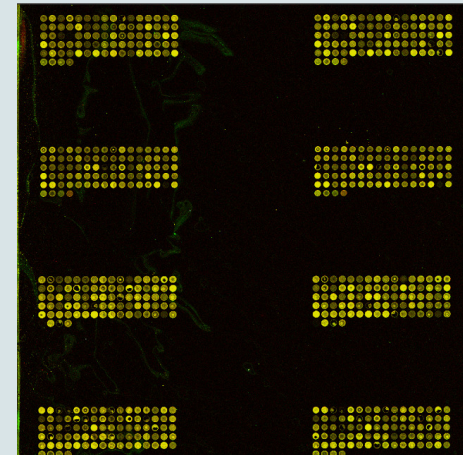
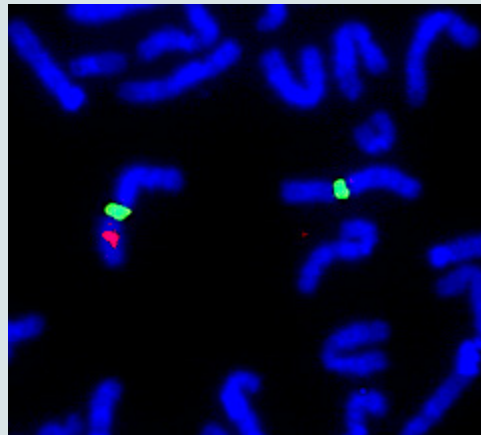
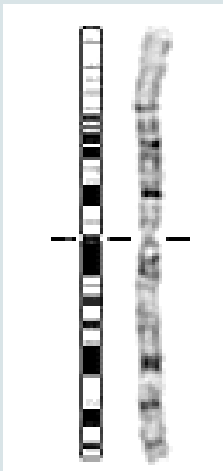


Detection of copy number imbalances in children with learning disabilities: where are we now?

Una Maye



Outline of Talk

- **Background to service**
- **Benefits of a diagnosis**
- **LWH data**
- **Interpretation difficulties**
- **Future**
- **Summary**

Background

- **Mental Retardation- heterogeneous condition affects 1-3% population.**
- **Significant proportion of children with LD do not present with a recognisable phenotype.**
- **New technologies discovery of novel cryptic chromosomal aberrations.**

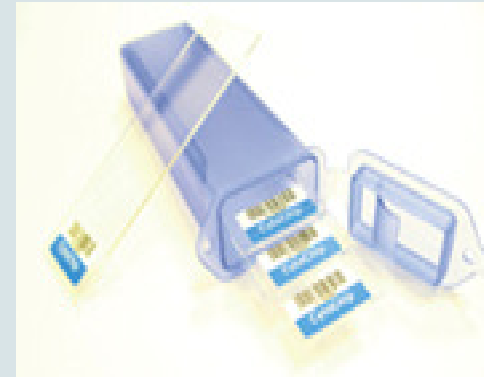


Association for
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Benefits of Microarray Testing

