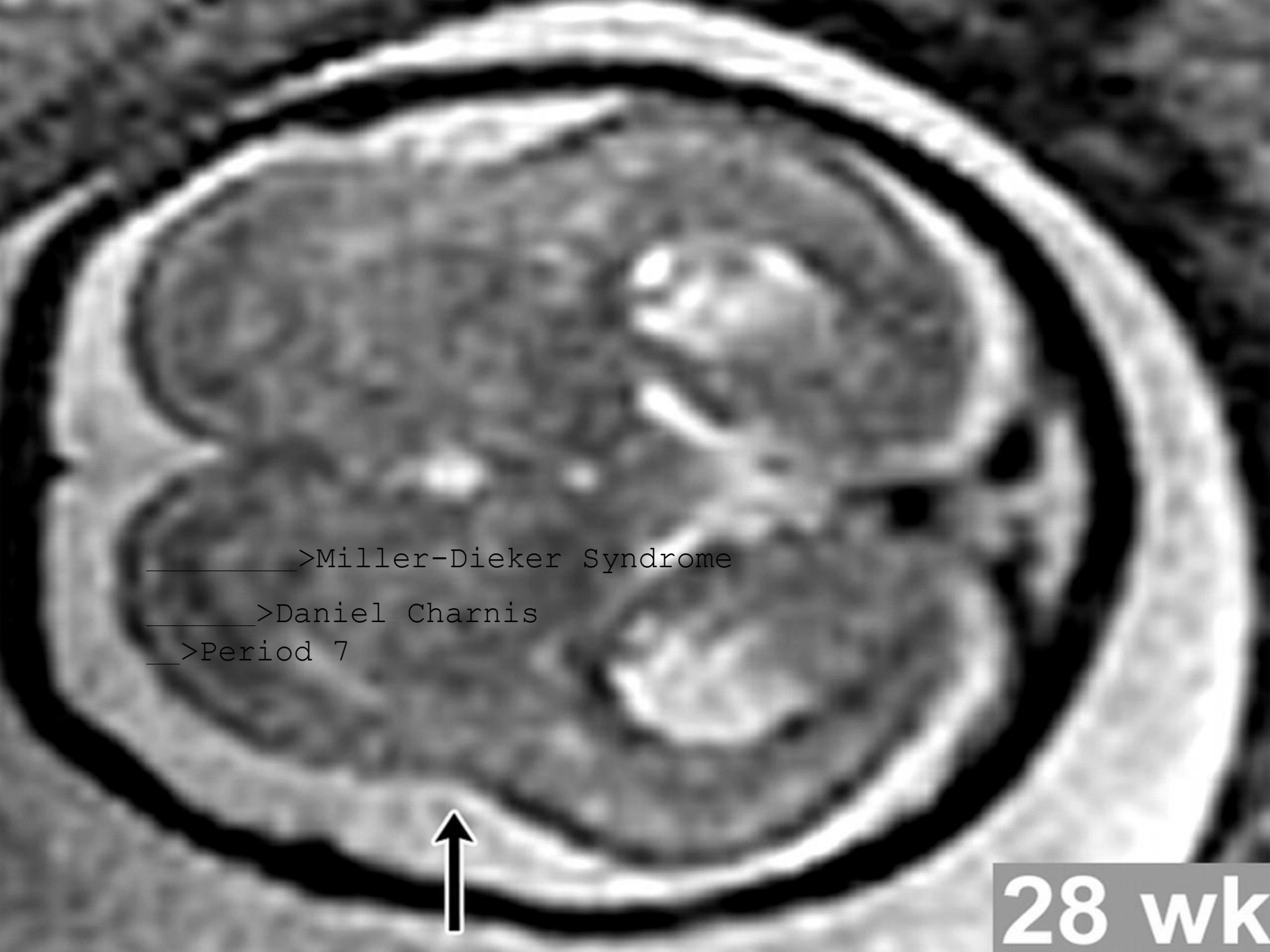

_____>Miller-Dieker Syndrome
_____>Daniel Charnis
__>Period 7
28 wk

Physiology

- MDS occurs once for about 100,000 people, and it is autosomal dominant
- Most MDS patients die before they are two years of age, due to the very complicated syndromes present in the disease.
- ***Miller Dieker patients have a host of physiological problems because MDS (Miller-Dieker Syndrome) is syndromic and affects multiple body systems***
- The most direct causes of problems is in the nervous system:
  - The brains of patients with MDS usually have fewer layers of folds in the brain called **gyri** and **sulci,** as depicted in Figure -> called lissencephaly
  - Patients also have facial dysmorphism, and have a short nose, a widened face, and a thickened lip, as depicted in Figure 2
  - These nervous system problems lead to cognitive and developmental delay

