MEDICAL ISSUES IN ADULTHOOD OF SELECTED GENETIC DISORDERS

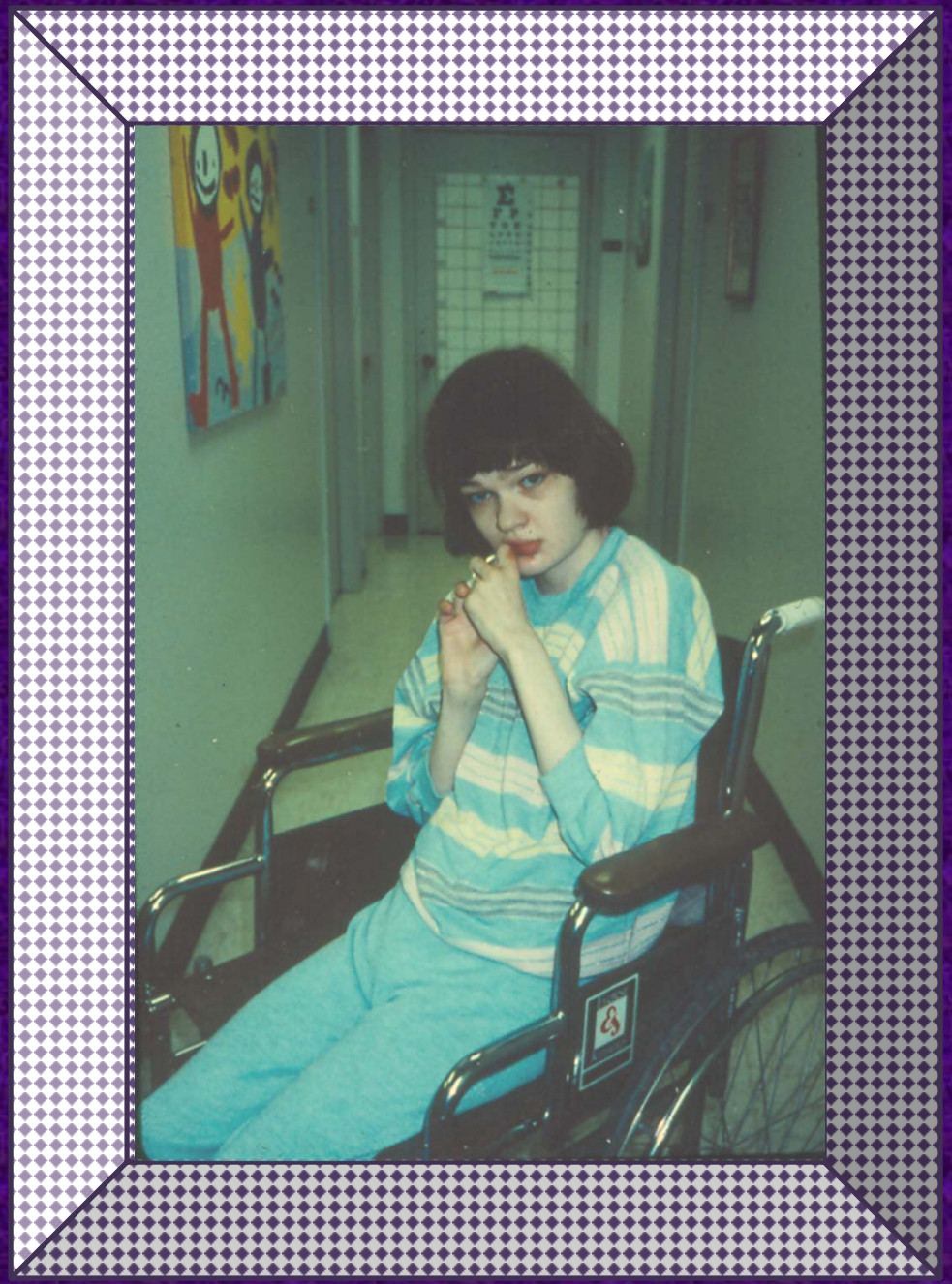
Joseph H. Hersh, M.D.

November 14, 2015

A 3 year old female acquired normal developmental milestones for the first 12 months of life. Subsequently, previous developmental milestones were lost, she no longer had speech and there was no functional hand use. Seizures developed at 2 years of age. She was found to have a MECP2 mutation.

Rett Syndrome

- ◊ Gradual or sudden loss of speech and hand function, loss of acquired gross motor skills and the development of stereotypic hand movements starting between 6 and 18 months of age
- ◊ Females are mostly affected with an incidence of 1:9000
- ◊ Secondary to mutations in MECP2



Long term outcome in Rett syndrome

- Survival:
  77.6% at 20 years
  71.5% at 25 years
  59.8% at 37 years
- Majority of adults living in the parental home and the remainder in group homes or residential settings
- Common medical problems included scoliosis, seizures, constipation, gall bladder disease, sleep disturbance, mental health problems, urinary tract infections and respiratory illness
- Independent walking in about 20% or with assistance in about 40% of cases

Phenylketonuria (PKU)

- ◊ Disorder of amino acid metabolism
- ◊ Effective dietary treatment restricting phenylalanine intake
- ◊ Risk for microcephaly, congenital heart disease and intellectual disability in offspring of affected women not on dietary restrictions

Medical Issues In Adulthood Of Selected Genetic Disorders

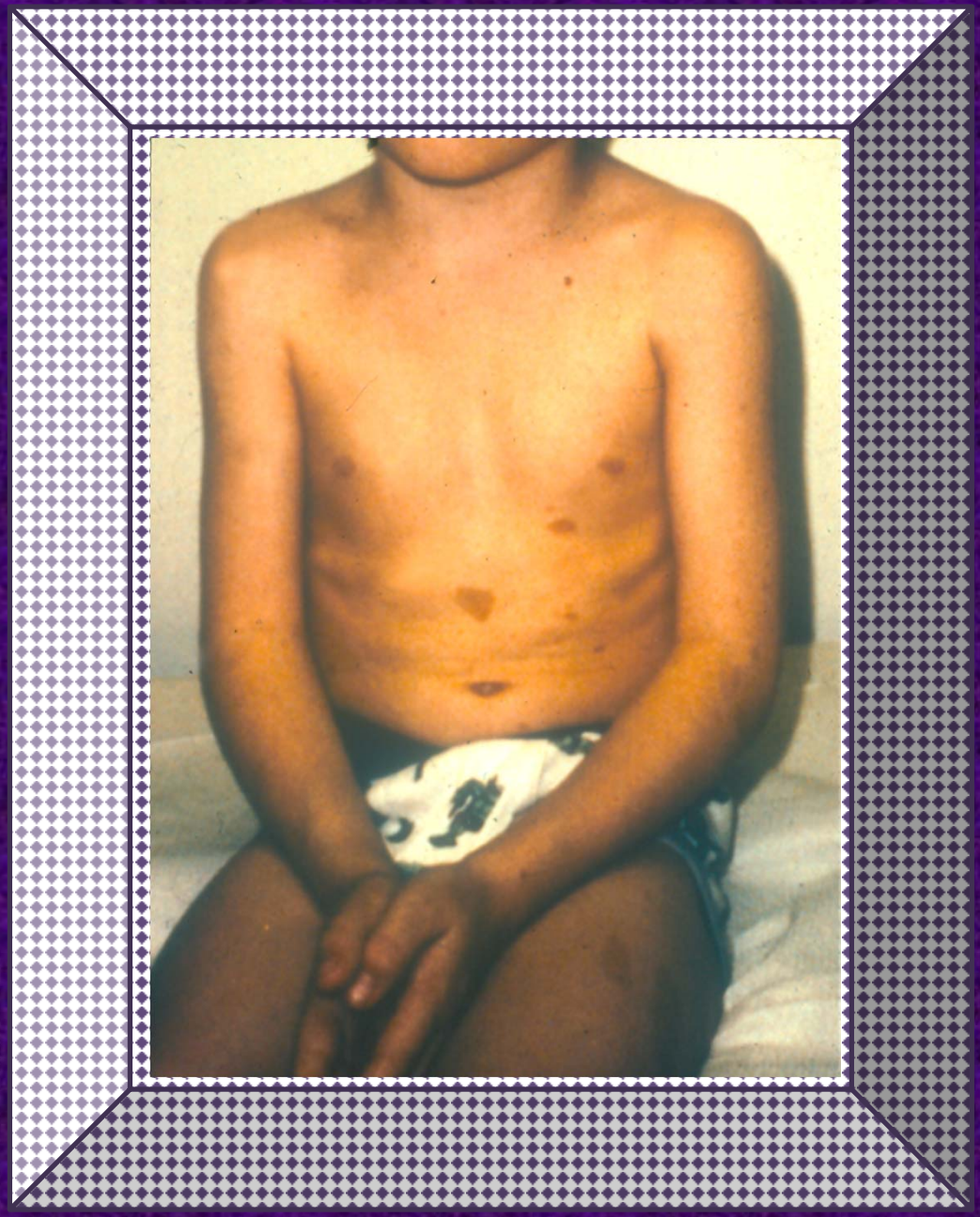
- Neurofibromatosis 1
- Down syndrome
- Fragile X syndrome

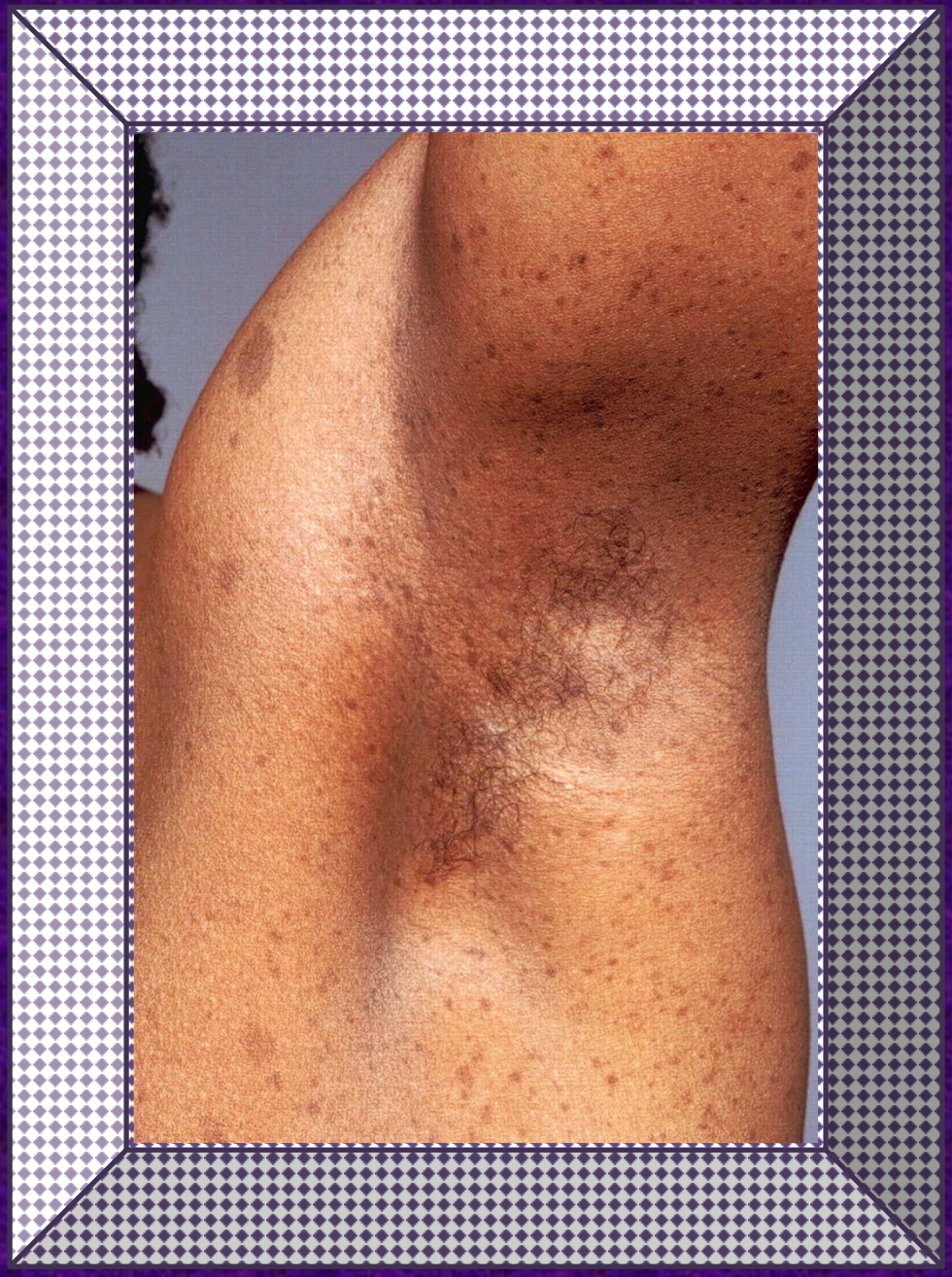
Establishing A Clinical Diagnosis Of Neurofibromatosis (Two Or More Of The Following Features)

