

# Natural history study of adults with Wolf-Hirschhorn syndrome

- Agatino Battaglia<sup>1,2</sup> and John C Carey<sup>2</sup>

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# Natural history study of adults with Wolf-Hirschhorn syndrome

(only 11 adults in literature)

Although more than 300 persons with WHS have been reported in the literature, there is/are:

- sparse long-term follow-up of these individuals
  - ↓
- little knowledge about course,
- potential further complications, and
- health risks during adulthood and advanced age.

# Natural history study of adults with Wolf-Hirschhorn syndrome

With this study we attempted to assess medical conditions and function of adult individuals with WHS.



- This overall investigation comprises two methodologies divided into two parts:

# Part 1: case series of personally observed 35 individuals

ORIGINAL ARTICLE

AMERICAN JOURNAL OF  
medical genetics  WILEY

## Natural history study of adults with Wolf–Hirschhorn syndrome 1: Case series of personally observed 35 individuals

Agatino Battaglia<sup>1</sup>  | Amanda Lortz<sup>2</sup> | John C. Carey<sup>3</sup> 

*Am J Med Genet* 2021; 185:1794-1802

*Agatino Battaglia*

# Part 2: Patient-reported outcomes

## Patient-Reported-Outcomes-Study (PROS)

ORIGINAL ARTICLE

AMERICAN JOURNAL OF PART **A** medical genetics WILEY

### Natural history study of adults with Wolf–Hirschhorn syndrome 2: Patient-reported outcomes study

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*AJMG* 185:2065, 2021

John C Carey

# Part 1: case series of personally observed 35 individuals

Agatino Battaglia<sup>1,2</sup>

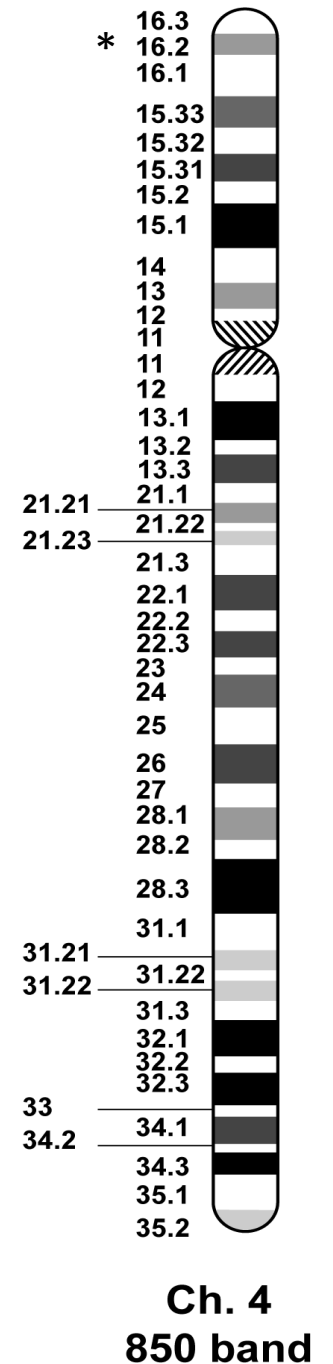
- *<sup>1</sup>IRCCS Stella Maris Foundation, Department of Developmental Neuroscience, Pisa, Italy*
- *<sup>2</sup>Dept. of Pediatrics, Division of Medical Genetics, University of Utah, Salt Lake City, UT, USA*

# Natural history study of adults with Wolf-Hirschhorn syndrome

- We recruited 35 individuals with WHS (26 females; 9 males), aged between 19 and 55 years.
- 25 were personally observed at the IRCCS Stella Maris Foundation by A.B., and **followed up** between 5 and 20 years
- 10 were recruited from the 4p- Support Group-USA.

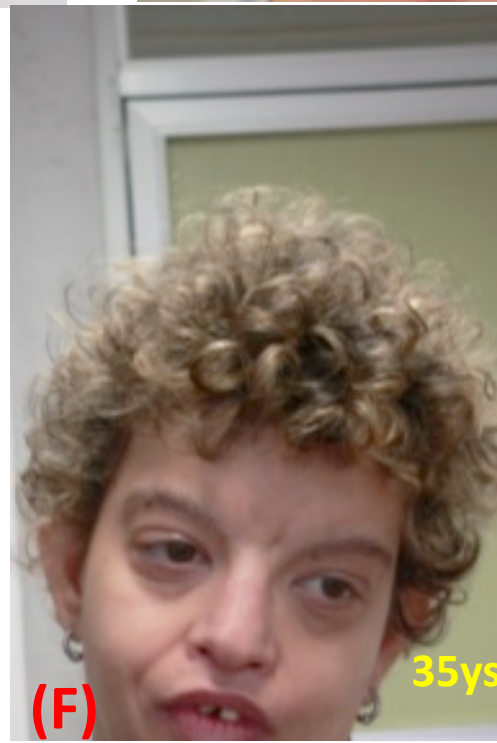
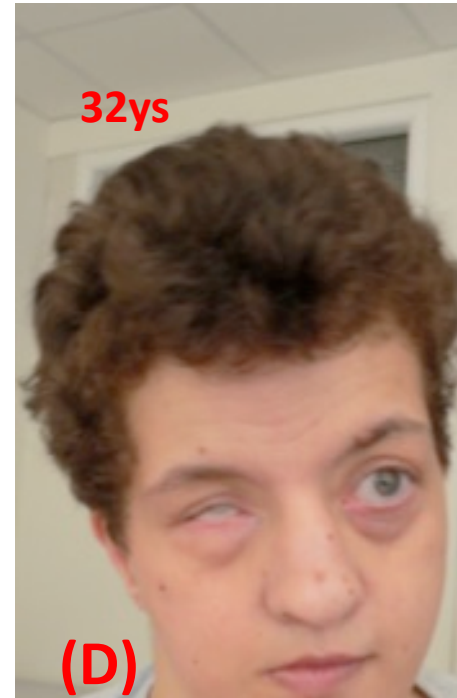
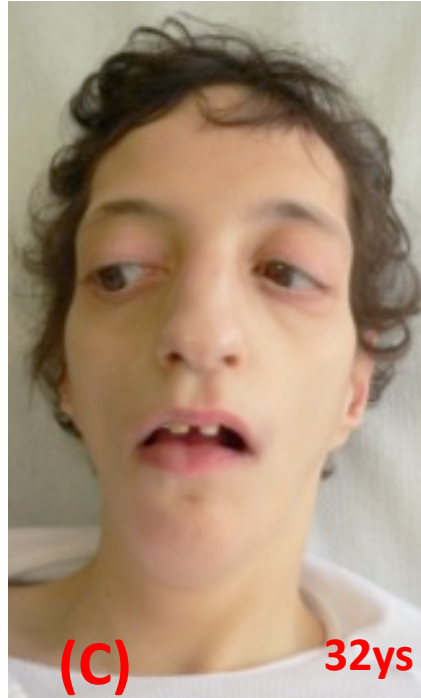
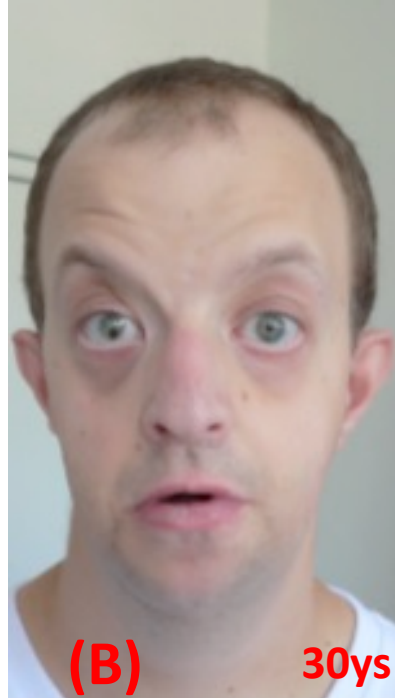
# Natural history study of adults with Wolf-Hirschhorn syndrome

- All of the participants had deletions involving the critical region of **4p16.3\***
- most deletions detected by a banded chromosome study or subtelomeric FISH due to their age of diagnosis being prior to the availability of cytogenomic microarray



# Behavioral features of adults with Wolf-Hirschhorn syndrome

- All persons were described by their caregivers as being happy, friendly, affectionate, outgoing adults that enjoy being around family and friends, mostly communicating by gestures.
- About 25%, when seen by us, showed some degree of anxiety with tendency to be frightened in new or, for them, incomprehensible situations.
- Less than 15% reportedly showed some aggressive behaviors in response to frustrations.



