RETT SYNDROME

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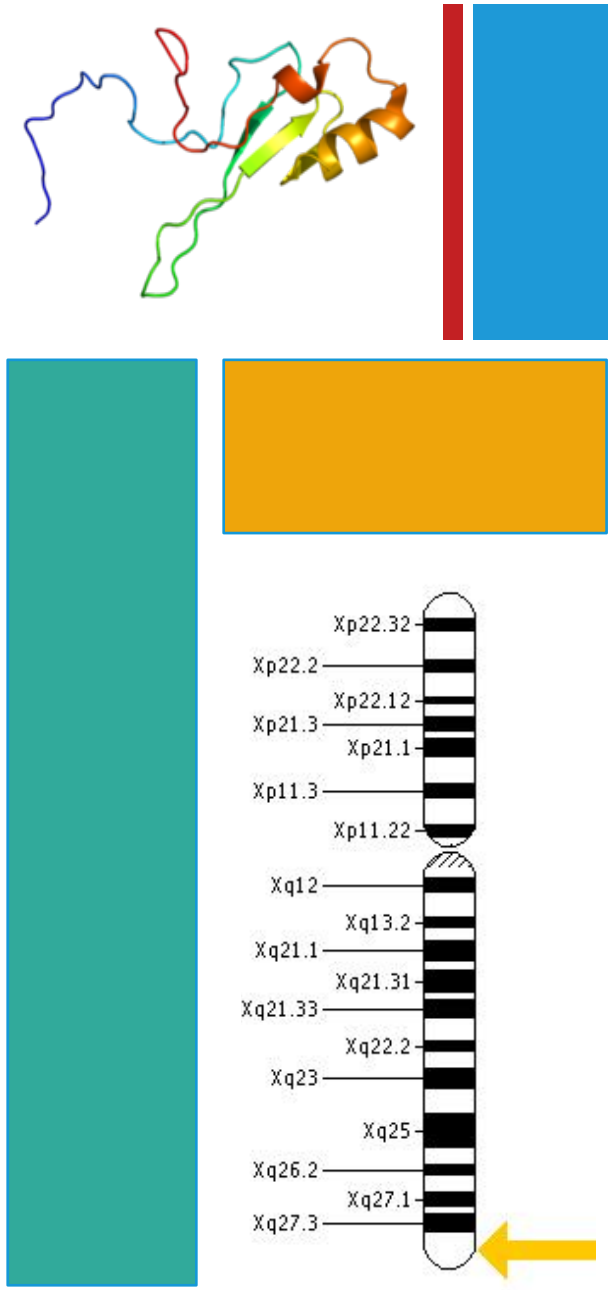
Pd. 6

