Rett Syndrome

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Bioinformatics Summer Workshop

Introduction:

❖What is Rett Syndrome?

Rett syndrome-

- inherited disease of the nervous system and a childhood neurodevelopment disorder.

That leads to:

-developmental reversals in the areas of expressive language and hand use

-slow progress of brain and head growth

-gait abnormalities

-seizures

-mental retardation

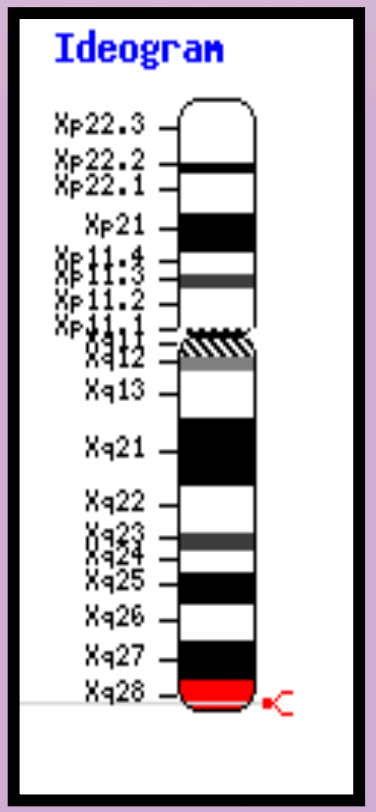
Objective:

- **Bioinformatics**-

  -came about from the **Human Genome Project**

  -a way to organize, search, analyze and store all of the millions of DNA gene sequences on the computer.

- **Rett Syndrome** relates to **Bioinformatics** because Rett Syndrome is an inherited disorder where the mutation is found on the X chromosome, which is part of the **human genome**.

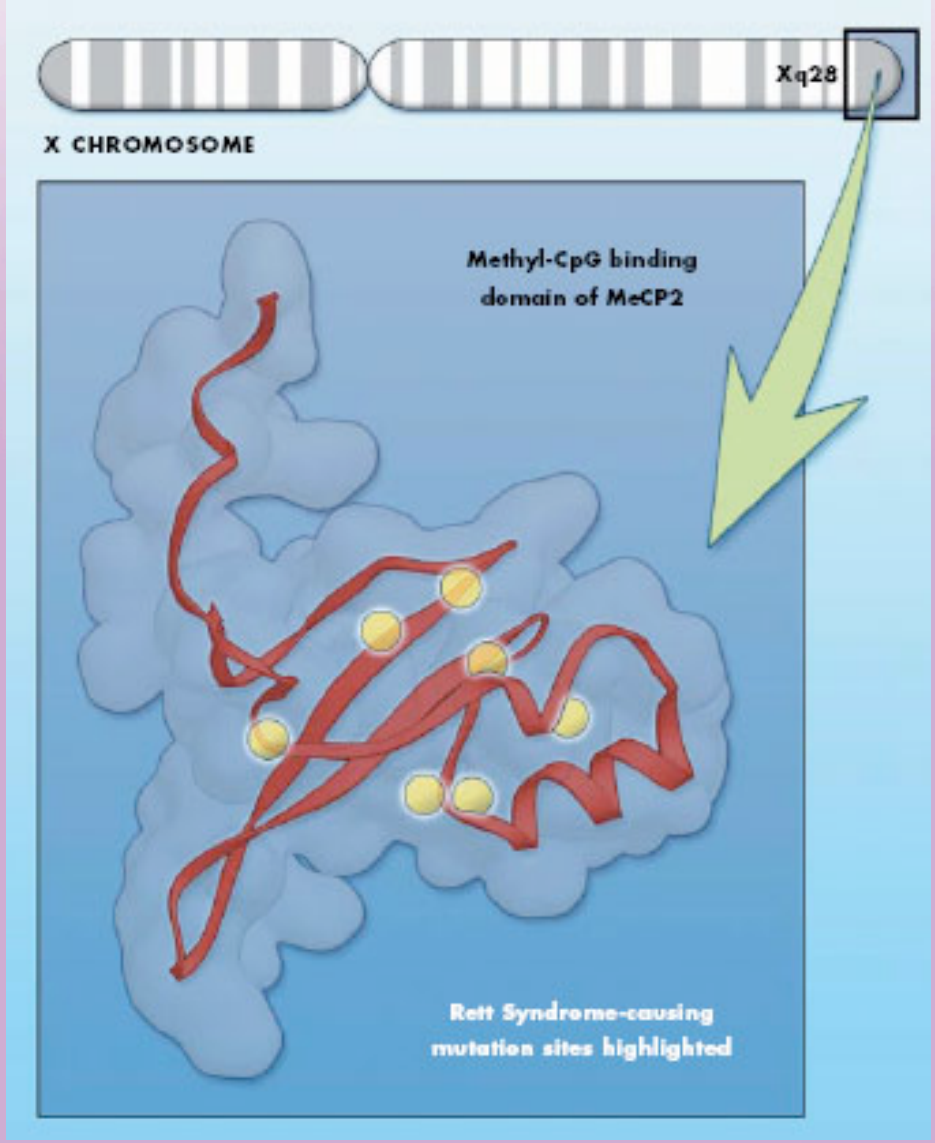


History:

