




**Advanced Genetic Testing:
Clinical Application and Benefits in Real Practice**

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คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

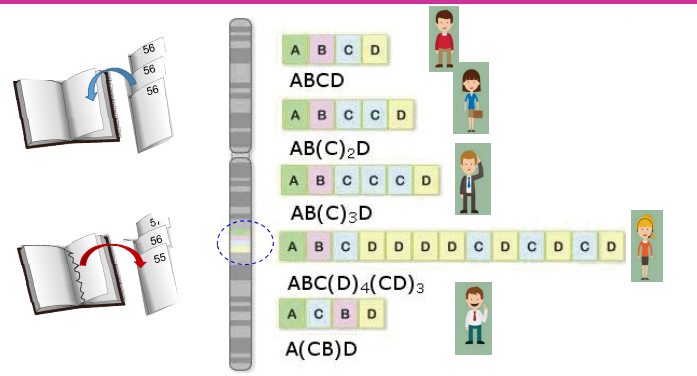
26 Oct 2019

Genetic Disorders: 4 types

- **Chromosomal disorders**
 - Multiple anomalies and/or Developmental delay, Intellectual disability, Dysmorphic features
 - Syndrome & Nonsyndrome
- **Single gene disorders/mutation**
 - Multiples organs - syndromes
 - Specific organs – muscle weakness, kidney etc.
 - Inborn metabolic disorders
- **Multifactorial disorders**
- **Others**
 - Epigenetic disorders, imprinting defects
 - Mitochondrial disorders



Chromosome variants: Copy number variation (CNV)



<http://lvwarren.blogspot.com/>
https://www.freepik.com/free-vector/people-cartoon-characters_761597.htm

CNV: inter-individual genetic polymorphism

- DNA segment size >1 Kb with variable copy number
- Gain or loss; the **average size 250 kb**
- Found in both **healthy and affected individuals**
- Contributes to **≈34% of the genome**
- **Benign, Variant of unknown significant, Pathogenic**
mean number of **benign CNVs** per person >800

Tyson et al. *Am J Med Genet* 2005
Lee, et al. 2007 *Nat Genet*

Clinical interpretation of CNV

- 3 categories: **Benign, Pathogenic, Unknown significance**
- **Pathogenic CNVs**
 - gene-rich
 - inherited from an affected parent
 - seen in multiple affected individuals
 - large deletion size >3Mb in size, etc.
- **Duplications:** better tolerated than deletions
- **Deletion**
 - higher likelihood of being pathogenic
 - benign deletion - average size of 15-20 kb
 - small, gene-rich CNVs are more likely to be pathogenic than larger, gene-poor CNVs

(Lee, et al. 2007 Nat Genet)

Clinical interpretation of CNV

Single-copy deletion can be phenotypically benign, **but it may also be associated with pathogenicity**

Lee C, et al. Nat Genet. 2007 Jul;39(7 Suppl) :S48-54.

Testing for **single gene disorders**

- **Conventional Sanger sequencing**
 - common mutations, familial mutation
 - All exons of one gene
- **Next generation sequencing**
 - Targeted disease panel
 - Whole exome sequencing
 - Whole genome sequencing
- Exon deletion/duplication
 - MLPA (multiple ligation-dependent probe amplification)
 - Ex: Duchenne muscular dystrophy, Spinal muscular atrophy etc.
- Trinucleotide repeat: PCR, Southern blot

Next generation sequencing = Multiple gene sequencing in one time

https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

- **100,000 variants**
- **Clinical history**
- **Known causing genes**
- **Allele frequency**
- **Inheritance pattern**

candidate variants

Clinical Application & Benefits

- Disease/disorder based example – Autism
- Individual patient based example – Case 1, 2,3...

Autism: Recurrence Risk

- Chromosome & Single gene dis: 1-50%
- Multifactorial: 4%

Old belief - idiopathic autism = multifactorial

Recent data - high recurrence risk indicating NOT simply multifactorial

Condition	Multi-factorial	Idiopathic autism	Ritvo, 1989, Am J Psychiatry	Constantino, 2010, Am J Psychiatry	Ozonoff S, 2011, Pediatrics
1 affected child; Next child to be affected	4%	4% M 7% F 1%	8.6% (Utah Epidemiology Survey)	14.6% (Utah, Autism Registry)	18.7% (Utah, Prospective 3 Yr Longitudinal 664 → 132 ASD) Risk Male x3
2 affected child; Next child to be affected	10%	35%			32%

Clinical Utility of CMA

References	Study population	Results
Rauch et al., 2006	Unexplained Dev Delay/Intellectual Disability (DD/ID)	<ul style="list-style-type: none"> •Missed 0.6% of cases with disease-causing balanced de novo aberration •Highest diagnostic yield of any single test (28.9%)
Miller et al., 2010	21,698 patients with DD/ID, MCA and/or ASD	<ul style="list-style-type: none"> •using CMA as First-line test → diagnostic yield +12.2% higher than G-banding
Hochstenbach et al., 2009	DD/ID	<ul style="list-style-type: none"> •pathogenic CNV in 19%
Shen et al., 2010	ASD	<ul style="list-style-type: none"> •abnormal CNV in 18.2% (abnormal G-banding 2.23%; abnormal FXS test 0.46%)

ACMG PRACTICE GUIDELINES

Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities

Melanie Manning, MD, MS, FACMG, and Louanne Hudgins, MD, FACMG, for the Professional Practice and Guidelines Committee