Clinical and Genetic Approach to LD

- **Diagnosis**
- **Prognosis**
- **Patient management**
- **Recurrence risks**

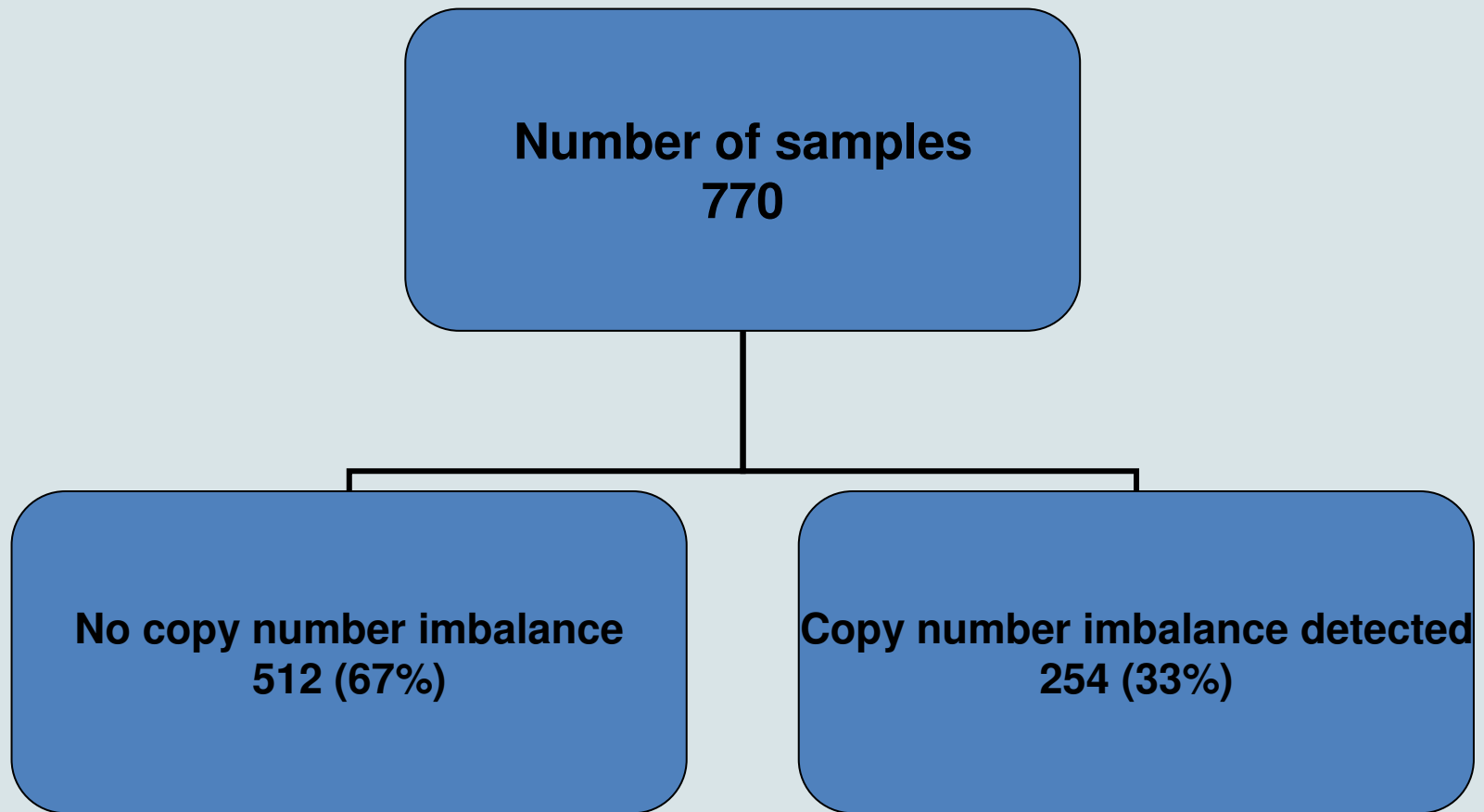


Regional Service

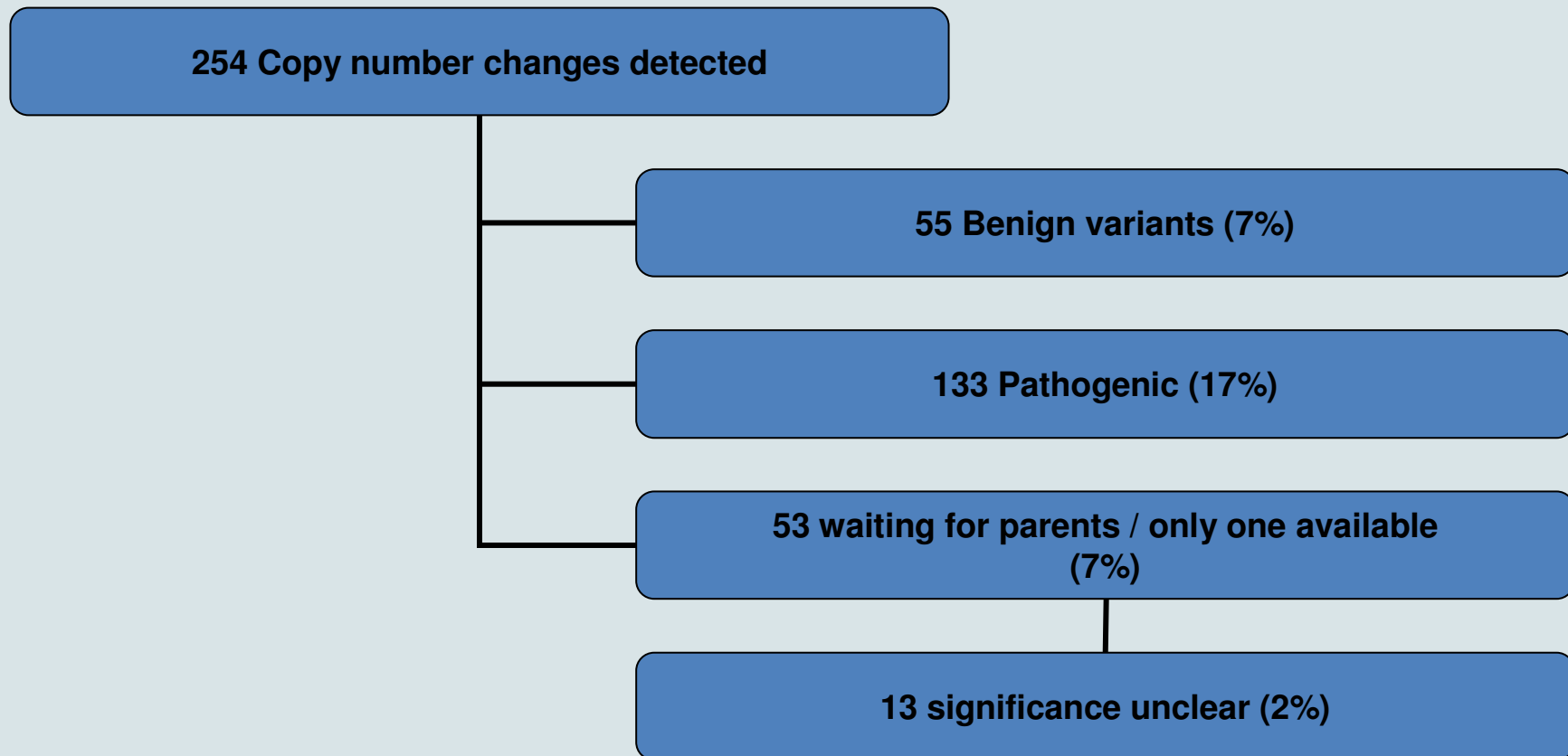
- **Population of 2.8 million**
- **1700 samples per year from children with developmental delay, congenital abnormalities and neonates**
- **Array service since January 2008**
- **BAC 0.5Mb Cytochip and 8 x 60k ISCA Oligo**



