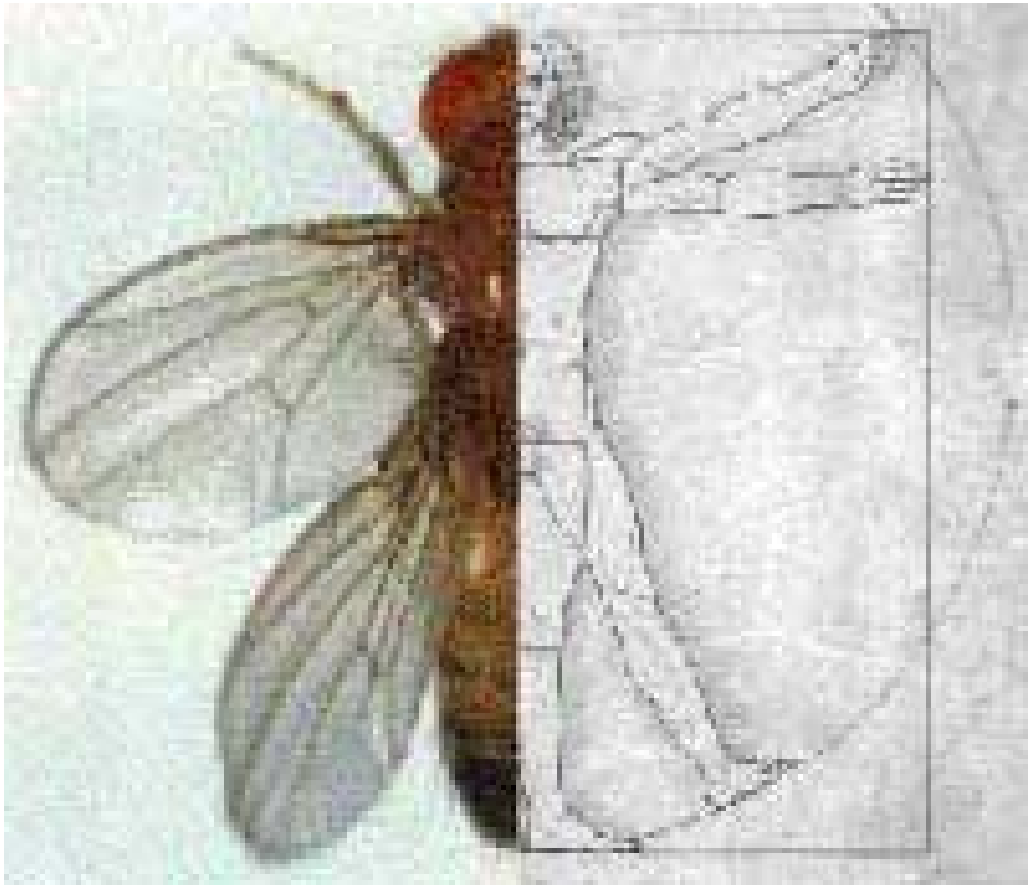
Invertebrate models of human disease

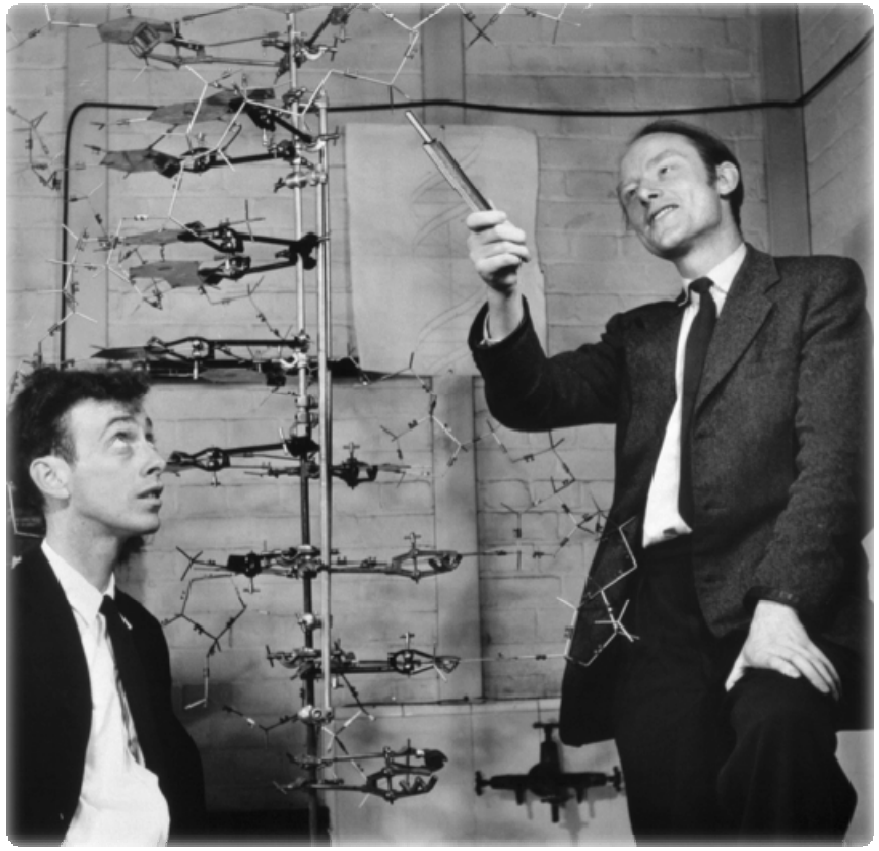


November 2015
NCBS, TIFR, Bangalore

Foundational Milestones in Genetics & Genomics

Mendel *1865*

The inheritance of traits

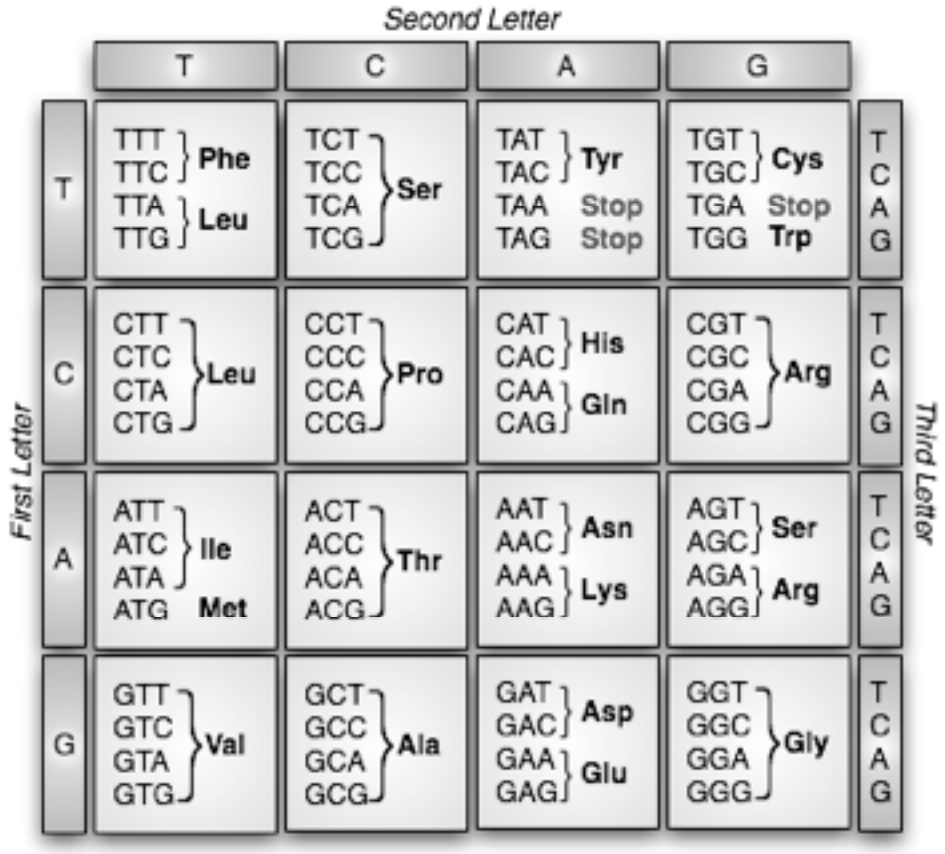


Watson and Crick *1953*

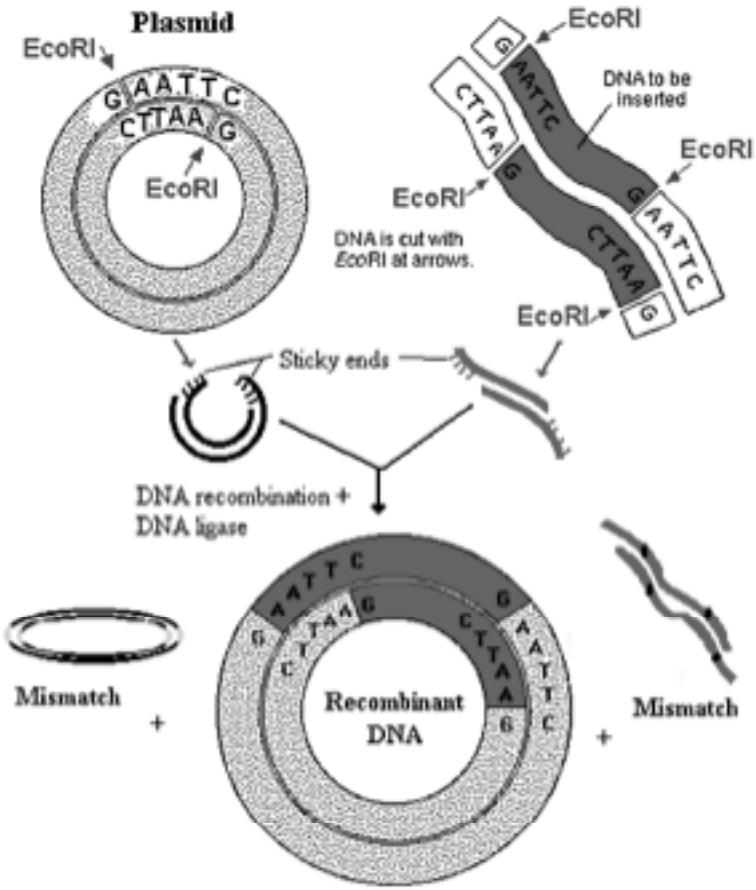
Double helical structure of DNA

1960's

1980's



The Genetic Code



DNA Cloning and sequencing

The Origin of "Genomics": 1987

EDITORIAL

A New Discipline, A New Name, A New Journal