Italian adult individuals with WHS at different ages

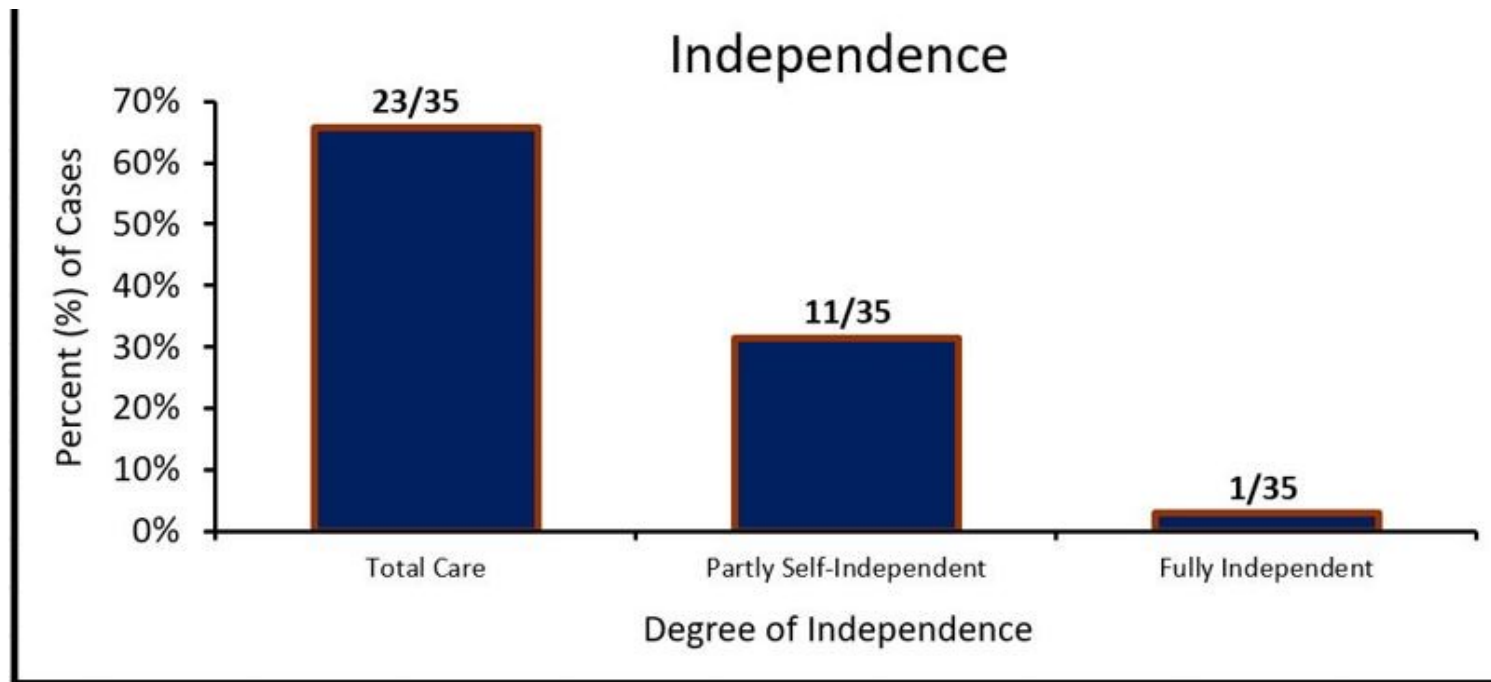


U.S. adult individuals  
with WHS at different  
ages

# Degree of Independence

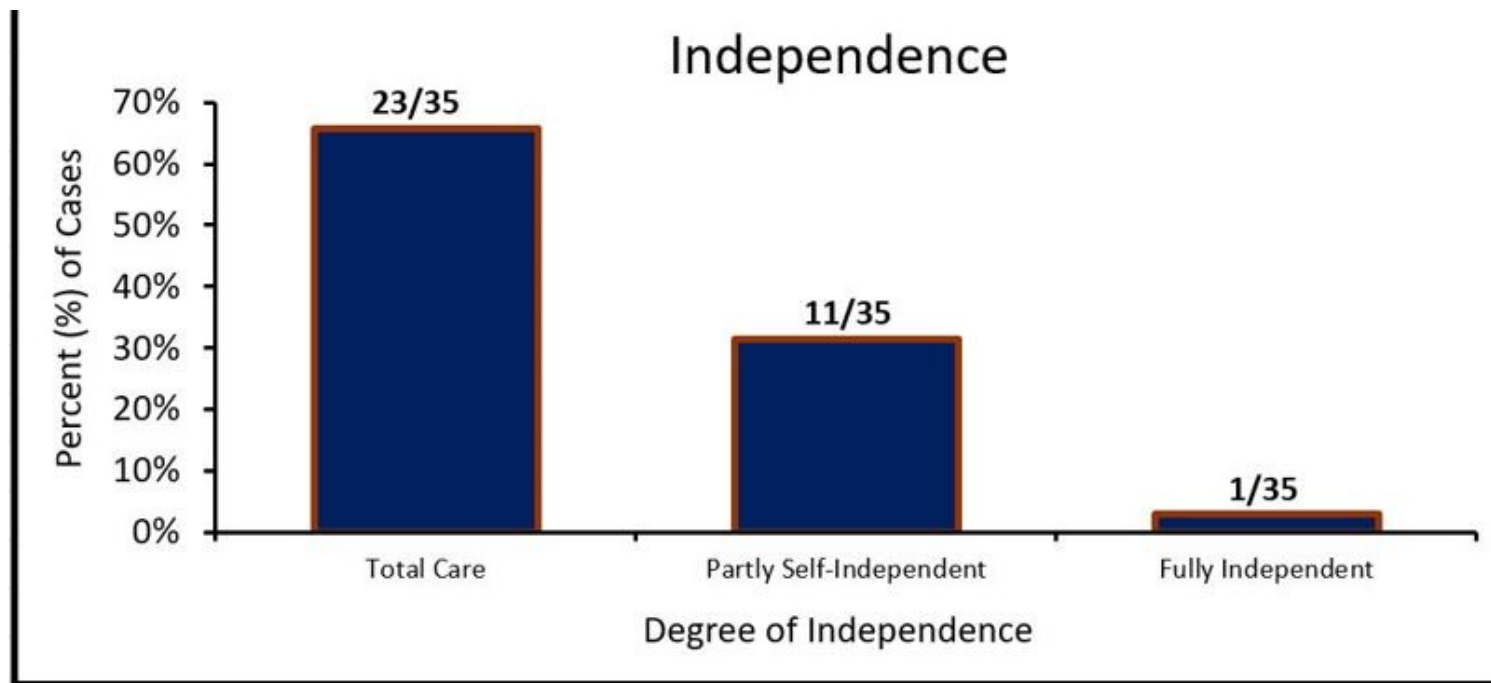
23 out of 35 (66%) were close to total care with needs to be assisted in feeding, diapering/toileting, bathing, dressing/undressing, and, when walking, needing assistance on uneven ground or transitioning from carpet to tile.

- Of note, 4 of them required a wheelchair for locomotion.



# Degree of Independence

- 11 out of 35 (31%) were partly self-independent, being able to feed and dress themselves, but needing supervision and some assistance with personal hygiene, and, at times, with walking on uneven ground.
- 1 out of 35 (3%) is fully independent and is volunteering at St. Vincent de Paul food bank



# Daily Living

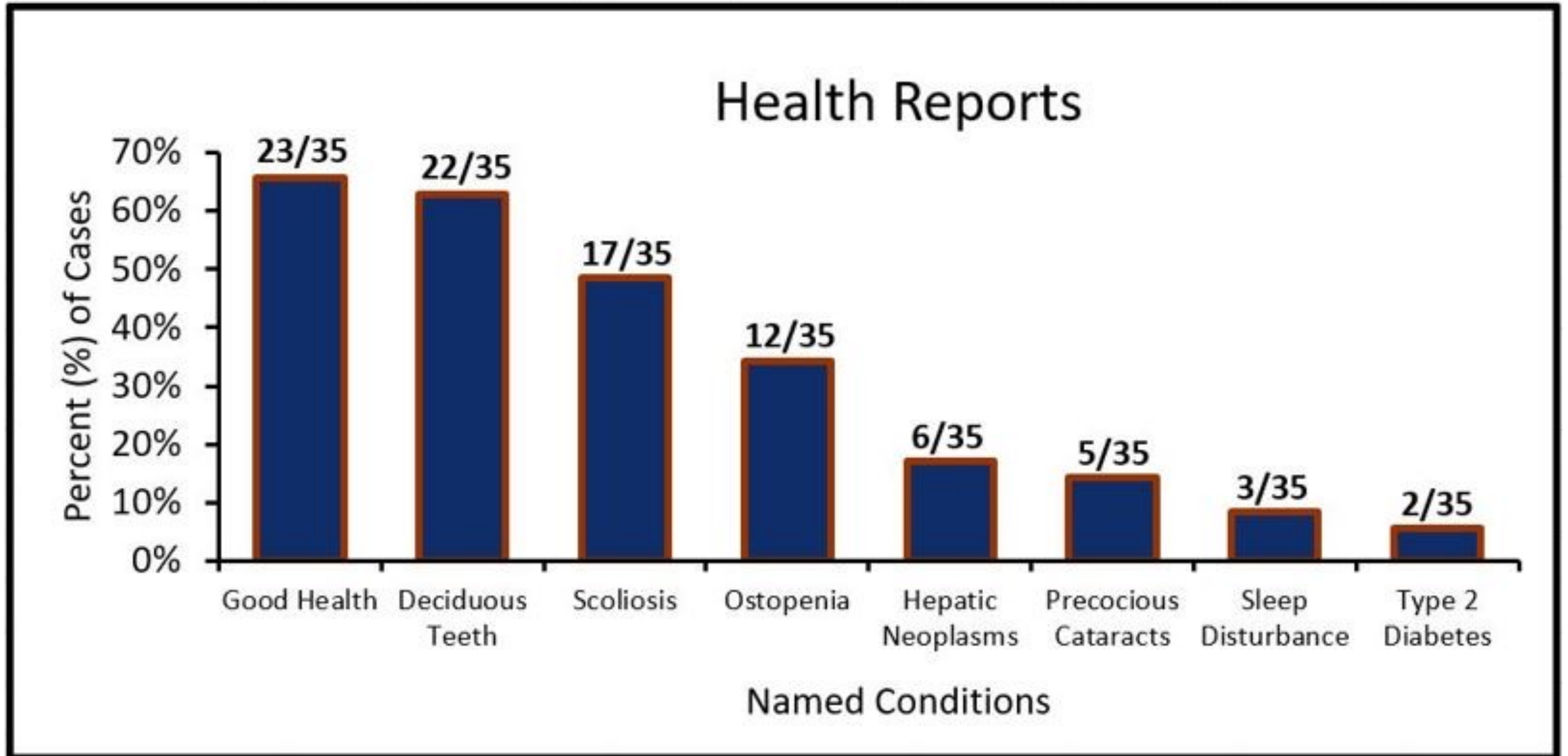
- Most individuals with WHS were living in their parents' home

# Cognitive features of adults with Wolf-Hirschhorn syndrome

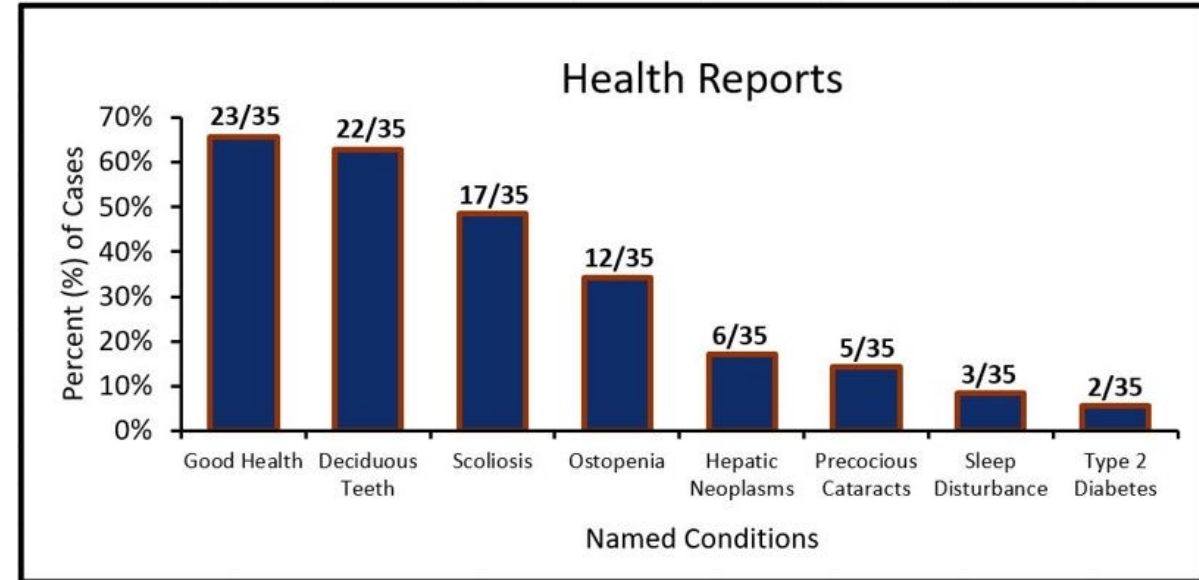
- All had a global executive slowness, and variable degrees of developmental disabilities, with a moderate to severe/profound cognitive deficit.
- The level of the adaptive development reached was at approximately 24 months of age.