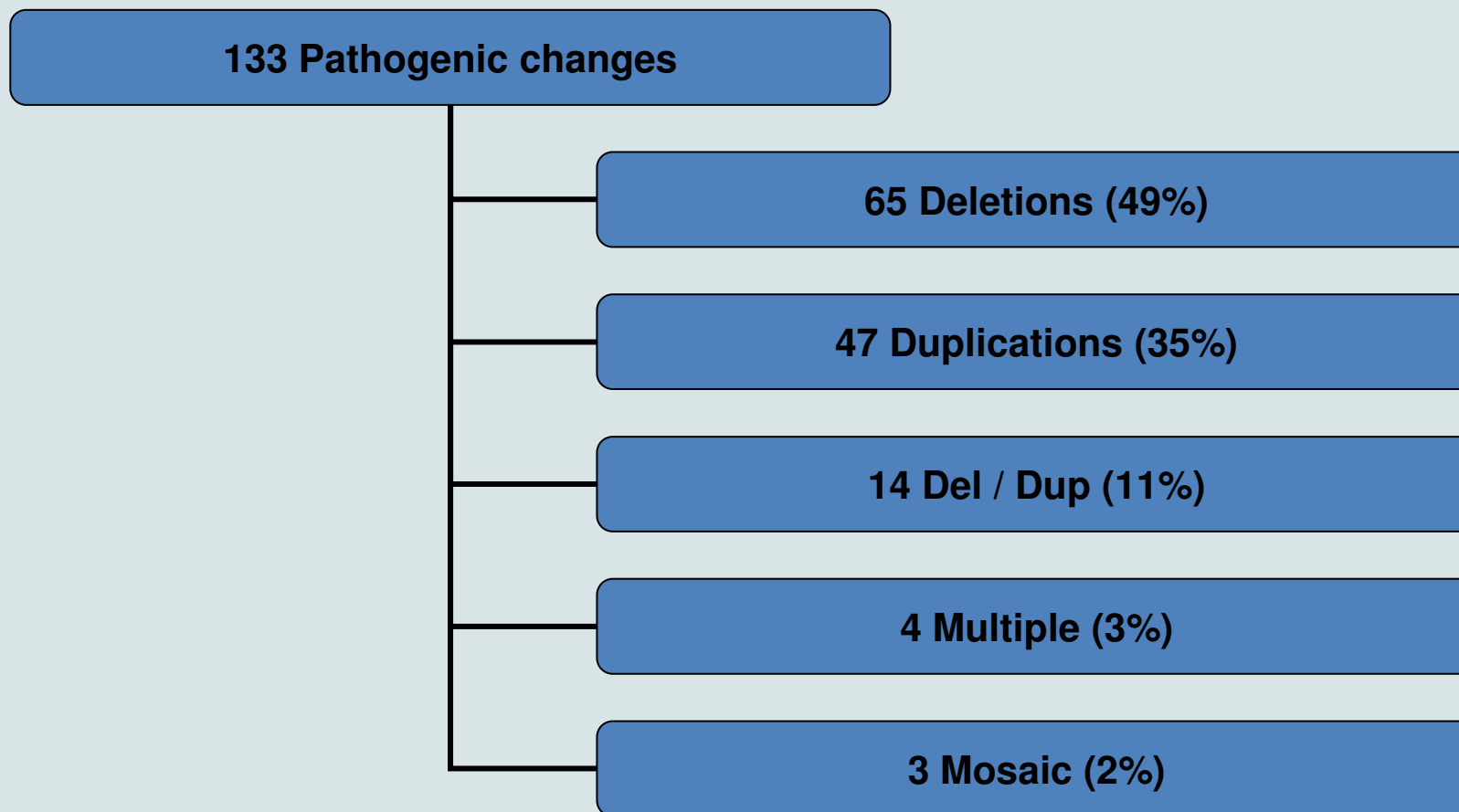
Array Data 2008-2011



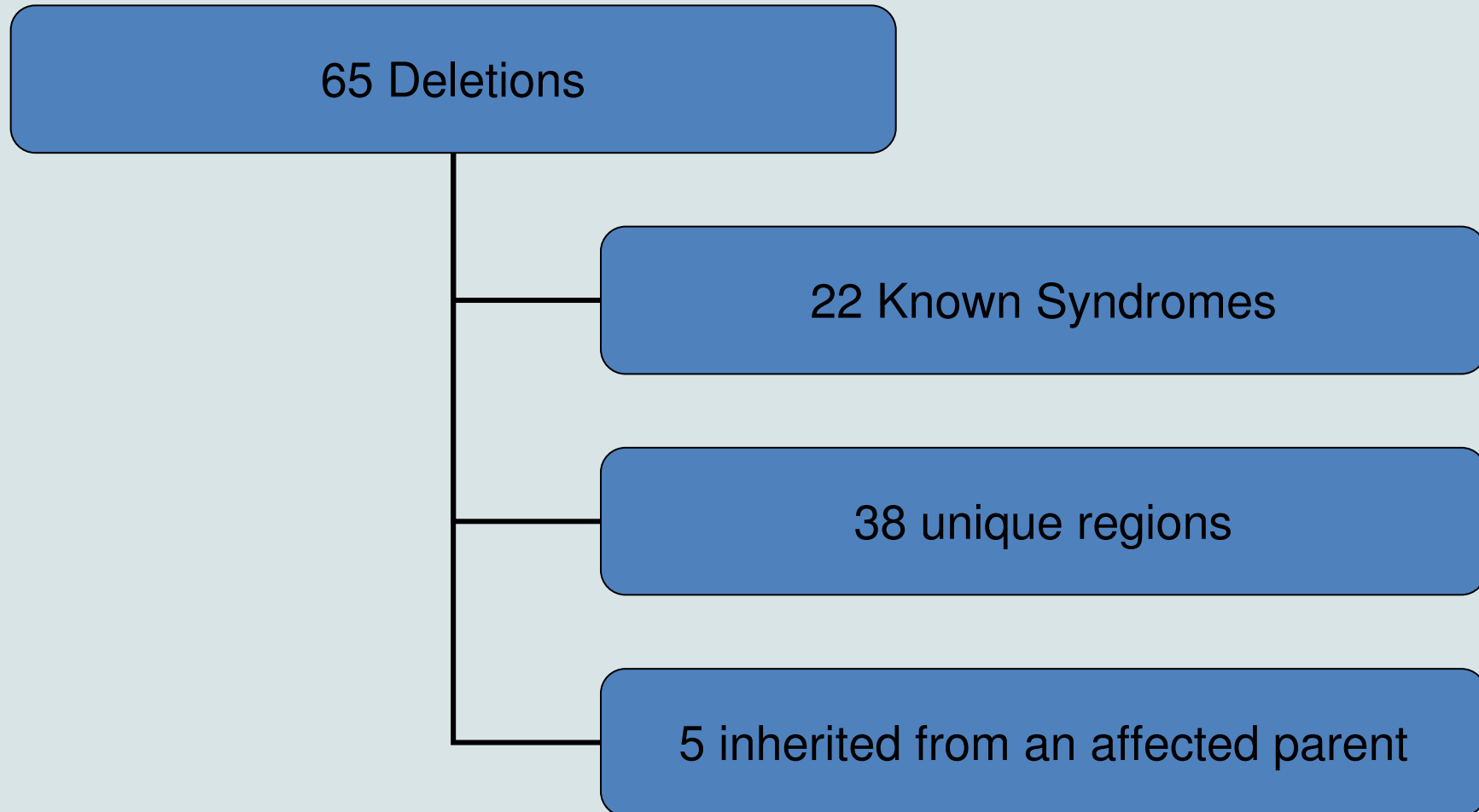
Array Data 2008-2011