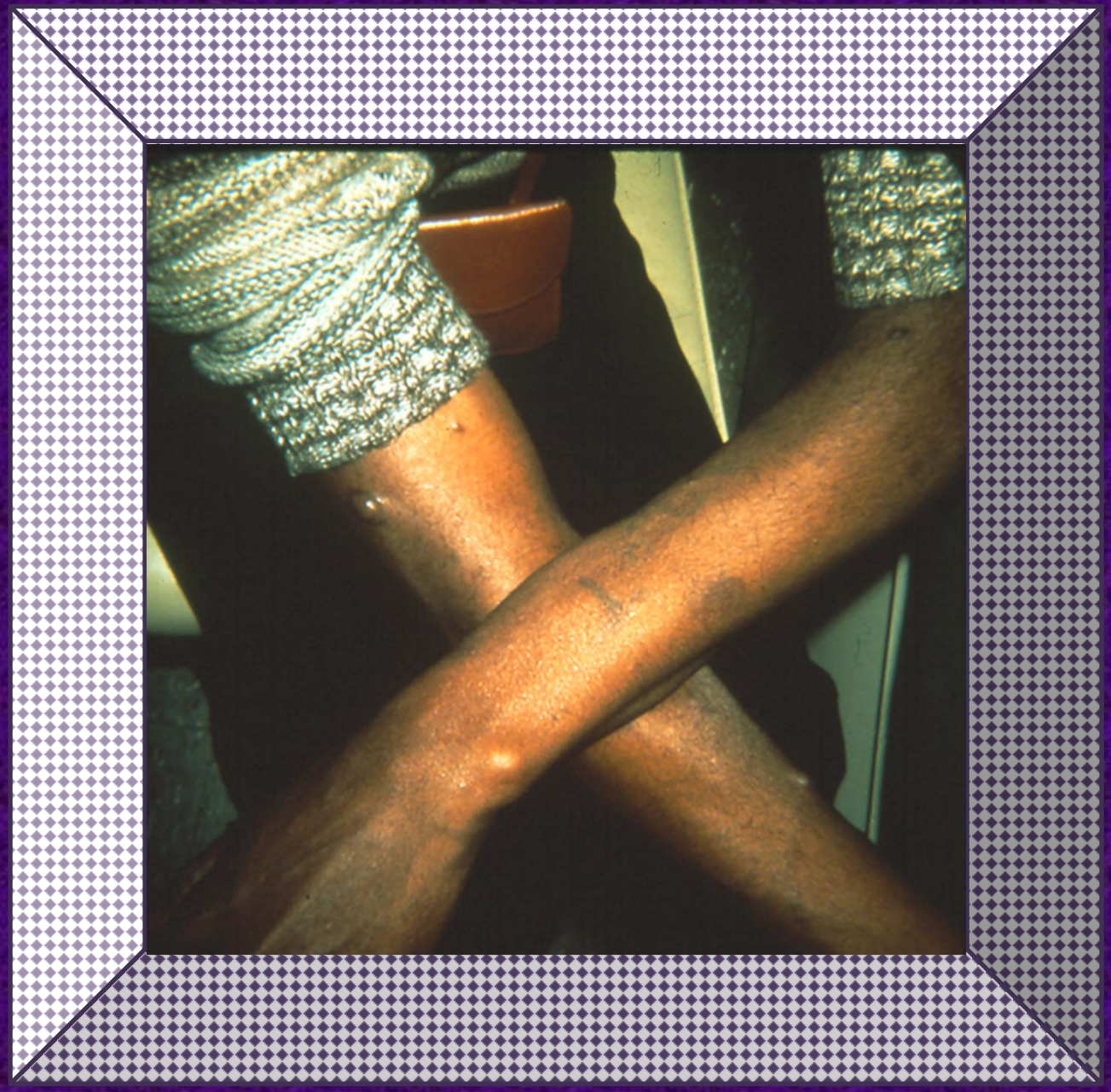
- ◊ Six or more café-au-lait spots over 5 mm. in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals
- ◊ Two or more neurofibromas of any type or one plexiform neurofibroma
- ◊ Freckling in the axillary or inguinal regions
- ◊ Optic glioma
- ◊ Two or more lisch nodules (iris hamartomas)
- ◊ Distinct osseous lesion such as sphenoid dysplasia or tibial pseudoarthrosis
- ◊ A first degree relative with NF1 (parent, sibling, offspring)

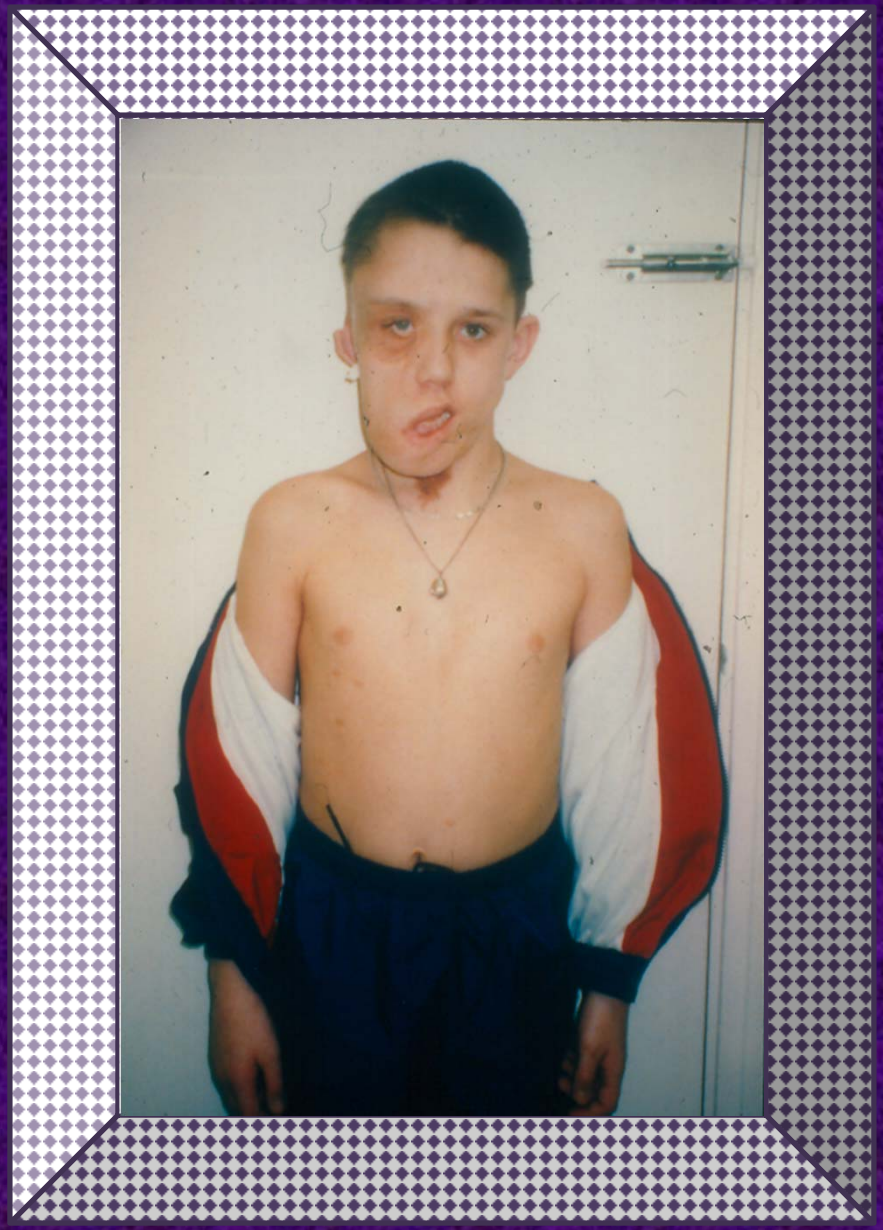
Neurofibromatosis 1 (NF1)

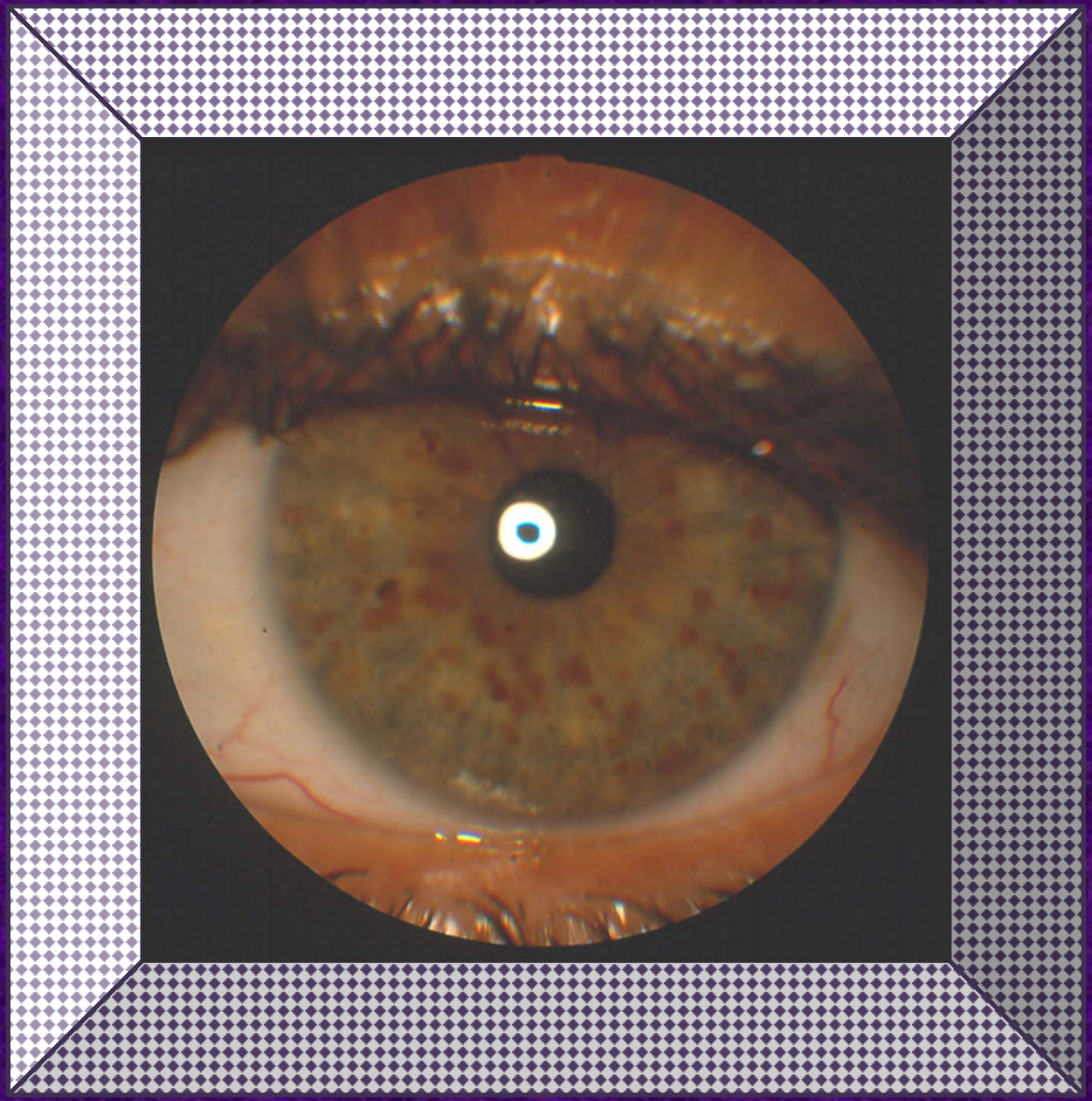
- Autosomal dominant
- 1:2700 Birth Incidence
- 50% of cases de novo

