

Module 1: Autism Spectrum Disorder: The Genetics Evaluation

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EXCEPTIONAL CARE. WITHOUT EXCEPTION.



Objectives

- Become familiar with certain syndromes in which autism spectrum disorders are more common
- Know which genetic tests are most useful when considering the etiology of autism spectrum disorders
- Understand that genetic diagnoses can help physicians, families, and schools understand and help people with certain disorders

Think Broad to Specific

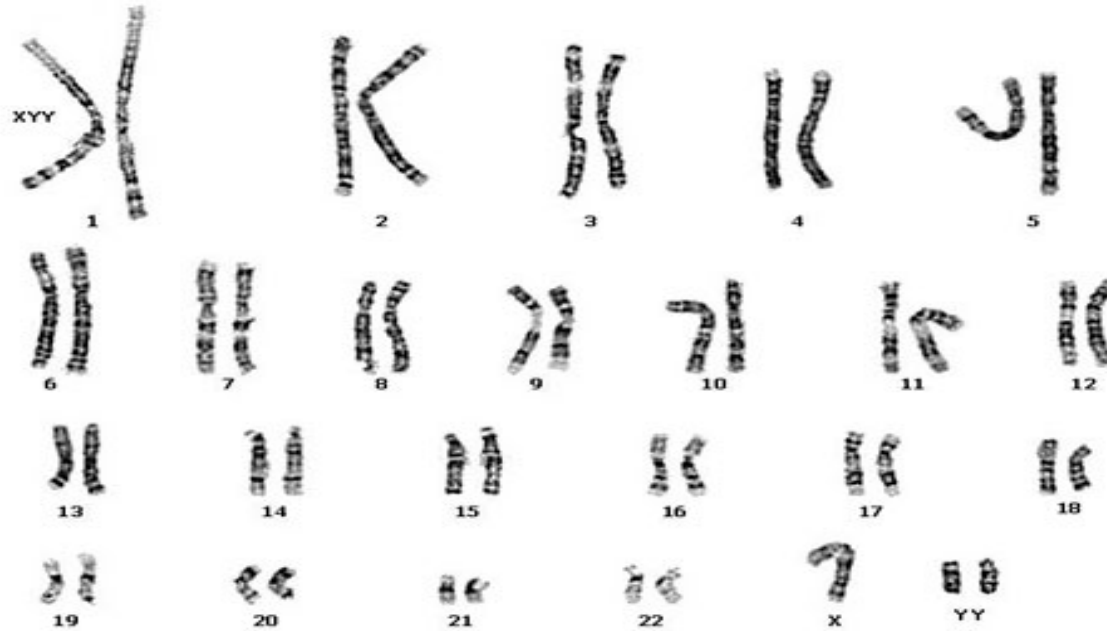
- Is it genetic?
 - We only find a genetic basis of autism in 10-15% of cases
- Chromosomal?
- Microdeletion/Microduplication?
- Methylation disorder?
- Single gene disorder?

Down syndrome

- Trisomy 21
 - About 1/780 live births
- Well known syndrome with distinctive features and physical characteristic
- Intellectual disability; variable degree
- Autism spectrum disorder in ~5-7 %



siadownsyndrome.net



- 1/1000 males
- 7cm taller than average – post-natal onset
 - Weight in lower percentile than height
- Prominent glabella, long ears
- Normal genitalia
 - May have delayed puberty
 - May have “immature sperm”, but are fertile
- Severe acne of adolescence

XYY Syndrome

- Development and Behavior
 - IQ in normal range, but lower than sibs
 - Speech delay, communication disorders and learning disabilities
 - Social impairment, withdrawal
 - Temper tantrums
 - Negativistic, disruptive
 - Myth of XYY as criminals
 - 3/1000 psychiatric patients vs. 1/1000 prevalence
 - **Increased risk of autism reported**
 - 2003 study showed 4x risk of general population
 - 2011 showed 10-20X risk of general population



