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
Chromosomes
46,XX Female
46,XY Male
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
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(20372901-29351062)x3

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

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

a.k.a.: idic(15)

inverted duplication 15
supernumerary marker
bisatellited supernumerary
tetrasomy 15
partial trisomy 15
Isodicentric 15

- Extra (supernumerary) bisatelleted 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
- \textit{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

PATERNAL  MATERNAL
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: 2\textsuperscript{nd} most common CNV in ASD
- \sim 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

RefSeq Genes

supernumerary

x 4

x 3

BP 1-3

BP 2-3

BP 1-2

x 3

BP 3-5

BP 4-5

x 3

BP 3-5

BP 4-5

x 3
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