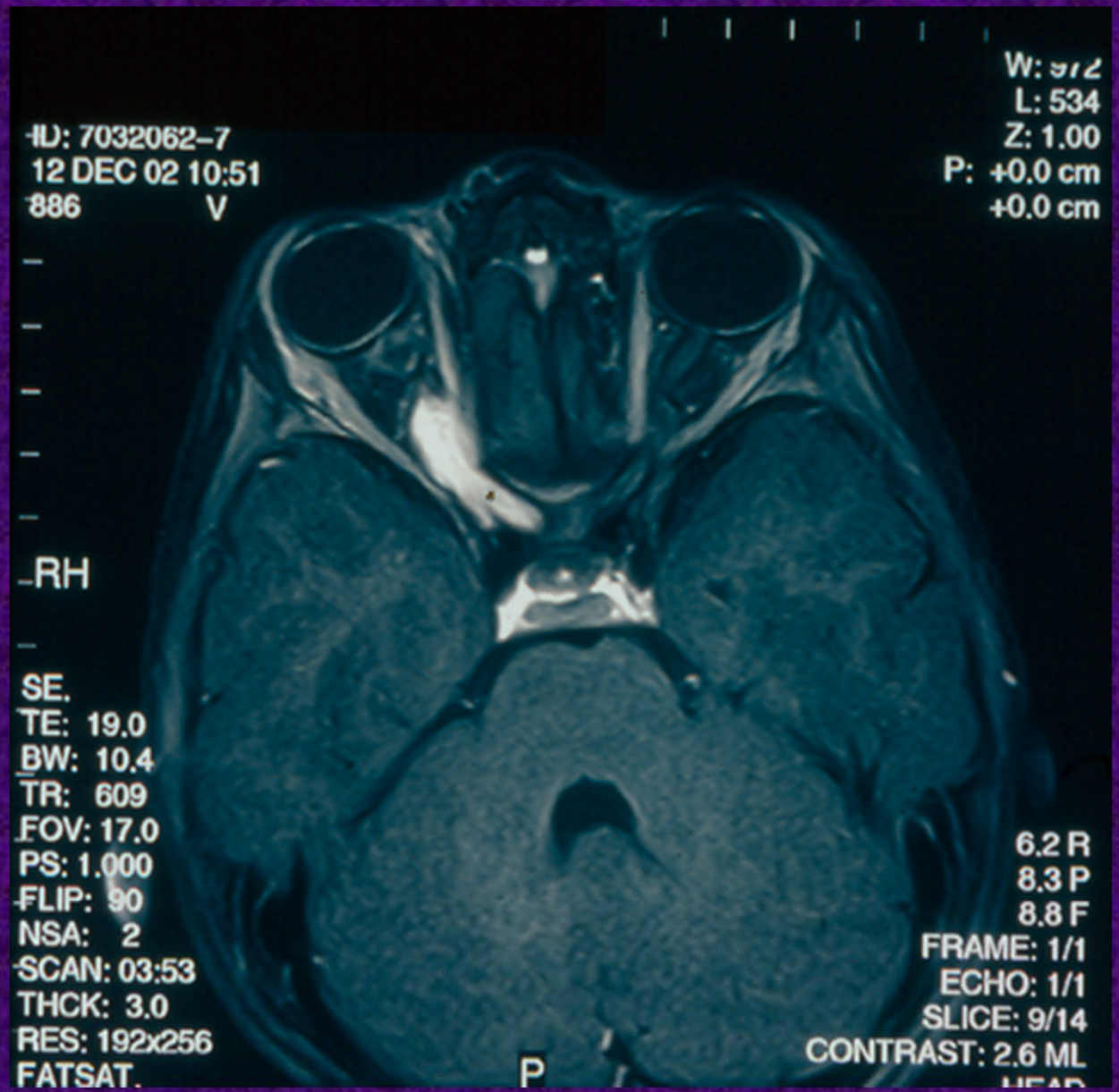


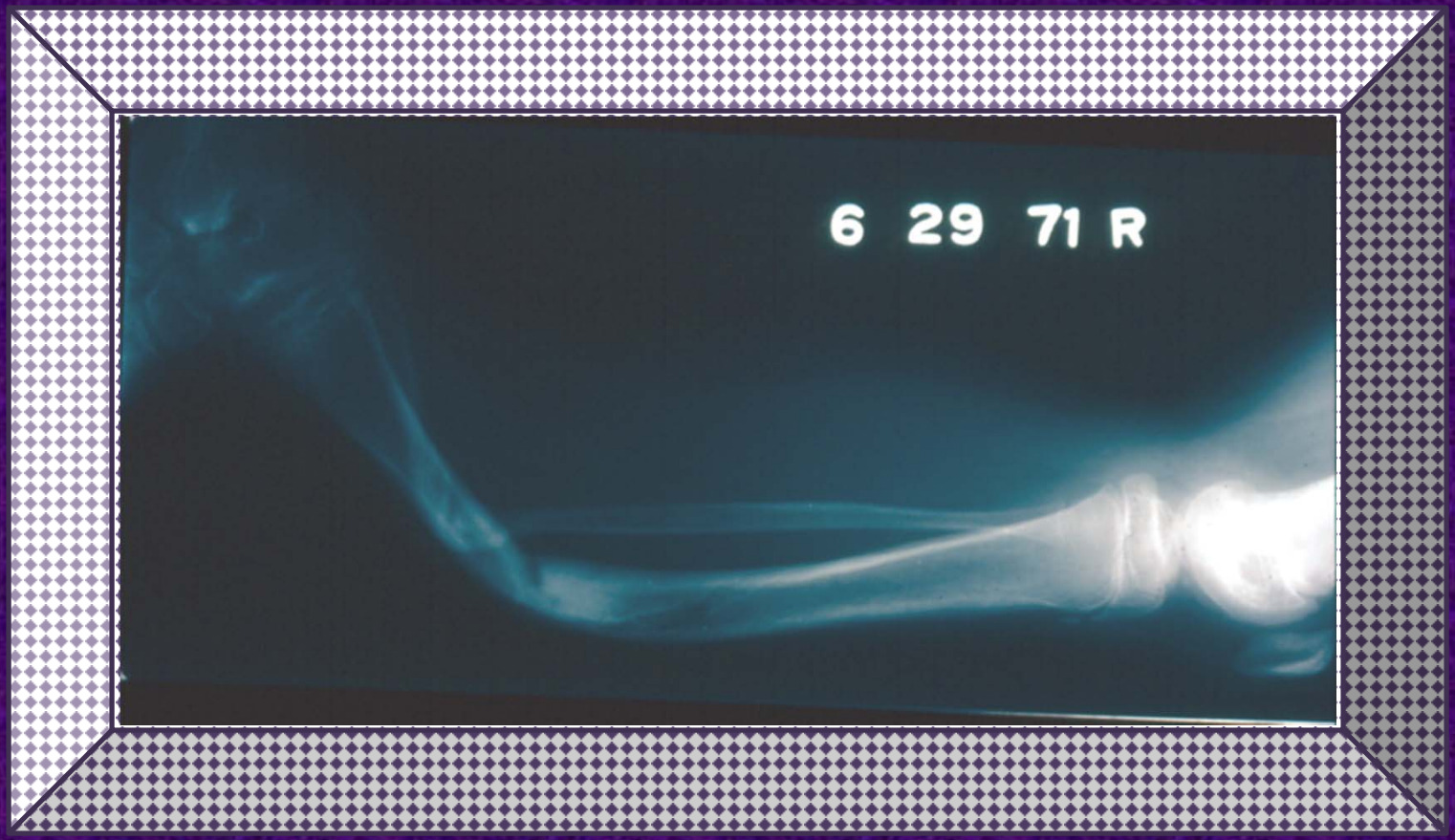


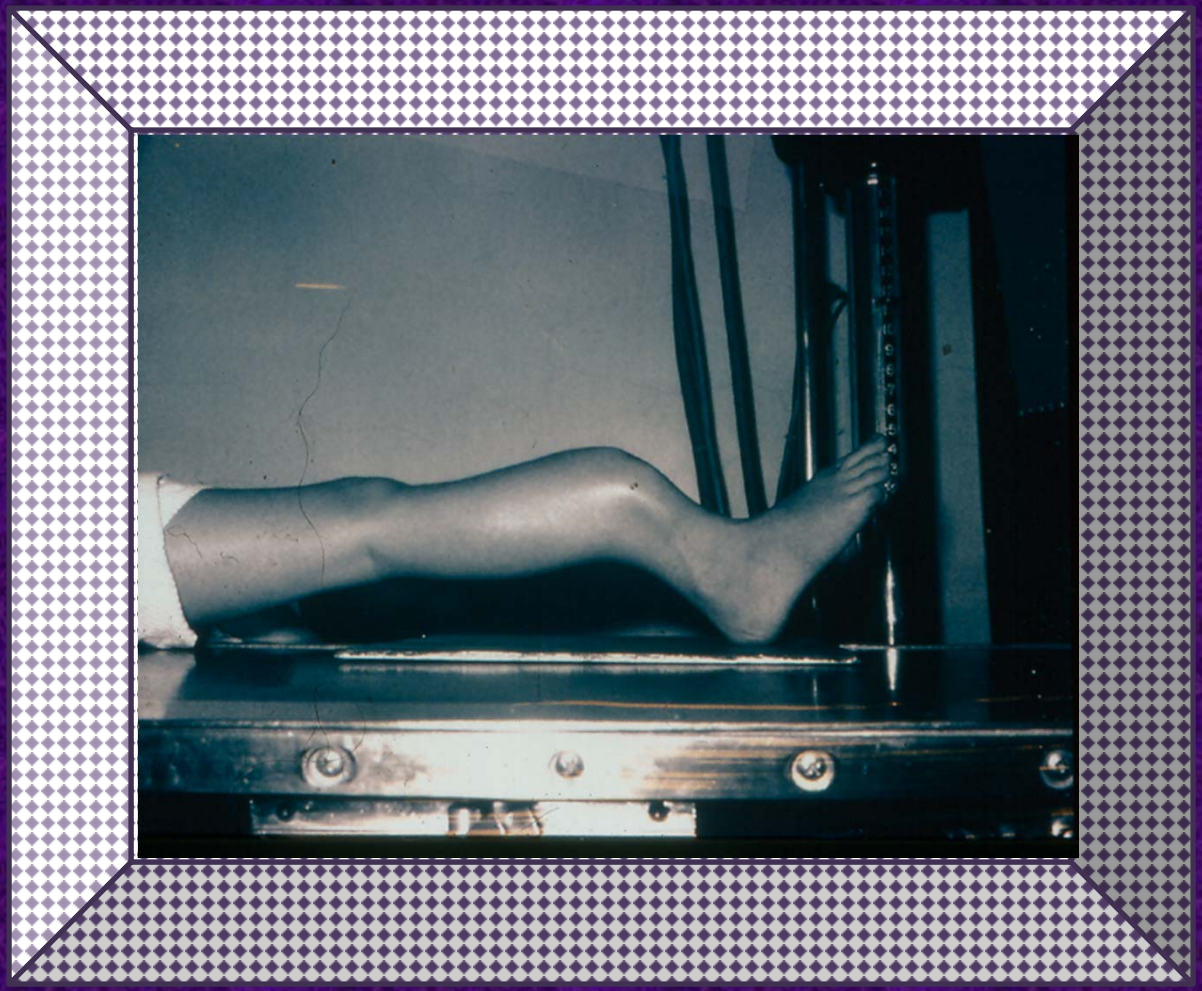


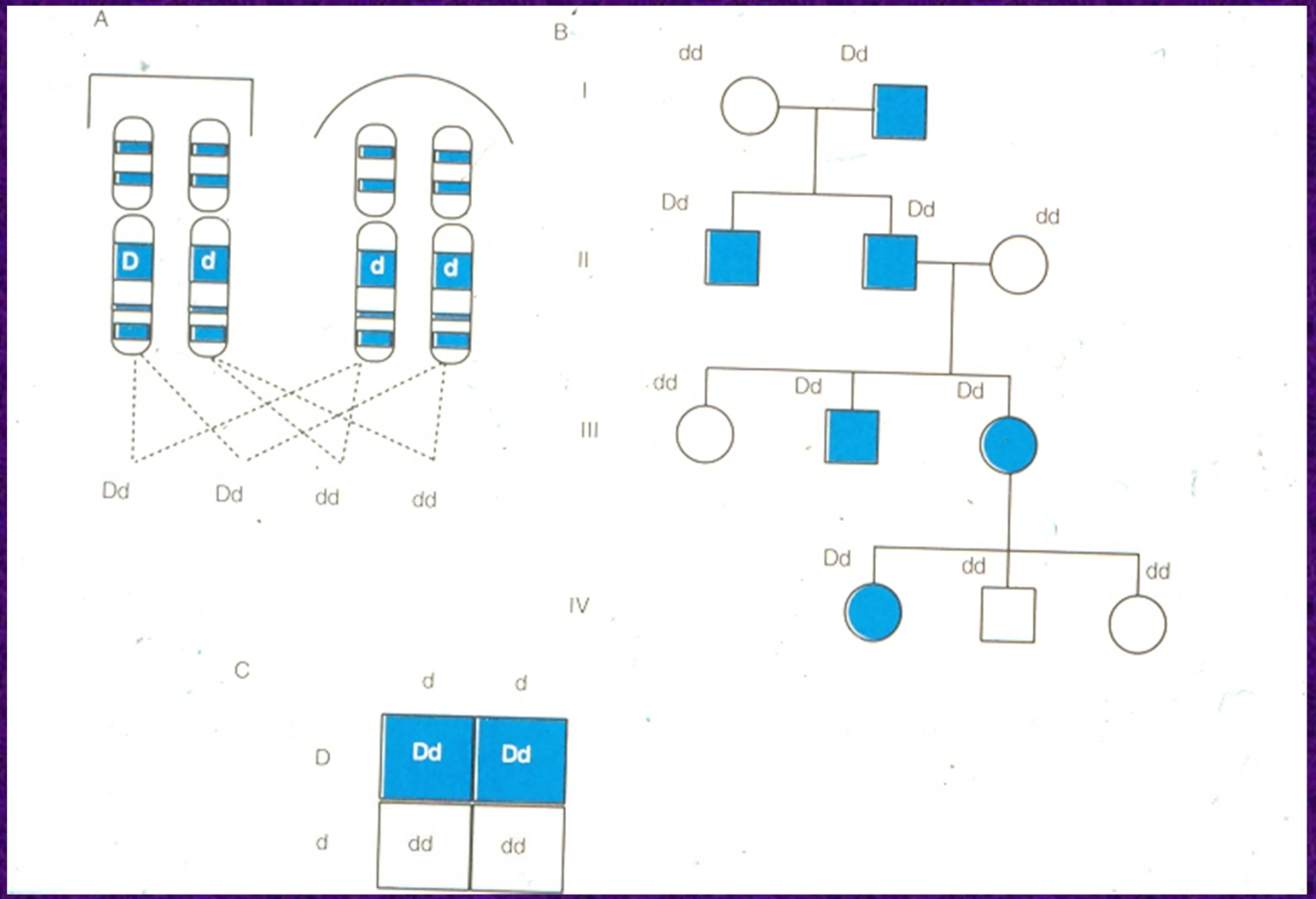





ID: 7032062-7
12 DEC 02 10:51
886 V
RH
SE.
TE: 19.0
BW: 10.4
TR: 609
FOV: 17.0
PS: 1.000
FLIP: 90
NSA: 2
SCAN: 03:53
THCK: 3.0
RES: 192x256
FATSAT.
W:
L: 534
Z: 1.00
P: +0.0 cm
+0.0 cm
6.2 R
8.3 P
8.8 F
FRAME: 1/1
ECHO: 1/1
SLICE: 9/14
CONTRAST: 2.6 ML
P


6 29 71 R




A
D
d
d
d
Dd
Dd
dd
dd
B
I
II
III
IV
dd
Dd
Dd
Dd
dd
dd
Dd
Dd
Dd
Dd
dd
dd
C
d
d
D
Dd
Dd
d
dd
dd

Neurofibromatosis 1 (NFI)

Complications resulting from NFI are widespread, unpredictable and variable

- ◊ Progressive
- ◊ Majority do not have severe medical complications
- ◊ Approximately 70-80% have some type of developmental problem

Neurofibromatosis 1 In Adulthood

Complications of NF1 in adulthood

- Disfiguring and sometimes symptomatic plexiform neurofibromas
- Hypertension
- Gastrointestinal tumors
- Bone abnormalities
- Pain from neurologic symptoms
- Increased risk of malignancy (Malignant nerve sheath tumor; Breast cancer)

NFI impacts on affected adults in five major ways (60 adults in Australia median age 29 (19-40)

1. Cosmetic burden of disease (both genders)
2. Learning difficulties; ADHD; Poor self image
3. Concerns about passing NFI to offspring (50%)
4. Uncertain disease progression
5. Pain – Headaches; back pain; Neurofibroma pain

