Aggression : *MAOA* gene and potential drugs

by Sin Ruow Tey

Image source: http://images.sussexpublishers.netdna-cdn.com/article-top/blogs/49143/2011/04/58689-51554.jpg

Overview of Aggression

ag·gres·sion

əˈgreSHən/

noun

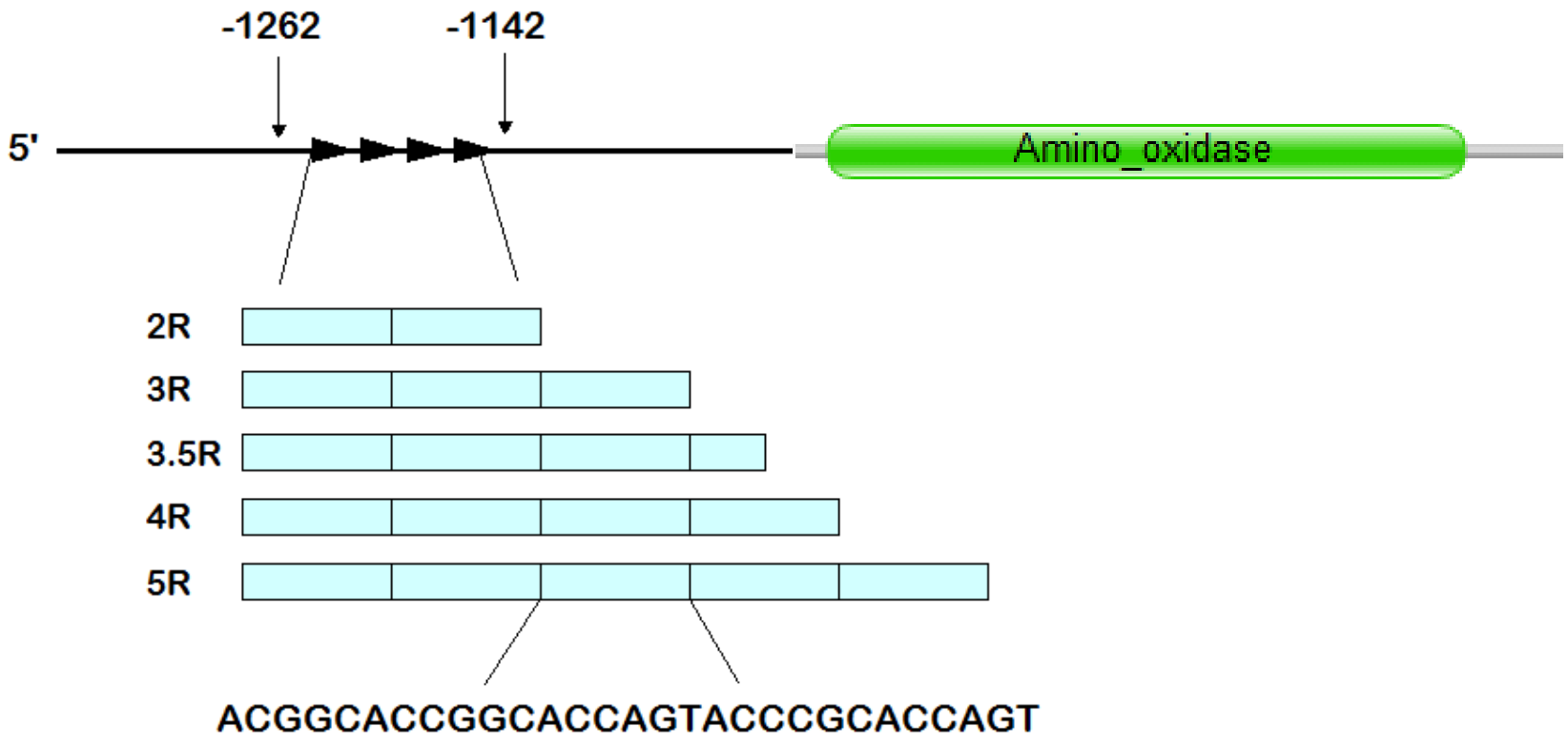
hostile or violent behavior or attitudes toward another; readiness to attack or confront.

