

GEPHE SUMMARY

		Gephebase Gene		GepheID
alcohol dehydrogenase (Adh) ( <a href="https://www.gephebase.org/search-criteria?/and+Gene">https://www.gephebase.org/search-criteria?/and+Gene</a> )			GP00001963	
Gephebase="alcohol dehydrogenase (Adh)"#gephebase-summary-title)				Main curator
	Entry Status		Courtier	
Published				

PHENOTYPIC CHANGE

	Trait Category
Physiology ( <a href="https://www.gephebase.org/search-criteria?/and+Trait">https://www.gephebase.org/search-criteria?/and+Trait</a> )	
Category="Physiology"#gephebase-summary-title)	
	Trait
Xenobiotic resistance (alcohol) ( <a (alcohol)"#gephebase-summary-title"="" href="https://www.gephebase.org/search-criteria?/and+Trait=" resistance="" xenobiotic="">https://www.gephebase.org/search-criteria?/and+Trait="Xenobiotic resistance (alcohol)"#gephebase-summary-title</a> )	
	Trait State in Taxon A
Drosophila santomea - lower enzyme activity	
	Trait State in Taxon B
Drosophila yakuba - higher enzyme activity	
	Ancestral State
Unknown	
	Taxonomic Status
Interspecific ( <a href="https://www.gephebase.org/search-criteria?/and+Taxonomic">https://www.gephebase.org/search-criteria?/and+Taxonomic</a> )	
Status="Interspecific"#gephebase-summary-title)	

Taxon A	Latin Name	Taxon B	Latin Name
Drosophila santomea ( <a drosophila="" href="https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=" santomea"#gephebase-summary-title"="">https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms="Drosophila santomea"#gephebase-summary-title</a> )		Drosophila yakuba ( <a drosophila="" href="https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=" yakuba"#gephebase-summary-title"="">https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms="Drosophila yakuba"#gephebase-summary-title</a> )	
-	Common Name	-	Common Name
	Synonyms		Synonyms
	Rank	Drosophila yakuba Burla, 1954	Rank
species		species	
	Lineage		Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Holometabola; Diptera; Brachycera; Muscomorpha; Eremoneura; Cyclorrhapha; Schizophora; Acalyptera; Ephydroidea; Drosophilidae; Drosophilinae; Drosophilini; Drosophila; Sophophora; melanogaster group; melanogaster subgroup		cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Holometabola; Diptera; Brachycera; Muscomorpha; Eremoneura; Cyclorrhapha; Schizophora; Acalyptera; Ephydroidea; Drosophilidae; Drosophilinae; Drosophilini; Drosophila; Sophophora; melanogaster group; melanogaster subgroup	
	Parent		Parent
melanogaster subgroup () - (Rank: species subgroup) ( <a href="https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 32351">https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 32351</a> )		melanogaster subgroup () - (Rank: species subgroup) ( <a href="https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 32351">https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 32351</a> )	
	NCBI Taxonomy ID		NCBI Taxonomy ID
129105 ( <a href="https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 129105">https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 129105</a> )		7245 ( <a href="https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 7245">https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 7245</a> )	
	is Taxon A an Infrasppecies?		is Taxon B an Infrasppecies?
No		No	

GENOTYPIC CHANGE

	Generic Gene Name	UniProtKB Drosophila melanogaster
Adh		P00334 ( <a href="http://www.uniprot.org/uniprot/P00334">http://www.uniprot.org/uniprot/P00334</a> )
	Synonyms	GenebankID or UniProtKB
adh; ADH; Adh3; BG:DS01486.8; CG32954; CG3481; dADH; DM-ADH; DmADH; Dmel\CG3481; Dreg-1; Reg-1; T16		()
	String	
7227.FBpp0100048 ( <a href="http://string-db.org/newstring.cgi/show_network_section.pl?identifier= 7227.FBpp0100048">http://string-db.org/newstring.cgi/show_network_section.pl?identifier= 7227.FBpp0100048</a> )		
	Sequence Similarities	
Belongs to the short-chain dehydrogenases/reductases (SDR) family.		
	GO - Molecular Function	
GO:0042803 : protein homodimerization activity ( <a href="https://www.ebi.ac.uk/QuickGO/term/GO:0042803">https://www.ebi.ac.uk/QuickGO/term/GO:0042803</a> )		
GO:0008774 : acetaldehyde dehydrogenase (acetylating) activity ( <a href="https://www.ebi.ac.uk/QuickGO/term/GO:0008774">https://www.ebi.ac.uk/QuickGO/term/GO:0008774</a> )		