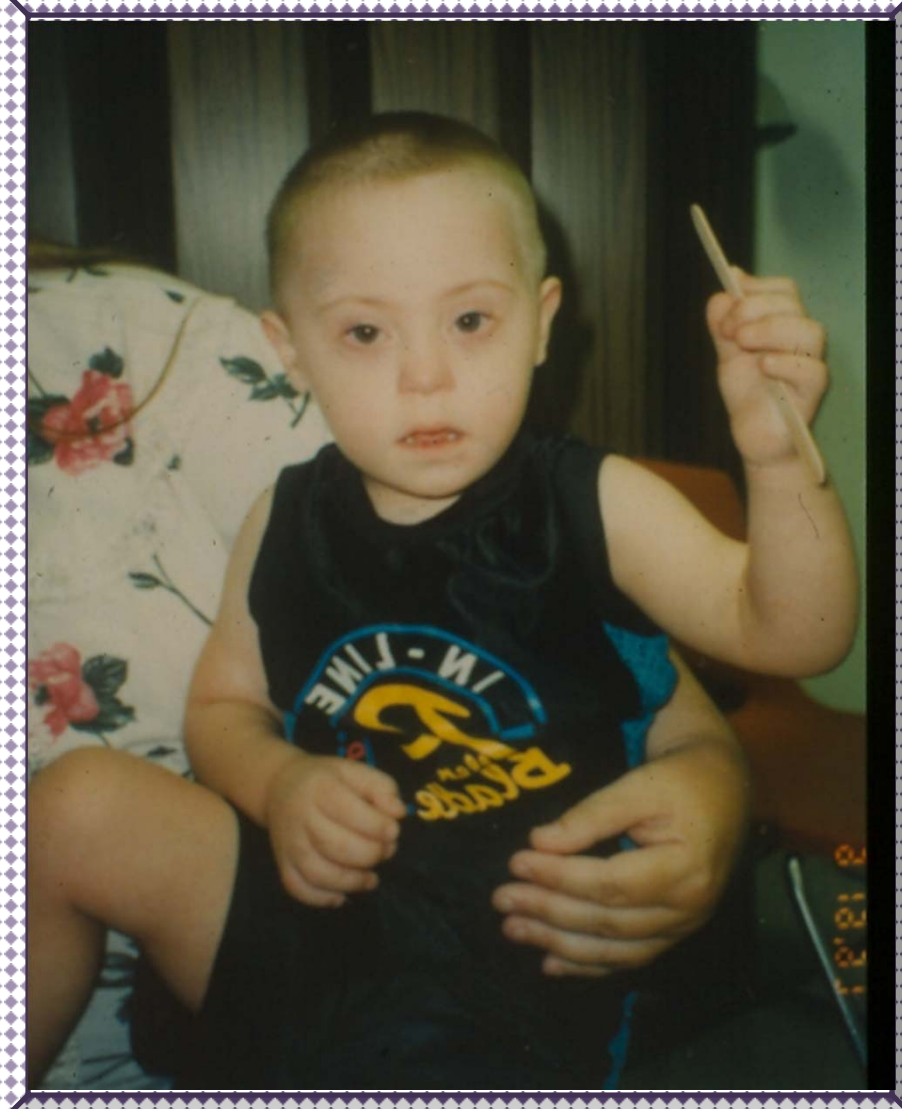
Greatest concern to adults with NF1

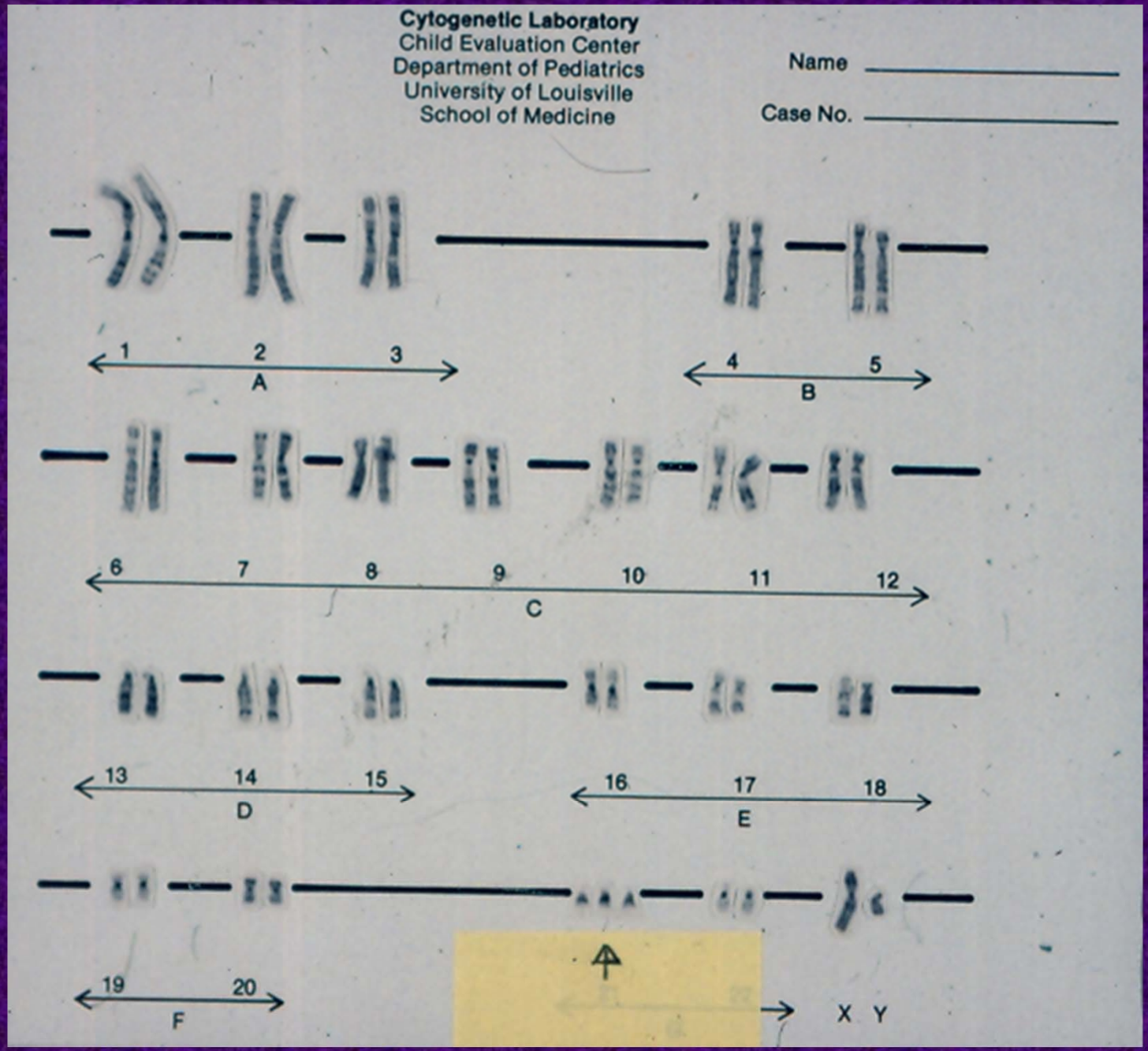
1. Disfiguring cosmetic. Neurofibromas whether mildly or severely affected
2. Learning difficulties impacting on career choices and in seeking employment

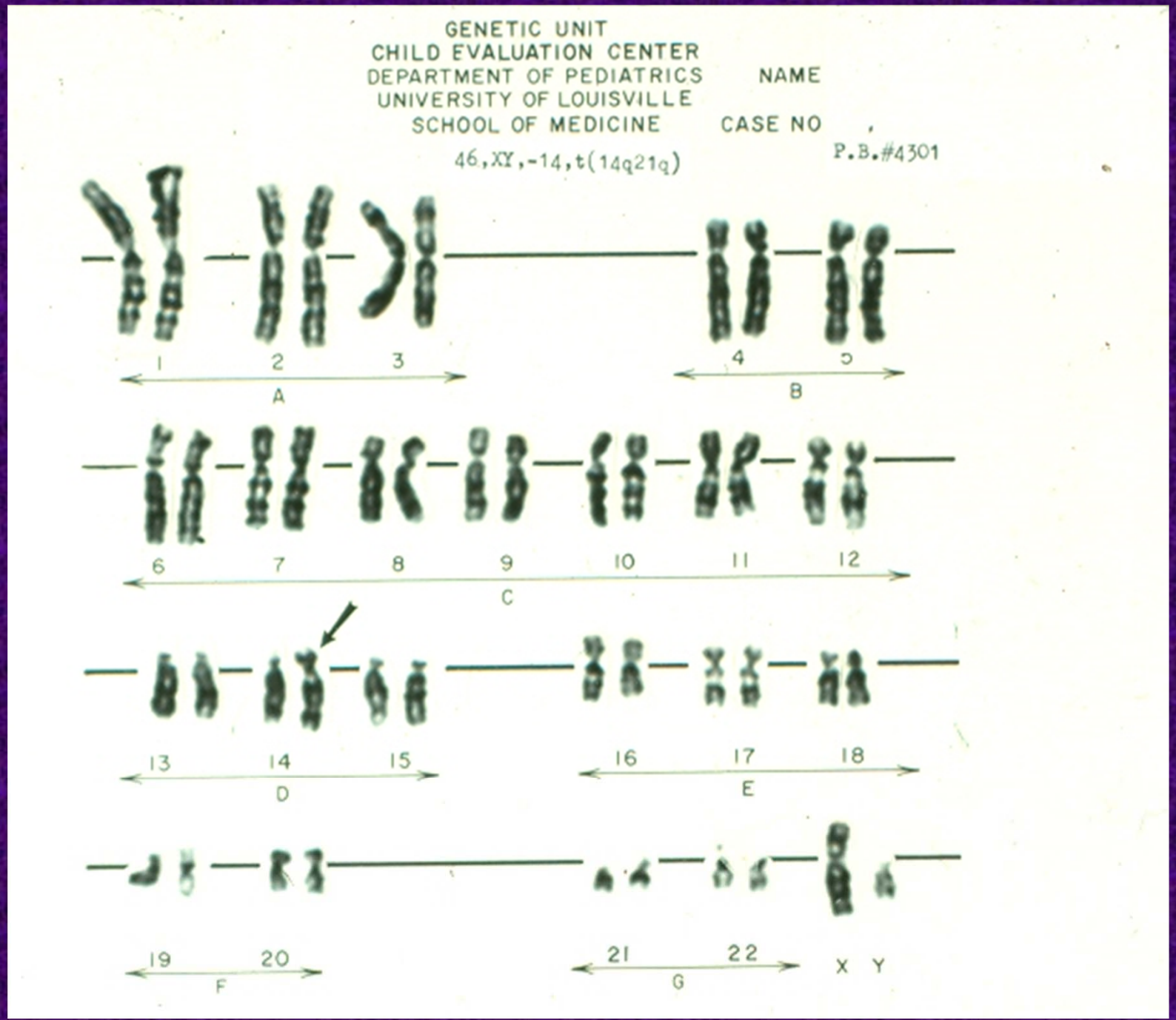
Down Syndrome

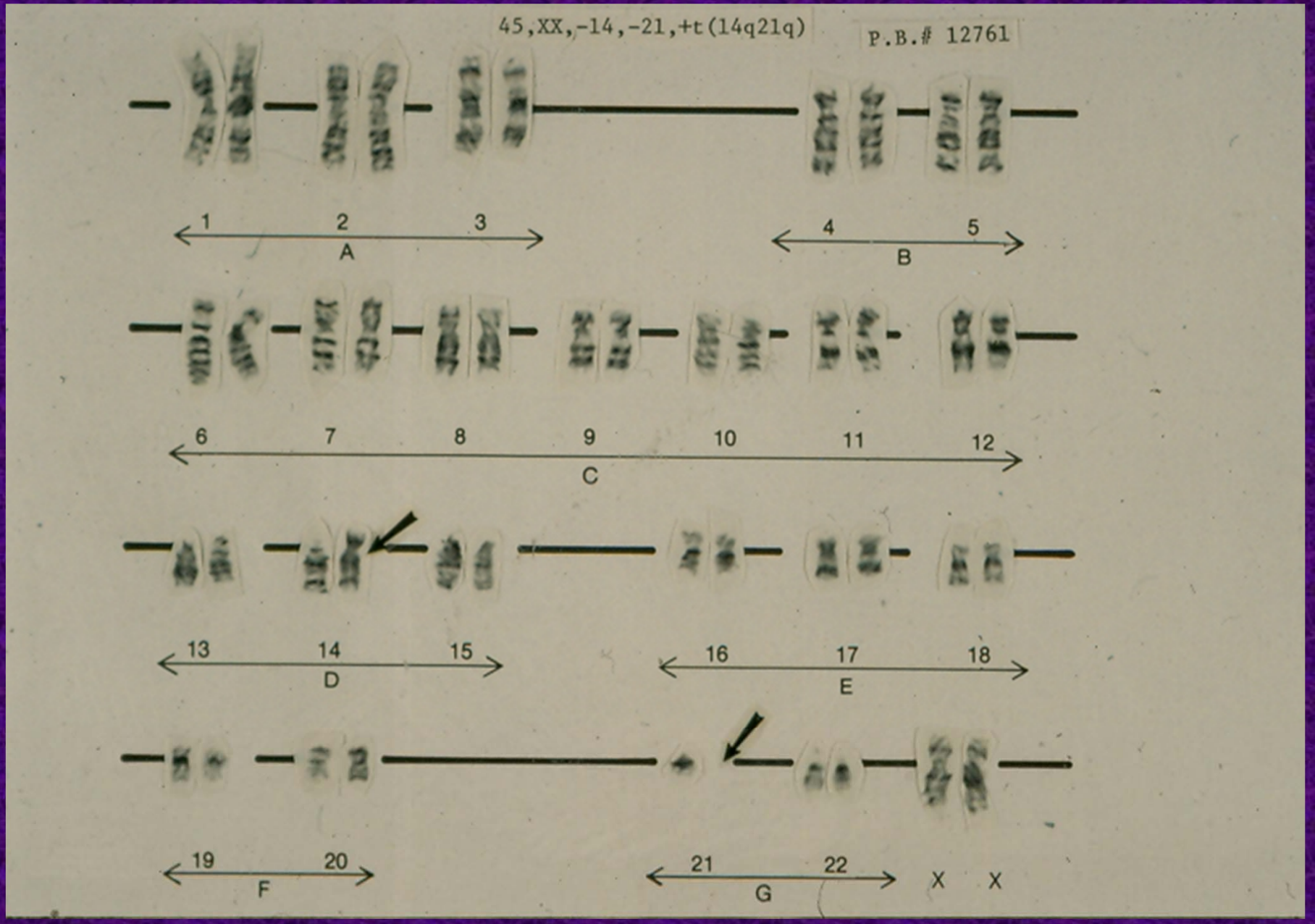
- Trisomy 21 (increases with advanced maternal age)
- Robertsonian translocation (usually 14;21)
- Mosaicism (possible milder phenotype)

Clinical phenotype in Trisomy 21 and Translocation Down syndrome is similar, but Trisomy 21 in almost all instances is sporadic, while 25-50% of Translocation Down syndrome is transmitted from a parent who is a balanced carrier




Cytogenetic Laboratory
Child Evaluation Center
Department of Pediatrics
University of Louisville
School of Medicine
Name
Case No.
1 2 3
A
4 5
B
6 7 8 9 10 11 12
C
13 14 15
D
16 17 18
E
19 20
F
X Y


GENETIC UNIT
CHILD EVALUATION CENTER
DEPARTMENT OF PEDIATRICS
UNIVERSITY OF LOUISVILLE
SCHOOL OF MEDICINE
NAME
CASE NO ,
46,XY,-14,t(14q21q)
P.B.#4301
1 2 3
A
4 5
B
6 7 8 9 10 11 12
C
13 14 15
D
16 17 18
E
19 20
F
21 22
G
X Y


45,XX,-14,-21,+t(14q21q)
P.B.# 12761
1
2
3
A
4
5
B
6
7
8
9
10
11
12
C
13
14
15
D
16
17
18
E
19
20
F
21
22
G
X
X

In the last two generations with increased survival, adults and elders with Down syndrome represent a new population with particular challenges to healthcare professionals, necessitating a greater understanding of the nature, timing and impact of comorbidities

Down Syndrome In Adulthood

Correction of congenital heart defects, more focused treatment of infections, improved general healthcare and psychosocial support have contributed to significantly longer life expectancy

Life Expectancy in Down syndrome

- 12 years in the 1950's
- 25 years in 1983
- 49 years in 1997
- 60 years in 2002

Challenges In Healthcare For Adults With Down Syndrome

a) Lack of data on the prevalence of chronic diseases and age-related conditions
   - Low prevalence of cardiovascular disease and high prevalence of obesity

b) Consensus on standardized protocols for adults with Down syndrome

c) Little is known about treatment of diseases in adults with Down syndrome

- Clinical trials with donepezil and memantine in Alzheimer-like dementia have not affected cognition
- Osteoporosis is prevalent but data on fracture risk and preventive treatment are limited

d) Are primary care physicians sufficiently knowledgeable to administer proper levels of care to adults with Down syndrome?