http://www.oxforddictionaries.com/us/definition/american_english/aggression

Video: https://www.youtube.com/watch?v=35cOqZI067E

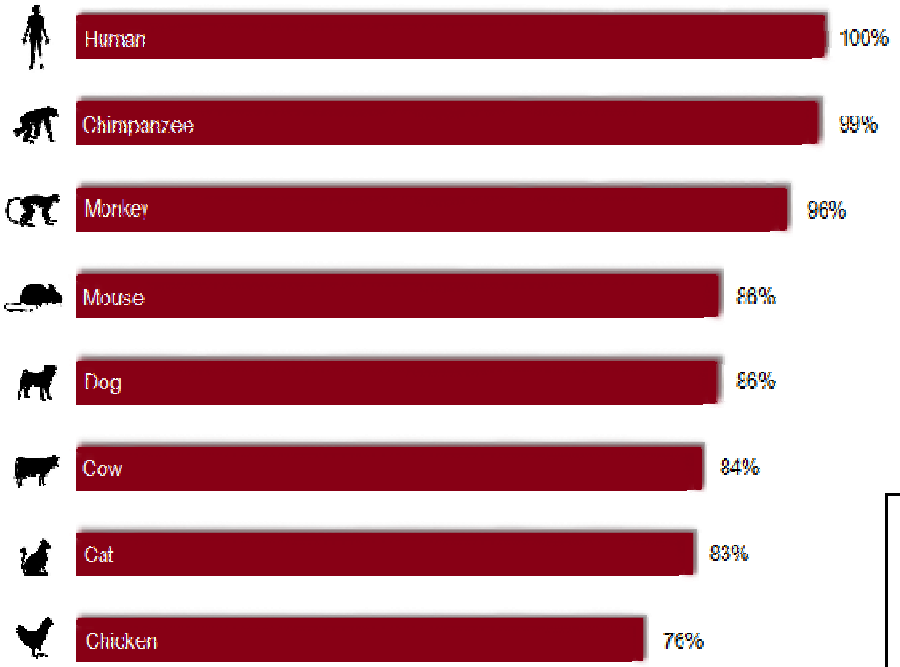
MAOA = Monoamine oxidase A

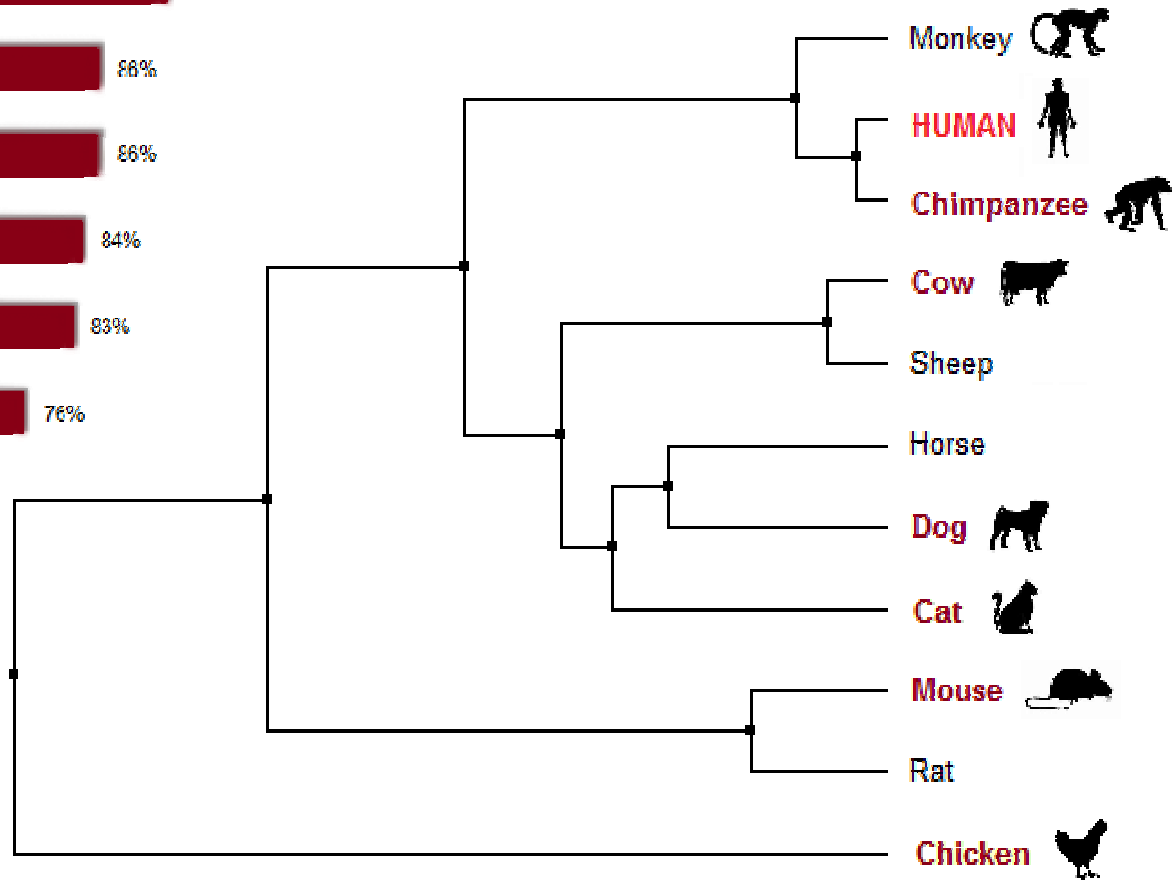
Polymorphism in VNTR upstream of MAOA promoter



Pfam

How well conserved is *MAOA* gene?

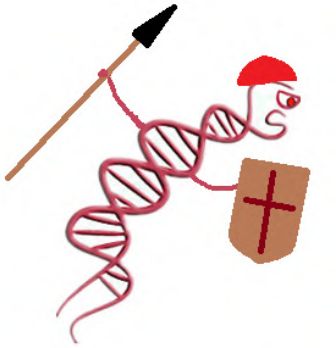




Clustal Omega

MAOA deaminates neurotransmitters

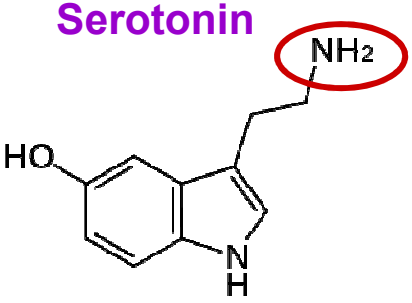
MAOA gene



MAOA protein

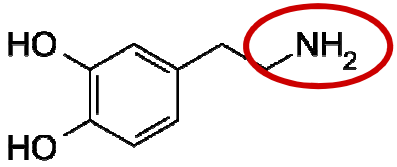
neurotransmitters

Serotonin



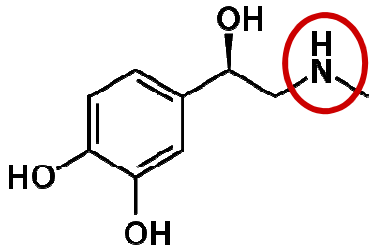
http://en.wikipedia.org/wiki/File:Serotonin-2D-skeletal.svg

Dopamine



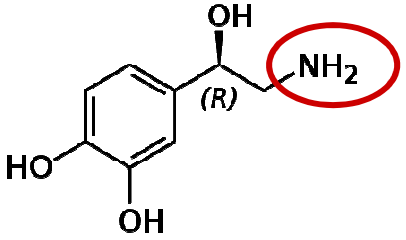
http://en.wikipedia.org/wiki/File:Dopamine2.svg

