ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
GREEK MINISTRY OF EDUCATION, RESEARCH AND RELIGIOUS AFFAIRS.
ΓΕΝΙΚΗ ΓΡΑΜΜΑΤΕΙΑ ΕΡΕΥΝΑΣ ΚΑΙ ΤΕΧΝΟΛΟΓΙΑΣ

FORTH
FOUNDATION FOR RESEARCH AND TECHNOLOGY-HELLAS
INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY

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PRESS RELEASE

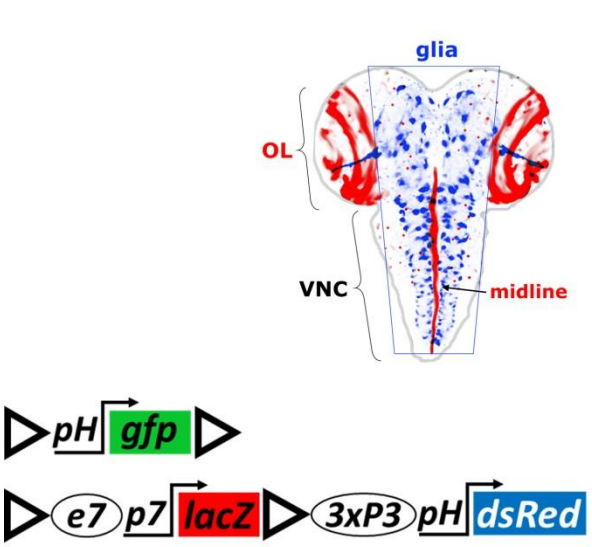
SUBJECT: NEW PUBLICATION

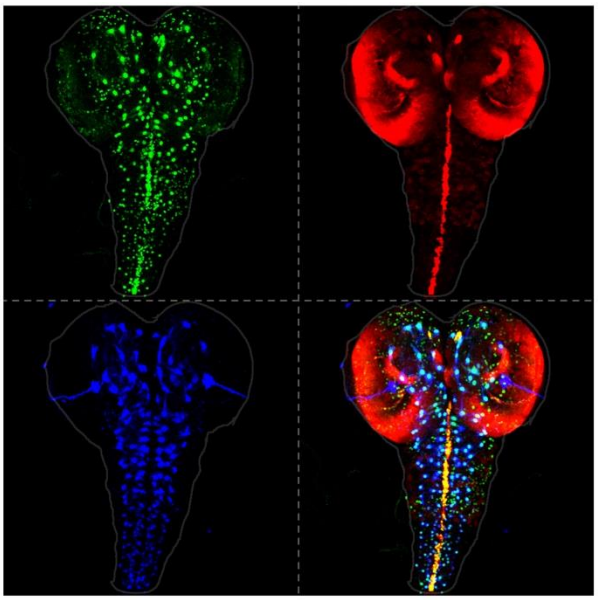
IMBB scientists describe a novel mechanism of interchromosomal gene regulation

Precise activity of a gene requires its promoter to be matched with an appropriate enhancer. Enhancers are stretches of DNA near a gene, which recruit transcption factors, a cohort of regulatory proteins that instruct the gene to get transcribed (turn on) or remain silent. They do so by looping the chromosome thread to bring the enhancer near the promoter, another DNA stretch at the start of the gene's coding sequence, where the transcriptional machinery is recruited to initiate copying of the DNA to RNA. Although promoters and enhancers are intensely studied, another less prominent type of DNA element in this fundamental process of gene regulation are the so-called insulators. Insulators serve to limit inappropriate enhancer-promoter interactions and are important players in subdividing animal genomes into domains of independent gene activity.

The PhD student Pawel Piwko and collaborators, led by the IMBB associate researcher and University of Crete professor Christos Delidakis, revisited a phenomenon of inter-chromosome gene regulatory interaction. The two homologous chromosomes (one from each parent) are closely aligned in all cells of the fruitfly *Drosophila melanogaster*. This apparently enables enhancers from one homologue to activate promoters on the opposing homologue. This is an unusual mechanism of gene regulation, since normally enhancers, promoters and coding regions are in proximity of each other on the *same* DNA molecule. When it was first recognized by Nobel laureate Ed Lewis in the 1950's, it was dubbed transvection.

In their work published in the journal GENETICS, the IMBB scientists used modern transgenesis techniques to insert artificially assembled genes in specific places (loci) in the fruitfly's genome. They then studied the activity of a large number of pairs of such transgenes, each member of the pair inserted in the same locus of two homologous chromosomes. They found that transvection requires the presence of an insulator element on both homologues. When the same insulator is placed next to a transgene in both homologues, an enhancer from the one transgene can robustly activate transcription from a promoter in the other. They showed that four different insulators can support transvection, and that this can happen at any of several loci in the genome, as long as chromosome pairing is not disrupted. Though necessary, the presence of homotypic insulators is not sufficient for transvection; their position, number and orientation matters. The identity of enhancers and promoters in the vicinity of a *trans*-interacting insulator pair is also important, indicative of complex insulator-enhancer-promoter interactions. It therefore appears that transvection is simply an epiphenomenon of normal gene regulatory mechanisms (that are traditionally thought to take place within the same chromatin thread) and the ability of *Drosophila* homologous chromosomes to pair with each other. As such, it highlights a heretofore little appreciated *positive* role of insulators in transcription and proposes that insulators could generally function as powerful and versatile gene regulators.





Two transgenes are placed opposite each other in the fruitfly's genome: one contains two tandem artificial genes: lacZ (red) is driven by promoter p7 and enhancer e7 and dsRed (blue) is driven by promoter pH and enhancer 3xP3. Their protein products are detected in Drosophila tissues in red and blue, respectively. The other transgene (pH-gfp) lacks an enhancer and, as a result, it is not expressed at all. As an example, a larval nervous system is shown with anatomical structures expressing the lacZ and dsRed proteins annotated in red and blue, respectively (In the schematic, OL= optic lobe, VNC = ventral nerve cord). In the micrographs, images of a nervous system are shown with lacZ, dsRed and GFP detected in red, blue and green, respectively. The opposition of the heretofore silent transgene ph-gfp across the active lacZ and dsRed transgenes results in its activation in the same anatomical structures where the opposed enhancers are active, namely glia, VNC midline and optic lobe: this is an example of transvection. Triangles in the transgene maps represent insulators; if omitted, no GFP is detected.

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Relevant links:

https://www.ncbi.nlm.nih.gov/pubmed/30948430
https://www.genetics.org/content/212/2/489
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