There is a wide range of comorbidities across the life span in Down syndrome from those in early childhood, such as congenital heart disease, decreased immunologic function, and increased risk for leukemia, to adulthood, with premature aging apparent by age 40, about 20+ years earlier than in the general population

Therefore, while longevity has improved appreciably, age-specified risk for morbidity is considerably increased compared with other individuals with intellectual disabilities, posing unique clinical problems that differ from those of the general population

From a healthcare prospective, it is likely that two clinically distinct populations of individuals exist. Those under 30 have likely received better attention in childhood based on available clinical protocols (AAP, 2011), for detection of congenital cardiac lesions, celiac disease, atlantoaxial instability, etc, and greater psycho-social support

Guidelines for Management of a Genetic Disorder

Down syndrome

Neonate

Establish diagnosis

Support to family

Evaluate heart

Monitor GI tract

Monitor heme status

Infant

Hypotonia

Feeding problems

Developmental delay

Infections

Monitor vision & hearing

Monitor thyroid

Child

School needs

Evaluate cervical spine

Monitor vision & hearing

Monitor thyroid

Follow growth especially weight

Adult

Supported living

Employment

Monitor heart

Premature aging

Dementia

Psychiatric disease

Over 30, the clinical profile reflects an early-onset aging process, with problems such as cataracts, dementia and musculoskeletal disorders

Spanish study of 144 adults with Down syndrome mean age 35 ½ years (17-65) and 51% male and 49% female

- 112 (78%) lived with family
- Parents were main caregivers (73%)
- Older adults lived more frequently in residential facilities

Each subject presented with an average of 5.2 clinical problems

- Eye: 117/144 (81%)
- Skin: 86/144 (60%)
- Thyroid: 81/144 (56%)
- Gastrointestinal: 73/144 (51%)
- Psychopathologic Disorders: 58/144 (40%)

Cataracts, Keratoconus, dementia and seizures were more frequent in affected individuals over 50 and no differences were found between genders

The medications most frequently prescribed were levothyroxine, vitamin D, antidepressants and antipsychotics

Comorbid conditions in adults with Down syndrome

1. Endocrine: Hypothyroidism (15-37%); Obesity; Osteoporosis (fracture risk > 50); Cervical spine degeneration
2. Cardiac: Mitral valve prolapse (45%); Aortic regurgitation
3. Gastrointestinal: GERD; Swallowing problems and aspiration risk (25%); Celiac disease
4. Hematology-Oncology; Leukopenia; Mild polycythemia; Macrocytosis; Leukemia is rare

Comorbid conditions in adults with Down syndrome continued . . .

5. Pulmonary: Pneumonia; Obstructive sleep apnea
6. Behavioral/Mental Health: Depression, anxiety, OCD, ASD
7. Neurology: Alzheimer Dementia (R/O Depression); Seizures

Thyroid dysfunction in adults with Down syndrome

- Of those who are euthyroid, the risk for becoming hypothyroid at 5 years is 0.9%
- Of those with subclinical hypothyroidism, only a small minority develop hypothyroidism
- Those on thyroid replacement often are still biochemically hypothyroid

The most common causes for a decline in skills younger than 40 are psychiatric issues and difficulty over coming a loss such as a death of a family member or caregiver; after 40, evaluation for Alzheimer's dementia should be included

Alzheimer's dementia in Down syndrome

- Neurofibrillary plaques and tangles in adults over 35 years
- Few cases<40, and alzheimer's dementia is not universal
- Presentation differences: Sleep disturbance, apathy, gait changes, personality changes, seizures, incontinence
- Treatment is mainly supportive

Children with Down syndrome are at lower risk for psychopathology than other children with intellectual disability. In youth externalizing behaviors may be problematic, where as a shift toward internalizing behaviors emerges with maturity.

Dementia or cognitive decline due to medical or mental health reasons?

Despite the high prevalence of obesity, dyslipidemia, and sedentariness in the elderly, the prevalence of metabolic syndromes, hematologic and solid tumors, cardiovascular disease and hypertension is low

Leading causes of death in Down syndromes

1) Cardiac, including congenital heart defects (25-43%)
2) Respiratory infections (20-40%)
3) Dementia after 40 (35%)

Regular medical screening in adults with Down syndrome

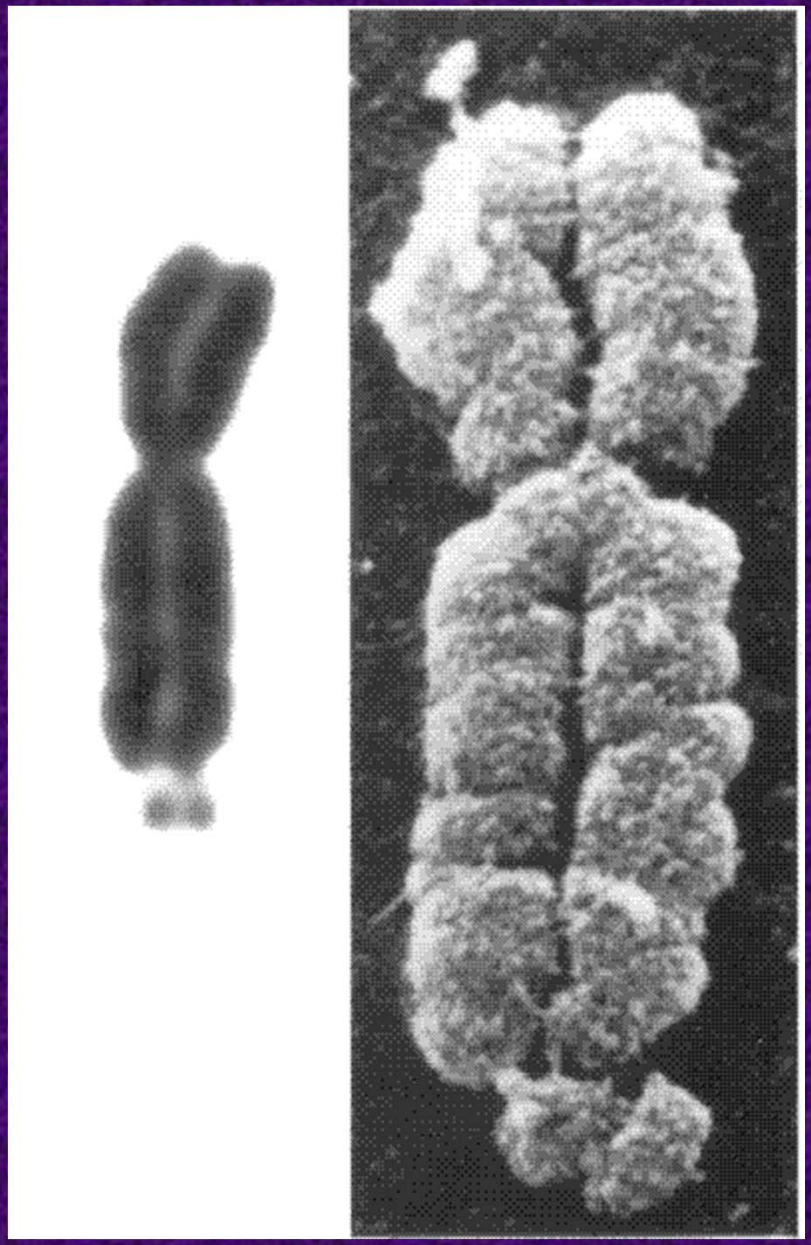
1. Thyroid screening
2. Bone density ≈40 y/o
3. Echocardiogram
4. Modified swallow study (cough, sigh, burp, throat clearing at mealtime)
5. Celiac screen (weight loss, diarrhea, mood or behavior change)
6. GERD (weight loss, decline in skills, behavior change)
7. Obstructive sleep apnea (change in mood and behavior, decline in skills, fatigue, daytime sleepiness, nocturnal gasping/choking)
8. Depression (withdrawal, decreased appetite, decrease in speech); Separation from parent, death in family

Adults with Down syndrome have a wide spectrum of potentially treatable medical conditions making specialty-trained and multidisciplinary teams potentially of great value in complementing services provided by PCP's

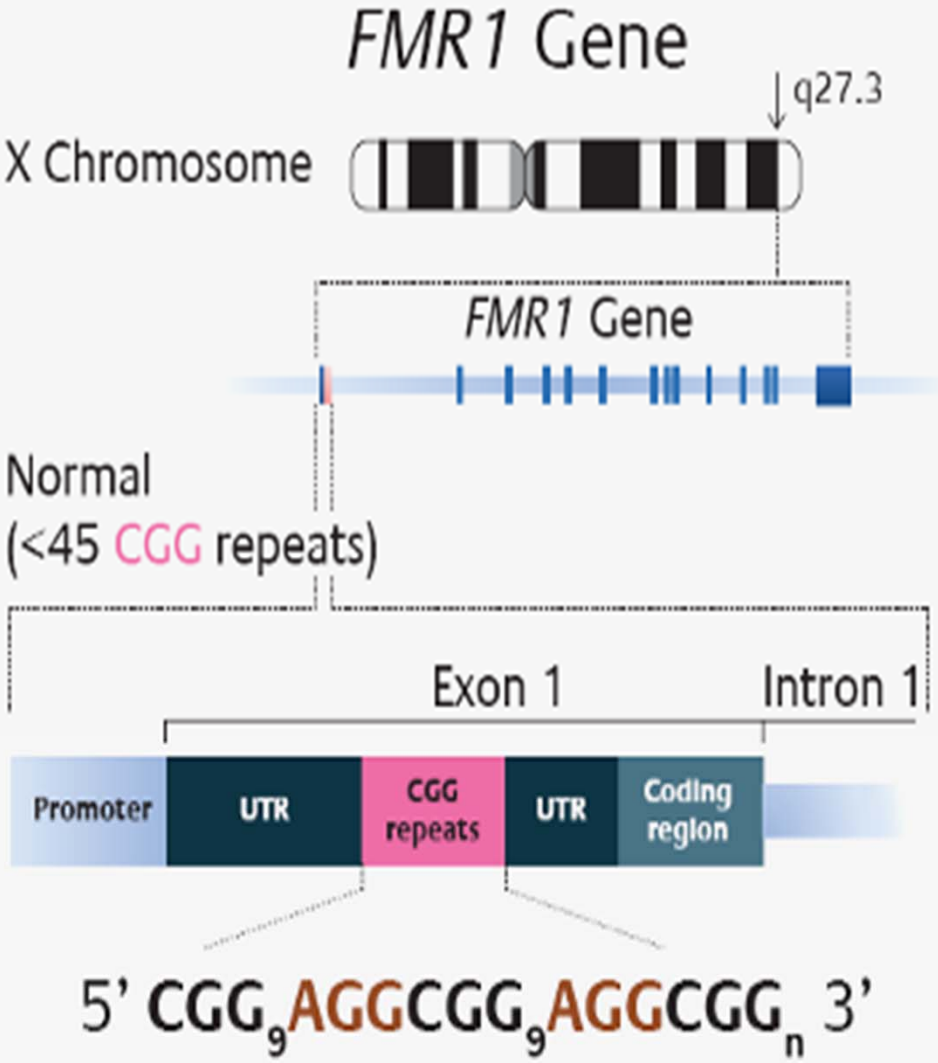
Fragile X Related Disorders In Adulthood

