Tangier Disease

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Sophomore Introsem: Genomics and Medicine

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Tangier Disease is a rare, autosomal recessive metabolic disorder

Background on Tangier Disease

- First identified in the island of Tangier, off the coast of Virginia
- Inhabitant had orange tonsils, low levels of high density lipoprotein ("good cholesterol"), and enlarged liver and spleen
- Rare disorder with approximately 50 cases identified worldwide

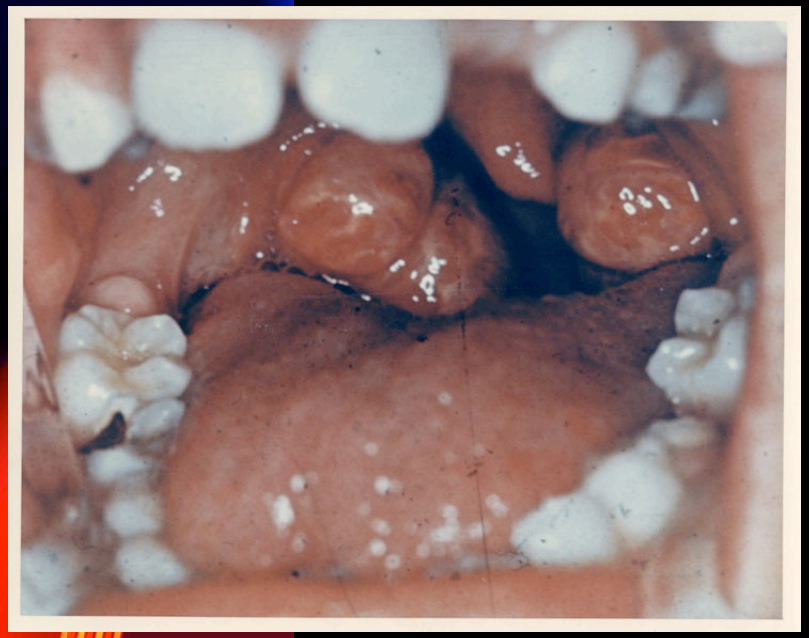
Classic Diagnosis

- Assessment of clinical symptoms
- Biochemical testing
- Examination of throat and tonsils

Classic Signs that indicate Tangier

- Enlarged, orange tonsils
- Low levels of high density lipoproteins (HDLs)
- Deposits of cholesterol on the cornea
- Virtually no HDL-C in bloodstream and severely reduced ApoA-1 levels (1-3% of normal)

Symptoms of Tangier



- Low HDL level
- High fat levels in blood
- Neuropathy
- Enlarged orange or yellow tonsils
- Premature atherosclerosis
- Enlarged spleen
- Enlarged liver
- Cloudy cornea
- Early-onset cardiovascular disease

Genetics

- Caused by mutations in the ABC1 (ATP-binding cassette gene) on chromosome 9q31
- Amino acid substitutions

What is ABC1?

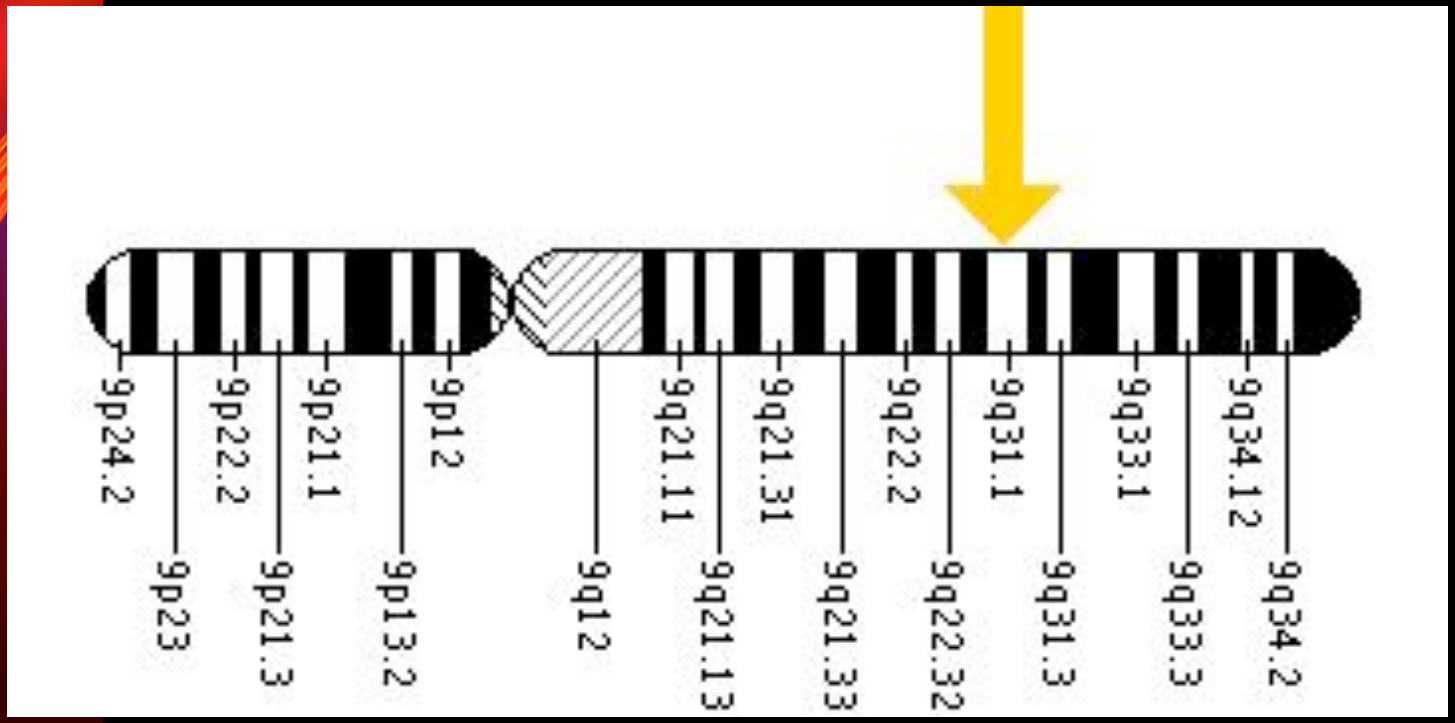
- Codes for a protein that rids cells of excess cholesterol