  - Seizures are also rampant in MDS
  - When these symptoms occur without any other
  - problems, it is called isolated lissencephaly
  - sequence
- Problems also in digestive and circulatory systems
  -Failures in peristalsis, muscles lining stomach, , electrical conduction system, etc
- Onset of these syndromes is prenatal, in the first trimester

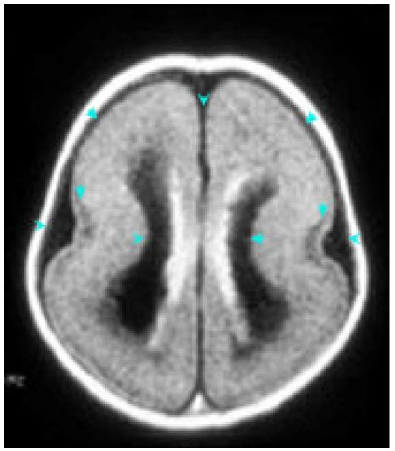


Figure 1

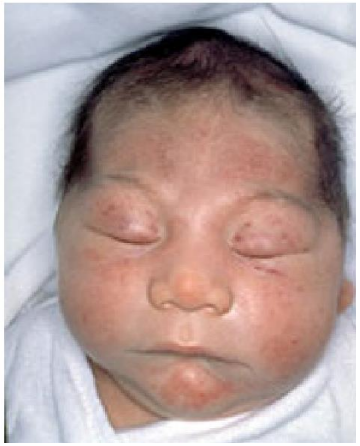
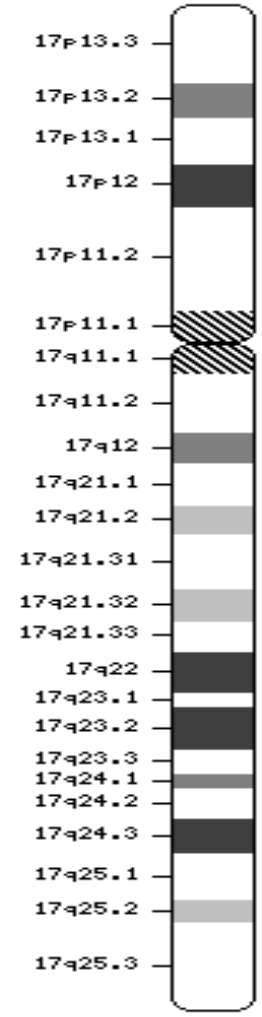


Figure 2

Molecular Cause

- Miller Dieker Syndrome occurs because of a microdeletion of 17p13.3 (figure 1), and specifically the LIS1 gene (lissencephaly) also known as the PAFAH1B1 gene
- The disease is classified as autosomal dominant, but since patients die before they are two the gene arises spontaneously.
- Miller-Dieker syndrome occurs because of a failure of neurons to migrate during development, called neuronal migration; specifically microtubules of the flagellum of the underdeveloped nerve cells fail to function. The explanation of that is the **dynein-kinesin motor system**.
- In short, the motor proteins dynein and kinesin walk along the microtubule. When you walk, you push against the ground. For dynein and kinesin, the "ground" is the microtubule. Pushing against the microtubule causes the microtubule to bend, which causes the flagellum to bend, which causes to cell to move.
- However, this process requires ATP, and for ATP to be used, it needs a way to interact with the motor proteins
- The LIS1 gene product, also known as LIS1, is the binding site for the ATP. Without it, the ATP cannot bind the the motor proteins, and the cell cannot move.