<http://drvitelli.typepad.com/>

Turner Syndrome

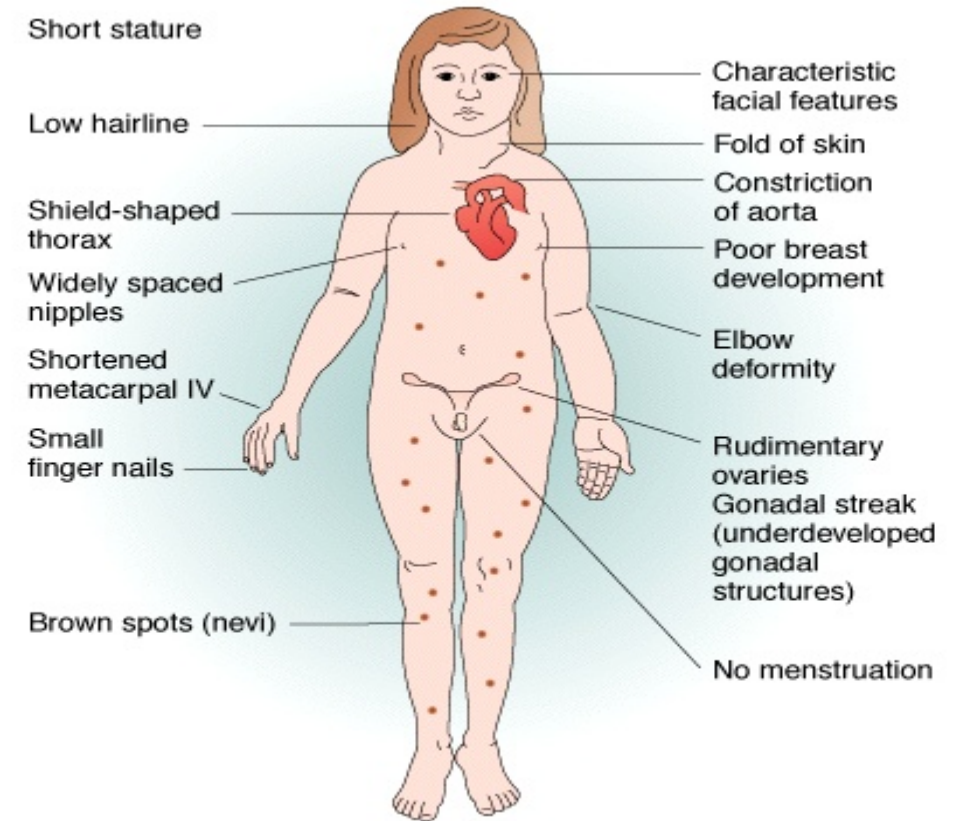
- 1/2000 live births
- Prenatal increased nuchal translucency, cystic hygroma; post-natal webbed neck
- Some present in adolescence with lack of puberty
- Aortic coarctation
- Short stature
- Streak gonads
- Due to loss of one X chromosome
 - Mosaicism tends to results in more mild presentation



assets.macthbin.com

Turner Syndrome

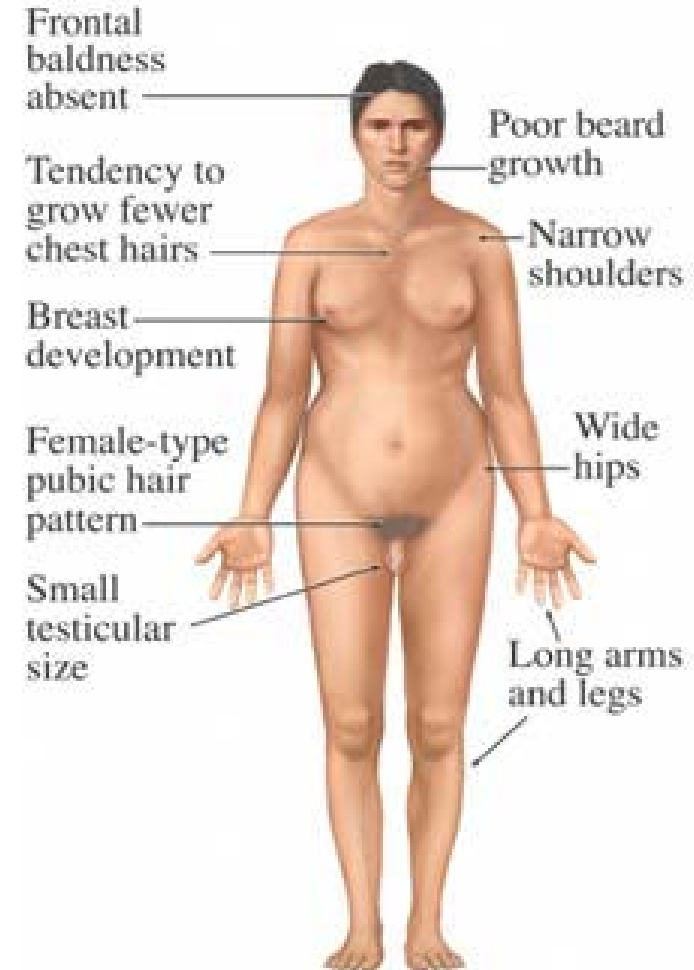
- Normal verbal intelligence
- Non-verbal challenges in social reciprocity and communication
 - Poor visuospatial memory
 - Difficulty with math
 - Issues with facial recognition
 - Difficulty reading others' emotions
- Autism spectrum disorder seen in > 25%



figcox.miami.edu

Klinefelter Syndrome (XXY)