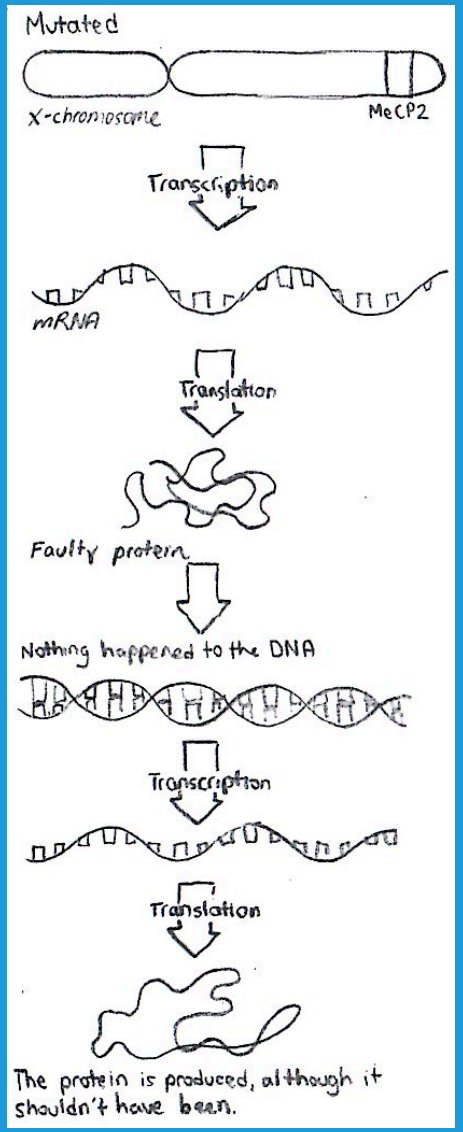
Physiology

- Rett syndrome is a progressive neural disorder affecting about 16,000 women and children in the US
- Inheritance pattern: X-linked dominant
  - Most cases are not inherited—instead, they're caused by spontaneous mutations
- Symptoms generally described in terms of four "stages"
  - Early onset
    - Less eye contact, reduced interest in toys, difficulty sitting or crawling, mild handwringing and mild decrease in head growth
  - Rapid destructive stage
    - Starts ages 1-4, lasts for weeks or months
    - Loss of control of hand movements begins, as does loss of ability to communicate through talking, handwringing increases, and there are breathing irregularities
  - Plateau or pseudo-stationary stage
    - Starts 2-10, lasts for years
    - improvement in behavior- more social interaction and interest in surroundings
    - many remain in this stage for much of their lives
  - Late motor deterioration stage
    - Most motor capabilities decline further with the exception that repetitive hand movements tend to decrease; communication abilities stay the same

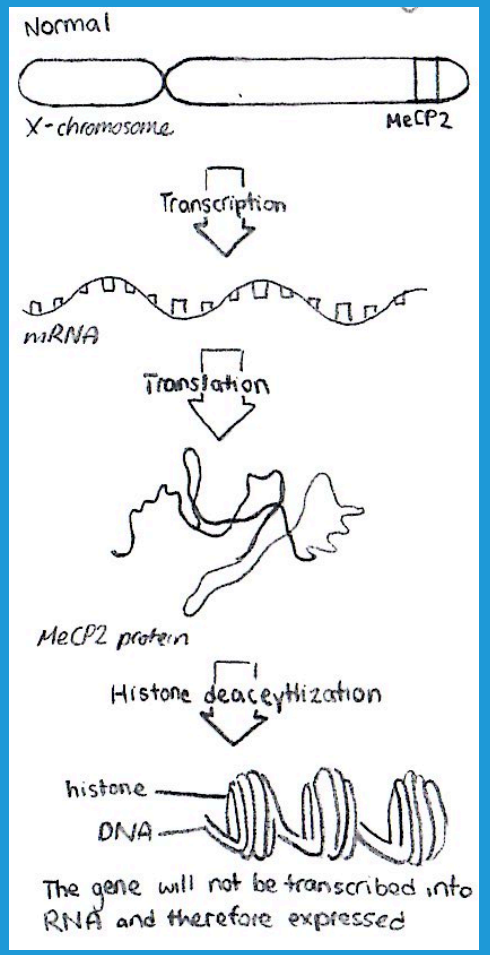
Molecular Cause

- Rett syndrome is caused by mutations in the MeCP2 gene
  - No one specific mutation; there are many
- The MeCP2 gene regulates the expression of other genes by silencing transcription and binding to methylated DNA throughout the genome
  - Most abundant in the brain, where it is believed to have a maintenance function
    - Would explain the delayed onset, which has been replicated in mice—even with mice, whose developmental stages are very different from ours, the onset takes about 9 months
- When there's a mutation in the gene, the structure of the MeCP2 protein is changed so that it can no longer bind either to the DNA or so to the other (transcription-repressing) enzymes
  - These genes are therefore overexpressed
- MeCP2 protein not functioning therefore doesn't directly cause the symptoms—it causes the malfunctions of other genes which then causes the symptoms
  - Explains the variation in the symptoms—not all caused by the one gene
- Very little is known about the genes the functioning MeCP2 gene represses
  - Just one found in mice: the BDNF gene, which is related to learning and neural plasticity, and none known in humans




Mutated
X-chromosome
MeCP2
Transcription
mRNA
Translation
Faulty protein
Nothing happened to the DNA
Transcription
Translation
The protein is produced, although it shouldn't have been.

vs.