2010
2013

1. Cytogenetic microarray (CMA) test for CNV **Yield 15-30%**
 “FIRST-line Test” in initial **postnatal** evaluation
 - Multiple anomalies not specific to well-delineated genetic syndrome
 - Non-syndromic developmental/intellectual disability
 - Autism spectrum disorders (ASD)
2. Growth retardation, speech delay, other less well-studied indication but prospective study required
3. Appropriate F/U when chromosome imbalance is identified
 chromosome/FISH study: patient, parents
 clinical genetic evaluation & counseling

ACMG PRACTICE GUIDELINES **2010, con't**
 American College of Medical Genetics

Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities

- When CMA should **NOT** be ordered
 - Rapid turnaround time is needed -- still true?
 - Suspected specific common aneuploidy
 - T21, T18, sex chromosome aneuploidy (conventional karyotype - more appropriate)
 - FISH with **single probe** to confirm suspected diagnosis eg, William syndrome, which would be more cost-effective

Experiences @ Ramathibodi Hosp.

Cohort 1: Nonsyndromic Autism
 positive 25.4% (29/114)

Cohort 2: DD/ID w/wo dysmorphic features, congenital anomalies, w/wo autism
 positive ≈ 30% (30/100)

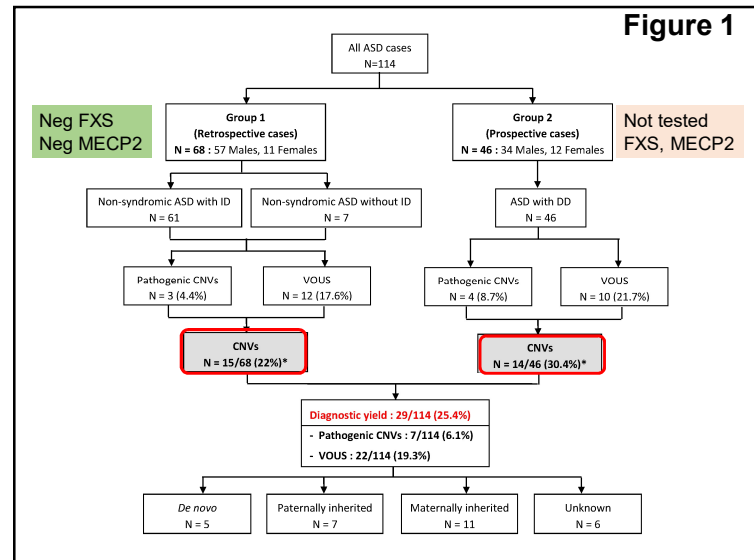
SCIENTIFIC REPORTS

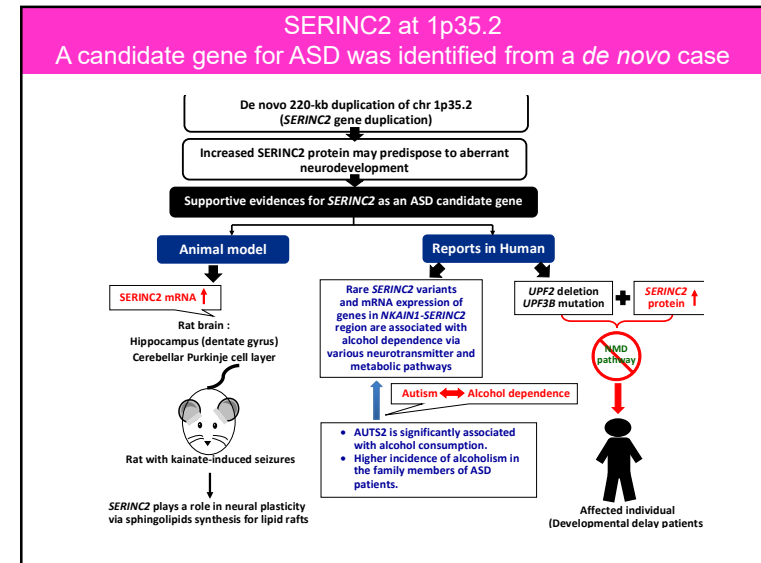
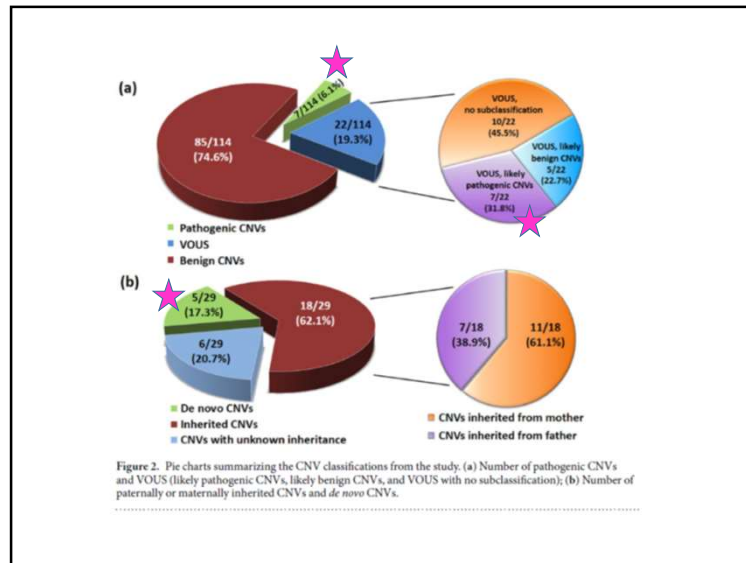
114 Nonsyndromic (idiopathic) ASD