- Extra X chromosome
- Affects 1 in 1000 males- underdiagnosed



Klinefelter Syndrome (XXY)

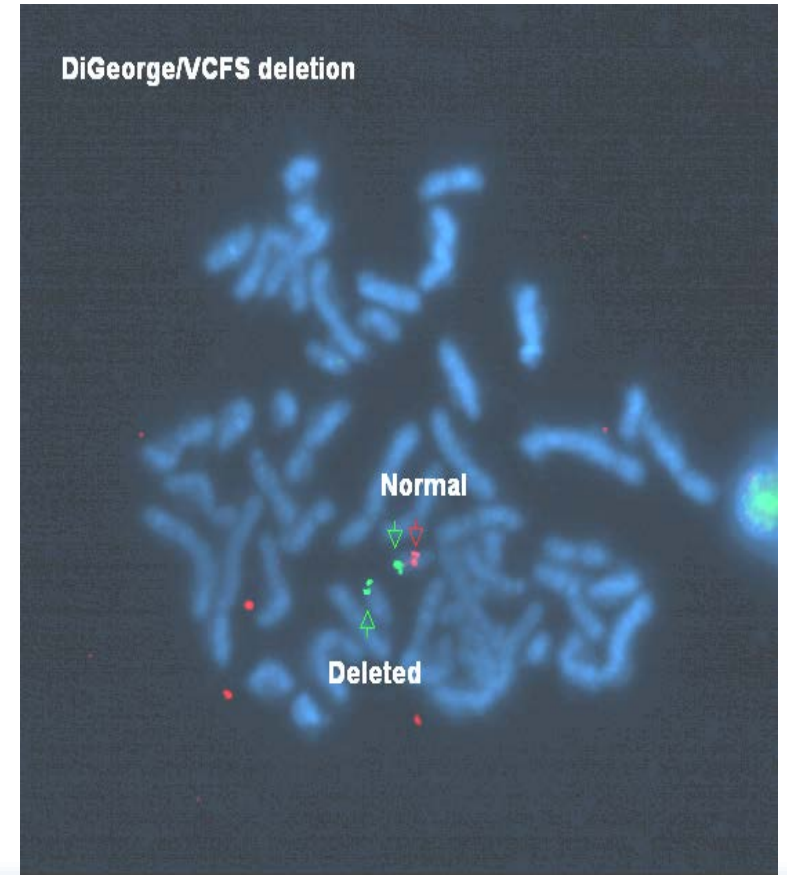
- Full scale IQ average 85 with wide range
 - Verbal deficits common
 - Overlap with symptoms of ASD
- Challenges
 - social cognition
 - expressive language
 - auditory processing and memory
 - reading and spelling
 - poor coordination skills, motor delay
- Immaturity, insecurity, shyness
- Psychosocial adjustment problems
 - poor judgment, poor impulse control
 - unrealistic boastful and assertive activity
 - outbursts with frustration
- Psychiatric diagnoses are rare
 - Early-onset schizophrenia/affective disorder
 - ADD



www.mf.uni-lj.si/acta-apa

22q11.2 deletion syndrome

- Also previously known as CATCH 22
 - Velocardiofacial / Shprintzen syndrome (VCFS)
 - DiGeorge Syndrome
 - 22q11 deletion syndrome (preferred)
- Autosomal dominant
 - Majority sporadic (87%)
 - Adult cases often identified from pediatric case
- Frequency of 1 in 2500-3000
 - 5-10% with classical autism
 - Up to 25% with some findings of autism



22q11.2 deletion syndrome

- Common issues
 - Pierre Robin sequence
 - Velopharyngeal insufficiency
 - Conductive hearing loss
 - Immune dysfunction-thymic hypoplasia
 - Cardiovascular malformations
 - Nasal GI reflux, severe constipation
 - Renal malformations
- Subtle dysmorphic features
 - Microcephaly, long face
 - Small palpebral fissures
 - Squared ears
 - Bulbous nasal tip, tubular nose, square root
 - Small mouth



www.ucdmc.ucdavis.edu

22q11.2 deletion syndrome

- Gross and fine motor delays
- Hypernasal speech with delays
- IQ usually 70-90
- Perseverative behavior
- Concrete thinking
- Good verbal and auditory skills
- Poor visual-spatial and executive function
- Psychiatric involvement-25%
 - Rapidly alternating bipolar disorder
 - Chronic schizophrenia with paranoid delusions
 - COMT gene and PRODH gene (Hyperprolinemia)
 - Anxiety, ADHD
 - Autism – 5-10% meet criteria, 25% with some features



www.specialchild.com

16p11.2

- Microdeletions -3/10,000 prevalence
 - found in 1% of people with ASD
 - speech and language delays
 - very minor unusual facial or physical features
 - hypotonia
 - tendency to overweight
 - Seizures (rare)
- Microduplications -1/10,000 prevalence
 - speech and language delays
 - very minor unusual facial or physical features
 - tendency to underweight
 - Seizures (rare)
 - Increased likelihood of difficult behavior/mental health issues
- Both contain KCTD13, thought to be associated with ASD



