Narcolepsy: Classical Diagnosis

Neurological condition: sleep disorder.

✓In the U.S. narcolepsy is roughly as common as Parkinson's disease or multiple sclerosis, affecting one in every 2,500 people.

✓Can be inherited, but usually occurs at random

✓ Having an immediate family member with narcolepsy increases one's chances of having the disease by 10 to 40 times. However, If you have narcolepsy, there is only a 1 to 2% chance that your child will have it.

Tetrad of Symptoms:

- Excessive Daytime Sleepiness
- Sleep Paralysis
- Hynagogic Hallucinations
- Cataplexy

Emmanuel Mignot and his colleagues at the Stanford sleep clinic used narcoleptic dogs to better understand the possible genetic causes of human narcolepsy.

Introducting…

Rusty the Narcoleptic Dog!

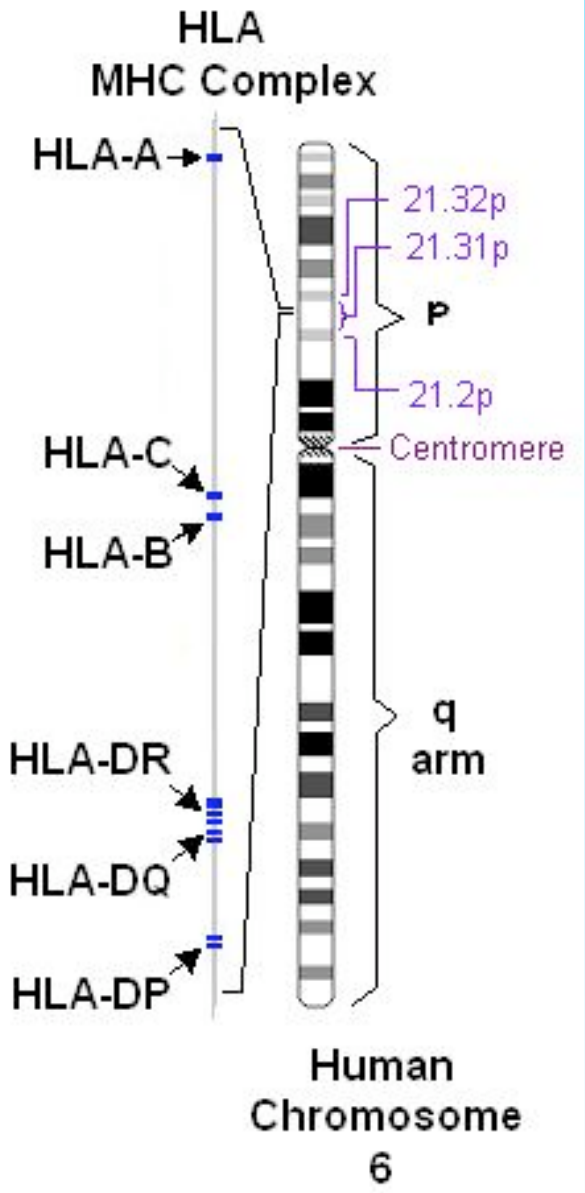
Narcolepsy: Classical Diagnosis

- MSLT: Multiple Sleep Latency Tests.

  Narcoleptic patients must have an average of less than 8 minutes sleep latency (greater than than ten minutes is normal) and 2 or more sleep onset REM periods.
- Polysomnogram
  - EEG determines what stage of sleep patient is in
  - EMG (muscle movement)
  - EKG (heart rate and rhythm)

  Normally, REM sleep occurs after an hour and a half of non-REM sleep, but narcoleptic patients fall into REM sleep at the onset of sleep.