The *PAFAH1B1* gene (also known as *LIS1*)

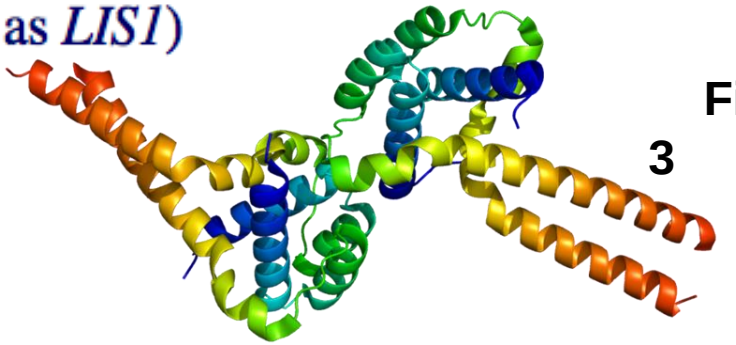
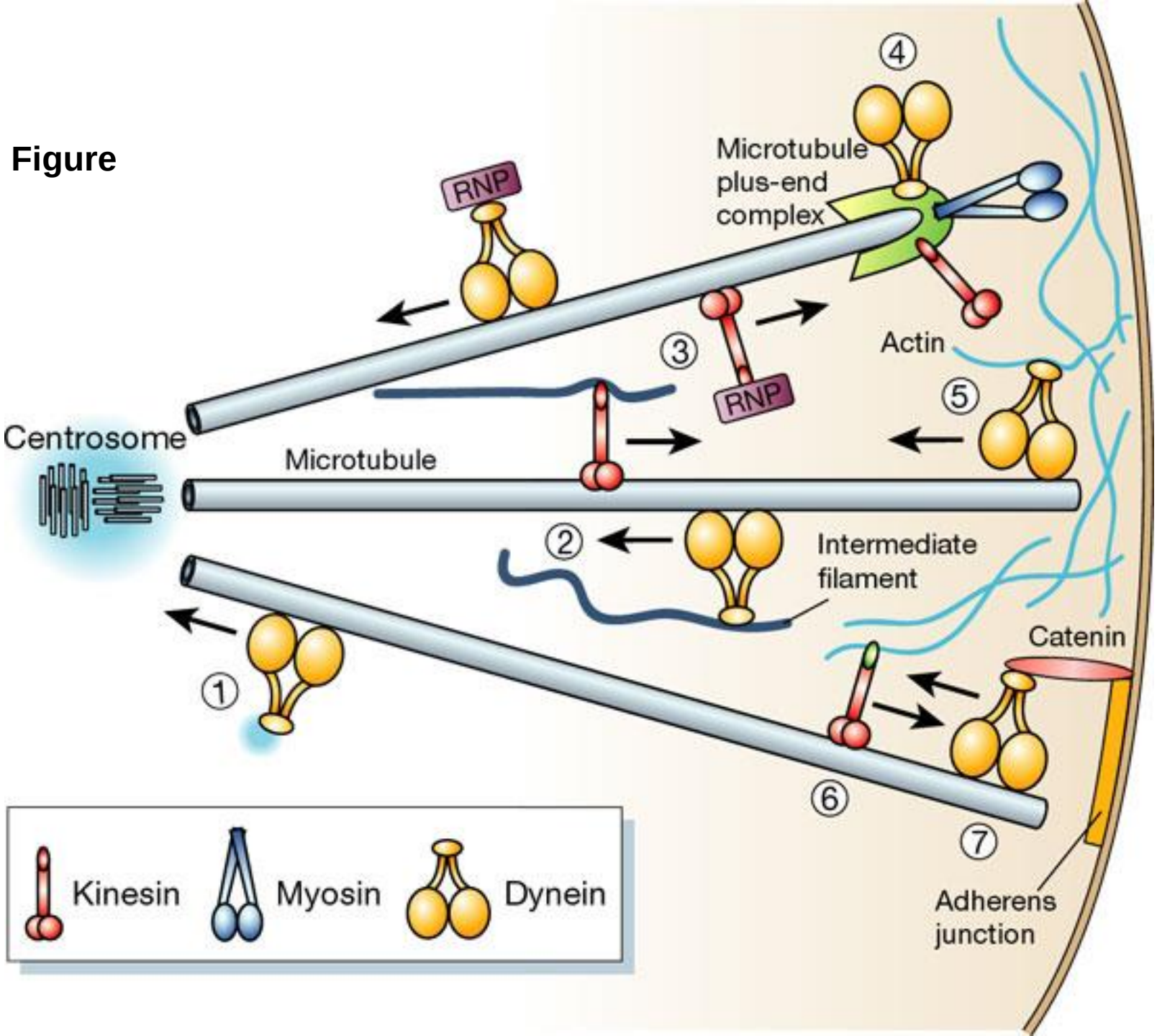