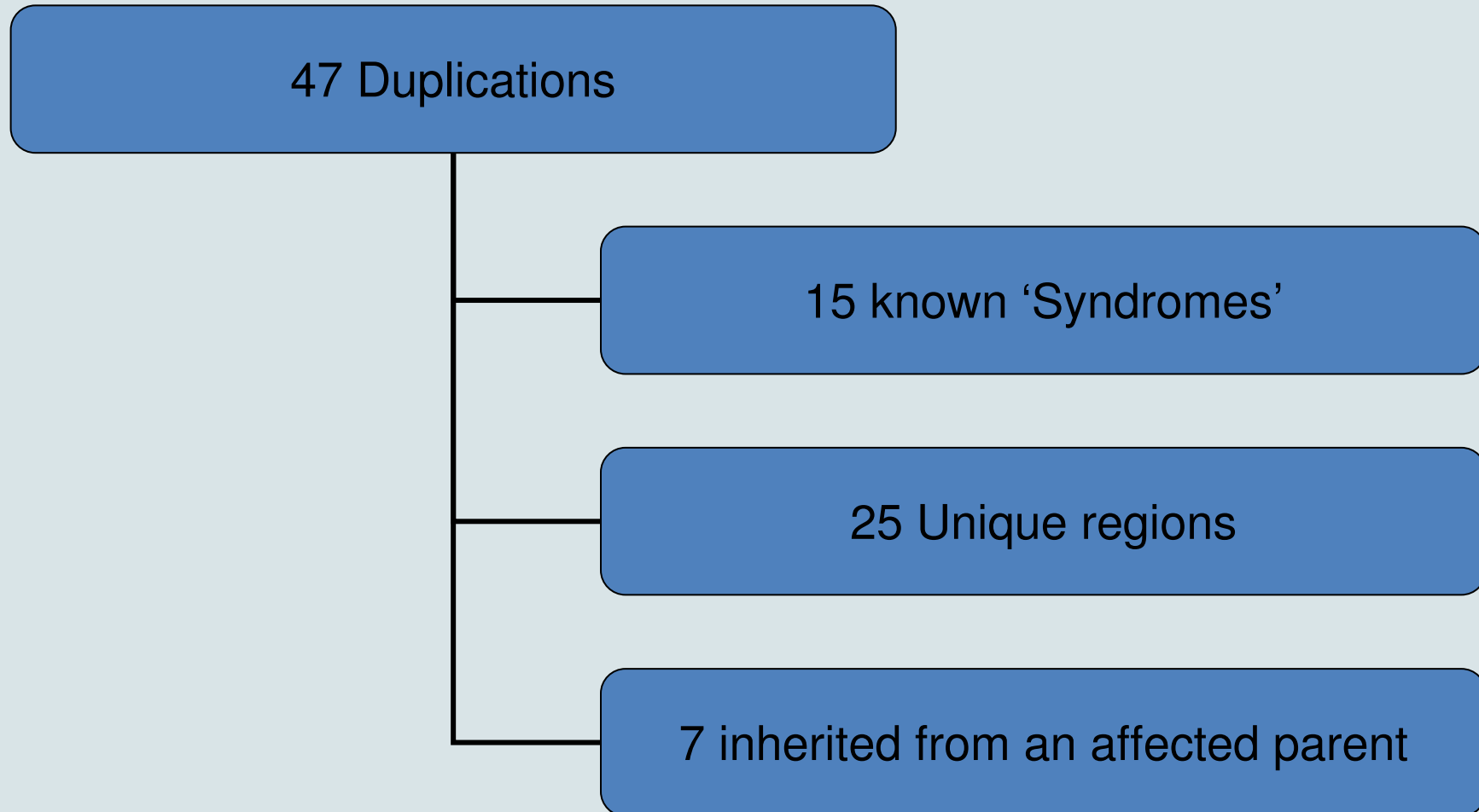
Pathogenic Changes



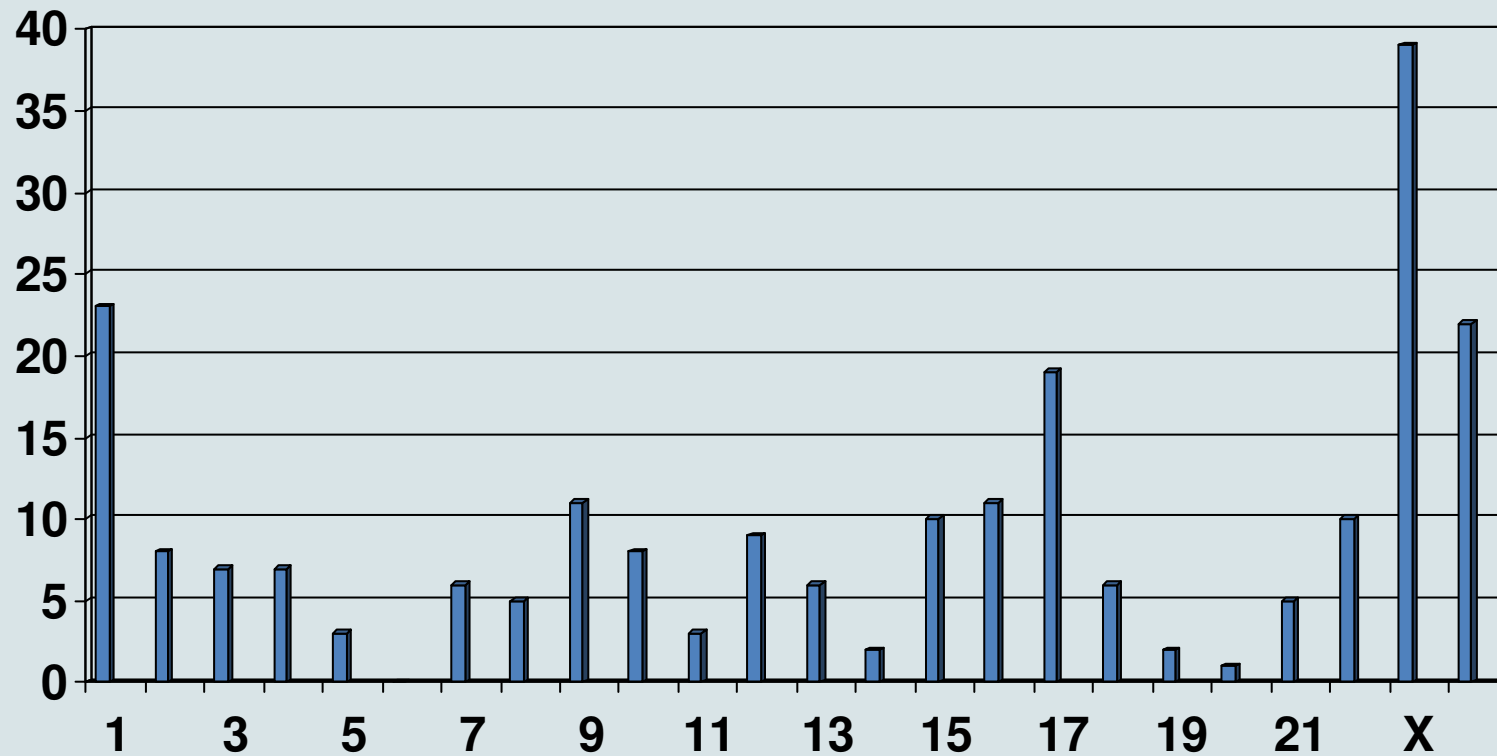
