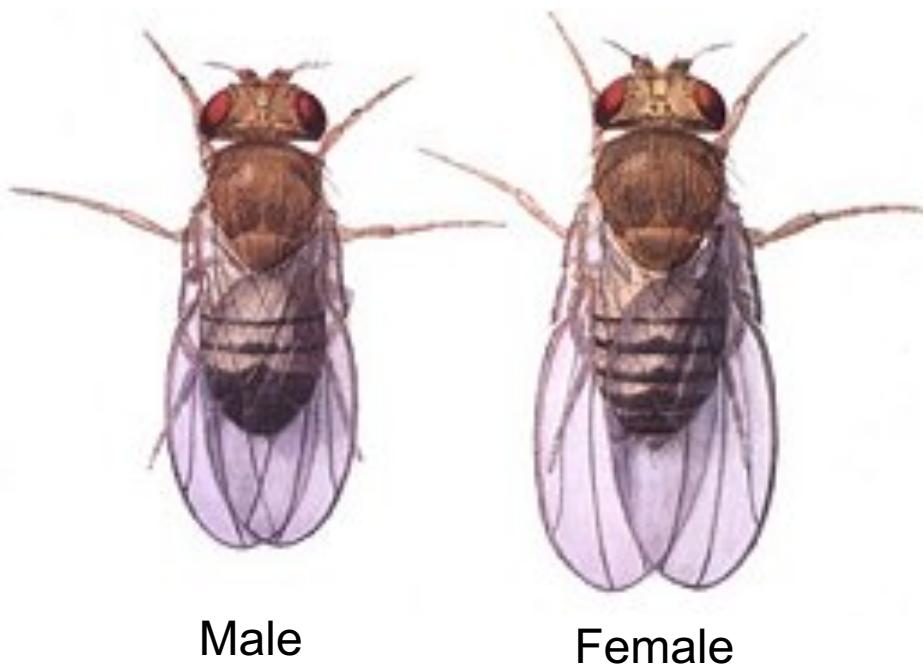


Model organisms and developmental biology

仲寒冰

zhong.hb@sustc.edu.cn

Drosophila (fruit fly)

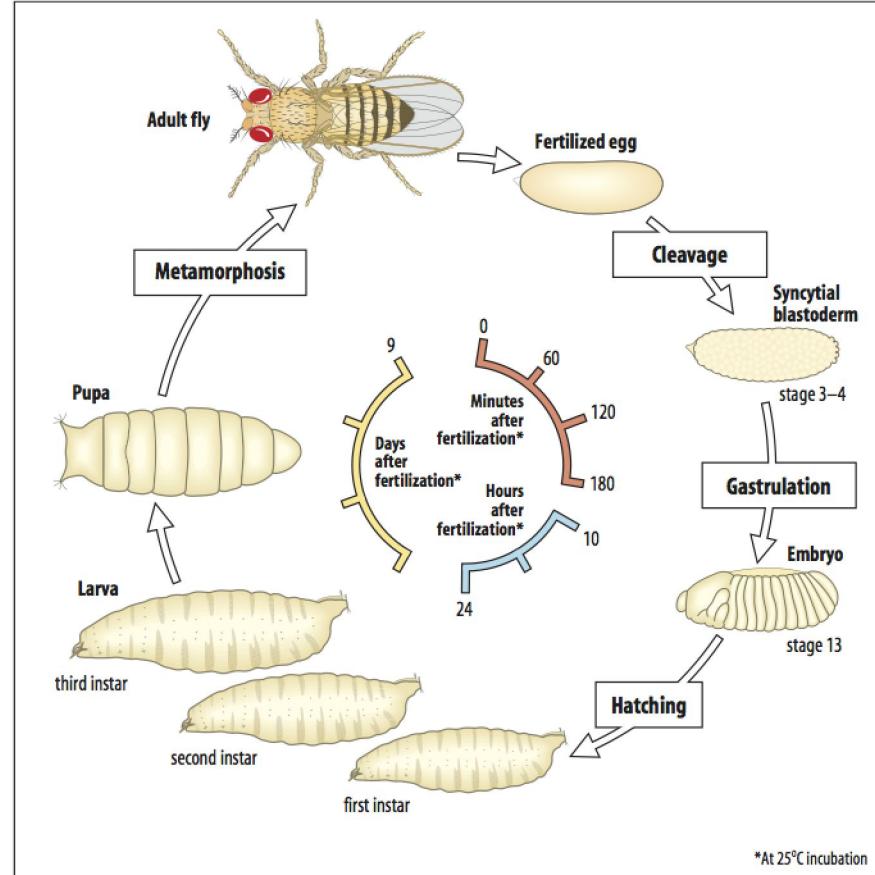
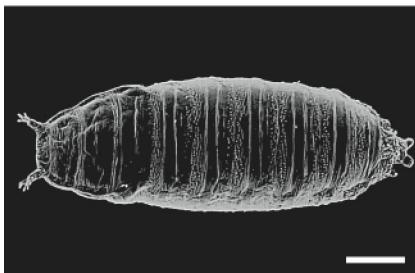
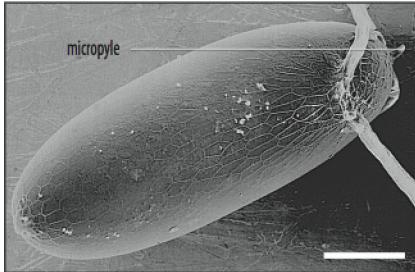


Male

Female

Drosophila melanogaster. Greek for *dark-bellied dew lover* : δρόσος = dew (**Droso**), φίλος = intimate friend, lover (**phila**), μέλας = dark-coloured (**melano**), γαστήρ = belly (**gaster**) .