- The disorder was identified by an Austrian physician **Dr. Andreas Rett** in 1966.
- In 1954, Dr. Andreas Rett first noticed two girls as they sat in his waiting room and observed these children making the same repetitive hand-washing motions.
- He then compared their clinical and developmental histories and discovered they were very similar to six other girls with the similar behavior.
- Surely, he thought, all these girls must have the same disorder.

Causes:

- In 1999, it was discovered that Rett syndrome is caused by mutations in the **MECP2 gene**.
- The discovery of the gene **MECP2** which is located at the **Xq28 site** on the **X chromosome** proved that Rett syndrome is an **X-linked disorder**.
- **Only one** of the **two X chromosomes** needs to have the mutation in order for it to cause the disorder.



Causes: (cont'd)

- The fact that Rett syndrome is an **X-linked dominant disorder** helps explain why it is usually found only **exclusively in girls**.
- Females have two X chromosomes, so even when one has this defect, the other X chromosome provides enough normal protein for the female to survive, still carrying the disorder.
- **70-80%** of girls given a diagnosis of Rett syndrome have the MECP2 genetic mutation.

MECP2 Gene Function:

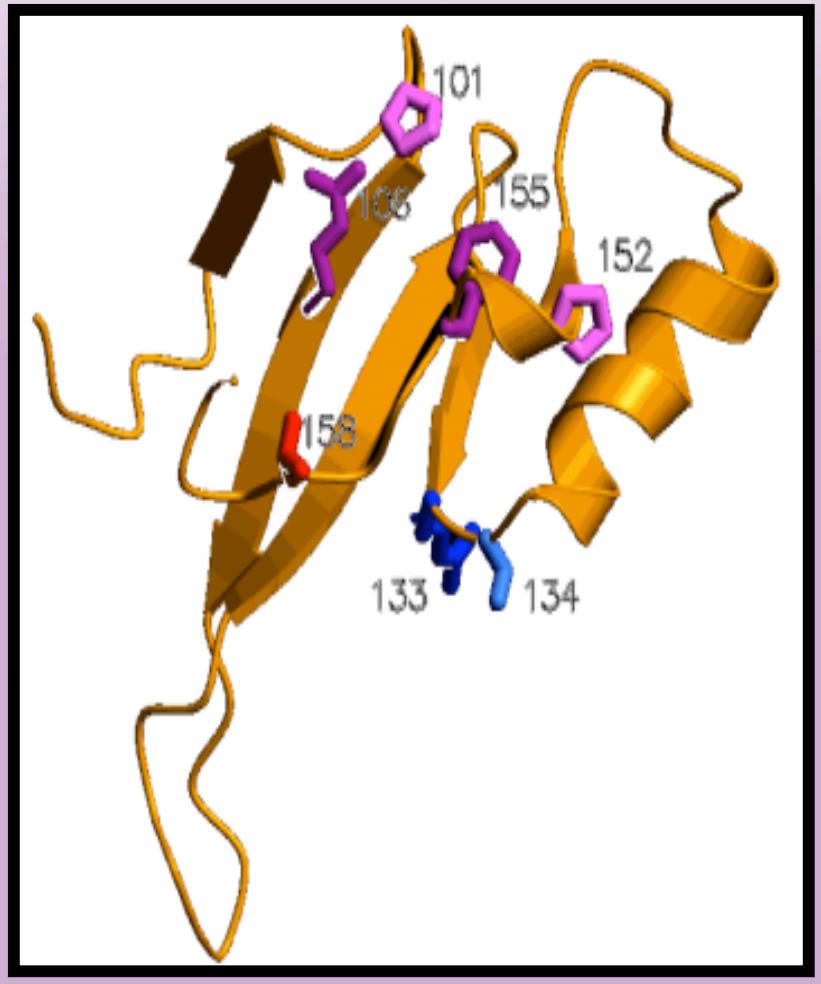
- **MECP2** is a member of a family of proteins all containing a **Methyl-CpG Binding Domain (MBD).** Other family members are **MBD1, MBD2, MBD3** and **MBD4**.