Pathogenic deletions



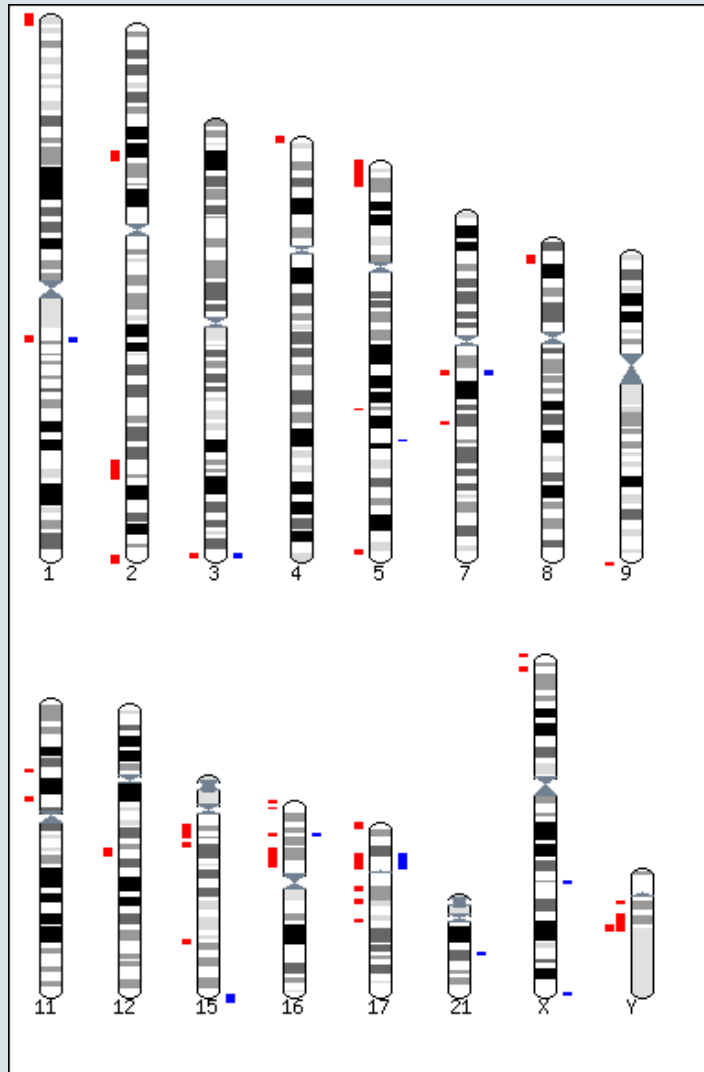
Pathogenic Duplications



CNVs by chromosome



Syndromic CNVs



Nearly all syndromes represented

37 Total

22/37 deletions

15/37 duplications

12/37 (32%) familial

Most common:

