CX12311, and 94 RILs was performed on 10 micrograms of DNA by the Rockefeller Genomics Resource Center using the manufacturer's protocol. Most of the SNPs were reliably identified by the Illumina software, but some SNPs were called as heterozygous; in some cases, these could be unambiguously assigned to a parental strain by visually inspecting the scatterplots. When heterozygous SNPs were clearly inconsistent with flanking markers, the heterozygous call was replaced with an ungenotyped call. The genotyping for a small number of SNPs, such as LSJ2_N2_II_7695720, was consistent with the SNPs being unfixed polymorphisms segregating within the parental LSJ2 population. Owing to differences in allele frequencies and the crossing strategy using distinct LSJ2 hermaphrodites and LSJ2 males for the RIL initial crosses, the LSJ2_N2_II_7695720 SNP appeared to be spuriously linked to the mitochondrial marker. A total of 16 SNPs showed no segregation and were excluded from the analysis.

Quantitative Trait Loci (QTL) mapping

The fraction of dauer animals formed in response to C3 ascaroside was used as a phenotype for nonparametric interval mapping in Rqtl[35]. Lod scores were computed at each marker.

Near-Isogenic Line (NIL) construction

To create CX13249, the RIL ln71-8 was backcrossed to N2 for 10 generations, selecting for the presence of the LSJ2 deletion. The resulting introgression was named *kyIR88(X, LSJ2>N2).*

To create CX13591, CC1 was backcrossed to N2 for 5 generations, selecting for the presence of the CC1 deletion in *srg-36* and *srg-37.* The resulting introgression was named *kyIR95(X,CC1>N2).*

To create CX13431, DR1690 was backcrossed to AF16 for 5 generations, selecting for the presence of the DR1690 deletion in *CBG24690.* The resulting introgression was named *kyIR94(X, DR1690>AF16).*

Molecular biology and generation of transgenic lines

The genomic region surrounding *srg-36/srg-37* was amplified using 5'-aaccttggccggccgctcacgctcaccaatttct-3' and 5'-tcttggccttacacgtcttgc-3' primers. The resultant PCR product was injected into CX13249 or CX13591 at a concentration of 100 ng/μl.

The genomic region surrounding *srg-37* was amplified using 5'-aaccttggccggccgctcacgctcaccaatttct-3' and 5'-tccagcagaattatttgatgaat-3' primers and injected into CX13249 at a concentration of 50 ng/μl.

The *srg-36* cDNA was amplified with 5'-aaccttgctagcatgacgctggcaagcttg-3' and 5'-aaccttggtacctcaccctgtgattgtaggtgc-3' primers from RNA that had been isolated from N2 animals and then reverse transcribed into cDNA. The cDNA we isolated matched the

prediction from www.wormbase.org.

The *srg-37* cDNA was amplified using 5'-aaccttgctagcatgccatcttcaagtcctttaaga-3' and 5'-aaccttggtacctcaccttaatatttggttagttcctgatgc-3' primers from RNA that had been isolated from N2 animals and then reverse transcribed into cDNA. The cDNA isolated multiple times for *srg-37 (srg-37.b)* did not match the prediction from www.wormbase.org *(srg-37.a)* as it also contained sequence that matched the first two introns of the gene prediction (Figure S5). Sequence analysis indicated that the second intron (51 bp) encoded 17 amino acid residues that were conserved in several *srg* genes from *C. elegans, C. briggsae, and C. remanei,* whereas the first intron did not encode sequences related to other SRG proteins. We therefore deleted the first intron from the *srg-37.b* cDNA to generate *srg-37.c* (Figure S5). Ectopic expression of *srg-37.c* conferred C3 sensitivity on ASH based on calcium imaging and behavior, but expression of *srg-37.b* did not; *srg-37.a* was not tested.

The *srg-36* promoter was amplified using 5'-aaccttggccggccgtgtgcggcaaactttgtaa-3' and 5'-aaccttggcgcgccaccaacaggaggagttgaaattt-3' primers.

The *srg-37* promoter was amplified using: 5'-aaccttggccggccgctcacgctcaccaatttct-3' and 5'-aaccttggcgcgccggtttttgtattcggccaaa-3' primers.

