

Dad
Clinical Geneticist
Researcher



Why am I at a 1p36 conference?

Question #1

Why does my son/daughter have medical problems?



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Clinical Geneticist
Researcher



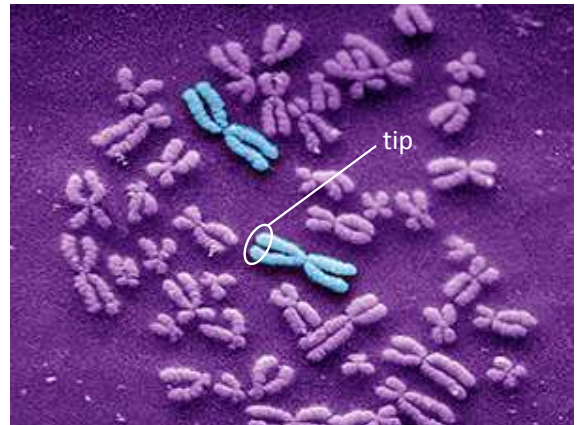
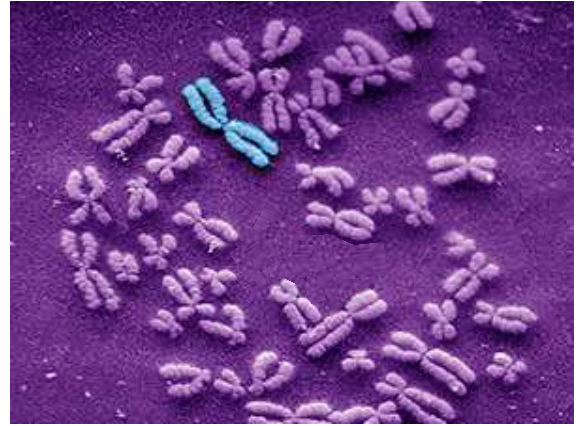
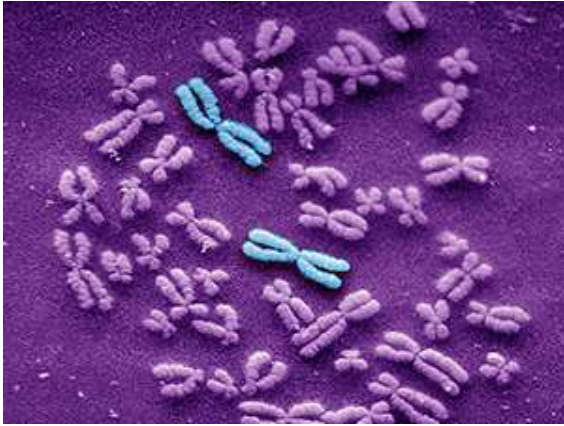
Why am I at a 1p36 conference?

[Answer your questions](#)

Question #1

Why does my son/daughter have medical problems?

Children with 1p36 deletions have an imbalance in their genetic material.



Question #1

Why does my son/daughter have medical problems?

Children with 1p36 deletions have an imbalance in their genetic material.



Question #1

Why does my son/daughter have medical problems?

Children with 1p36 deletions have an imbalance in their genetic material.



Ingredients

Flour
White sugar
Brown sugar
Eggs
Butter
Vanilla
Baking soda
Chocolate chips

Question #1

Why does my son/daughter have medical problems?

Children with 1p36 deletions have an imbalance in their genetic material.

Ingredients

Water
Proteins
Fats
Minerals
Carbohydrates
DNA

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Ingredients

Water
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Carbohydrates
DNA
645 Genes

Question #2

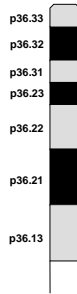
Why do some children with 1p36 deletions have more medical problems than others?

Question #2

Why do some children with 1p36 deletions have more medical problems than others?

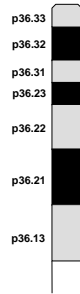
1p36 deletions can be of different sizes and affect different genes.

1p36 Deletions



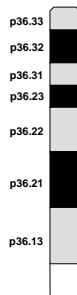
1p36 Deletions

Terminal Deletions



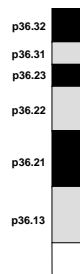
1p36 Deletions

Terminal Deletions
99 Genes



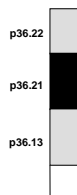
1p36 Deletions

Terminal Deletions
99 Genes



1p36 Deletions

Terminal Deletions
186 Genes

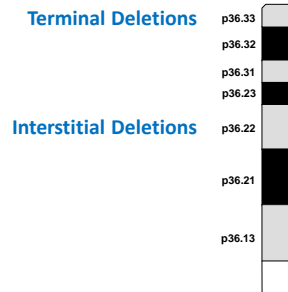


1p36 Deletions

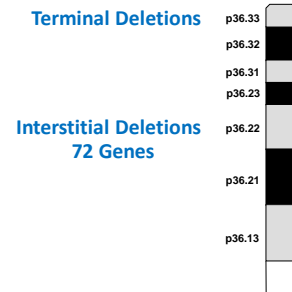
Terminal Deletions



1p36 Deletions



1p36 Deletions



Question #2

Why do some children with 1p36 deletions have more medical problems than others?

1p36 deletions can be of different sizes and affect different genes.



Other genetic differences not associated with a 1p36 deletion

Question #2

Why do some children with 1p36 deletions have more medical problems than others?

1p36 deletions can be of different sizes and affect different genes.



Other genetic differences not associated with a 1p36 deletion (Genetic background)

Question #2

Why do some children with 1p36 deletions have more medical problems than others?

1p36 deletions can be of different sizes and affect different genes.

Genetic background.

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Why do some children with 1p36 deletions have more medical problems than others?

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Genetic background.

Every child with a 1p36 deletion is unique!

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Why do some children with 1p36 deletions have more medical problems than others?

1p36 deletions can be of different sizes and affect different genes.

Genetic background.

Every child with a 1p36 deletion is unique!
They are genetically unique!

Question #3

How do doctors know which region of 1p36 is deleted?

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How do doctors know which region of 1p36 is deleted?