• วามชิบิตติ มหิตล
 • สงขลานครินทร์
 • ธรรมศาสตร์

CMA Diagnostic yield 25.4%

Case ID	Sex	Clinical diagnosis	Additional clinical features	Chromosome region	Coordinates (hg19)	Size (kb)	Gene involved*	Inheritance
A. Pathogenic CNVs (N = 7 of 114)								
14882.2	M	Non-syndromic ASD	Microcephaly	1q21.1 (q21.1)	chr1:100113364-100121348	10.0	11 genes	Maternal
17222	M	Non-syndromic ASD	Microcephaly, autism	9q31.3	chr9:48362-100756	1.01	11 genes	NA
2713	M	ASD, ID	Thrombocytopenia, autism	10q11.23 (q11.2)	chr10:726648-726686	1.0	18 genes	De novo
14882.3	F	Non-syndromic ASD	None	17q21.31 (q21.3)	chr17:2017174-221498	1.0	21 genes	Maternal
17622.2	M	Non-syndromic ASD	None	10q21.1	chr10:1122474-1441784	1.0	15 genes	Paternal
B. VUS/NA likely pathogenic CNVs (N = 7 of 114)								
7137	F	ASD, ID, MCA	Microcephaly, ID, ID (probable) (probable), abnormal ear and eye appearance, NA	19q21.31 (q21.3)	chr19:388384-7861336	1.0	18 genes	NA
2890	F	ASD	Microcephaly, ID	22q13.1	chr22:3017861-3322192	1.0	27 genes	De novo
C. VUS/NA likely benign CNVs (N = 8 of 114)								
17612.2	M	Non-syndromic ASD	None	10q11.2	chr10:1070761-1028367	1.0	22 genes	NA
14882.4	F	Non-syndromic ASD	None	10q21.1	chr10:1122474-1441784	1.0	15 genes	NA
17612.3	M	Non-syndromic ASD	None	10q11.2	chr10:1070761-1028367	1.0	22 genes	NA
17612.4	F	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.5	M	Non-syndromic ASD	Abnormal hearing ear	17q21.31	chr17:2017174-221498	1.0	21 genes	NA
14882.6	M	Non-syndromic ASD	Abnormal hearing ear	17q21.31	chr17:2017174-221498	1.0	21 genes	NA
17612.5	M	Non-syndromic ASD	None	10q11.2	chr10:1070761-1028367	1.0	22 genes	NA
17612.6	M	Non-syndromic ASD	None	10q11.2	chr10:1070761-1028367	1.0	22 genes	NA
14882.7	M	Non-syndromic ASD	None	17q21.31	chr17:2017174-221498	1.0	21 genes	NA
14882.8	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.9	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.10	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.11	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.12	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.13	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.14	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.15	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.16	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.17	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.18	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.19	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA
14882.20	M	Non-syndromic ASD	None	10q11.2	chr10:1122474-1441784	1.0	15 genes	NA





Case 1: A 6 y-old boy

Severe dev delay & autism, blindness, multiple congenital anomalies

Clinical

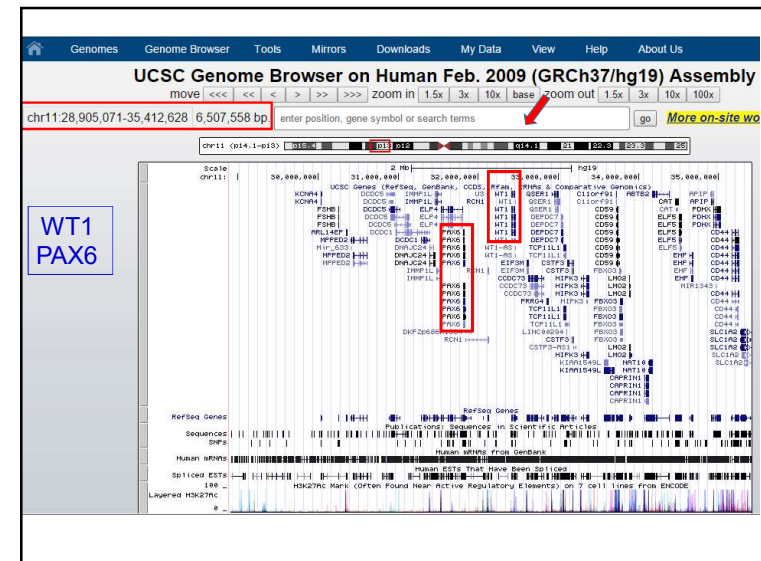
- small & cup-shaped ear
- congenital cataract & glaucoma
- autistic-like behavior
- double opening urethra
- KUB U/S: bilateral VUR grade III