The *srg-47* promoter was amplified using: 5'-ggaaccggccggcctgaaccatcgatgaaaaacg-3' and 5'-ggaaccggcgcgccttttaattcgaagaaaagattatcaaaaa-3' primers.

The *srg-36* and *srg-37* cDNAs were inserted into the pSM-sl2-gfp and the pSM-P_{sra-6} backbone backbone using NheI and AspI restriction sites. The *srg-36*, *srg-37,* and *srg-47* promoters were inserted the pSM-*srg*-sl2-gfp vectors using FseI and AscI restriction enzymes.

To create a GFP fusion to the SRG-36 protein, a cDNA lacking a stop codon was amplified from a vector containing the *srg-36* gene using the primers 5'-aaccttgctagcatgacgctggcaagcttg-3' and 5'-aaccttaccggtaaccctgtgattgtaggtgctc-3'. This cDNA was cloned into the pSM-P_{str-3}-GFP vector using the NheI and AgeI restriction enzymes.

The genomic region surrounding the *CBG24690* gene was amplified from AF16 using 5'-tgtgctgcgtacaagtaattgag-3' and 5'-gtaaaaatggctggctctgc-3' primers. The resulting PCR product was injected into CX13431 at a concentration of 50 ng/μl.

The *CBG24690* cDNA was amplified with 5'- aaccttgctagcatgttagatcttcttttaaaaccctcttt-3' and 5'- aaccttggtaccttacaatttatatttcacattggtagctac-3' primers from RNA that had been isolated from AF16 animals and then reverse transcribed into cDNA. The cDNA we isolated did not match the prediction from www.wormbase.org due to the presence of a one base pair insertion near the 3' end of the gene. The corrected sequence has been submitted to Wormbase.

Calcium Imaging and Drop Test

The extrachromosomal array *kyEx2865* expresses the genetically encoded calcium indicator GCaMP3.0[30] under the *sra-6* promoter, which drives expression in ASH, ASI and PVQ. cDNAs encoding *srg-36, srg-37.c,* or *CBG24690* were expressed ectopically in ASH by injecting P_{sra-6}::*srg-36,* P_{sra-6}::*srg-37.c, or* P_{sra-6}::*CBG24690* into a strain bearing *kyEx2865*. These animals were tested for avoidance of 1 μM of C3 or C6 ascaroside using the drop test[28]. At least 50 animals were tested blind for each condition from three independent lines. After determining if the animal responded, the presence of the extrachromosomal array containing the P_{sra-6}*::srg-36* transgene was determined by the presence or absence of the coinjection marker.

For imaging, young adult worms were trapped in a custom-designed microfluidic device made of the transparent polymer PDMS, where their noses were exposed to liquid streams under laminar flow[29, 36]. Switching between odor streams was accomplished by means of two alternative side-streams in order to minimize changing fluid pressure with odor delivery. Movement artifact was reduced using 1 mM tetramisole in the worm-loading channel. Wide-field microscopy was used to monitor fluorescence from the cell of interest as six sequential 10-second pulses of C3 ascaroside (1 μM in S. basal medium) were presented to the worm's nose. Fluorescein (1:250,000 dilution) was added to the C3 stream to measure accurate switching between C3 and buffer in each trial.

Metamorph and a Coolsnap HQ (Photometrics) camera were used to capture stacks of TIFF images at 10 frames/sec during the odor presentation sequence. Metamorph was used to identify the region of interest encompassing the ASH cell body in all frames. The background intensity and the average fluorescence intensity of the cell in each frame were determined by running a journal script based on the Metamorph "track objects" function using a threshholding algorithm. A Matlab (7.0R14, MathWorks) script generated cell response plots using log files generated by Metamorph. The average fluorescence of the region of interest was generated by subtracting the recorded value from the average intensity of the background region of a similar area. The average fluorescence in a 3s window (t=1-4s) was set as F0. For figures, the percent change in fluorescence intensity for the region of interest relative to F0 was plotted for each trial individually. A second Matlab script was used to plot the average of all trials with standard errors for each time-point.

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