Fragile X Syndrome

- ◊ Most common inherited cause of intellectual disability and most common known single gene cause of autism spectrum disorder
- ◊ First recognized in 1969 when a fragile site on the distal end of the long arm (q) of the X chromosome
- ◊ FMR1 gene discovered in 1991



Fragile X Chromosome


FMR1 Gene
q27.3
X Chromosome
FMR1 Gene
Normal
(<45 CGG repeats)
Exon 1
Intron 1
Promoter
UTR
CGG repeats
UTR
Coding region
5' CGG9AGGCGG9AGGCGGn 3'

Fragile X related disorders are due to expansion of a CGG trinucleotide repeat in exon resulting in silencing of the gene and absence or significant reduction of the gene product, fragile X mental retardation protein (FMRP)

◊ Normal : 10-45 CGGs
◊ Pre mutation : 55-200
◊ Full mutation : >200 CGGs and aberrant methylation of FMR1

FMRP is essential for proper brain synaptic plasticity, neuronal morphology and cognitive development and its absence leads to varying degrees of intellectual disability

In fragile X syndrome, boys are typically more severely affected than girls because of the presence of an unaffected second X chromosome in girls

Fragile X Phenotype

◊ Prominent forehead

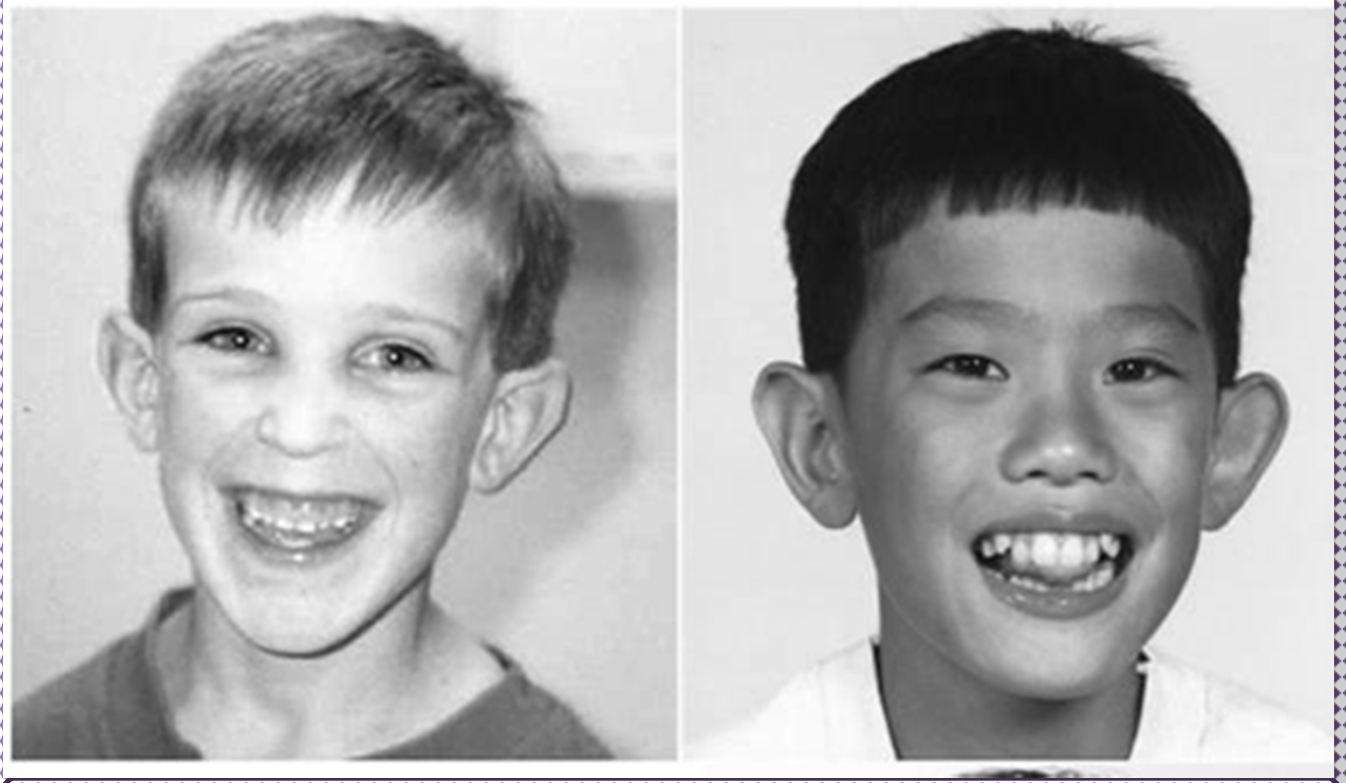
◊ Protruding ears

◊ High-arched palate

◊ Strabismus

◊ Macro-orchidism

◊ Connective tissue dysplasia



Associated medical conditions in fragile X syndrome

Otitis media
GI problems
Seizures
Ocular disorders
Sleep problems
Growth abnormalities
Cardiac conditions

Fragile X-associated tremor/ataxia syndrome (FXTAS) primarily occurs in males with an FMRI pre-mutation (and some females) and is characterized by late-onset progressive cerebellar ataxia and intention tremor

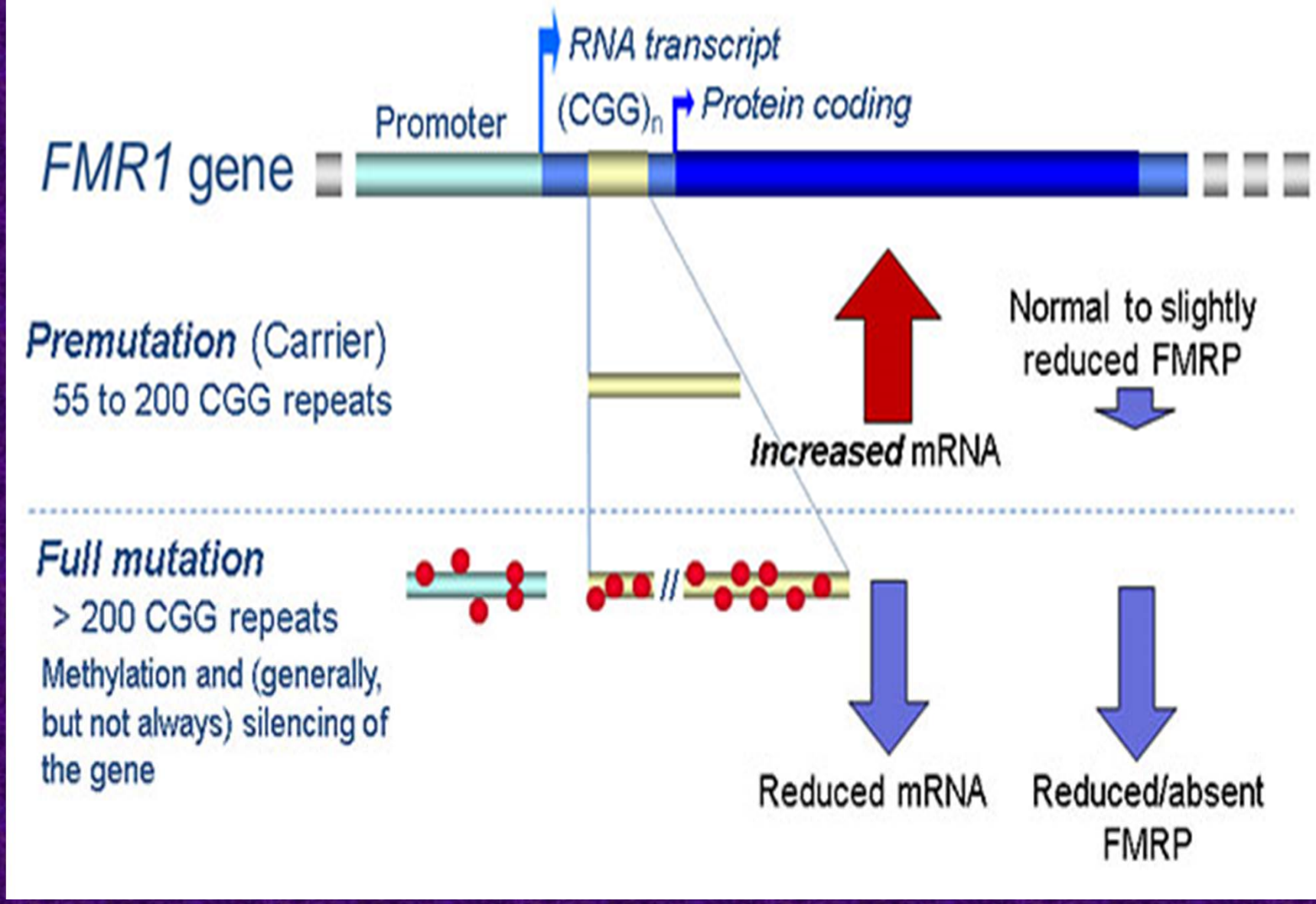
FXTAS Clinical Features

- Progressive cerebellar ataxia, tremor, parkinsonism and cognitive decline specifically executive functioning
- Psychiatric disturbances with anxiety, irritability, apathy, OCD, depression
- Autonomic and peripheral neuropathies
- Dementia

Risk of FXTAS in Males

Age	Risk
50-59	17%
60-69	38%
70-79	47%
≥ 80	75%

The pathogenic mechanism causing FXTAS is related to overexpression and toxicity of the FMR1 messenger RNA


RNA transcript
Promoter
(CGG)n
Protein coding
FMR1 gene
Premutation (Carrier)
55 to 200 CGG repeats
Increased mRNA
Normal to slightly reduced FMRP
Full mutation
> 200 CGG repeats
Methylation and (generally, but not always) silencing of the gene
Reduced mRNA
Reduced/absent FMRP

FMRI-related premature ovarian insufficiency (age at cessation of menses <40 years) occurs in approximately 20% of females who have an FMRI pre-mutation

Fragile X-associated primary ovarian insufficiency

POI:≥4 months of disordered menses in association with menopausal FSH levels, in a woman <40

a. 1:100 women in general population compared to 20% with an FMR1 premutation
b. Highest risk is with 80-100 CGG repeats