Rarechromo.org

15q13.3 microdeletion

- 1 in 30-40,000
 - Generally no obvious birth defects
 - Learning disability
 - Seizures or abnormal results on EEG
 - Autistic spectrum disorder
 - Behavioral difficulties such as aggressive behavior and rage
 - ADHD
 - Subtly unusual facial features
 - Contains CHRNA7
-
- Other microdeletion/microduplication syndromes are also associated with ASD

Fragile X Syndrome



www.fragilex.org

- Most common genetic cause of ID
 - 1 in 4000 boys
- Long face, large ears
- Macro-orchidism after puberty
- X-linked CGG trinucleotide repeat expansion
 - Occurs in maternal meiosis
- 30-50% with autism spectrum disorder
 - 2% of ASD caused by Fragile X

Fragile X Syndrome

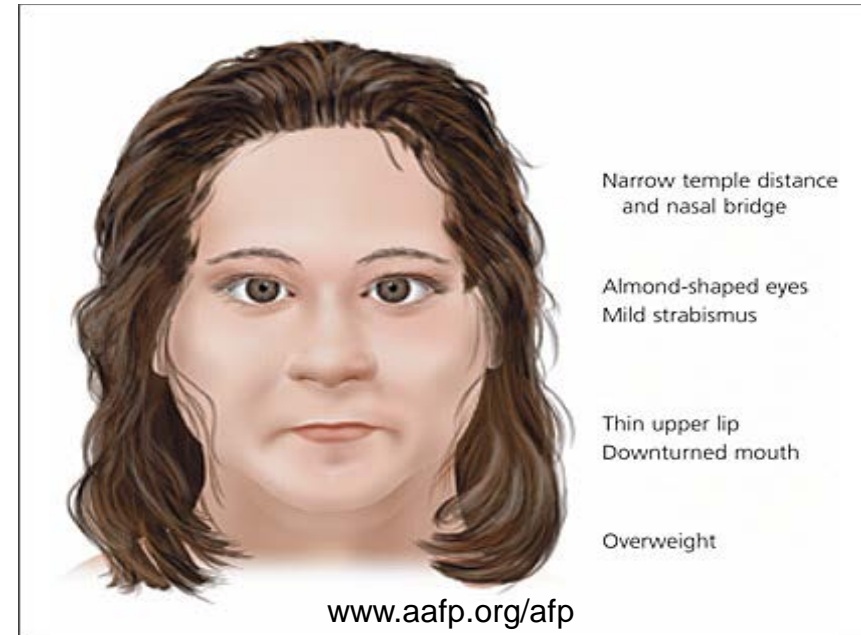
- Mild dysmorphic features
 - Long face, prominent forehead and chin
 - Striking blue eyes with mild down-slant
 - Prominent, large ears
- Other physical findings
 - large growth parameters
 - Post-pubertal macro-orchidism
 - Connective tissue involvement-hypermobility joints, MVP, Aortic dilatation
- Prader-Willi subphenotype
 - Excessive weight gain
 - Small, broad hands
 - No infantile failure to thrive



152.16.198.53/GeneticsModules/Design/images/fragileX

Prader-Willi syndrome

- Etiology- absence of paternal SNRPN (15q11-13)
- Prevalence- 1 in 10-25,000
- Infancy-
 - Severe hypotonia
 - Failure to thrive, poor suck
 - Often require tube feedings
 - No vomiting
- Early childhood (6mos-6y)
 - Severe weight gain –lower abdomen, buttocks and thighs



Prader-Willi Syndrome

- Development
 - Global delays
 - Intellectual disability- mild in 63%, moderate in 31%
 - Speech articulation problem
- Behavior
 - Compulsive eating, lack of satiety
 - Oppositional behavior, Stealing
 - Stubbornness, tantrums, rage
 - Unusual skill with jigsaw puzzles
 - Picks sores (decreased pain sensitivity)
- Psychiatric
 - Obsessive compulsive disorder, Anxiety
 - Psychotic features (cycloid and affective psychosis)
 - Autistic spectrum in ~18% (38% with mUPD) (vs. 2% in Angelman syndrome)



Fig 1. Patient at the age of 6 years and 4 months. (photo published with parents consent).