Life cycle



Advantages

- The care and culture requires little equipment and use little space.
- Their morphology is easy to identify (need to be anesthetized).
- It has a short generation time (about 10 days at room temperature).
- It has a high fecundity (females lay up to 100 eggs per day, and perhaps 2000 in a lifetime).
- Males and females are readily distinguished and virgin females are easily isolated, facilitating genetic crossing.
- The mature larvae show giant chromosomes in the salivary glands called polytene chromosomes.
- It has only four pairs of chromosomes: three autosomes, and one sex chromosome.

Pubmed @ 2009

- Animal, 4,563,882
- Mouse, 1,047,200
- *Drosophila*, 70,302
- *C. elegans*, 16,523
- Zebrafish, 12,734

Pubmed @ 2015

- Animal, 5,614,647
- Mouse, 1,412,077
- *Drosophila*, 91,249
- *C. elegans*, 25,052
- Zebrafish, 25,018
- Human, 14,579,283

History of use in genetic analysis



Charles W. Woodworth (吴伟士)

Founded the Entomology Department at the UC, Berkeley

Credited with first breeding Drosophila in quantity while he was at Harvard

Four years in China, 江苏昆虫局

Thomas Hunt Morgan



PhD from Johns Hopkins University in 1890

Used Drosophila to study genetics in Columbia University

Moved to California Institute of Technology in 1928 and headed its division of biology until 1942.

Awarded Nobel prize in 1933 "for his discoveries concerning the role played by the chromosome in heredity".

The Division of Biology he established at the California Institute of Technology “produced” seven Nobel Prize winners.

Fly room



Famous students



A.H. Sturtevant

C.B. Bridges

H.J. Muller

Courtesy of the Caltech Archives

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Sturtevant proposed the first linkage map when he's a Sophomore



A.H. Sturtevant in the *Drosophila* stock room of the Kerckhoff Laboratories.

Courtesy of the Caltech Archives

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Sturtevant, A. H. 1913. The linear arrangement of six sex-linked factors in *Drosophila*, as shown by their mode of association. *Journal of Experimental Zoology*, 14: 43-59.

THE LINEAR ARRANGEMENT OF SIX SEX-LINKED FACTORS IN DROSOPHILA, AS SHOWN BY THEIR MODE OF ASSOCIATION

A. H. STURTEVANT

HISTORICAL

The parallel between the behavior of the chromosomes in reduction and that of Mendelian factors in segregation was first pointed out by Sutton (1902) though earlier in the same year Boveri (1902) had referred to a possible connection. In this paper and others Boveri brought forward considerable evidence from the field of experimental embryology indicating that the chromosomes play an important role in development and inheritance. The first attempt at connecting any given somatic character with a definite chromosome came with McClung's (1902) suggestion that the accessory chromosome is a sex-determiner. Stevens (1905) and Wilson (1905) verified this by showing that in numerous forms there is a sex chromosome, present in all the eggs and in the female-producing sperm, but absent, or represented by a smaller homologue, in the male-producing sperm. A further step was made when Morgan (1910) showed that the factor for color in the eyes of the fly *Drosophila ampelophila* follows the distribution of the sex chromosome already found in the same species by Stevens (1908). Later, on the appearance of a sex-linked wing mutation in *Drosophila*, Morgan (1910a, 1911) was able to make clear a new point. By crossing white-eyed, long-winged flies to those with red eyes and rudimentary wings (the new sex-linked character) he obtained, in F_2 , white-eyed,

Sturtevant proposed the first linkage map when he's a Sophomore



A.H. Sturtevant in the *Drosophila* stock room of the Kerckhoff Laboratories.

Courtesy of the Caltech Archives

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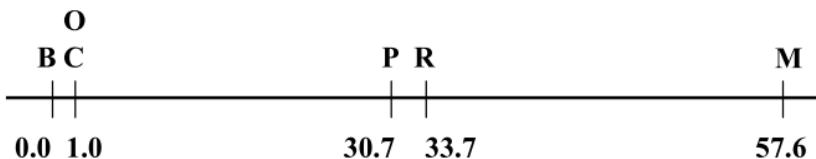
Sturtevant, A. H. 1913. The linear arrangement of six sex-linked factors in *Drosophila*, as shown by their mode of association. *Journal of Experimental Zoology*, 14: 43-59.

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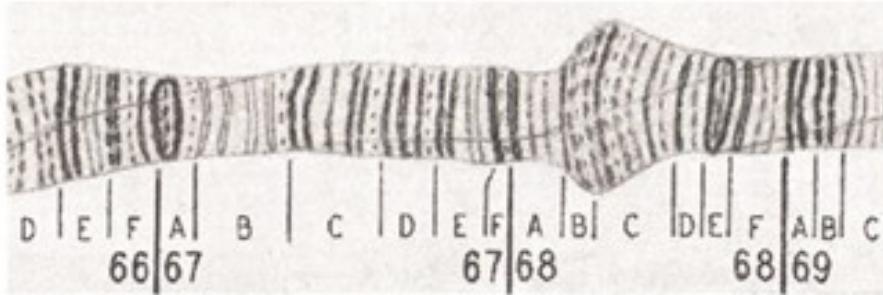
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Bridges and polytene chromosome



- The banding patterns of the polytene chromosomes of *Drosophila melanogaster* were sketched in 1935 by Calvin B. Bridges, in such detail that his maps are still widely used today.