Microarray analysis.

Microarray Analysis



Blood sample

Microarray Analysis

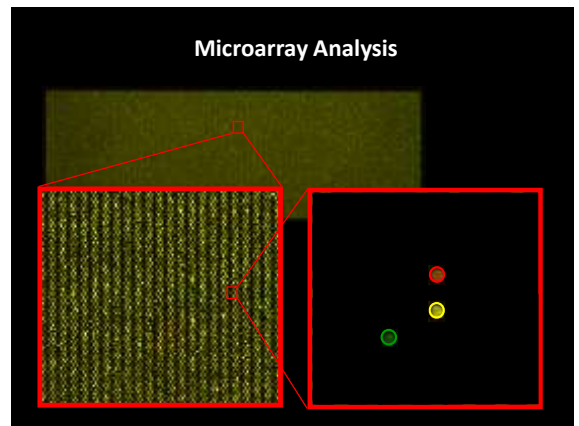
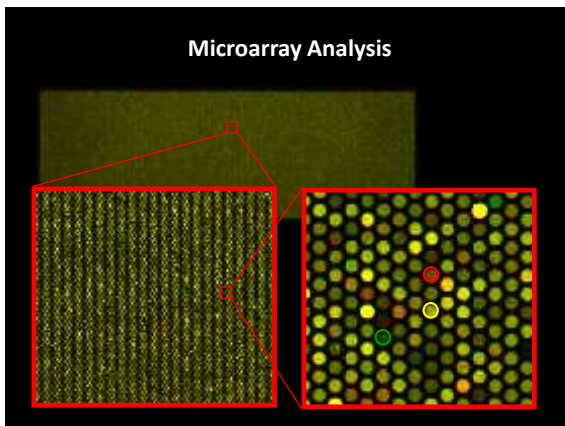
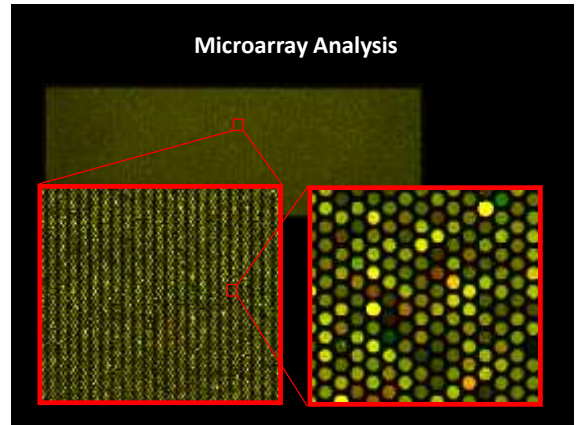
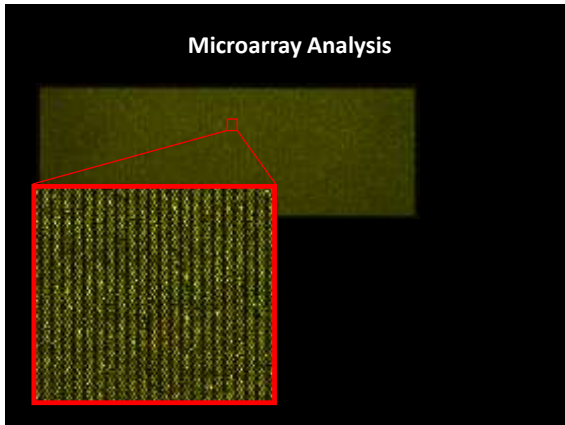
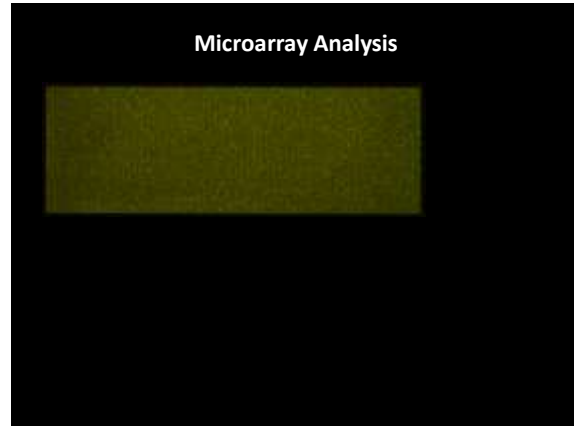
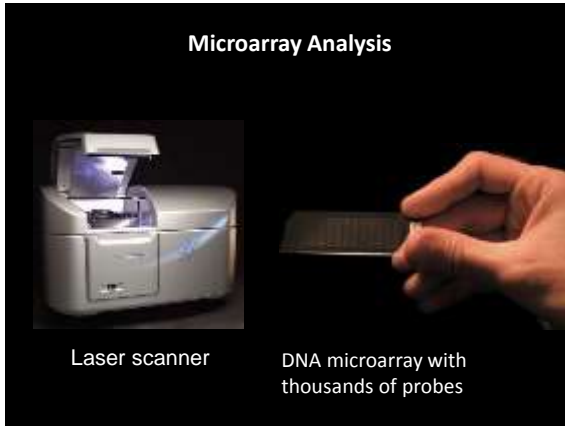