***Genomics* (1987)**

For the newly developing discipline of [genome] mapping/sequencing (including the analysis of the information), we have adopted the term GENOMICS… The new discipline is born from a marriage of molecular and cell biology with classical genetics and is fostered by computational science.

October, 1990

Human Genome Project Begins

April, 2003

Human Genome Project Ends

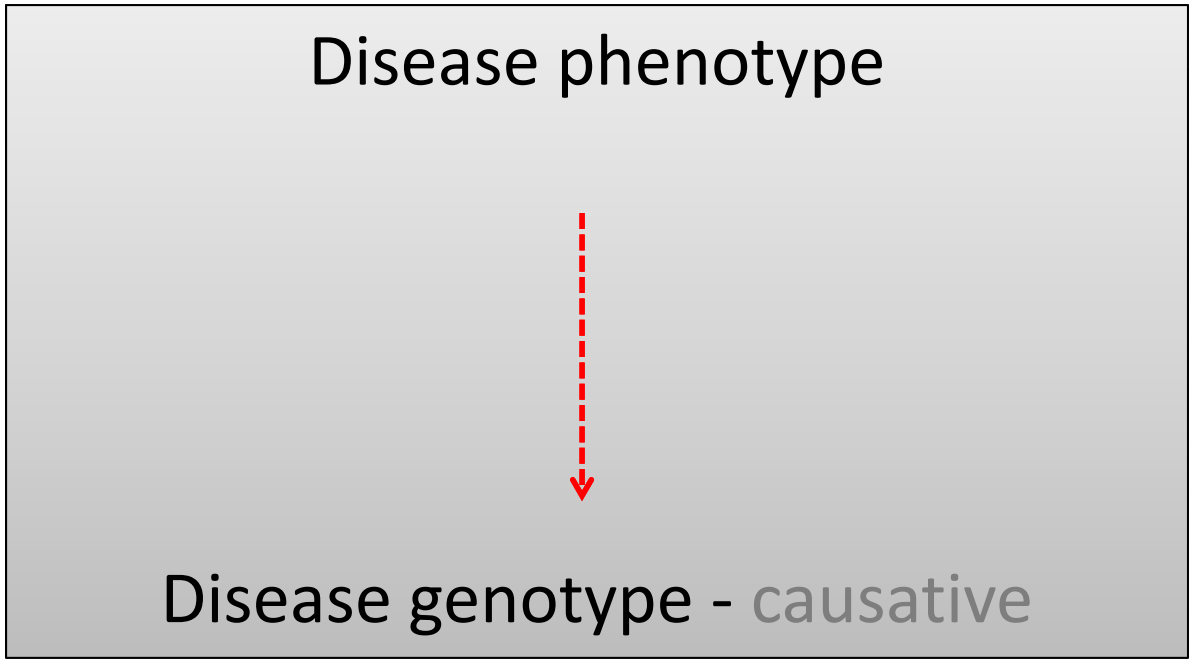
The Path to Genomic Medicine

Human Genome Project

Realization of Genomic Medicine

"Fulfilling the Promise"