Narcolepsy: Genetic Diagnosis



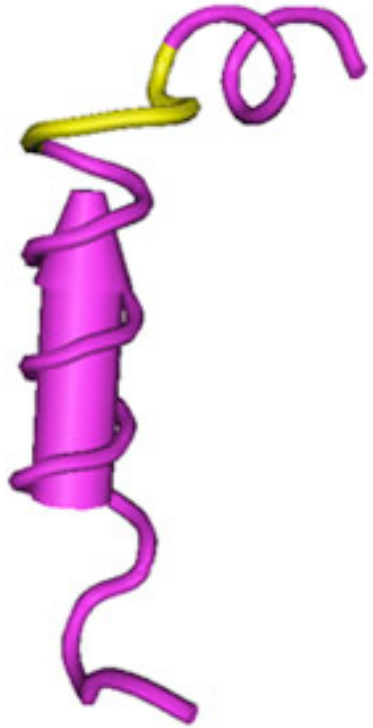
Human Leukocyte Antigens

- HLA genes keep immune system in check.
- Narcolepsy associated with HLA protein DQB1*0602, located on chromosome 6.
- Kawashima et al. (2006) performed a genomewide association study and found that all patients with narcolepsy carried the HLA susceptibility haplotype. (DQB1*602)
- However, it is unreliable to use HLA testing to diagnose narcolepsy because about 20% of the general population carry the exact same HLA subtypes (HLA-DR2, DQB1*0602, etc).
- DQB1*0602 is correlated with auto-immune response to protein-producing neurons in the hypothalamus of the brain.
- This protein is called hypocretin, or orexin, and it's job is to regulate sleep patters.
- Scientists think that the body's immune cells attack and damage the neurons that secrete hypocretin, probably at some point during adolescence.

Narcolepsy: Genetic Diagnosis

Hypocretin/Orexin:

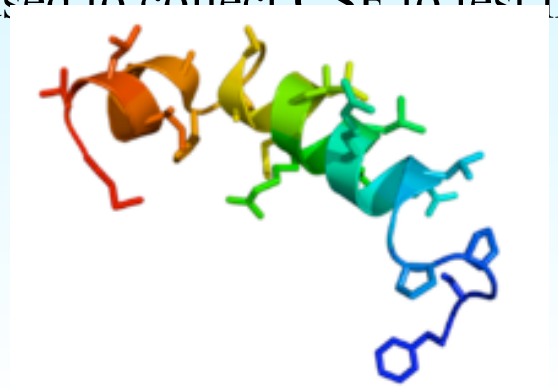
Regulates Sleep Patterns



The human hypocretin-2 protein is 28 amino acids long. It contains two alpha-helix domains (shown in purple) that are connected by a flexible loop (shown in yellow).

Recent studies have shown that narcolepsy with cataplexy is usually caused (>90%) by the lack of two related brain chemicals called "**hypocretin-1**" and "**hypocretin-2**", found in the hypothalamus.

90% narcoleptic patients have undetectable hypocretin levels in their cerebrospinal fluid, while all the normal individuals do have hypocretins in their CSF. A spinal tap is used to collect CSF to test hypocretin levels.



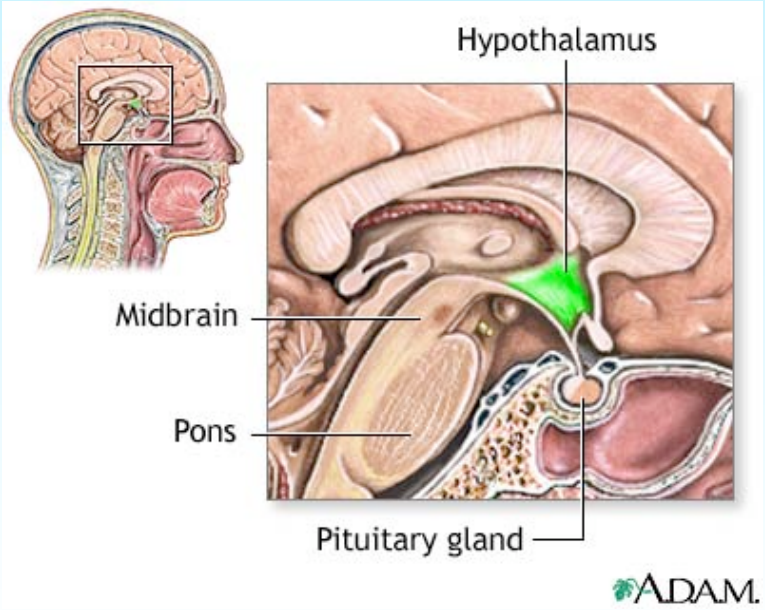
Narcolepsy: Classical Treatment

- Treatment: No cure, we can only control symptoms.
- -planned naps, to reduce drowsiness and sleep attacks
- -eating light or vegetarian meals during the day, napping after meals
- Gamma-hydoxybutyrate (GHB) (for cataplexy)
- amphetamine-like stimulants such as methylphenidate, (Ritalin) racemic amphetamine, dextroamphetamine, methamphetamine, modafinil (for drowsiness)
- Antidepressants: clomipramine, imipramine, or protriptyline.

  (Cataplexy and REM sleep symptoms)

Narcolepsy: Genetic Treatment

- Current treatments correct the symptoms rather than the cause of the problem. Need to replace missing hyocretin molecules.
- Can't be given by mouth or injected by blood
- Better option: drug that can "replace" the missing molecule. Will not be a cure.
- Ideally, we will have a breakthrough that allows us to transplant cells that could produce hypocretins in the brain.
- A recent study reported that transplantation of hypocretin neurons into rats is feasible.



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