GO:0004022 : alcohol dehydrogenase (NAD) activity  
 (https://www.ebi.ac.uk/QuickGO/term/GO:0004022)  
 GO:0016491 : oxidoreductase activity (https://www.ebi.ac.uk/QuickGO/term/GO:0016491)  
 GO - Biological Process

GO:0006117 : acetaldehyde metabolic process  
 (https://www.ebi.ac.uk/QuickGO/term/GO:0006117)  
 GO:0046164 : alcohol catabolic process  
 (https://www.ebi.ac.uk/QuickGO/term/GO:0046164)  
 GO:0006066 : alcohol metabolic process  
 (https://www.ebi.ac.uk/QuickGO/term/GO:0006066)  
 GO:0048149 : behavioral response to ethanol  
 (https://www.ebi.ac.uk/QuickGO/term/GO:0048149)  
 GO:0006067 : ethanol metabolic process  
 (https://www.ebi.ac.uk/QuickGO/term/GO:0006067)  
 GO:0006069 : ethanol oxidation (https://www.ebi.ac.uk/QuickGO/term/GO:0006069)  
 GO:0055114 : oxidation-reduction process  
 (https://www.ebi.ac.uk/QuickGO/term/GO:0055114)

GO - Cellular Component

GO:0005829 : cytosol (https://www.ebi.ac.uk/QuickGO/term/GO:0005829)  
 GO:0032991 : protein-containing complex  
 (https://www.ebi.ac.uk/QuickGO/term/GO:0032991)

Mutation #1

No (https://www.gephebase.org/search-criteria?/and+Presumptive Null=^No^#gephebase-summary-title) Presumptive Null  
 Coding (https://www.gephebase.org/search-criteria?/and+Molecular Type=^Coding^#gephebase-summary-title) Molecular Type  
 SNP (https://www.gephebase.org/search-criteria?/and+Aberration Type=^SNP^#gephebase-summary-title) Aberration Type  
 Nonsynonymous SNP Coding Change  
 In vitro assay by replacement of the entire coding region. Three possible amino acid changes. Exact causal amino acid change(s) not identified. Molecular Details of the Mutation  
 Candidate Gene (https://www.gephebase.org/search-criteria?/and+Experimental Evidence=^Candidate Gene^#gephebase-summary-title) Experimental Evidence

	Taxon A	Taxon B	Position
Codon	-	-	-
Amino-acid	-	-	-

A major role for noncoding regulatory mutations in the evolution of enzyme activity. (2019) (https://pubmed.ncbi.nlm.nih.gov/31152141) Main Reference  
 Loehlin DW; Ames JR; Vaccaro K; Carroll SB Authors  
 The quantitative evolution of protein activity is a common phenomenon, yet we know little about any general mechanistic tendencies that underlie it. For example, an increase (or decrease) in enzyme activity may evolve from changes in protein sequence that alter specific activity, or from changes in gene expression that alter the amount of protein produced. The latter in turn could arise via mutations that affect gene transcription, posttranscriptional processes, or copy number. Here, to determine the types of genetic changes underlying the quantitative evolution of protein activity, we dissected the basis of ecologically relevant differences in Alcohol dehydrogenase (Adh) enzyme activity between and within several *Drosophila* species. By using recombinant Adh transgenes to map the functional divergence of ADH enzyme activity in vivo, we find that amino acid substitutions explain only a minority (0 to 25%) of between- and within-species differences in enzyme activity. Instead, noncoding substitutions that occur across many parts of the gene (enhancer, promoter, and 5' and 3' untranslated regions) account for the majority of activity differences. Surprisingly, one substitution in a transcriptional Initiator element has occurred in parallel in two species, indicating that core promoters can be an important natural source of the tuning of gene activity. Furthermore, we show that both regulatory and coding substitutions contribute to fitness (resistance to ethanol toxicity). Although qualitative changes in protein specificity necessarily derive from coding mutations, these results suggest that regulatory mutations may be the primary source of quantitative changes in protein activity, a possibility overlooked in most analyses of protein evolution.  
 Copyright © 2019 the Author(s). Published by PNAS. Additional References