23 out of 35 (66%) enjoyed good health

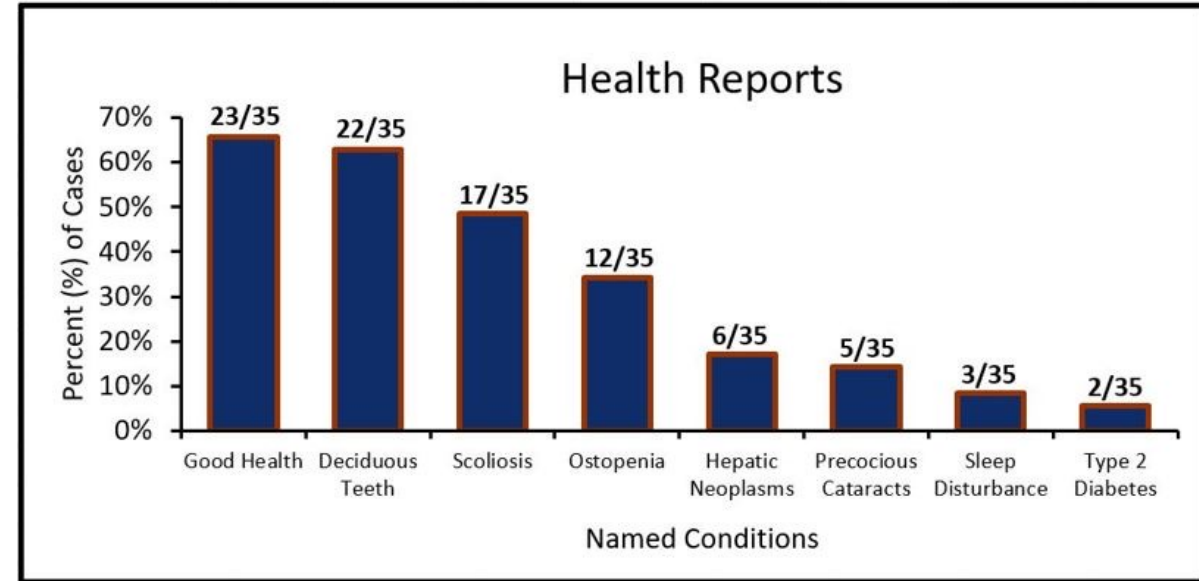


# Dentition in WHS



- Persistence of deciduous teeth/dental agenesis/oligodontia was observed in **22** (63%) adults
- 9 individuals (26%) were still having feeding difficulties, due to chewing inefficiency and needed to assume semisolid or liquid food.
- Most adults tended to keep the food in their mouth for a long time, eating small quantities

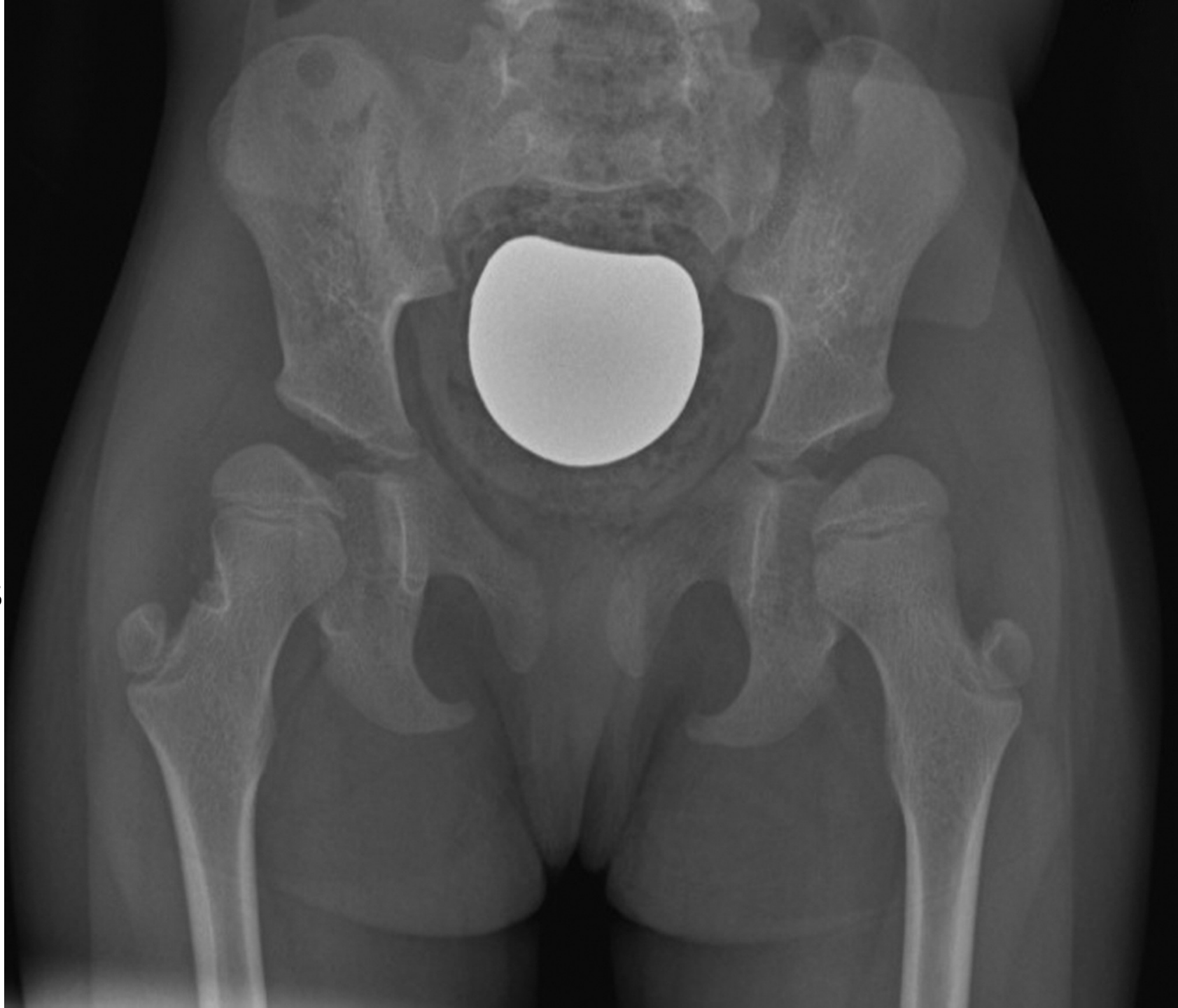
# Scoliosis in WHS



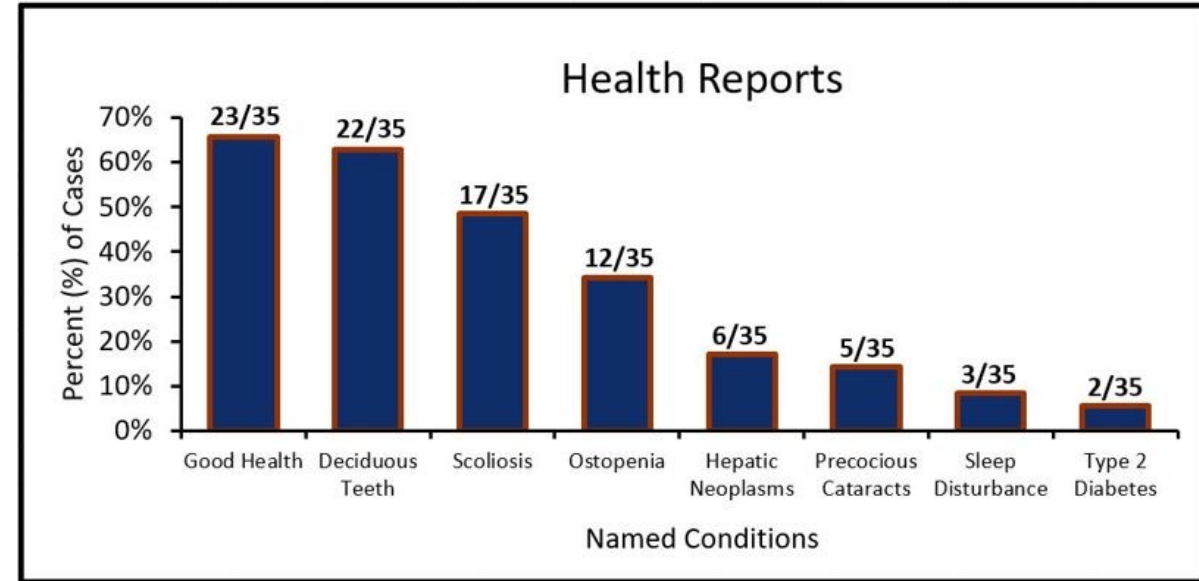
- About **50%** developed mild-to-severe thoraco-lumbar scoliosis between the age of 3 and 20 years.
- DEXA scan (**MOC**) showed low bone density in 12 individuals (34%) at different ages;
- only 4 of them suffered severe limited mobility.

