Dup15q Syndrome: Basic Concepts in Genetics and Diagnosis

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Duplication 15q Syndrome

Syndrome: recognizable pattern of physical and behavioral characteristics

- Dup15q a.k.a. inverted dup15q; isodicentric 15q; partial trisomy 15; tetrasomy 15q; interstitial dup15q; etc.
  - Infantile hypotonia (poor muscle tone)
  - Subtle facial differences
  - Intellectual disability
  - Epilepsy, particularly infantile spasms
  - Autism spectrum disorder in majority
  - Sudden unexplained death in minority
  - Duplication of PWACR
DNA: the Molecule of Life

DNA:

Chromosomes:

Cell:

Gene:
Chromosomes
46,XX Female
47,XY+21  Male
Copy number variations (CNV):
- Deletion: *missing* segment of genetic material
- Duplication: *extra* segment of genetic material
- Benign, pathogenic, and VUS (variants of unknown significance)

Microdeletions / microduplications:
cannot be detected visually; diagnosed using molecular methods (FISH, microarray)

Mosaicism: Two or more different genetic patterns in the same individual
47,XX,idic(15)(q11q13)   Female
FISH: Fluorescence In Situ Hybridization
Chromosomal Microarray
DNA Chip Technology that Reveals Copy Number Variation in the Human Genome

Reference DNA
Test DNA
specific region of DNA being studied

deletion

duplication

no deletion / duplication
15q11.2-13.1 includes the PWACR

Deletion of genes within the 15q11.2-13.1 region cause two well-known genetic syndromes:
- Prader-Willi syndrome (PWS): paternal
- Angelman syndrome (AS): maternal

- Smallest deleted region associated with these disorders is the Prader-Willi Angleman Critical Region (PWACR)
- **Core duplications**: include the PWACR, cause dup15q syndrome (characteristic pattern of physical, medical, behavioral findings)
- **Edge duplications**: adjacent to the region but not including the PWACR, may have effects on behavior, learning but not a cause of “dup15q syndrome”
The Lab Report is Key!

Karyotype (chromosome study)
- 47,XX,idic(15)(q11)
- 47,XX,+psu dic(15)(q11q13)
- 47,XY,+inv dup(15)(q13q13)
- 46,XX,dup(15)(q11q13)

FISH (fluorescence in situ hybridization)
- 47,XY.ish idic(15)(q13)(D15Z1x2,SNRPNx2,PML-)
- 47,XX,+idic(15).ish15q12 SNRPN x 4, 15qter X2

Microarray
- arr[hg19] 15q13.3(30,960,781-32,444,196)x3
- arr[hg18] 15q11.2q13.3(20372901-29351062x3)

Find a genetic counselor: www.nsgc.org
Dup15q Variables

- extra chromosome vs interstitial
- de novo vs familial
- Copy number
- Breakpoints
- Parent of origin (maternal vs paternal)
- Mosaicism
The 15q11-13 region

PWACR
Isodicentric 15

a.k.a.: idic(15)

inverted duplication 15

supernumerary marker

bisatelleted supernumerary

tetrasomy 15

partial trisomy 15
Isodicentric 15

- Extra (supernumerary) bisatellited chromosome
- Duplication of all of the p arm and part of the q arm
- With 2 normal 15s, results in tetrasomy
- When it includes the PWACR, causes dup15q syndrome
- Maternal origin
- *de novo*
- Sometimes “mosaic”
Isodicentric 15

PATERNAL

MATERNAL
Interstitial duplication 15q

- No extra chromosome
- Often inherited
- Maternal or paternal
- In past, often missed on chromosome studies
- Detected through FISH, microarray
- When dup includes the PWACR, causes dup15q syndrome
Interstitial Duplication 15q
Common Idic(15) Chromosomes

courtesy of Carolyn Schanen
Common Isodicentric 15 Chromosomes

BP3:BP3
BP4:BP5

Tetrasomy
Trisomy

courtesy of Carolyn Schanen
Mapping the 15q11-13 region
Prevalence in Clinical Samples

• 15q11-13 dups: 2nd most common CNV in ASD
• ~1 in 500 clinical samples
• 1 - 3% of ASD

• Mutations in GABRB3: among most common findings in epilepsy

Moreno-De-Luca et al., 2012
Epi4K Consortium & Epilepsy Phenome/Genome Project, 2013
Mapping the 15q11-13 region

- **Segmental Dups**: Various segments highlighted in different colors with labels BP 1-2, BP 1-3, BP 2-3, BP 3-4, BP 3-5.
- **RefSeq Genes**: Genes listed vertically, including POTEB, CYFIP1, NIPA1, NIPA2, SNRPN, SNURF, GABRB3, GABRA5, GABRG3, HERC2, QCA2, ARHGAP11B, GOLGA8O, RYR3, TJP1, TRPM1, LOC283710, CHRFAM7A, KLF13, GREM1, SCG5, FMN1.
15q Duplications not involving PWS/AS Region

- 15q13.2 – q13.3 microduplication: (BP 4-5)
  - CHRNA7 implicated in ID, schizophrenia, ASD, ADHD
  - Recognized deletion syndrome
  - Evidence for pathogenic duplication
  - Familial and highly variable

- 15q11.2 microduplication (BP 1-2)
  - Variant of unknown significance
  - Reports of association with ADHD, ASD, S/L disorders
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Dup15q Alliance

- >800 families internationally
- Professional Advisory Board
- Major research collaborations / initiatives
  - NIGMS / Coriell Cell Repository
  - Dup15q International Registry
  - Dup15q Clinics!

www.dup15q.org