- The **MECP2 gene** provides instructions for making a **MECP2 protein** that is critical for normal brain development.

- The **MECP2 protein** plays a role in forming connections between nerve cells, including regulating other genes in the brain by switching them off when they are not needed.

MECP2 Protein Function:

- A **missence mutation** occurs in the MECP2 gene, which **changes only one amino acid** of the gene, that changes the whole configuration of the protein, and makes the proteins tightly packed in the MBD.
- Therefore, the **MBD** is **crucial for MECP2 function**.



Binding of MBD:

This picture demonstrates the structure of the MBD from the MBD1 protein. The methyl group marked as bubbles point to the major DNA movement, where it makes contact with amino acids within the MBD.

Symptoms:

- Before the symptoms begin an **infant** with Rett syndrome usually has **normal development** for the **first 6-8 months**.
- Then, gradually, **mental and physical symptoms** appear, such as:

  -Hypotonia (loss of muscle tone)-
  (frequently the first symptom)
  -diminished eye contact
  -Severe development of language
  (loss of speech)
  -Loss of purposeful hand movements
  (often wringing and washing)
  -Apraxia (problems crawling or walking)
  -Loss of social engagement

Stages of Rett Syndrome:

1) **Early Onset Phase** – Development stops after 6-18 months

2) **Rapid Destructive Phase** – (**Hypotonia)** hand movements and speech are the first skills lost

3) **Plateau Phase** – symptoms may seem to lessen (**most people spend their lives in stage**)

4) **Late Motor Deterioration Phase** – (**apraxia)** loss of movement and muscle tone, some may become immobile.

Treatment:

- Unfortunately, Rett syndrome has **no cure**. However, the **symptoms** that are associated with the disorder **can be treated**.
- These treatments aim to **slow** the **loss of abilities**, **improve movement**, and **encourage communication**. Such treatments include:

-**Therapy**- help slow progress of movement loss. Therapies includes:

hysical therapy- help patients
y

ccupational therapy- help
e of hand

peech-language therapy- help
-verbal ways of
improve social
interaction.

What are the chances?

- Rett syndrome occurs in **all racial and ethnic groups,** worldwide in **1 of every 10,000 to 23,000 female births.**
- Although Rett syndrome is a **genetic disorder**, the **inheritance is dominant** if **one copy of the mutated gene** which is **MECP2** in **each cell** of the **X chromosome** is **sufficient** to **cause the condition**.
- **Boys** who have an MECP2 mutation only have **one X chromosome**, which means if they have the mutation they **lack** the **back-up copy** that could **compensate,** therefore, boys with this mutation **die shortly after birth**.