**Hip displacement in WHS** as a consequence of hypotonia, observed in almost all our adult individuals

Preoperative AP Pelvis Radiograph of WHS Pt., at the age of 7, showing bilateral hip migration and right femoral neck cortical bone defect



# Neoplasia in WHS



- 6/35 (17%) were diagnosed with hepatic neoplasms
- 2/35 (6%) with hepatic angioma, 4/35 with adenomas

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WILEY AMERICAN JOURNAL OF PART **A**  
medical genetics

## ORIGINAL ARTICLE

### Risk of hepatic neoplasms in Wolf–Hirschhorn syndrome (4p-): Four new cases and review of the literature

Agatino Battaglia<sup>1\*</sup> | Amy R.U.L. Calhoun<sup>2\*</sup> | Amanda Lortz<sup>3</sup> | John C. Carey<sup>4</sup>

Patient number	Sex	Age at WHS diagnosis	WHS testing method	Deletion size	Age at adenoma diagnosis	Adenoma(s)	Seizures	Antiepileptic medications	Age at most recent evaluation
Pt.1	F	7 years	Subtelomeric FISH	3.5 Mb 4p16.3 del	15 years 6 months	Multiple hepatic adenomas	Onset at 1 year	Phenobarbital, valproate	17 years 8 months
Pt.2	F	17 months	Standard Karyotype	4p terminal deletion	32 years	Two hepatic adenomas	Onset at 9 months	Phenobarbital, valproate, ethosuccimide	34 years
Pt.3	F	5 years, 5months	Subtelomeric FISH	De novo del(4)(p16.3p16.3) (D4S3359)	18 years	Multiple hepatic adenomas	Onset at 8 months	Topiramate, oxcarbazepine	20 years
Pt.4	F	<12 months	Standard Karyotype	Large terminal del 4p15.2	?12-22 years	Multiple hepatic adenomas progressing to hepatocellular carcinoma	Onset at 23 months, intractable	Diazepam, valproate, lamotrigine, phenytoin	22 years

Axial abdominal CT image of a WHS Patient which demonstrates the hypodense mass in the right lobe of the liver, representing a multifocal hepatic adenoma.



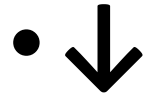
Prunotto G, et al. Two cases of hepatic adenomas in patients with WHS: A new rare complication? Am J Med Genet 2013, 161A:1759–1762.  
Dx: 11-20 ys

# Hepatic neoplasms in WHS

Because WHS is rare, the occurrence of liver neoplasms in nine individuals, with progression in two of them, raises concern that hepatic neoplasms may be a **component feature** of WHS

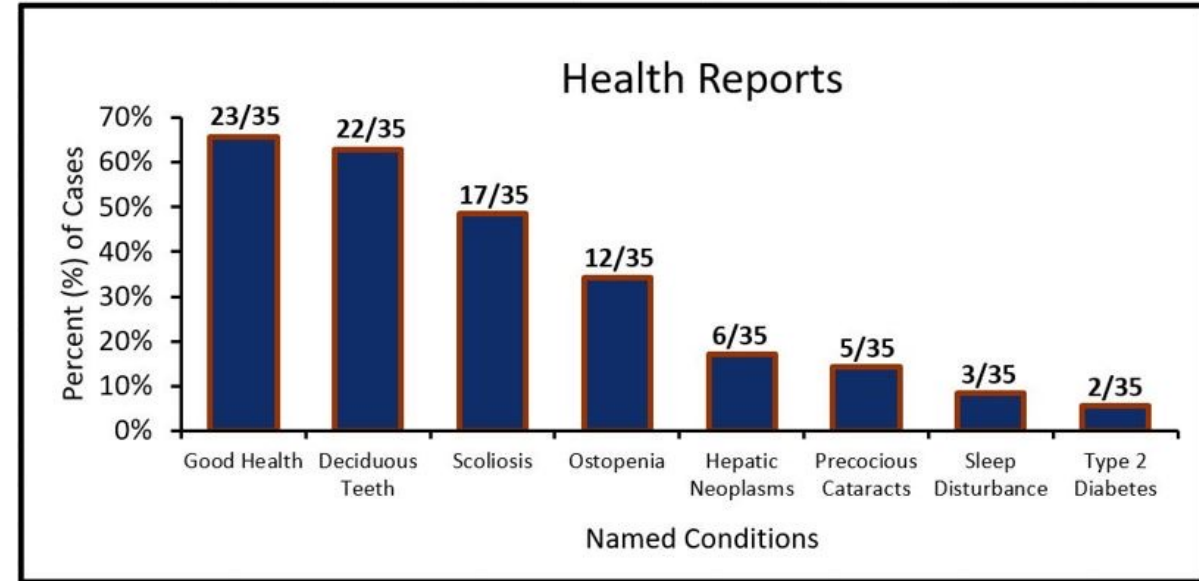
# Structural defects of the urinary tracts in 37% of our WHS cohort

- Renal hypoplasia in 20%



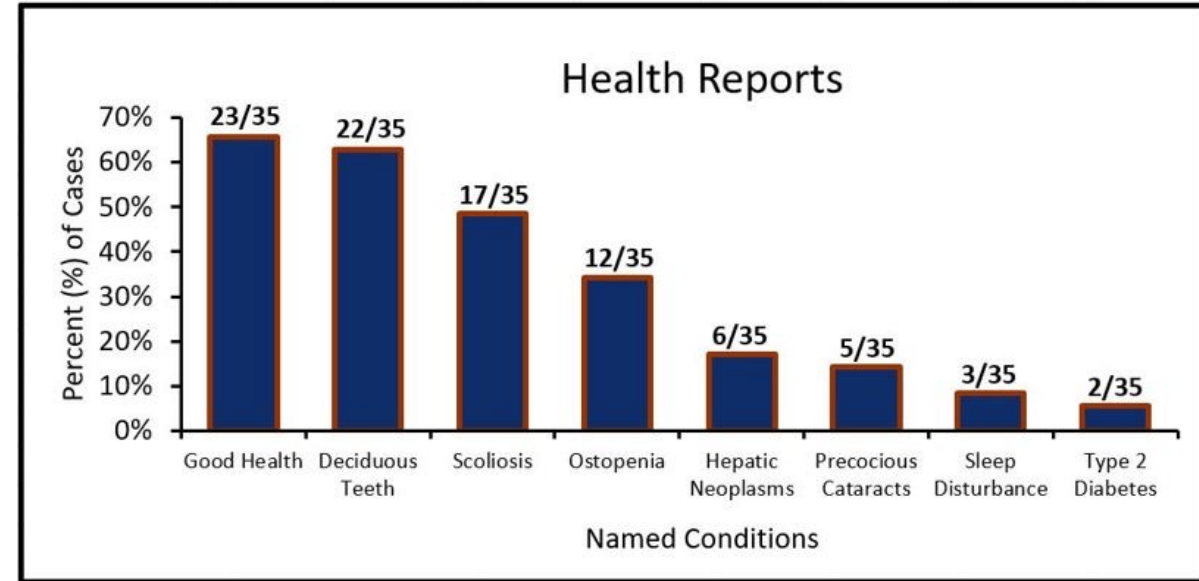
- Careful assessment of renal function should be pursued periodically, in order to prevent a possible **renal insufficiency**.

# Ophthalmologic in WHS



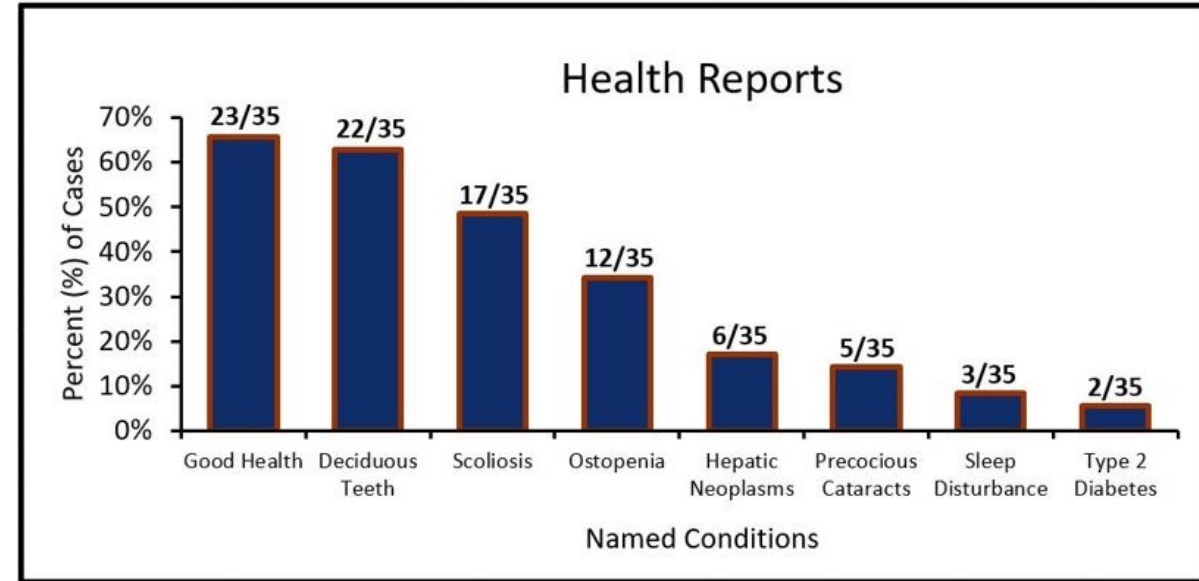
- Precocious cataracts
- Unilateral/bilateral cataracts diagnosed in **5** (14%) individuals between ages 22 and 28