Mutation #2

No (https://www.gephebase.org/search-criteria?/and+Presumptive Null=^No^#gephebase-summary-title) Presumptive Null  
 Cis-regulatory (https://www.gephebase.org/search-criteria?/and+Molecular Type=^Cis-regulatory^#gephebase-summary-title) Molecular Type  
 Unknown (https://www.gephebase.org/search-criteria?/and+Aberration Type=^Unknown^#gephebase-summary-title) Aberration Type  
 5' flanking region. Exact mutation(s) not identified. Molecular Details of the Mutation  
 Candidate Gene (https://www.gephebase.org/search-criteria?/and+Experimental Evidence=^Candidate Gene^#gephebase-summary-title) Experimental Evidence  
 A major role for noncoding regulatory mutations in the evolution of enzyme activity. (2019) (https://pubmed.ncbi.nlm.nih.gov/31152141) Main Reference  
 Authors

The quantitative evolution of protein activity is a common phenomenon, yet we know little about any general mechanistic tendencies that underlie it. For example, an increase (or decrease) in enzyme activity may evolve from changes in protein sequence that alter specific activity, or from changes in gene expression that alter the amount of protein produced. The latter in turn could arise via mutations that affect gene transcription, posttranscriptional processes, or copy number. Here, to determine the types of genetic changes underlying the quantitative evolution of protein activity, we dissected the basis of ecologically relevant differences in Alcohol dehydrogenase (Adh) enzyme activity between and within several *Drosophila* species. By using recombinant Adh transgenes to map the functional divergence of ADH enzyme activity *in vivo*, we find that amino acid substitutions explain only a minority (0 to 25%) of between- and within-species differences in enzyme activity. Instead, noncoding substitutions that occur across many parts of the gene (enhancer, promoter, and 5' and 3' untranslated regions) account for the majority of activity differences. Surprisingly, one substitution in a transcriptional Initiator element has occurred in parallel in two species, indicating that core promoters can be an important natural source of the tuning of gene activity. Furthermore, we show that both regulatory and coding substitutions contribute to fitness (resistance to ethanol toxicity). Although qualitative changes in protein specificity necessarily derive from coding mutations, these results suggest that regulatory mutations may be the primary source of quantitative changes in protein activity, a possibility overlooked in most analyses of protein evolution.

Copyright © 2019 the Author(s). Published by PNAS.

Additional References

#### Mutation #3

No ([https://www.gephebase.org/search-criteria?/and+Presumptive Null="No`#gephebase-summary-title](https://www.gephebase.org/search-criteria?/and+Presumptive+Null=))

Presumptive Null

Cis-regulatory ([https://www.gephebase.org/search-criteria?/and+Molecular Type="+Cis-regulatory`#gephebase-summary-title](https://www.gephebase.org/search-criteria?/and+Molecular+Type=))

Molecular Type

Unknown ([https://www.gephebase.org/search-criteria?/and+Aberration Type="+Unknown`#gephebase-summary-title](https://www.gephebase.org/search-criteria?/and+Aberration+Type=))

Aberration Type

5' UTR region. Exact mutation(s) not identified.

Molecular Details of the Mutation

Candidate Gene ([https://www.gephebase.org/search-criteria?/and+Experimental Evidence="+Candidate Gene`#gephebase-summary-title](https://www.gephebase.org/search-criteria?/and+Experimental+Evidence=))

Experimental Evidence

A major role for noncoding regulatory mutations in the evolution of enzyme activity. (2019) (<https://pubmed.ncbi.nlm.nih.gov/31152141>)

