Dels and Dups and Idics, Oh My!

Clinical and Genetic Aspects of the 15q11-13 Region

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Neurogenetic Disorders

>1000 genetic conditions associated with neurodevelopmental disorders (OMIM, 2012)

- Down syndrome: described in 1866
- Cornelia de Lange syndrome: 1933
- Prader-Willi syndrome: 1956
- Williams syndrome: 1961
- Angelman syndrome: 1965
- Smith-Magenis syndrome: 1986
- Phelan-McDermid syndrome: 1998
- Potocki-Lupski syndrome: 2000

…..plus hundreds of newly-identified CNVs and mutations!

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Prader-Willi Syndrome

First described in 1956

Clinical diagnosis based on specific pattern of physical and behavioral findings

The three H's:

- Hypotonia
- Hypogonadism
- Hyperphagia

Mild intellectual disability

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Angelman Syndrome

First described in 1965

Clinical diagnosis based on specific pattern of physical and behavioral findings

Key features:

- Characteristic facial appearance
- Frequent unprovoked laughter
- Wide-based unsteady gait, uplifted arms
- Severe intellectual disability

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Supernumerary Markers

- Through 1980s, reports of unidentified extra chromosomal material associated with intellectual disability (ID), autism
- Some markers benign, others associated with severe disability
- Advances in chromosomal staining techniques pointed to 15q in many cases
- Apart from ID, not thought to have a specific clinical phenotype

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Prader-Willi / Angelman / Dup15q

- 1981: PWS linked to 15q11-13 deletion
- 1987: 15q11-13 chromosomal deletions reported in Angelman syndrome
- 1989: PWS and AS involve differentially imprinted genes in 15q region (paternal deletion in PWS, maternal deletion in AS)
- 1990s: Maternally inherited supernumerary markers involving inverted duplications of PWS/AS region; linked to autism, ID, and subtle but recognizable clinical phenotype

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Duplication 15q Syndrome

- a.k.a. inverted dup15q; isodicentric 15q; partial trisomy 15; tetrasomy 15q; interstitial dup15q; etc.
- Severe infantile hypotonia
- Subtle facial differences
- Intellectual disability
- Epilepsy, particularly infantile spasms
- Autism spectrum disorders in majority
- Sudden unexplained death in minority

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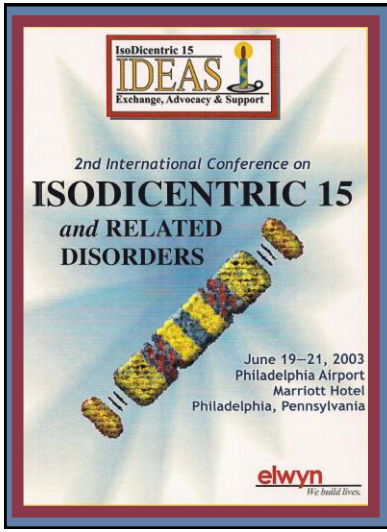


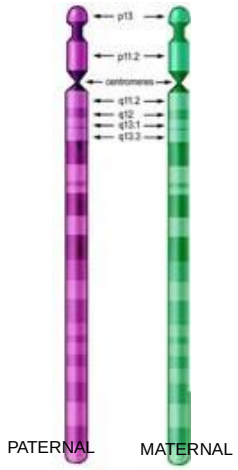
- 1994: IDEAS established (13 families) Inverted Duplication Exchange, Advocacy and Support
- 1997: Name change IsoDicentric 15 Exchange, Advocacy and Support
- 2001, 2003: First international conferences in Philadelphia
  - Dup15q "syndrome"
  - Professional Advisory Board
- 2004: Incorporation of IDEAS
- 2011: Name change to Dup15q Alliance
- 2012, 2013: Research meetings

Dup15q Alliance

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

DUP15q ALLIANCE

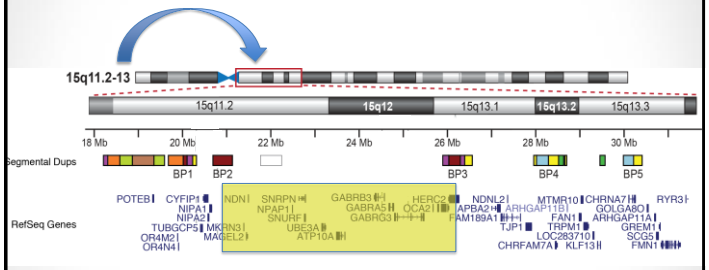
www.dup15q.org



Dup15q Variables

- Supernumerary vs interstitial
- De novo vs familial
- Copy number
- Breakpoints
- Parent of origin