Hermann J. Muller

- In 1919, Muller made the important discovery of a mutant (later found to be a chromosomal inversion) that appeared to suppress crossing-over, which opened up new avenues in mutation rate studies and leaded to generation of balancer chromosomes.
- Balancer chromosomes always contain a lethal recessive allele.
- X-ray mutagenesis.

Morgan's Chinese students



李汝祺



谈家桢

Edward Lewis

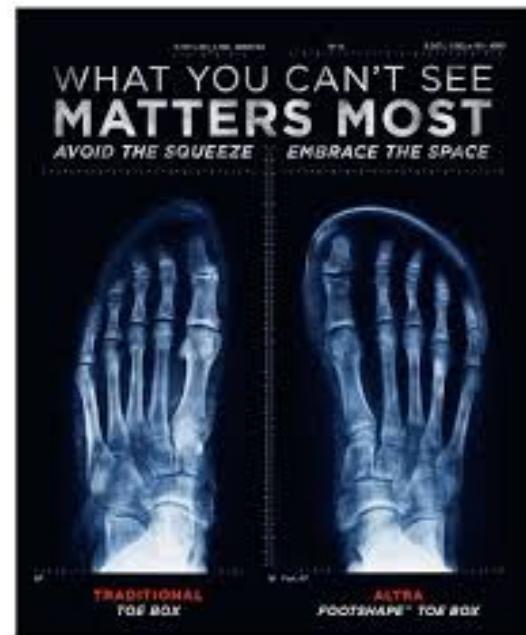


Edward B. Lewis with
Drosophila.

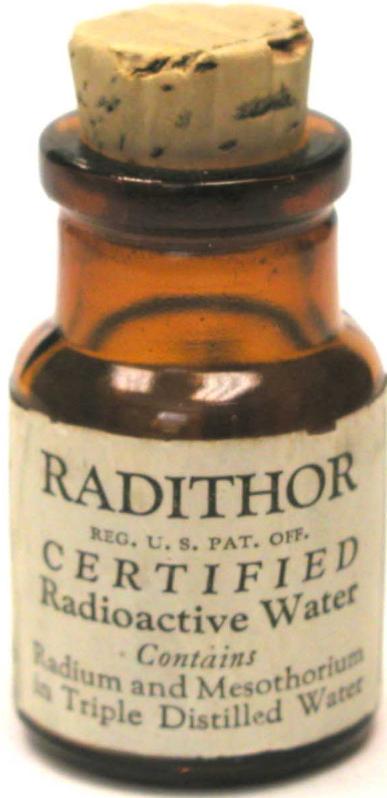
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- Lewis和Bacher (1968)发现 ethyl methanesulfonate (EMS, 甲基磺酸乙酯) 是很好的化学诱变剂。EMS通常造成很小的突变(常常是点突变), 而突变位点分布相对比较均匀, 被应用于果蝇和其他动物的遗传研究, 目前仍与ENU (N-ethyl-N-nitrosourea) 为常用的化学致变剂。
- 1950到1960年代Lewis研究辐射与癌症的关系时, 他认为“辐射可以致癌”的结论与美国政府主持原子能的将军发生冲突, 遭多方面攻击, 包括有科学家声称他的分析不科学。

Shoe-fitting fluoroscope (X-ray Shoe Fitter)



Radithor



1918 to 1928 by the Bailey Radium Laboratories, Inc.

- **Size:** 2 1/8" high (not including cork)
- **Exposure Rates:** ca. 2 uR/hr above background at one foot, ca. 35 uR/hr above background on contact.
- **Price:** one dollar a bottle
- **The bottle** pictured at left contained one-half ounce of Radithor - triple distilled water guaranteed to contain at least 1 microcurie each of Ra-226 and Ra-228. The manufacturer of the product, William J. Bailey, offered \$1,000 to anyone who could prove the product contained less than the stated amount. No one ever did.

SA1-3 Personal income summary

Per capita personal income (dollars) 2/

Bureau of Economic Analysis

Fips	00000
Area	United States
1929	697
1930	618
1931	525
1932	398
1933	372
1934	424
1935	473
1936	535
1937	574
1938	526
1939	556
1940	593
1941	717
1942	908
1943	1106
1944	1194
1945	1235

1924年8月，凯恩斯检查了一位47岁的乳腺癌患者，她身形消瘦，体质虚弱，乳腺中有溃疡性恶性肿块。如果是在巴尔的摩或者纽约的话，这种病人会被立即实施激进的手术。但是，凯恩斯注意到这位患者的虚弱体质，所以并没有不加区别地采取激进疗法（激进疗法很可能让她命丧手术台），而是采取了一种相对更加保守的策略。凯恩斯注意到一些放疗师，如艾米尔，已经证实X射线在治疗乳腺癌方面的有效性，于是他在这名患者的乳房里置入了50毫克的镭，以照射肿瘤并监测治疗效果，希望能减轻她的症状。令他惊讶的是，病人有了明显的改善。他写道，“溃疡很快被治愈了，肿块变小、变软，也不那么顽固了。”她的肿块消退得很快，凯恩斯觉得自己也许可以采用较小的非根治性外科手术来彻底去除肿瘤。

The Nobel Prize in Physiology or Medicine 1995

For their discoveries concerning the genetic control of early embryonic development.