www.scielo.br/img/fbpe/anp

Single Gene Disorders

- Syndromic examples:
 - **Neurofibromatosis type 1 (NF1)** –café au lait spots, freckling, neurofibromas, optic gliomas, ADHD, learning disability, autism
 - **Tuberous sclerosis complex (TSC1 and 2)** –seizures, brain tubers, cutaneous findings, ID, autism
 - **Creatine Transport Deficiency (SLC6A8)**-one study reports 2.1% of males with XL ID and autism
 - Seizures, dysmorphic features, myopathy
 - **Rett syndrome (MECP2)**-
 - Classically -females with progressive microcephaly, regression, hand-wringing, unsteady gait, seizures, ASD
 - Less typically –males and females with decreased communication and social interactions

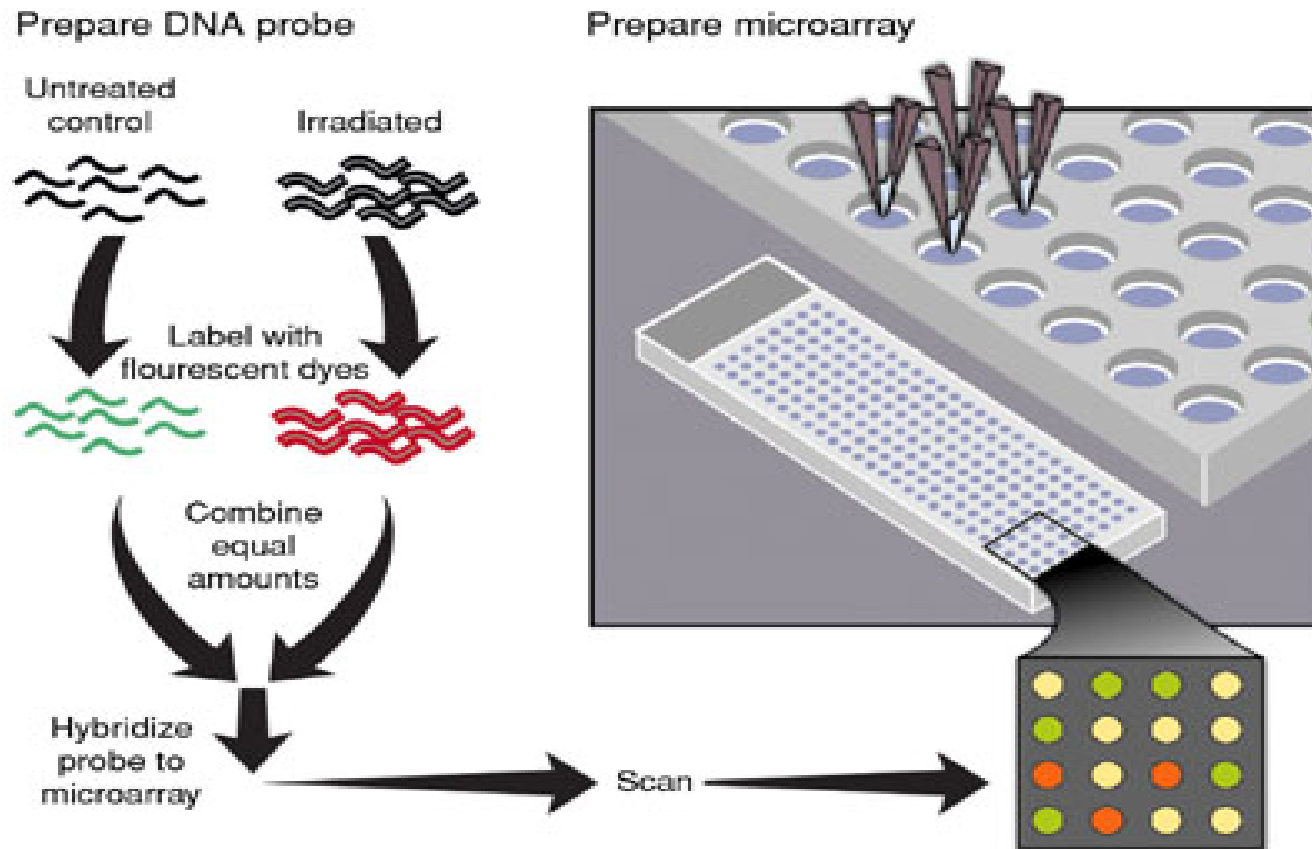
Single Gene Disorders

- Non-syndromic AUTS1 through AUTX
 - many regions mapped that are associated with autism
- Examples
 - CNTNAP2, SLC9A9, SHANK2, PTCHD1, TMLHE
 - NLGN3 and NLGN4- rare cause of ID and autism, few families
- Large Nextgen sequencing panels are offered by several labs
 - Diagnosis can be meaningful for family and reproductive risk
 - Insurance coverage is rare due to lack of current medical utility
 - Due to large number of genes on such panels, many are found to have variants of uncertain significance

What tests might be relevant?