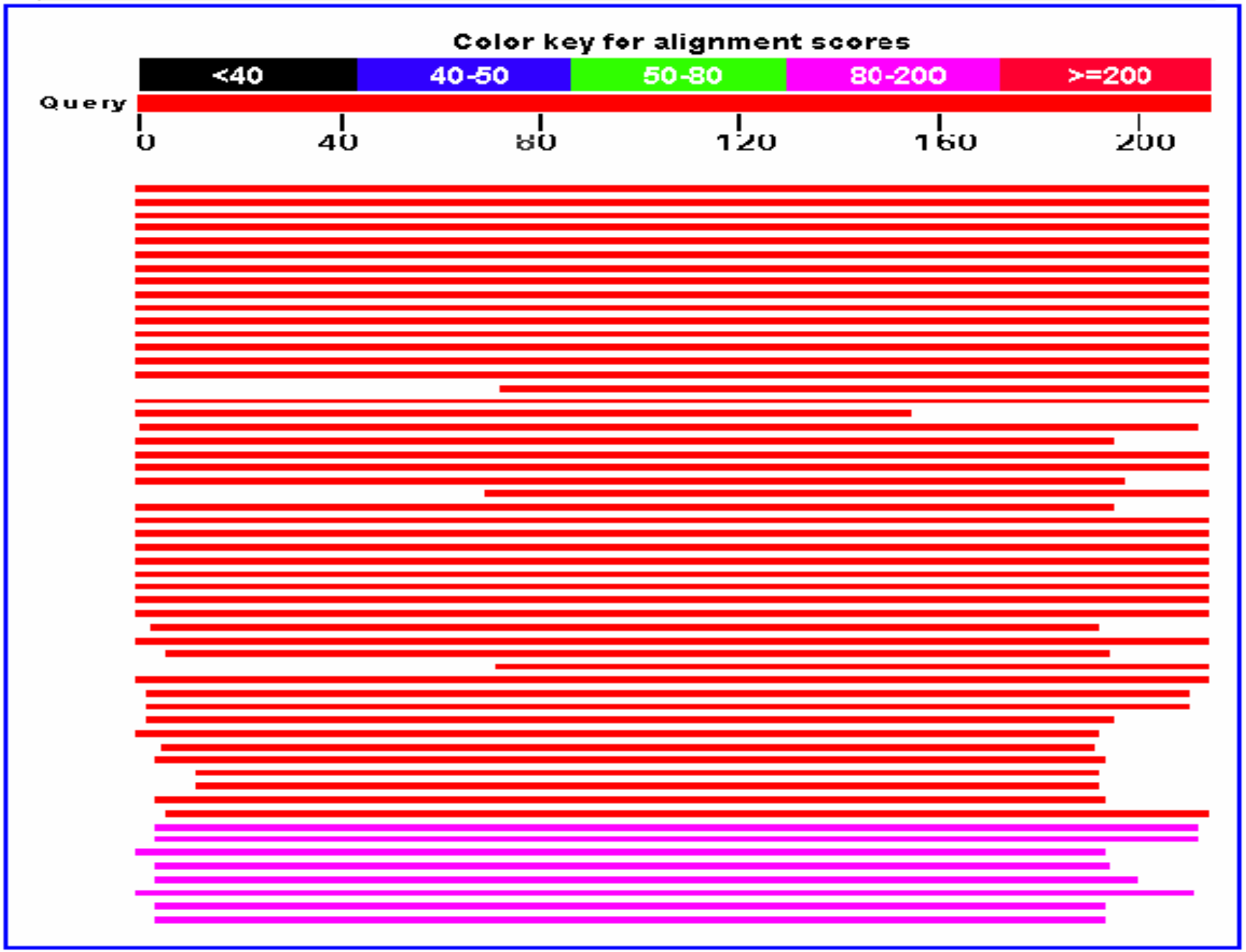
Experiment:

- **Goal:** I would like to **understand** the **alignment of MECP2 sequences** from **different species** with the positions of the mutations in Rett Syndrome using the **National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST)** program.

Procedure:

- First, I obtained the messenger RNA sequence of the MECP2 gene using the **National Center for Biotechnology Information (NCBI)** website.
- Next, I used the program:
  - **Basic Local Alignment Search Tool (BLAST)-** database designed to explore all of the available gene sequences.

  To receive the different sequences that the MECP2 will compare.
- After that, the results from BLAST of the sequences were analyzed.
- Finally, the search was narrowed down with three other organisms to compare the human MECP2 sequence with three other organisms sequences, such as the mouse, chicken, and X-*laevis* (African Clawed frog).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<40
40-50
50-80
80-200
>=200
Query
0
40
80
120
160
200

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(Over 10 PubMed links)