Epinephrine



http://en.wikipedia.org/wiki/File:Epinephrine_structure.svg

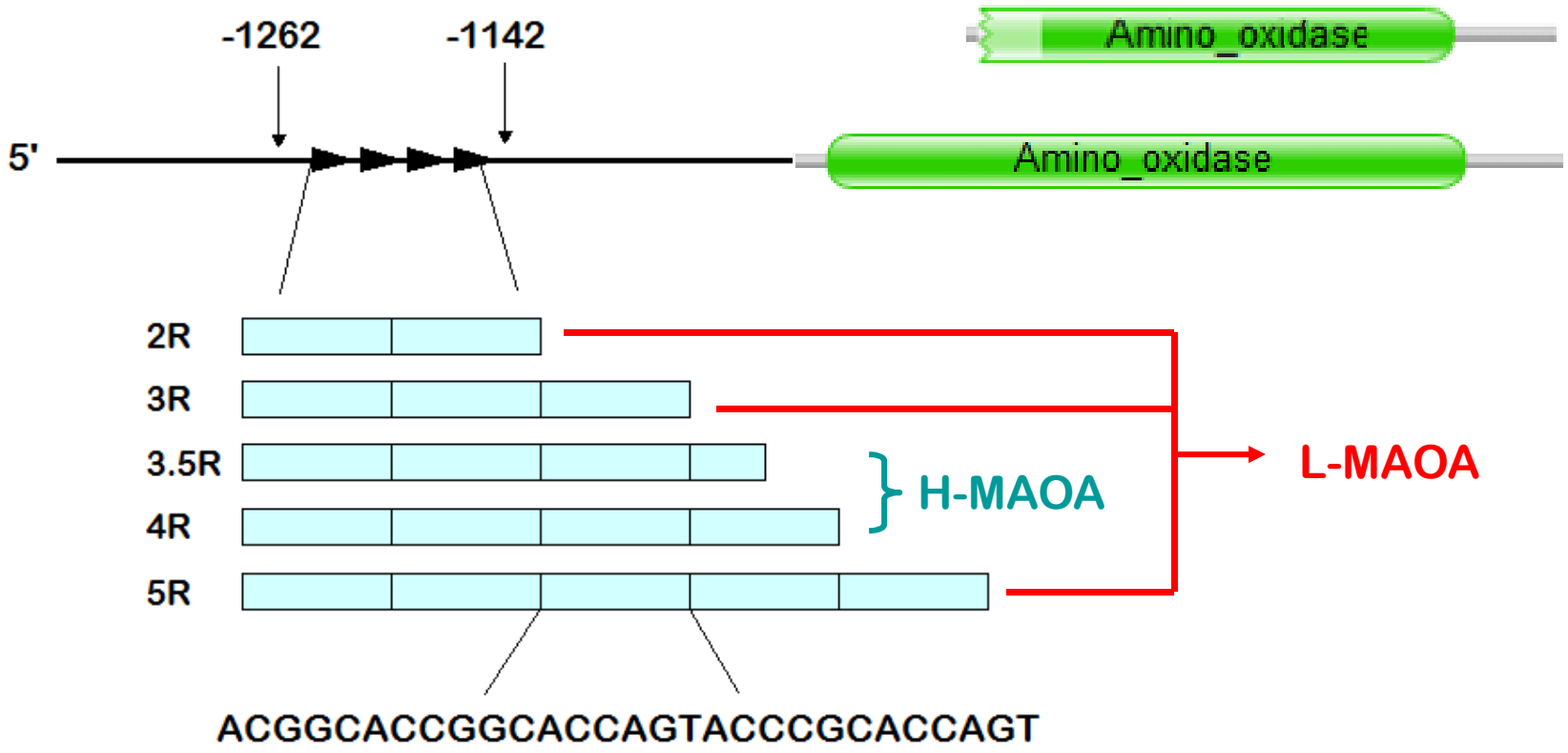
Norepinephrine



http://en.wikipedia.org/wiki/File:Norepinephrine_structure_with_descriptor.svg

Polymorphism of MAOA

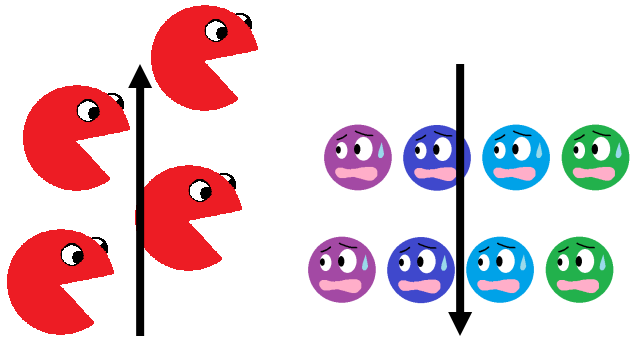
Polymorphism in VNTR upstream of MAOA promoter