Main Reference

Loehlin DW; Ames JR; Vaccaro K; Carroll SB

Authors

Abstract

The quantitative evolution of protein activity is a common phenomenon, yet we know little about any general mechanistic tendencies that underlie it. For example, an increase (or decrease) in enzyme activity may evolve from changes in protein sequence that alter specific activity, or from changes in gene expression that alter the amount of protein produced. The latter in turn could arise via mutations that affect gene transcription, posttranscriptional processes, or copy number. Here, to determine the types of genetic changes underlying the quantitative evolution of protein activity, we dissected the basis of ecologically relevant differences in Alcohol dehydrogenase (Adh) enzyme activity between and within several *Drosophila* species. By using recombinant Adh transgenes to map the functional divergence of ADH enzyme activity *in vivo*, we find that amino acid substitutions explain only a minority (0 to 25%) of between- and within-species differences in enzyme activity. Instead, noncoding substitutions that occur across many parts of the gene (enhancer, promoter, and 5' and 3' untranslated regions) account for the majority of activity differences. Surprisingly, one substitution in a transcriptional Initiator element has occurred in parallel in two species, indicating that core promoters can be an important natural source of the tuning of gene activity. Furthermore, we show that both regulatory and coding substitutions contribute to fitness (resistance to ethanol toxicity). Although qualitative changes in protein specificity necessarily derive from coding mutations, these results suggest that regulatory mutations may be the primary source of quantitative changes in protein activity, a possibility overlooked in most analyses of protein evolution.

Copyright © 2019 the Author(s). Published by PNAS.

Additional References

#### Mutation #4

No ([https://www.gephebase.org/search-criteria?/and+Presumptive Null="+No`#gephebase-summary-title](https://www.gephebase.org/search-criteria?/and+Presumptive+Null=))

Presumptive Null

Cis-regulatory ([https://www.gephebase.org/search-criteria?/and+Molecular Type="+Cis-regulatory`#gephebase-summary-title](https://www.gephebase.org/search-criteria?/and+Molecular+Type=))

Molecular Type

Unknown ([https://www.gephebase.org/search-criteria?/and+Aberration Type="+Unknown`#gephebase-summary-title](https://www.gephebase.org/search-criteria?/and+Aberration+Type=))

Aberration Type

3' UTR region. Exact mutation(s) not identified.

Molecular Details of the Mutation

Candidate Gene ([https://www.gephebase.org/search-criteria?/and+Experimental Evidence="+Candidate Gene`#gephebase-summary-title](https://www.gephebase.org/search-criteria?/and+Experimental+Evidence=))

Experimental Evidence

A major role for noncoding regulatory mutations in the evolution of enzyme activity. (2019) (<https://pubmed.ncbi.nlm.nih.gov/31152141>)

Main Reference

Loehlin DW; Ames JR; Vaccaro K; Carroll SB

Authors

Abstract

The quantitative evolution of protein activity is a common phenomenon, yet we know little about any general mechanistic tendencies that underlie it. For example, an increase (or decrease) in enzyme activity may evolve from changes in protein sequence that alter specific activity, or from changes in gene expression that alter the amount of protein produced. The latter in turn could arise via mutations that affect gene transcription, posttranscriptional processes, or copy number. Here, to determine the types of genetic changes underlying the quantitative evolution of protein activity, we dissected the basis of ecologically relevant differences in Alcohol dehydrogenase (Adh) enzyme activity between and within several *Drosophila* species. By using recombinant Adh transgenes to map the functional divergence of ADH enzyme activity *in vivo*, we find that amino acid substitutions explain only a minority (0 to 25%) of between- and within-species differences in enzyme activity. Instead, noncoding substitutions that occur across many parts of the gene (enhancer, promoter, and 5' and 3' untranslated regions) account for the majority of activity differences. Surprisingly, one substitution in a transcriptional Initiator element has occurred in parallel in two species, indicating that core promoters can be an important natural source of the tuning of gene activity. Furthermore, we show that both regulatory and coding substitutions contribute to fitness (resistance to ethanol toxicity). Although qualitative changes in protein specificity necessarily derive from coding mutations, these results suggest that regulatory mutations may be the primary source of quantitative changes in protein activity, a possibility overlooked in most analyses of protein evolution.

Copyright © 2019 the Author(s). Published by PNAS.

## RELATED GEPHE

No matches found.

Related Genes

No matches found.

Related Haplotypes

## EXTERNAL LINKS

## COMMENTS

@SeveralMutationsWithEffect - There is a consensus phenotype of moderate ADH activity in the broader taxonomic group (Mercot et al. 1994). With the transformed alleles David Loehlin also observed "moderate" activity in *mel-slow*; *D. erecta* and *D. yakuba*. This suggests that *D. santomea* and *D. orena* have derived low phenotypes but the phylogenetic signal is weak. - Entry validated by David Loehlin