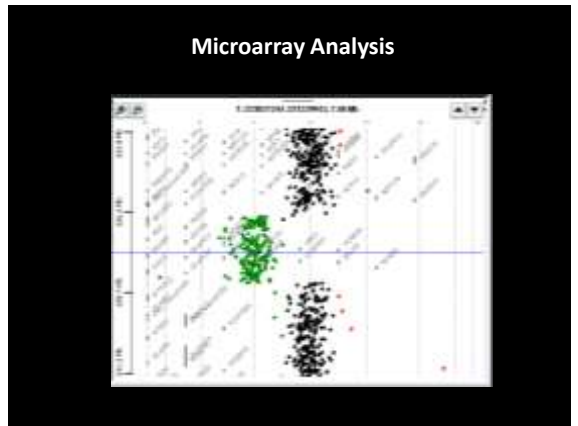
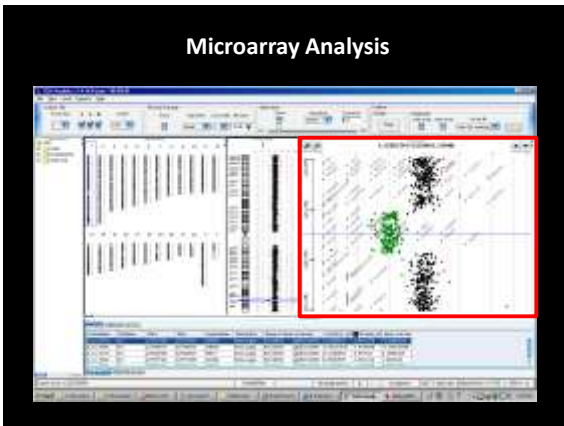
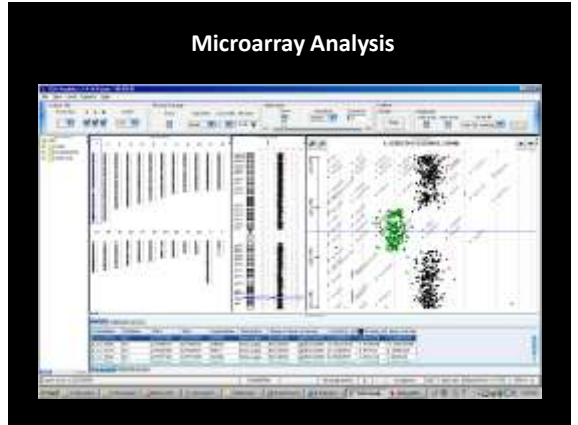
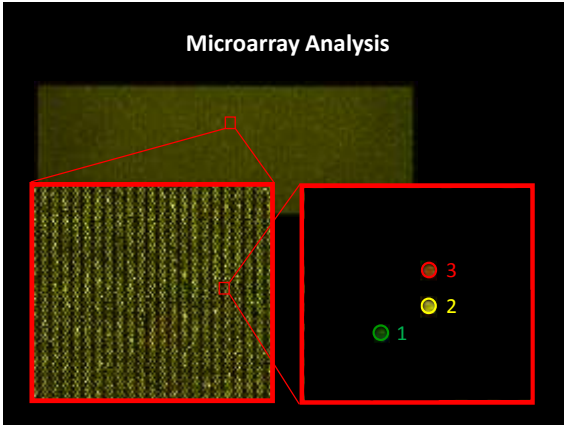
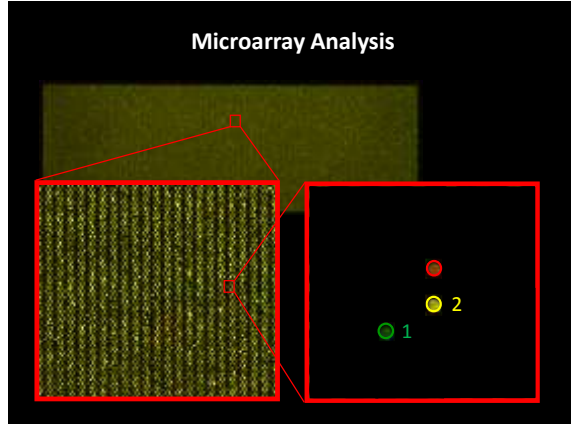
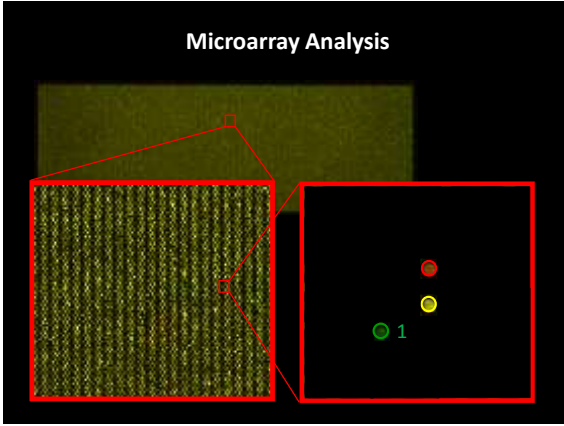
Blood sample
White blood cells

Microarray Analysis

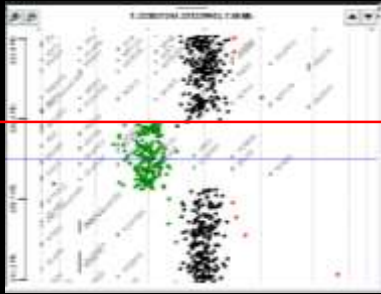


Blood sample
White blood cells
Extract DNA

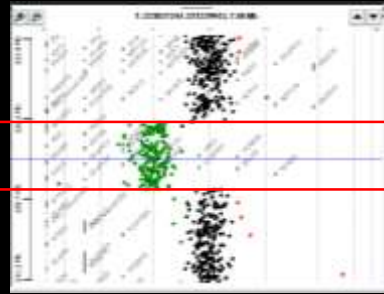




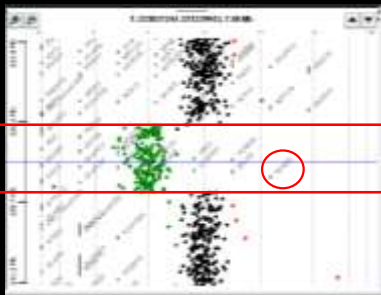
Microarray Analysis



Microarray Analysis



Microarray Analysis



BCM MEDICAL GENETICS LABORATORIES
 300 Research Blvd., Houston, TX 77030 • 832-855-4532
 Fax: 832-855-6800 • email: genmed@bcm.tmc.edu • genmed@bcm.tmc.edu

CLINICAL CYTOGENETICS LABORATORY

Name:	Sample Report:
Date of birth: 07/01/2005	Sample Type: 01-ABD
Request #: 00140002	Date collected: 08/22/2009
Accession #: 00000000	Date received: 08/22/2009
Ref. Lab #:	Request date: 01/22/2010
Panel #:	Telephone: 832-754-4400
Referring Physician: Stephen D. Glick, MD, PhD	Fax No.: 832-754-4400

CHROMOSOMAL MICROARRAY ANALYSIS (CMA)

Method: CMA-01-010-V12

Result: **ABNORMAL - 4,200**

Copy	Chromosome	Copy Number*	Min Size (kb)	Max Size (kb)	Min Size (Mb)	Max Size (Mb)
2.00	1	1.00	1,421,500	1,421,500	1.15	1.15

*Normal copy number is 2.00. An up to 10% deviation is considered an artifact from CNV or other CNV.