# Sleep disturbance in WHS



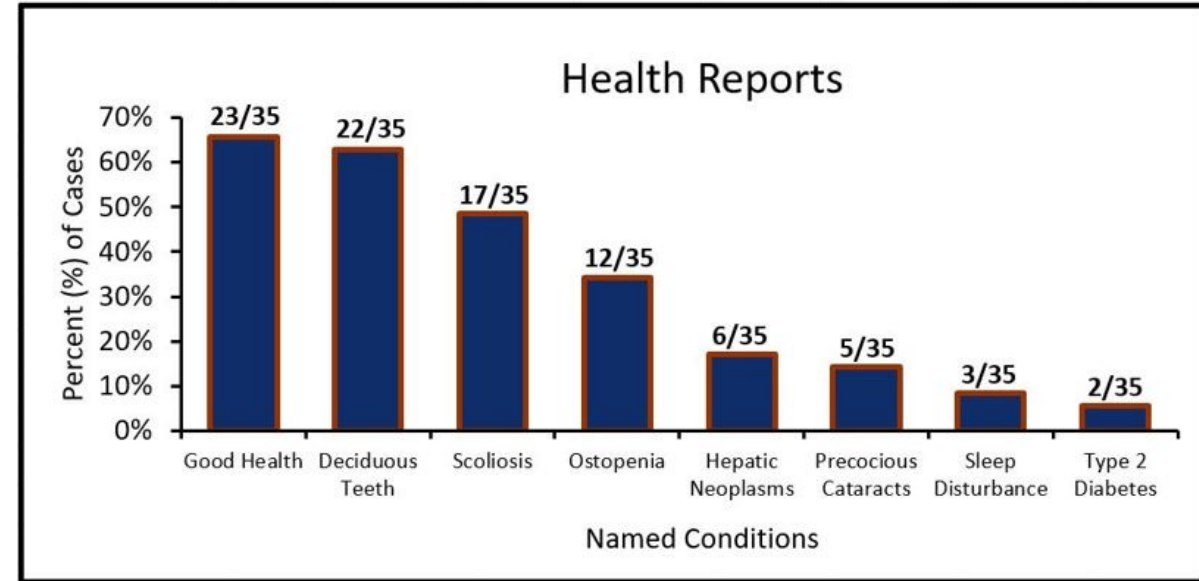
- Frequent awakenings during the night (midnight→4 a.m.) were reported in **3** (9%)

# Other clinical issues in WHS



- Type 2 diabetes was reported in **2/35** (6%), diagnosed at age 13 and 33
  - Nonfamilial hypercholesterolemia in **2/35** (6%)
- **1/35** female never experience her menarche, & **1/35** had amenorrhea from age 33
- About **13/35** (37%) underwent major surgery for various indications

# Other clinical issues in WHS



- About **13/35 (37%)** underwent major surgery for various indications:
  - Thyroid carcinoma (**1**, age 30), right mastitis (**2**, age 19), pancreatitis (**1**, age 25), bladder exstrophy (**2**, age 9/12), intussusception (**1**, age 1), cholecystectomy (**1**, age 12), uni-bilateral cataracts (**5**, between ages 22 and 28)

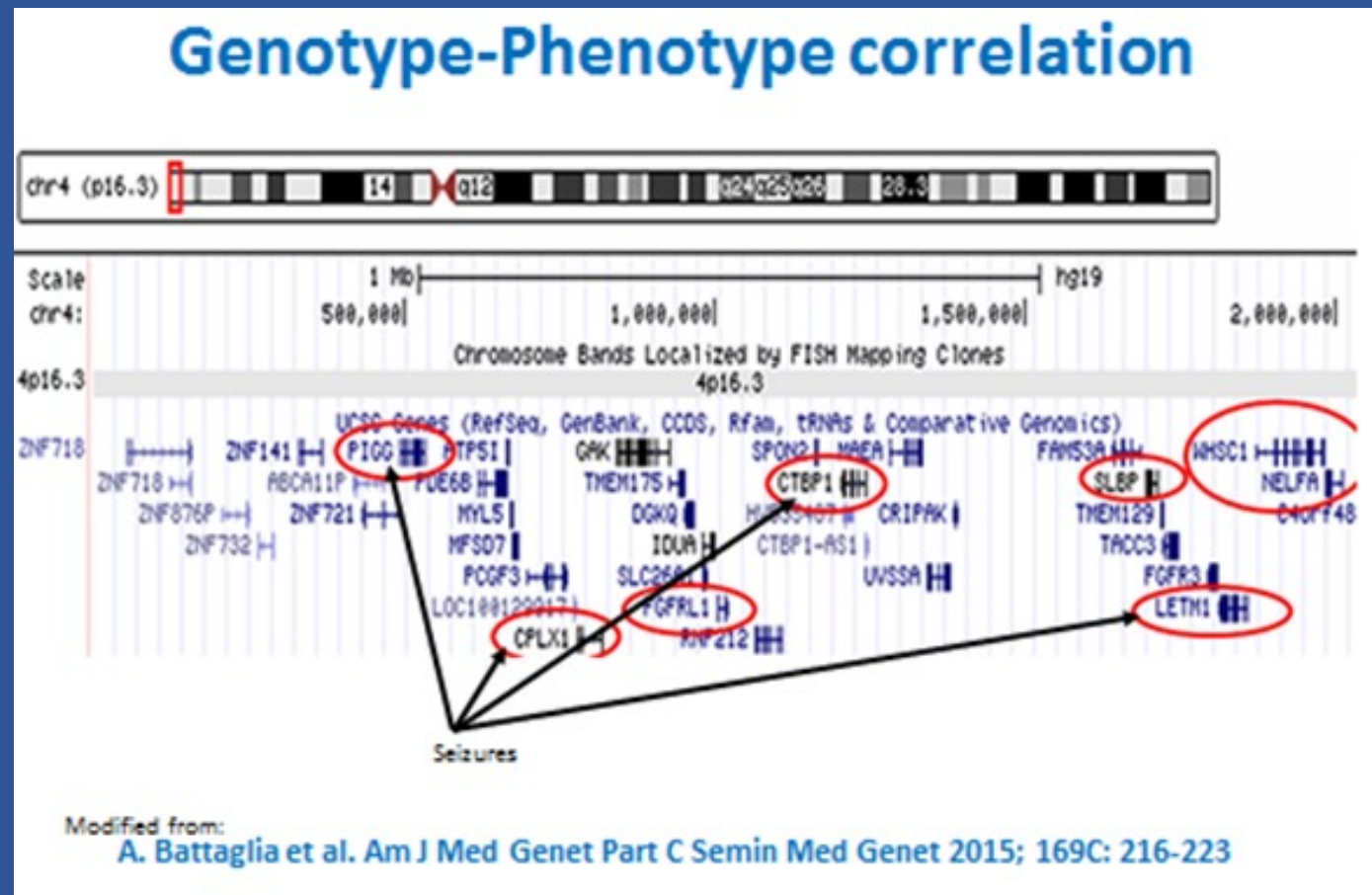
# Seizures outcome in WHS

- All but 1 adult (on CBZ, PHT, LTG, DZP) were ***seizures free***.
- Although, in 34/35 seizures stopped between ages 2 and 14 years,
- 10 individuals, aged between 16 and 34 years, were ***still receiving*** antiepileptic drugs

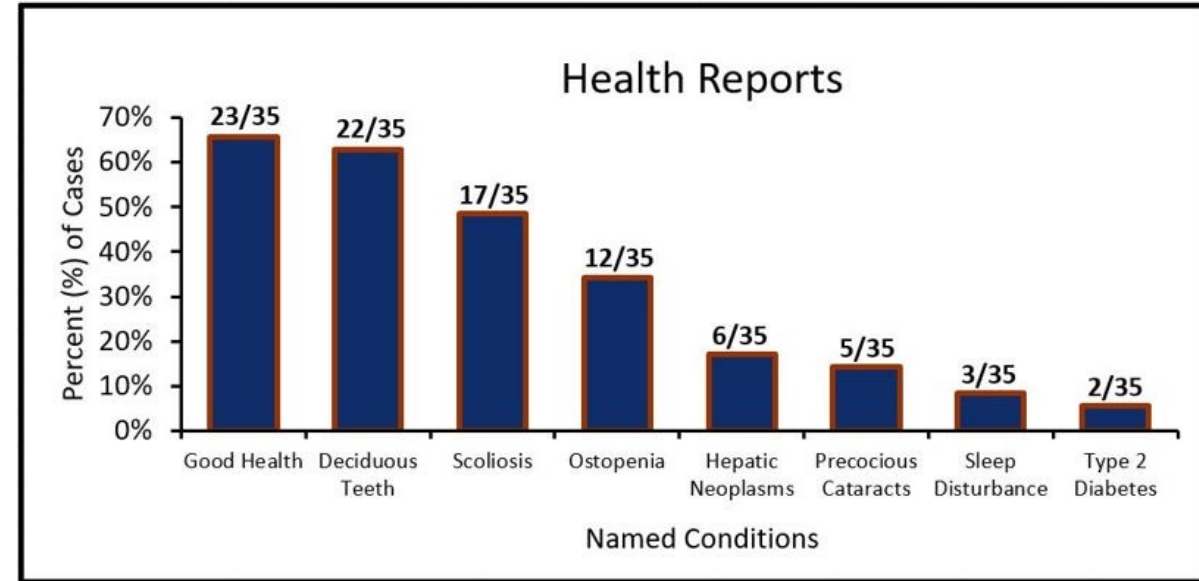
# The “Genotype-First” Era

## Cytogenomic microarray (CMA) period

- Ho et al (2016) reviewed the relevant patients with microdeletions of distal 4p16 and proposed that **PIGG** was a good candidate gene besides **LETM1** underlying seizures in WHS.



# Recommendations on routine care in adults with WHS




- Annual abdominal sonograms of the liver looking for hepatic adenomas
- Annual ophthalmology examination
- Annual assessment of renal function, CBC, cholesterolemia
- Referral to an orthopedist to check on the severity of scoliosis and plan its treatment (? Hip displacement/subluxation)
- DEXA scan at around 20-30 years of age or if any occurrence of fractures
- Routine dental evaluations (hygiene & care)

# Part 2: Patient-reported outcomes PROS

ORIGINAL ARTICLE

AMERICAN JOURNAL OF PART  
medical genetics **A** WILEY

## Natural history study of adults with Wolf–Hirschhorn syndrome 2: Patient-reported outcomes study

John C. Carey<sup>1</sup>  | Amanda Lortz<sup>2</sup> | Alyssa Mendel<sup>3</sup> | Agatino Battaglia<sup>4</sup> 

*AJMG* 185:2065, 2021

John C Carey

# Methods- the CoRDS registry study

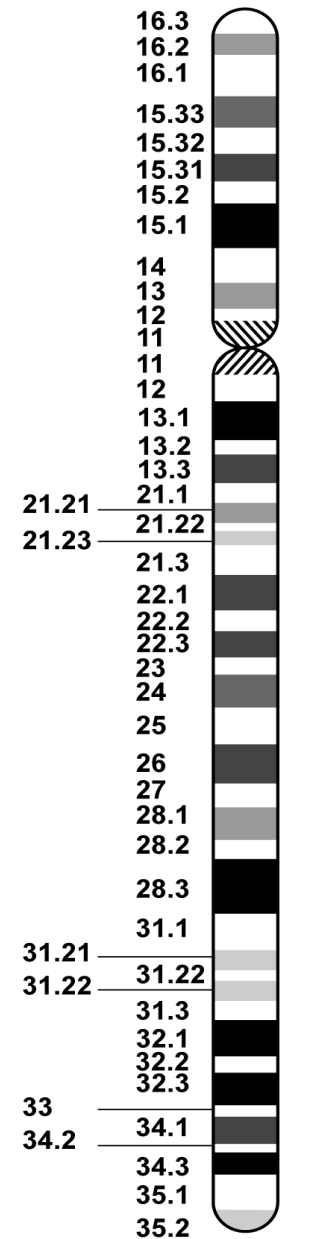
- 30 caretakers/parents of individuals >18ys of age voluntarily answered a survey consisting of demographic, cytogenetic, and medical issues.
- These data were entered into the online CoRDS.