Normal
X-chromosome
MeCP2
Transcription
mRNA
Translation
MeCP2 protein
Histone deaceytlization
histone
DNA
The gene will not be transcribed into RNA and therefore expressed

+ Management

- Diagnosis
  - Clinically diagnosed by observing the symptoms listed previously
  - Three main types of criteria in terms of diagnosis:
    - Main:
      - include things necessary for diagnosis of Rett syndrome, like loss of motor skills, loss of language skills, repetitive movements, and abnormalities in gait
    - Supportive:
      - not necessary for diagnosis but are often found in patients with the syndrome, and include things like scoliosis and abnormal sleep patterns
    - Exclusion:
      - show the patient does not have Rett syndrome; include things such as known brain trauma that would explain the symptoms shown
  - Genetic testing is available to verify the diagnosis and to give some insight into the patient's specific mutation. However, as there are MeCP2 mutations that do not cause Rett syndrome, the genetic test itself is often not enough.

- There is currently no viable gene therapy, but research is being done:
  - Figuring out what parts of the brain correspond to what symptoms so that cells in certain areas can be genetically engineered to have two normal copies of the MeCP2 gene
  - Researching molecular pathways
  - In mice, lifespan was significantly lengthened with a bone-marrow transplant after specific cells with faulty MeCP2 genes/ proteins were killed off
  - "Modifiers" which suppress specific subsets of Rett syndrome symptoms
  - Not enough is known about any of these for them to be helpful

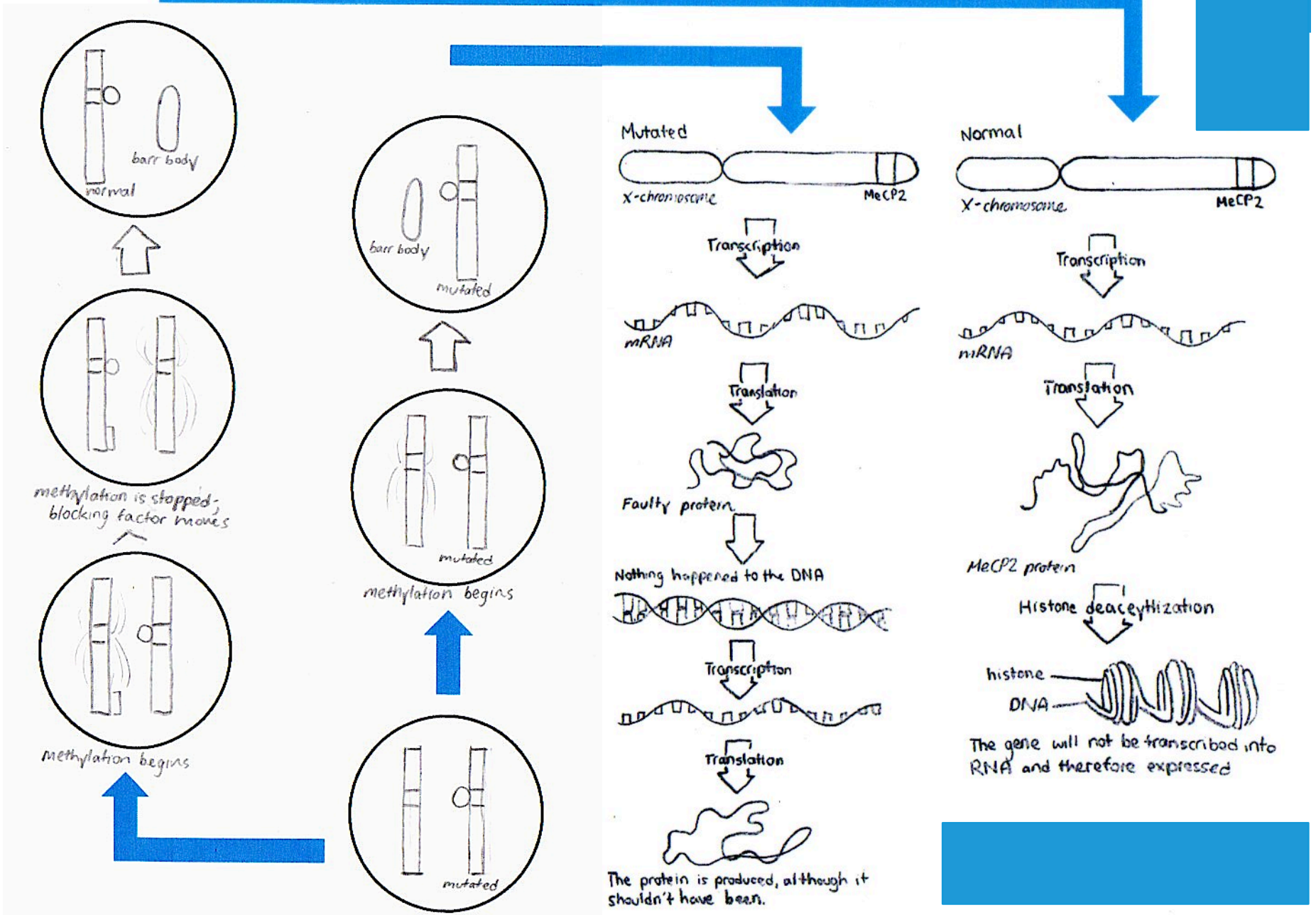
- Current Therapies
  - Physical therapy
    - Different focus for each stage: 1—standing, sitting, walking; 2—range of motion; 3—sitting; 4—everything from before
    - May use splints to help prevent repetitive motions (specifically hands)
    - First form of therapy that should be pursued—the earlier the better
  - Speech therapy
    - Help language skills
    - May use non-verbal forms of communication
  - Nutritional support
    - Needed to maintain adequate weight—high-fat, high-calorie diet
    - Can deliver nutrients directly to the stomach through tubes
  - Medications
  - Anticonvulsant medications for seizures
    - L-dopa helps alleviate muscle stiffness
    - Stabilize breathing
  - Obvious drawbacks: none of these constitutes an actual cure
    - Treatment must be specialized for each individual child