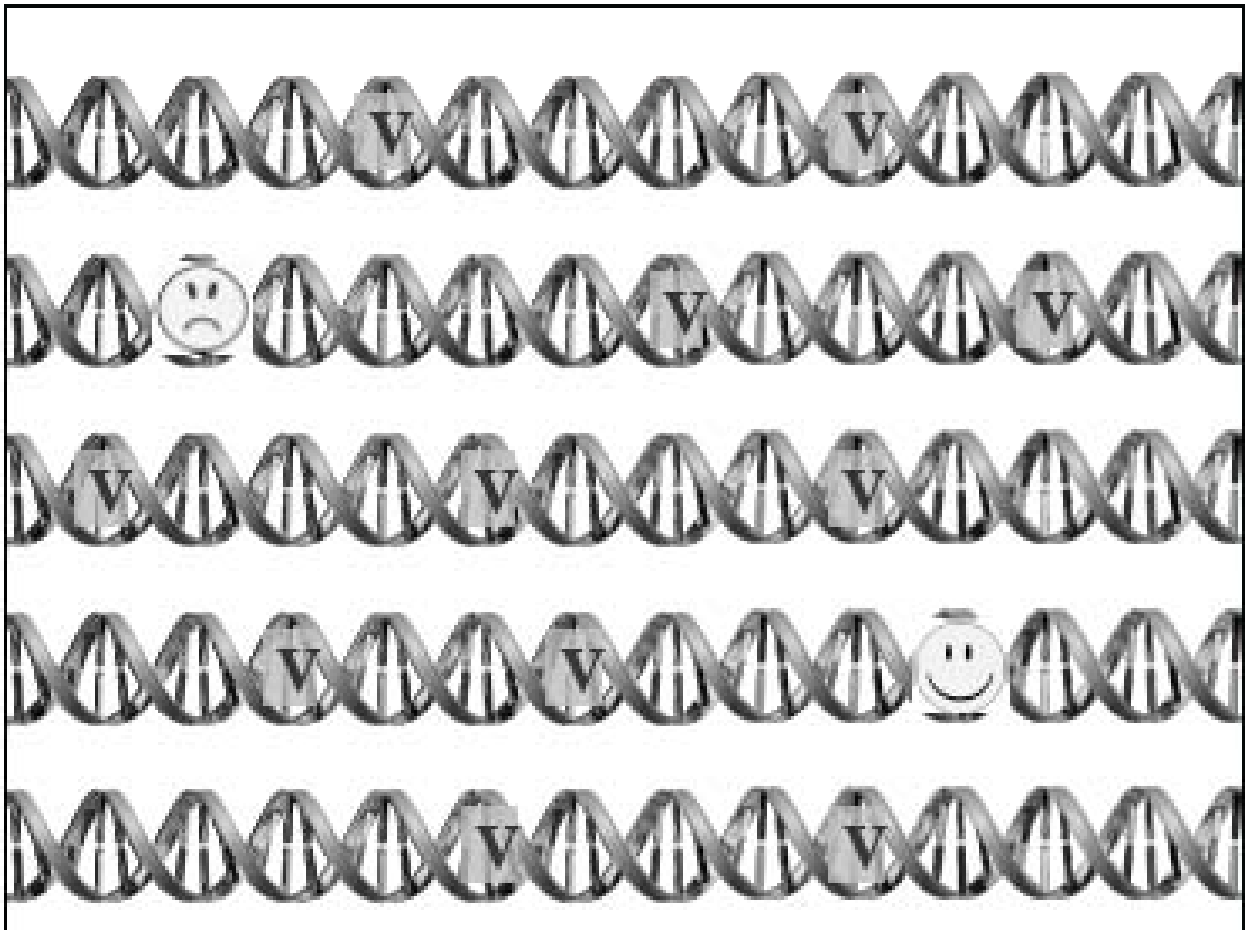
Challenges



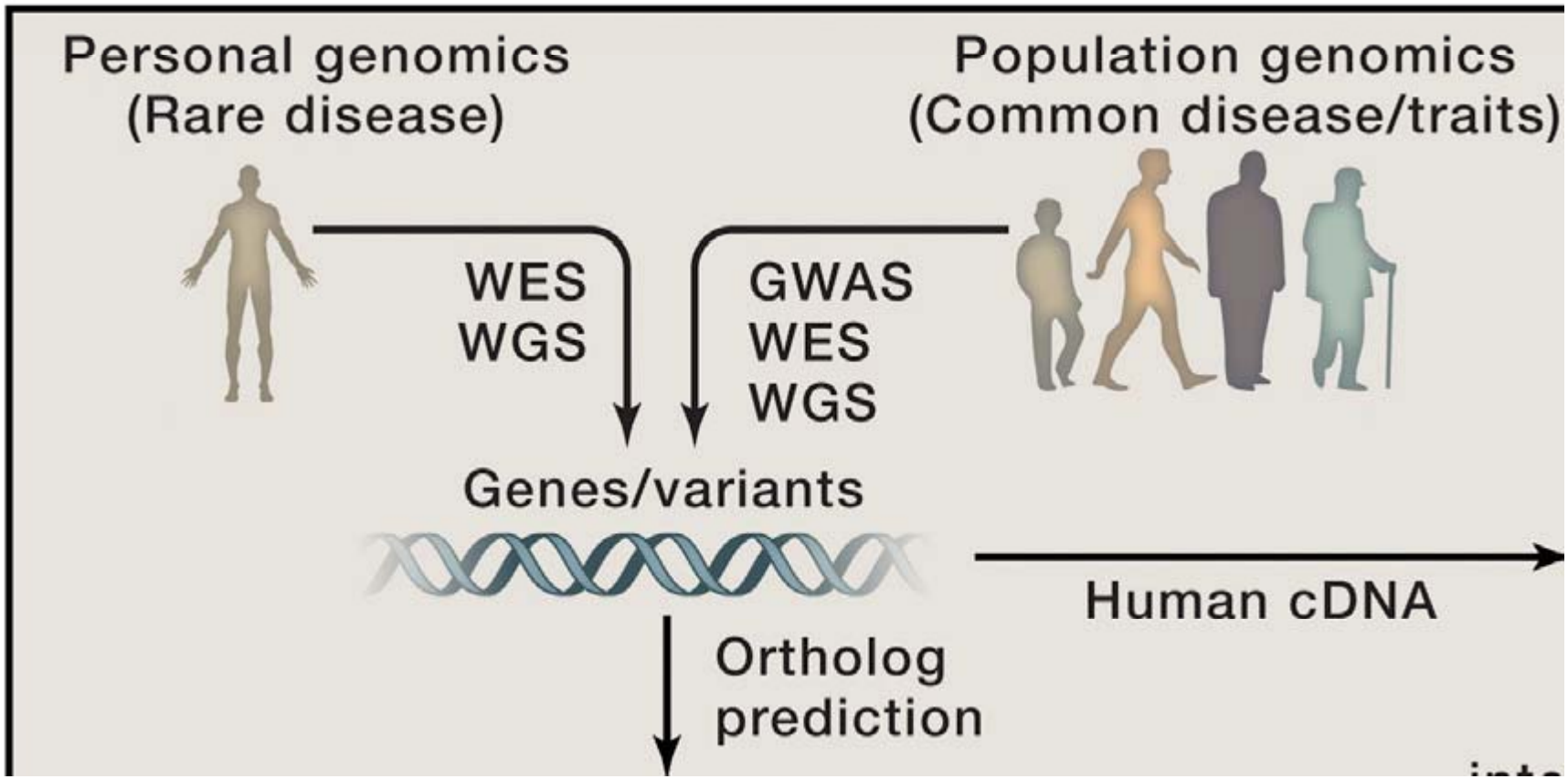
~30,000 genes in the human genome

Vast regions of the human genome are non-coding

Which mutation is causative for the disease?