# Methods- the CoRDS registry study

- CoRDS (Coordination of Rare Diseases at Sanford) is a registry of rare disease conditions based in South Dakota  
and sponsored by Sanford Research  
<https://research.sanfordhealth.org/rare-disease-registry>
- Has over 80 “partners”, >50 having registries
- 4p- support group joined in 2014
- As of 2021, 103 families of persons with WHS /4p- had entered information on their family member
- Online survey of demographic and medical information of family member with WHS/4p-

# Summary of major sections, CoRDS registry survey and Number of caretakers completing the sections

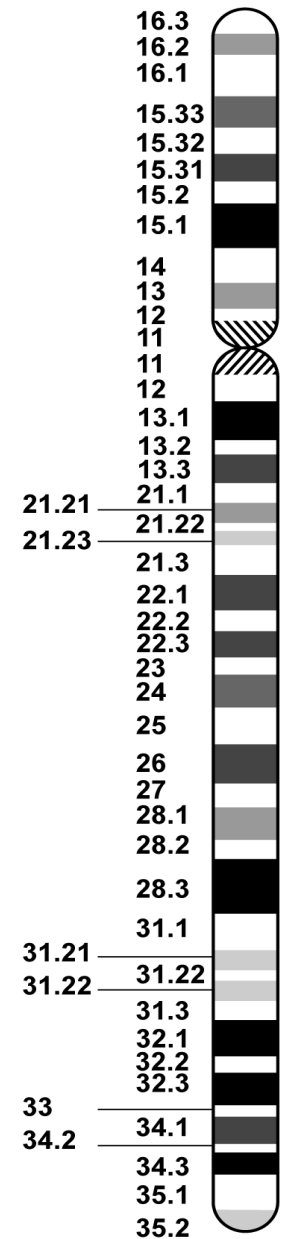
- Surveys: 30 persons over 18 years of age
- 26 were from the USA and 4 from EU, Canada, Australia
- All had deletion of **4p16.3**, most determined by karyotype, due to their age of Dx being prior to CMA
  - 4 had 4p deletion as part of unbalanced translocation
- 2 of the 30 individuals were deceased



Ch. 4  
850 band

# Summary of major sections, CoRDS registry survey and Number of caretakers completing the sections

- Surveys: 30 persons over 18 years of age (2/30 were deceased)
- 30 surveys with demographic, genetic diagnosis, and some medical information: 21 of 28 were female, average age of persons 30 years (range 22-64 years)
- Only 12 completed surveys with Daily Living sections

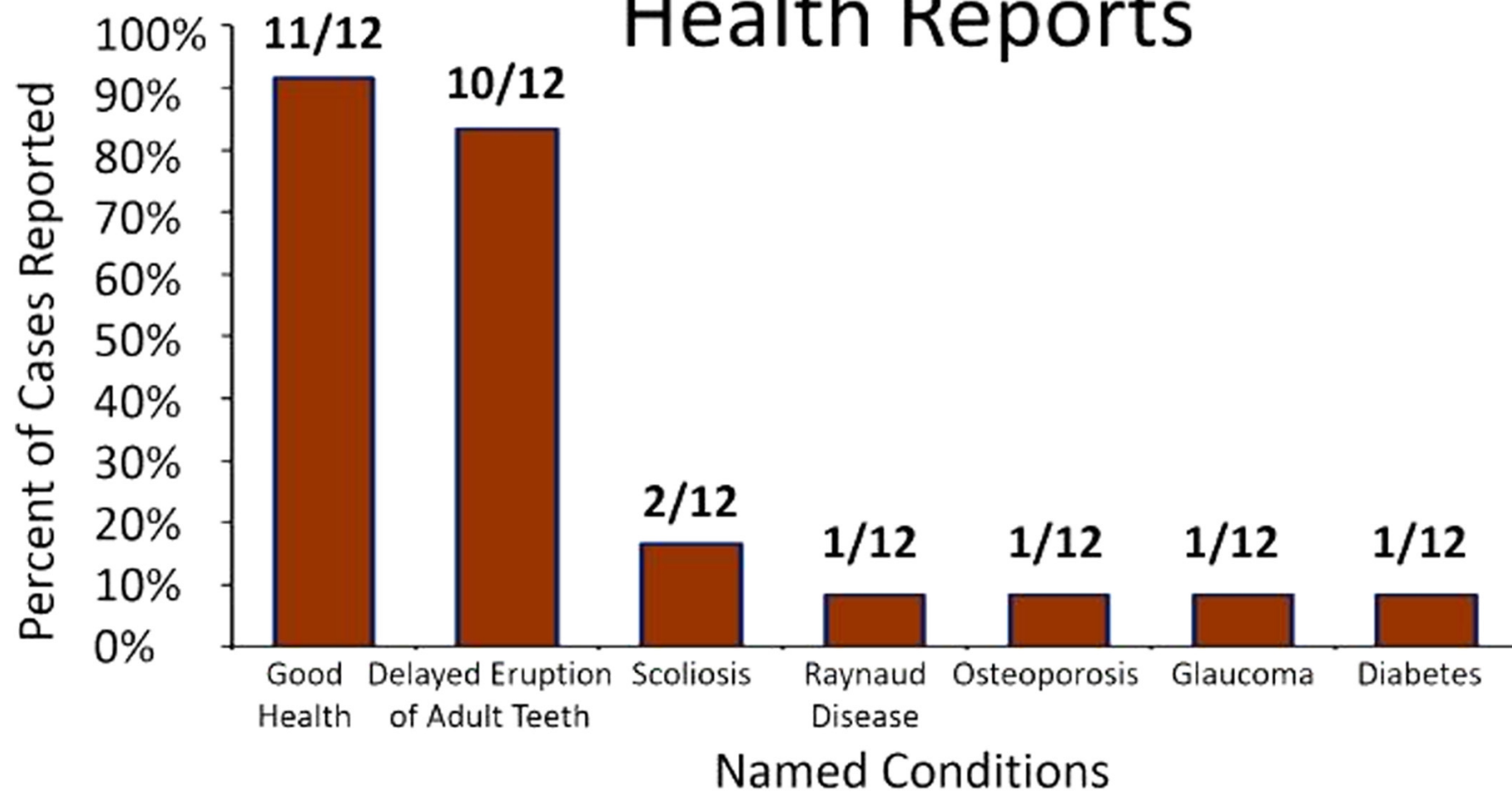


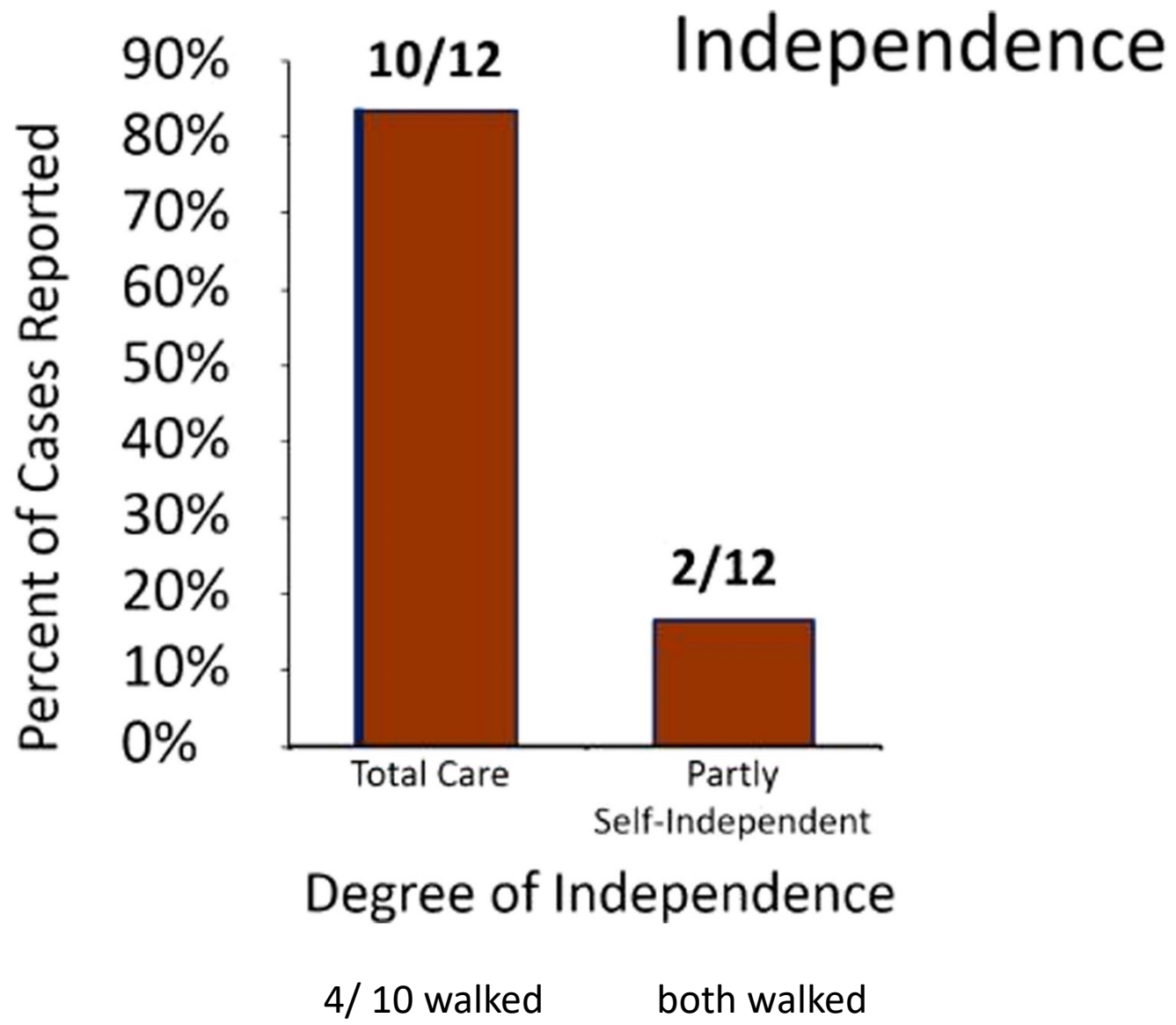
# Summary of major sections, CoRDS registry survey and Number of caretakers completing the sections

