Lesch-Nyhan Syndrome

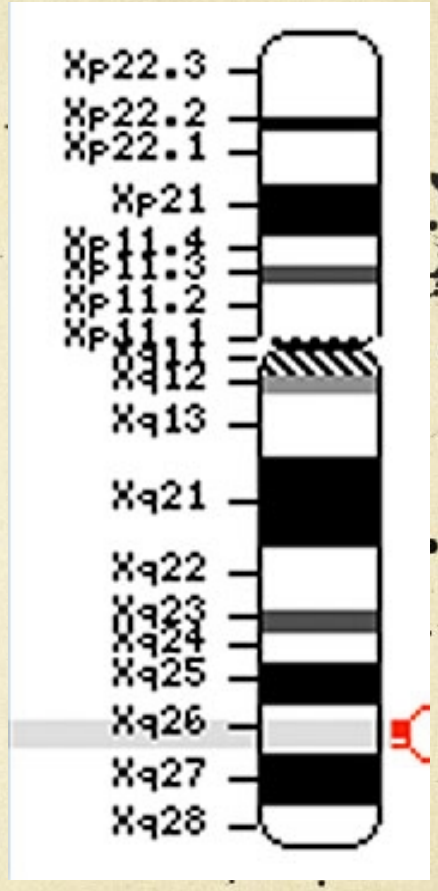
Kima Uche

BIOC 118Q: Genomics and Medicine

What is Lesch-Nyhan Syndrome?

LNS is a genetic disorder caused by a mutation in the HRPT(1) gene of the X-chromosome. This mutation results in deficient production of *hypoxanthine guanine phosphoribosyltransferase*, an enzyme that is vital in metabolizing Vitamin B_{12} and recycling purines[1].

The condition Affects 1 in 380,000 People



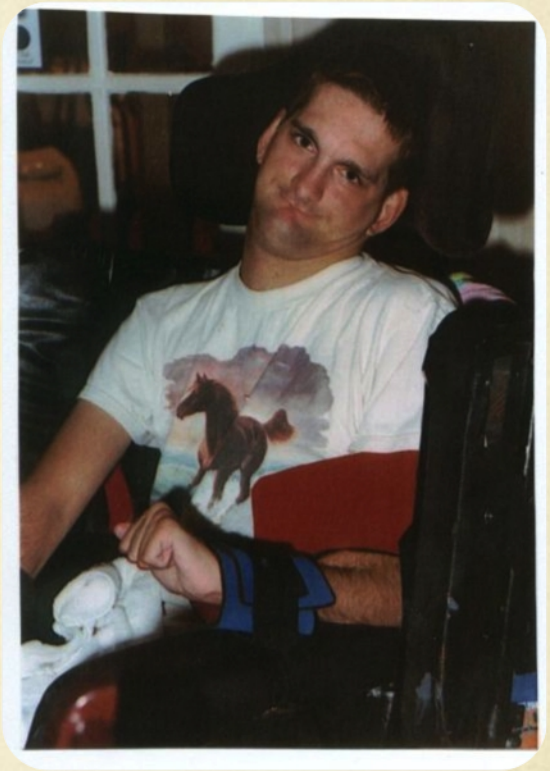
Xq26-q27.2, The Locus of LNS

Symptoms

- **LNS is characterized by the following**
  - Cognitive and Behavioral Disturbances[2]
    - **LNS's infamous symptom is** persistent self-mutilation
      - Such as biting fingers, lips and banging one's skull or limbs
  - Delayed Development
  - Onset of Huntington Disease-like symptoms
    - Facial grimacing, repetitive involuntary leg/arm movements and involuntary writhing
  - Low Muscle Tone **(Hypertonia)**
  - Overproduction of Uric Acid **(Hyperuricemia)**
    - ^This is a side effect of being unable to recycle purines
  - Motor Dysfunction (≈ Similar to that of Cerebral Palsy)
  - In most cases, an inability to walk from childhood