Topography of the 15q11-13 region



PWS/AS

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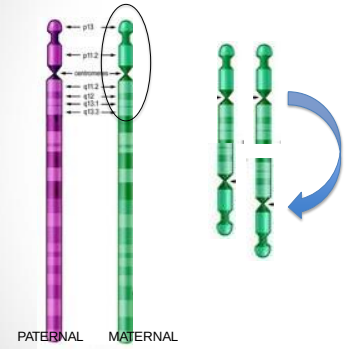
Isodicentric 15



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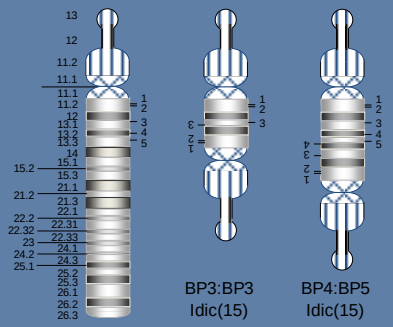
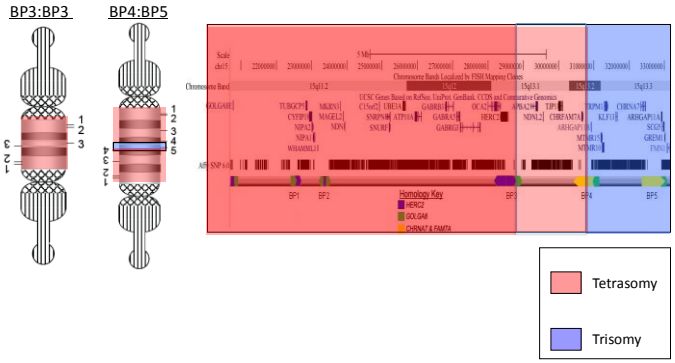
Common Idic(15) Chromosomes



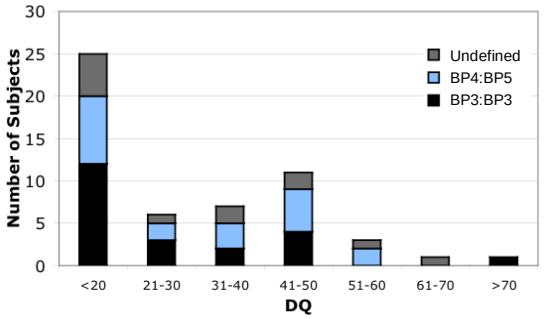
courtesy of Carolyn Schanen

Common Isodicentric 15 Chromosomes



courtesy of Carolyn Schanen

Common Idic15q: Cognition Not Correlated with Breakpoint



courtesy of Carolyn Schanen

UCLA / Nemours Data:

Isodicentric 15:

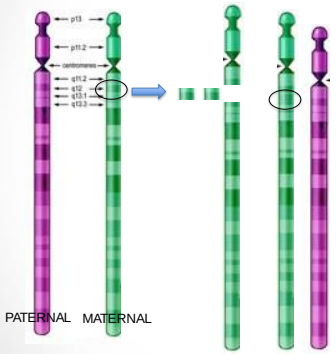
Typical Duplications	Male	Female
BP3:BP3	13	11
BP4:BP5	17	18

Atypical Duplications	Male	Female
BP1:BP1	2	0
BP1:BP3	1	0
BP3:BP4	2	0
BP4:BP4	1	0
BP5:BP5	1	2
Complex	2	0
Translocation	1	0

Interstitial Duplications	Male	Female
BP1-BP3	5	2
BP2-BP3	1	0
Complex	2	0

courtesy of Carolyn Schanen

Interstitial Duplication 15q



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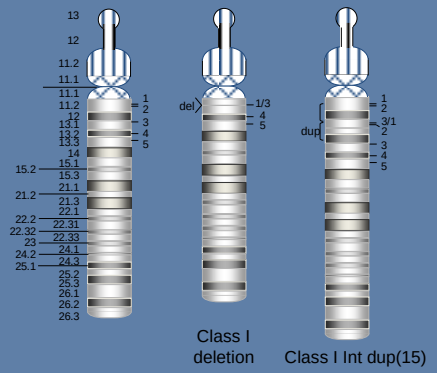
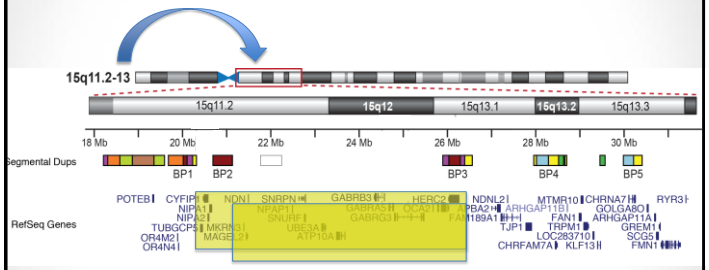
Interstitial Duplications