Major sections <sup>a</sup>	# of parents/caretakers completing section
Instructions	30
Permissions and data sharing <sup>b</sup>	30
Demographic information <sup>b</sup>	30
Diagnosis	30
Primary diagnosis	
Rare disease symptoms	
Anomalies	
Genetic diagnosis	30
Gestation/Birth	30
Medical history	30
Seizures/Epilepsy	30
Daily living	12

PROS N= 12 adults

## Health Reports





# PROS: Daily Living

- 5 of the 12 individuals with WHS lived in their parents' home
- 5 lived in a group home
- 2 resided in a care facility

# Summary & Conclusions

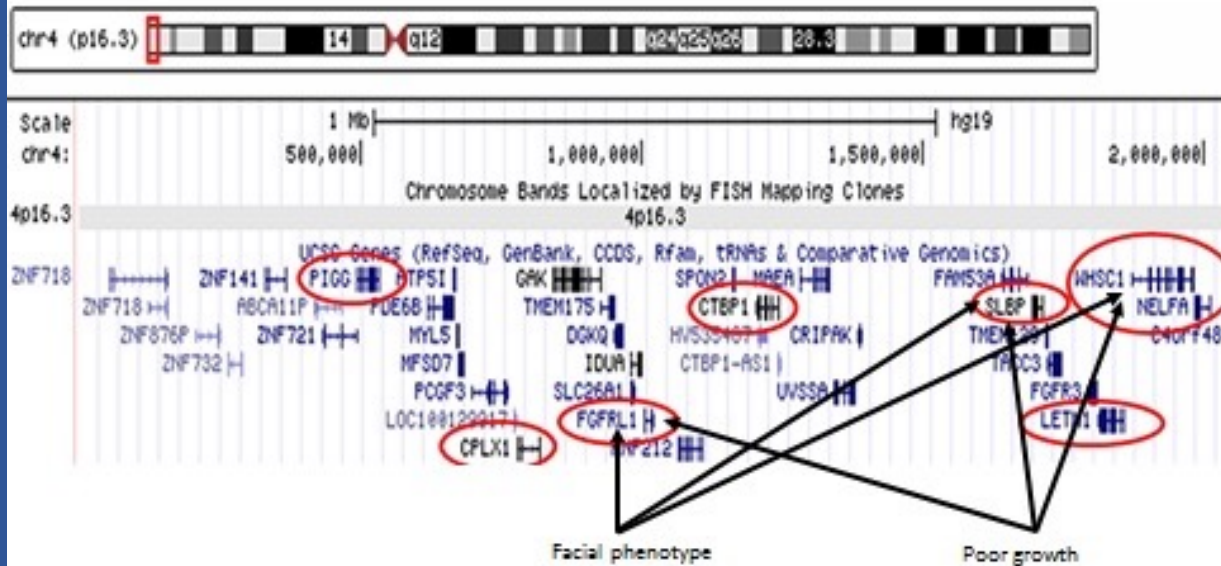
- Report on **47 adult persons** with WHS (only 11 in the literature)
- Both samples have a selection **bias** toward one end of spectrum of medical issues and daily living
- Despite limitations adds to our knowledge of medical conditions and help inform guidelines of **health supervision**

# The “Genotype-First” Era

## Clinical Exome Sequencing (ES) period

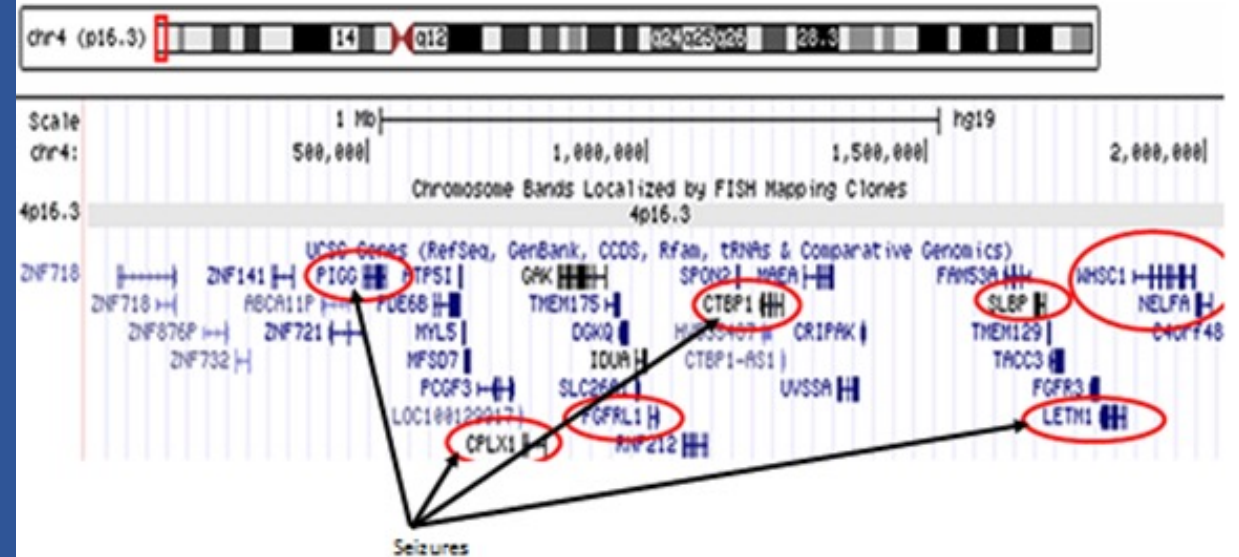
- There is convincing clinical evidence that the pathogenesis of the WHS phenotype is **multigenic**
- The WHS core phenotype (PPNGD, Distinctive craniofacial features, ID, seizures) is due to haploinsufficiency of several closely linked genes

### Genotype-Phenotype correlation



Modified from:  
A. Battaglia et al. Am J Med Genet Part C Semin Med Genet 2015; 169C: 216-223

### Genotype-Phenotype correlation



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A. Battaglia et al. Am J Med Genet Part C Semin Med Genet 2015; 169C: 216-223

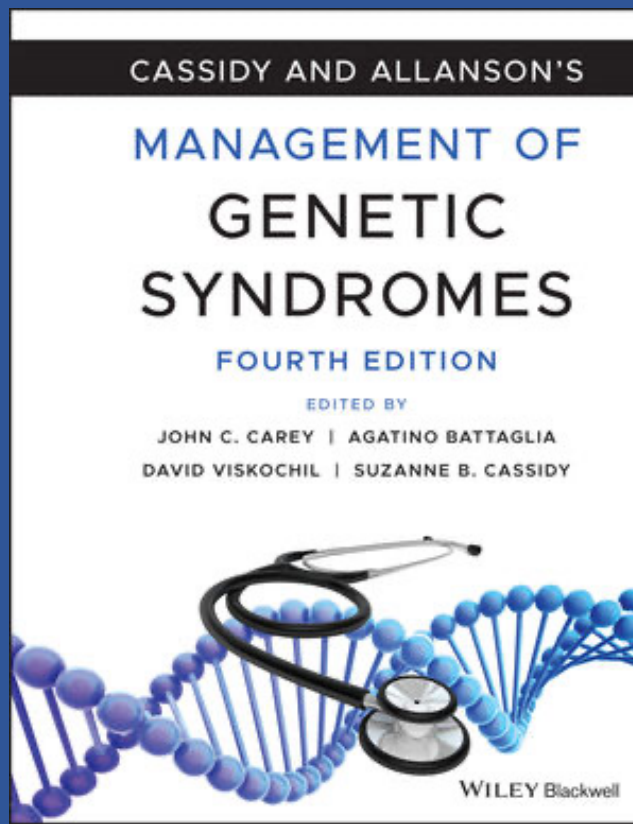


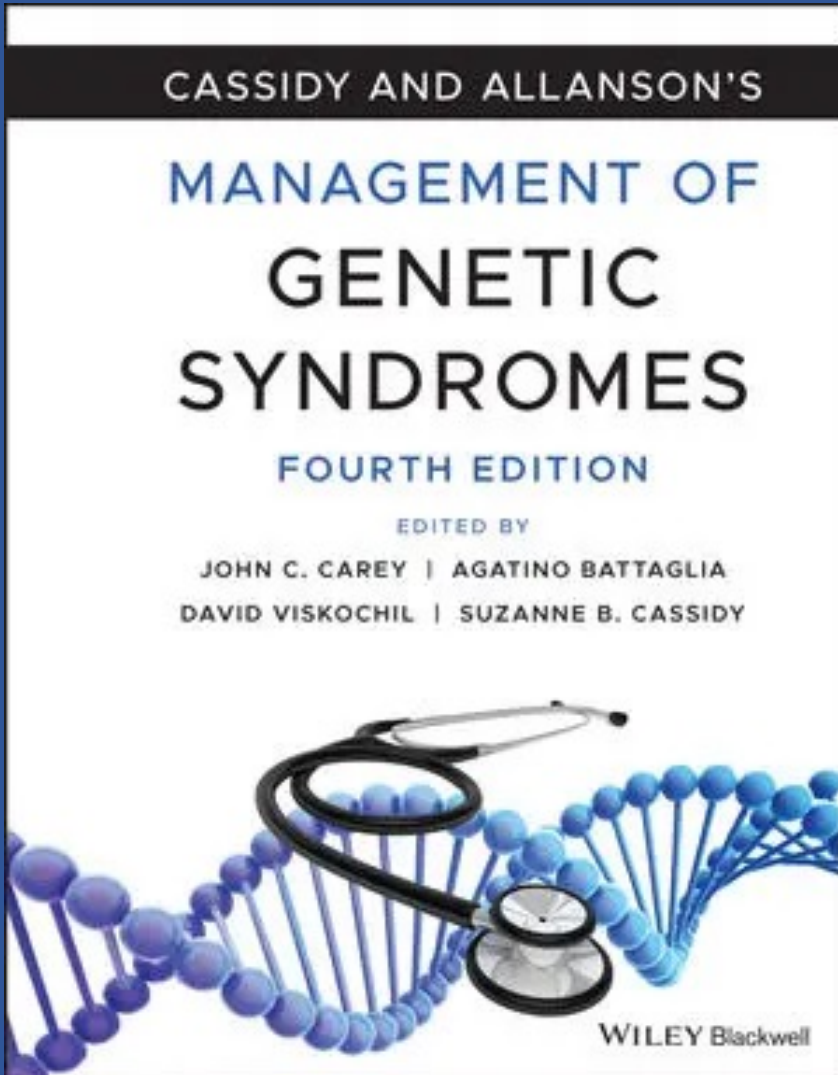
Oligodontia in an individual with WHS



Peg  
lateral  
incisor

Possiamo avere in salotto la più preziosa libreria del mondo, ma se nessuno ci guida, tenendoci per mano, non sapremo mai quale libro scegliere.





