### WBO 10

Gene families and Gene function annotation

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### Many genes have conserved sequence and function over milions of years of evolution





# How did the gene families originate

- As we discussed earlier, we cannot answer questions about the pre-cellular origins of life
- We know that the simplest autnomous cellular life forms have ~1000 protein coding gene and some parasitic life forms can function with ~500 genes
- How do we arrive at a certain number of genes and do they evolve intependently?
- What processess lead to evolution of organisms with tens of thousands of genes with hundreds of thousands gene products.

### Duplication and speciation

- As we discussed earlier, some events during DNA replication (e.g. non-homologous recombination) can create duplicates of genes or gene clusters
- If the duplication of a gene did not lead to deleterious effects and the resulting organism is viable, there is a lesser selective pressure on maintaining the function of each of the gene copies, i.e. one of them can randomly mutate to potentially perform a different function, while the other remains to perform the original function

### Specialization after duplication

- Since one copy of a gene was enough before duplication, there is now an additional gene copy, that can acquire mutations leading to potential for a more specialized function (subfunctionalization) or a new function (neofunctionalization)
- If the mutations are deleterious, the gene becomes non-functional **pseudogene**
- If the mutated gene provides some new function, this can contribute to a speciation event – organisms with a single copy might not be able to cross

# Evolution of duplicated genes

- Selekcja osobników przebiega na podstawie fenotypu, a nie genotypu, zaś posiadanie dwóch kopii tego samego genu często nie wpływa bezpośrednio na fenotyp
- Chyba, że mamy do czynienia z genem, który musi mieć ściśle regulowaną liczbę produktów (transkryptów, białek), bo zwiększenie liczby kopii DNA genu prowadzi często do zwiększonej ekspresji genu

# What is a gene's *function*?

- We are using the word *function* here in a very informal way
- It basically means any ablility of a gene product (RNA or protein) to change the behavior of the cell containing this gene versus the one without it
- Usually this may mean taking part in a chemical reaction or some other molecular interaction
- These are usually non-unique (i.e. many functions for a single gene) and somewhat arbitrary, as it is difficult to prove exactly what the function is

# Gene homologs

- Genes with a common ancestral sequence are called homologous, or homologs. Theoretically, this would be an equivalence relation, however, the number of classes of this relation depends on how far back we look.
- In practive, genes with a certain level of sequence similarity, making the probability of their independent evolution extremely small, to be homologs. It is not an equivalence relationship, as the sequence similarity is not transitive.
- Sometimes people distinguish this second raltion as "sequence homology" as opposed to "true homology"

# Types of homologs

- Homologous genes originated from gene duplication are called paralogs
- Homologous genes originated from speciation are called **orthologs**
- Lesser frequently used types of homologs are xenologs – originating from horizontal gene transfers, and ohnologs – originating from whole genome duplication

# The timing of evolutionary events makes a difference

- We have very different expectations from paralogs and orthologs
  - Evolving orthologs usually maintain their function
  - Paralogs are much more prone to neofunctionalization



### Two examples – PAH and TPH

- PAH phenylalanine hydroxylase, a very well known and old enzyme, that is almost always existing in a single copy - a gene that has a very well defined function,
- mutations in it cause a genetic disease called phenylketonuria
- A paralog of PAH is TPH tryptophan hydroxylase, not a dosage sensitive gene, exists in multiple copies in many genomes

### Example 2 - histones

- Histones are the proteins that are combined to create nucleosomes that are used to organized chromatin.
- Every eukaryotic cell needs milions of nucleosomes, so they exist in many copies in the genome, with some functionalization (H2A, H2B, H3, H4 and linker histone H1)



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# Using BLAST to find homologs

- Bidirectional BLAST Best hits proteins that are mutally most similar to each other in two genomes
- We can construct a graph where any two genes from different genoms are connected if they are BBB hits
- This graph can be searched for dense structures, similar to cliques, to identify Clusters of Orthologous Genes, or COGs (Koonin 1997)