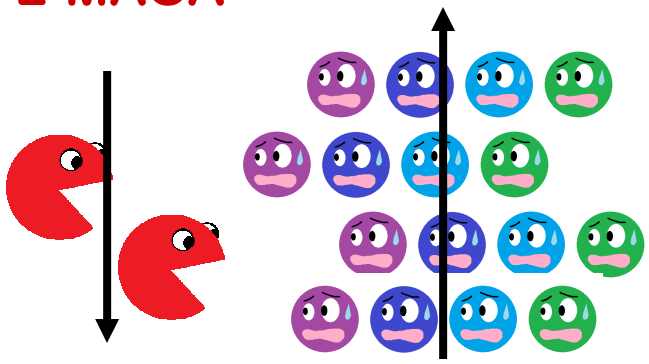
Pfam

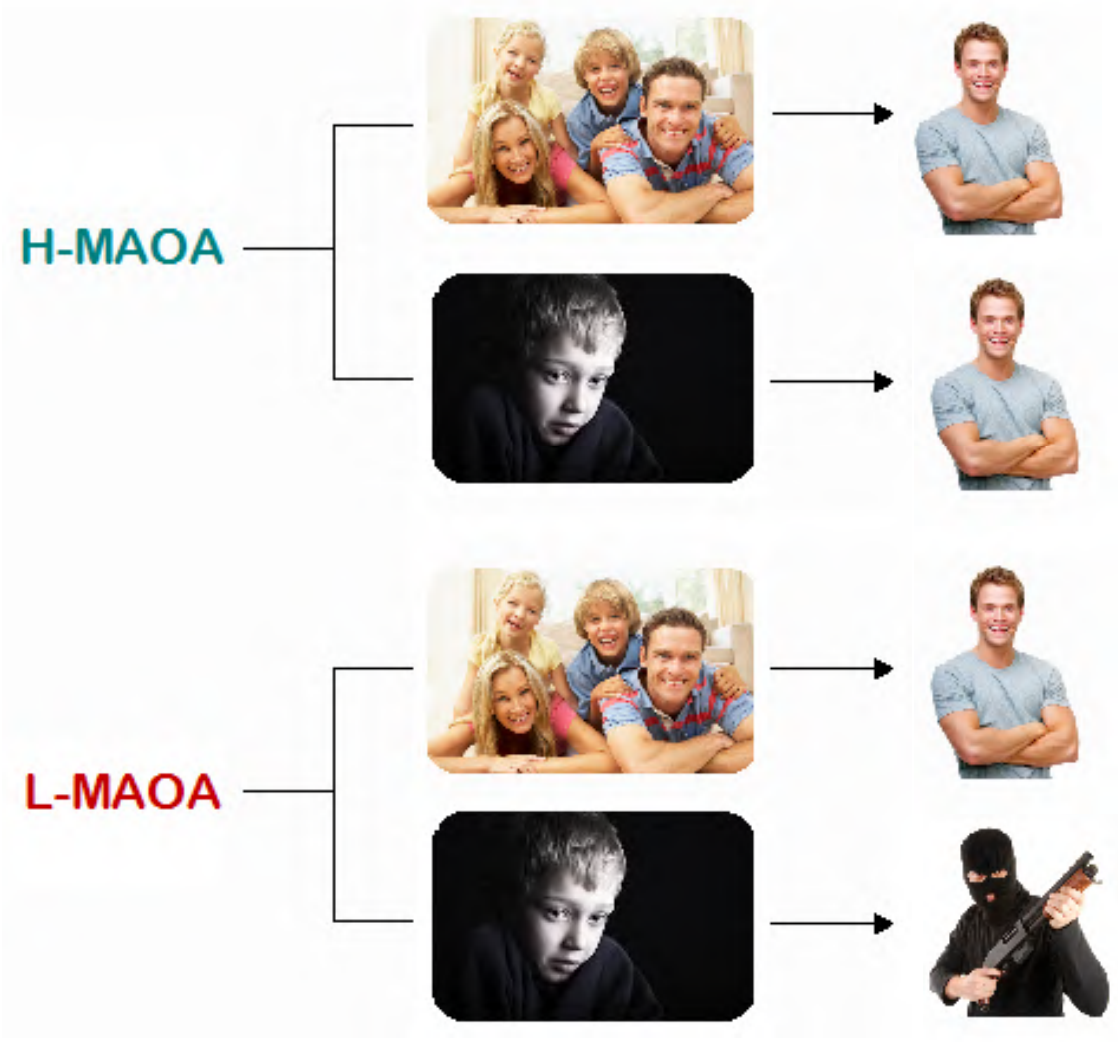
L-MAOA + environment = Aggression ?

H-MAOA



L-MAOA





Family: http://www.southpointefamilyresourcecenter.com/images/family-on-stomachs-smile.jpg

Healthy adult: http://blog.myskin.com/wp-content/uploads/2010/07/iStock_000006947588XSmall.jpg

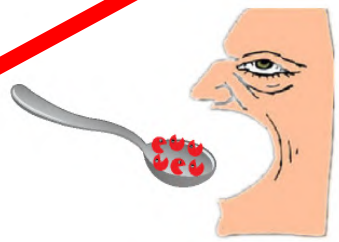
Traumatic childhood: http://www.renownscribbles.org/wp-content/uploads/2012/08/shutterstock_42899995.jpg

Criminal: http://blogs.lawyers.com/wp-content/uploads/2013/04/masked-robber-gun-300.jpg

Potential treatment for aggression

Direct supplementation of MAOA?

- difficult procedures
- slow production
- high cost



Criteria for potential drugs:

- can increase transcription of *MAOA*
- orally biodegradable
- active *in vivo*
- potent

Main hypothesis

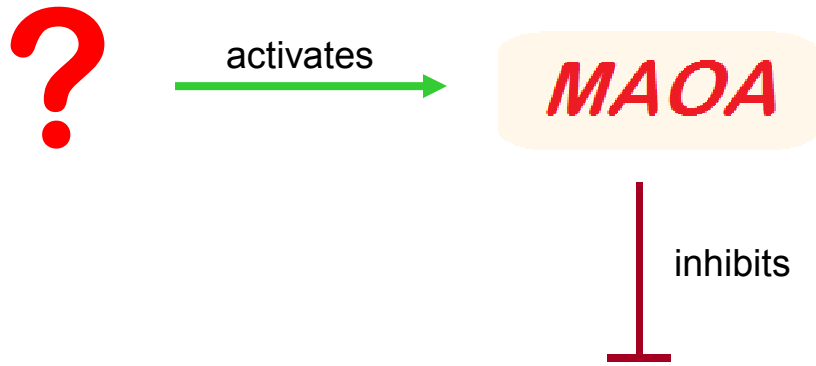
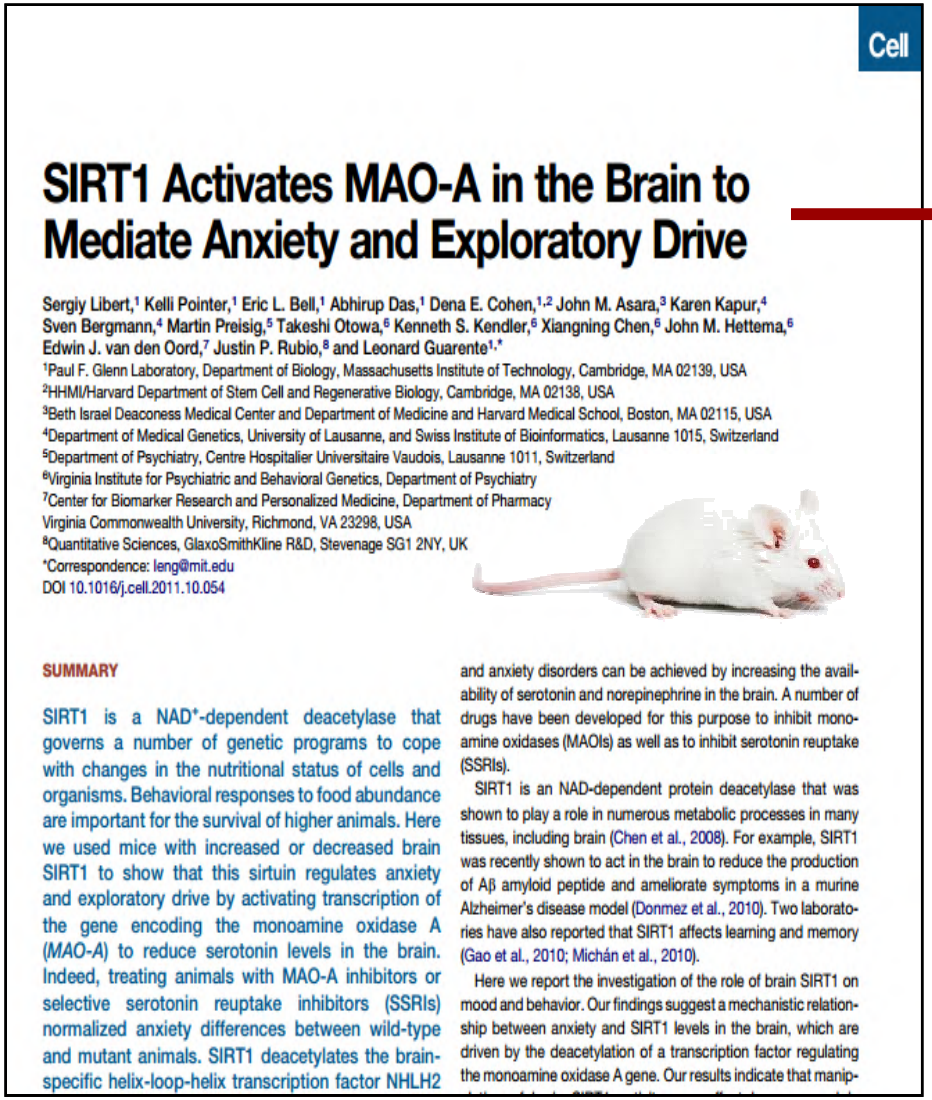