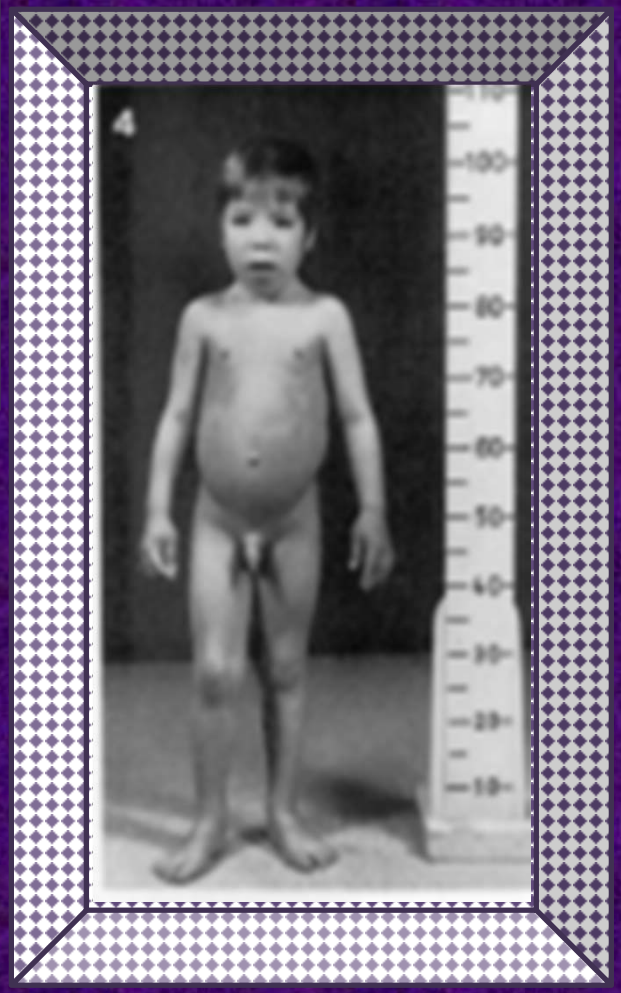
Women who have a premutation and normal ovarian function are at risk for FXTAS. Of the 20% of women with a premutation who develop FXPOI, they do not seem to be at increased risk for developing FXTAS

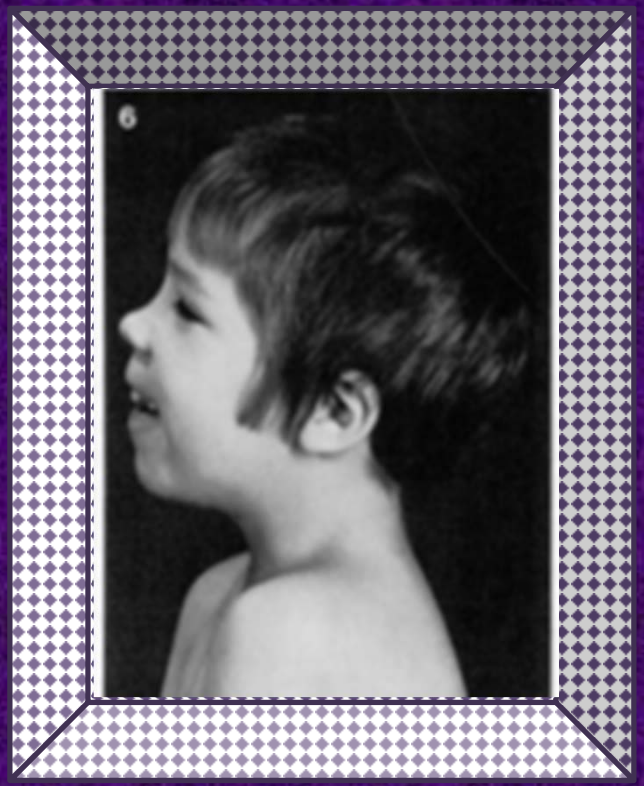
Whole exome sequencing identifies variants in the protein coding regions of the exons of all genes in the human genome. The potential for detecting single gene abnormalities using this technology has increased significantly

Whole exome sequencing establishing diagnostic entities in individuals with unexplained developmental disorders or birth defects after a chromosome abnormality has been ruled out by chromosome microarray analysis

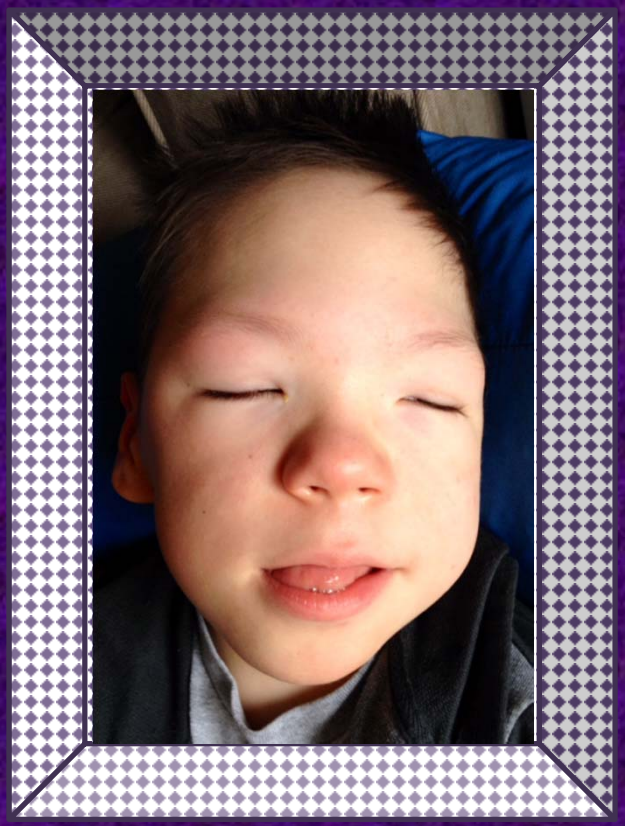
In 1989, Wiedemann reported on a boy with severe hypertelorism, narrow palpebral fissures, pre and postnatal growth deficiency , short hands and severe psychomotor retardation

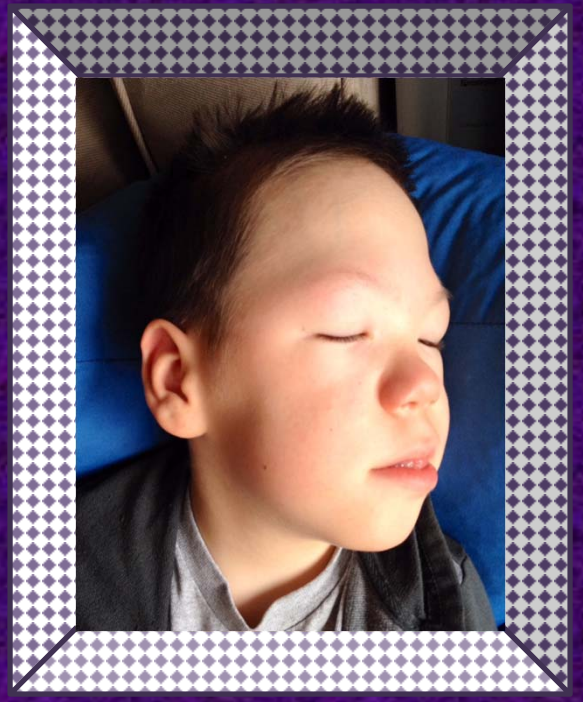

2

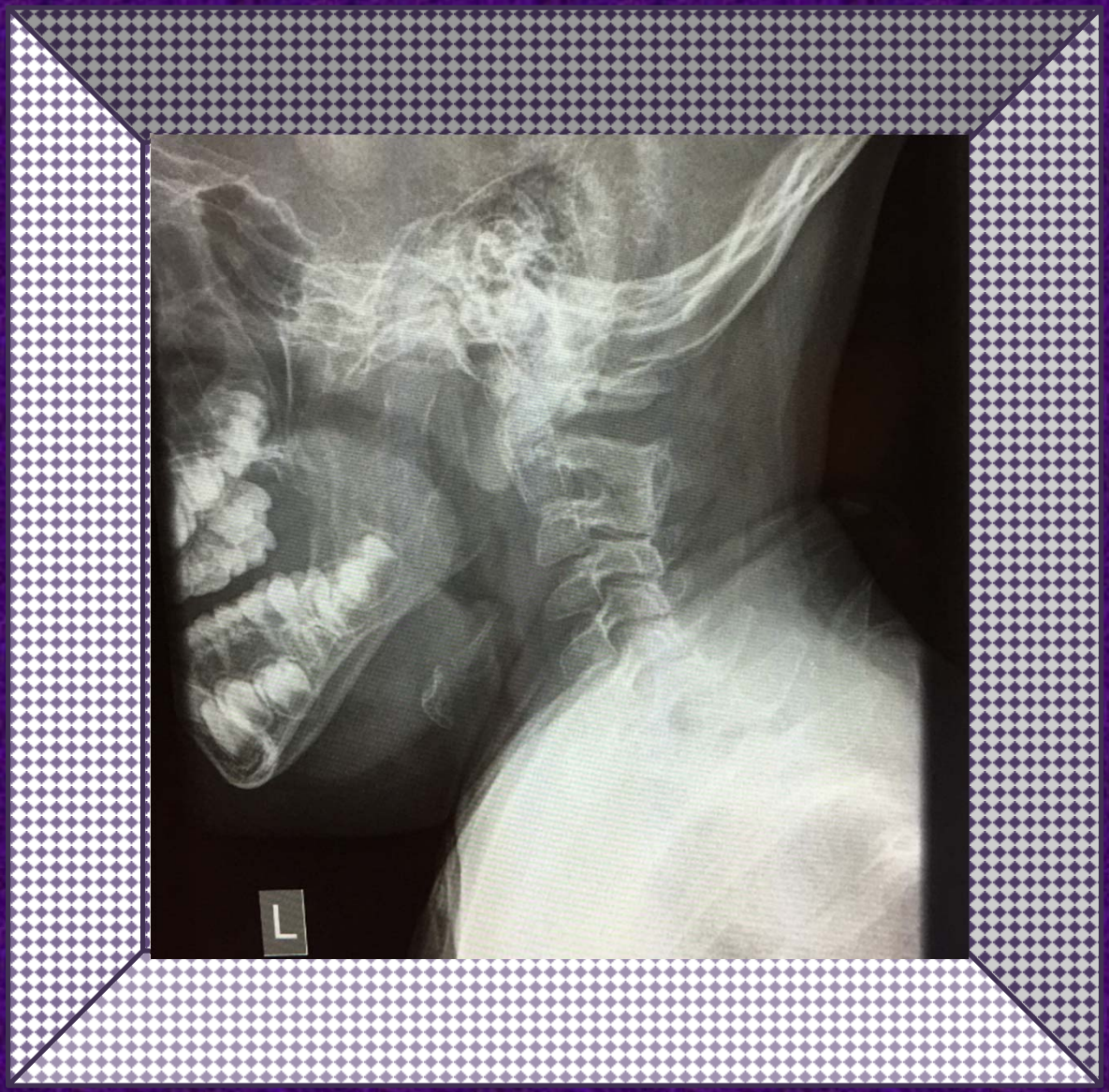

4


6

Steiner and Marques, in 2000, described an eight year old girl with short stature, thick eyebrows, telecanthus, broad nasal bridge, long philtrum, thin upper lip, fifth finger clinodactyly and mild to moderate psychomotor delay







Fusion of the vertebral bodies and posterior elements of C2 and C3.

Advances in genetic technology is enabling diagnosis of new disorders or previously unrecognized conditions. This gene discovery should enhance the ability of healthcare professionals to provide better care for those adults with special needs