Interpretation: Chromosomal Microarray Analysis revealed a 1.15 Mb copy number loss in the distal short arm of chromosome 1, spanning a minimum of 1,421,500 and a maximum of 1,15 Mb, which was confirmed by FISH analysis. Clinical correlation is recommended.

BCM MEDICAL GENETICS LABORATORIES
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Question #4

Is each medical problem caused by deletion of a specific gene?

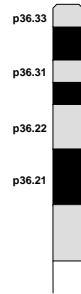
Question #4

Is each medical problem caused by deletion of a specific gene?

Good question!

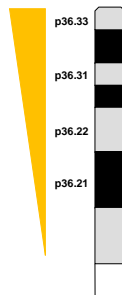
1p36 Deletions

Terminal deletions



1p36 Deletions

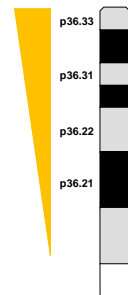
Terminal deletions



1p36 Deletions

Terminal deletions

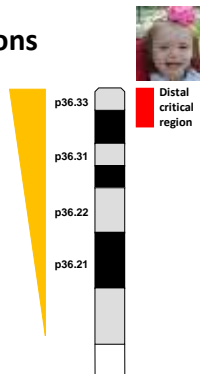
- Eye/vision problems
- Postnatal growth deficiency
- Cognitive impairment
- Brain anomalies
- Delayed motor development
- Facial Clefting
- Hearing loss
- Cardiovascular malformations
- Cardiomyopathy
- Renal anomalies



1p36 Deletions

Terminal deletions

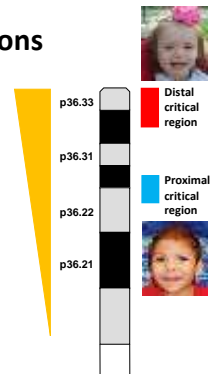
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1p36 Deletions

Interstitial deletions

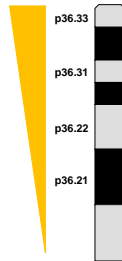
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1p36 Deletions

Interstitial deletions

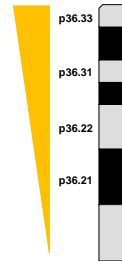
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- Postnatal growth deficiency
- Cognitive impairment
- Brain anomalies
- Delayed motor development
- Facial Clefting
- Hearing loss
- **Cardiovascular malformations**
- **Cardiomyopathy**
- Renal anomalies



1p36 Deletions

1p36 Deletions

- Isolated
- **Microarray data**
- **Cardiovascular malformations**
- **Cardiomyopathy**



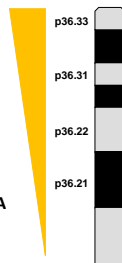
1p36 Deletions

1p36 Deletions

- Isolated
- **Microarray data**
- **Cardiovascular malformations**
- **Cardiomyopathy**

Data Sources

- Patients recruited to 1p36 study
- Patients referred to Baylor for CMA
- DECIPHER database
- Literature search



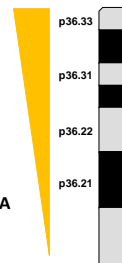
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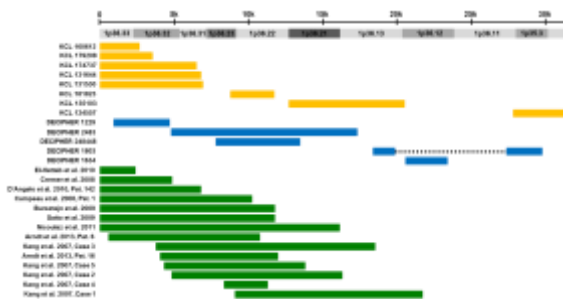
- Isolated
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Data Sources

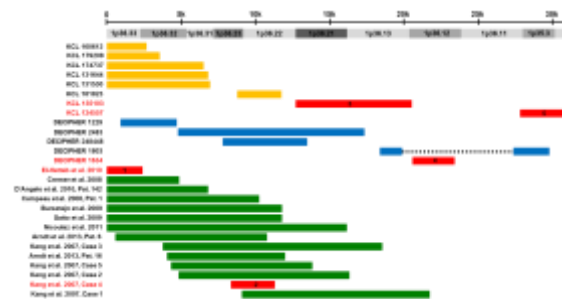
- Patients recruited to 1p36 study
- Patients referred to Baylor for CMA
- DECIPHER database
- Literature search
- **Surprisingly few cases**



Cardiovascular Malformations

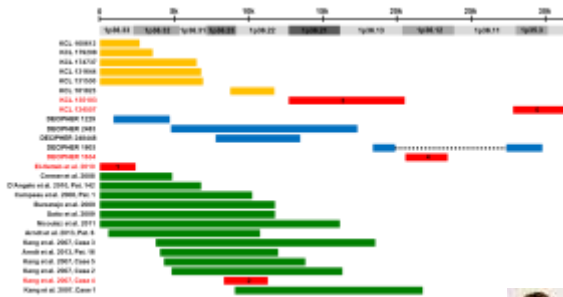


Cardiovascular Malformations



Five non-overlapping critical regions

Cardiovascular Malformations



Five non-overlapping critical regions



GeneDistiller 2 interface showing search filters and results. The 'target genes' section is highlighted with a red box, showing a list of genes and their associated data.