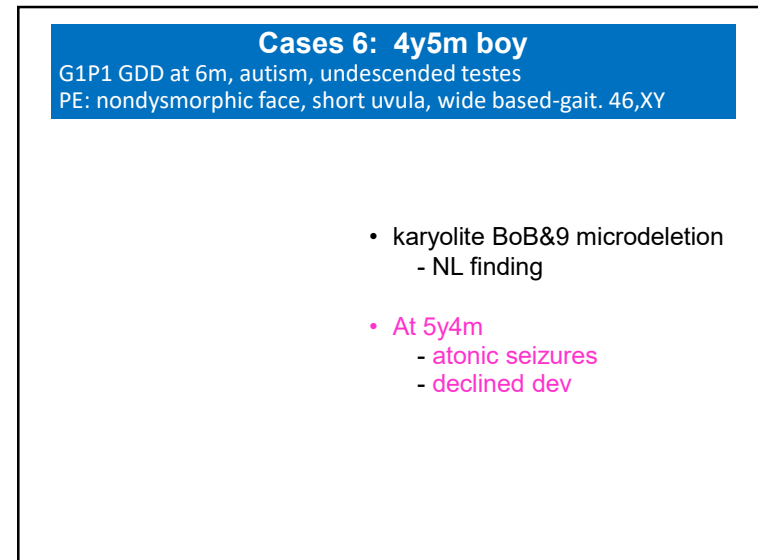
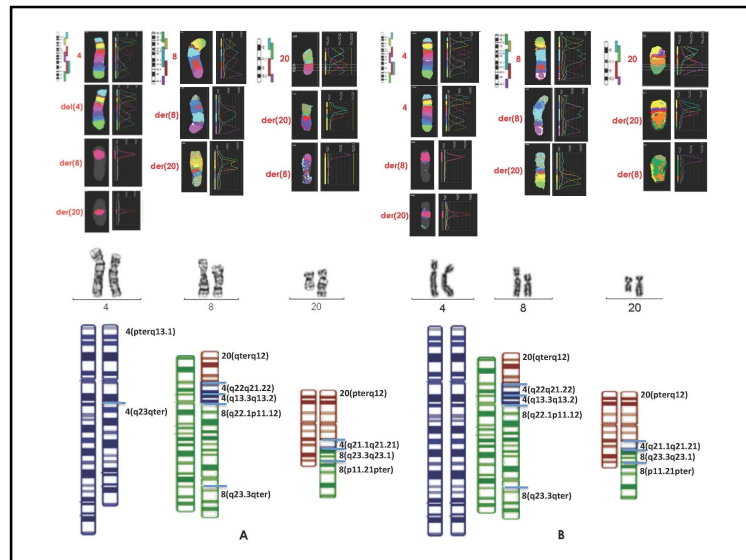
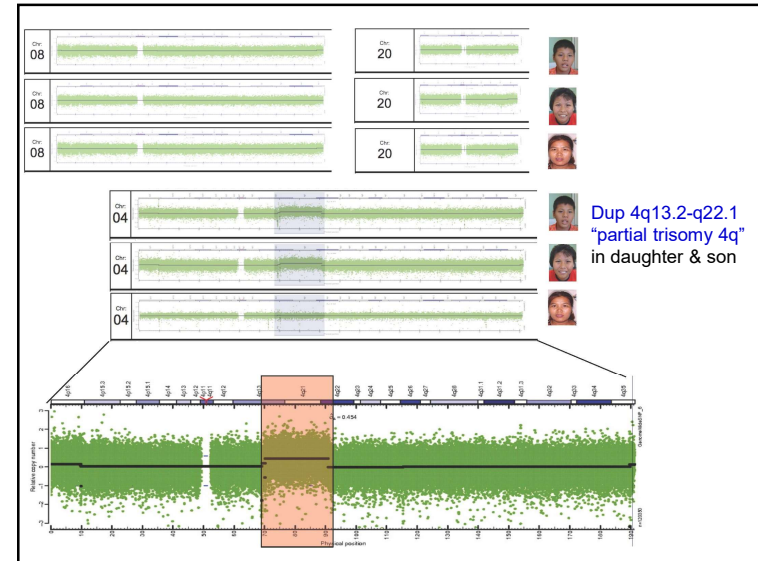
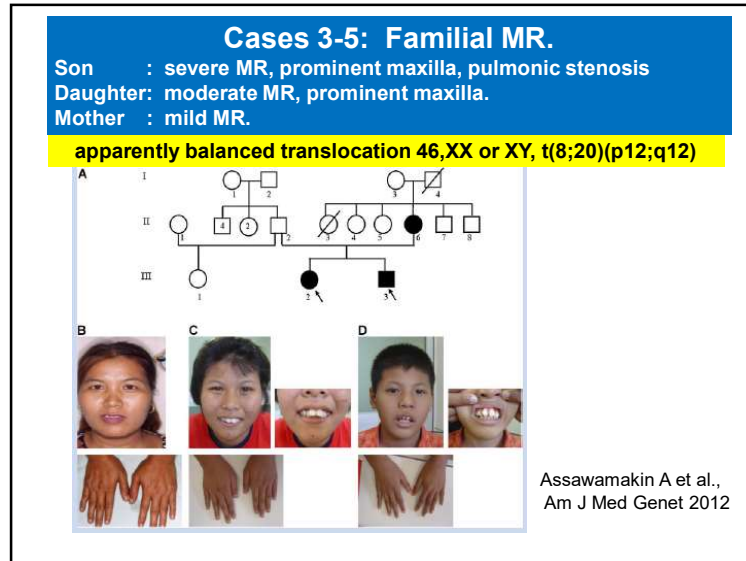
Previous Lab test

- 46,XY
- MRI Brain suggestive Lowe syndrome
- Mutation analysis of OCRL gene → no mutation identified

aCGH: deletion 11p13-p14.1 chr11:28,905,071-35,412,628 (6.5 Mb deletion)

