The Gene Concept

Sonja Prohaska

Computational EvoDevo
Universitaet Leipzig

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What is a gene?

"I can't tell but I recognize a gene when I see one."
a biologist

"Something is a gene when a biologist says it is one."
a bioinformatician

"A gene is a database entry with an Ensembl gene ID."
a computer scientist

"A gene is what Wikipedia says it is."
a student

"A gene is a locatable region of genomic sequence, corresponding to a unit of inheritance, which is associated with regulatory regions, transcribed regions and/or other functional sequence regions." Wikipedia

Historical view – really short

In the beginning...

- a *phenotype* has characteristics
- some characteristics are independent
- some characteristics are heritable
- all heritable characteristics need to go through a single cell (gamete)

How to put (all) characteristics of a phenotype into a gamete?

- miniature organism within gamete?
- gemmule, shed by the organs accumulated in gametes? (Darwin 1868)
- distinct, discrete entities that specify characteristics (Mendel 1866)

"special conditions, foundations and determiners which are present [in the gametes] in unique, separate and thereby independent ways [by which] many characteristics of the organism are specified" by Johannsen (1909)

... the **gene** is a (unknown) substance **representing a characteristic**.

Historical view – really short

linkage of genes

- Morgan (1915)
- segregation experiments and crossbreeding
- the observed linkage of genes best fitted a model of a linear arrangement
- size of genes and distance between genes could be inferred
- the model had predictive power in breeding

How did this change the understanding of a gene?

- genes are continuous
- genes are nonoverlapping
- distinct genes have distinct dimensions
- genes are linked to verying degrees

A gene is an abstract entity whose existance is reflected in the way a phenotype is transmitted between generations.

Historical view – really short

- **1941** Beadle and Tatum: *"one gene, one enzyme"*
  The gene is the information behind the individual molecule.
- **1955** Hershey and Chase: the substance for genes is DNA
- **1955** Benzer: a cistron (gene) is a region of DNA defined by mutations that in *trans* could not genetically complement each other.
- **1953** Watson and Crick: how DNA could function as a molecule of heredity
- **1958** Crick: flow of information from DNA → RNA → protein
- **1970 – 1980** Fiers: RNA and DNA sequencing
- understanding of how genes are expressed, discovery of splicing
- development of computational tools
- **the "nominal gene"** is defined by its **predicted sequence** rather than a genetic locus
- **1986** the gene effectively became identified as an annotated open freading frame (ORF)

pre-ENCODE: the birth of the structural gene

a gene is...

"... a DNA segment that contributes to phenotype/function. In the absence of demonstrated function a gene may be characterized by sequence, transcription or homology." Human Genome Nomenclature Organization

"... the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding region (leader and trailer) as well as intervening sequences (introns) between individual coding seqments (exons)." textbook *Genes V* by Lewin (1994)

" ... the entire nucleic acid sequence that is necessary for the synthesis of a functional polypeptide (or RNA)" by Lodish (2000)

Servey – “Representing Genes” by Griffiths and Stotz

Problematic issues with the gene concept

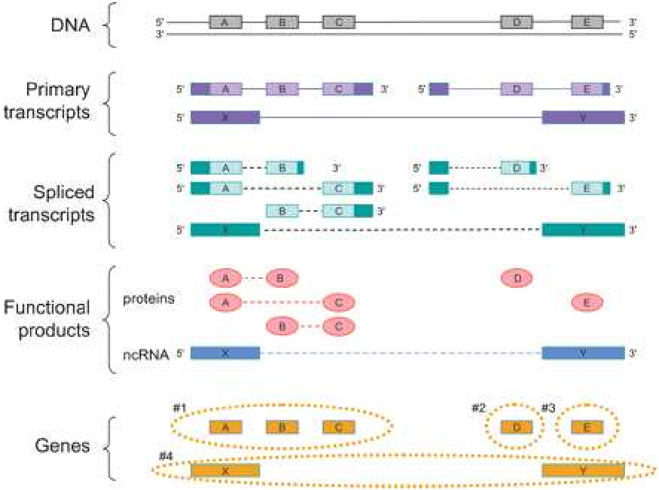
- **regulatory sequence**: part of a gene or associated with a gene?
- **overlapping genes**: same strand different reading frame or readingframes on opposite strands
- **splicing**: open reading frame is segmented
- **alternative splicing**: multiple different transcripts with different function
- **trans-splicing**: distinct transcripts can be joint
  the gene as a single locus no longer applies
- **run-through transcripts and fusion proteins**
- **parasitic and mobile elements**
- **pseudogenes**: retrotranscposed "dead" genes

A gene is a set of connected transcripts where "connected" means sharing of exons.

How ENCODE ruined/challenged the gene concept

- functional non-coding RNAs
- unannotated transcription: only 50% of spliced transcripts are annotated
- transcription from (distal) alternative transcription start sites (TSS)
- alternative 3'UTRs
- transcription at regulatory elements
- dispersed regulation and elements (upstream, downstream, within the first exon, within the first intron, anywhere else)
- blurring of the destinction between genic and intergenic, exonic and intronic
- act of transcription of functional importance, transcript irrelevant
- pseudogenes
- highly conserved elements, only 20% in annotated regions

The Gerstein-Snyder gene definition



"The gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products." Gerstein et al. 2007

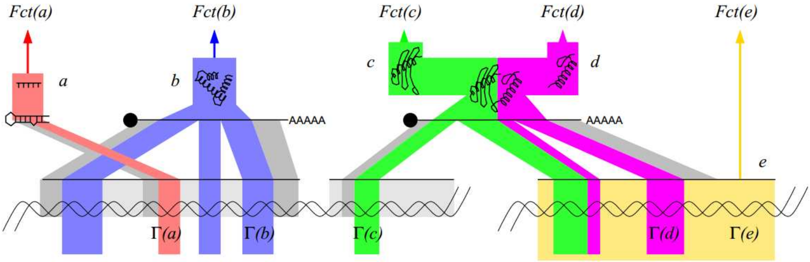
What any good gene concept needs

A **structural** and a **functional** component.

- a well-defined structural representation on the genetic material
- a well-defined notion of function (by measurement)
- **heritability** (conveyed by the genetic material)
- compartibility with the concept of **homology** on structural and/or functional level
- processes of **gene expression** connecting the structural and functional components
- relation between mutations and changes in a gene product

A gene is a heritable elementary functional unit.

The Stadler-Prohaska gene definition



Functional objects (a to e) and relationships with their genomic footprints (Γ(*a*) to Γ(*e*)).

Btw. **Genes** are irrelevant for **genome annotation**! Annotation should focus on the observable intermediates (transcripts, translation products, precursors, etc.) of the expression cascade.

Literature

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Teaser

- What is “function” or a “functional gene”?
- Does function answer the question:

  “What is it (good) for”?
  “What does it do”?
  “What has it been doing in the past”?
- How are the relations between “unit of function”, “unit of selection” and “unit of heredity”?

- Can a small peptide be encoded in a non-coding RNA?
- Is a functional pseudogene a “gene zombie”?