GeneDistiller 2 interface showing search filters and results. The 'target genes' section is highlighted with a red box, showing a list of genes and their associated data.



target genes

Linkage interval

chromosome 1 from to

1p24p11 (NCBI Build 37) 20,540,117

gene symbol

dbSNP ID / Affymetrix ID

microRNA

type

Count

GeneDistiller 2 interface showing search filters and results. The 'display options' section is highlighted with a red box, showing a list of checkboxes for various data sources and display settings.

display options

auto size (in: UI)

NCBI synonyms

Concepts (NCIT) / Trivial Names

Protein families (EPRO) / EPRO

Protein domains (PFAM)

Pathways (Kegg)

UniProt repeats (show full repeats)

Condam's Box

STR/CP/Alu repeats

Show table with expression values

NCBI geneRFs

Protein domains (trn/Pro)

Ankyrin/sequence variants (from ENSEMBL)

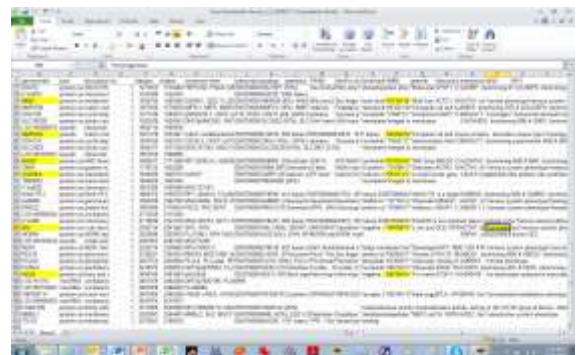
Human Phenotype Ontology

With phenotypes (show related exceptions)

GeneOntology terms

Translate above threshold for prediction

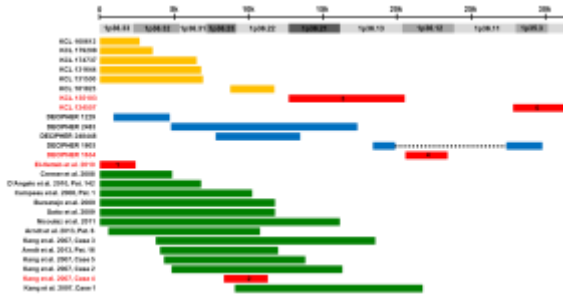
Show expression dot plot



“Cardiac” “Heart” “Cardio”

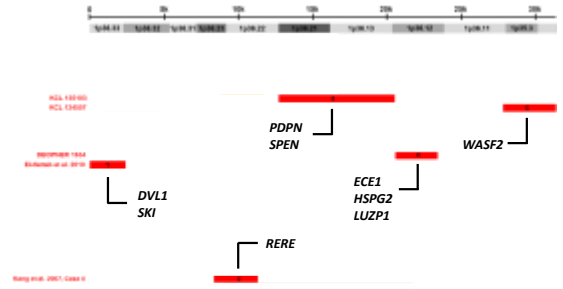
“Cardiac” “Heart” “Cardio”

Cardiovascular Malformations



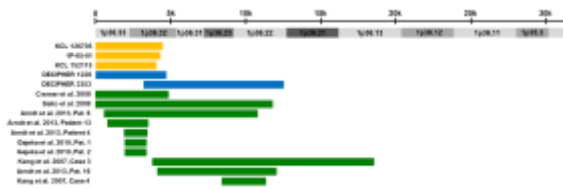
Five non-overlapping critical regions

Cardiovascular Malformations



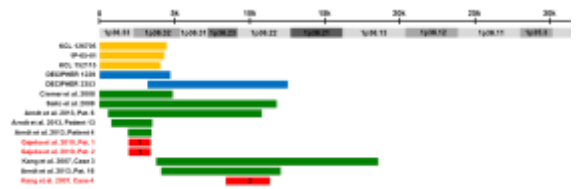
Five non-overlapping critical regions = Candidate genes

Cardiomyopathy

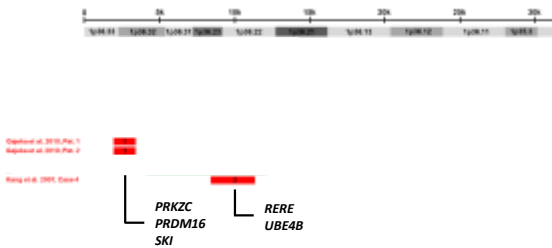


Two non-overlapping critical regions

Cardiomyopathy



Cardiomyopathy



Two non-overlapping critical regions

Question #4

Is each medical problem caused by deletion of a specific gene?

Good question!

Some medical problems may be caused by loss of a single gene.

Question #4

Is each medical problem caused by deletion of a specific gene?

Good question!

Some medical problems may be caused by loss of a single gene.

Other medical problems may be caused by loss of several genes.

Question #4

Is each medical problem caused by deletion of a specific gene?

Good question!

Some medical problems may be caused by loss of a single gene.

Other medical problems may be caused by loss of several genes.

The same medical problem can be caused by different genes in different people.

Question #5

How does knowing the genes involved help people?

Question #5

How does knowing the genes involved help people?

Help doctors make good medical decisions.

Question #5

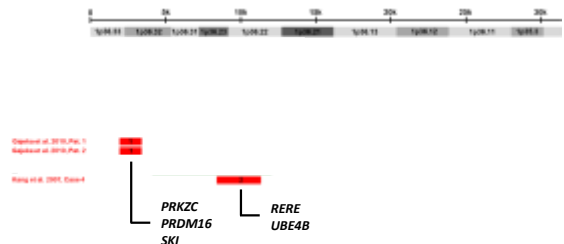
How does knowing the genes involved help people?

Help doctors make good medical decisions.

Child with 1p36 deletion.

Should we screen for cardiomyopathy?

Cardiomyopathy



Two non-overlapping critical regions

Cardiomyopathy



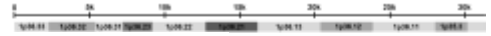
Optimal at 2010, Pac 1
Equivalent at 2010, Pac 2
Rang et al. 2005, Case4

PRKZ
PRDM16
SKI

RERE
UBE4B

Two non-overlapping critical regions

Cardiomyopathy



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Question #5

How does knowing the genes involved help people?