- **1q21.1 duplications / deletions**
- **17q12 duplications**
- **16p11.2 deletions**
- **Distal 22q deletions**



Evidence of Pathogeneticity

- Normal control population
 - Size of imbalance
 - Clinical findings
 - Gene content
 - Familial or de novo
 - Penetrance issues
-
- **Interpretation can be complex!**



Size of imbalance

Range from 25kb to whole chromosome gain

Smallest deletion



Deletion of 84kb Gli3 gene

The Clinical Atlas of Greig Cephalopolysyndactyly Syndrome

Katherine Balk¹ and Leslie G. Biesecker^{2*}

¹National Institute of Nursing Research, National Institutes of Health, Bethesda, Maryland

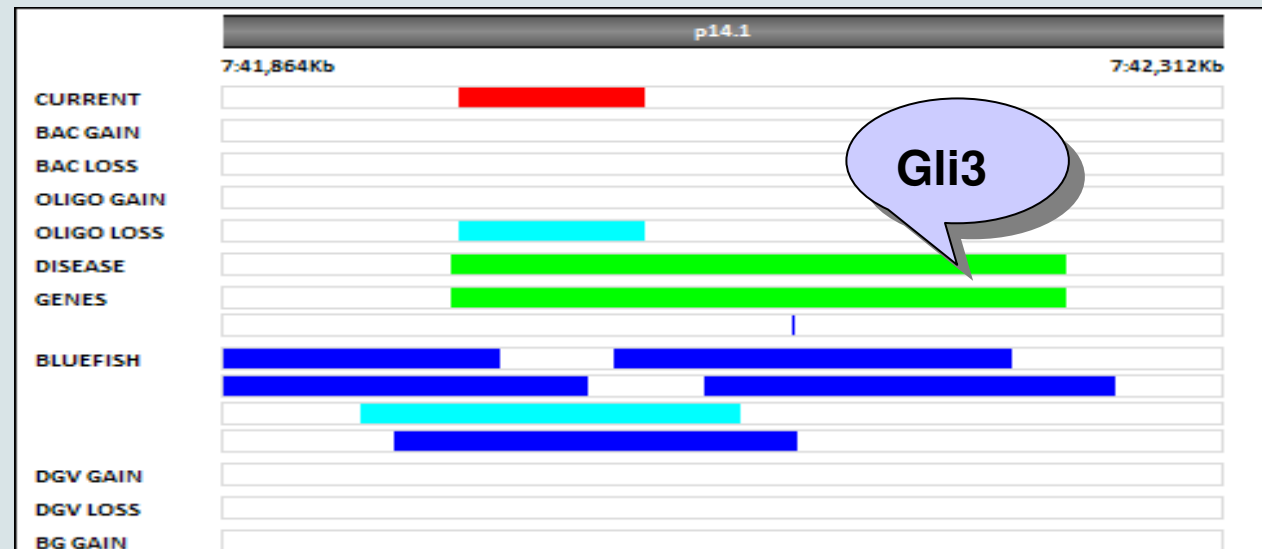
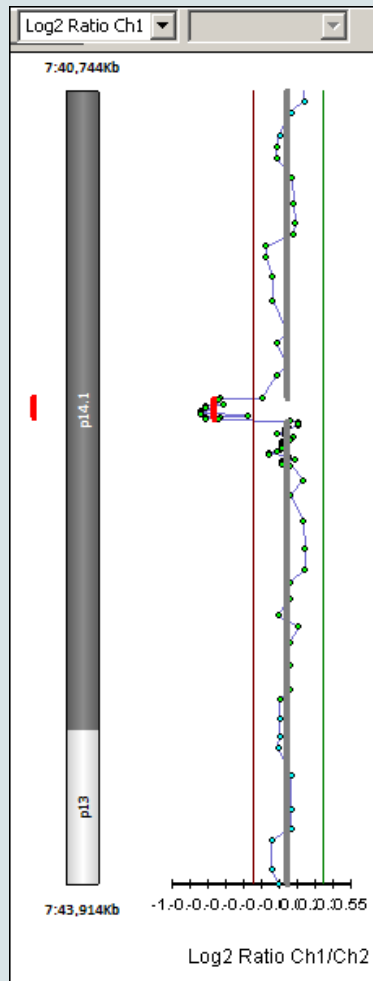
²National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland