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7 more sequence titles
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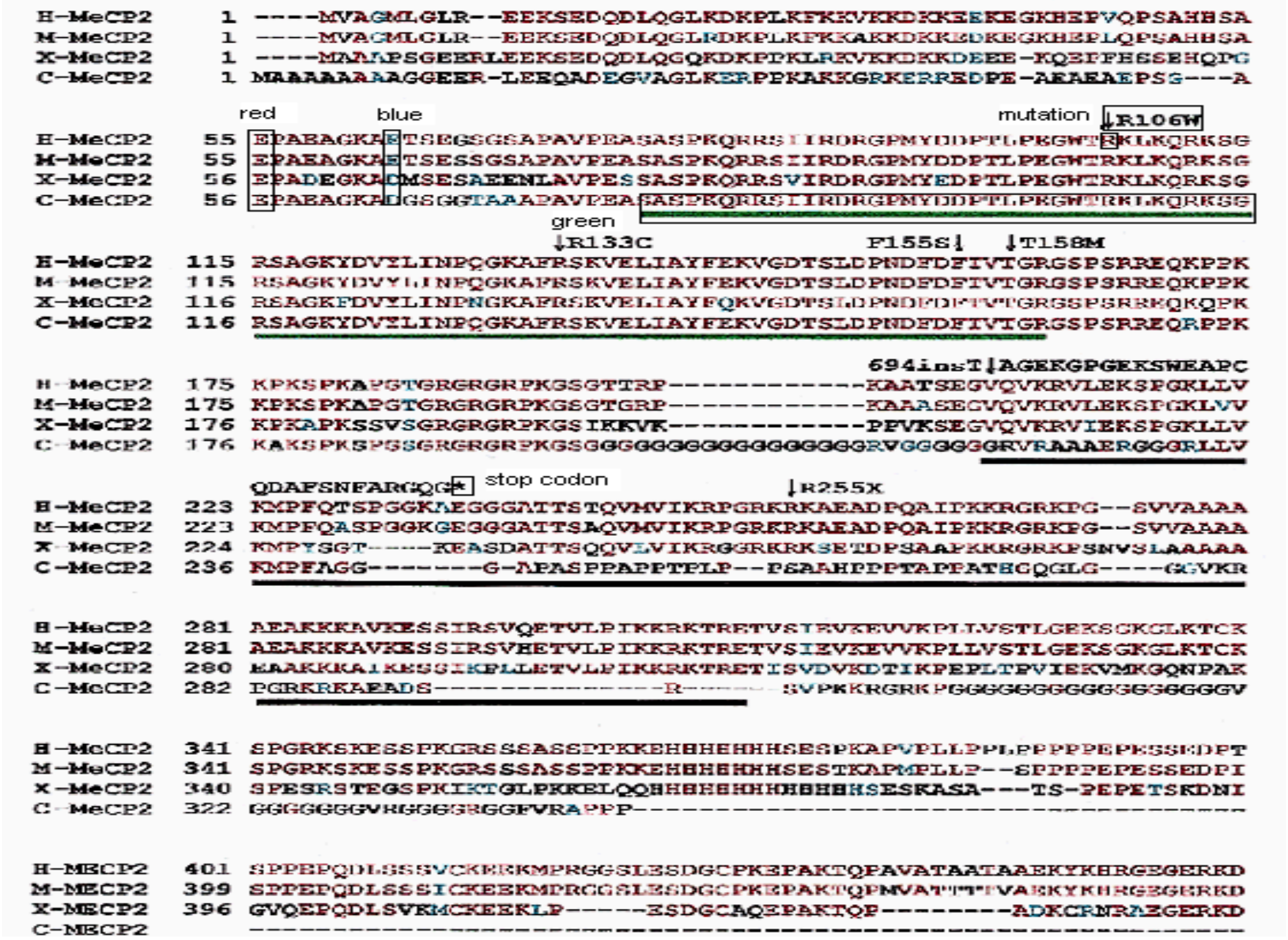
GENE ID: 67790 Rab39b | RAB39B, member RAS oncogene family [Mus musculus]
(Over 10 PubMed links)


red
blue
mutation
R106W
green
R133C
F155S
T158M
694insT
AGEEGPGEESWEAPC
stop codon
R255X

Future Research:

- **The National Institute of Neurological Disorders and Stroke (NINDS)** and the **National Institute of Child Health and Human Development (NICHD)**, two of the **National Institutes of Health (NIH)** facilities, are trying to find out how the **MECP2 protein functions**.
- Information from this study will increase understanding of the disorder, a basis which may lead to **new therapies**.
- **One outcome** might involve **manipulating** other **biochemical pathways** to **compensate** for the **malfunctioning MECP2 gene**, thus **preventing progression** of the disorder.

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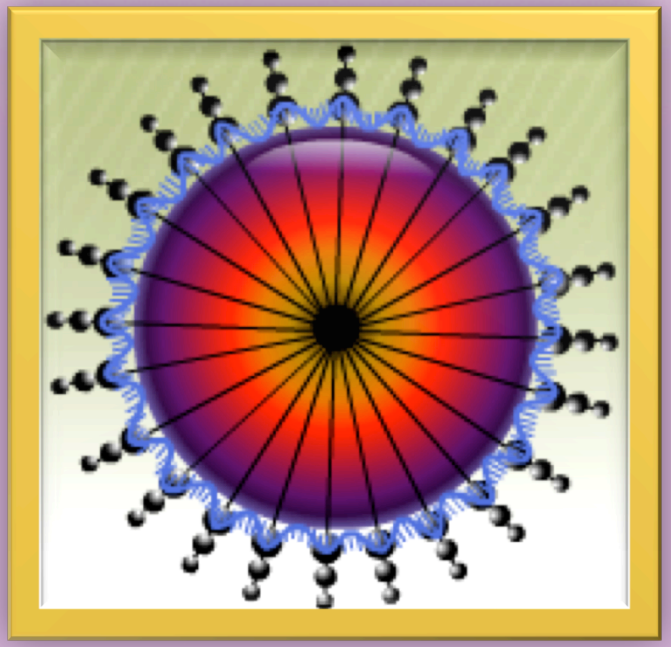

Thank You!