Edward B. Lewis

◐ 1/3 of the prize

USA

California Institute of
Technology (Caltech)

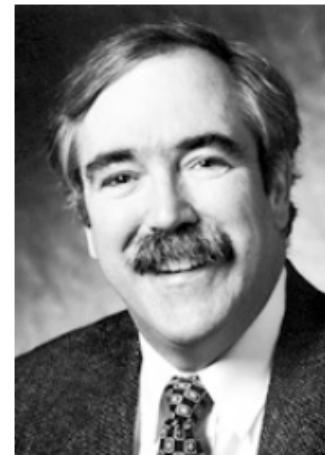


Christiane Nüsslein-Volhard

◐ 1/3 of the prize

Federal Republic of
Germany

Max-Planck-Institut für
Entwicklungsbiologie



Eric F. Wieschaus

◐ 1/3 of the prize

USA

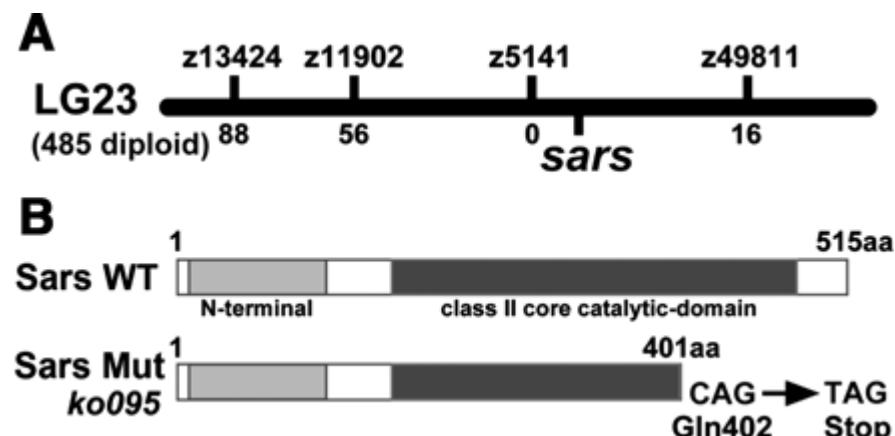
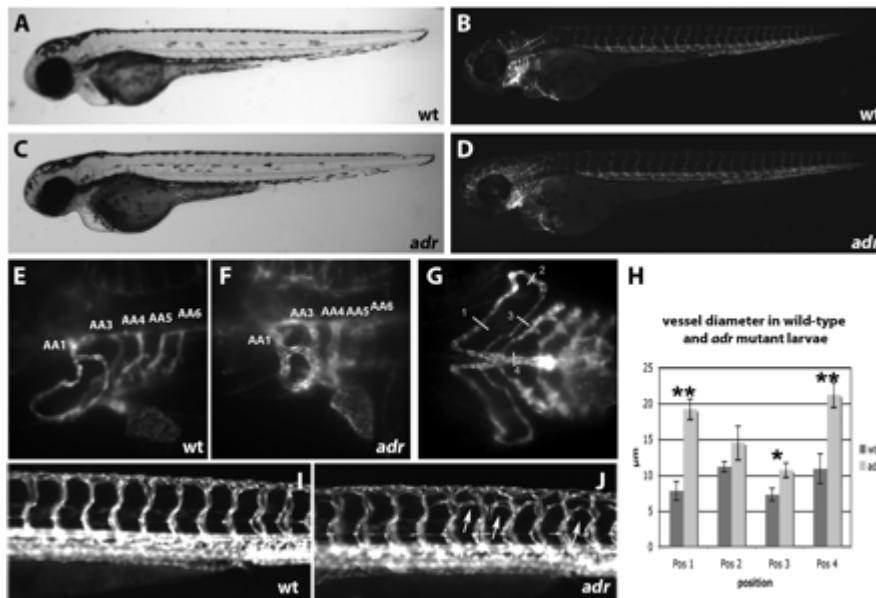
Princeton University
Princeton, NJ, USA

- 遗传学
- 发育的基因调控
- 各类神经疾病的研究: 帕金森氏病 (Parkinson's disease), 老年痴呆症(Alzheimer disease)
- 药物成瘾(addiction)和酒精中毒(Alcoholism)
- 衰老与长寿(aging and longevity)
- 学习记忆(learning and memory)和某些认知行为 (Cognitive behavior)

Acknowledgement

- 饶毅的博客
- Nobelprize.org

Genetic evidence for a noncanonical function of seryl-tRNA synthetase in vascular development