Without it, unable to eliminate cholesterol from cells, which leads to buildup

ATP-binding cassette, sub-family A (ABC1), member 1

Cytogenetic Location: 9q31.1

Molecular Location on chromosome 9: base pairs 106,583,103 to 106,730,256



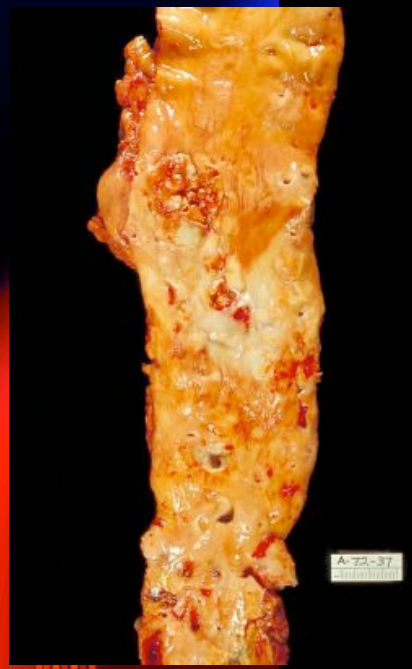
Impact of Mutation

- Mutations prevent the ABCA1 protein from effectively transporting cholesterol and phospholipids out of cells for pickup by lipid poor Apo-A1 lipoprotein in the bloodstream

What is ApoA1?

- Human gene
- Protein encoded by this gene is an apolipoprotein (lipoprotein)
- Component of high density lipoprotein (HDL)

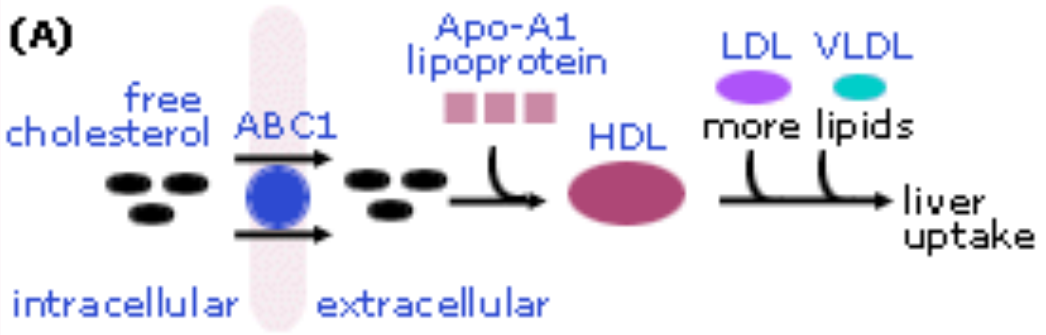
Implication of Impaired Pathways



1. Inability to transport cholesterol out of cells leads to a deficiency of high-density lipoproteins in the circulation
2. Buildup of cholesterol in cells can be toxic, causing cell death or impaired function.
3. Results in decreased amounts of cholesterol available on the surface of the cell to bind to ApoA-1 and decreased cholesterol available to form HDL-C (good cholesterol)

HDL needed to transport cholesterol to liver

Pathway



(A) In normal cells ABC1 helps cholesterol exit the cell where it combines with lipid poor Apo-A1 lipoprotein to form high density lipoprotein (HDL). HDL picks up more lipids from low density (LD) and very low density (VLDL) lipoproteins and transfers the cholesterol to the liver, where it is processed.

(B) In Tangier disease, mutations in ABC1 cause cholesterol to accumulate within the cell.

[Adapted from Young and Fielding (1999) Nat Genet. Aug;22(4):316-8, with permission]

Genetic Diagnosis

- DNA/Genetic testing for Tangier disease
- Identification of ABCA1 gene changes by analysis of entire coding region
- Prenatal testing is only available if ABC1 gene changes are identified in the parents
- Specific HDL testing
  - Main function of HDL is to help soak up excess cholesterol from the walls of blood vessels and carry it to the liver

Classic Treatment

- Based on severity and presence of various symptoms
- Heart surgery
- Organ Removal and Transplants
- Arteriosclerosis may be treated through angioplasty or bypass surgery

Genetic Treatment and Implications of Genomics

- Gene therapy options
- Structural versus Pathway Disorder
- New drugs that can be developed for regulation of HDL levels

More important than treatment advances is the access genomics information has given us into the finding and research of other diseases.

- New Understanding of Cholesterol Transport Pathways
- New understanding of inverse relationship between HDL and heart disease

Familial hypoalphalipoproteinemia

- Dominantly inherited disorder
- Caused in some families by mutation in the ABC1 gene (like Tangier!)
- Additional mutations in the apolipoprotein A1 gene (maps to 11q23.3)
- Concentrations of alpha-lipoproteins or high-density lipoprotein (HDL) are reduced
- Reduction in cellular cholesterol efflux

Resources

Human Genome Resources

- Genes and Diseases
- GeneTests
- Karolinska Library
- National Center for Biotechnology Information
- Online Mendelian Inheritance in Man (OMIM)
- Entrez Gene