[2]Cognitive-Behaviorial Symptoms

- Nervous System Dysfunctions include
  - Mental retardation
  - Spasticity (Lack of Muscle Inhibition)
  - Hyperreflexia (Exaggerated Reflexes)
  - Opisthotonus (Bridging formation of the head, spine and neck)
  - Dysarthria (Motor Speech Disorder)
  - Dysphagia (Swallowing Problems)
  - Mental retardation



Living with LNS

Diagnosing LNS

- Check phenotype (cognitive, behavioral or neurological) indications of Lesch-Nyhan Syndrome
  - Confirmed through a series of diagnostic tests:

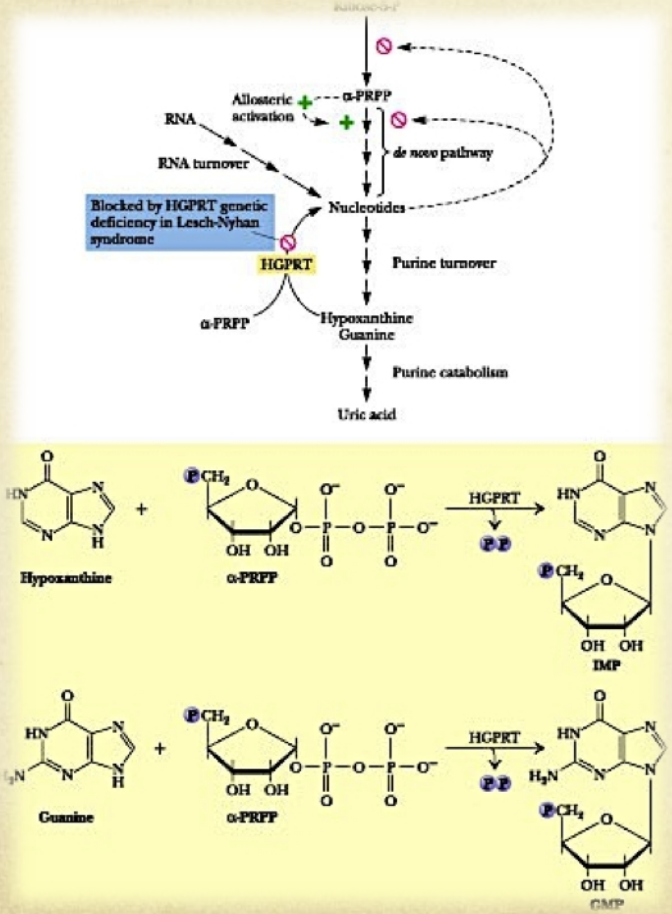
Though used in initial diagnosis, these tests aren't considered diagnostic.

  - **Urate v. Creatinine Ratio > 2.0** is characteristic of LNS
  - **24-Hour Urate Excretion > 20mg/kg** is also characteristic

- **HPRT(1) Enzyme Activity**
  - **Males:** HPRT Activity < 1.5% in cells is diagnostic
  - **Females:** Technically demanding and some inaccuracies

- **Proliferation of Blood T-lymphocytes:** blood test available on a research basis only

Diagnosing LNS: Molecular Genetic Testing



- **Sequence Analysis/Mutation Scanning:**
  - Using multiple methods to screen DNA to find the locus that has a variant gene; >90% accuracy in affected males; ≈ 80% in carrier females.

- **Deletion/Duplication Analysis:**
  - Analyzes the 20-24% of HPRT(1) large deletions in females that are undetectable in Sequence Analysis[3].