Fukui, et al, *Circulation Research*, 2009

Herzog, et al, *Circulation Research*, 2009

ARTICLE

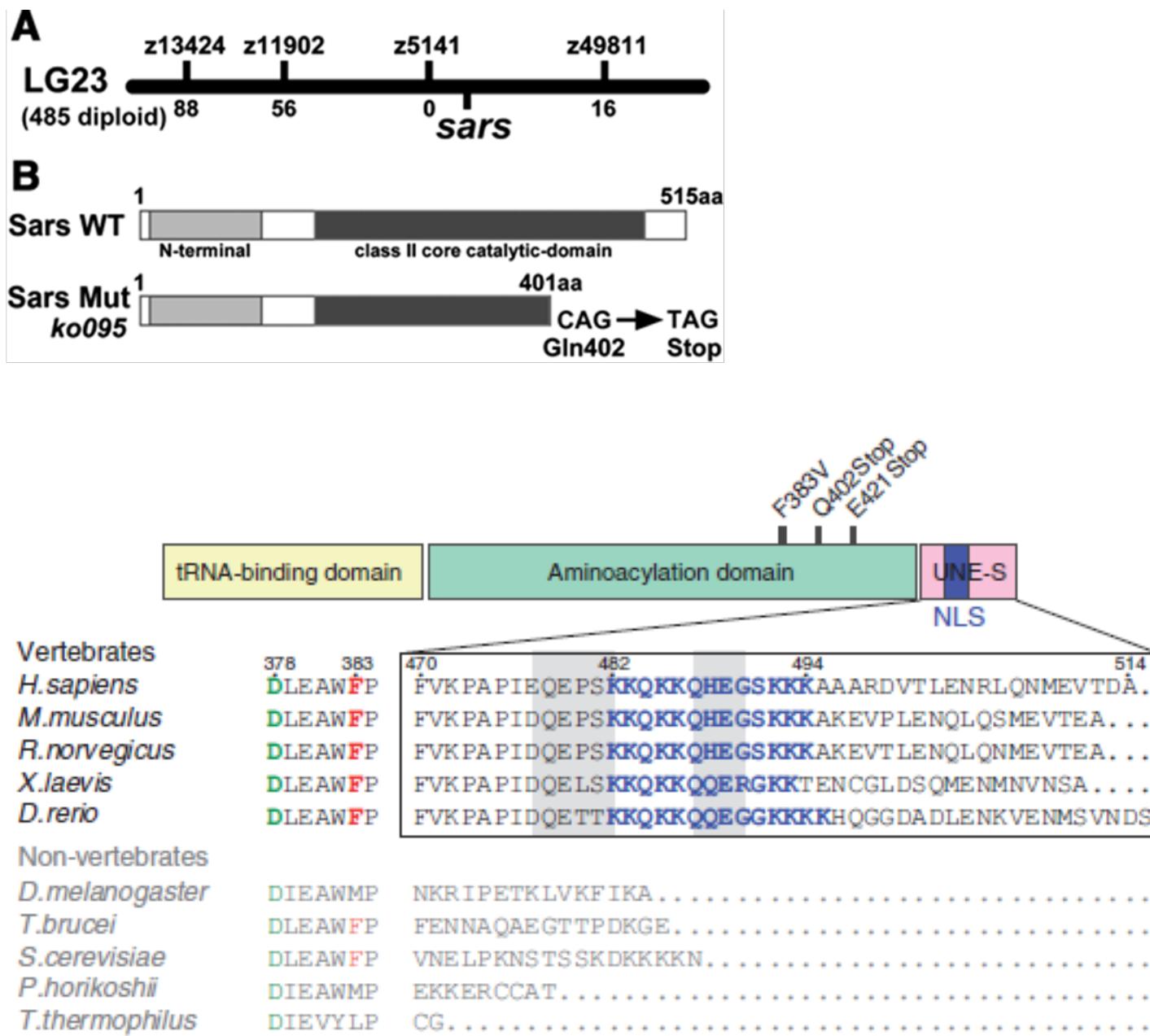
Received 24 Oct 2011 | Accepted 16 Jan 2012 | Published 21 Feb 2012

DOI: 10.1038/ncomms1686

Unique domain appended to vertebrate tRNA synthetase is essential for vascular development

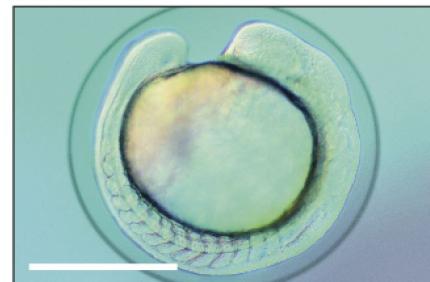
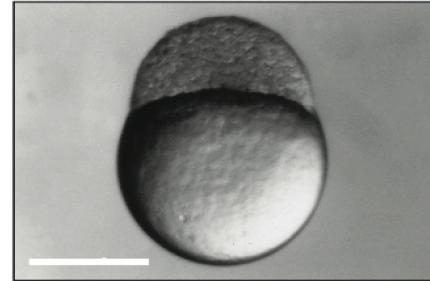
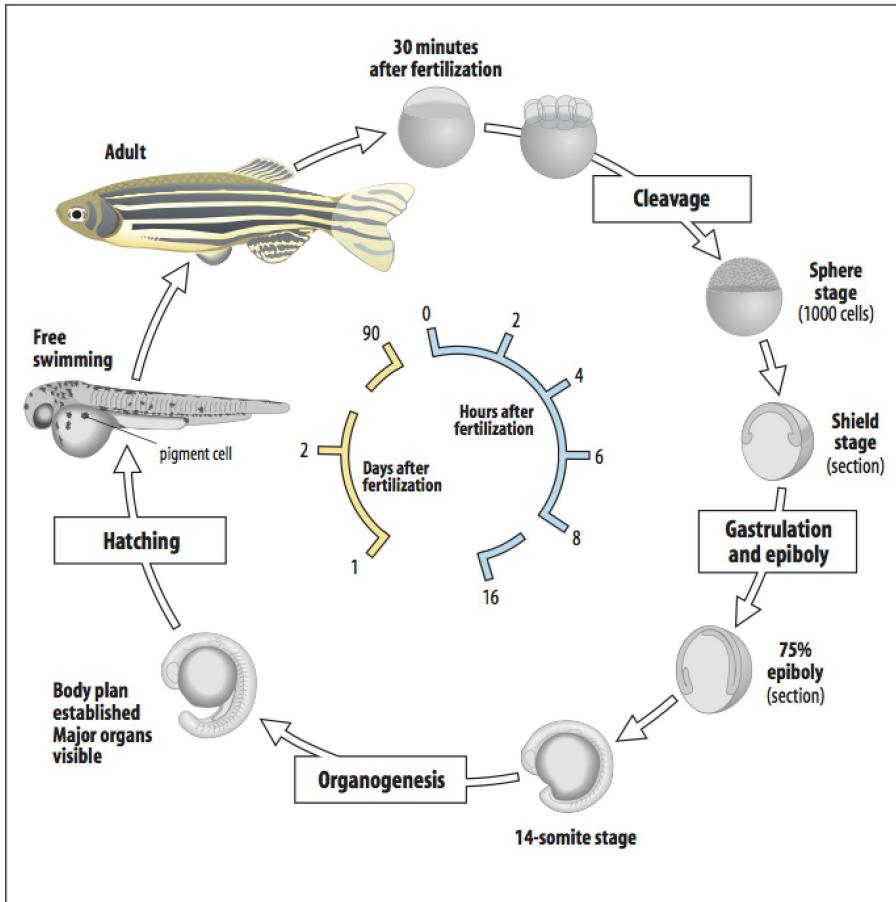
Xiaoling Xu^{1,*}, Yi Shi^{1,*}, Hui-Min Zhang^{2,†}, Eric C. Swindell³, Alan G. Marshall^{2,4}, Min Guo⁵, Shuji Kishi⁶ & Xiang-Lei Yang¹