WT1 – tumor suppressor gene
 PAX6 – anterior eye segment





Cases 6: 4y5m boy
 G1P1 GDD at 6m, autism, undescended testes
 PE: nondysmorphic face, short uvula, wide based-gait. 46,XY

ID 2709: chr X
 ISCN
arr[GRCh37] Xq28(152,966,348-153,781,876)x2

Size (bp)
815,529 (0.85 Mb)

2709 1000285966 RDSECF Karyotype Chart (GRCh37) - 22/01/2015

Genes at Xq28

MECP2	Male	Female
Loss/deletion or point mutation	still birth, neonatal encephalopathy	Rett syndrome
Duplication: Xq28 duplication syndrome*	X-linked DD/ID, behavioral and psychiatric phenotypes (ADHD, autism, anxiety, psychotic), dev regression	No clinical symptoms or mild phenotype: LD

*Testing of maternal samples is important in determining recurrence risk.

<https://www.ncbi.nlm.nih.gov/books/NBK349624/>

<http://www.rarechromo.org/>

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Support and Information

Rare Chromosome Disorder Support Group,
 PO Box 2189,
 Caterham,
 Surrey CR3 5GN,
 UK
 Tel/Fax: +44(0)1883 330766
 info@rarechromo.org
 www.rarechromo.org

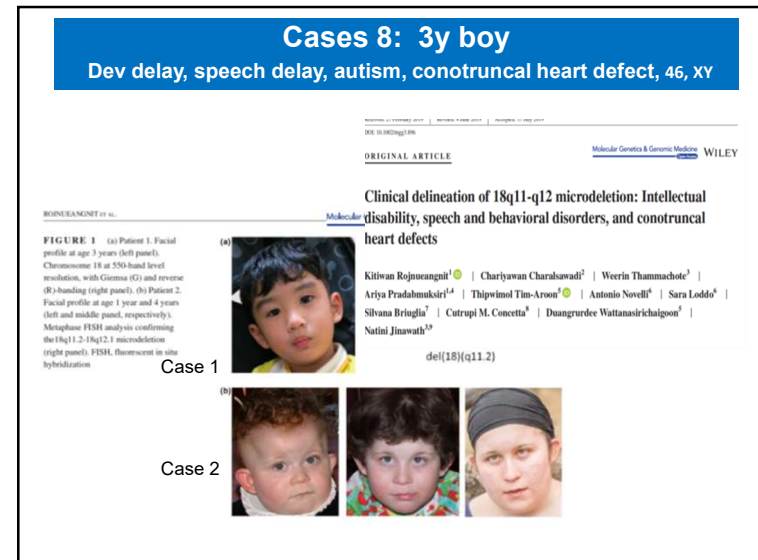
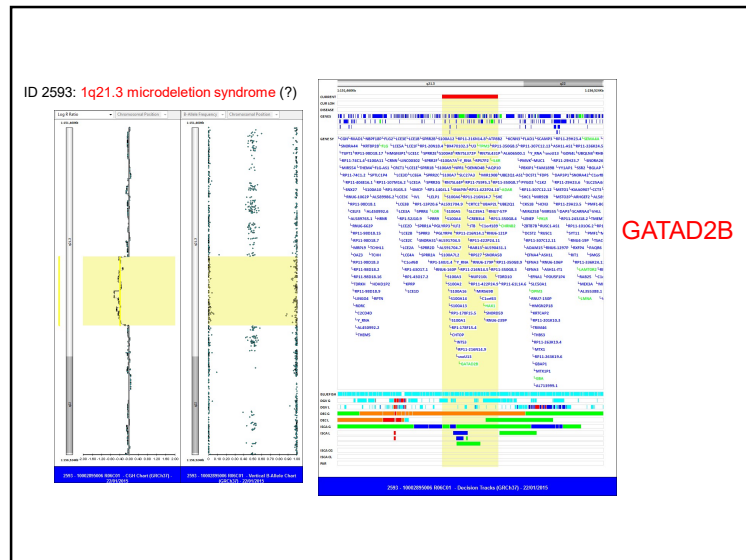
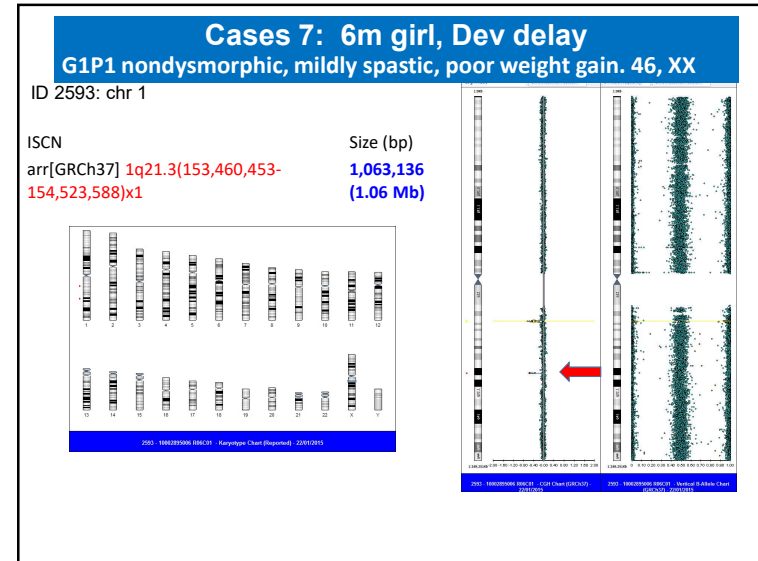
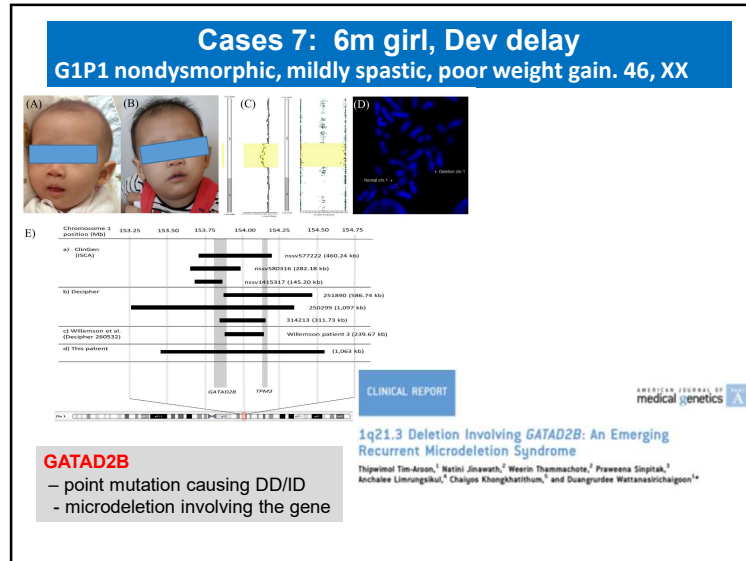
Xq28 duplications