- Chromosomal microarray
 - Counts chromosomes AND detects small deletions/duplications
- Trinucleotide repeat analysis
 - Useful for conditions like Fragile X due to repeat expansion
- Methylation studies
 - Useful for Prader Willi/Angelman syndromes
- Single gene sequencing with del/dup
 - Useful for conditions due to isolated DNA mutations such as NF1, TSC, SHANK, etc.

Chip technology



www.llnl.gov

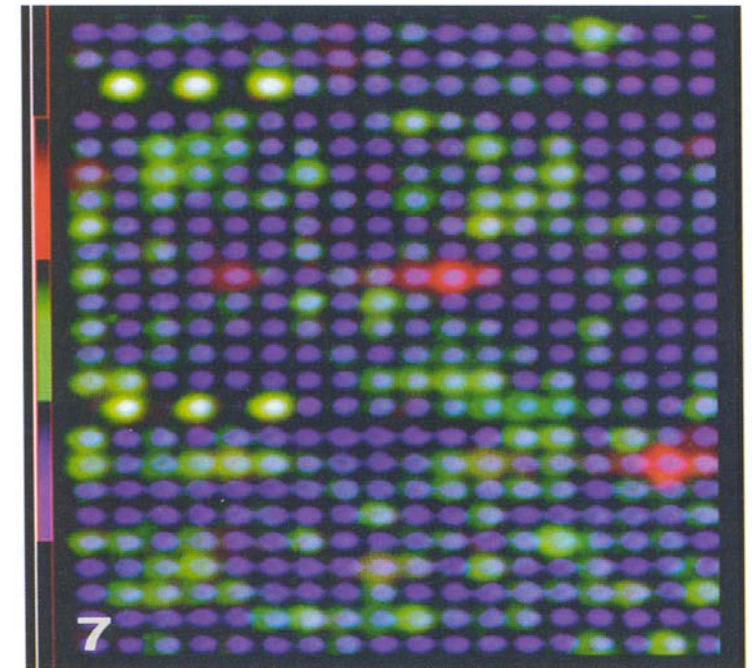
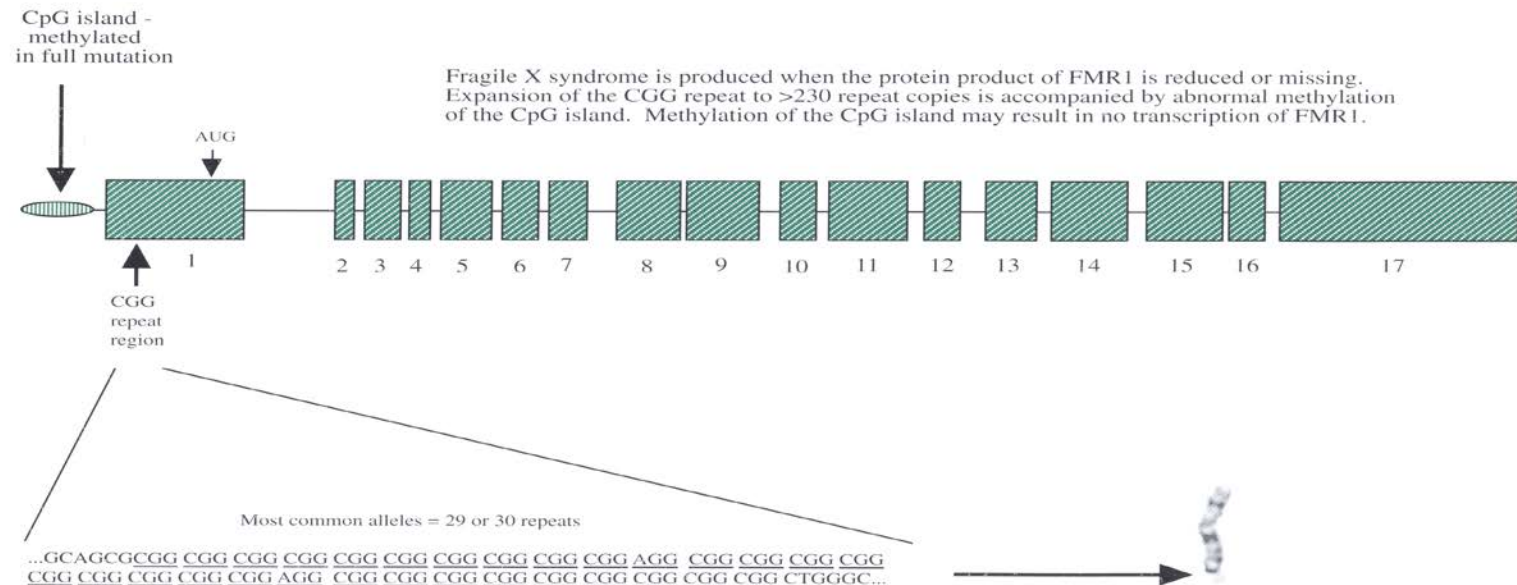


Fig. 7. Partial image of microarray hybridization on Human Gene Filter Release 1 (Research Genetics). Blue color is used to show the location of the cDNA spots on the filter. Yellow spots indicate genes that show balanced expression between tumor and reference. Spots with increased green intensities indicate overexpressed tumor genes, while increased red intensities indicate underexpressed tumor genes (photo courtesy of S. Knuutila).