New domains were progressively added to cytoplasmic aminoacyl transfer RNA (tRNA) synthetases during evolution. One example is the UNE-S domain, appended to seryl-tRNA synthetase (SerRS) in species that developed closed circulatory systems. Here we show using solution and crystal structure analyses and *In vitro* and *In vivo* functional studies that UNE-S harbours a robust nuclear localization signal (NLS) directing SerRS to the nucleus where it attenuates vascular endothelial growth factor A expression. We also show that SerRS mutants previously linked to vasculature abnormalities either deleted the NLS or have the NLS sequestered in an alternative conformation. A structure-based second-site mutation, designed to release the sequestered NLS, restored normal vasculature. Thus, the essential function of SerRS in vascular development depends on UNE-S. These results are the first to show an essential role for a tRNA synthetase-associated appended domain at the organism level, and suggest that acquisition of UNE-S has a role in the establishment of the closed circulatory systems of vertebrates.

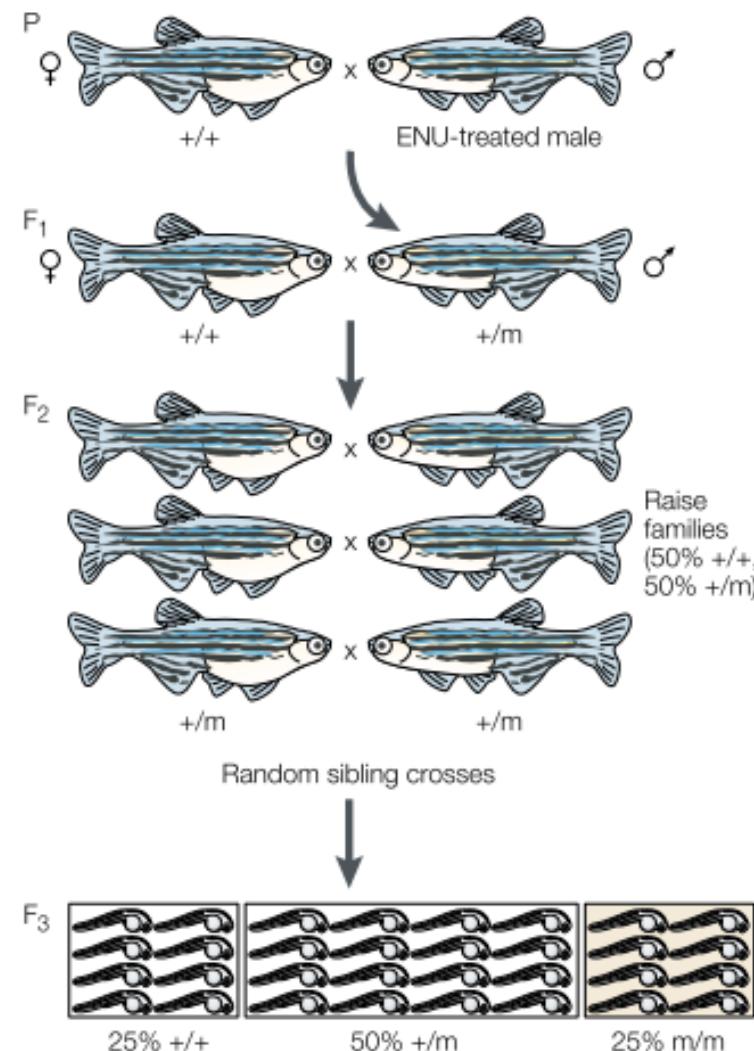


Comparison of mutagenesis in zebrafish and Drosophila

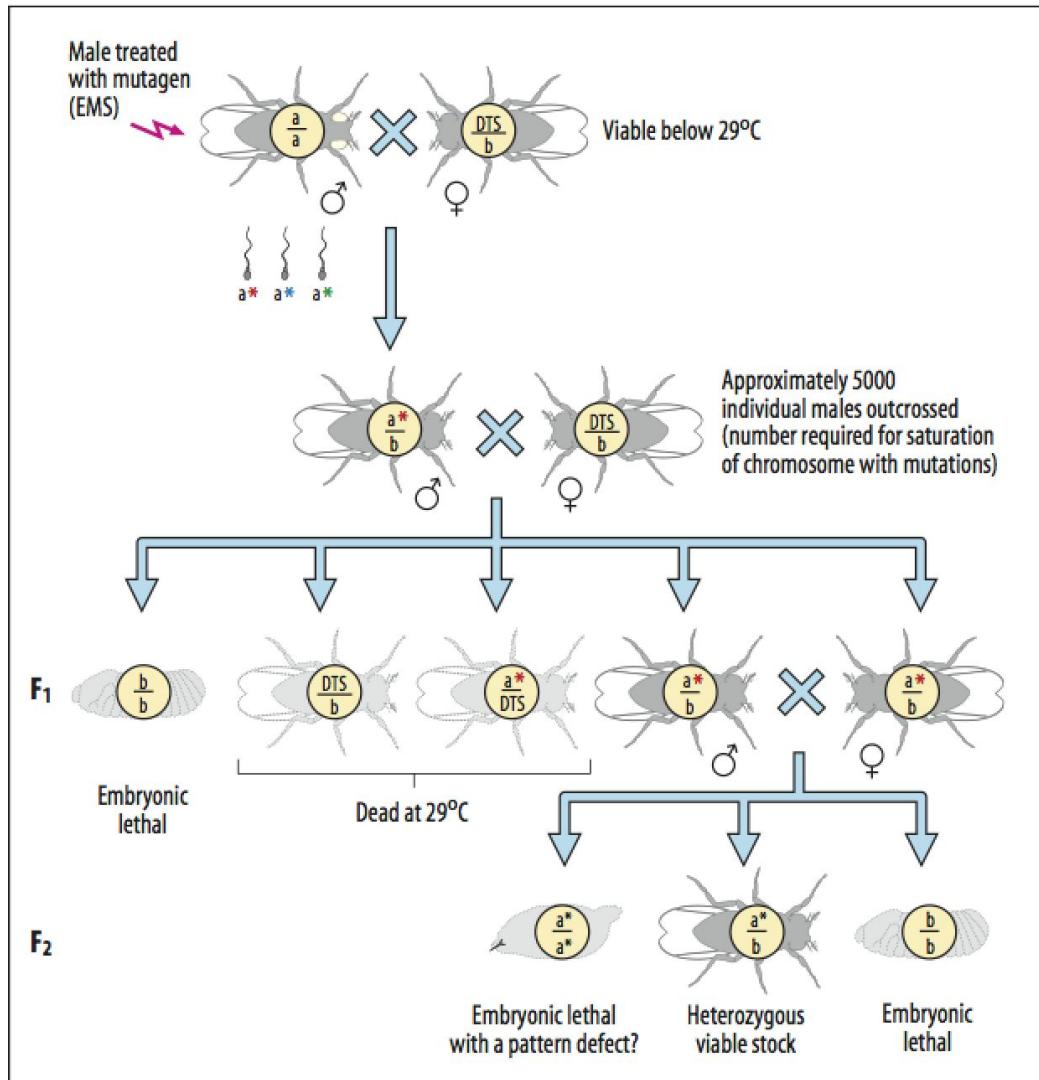
The life cycle of zebrafish



Mutagenesis and genetic screening strategy for identify developmental mutants in zebrafish



Mutagenesis and genetic screening strategy for identify developmental mutants in *Drosophila*



Forward-genetics analysis of sleep in randomly mutagenized mice