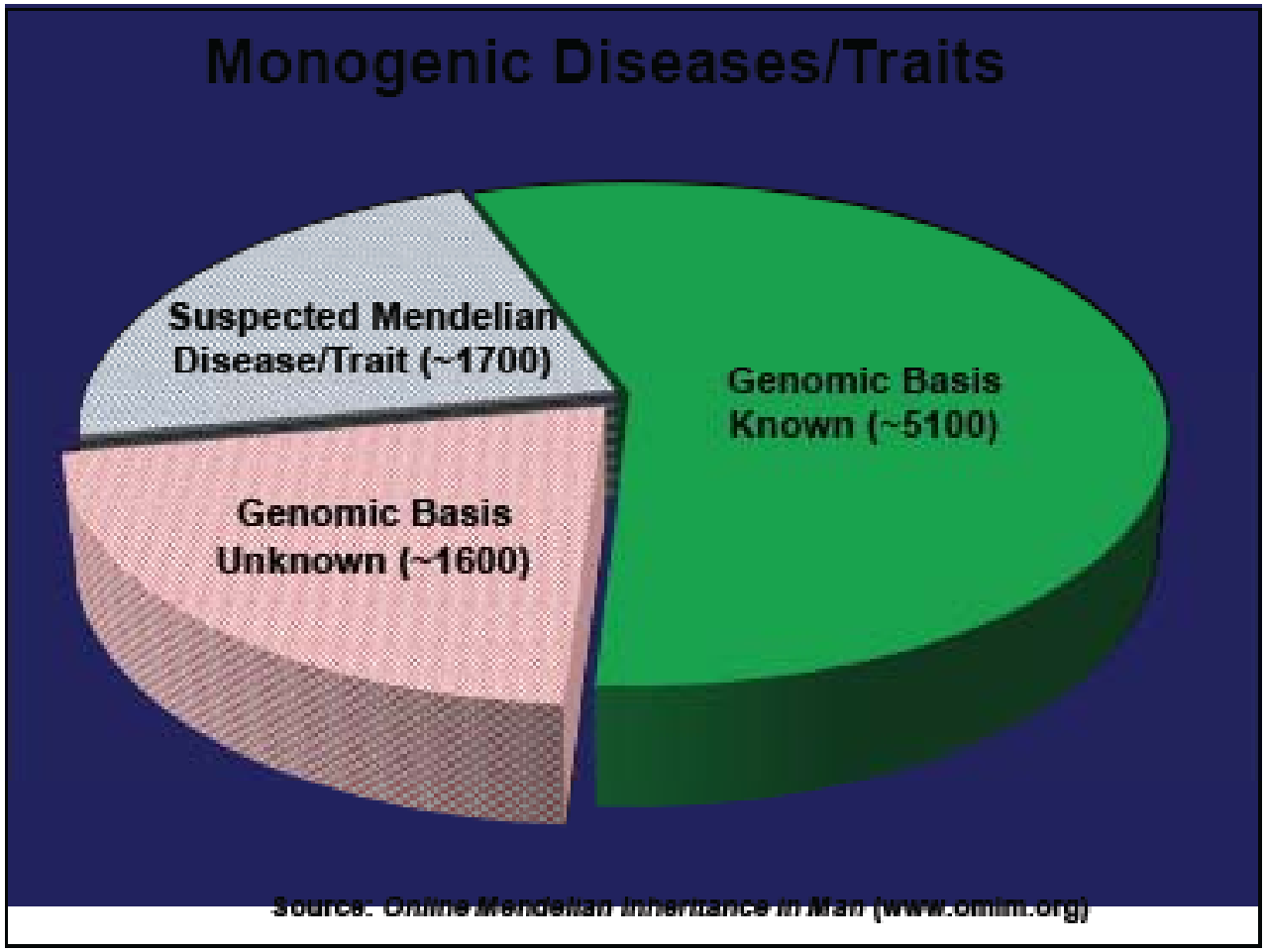


Many human diseases have a genetic component



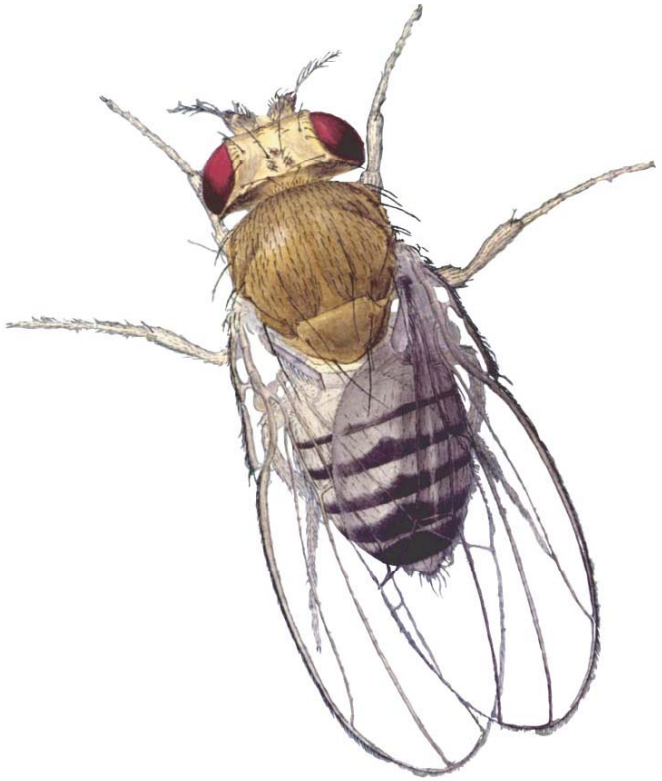
Normal Gene Function and mechanism of disease causation

OMIM database: Online mendelian inheritance in man



Yeast

C. elegans



Drosophila

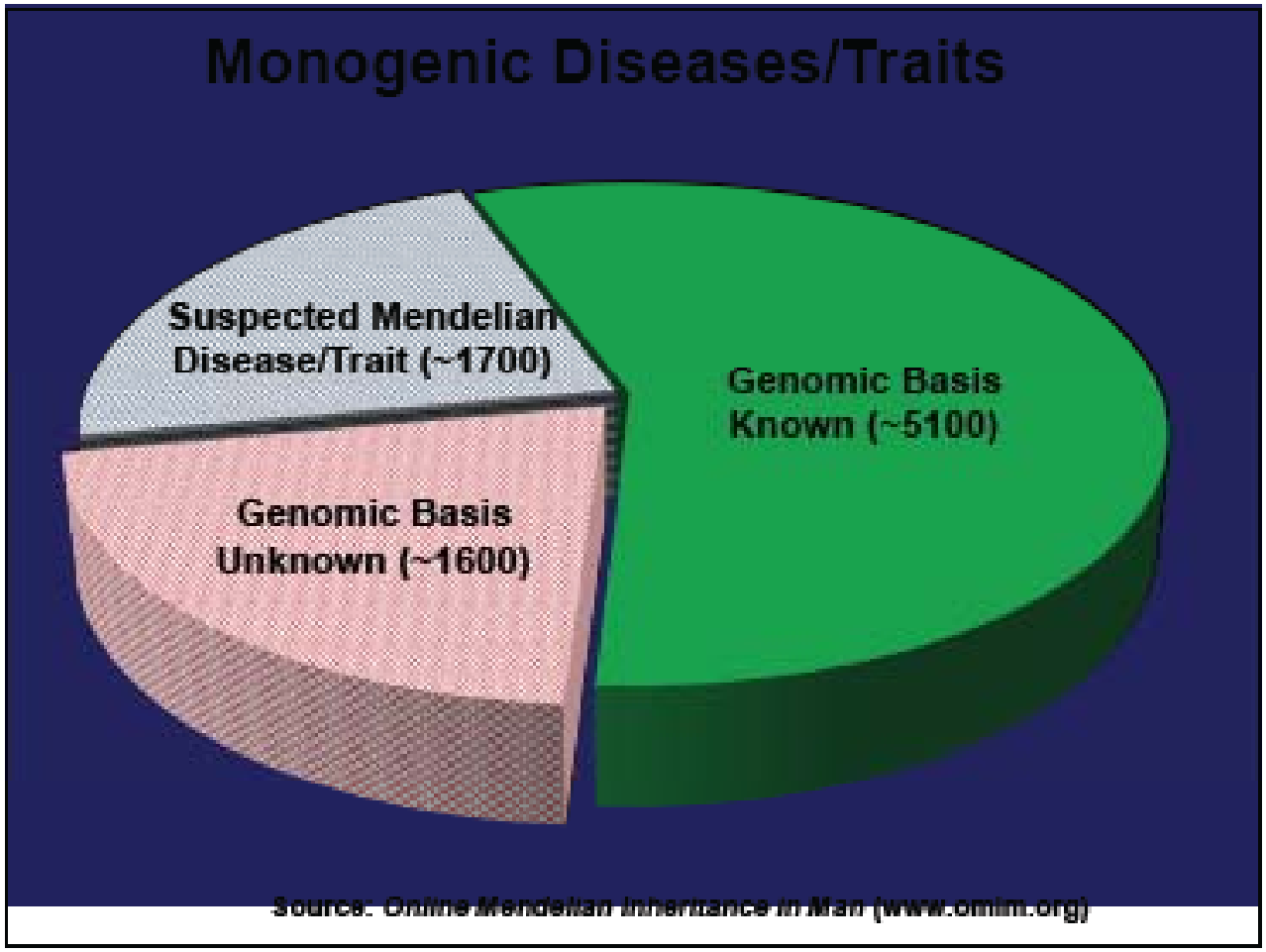
Some key examples

Cancer pathways – e.g **Ras, wingless, hedgehog and notch** - were identified as causative because their cellular function had been understood in invertebrate development. **Several anti-cancer drugs are targeted to molecules in these pathways**

Cardiac diseases, Epilepsy, Deafness – caused by mutations in a class of **Potassium channels** that were originally identified and characterized in *Drosophila* (the *Shaker* family) and *C. elegans*

Discovery of **innate immune receptors** in *Drosophila* followed by their identification in humans and their role in **microbial and viral immunity, autoimmune diseases and allergies**. More recently in **cancer**