This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. It was compiled by Unique and reviewed by Dr Damien Sanlaville, Hospices Civils de Lyon, France; Professor Dian Donnai, University of Manchester, UK and by Professor Maj Hultén BS, PhD, MD, FRCPath, Professor of Reproductive Genetics, University of Warwick, UK, 2010.
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Rare Chromosome Disorder Support Group
 Charity Number 1110661

Recommend Follow-up test following positive CMA

- patient:
- parents: inherited or *de novo*, Recurrence risk, PND
- methods: high resolution chromosome / FISH



หน้าหลัก ค้นหา ติดต่อเรา ติดต่อเรา Gmail เอกสาร ปฏิทิน แอปภาษา ภาพถ่าย อื่นๆ »

rare chromosome

ค้นหา ผลการค้นหาพบจำนวน 7,650,000 รายการ (0.35 วินาที)

เว็บไซต์ Unique - The Rare Chromosome Disorder Support Group - www.rarechromo.org/ - แครช - แปลงหน้า

ค้นพบ Unique - Rare Chromosome Disorder Support Group for families affected by any rare chromosome disorder such as deletions, duplications, translocations, ...

แผนที่ [Chromosomes & Disorders](#)
Consequences of Rare Chromosomal Disorders. All ...

วิดีโอ [The Little Yellow Book](#)
The Little Yellow Book. We have prepared this booklet to give ...

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Chromosome Disorder Leaflets. We have been collecting ...

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Chromosome Disorder Leaflets

We have been collecting information about specific chromosome disorders in our comprehensive online database for nearly 25 years and since 2003 have spent many thousands of hours producing family friendly, medically verified, disorder specific information leaflets. These leaflets are dynamic documents and will be updated as new information becomes available. New leaflets about other chromosome disorders will be coming on stream all the time. To find out about the exacting process we adopted to produce these leaflets, please view our leaflet protocol descriptions.

We have produced two levels of information leaflet about many of the rare chromosomal disorders affecting our members (see the table below for the specific titles), including:

- A brief introduction in tri-fold format (Quick Read Version), suitable for families with a new or recent diagnosis and for couples with an unborn baby.
- A more detailed and descriptive leaflet that includes many references to families' individual experiences of having a child with a particular disorder. The longer leaflets are suitable for families who wish to know in greater detail how other people have been affected by a particular disorder and understand the often broad range of outcomes that are possible for their own child. The longer leaflets are available as:
 - A Web Version formatted for viewing online.
 - A Print Version formatted to be printed so it can be stapled together as a booklet.

Just click on the relevant title in the table below to download the Unique Information Leaflets on the disorders in which you are interested.

Whether you are a family or professional or a member of the general public, please help us to continue this work by being generous with your donations, fund raising or sponsorship. We receive no government funding and can only continue our work with your support. If you are a family affected by a rare chromosome disorder, please do join us and contribute to the collective knowledge so that we can continue to make our leaflets even more comprehensive.

Before downloading any of our leaflets, we ask you to please read and adhere to our [disclaimer and copyright notice](#).

Chromosome	Title	Web Version	Print Version	Quick Read	Other Versions
Chromosome 1					
1p Interstitial Deletions		Web Version	Print Version		
1p36 Deletion		Web Version	Print Version		

Inform Network Support

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Rare Chromosome Disorder Support Group
c/o The Children's Hospital, 18 West, 2000 Century Blvd
St. Louis, Missouri 63104
info@rarechromo.org | www.rarechromo.org

The Chromosome 18 Research & Registry Society
18q Deletions and Beyond
www.18q.org

18q deletions: from 18q21 and beyond

Looking at 18q
Chromosomes can be seen with the naked eye, but if they are stained and magnified under a microscope it is possible to see that each one has a distinctive pattern of light and dark bands. By looking at your child's chromosomes in this way, it is possible to see that your child's chromosome has broken and to see what material is missing.

In 18q, part of the long arm of chromosome 18 is missing. Most deletions of this arm are terminal. This means that the tip of the long arm is included in the deletion. Deletions of the long arm of chromosome 18 are missing, but the tip is still present.