- **Prenatal and Carrier Testing**
  - Search for the presence of a Purine analolgue

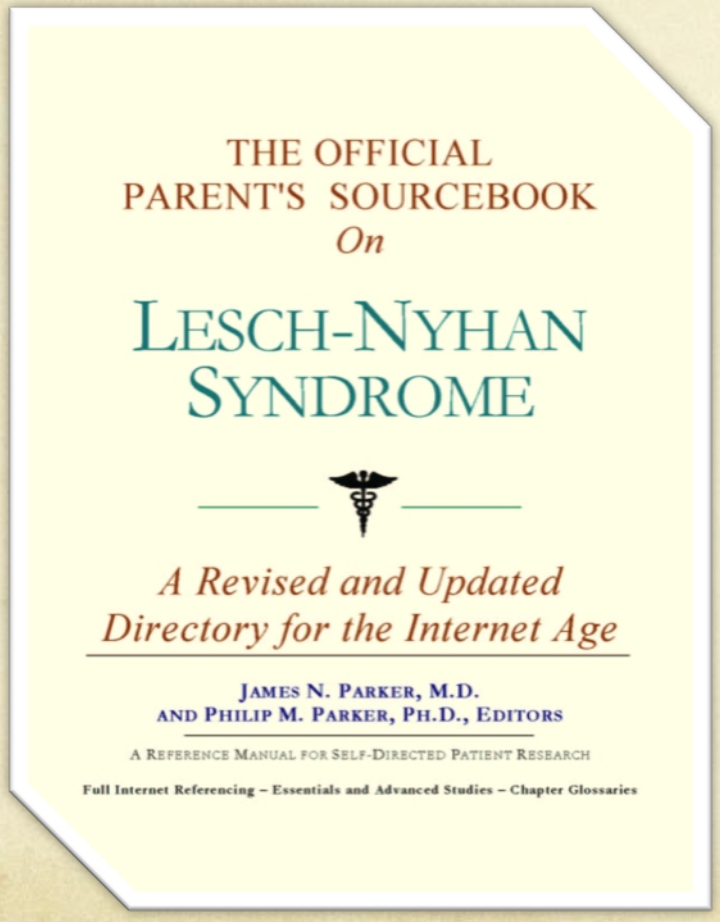
A Clinical Synopsis

- LNS is X-Linked and therefore has 100% Genetic Penetrance in Males
  - Female carriers are usually asymptomatic, rarely showing any symptoms of the disorder
- The Deficient **HPRT** enzyme (as a consequence of mutation) has very limited functionality in a LNS patient
- In general, life expectancy caps at the 2nd or 3rd decade of life
- Finger biting is a **behavioral phenotype**[3] for LNS, often serving to distinguish from other self-injurious prone conditions (i.e. Tourette syndrome and other psychiatric conditions).
- Overproduction of Uric Acid (also, inability to recycle the acid) may lead to deposits in kidneys, bladders or ureters
  - Causing sever kidney problems and exacerbating joint swelling (**Gout**)

Treatment and Novel Therapies

- Bill's ordeal epitomizes the nature of treatment for Lesch-Nyhan Syndrome
  - The disease is dealt with symptomatically, since there is no cure for the condition itself
    - Physical therapy as well as medicinal treatment specific to the patient
  - Essentially a multidrug approach to treating LNS
    - Gout Medication (**Allopurinol**) for decreasing uric acid levels
    - "*Some may be relieved with the drugs carbidopa/levodopa, diazepam, phenobarbital, or haloperidol*" (NINDS).

Misc. Definitions/Research



- 1 – Purines: aromatic, organic compounds that are biochemically significant components in a number of other important biomolecules
- 3 – Here is an interesting article on a deletion mutation associated with **HPRT(1).**
- 4 – Behavioral Phenotype: A characteristic pattern of motor, cognitive, linguistic and/or social abnormalities which is consistently associated with a biological disorder.
- New Yorker Article on **LNS**

Works-Cited

- http://www.ncbi.nlm.nih.gov/omim/300322?dopt=Synopsis
- http://www.ncbi.nlm.nih.gov/books/NBK1149/
- http://www.ncbi.nlm.nih.gov/omim/308000
- http://www.ncbi.nlm.nih.gov/gene/3251
- http://www.dmid.org/clinchap3.htm
- http://www.ninds.nih.gov/disorders/lesch_nyhan/lesch_nyhan.htm
- http://www.nlm.nih.gov/medlineplus/ency/article/001655.htm
- http://embryology.med.unsw.edu.au/Defect/leschnyhan.htm