OMIM database: Online mendelian inheritance in man



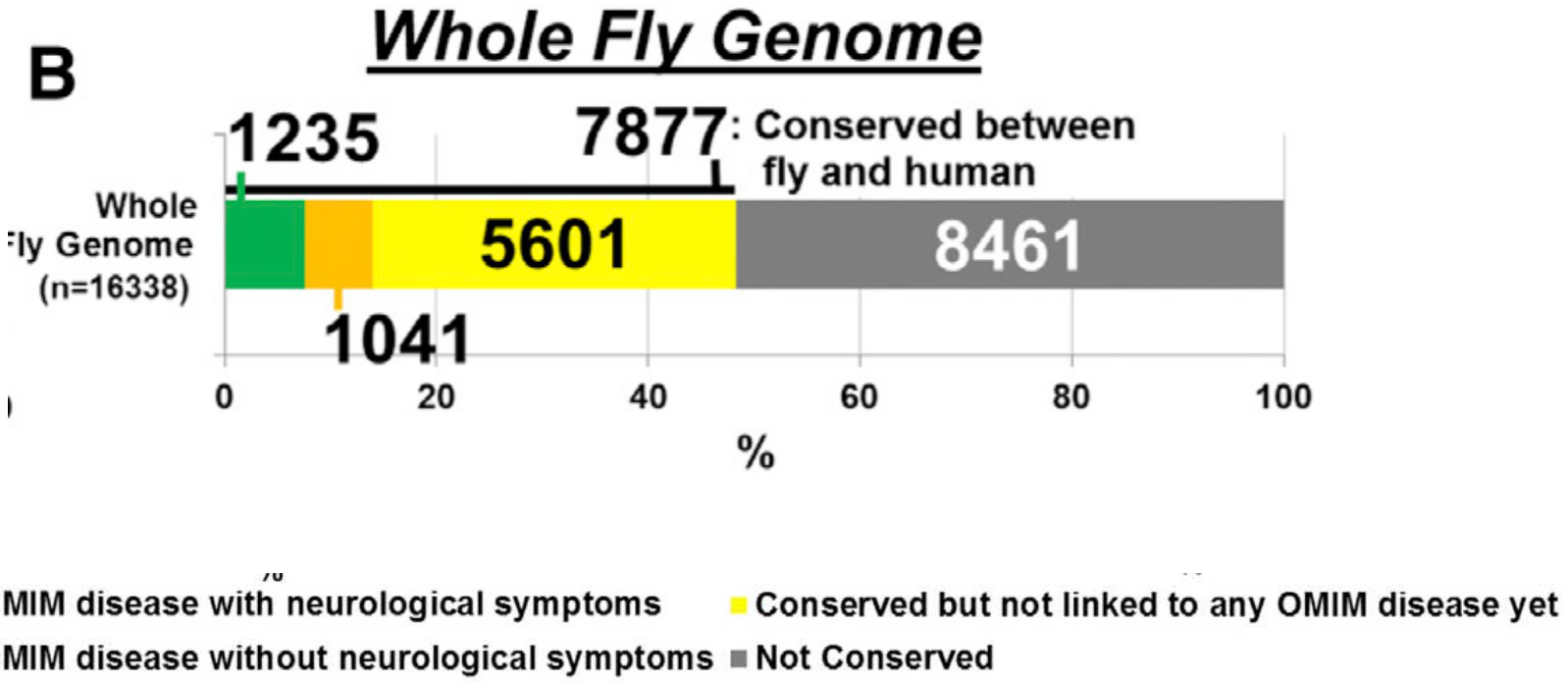
A *Drosophila* Genetic Resource of Mutants to Study Mechanisms Underlying Human Genetic Diseases

Cell 159, 200–214, September 25, 2014

Bellen Lab, Baylor College of Medicine, Houston, Texas, USA

Nearly 75% OMIM genes have fly homologs

Nearly 50% of the fly genome is conserved with human



Hypothesis:

Genes that cause neurodegeneration have not been identified successfully in model organisms because they are present as one copy and their encoded protein is essential. Thus most mutants die as embryos

In humans multiple genes encode such essential protein. A mutation may only affect the gene whose function is required in neurons. Such individuals will be viable but will show disease symptoms with age

Essential genes with effects on the nervous system = candidate neurodegeneration gene

Experimental design:

Carried out a genetic screen to identify novel genes on the X chromosome of Drosophila that cause neural defects - possibly linked to neurodegeneration in humans. Among the identified genes (**153**) many were already associated with neurological disease

WES from ~2000 individuals belonging to families with rare genetic disorders where the underlying genetic defect was not identified

Obtained sequence of ALL variants for ALL genes identified in the *Drosophila* screen and followed their Mendelian inheritance to classify them as disease candidates

Disease genes identified in human patients as a consequence of the dual screening strategy

Two patients with symptoms of Charcot-Marie-Tooth disease were diagnosed with mutations in the dynamin 2 gene – it is a human homolog of the *Drosophila* gene for Dynamin

Human homolog (CRX) of a *Drosophila ocelliless* – was identified as the mutant gene underlying a late onset retinal degeneration disease in 3 unrelated individuals with no previous family history of disease. In the past CRX mutants have been identified in **early** onset of retinal degeneration

Mutations in the Ankle2 gene were identified in a family with microcephaly. The Ankle2 gene was screened because it had shown up in the Drosophila screen as affecting sensory organ development

Disease mechanisms

Identify new disease genes

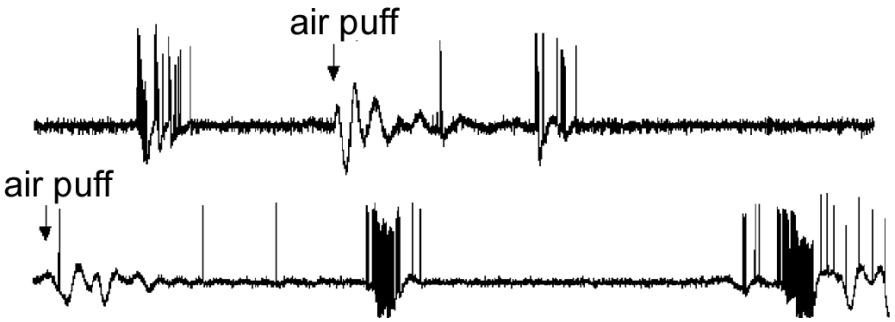
Cellular function of disease gene leading to an understanding of its role in organismal physiology

Identify modifiers of disease gene function to find therapeutic targets for the disease