Image source: http://images.sussexpublishers.netdna-cdn.com/article-top/blogs/49143/2011/04/58689-51554.jpg

What gene can activate *MAOA* ?



Cell

SIRT1 Activates MAO-A in the Brain to Mediate Anxiety and Exploratory Drive

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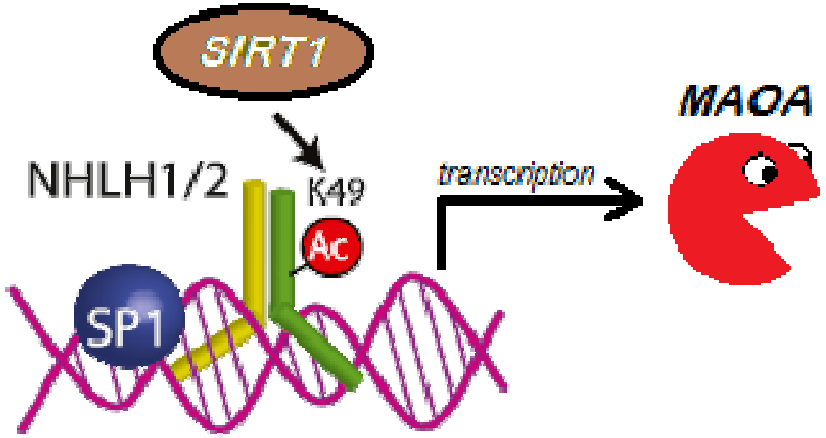
SUMMARY

SIRT1 is a NAD⁺-dependent deacetylase that governs a number of genetic programs to cope with changes in the nutritional status of cells and organisms. Behavioral responses to food abundance are important for the survival of higher animals. Here we used mice with increased or decreased brain SIRT1 to show that this sirtuin regulates anxiety and exploratory drive by activating transcription of the gene encoding the monoamine oxidase A (*MAO-A*) to reduce serotonin levels in the brain. Indeed, treating animals with MAO-A inhibitors or selective serotonin reuptake inhibitors (SSRIs) normalized anxiety differences between wild-type and mutant animals. SIRT1 deacetylates the brain-specific helix-loop-helix transcription factor NHLH2 and anxiety disorders can be achieved by increasing the availability of serotonin and norepinephrine in the brain. A number of drugs have been developed for this purpose to inhibit monoamine oxidases (MAOIs) as well as to inhibit serotonin reuptake (SSRIs).

SIRT1 is an NAD-dependent protein deacetylase that was shown to play a role in numerous metabolic processes in many tissues, including brain (Chen et al., 2008). For example, SIRT1 was recently shown to act in the brain to reduce the production of Aβ amyloid peptide and ameliorate symptoms in a murine Alzheimer's disease model (Donmez et al., 2010). Two laboratories have also reported that SIRT1 affects learning and memory (Gao et al., 2010; Michán et al., 2010).

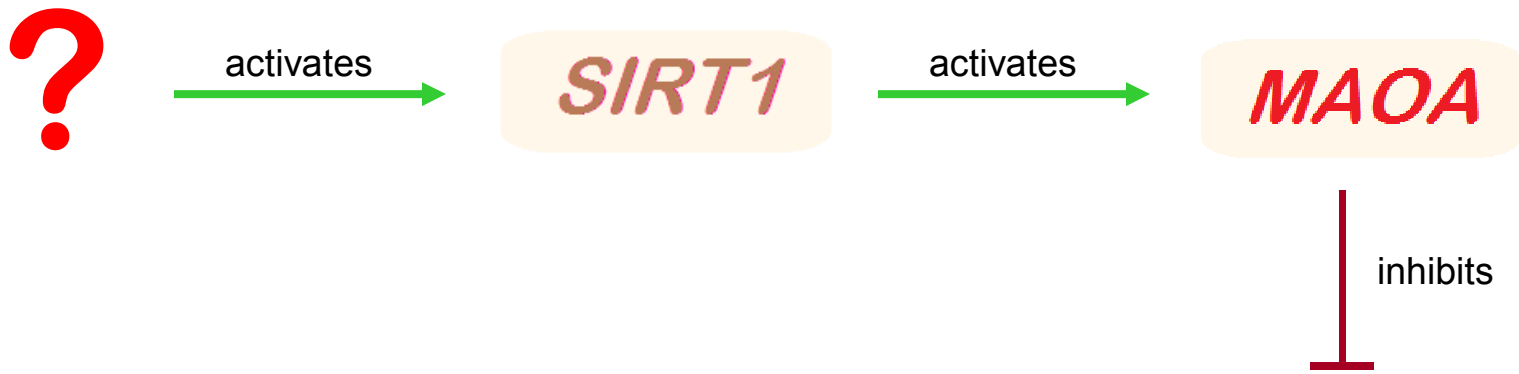
Here we report the investigation of the role of brain SIRT1 on mood and behavior. Our findings suggest a mechanistic relationship between anxiety and SIRT1 levels in the brain, which are driven by the deacetylation of a transcription factor regulating the monoamine oxidase A gene. Our results indicate that manip-