Hiromasa Funato^{1,2}, Chika Miyoshi^{1*}, Tomoyuki Fujiyama^{1*}, Takeshi Kanda^{1*}, Makito Sato^{1,3*}, Zhiqiang Wang¹, Jing Ma¹, Shin Nakane⁴, Jun Tomita⁴, Aya Ikkyu¹, Miyo Kakizaki¹, Noriko Hotta-Hirashima¹, Satomi Kanno¹, Haruna Komiya¹, Fuyuki Asano¹, Takato Honda¹, Staci J. Kim¹, Kanako Harano¹, Hiroki Muramoto¹, Toshiya Yonezawa¹, Seiya Mizuno⁵, Shinichi Miyazaki¹, Linzi Connor¹, Vivek Kumar^{6,7}, Ikuo Miura⁸, Tomohiro Suzuki⁸, Atsushi Watanabe⁹, Manabu Abe¹⁰, Fumihiro Sugiyama⁵, Satoru Takahashi⁵, Kenji Sakimura¹⁰, Yu Hayashi^{1,11}, Qinghua Liu^{1,12}, Kazuhiko Kume⁴, Shigeharu Wakana⁸, Joseph S. Takahashi^{1,6,13} & Masashi Yanagisawa^{1,3,13,14}

Sleep is conserved from invertebrates to vertebrates, and is tightly regulated in a homeostatic manner. The molecular and cellular mechanisms that determine the amount of rapid eye movement sleep (REMS) and non-REMS (NREMS) remain unknown. Here we identify two dominant mutations that affect sleep and wakefulness by using an electroencephalogram/electromyogram-based screen of randomly mutagenized mice. A splicing mutation in the *Sik3* protein kinase gene causes a profound decrease in total wake time, owing to an increase in inherent sleep need. Sleep deprivation affects phosphorylation of regulatory sites on the kinase, suggesting a role for SIK3 in the homeostatic regulation of sleep amount. *Sik3* orthologues also regulate sleep in fruitflies and roundworms. A missense, gain-of-function mutation in the sodium leak channel NALCN reduces the total amount and episode duration of REMS, apparently by increasing the excitability of REMS-inhibiting neurons. Our results substantiate the use of a forward-genetics approach for studying sleep behaviours in mice, and demonstrate the role of SIK3 and NALCN in regulating the amount of NREMS and REMS, respectively.