Drosophila inositol 1,4,5 trisphosphate receptor (*itpr*) mutants are flightless

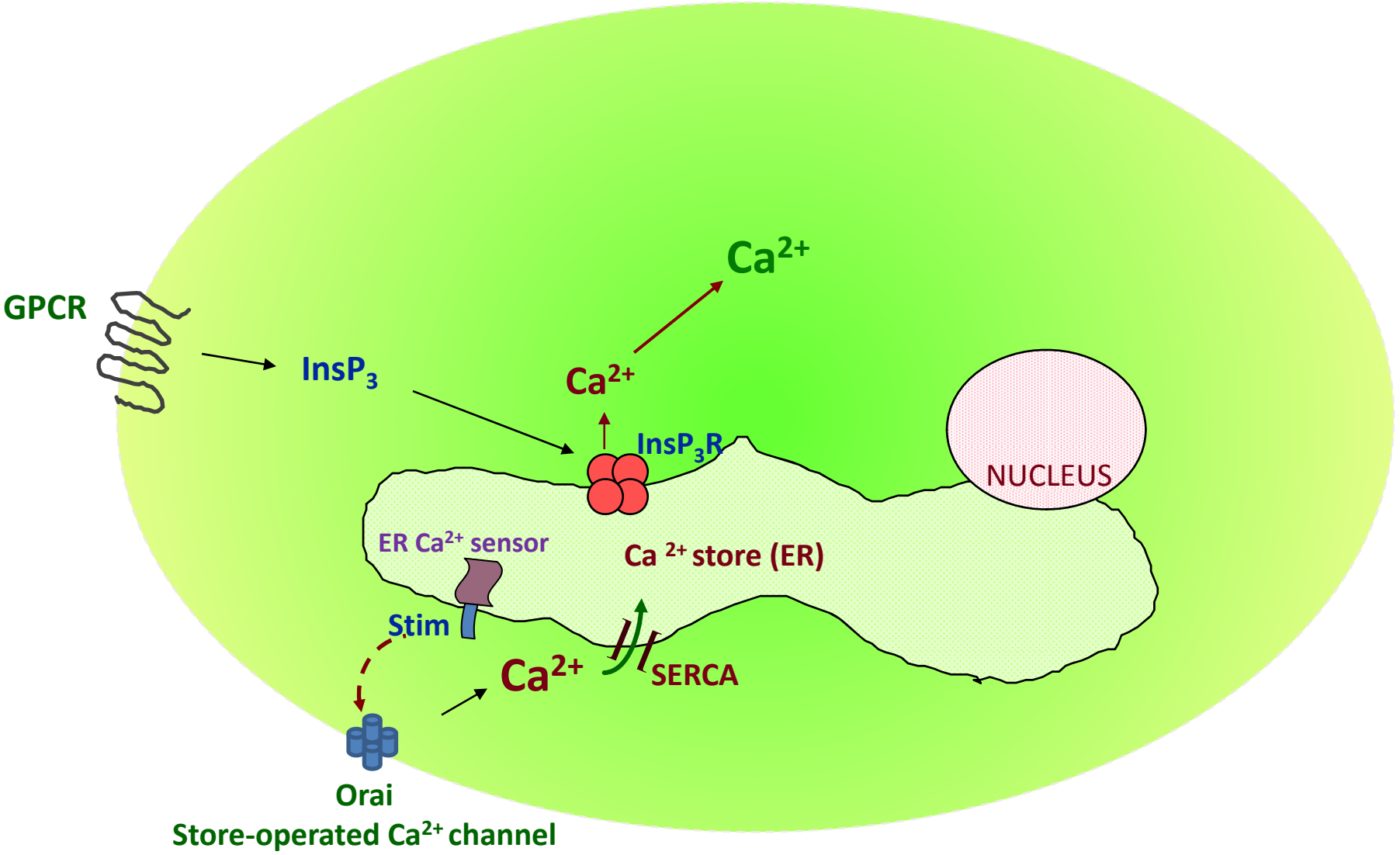
Wild type

***itpr* mutant**

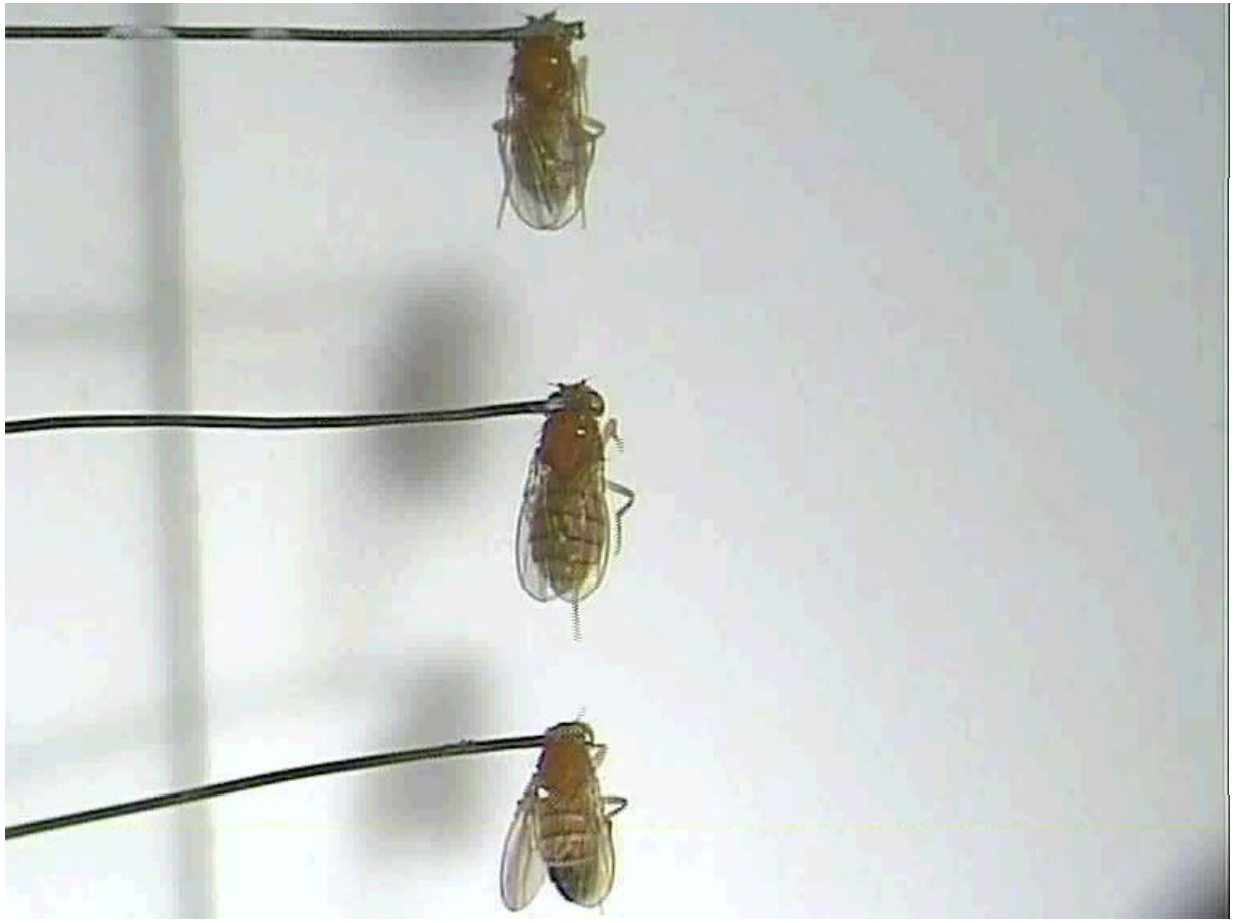


Banerjee et al., J. Neurosci 2004

Intracellular Ca^{2+} release and Store-operated calcium entry or SOCE



$InsP_3$ receptor mutants can fly!



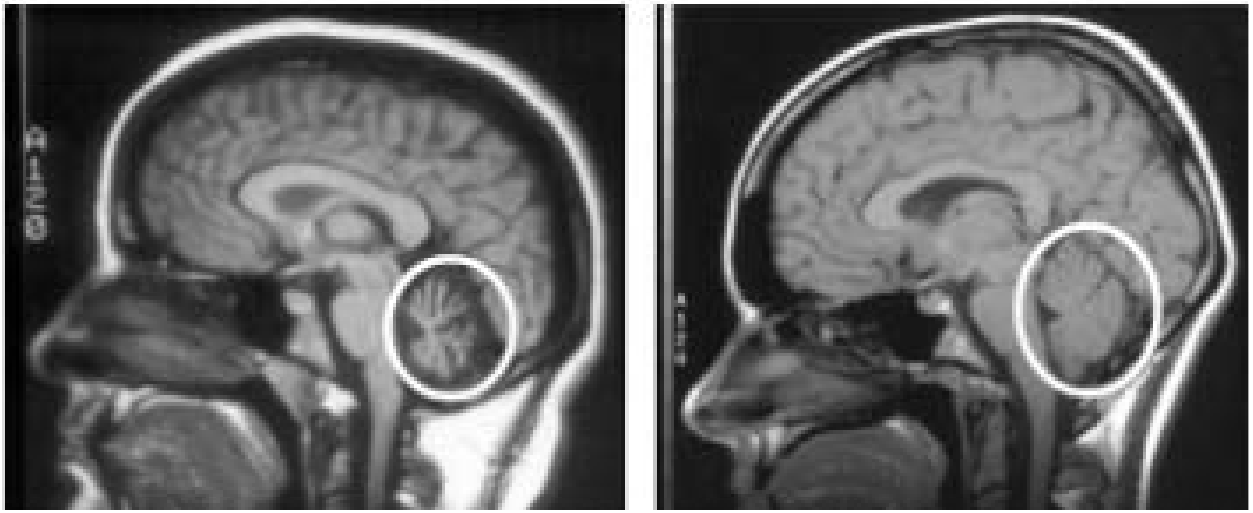
Normal

Mutant with a genetic modifier

Mutant

Venkiteswaran and Hasan, PNAS 2009,
Agarwal et al., J. Neurosci 2010