From: Nath and Johnson, *Biotechnology and Histochemistry* 2000; 75: 54-78.

Southern Blots: Expansion of tandem repeats

GENE ORGANIZATION OF FMR1, THE GENE RESPONSIBLE FOR FRAGILE X SYNDROME

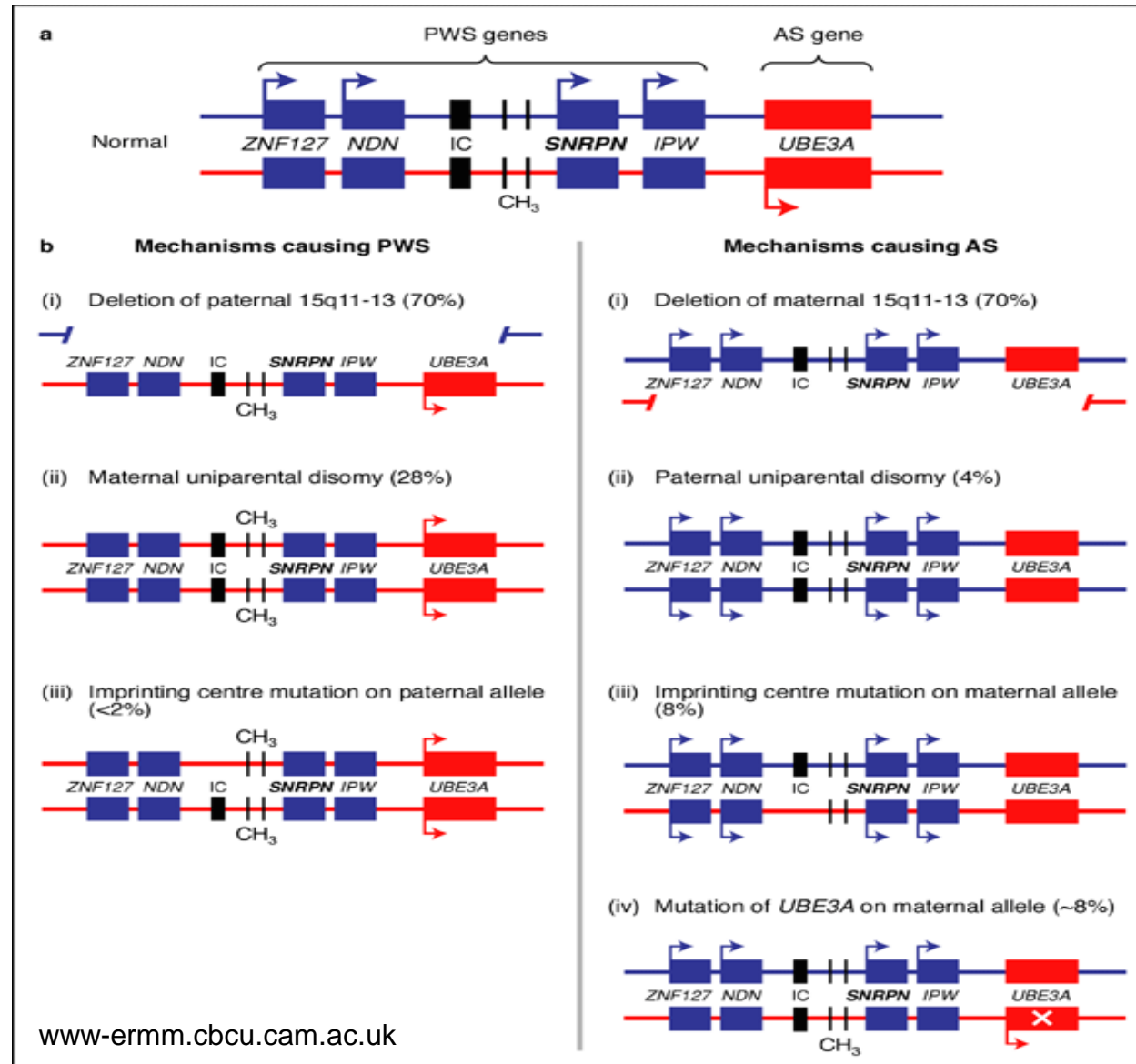


www.ikm.jmu.edu

From: Counseling Aids for Geneticists, 2nd edition

Paternal copy

Maternal copy



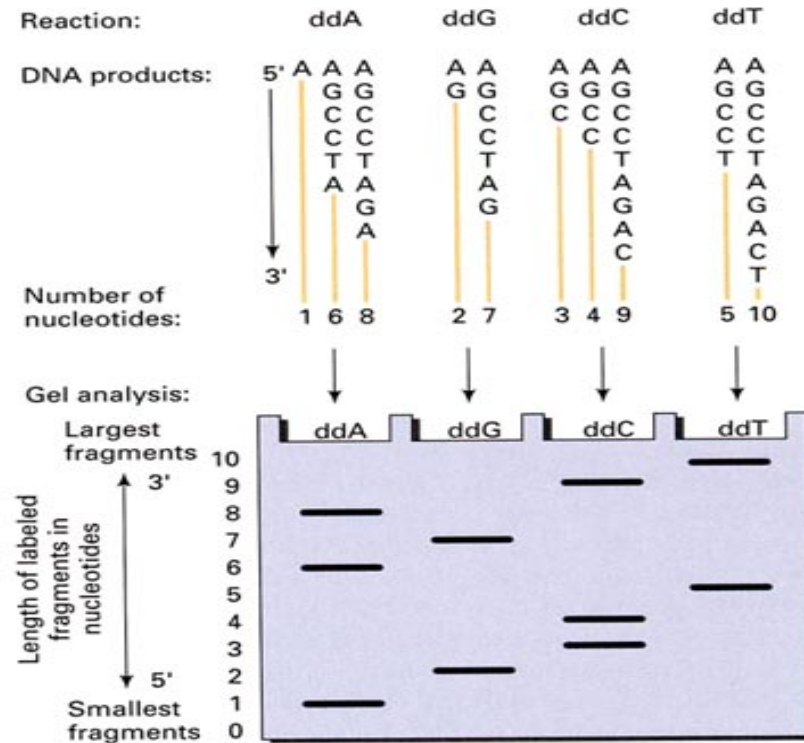
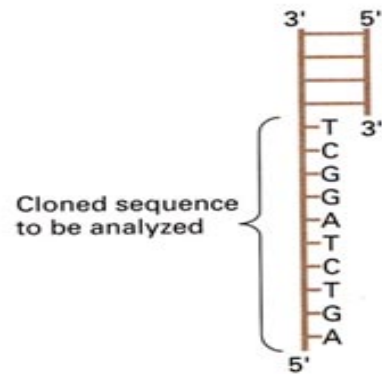
www-ermm.cbcu.cam.ac.uk

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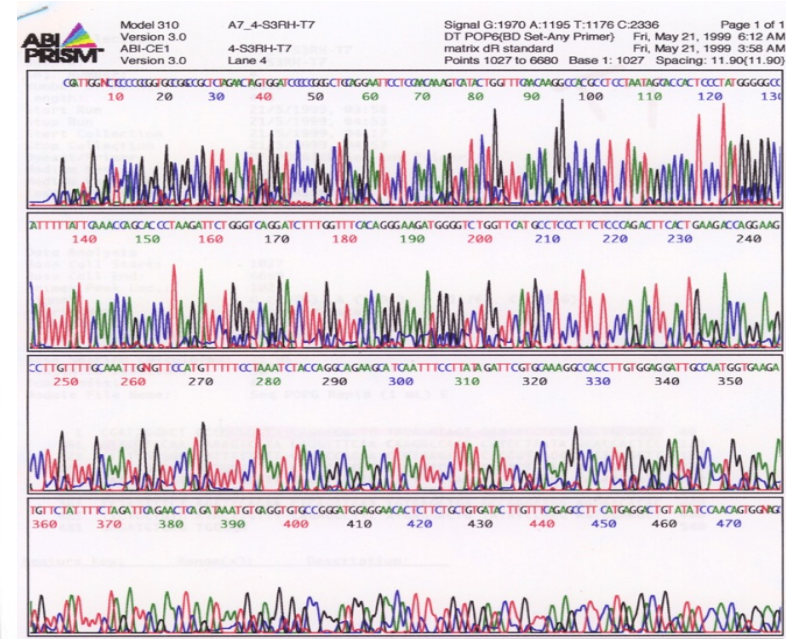
BOSTON
UNIVERSITY

Direct Sequencing



Sequence deduced from banding pattern of autoradiogram made from gel:

5' A-G-C-C-T-A-G-A-C-T 3'



www.genelink.com

www.dakotacom.net

Summary

- Usual combination of physical and medical issues?
 - Differences in growth and development?
 - Family history of autism or intellectual disability?
 - THINK GENETICS!
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- References:
 - Schaefer GB and Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2008, 10(4): 301–305.
 - Marco EI and Skuse DH. Autism-lessons from the X chromosome. SCAN 2006 I, 183-193.