Figure 3

Figure 4


4
Microtubule plus-end complex
RNP
Actin
3
RNP
5
Centrosome
Microtubule
2
Intermediate filament
Catenin
1
6
7
Adherens junction
Kinesin
Myosin
Dynein

Treatments

- As stated previously, most MDS patients don't live past two years of age, so treatments are limited
- Most treatments do not treat the actual cause of the disease, but rather the effects (symptomatic treatment)
- For example, to treat the failure of the digestive system, nasogastric tube feedings are administered
- Furthermore, a gastronomy may be performed
- Many patients of MDS also have seizures, to the point of epilepsy
- To help aid in quality of living, antiepileptic drugs such as Gabapentin and Pregabalin are used.
- That being said, none of these treatments actually "treat" the disease; rather, they treat the symptoms of the disease.
- Furthermore, it is almost impossible to develop a cure since a cure would involve rearranging the neurons of the brain into their proper positions, which is impossible because 1) neurons can't just be moved around and 2) the brain hasn't been mapped down to the neuron yet

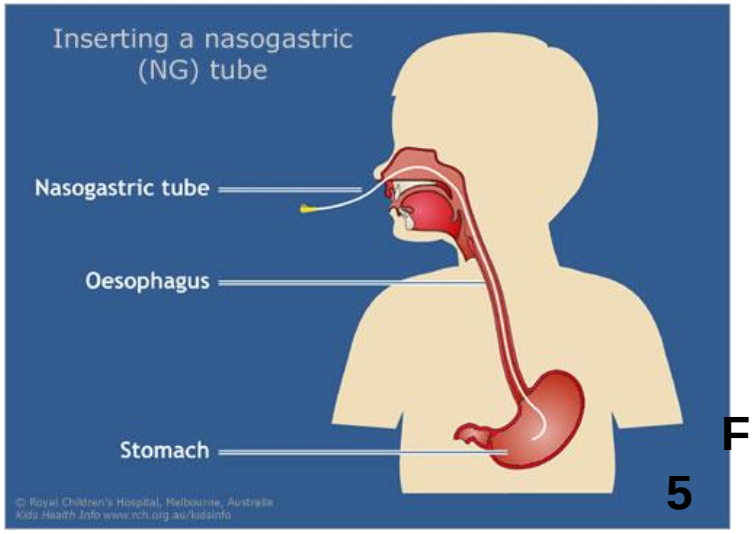


Figure 5

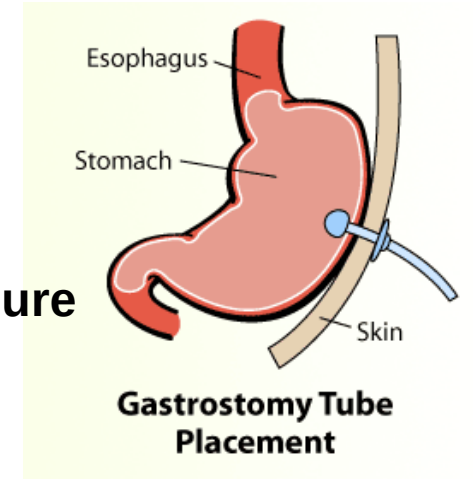
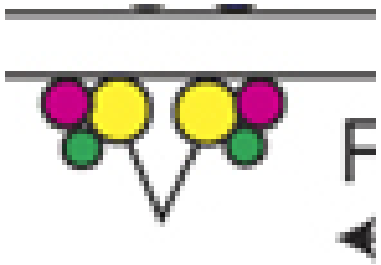