Heterozygosity of $InsP_3R1$ in humans - Spino-cerebellar ataxia (SCA15/16)
van de Leemput et al., 2007; di Gregorio et al., 2010



•SCAs are generally characterized by cerebellar atrophy and a progressive loss in coordination of movement known as ataxia

Advantages of *Drosophila*

$InsP_3$ receptor and SOCE requirement for flight:

What tissue?

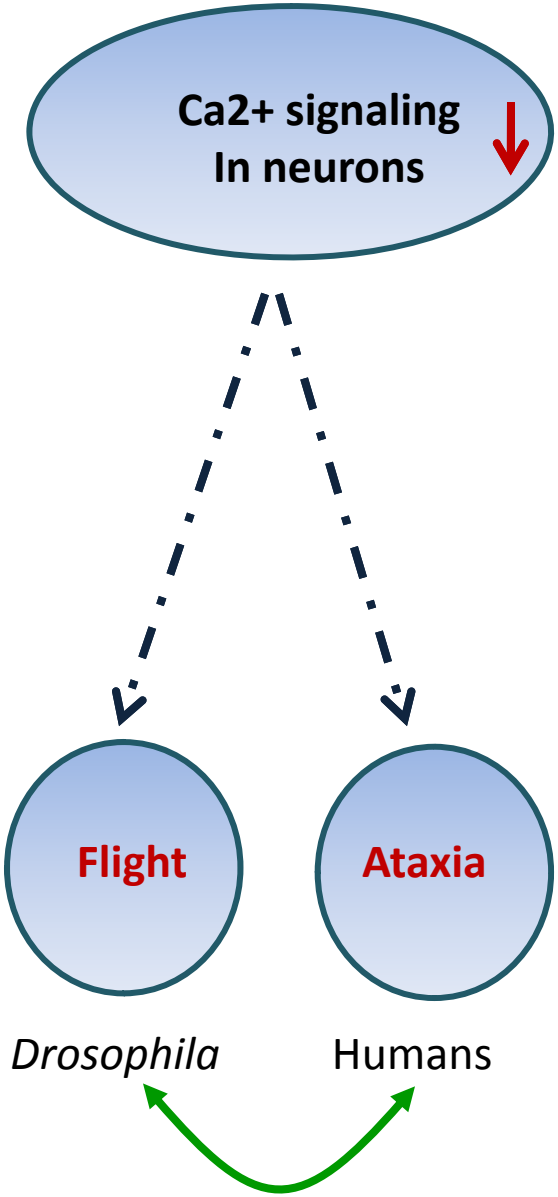
What stage?

Which cells?

Mechanisms of Ca2+ signaling?

Cellular changes downstream of Ca^{2+}?

Testing of potential therapeutic drugs



The Team - 2015