In the diagram of chromosome 18 on the right the bands are numbered downwards starting from where the short and long arms meet (the centromere). A centromere at 11 in the long arm, is close to the centromere. Regions closer to the centromere are called proximal. A region further from the centromere is called distal.

Deletions of 18q include both interstitial and terminal deletions. In general, the breakpoints in terminal deletions occur in the distal region of the chromosome. In contrast, interstitial deletions tend to occur in the proximal region of the chromosome. The sites of these breaks can be on terminal deletions. These deletions typically have a breakpoint between 18q21.1 and the end of the chromosome and include the end of the chromosome. Proximal deletions of 18q are covered in a separate leaflet available from Clinique.

Your geneticist or genetic counsellor will be able to tell you about the position where chromosome 18 breaks in your child. We will discuss options for genetic testing for your child, which is different to that for your chromosome map.

www.rarechromo.org

How can 18q deletion affect a child's development and mobility?
The symptoms that a person has when they have a 18q deletion depend on the size of the deletion. The larger the deletion, the more symptoms a person will have. Missing some material means that some of the genes that code for proteins are missing.

Each child with 18q deletion will have their own set of symptoms. Some children have mild symptoms, some have moderate symptoms, some have severe symptoms. Some children have developmental delays, some have physical disabilities, some have learning difficulties, some have behavioural problems, some have speech and language difficulties, some have hearing loss, some have vision problems, some have epilepsy, some have heart problems, some have kidney problems, some have immune system problems, some have endocrine system problems, some have reproductive system problems, some have dental problems, some have hearing loss, some have vision problems, some have epilepsy, some have heart problems, some have kidney problems, some have immune system problems, some have endocrine system problems, some have reproductive system problems, some have dental problems.

Case 10: A 6.5 y old boy
prenatal diagnosis of multicystic dysplastic kidney, 46,XY
Early childhood: dev delay, autism

METHOD OF ANALYSIS:
Array SNP based analysis (Infinium CytoSNP-850Kv1.1 BeadChip, Illumina) for patient

CYTOGENETIC AND/OR MOLECULAR DIAGNOSIS:
[arr\[hg19\] 17q12\(34,466,631-36,307,189\)x1](#)

Chromosome band: 17q12
Deleted region – genomic location (hg19): 34,466,631-36,307,189
Size (bp): 1,840,559
Number of SNP/markers within deleted region: 551
Normal flanking loci – genomic location: 34,465,375-36,450,598

Inform Network Support

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Rare Chromosome Disorder Support Group
c/o The Children's Hospital, 18 West, 2000 Century Blvd
St. Louis, Missouri 63104
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17q12 microdeletions

www.rarechromo.org

Case 10: A 6.5 y old boy prenatal diagnosis of multicystic dysplastic kidney, 46,XY Early childhood: dev delay, autism

NARRATIVE SUMMARY:

SNP array analysis showed a 1.84 Mb interstitial deletion on the long arm of chromosome 17 within band 17q12 from nucleotide 34,466,631-36,307,189, encompassing 2 OMIM genes that are known to be frequently deleted in chromosome 17q12 microdeletion syndrome. These genes are *HNF1B* (OMIM*189907) and *LHX1* (OMIM*601999).

Chromosome 17q12 microdeletion syndrome (OMIM*614527) is characterized by variable combinations of the three following findings: structural or functional abnormalities of the kidney and urinary tract (80% of affected individuals), maturity-onset diabetes of the young type 5 (MODY5) (40%), and neurodevelopmental or neuropsychiatric disorders e.g., global developmental delay, intellectual disability, autism spectrum disorder, schizophrenia, anxiety, and bipolar disorder (50%).

This recurrent deletion has high penetrance, with about 70% occurring *de novo* and 30% inherited from an affected parent who may have variable expressivity. Therefore, clinical correlation and genetic counseling are suggested. If indicated, parental array study is also recommended.

For more information, please refer to <https://ghr.nlm.nih.gov/condition/17q12-deletion-syndrome> and <https://www.ncbi.nlm.nih.gov/books/NBK401562/>.

CLINICAL INTERPRETATION:
17q12 microdeletion syndrome

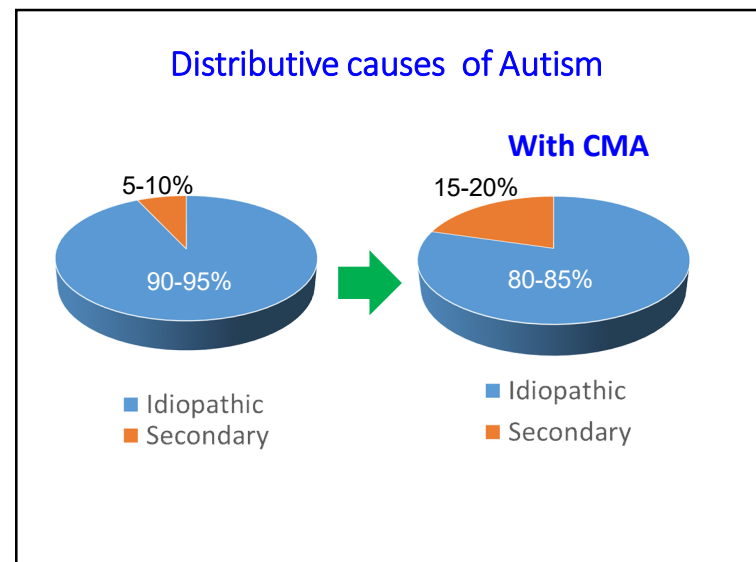
- Structural or functional defect of KUB system 80%
- ID, ASD, schizophrenia, bipolar 50%
- Maturity onset of diabetes of the young 40%