Received 21 March 2007; Accepted 11 October 2007



Gli3 Gene at 7p14.1

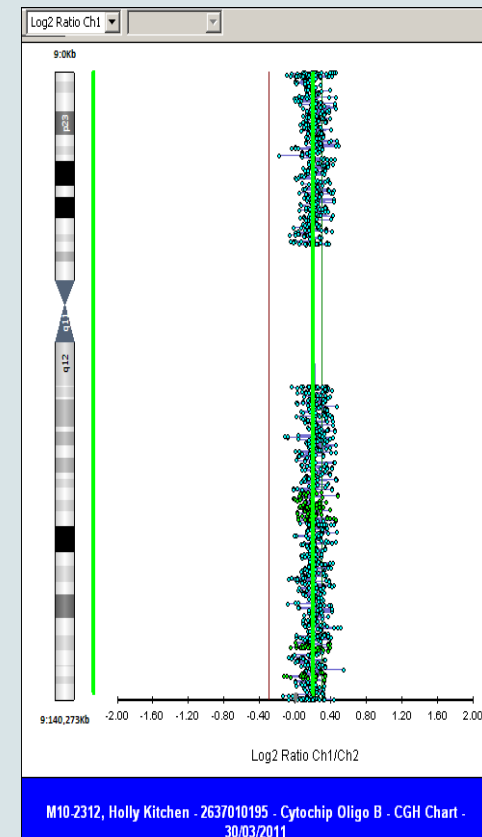
Newborn baby, frontal bossing,
 hypertelorism, postaxial polydactyly of the
 hands and feet with bilateral duplicated
 broad great toes → 84kb deletion



Mosaicism

3 cases

- Mosaic Trisomy 9 (30%)
- Mosaic Trisomy 13 (25%)
- Mosaic Dup (2)(p21-p16.1)
27Mb (60%)



ARTICLE

Genomic Imbalances in Neonates With Birth Defects: High Detection Rates by Using Chromosomal Microarray Analysis

Xin-Yan Lu, MD^{a,b}, Mai T. Phung, MD^{b,c}, Chad A. Shaw, PhD^a, Kim Pham, BS^a, Sarah E. Neil, BS^a, Ankita Patel, PhD^a, Trilochan Sahoo, MD^a, Carlos A. Bacino, MD^{a,b}, Pawel Stankiewicz, MD, PhD^a, Sung-Hae Lee Kang, PhD^a, Seema Lalani, MD^{a,b}, A. Craig Chinault, PhD^a, James R. Lupski, MD, PhD^{a,b}, Sau W. Cheung, PhD^a, Arthur L. Beaudet, MD^{a,b}

Departments of ^aMolecular and Human Genetics and ^bPediatrics, Baylor College of Medicine, Houston, Texas; ^cDepartment of Neonatal Medical Services, Winnie Palmer Hospital for Women and Babies, Orlando, Florida

Penetrance issues

- CREBBP gene 136kb dup 16p13.3 mat inherited

Thienpont et al 2010

- Duplication of critical Rubinstein-Taybi deletion region on 16p13.3 cause a novel syndrome
- Inheritance of the duplication from a clinically normal parent in 2 cases indicating incomplete penetrance

Complex cases

Multiple changes seen in 4 cases

- Patient AF
 - Deletion 16p11.2 syndrome De novo
 - Duplication 3q29 syndrome (Paternal)
 - Deletion 10p11.22-p11.23 (1.8-1.9Mb) 8 HGNC genes and 4 OMIM De novo
 - **?Interpretation**

Parental Follow-Up

- **Do not assume parents are normal!**
- **Detailed clinical history important**

Patient CR

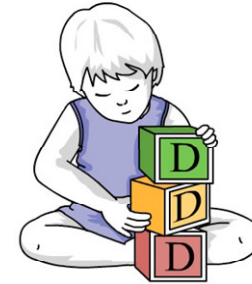
- **Deletion 500-800kb 12q14 spans known microdeletion region includes HMGA2**
- **Growth and Development**
- **Paternally inherited**
- **Dad low birth weight and short stature**



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Future?

- Higher resolution arrays
- DDD project
- Next gen sequencing
- Prenatal arrays



Deciphering Developmental
Disorders

nature
genetics

LETTERS

A de novo paradigm for mental retardation

Lisenka E L M Vissers^{1,2}, Joep de Ligt^{1,2}, Christian Gilissen¹, Irene Janssen¹, Marloes Steehouwer¹,
Petra de Vries¹, Bart van Lier¹, Peer Arts¹, Nienke Wieskamp¹, Marisol del Rosario¹, Bregje W M van Bon¹,
Alexander Hoischen¹, Bert B A de Vries¹, Han G Brunner^{1,3} & Joris A Veltman^{1,3}

NHS

Liverpool Women's

Summary

- **Array CGH has increased diagnostic yield for children with LD**
- **New syndromes**
- **Gene discovery**
- **Cellular pathways**
- **Genome architecture**
- **Greater understanding of genetic basis of disease**

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- **Cytogenetic staff at Liverpool Women's Hospital**
 - **Molecular genetic Colleagues**
 - **Clinical Genetics Department**