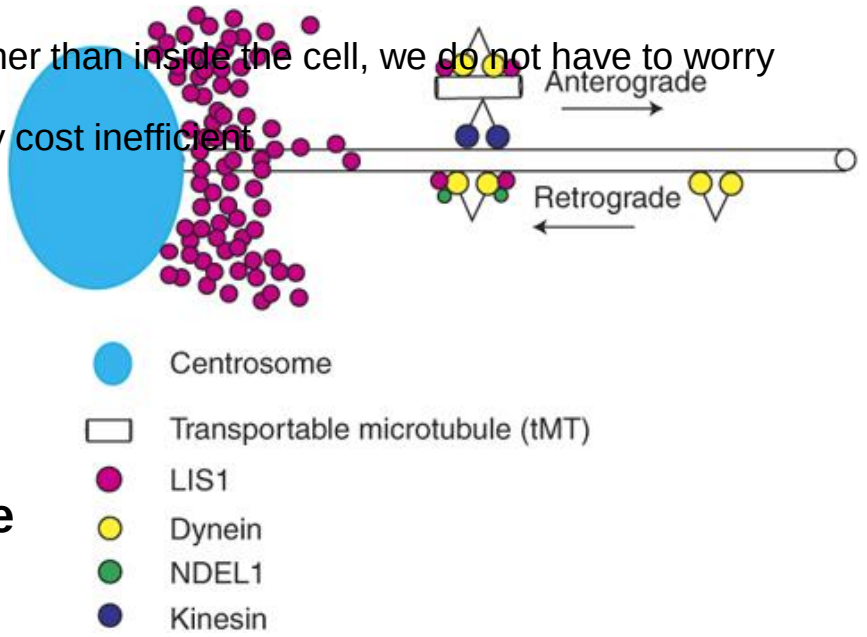
Figure 6

Cure Proposal

- Since the only thing wrong with Miller Dieker patients is a problem that takes place during development, if we can interfere during development, we cure MDS.
- First, we would need to determine if the patient has MDS. We retrieve a DNA sample via amniocentesis and run a FISH on the DNA to determine if they have MDS
- If so, we proceed with my cure:
- When LIS1 gets produced, it is co-translated with a protein called NDEL1 (which is in 17p13.3)
- NDEL1, in a laboratory setting, has been shown to be able to interact with ATP, dynein, kinesin, and LIS1
- The cure takes place on the premise that NDEL1 would be able to form an ATP-dynein/kinesin-NDEL1 complex and sufficiently bring the ATP to the motor protein
- This would solve the motor protein's dilemma of not being able to bind to ATP
- Delivery would be complicated:
- First, we would inject the NDEL (a protein) into an area close to the uterus in the mother, under the premise that it would be able to diffuse through the placenta
- Once in the circulatory system of the fetus, NDEL1 would naturally go to the brain since it is specific for LIS1-dynein in the brain
- Since the extracellular matrix is outside the cell rather than inside the cell, we do not have to worry about any solubility problems.
- Limits: FISH for every pregnant female is extremely cost inefficient



Figure



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- Images
-
- Figure 1 brain CT: http://radiographics.rsna.org/content/26/2/389/F26.large.jpg
- Figure 2 dysmorphism: http://dc96.4shared.com/doc/QibwAO-f/preview007.png
- Figure 3 gene structure: http://www.ncbi.nlm.nih.gov/mapview/maps.cgi?ORG=hum&query=uid(644,1172,5082,6793,9430,18595,18734,20180,20182,20183,20184,20185,20186,20187,20188,20192,20193,9026036,9026651,9027263)&qstr=p53+OR+CMT1A+OR+BRCA1&CHR=17&MAPS=ideogr[17pter%3A3896.000000],morbid[0.000000%3A3896.000000]&ZOOM=100.000000
- Figure 4 dynein: http://www.nature.com/nature/journal/v422/n6933/images/nature01601-f5.2.jpg
- Figure 5 naso feeding: http://www.rch.org.au/uploadedImages/Main/Content/kidsinfo/nasogastric-tube-RCH-KHI500.jpg
- Figure 6 gastronomy: http://pedsurg.ucsf.edu/media/85846/main_img.gif
- Figure 7 LIS1 connection to NDEL1: http://www.nature.com/emboj/journal