Advantages of CMA

- Identify small deletion/duplication of chromosomal segment
- Identify gain/loss of genetic material in **individual with physical/cognitive impairment but with apparently balanced translocation - actually unbalanced rearrangement**
 - 20% of individuals with apparently balanced translocation (de novo or familial) have loss/gain of genetic material
- Accurate information on microdeletion of **tumor susceptibility gene** in the deleted segment
- May **identify genes** that are disrupted by breakpoint

Benefits of CMA to Patients

- Avoid other unnecessary investigations
- Patient
 - Precise patient care & complication surveillance
- Family
 - Precise genetic counseling
 - Recurrence risk estimation
 - Prevention & PND



Advantage of Whole Exome Sequencing (WES) in ASD

- Detect smaller deletion & duplications not identified by microarray in **7% of ASD cases**
- Single nucleotide variants (SNV) & very small deletion & duplication of individual gene
- Trio data using NGS

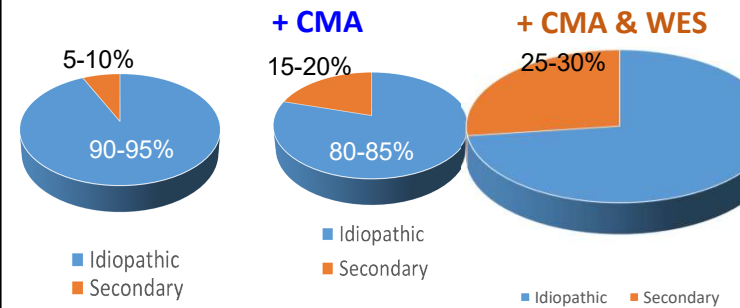
NGS	germline SNV mutation rate*	# de novo SNVs
WGS	1.1-1.2x10 ⁻⁸	70
WES	1.3-2.17x10 ⁻⁸	0.6-1.3

Most de novo SNVs, CNV, small indels – paternal origin

*per position per generation

Rubies SD and Buxbaum JD, 2015
Loke YJ et al, 2015

Distributive causes of Autism



Rubies SD and Buxbaum JD, 2015
Loke YJ et al, 2015

Reminders

Disorder	Karyotype	CMA	Other test
Down	√		
Cri du chat	√		
Unexplained DD/MR w/wo malformation	√	√**	
MCA or Autism	√	√**	?? future: WES
FXS			FMR1**Methylation PCR PCR-Southern
Angelman	FISH 75%	√ 80% (75%del +5% if using SNP array)	SNRPN-methylation PCR (80%)** FISH 75%
Prader-Willi	FISH 75%	√ 75% del	SNRPN-methylation PCR (99%)** FISH 75%
Rett			DNA sequencing**
Williams/ VCFS	FISH		

Take Home Message

When to order CMA 'If affordable'

- Multiple anomalies not specific to well-delineated genetic syndrome
- Non-syndromic developmental/intellectual disability
- Autism spectrum disorders (ASD)

When not to order CMA

- Suspected specific common aneuploidy / microdeletion syndrome

Limitation of CMA

- Clinical interpretation of VUS
- does not include FXS
- partially include PWS, Angelman

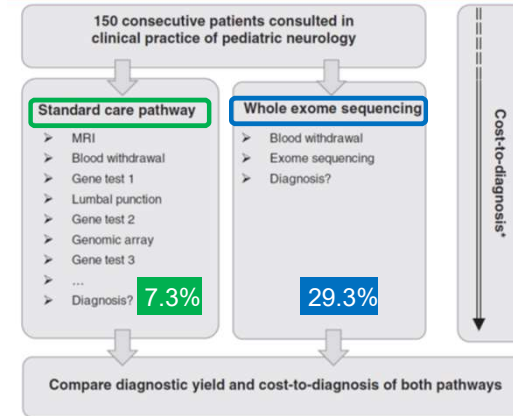
NGS

Pretest counseling is **IMPORTANT**

Use of Clinical WES in Pediatric Practice

- Yang Y et al, (NEJM 2013;369:1502-11)
Diagnostic yield 25-30% for undiagnosed disorder

A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology



Vissers LELM, et al. Gene Med 2017

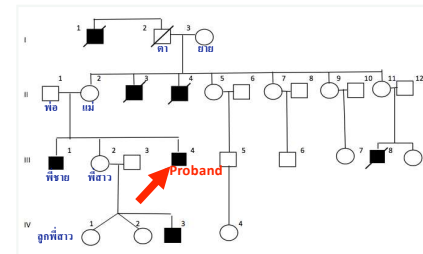
Unknown diagnosis case 1

- Girl 1y2m
- **Acute Liver failure** **Reye syndrome?**
- **Bicytopenia**
- Failure to thrive since 9m
- Minor dysmorphic features
- **UOA, PAA, eye exam, acylcarnitine: NL**
- Liver bx: mixed micro-macrovesicular fatty change

NBAS mutations → infantile liver failure, short stature, and atypical osteogenesis imperfecta.

Unknown diagnosis case 2

- Familial intellectual disability
- CT brain: Dandy-Walker syndrome



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