# How to identify gene function

- It is not easi to test protein functions experimentally
- It is costly, takes time and effort and is never 100% reliable
- Still, for majority of genes, even in humans, we don't know their function
- However, We still have lot of data on gene function of thousands of genes and need to systematize it

# Different approaches to gene function annotation

- Gene Ontology a systematic effort of manual curation of both an ontology of function terms (A directed acyclic graph with terms in nodes, and is\_a and part\_of relationships) and annotations of genes to this graph
- Wikigenes, genecards, etc. many commercial or open approaches to start a knowledge-base using text-mining tools and published articles and open it to human annotation at some point in "wikipedia" style

the Gene Ontology						
	Search	Browse	BLAST	Homolog Annotations	Tools & Resources Help	
Search GO			● terms ○ genes o	r proteins exact match Sub	mit Query	

PAH

### Phenylalanine-4-hydroxylase

protein from Homo sapiens (human)

	Term associations    Gene product information	on 🌩 Peptide Sequence 🖣	<ul> <li>Sequence information •</li> </ul>		
Term Associations					
Download all association information in: U gene association format	RDF-XML				
<ul> <li>▼ Filter associations displayed </li> <li>Filter Associations         <ul> <li>Ontology</li> <li>Evidence Code</li> <li>All</li> <li>Diological process</li> <li>Cellular component</li> <li>DA</li> <li>EA</li> </ul> </li> </ul>					
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GO:0042423 : catecholamine biosynthetic process	71 gene products view in tree	biological process	NAS		
GO:0008652 : cellular amino acid biosynthetic process	6303 gene products view in tree	biological process	TAS		

### Gene ontology graph





### Hoffmann, R. A wiki for the life sciences where authorship matters. Nature Genetics

Gene Review

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PAH - phenylalanine hydroxylase Synonyms: PH, PKU, PKU1, Phe-4-monooxygenase, Phenylalanine-4-hydroxylase

### Green, E.K. et al., Chao, H.M. et al., Maass, A. et al., Teigen, K. et al., Ramus, S.J. et al., et al.

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Ideally this entry shall become one comprehensive and continuous article. Bulleted lists, for instance, were only used because it is

### Disease relevance of PAH

- We present the case of a girl affected by <u>classical phenylketonuria</u> who has been screened for mutations in the PAH gene [1].
- Benzo[a]pyrene-induced <u>DNA damage</u> and <u>p53</u> modulation in human <u>hepatoma</u> HepG2 cells for the identification of potential biomarkers for <u>PAH</u> monitoring and <u>risk assessment [2]</u>.

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### Homo sapiens

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# Testing for annotation enrichment

- For many sets of genes (usually originating from some experiment) we might be interested if there is a common function to them.
- Usually this comes from a set of genes changed in a disease state, developmental stage or stress condition
- Sometimes, this can be a ranking of genes from most to least "affected", and we can ask if there is anything non random in functions of genes at both ends of the ranking.
- How to answer these questions statistically?

# Significant overlap of gene sets

- The most straightforward approach is to ask if the overlap of the set of genes in question with a set of genes annotated with a given function is greater than expected by chance
- This can be answered by Fisher's exact test, that uses the hypergeometric distribution to describe the overlap distribution under the null hypothesis
- This is similar to an urn scenario: What is the probability that I draw more than x black balls while taking N balls from an urn originally containing M balls of which k were black

### Gene set enrichment analysis

• Assuming that we have a ranking of genes, we can ask, similarly to the Kolmogorov-Smirnov test, if there is a significant difference in the enrichment at any point in the ranking



# Mulitple hypothesis testing corrections

- Multiple hypothesis testing corrections are very important in gene function enrichment testing as they are thousands of known functions and we usually test all of them
- The simplest correction is to multiply the p-value by the number of hypotheses – the Bonferroni correction
- Usually, more useful results are obatined with False Discovery Rate – FDR, that indicates what is the percentage of false positive predictions under a given p-value threshold.