SIRT1 deacetylates the brain-specific transcription factor NHLH2 on lysine 49 to increase its activation of the MAOA promoter

Mouse image: http://jaxmice.jax.org/images/jaxmicedb/featuredImage/001803_lg.jpg

Main hypothesis



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What can activate *SIRT1* ?

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Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes

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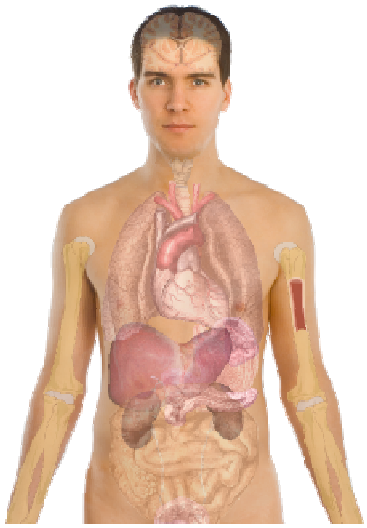
Abstract

Calorie restriction extends lifespan and produces a metabolic profile desirable for treating diseases of ageing such as type 2 diabetes[1,2]. SIRT1, an NAD^+-dependent deacetylase, is a principal modulator of pathways downstream of calorie restriction that produce beneficial effects on glucose homeostasis and insulin sensitivity[3–9]. Resveratrol, a polyphenolic SIRT1 activator, mimics the anti-ageing effects of calorie restriction in lower organisms and in mice fed a high-fat diet ameliorates insulin resistance, increases mitochondrial content, and prolongs survival[10–14]. Here we describe the identification and characterization of small molecule activators of SIRT1 that are structurally unrelated to, and 1,000-fold more potent than, resveratrol. These compounds bind to the SIRT1 enzyme—peptide substrate complex at an allosteric site amino-terminal to the catalytic domain and lower the Michaelis constant for acetylated substrates. In diet-induced obese and genetically obese mice, these compounds improve insulin sensitivity, lower plasma glucose, and increase mitochondrial capacity. In Zucker *fa/fa* rats, hyperinsulinaemic-euglycaemic clamp studies demonstrate that SIRT1 activators improve whole-body glucose homeostasis and insulin sensitivity in adipose tissue, skeletal muscle and liver. Thus, SIRT1 activation is a promising new therapeutic approach for treating diseases of ageing such as type 2 diabetes.

SRT 2183

SRT 1460

SRT 1720



Rat: http://www.ocoee.org/Departments/PR/includes/images/rat.jpg

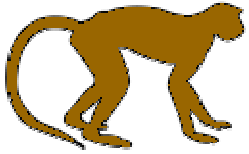
Human: http://www.clker.com/cliparts/q/v/6/E/J/L/human-body-anatomy-basics-hi.png

Candidancy of SRT 2183 SRT 1460 SRT 1720

Criteria for potential drugs:

- can increase transcription of MAOA ?
- orally biodegradable ✓
- active *in vivo* ✓
- potent ✓

Main hypothesis



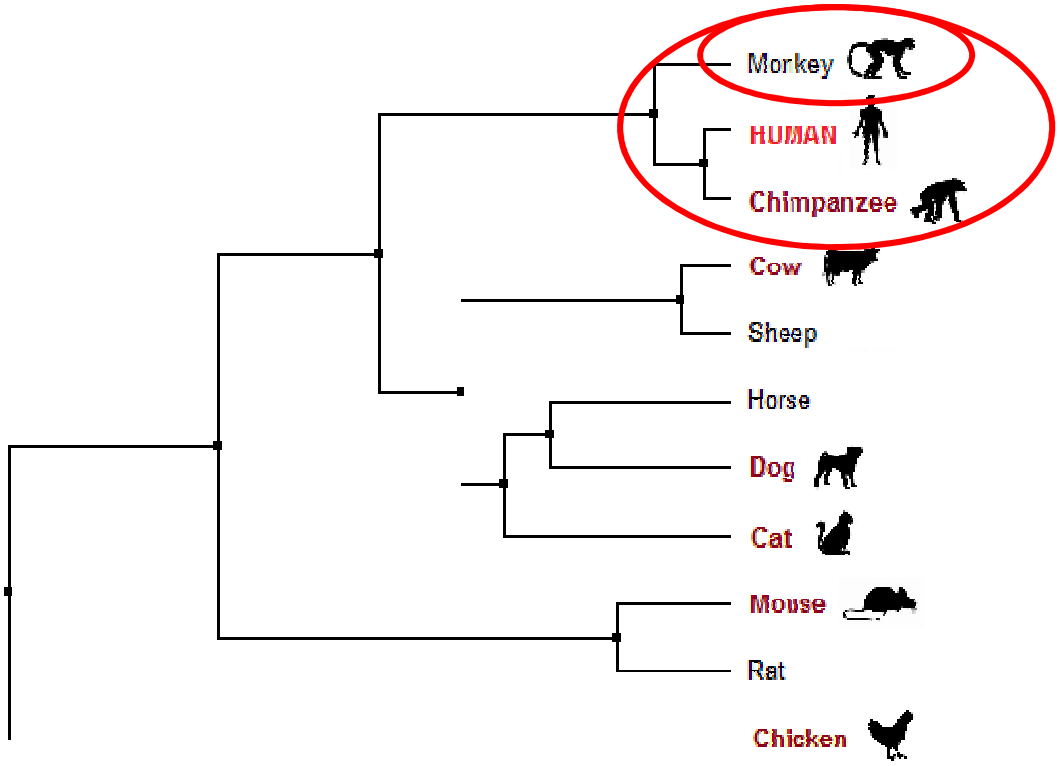
Model organism: Rhesus monkey
(*Macaca mulatta*)

Image source: http://images.sussexpublishers.netdna-cdn.com/article-top/blogs/49143/2011/04/58689-51554.jpg

Why choose rhesus monkey?