+ Proposed Cure

- Because of the large number of genes the MeCP2 protein regulates the expression of, it would be impractical to focus on preventing those proteins from working. Instead, it makes sense to target the X-chromosome, where the MeCP2 gene is located.

- Use the process of X inactivation to our advantage
  - Every girl with Rett syndrome has, in addition to the mutated copy of the MeCP2 gene, a normal copy of it; it's just inactivated in about 50% of the cells
  - Activating the silent copy would theoretically cure Rett syndrome
  - How x inactivation works:
    - Each x chromosome has an XIST gene on the long arm of the x chromosome (q13)
    - The presence of this gene is what causes x inactivation
    - Usually a blocking factor binds to one of the X-chromosomes' XIST, preventing the chromosome from being inactivated
    - DNA methyl transferases methylate the XIST promoter, resulting in its inhibition and thus the expression of the XIST gene
    - If bound a small molecule to the blocking factor it wouldn't fit quite as well, inducing some looseness and ability to un-bind
    - Also have a protein which binds specifically to the MeCP2 gene
      - Will only recognize the correct version
      - Stops methylation that usually occurs
        - XIST gene will not be expressed; gene with correct version will not be inactivated
    - Because of looseness blocking factor will be more inclined to switch between genes when one doesn't work
      - Goes to other gene when are still two activated, normal gene is left activated and other is inactivated

- Problems:
  - We don't know whether or not X inactivation can be 'redone' in a cell after an X chromosome has already been inactivated
    - If not, it would have to be done before birth
    - Presents an added problem as Rett syndrome is mostly diagnosed through symptoms
  - Although random small molecules are available (used in drug-making etc) would have to experiment to see what was big enough to have an effect but too small to prevent binding altogether
  - Need to know more about structure/behavior of blocking factor


barr body
normal
methylation is stopped- blocking factor moves
Methylation begins
barr body
mutated
mutated
methylation begins
mutated
Mutated
X-chromosome
MeCP2
Transcription
mRNA
Translation
Faulty protein
Nothing happened to the DNA
Transcription
Translation
The protein is produced, although it shouldn't have been.
Normal
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MeCP2
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MeCP2 protein
Histone deaceytlization
histone
DNA
The gene will not be transcribed into RNA and therefore expressed

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