- Commonly, reciprocal of AS or PWS deletions
- May extend to BP4 or BP5
- Sometimes complex rearrangements, triplications
- Often de novo
- Familial cases show imprinting effects
- Variable phenotype, including ASD

courtesy of Carolyn Schanen

Topography of the 15q11-13 region



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Interstitial Duplications of 15q11.2 – q13

- Int dup(15) highly associated with ASD
- Size of duplication not correlated with ASD severity
- UBE3A implicated in ASD phenotype
- Clinical findings in both mat and pat dups
- Clinical phenotype in int dup(15) more subtle than in idic15q: dosage effect
- Additional findings:
  - Subtle but characteristic facial dysmorphism
  - Sleep disturbance
  - Characteristic EEG pattern

Urraca et al., INSAR, 2013

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Inherited Duplications of 15q11-q13

- Several reports, mostly involving interstitial dup15q
- Pedigrees confirm imprinting effect
- Absent or minimal phenotypic consequences in paternally derived dups
- Anecdotal / published reports of variable psychiatric phenotypes

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Inherited Duplications of 15q11-q13

Piard J. et al. (2010). Clinical and molecular characterization of a large family with an interstitial 15q11q13 duplication. Am J Med Genet Part A 152A:1933-1941.

- Consistent with imprinting effect
- Absent / minimal phenotype in paternal dups
- No association with autism*

*no standardized tests for autism were done

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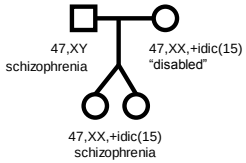
Inherited Duplications of 15q11-q13

Boot, E. et al. (2012). Overexpression of chromosome 15q11-q13 gene products: A risk factor for schizophrenia and associated psychoses? Am J Psychiat 169:96-97.



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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 epileptic encephalopathies

Moreno-De-Luca et al., 2012
Epi4K Consortium & Epilepsy Phenome/Genome Project, 2013

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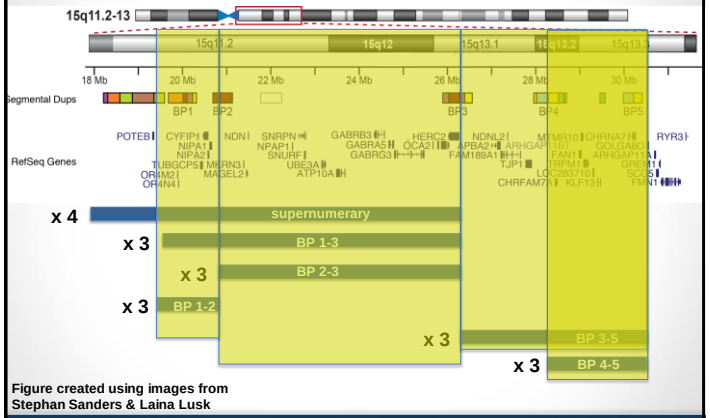
Topography of the 15q11-13 region



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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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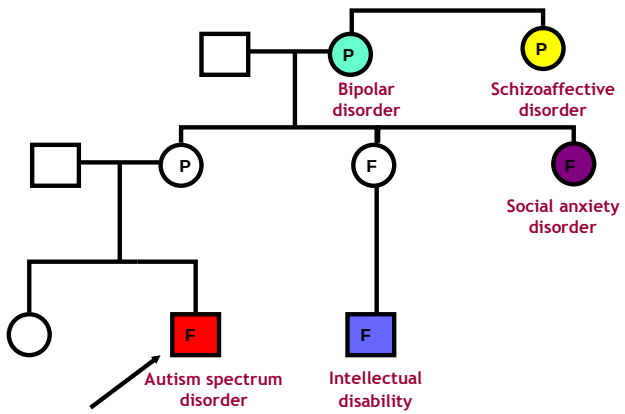
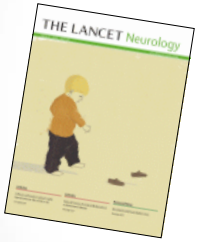
5 psychiatric diagnoses
1 etiological diagnosis: Fragile X syndrome



Developmental Brain Dysfunction



Moreno-De-Luca A, Myers SM, Challman TD, Moreno-De-Luca D, Evans DW, Ledbetter DH.

Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence.

Lancet Neurol. 2013 Apr; 12(4):406-14. Epub 2013 Mar 18.

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Dup15q Research: Future Directions

- Neurodevelopmental / psychiatric aspects
- Seizures, particularly infantile spasms
- Potential clinical associations: sleep disorders, GI issues, anxiety
- Sudden unexplained deaths
- Imprinting effects / paternal duplications
- Familial duplications, "the DBD pedigree"
- Dups not involving the PWS/AS region
- Assessment, online phenotyping
- Shared neurobiological pathways
- Targeted pharmacological and behavioral interventions

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