Why choose primates?

- similar cognitive and emotional functioning as humans



http://www.monkeyworlds.com/wp-content/uploads/Rhesus_Macaque_Monkey_Sitting_On_A_Tree_600.jpg

Aim 1: Determine if ***SRT2183***, ***SRT1460*** and ***SRT1720*** can increase ***MAOA*** levels in the brain and reduce aggression levels in *L-MAOA* rhesus monkeys

Selectively breed highly-aggressive *L-MAOA* rhesus monkeys

↓

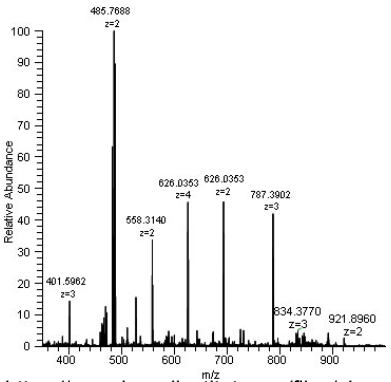
Feed them with *SRT2183, SRT1460* and *SRT1720*

SRT 2183

SRT 1460

SRT 1720

↓



https://www.broadinstitute.org/files/shared/proteomics/ms.jpg

Monitor their behavioral changes

↓

Examine the levels of brain-specific *MAOA* using **quantitative mass spectrometry**

Aim 2: Elucidate the mechanism of how ***SIRT1*** expression affect brain-specific ***MAOA*** expression in rhesus monkeys

Extract brain samples of *L-MAOA* and *H-MAOA* rhesus monkeys

↓

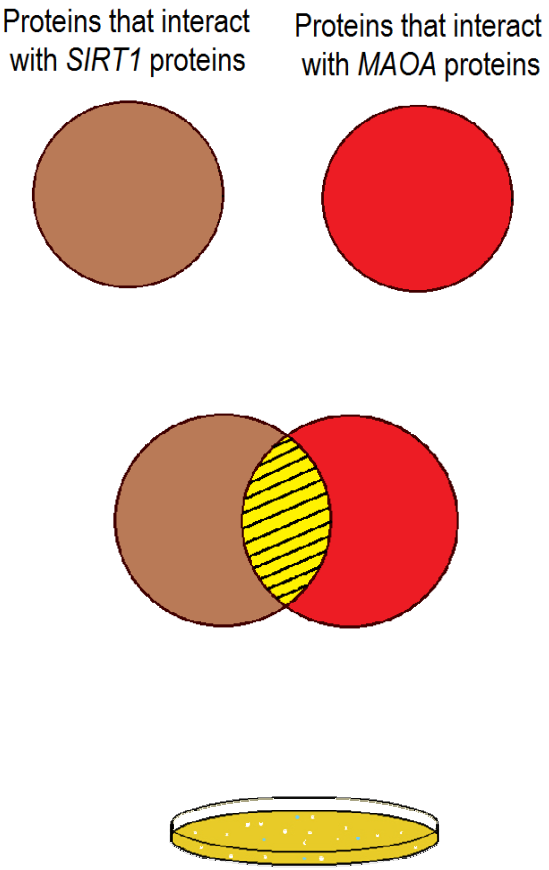
Use **TAP-tags** to identify all proteins that interact with *SIRT1* protein and *MAOA* protein, respectively

↓

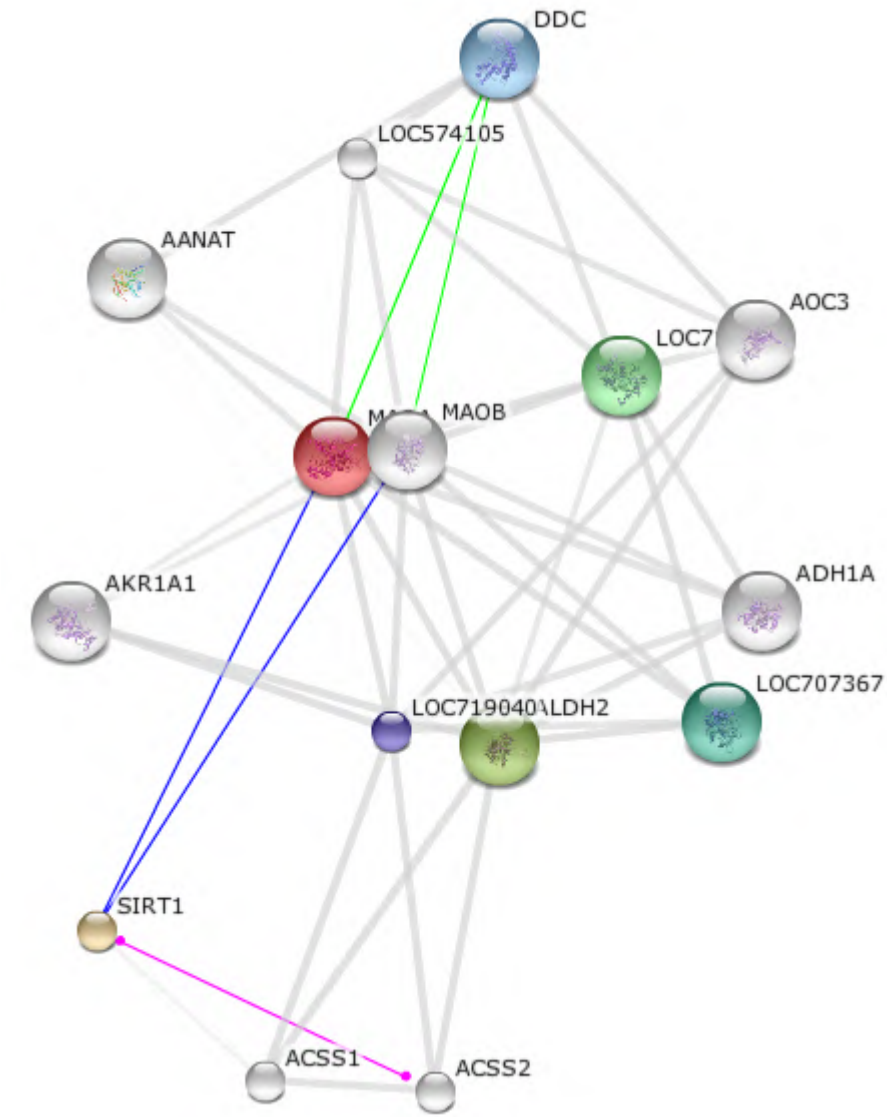
Identify proteins that interact with <u>both</u> *SIRT1* protein and *MAOA* protein