Help doctors make good medical decisions.

Identifying the genes involved is the first step to developing new treatments.

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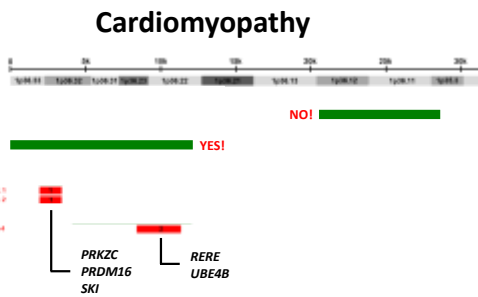
Identifying the genes involved is the first step to developing new treatments.

The second step is learning what these genes do in the body and how they do it.

Question #6

How do scientists learn what each gene does?

Sometimes we learn from individuals with mutations in a specific gene.

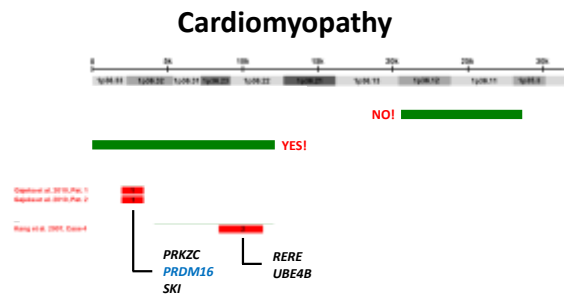


Two non-overlapping critical regions

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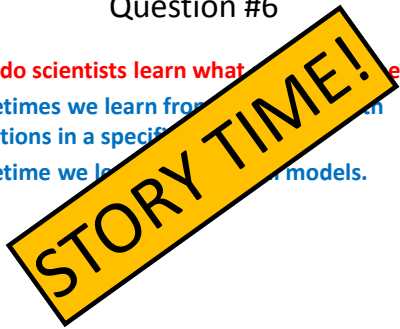
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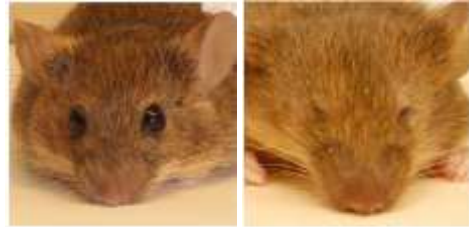
Sometime we learn from animal models.

Question #6

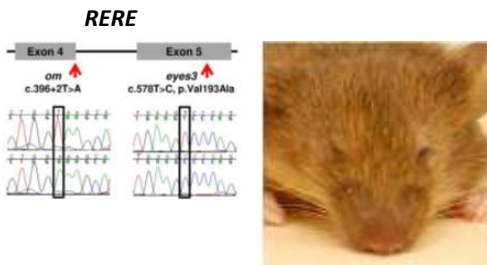
How do scientists learn what genes do?
 Sometimes we learn from studies of natural mutations in a specific gene.
 Sometime we learn from studies of mutant models.



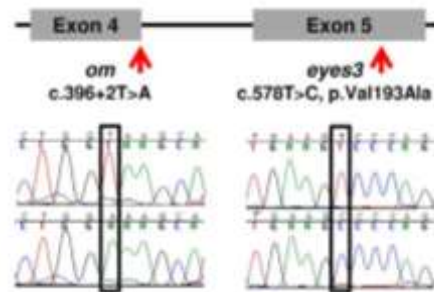
Blind Mice



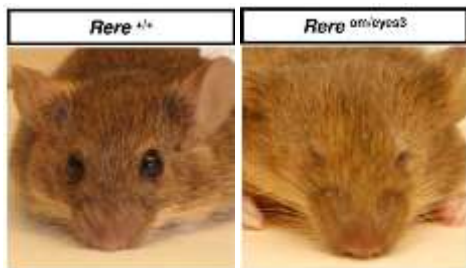
Blind Mice



Blind Mice



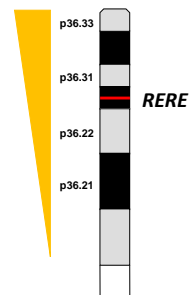
Blind Mice



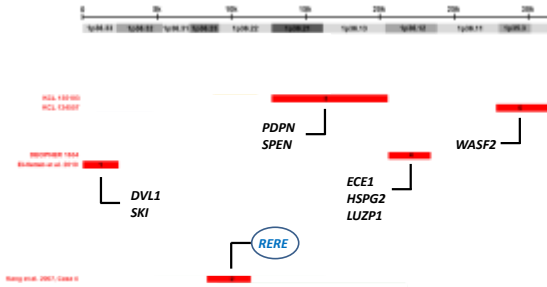
1p36 Deletions

Interstitial deletions

- Eye/vision problems
- Postnatal growth deficiency
- Cognitive impairment
- Brain anomalies
- Delayed motor development
- Facial Clefting
- Hearing loss
- Cardiovascular malformations
- Cardiomyopathy
- Renal anomalies



Cardiovascular Malformations



RERE-Deficient Mice



RERE-Deficient Mice



⇒ Descending aorta

RERE-Deficient Mice



⇒ Descending aorta
 → Ascending aorta

RERE-Deficient Mice



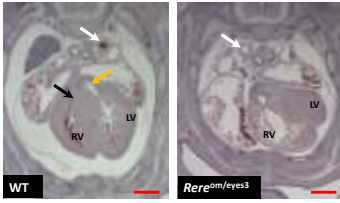
⇒ Descending aorta
 → Ascending aorta
 → Ventricular septum

RERE-Deficient Mice



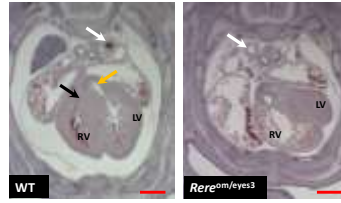
⇒ Descending aorta
 → Ascending aorta
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RERE-Deficient Mice