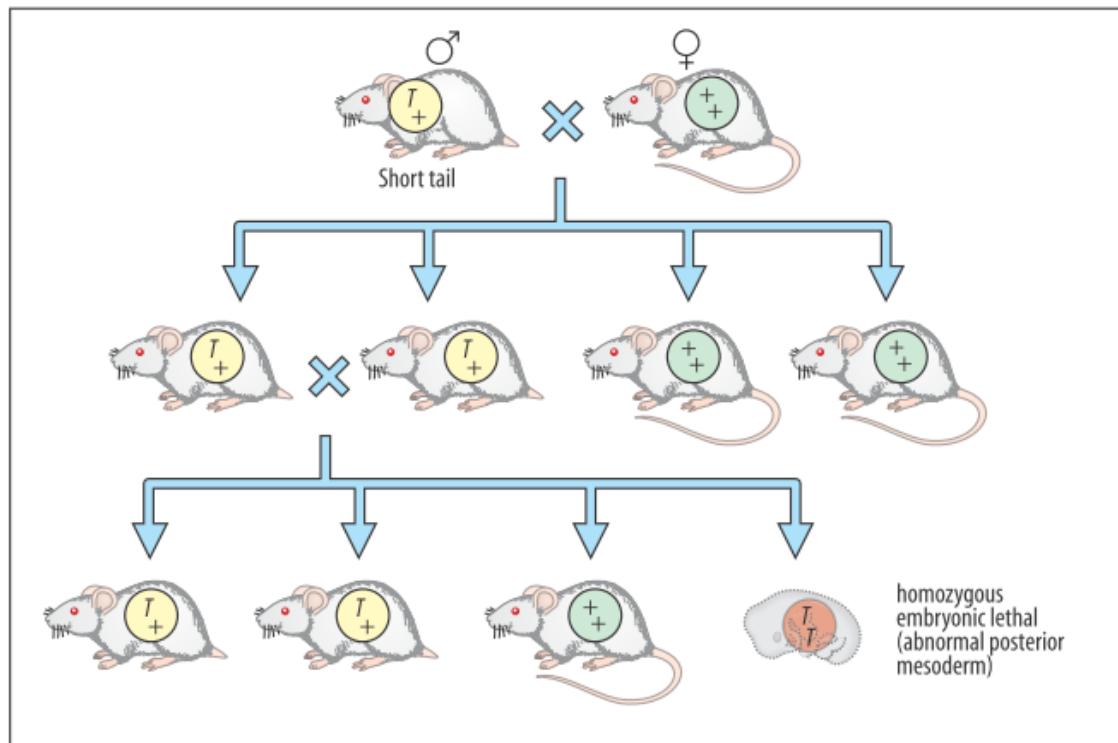
Sleep is an animal behaviour ubiquitously conserved from vertebrates to invertebrates, including flies and nematodes^{1–3}, and is tightly regulated in a homeostatic manner. Sleep in mammals exhibits the cycles of REMS and NREMS that are defined by characteristic activity of electroencephalogram (EEG) and electromyogram (EMG). Time spent in sleep is determined by a homeostatic sleep need, a driving force for sleep/wakefulness switching, which increases during wakefulness and dissipates during sleep^{4,5}. The spectral power in the delta-range frequency (1–4 Hz) of EEG during NREMS has been regarded as one of best markers for the current level of sleep need. Conversely, the level of arousal is positively correlated with sleep latency, which can be regulated independently of sleep need⁶, reflecting the overall activity of wake-promoting neurons. Traditional approaches to locate the neural circuits regulating sleep and wakefulness behaviour included local ablation of brain regions^{7–9}. Recent advances in optogenetic and chemogenetic research have directly demonstrated that switching between sleep and wake states is executed by subsets of neurons in

and mice successfully uncovered the molecular network of the core clock genes regulating circadian behaviours^{17–19}. Sleep-regulating genes were also discovered through the screening of mutagenized flies^{1,2}. However, genetic studies for sleep using mice has been challenging because of the effective compensation and redundancy in the regulation of sleep and wakefulness, and the need for EEG and EMG monitoring of the staging of wakefulness, NREMS and REMS.

Sik3 splice mutation increases NREMS

We induced random point mutations into C57BL/6J (B6J) male mice (G_0) by ethylnitrosourea (ENU) and screened more than 8,000 heterozygous B6J \times C57BL/6N (B6N) F_1 mice for dominant sleep and wakefulness abnormalities through EEG/EMG-based sleep staging (Extended Data Fig. 1a). B6N was chosen as a counter strain because its sleep and wakefulness parameters are highly similar to B6J (Extended Data Fig. 1b), and the entire list of single nucleotide polymorphisms has recently become available²⁰.

Genetics of the semi-dominant mutation *Brachyury* (*T*) in the mouse.



Brachyury (*T*) is *ntl* (*no tail*) in zebrafish.

Thanks!