↓

Use **Y2H system** to examine protein-protein interactions



Predicted protein-protein interactions



STRING 9.1

Aim 3: Study the homology of ***SIRT1*** and ***MAOA*** variants (genes and proteins) between rhesus monkeys and humans

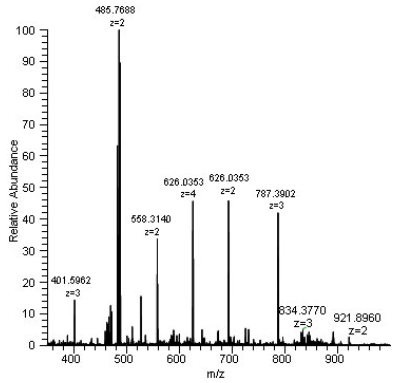
Extract samples of rhesus monkeys and humans

Gene

Protein

Roche 454 sequencing

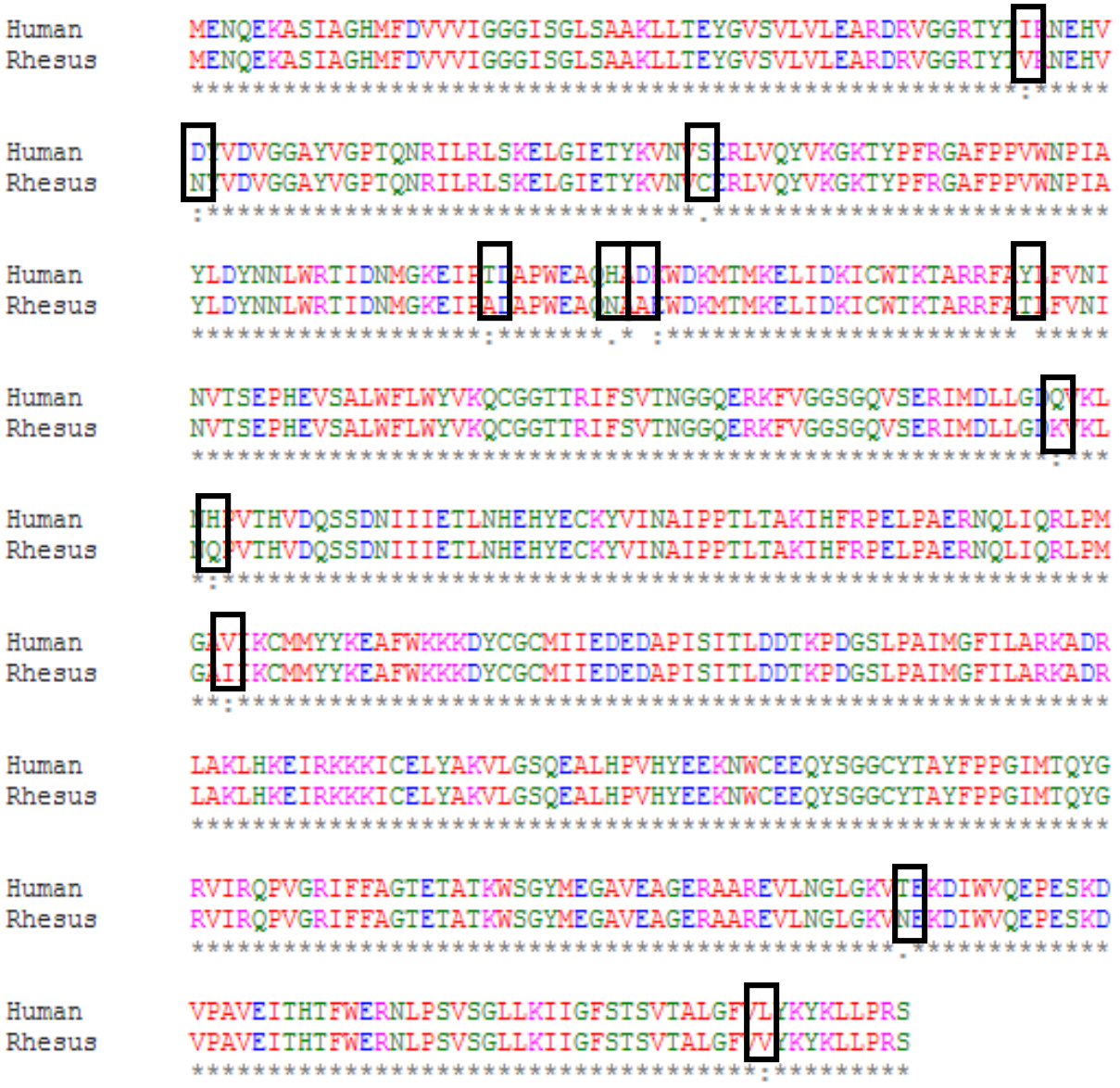
Mass spectrometry



http://www.langebio.cinvestav.mx/bioinformatica/jacob/wp-content/uploads/2013/08/roche.png

https://www.broadinstitute.org/files/shared/proteomics/ms.jpg

Proteins: Human vs. Rhesus monkey



Clustal Omega

Future implications

- a better understanding of the mechanisms between ***SIRT1***, ***MAOA*** and **aggression**
- potential drugs to upregulate ***MAOA***
- possible medical treatment for affected *L-MAOA* individuals
- a different view of criminality

Questions?

Image source: http://images.sussexpublishers.netdna-cdn.com/article-top/blogs/49143/2011/04/58689-51554.jpg