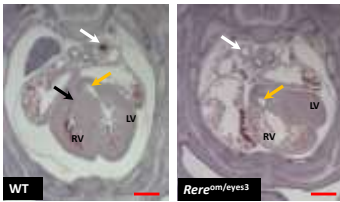
- ⇨ Descending aorta
- ⇨ Ascending aorta
- ⇨ Ventricular septum

RERE-Deficient Mice



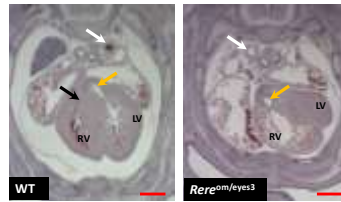
- ⇨ Descending aorta (right sided aorta)
- ⇨ Ascending aorta
- ⇨ Ventricular septum

RERE-Deficient Mice



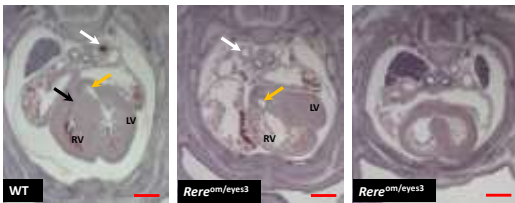
- ⇨ Descending aorta (right sided aorta)
- ⇨ Ascending aorta
- ⇨ Ventricular septum

RERE-Deficient Mice



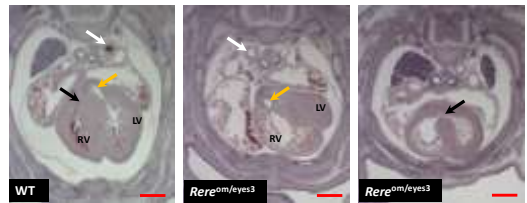
- ⇨ Descending aorta (right sided aorta)
- ⇨ Ascending aorta (double outlet right ventricle)
- ⇨ Ventricular septum

RERE-Deficient Mice



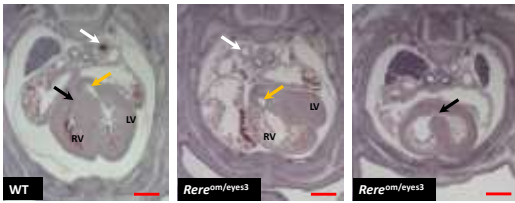
- ⇨ Descending aorta (right sided aorta)
- ⇨ Ascending aorta (double outlet right ventricle)
- ⇨ Ventricular septum

RERE-Deficient Mice



- ⇨ Descending aorta (right sided aorta)
- ⇨ Ascending aorta (double outlet right ventricle)
- ⇨ Ventricular septum

RETE-Deficient Mice

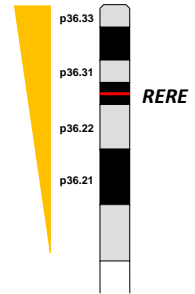


- ⇨ Descending aorta (right sided aorta)
- ⇨ Ascending aorta (double outlet right ventricle)
- ⇨ Ventricular septum (ventricular septal defect)

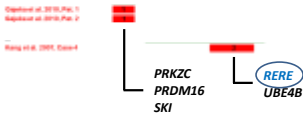
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Cardiomyopathy

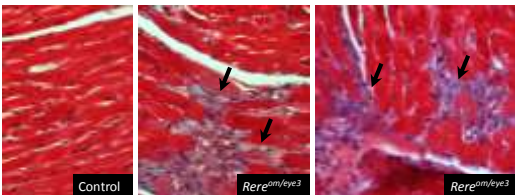


Two non-overlapping critical regions

RETE-Deficient Mice



RETE-Deficient Mice

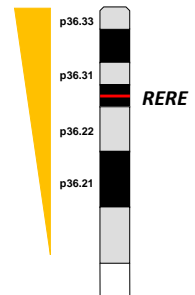


⇨ Cardiac fibrosis

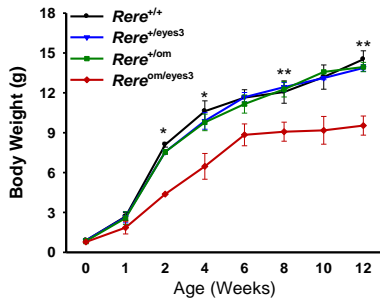
1p36 Deletions

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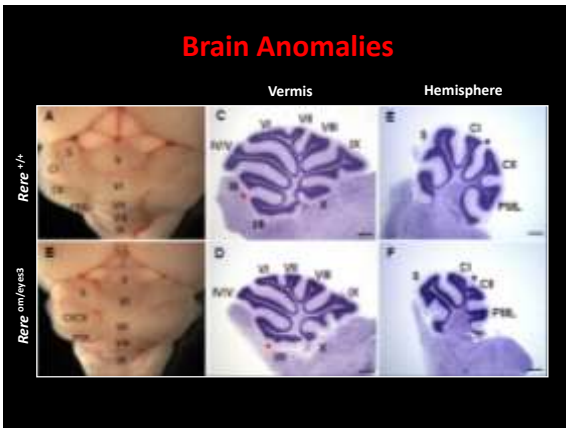
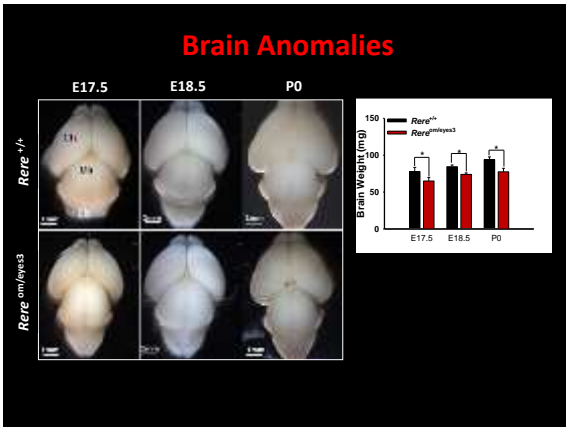


Postnatal Growth Deficiency?



