CLOVES Syndrome and the PI3K/AKT Pathway

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Method to Identify the Genetic Cause of CLOVES Syndrome

Archival Lesional Tissue
- Bar-coded Genomic Libraries
- Targeted/Exome Sequencing

Fresh or Frozen Lesional Tissue
- Bar-coded RNA Libraries
- RNA Sequencing

Unaffected Blood
- Bar-coded Genomic Libraries
- Exome Sequencing

Biologic Analysis

Tissue Validation

Genes with variants in >2 patients, or Variants in different patients but affecting genes in the same pathway

Total Lesional Variants

Lesional vs. Unaffected Comparison

Unique Lesional Variants

De Novo Patient Variants

Parental Variants
- Shared Variants (lower priority)
- Familial Polymorphisms

Unaffected Variants
The PI3K/ AKT/ mTOR Pathway

Tyrosine kinase receptor

PIK3CA

Outside Cell

Inside Cell
The PI3K/ AKT/ mTOR Pathway

Tyrosine kinase receptor

PIK3CA

Outside Cell

Inside Cell
The PI3K/ AKT/ mTOR Pathway
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Tyrosine kinase receptor

Outside Cell

PIK3CA

PIP2

PI3K/ AKT/ mTOR Pathway

PIP3

PDK1

AKT

mTOR
The PI3K/ AKT/ mTOR Pathway

Cell growth, size, & proliferation regulation / fat metabolism/ blood vessel growth
The PI3K/ AKT/ mTOR Pathway

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The PI3K/ AKT/ mTOR Pathway

1. Growth factors from the blood (such as insulin & vascular growth factors) bind cell surface receptors. Each cell has many, many receptors on its surface

2. The receptor is turned on and starts a cascade of signals inside the cell

3. Proteins in the cell are activated or deactivated by enzymes that add or remove phosphate molecules

4. The ON receptor then turns on the enzyme PIK3CA attached to its base

5. PIK3CA adds a P to PIP2 to make the active form, PIP3

6. PTEN eventually removes the P to inactivate PIP3 and slow down the process

7. PIP3 Activates an enzyme (PDK1) that adds a P to AKT

8. AKT is fully activated by a second P from mTOR

9. Multiple paths to activate genes & make proteins

10. Cell growth, size, & proliferation regulation / fat metabolism/ blood vessel growth
PIK3CA Mutations & CLOVES Syndrome
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CLOVES Syndrome/ Klippel-Trenaunay Syndrome (PIK3CA)
Megalencephaly ± Capillary Malformation/ MPPH (PIK3CA, PIK3R2)

Cell growth, size, & proliferation regulation / fat metabolism/ blood vessel growth
PTEN Hamartoma Tumor Syndrome

Cell growth, size, & proliferation regulation / fat metabolism/ blood vessel growth
Proteus Syndrome (AKT1)
Overgrowth-Hypoglycemia (AKT2) / Hemimegalencephaly (AKT3)

Cell growth, size, & proliferation regulation / fat metabolism
CLOVES Syndrome/ Klippel-Trenaunay Syndrome (PIK3CA)
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CLOVES Syndrome - New Therapies

Cell growth, size, & proliferation regulation / fat metabolism / blood vessel growth
CLOVES Syndrome - New Therapies

**Cell growth, size, & proliferation regulation / fat metabolism/ blood vessel growth**

- **PIK3CA**
- **PTEN**
- **PDK1**
- **AKT**
- **PIP2**
- **PIP3**
- **mTOR**
- **FOXO/p27**
- **GSK3B/MYC/JUN**
- **pS6K**

**Siroliums** (Rapamycin)

Tyrosine kinase receptor

Outside Cell

Inside Cell