Brain Anomalies
Cognitive Impairment
Behavioral Problems

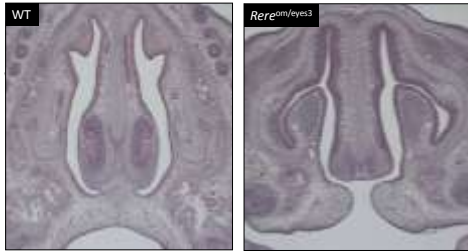
Brain Anomalies



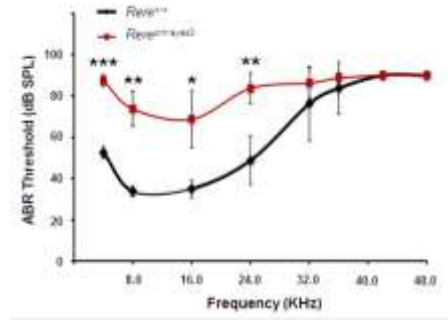
Cleft Palate?



Cleft Palate?



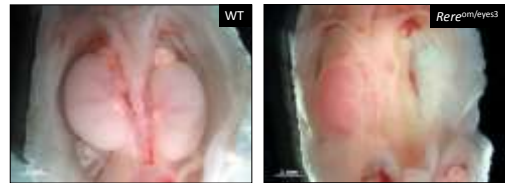
Hearing Loss?



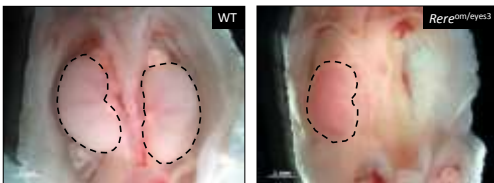
Renal Problems?



Renal Problems?



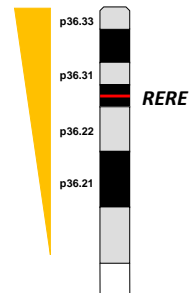
Renal Problems?



1p36 Deletions

RE-re deficiency

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Question #7

Does *RERE* cause 1p36 deletion syndrome?

Question #7

Does *RERE* cause 1p36 deletion syndrome?

No. Not all 1p36 deletions include *RERE*.

Question #7

Does *RERE* cause 1p36 deletion syndrome?

No. Not all 1p36 deletions include *RERE*.

Deletion of *RERE* may be sufficient to cause some problems and may contribute to others.

Question #8

Is there hope for a cure?

Is there hope for new treatments?

Question #8

Is there hope for a cure?

Is there hope for new treatments?

A cure would be very difficult.

Question #8

Is there hope for a cure?

Is there hope for new treatments?

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New treatments may be possible.

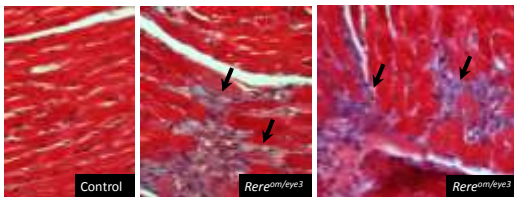
Question #8

Is there hope for a cure?
 Is there hope for new treatments?
 A cure would be very difficult.
 New treatments may be possible.
 Identifying the genes involved is the first step to developing new treatments.
 The second step is learning what these genes do in the body and how they do it.

Question #8

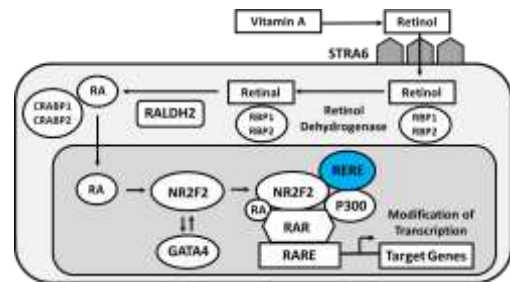
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RERE-Deficient Mice

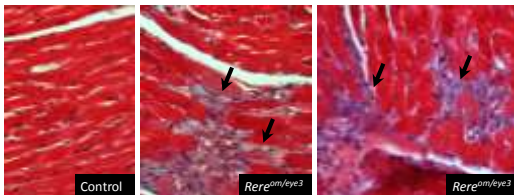


➔ Cardiac fibrosis

RERE and Vitamin A



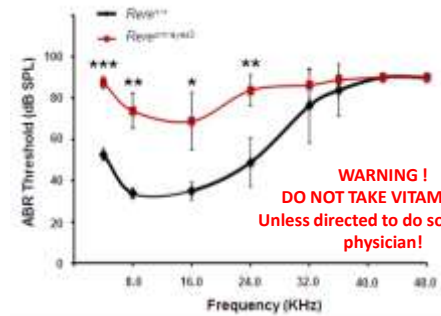
Vitamin A as a Therapy?



➔ Cardiac fibrosis

WARNING !
DO NOT TAKE VITAMINE A
 Unless directed to do so by your physician!

Vitamin A as a Therapy?



WARNING !
DO NOT TAKE VITAMINE A
 Unless directed to do so by your physician!

**WARNING !
DO NOT TAKE VITAMINE A!**

Vitamin A is a **TERATOGEN** meaning that if a pregnant mother takes too much it can cause birth defects!

Vitamin A can also be **TOXIC!** If you take too much it can kill you!

If Vitamin A **EVER** becomes a therapy, the dosage taken will need to be determined by a physician!

DO NOT TAKE VITAMIN A OR GIVE VITAMIN A TO YOUR CHILD unless directed to do so by a physician!

Question #8

Is there hope for a cure?

Is there hope for new treatments?

A cure would be very difficult.

New treatments may be possible.

New therapies will need to take into account the genes involved.

Question #8

Is there hope for a cure?

Is there hope for new treatments?

A cure would be very difficult.

New treatments may be possible.

New therapies will need to take into account the genes involved.

New therapies will take time to develop.

Question #9

What can we do to help?

Question #9

What can we do to help?

Encourage financial support for 1p36 research.

Question #9

What can we do to help?

Encourage financial support for 1p36 research.

Become involved in research projects.

Question #9

What can we do to help?

Encourage financial support for 1p36 research.

Become involved in research projects.

Mapping projects

- Microarray test results
- Clinical summary
- Learn more e-mail me! dscott@bcm.edu

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