19

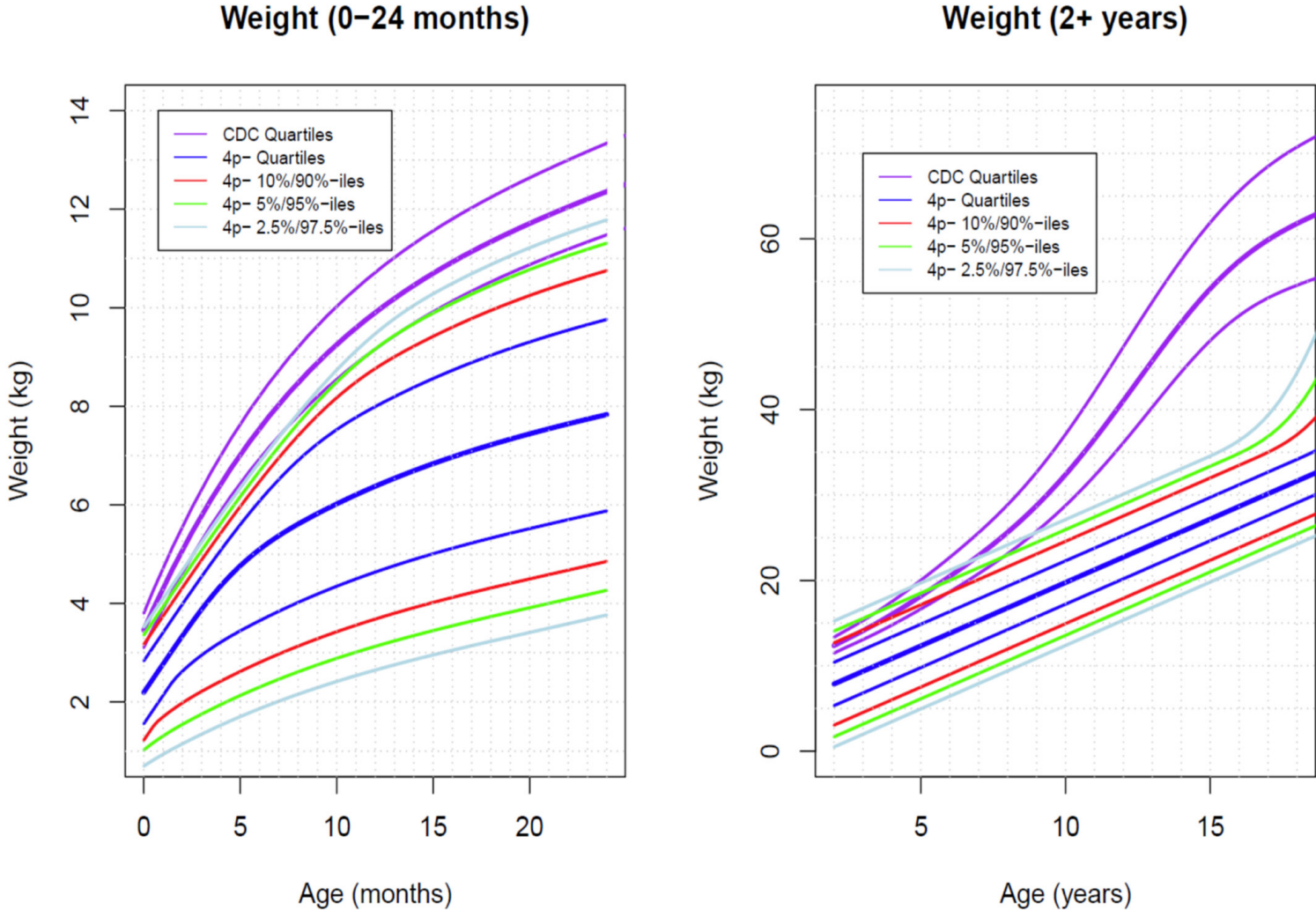
## DELETION 4p: WOLF-HIRSCHHORN SYNDROME

AGATINO BATTAGLIA

*Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry, Calambrone, Pisa, Italy; and Division of Medical Genetics, Department of Pediatrics, **University of Utah** School of Medicine, Salt Lake City, Utah, USA; and Division of Medical Genetics, Department of Pediatrics, Sanford School of Medicine, **University of South Dakota**, Sioux Falls, South Dakota, USA*

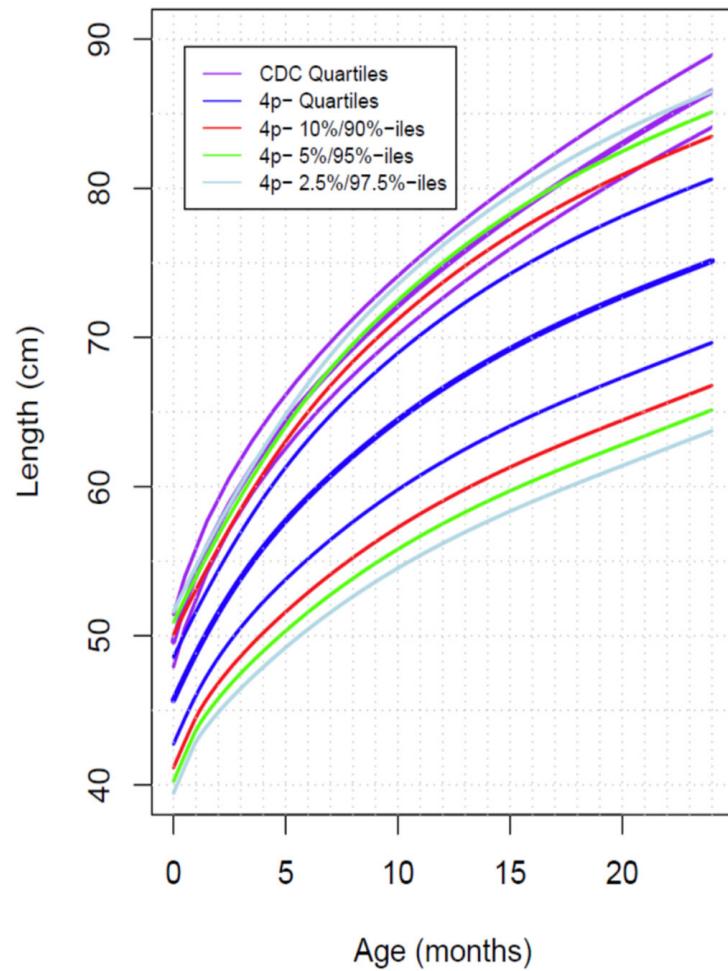
# Extended Growth Curves for the Wolf-Hirschhorn Syndrome (4p-)

(Calhoun et al. 2025. Am J Med Genet A197. <https://doi.org/10.1002/ajmg.a.64075>).

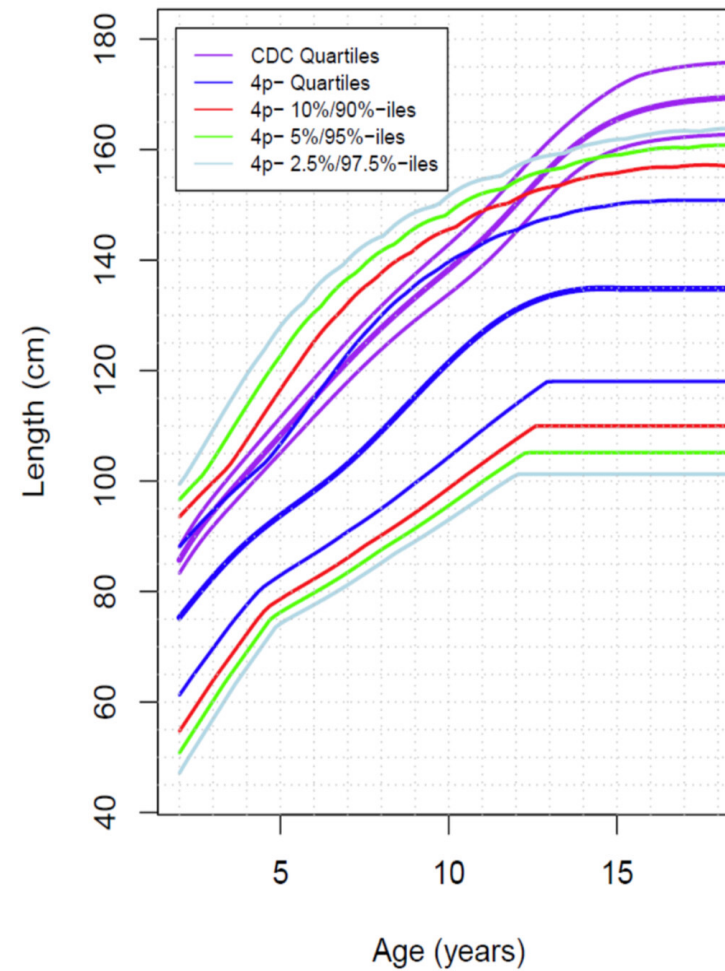


# Extended Growth Curves for the Wolf-Hirschhorn Syndrome (4p-)

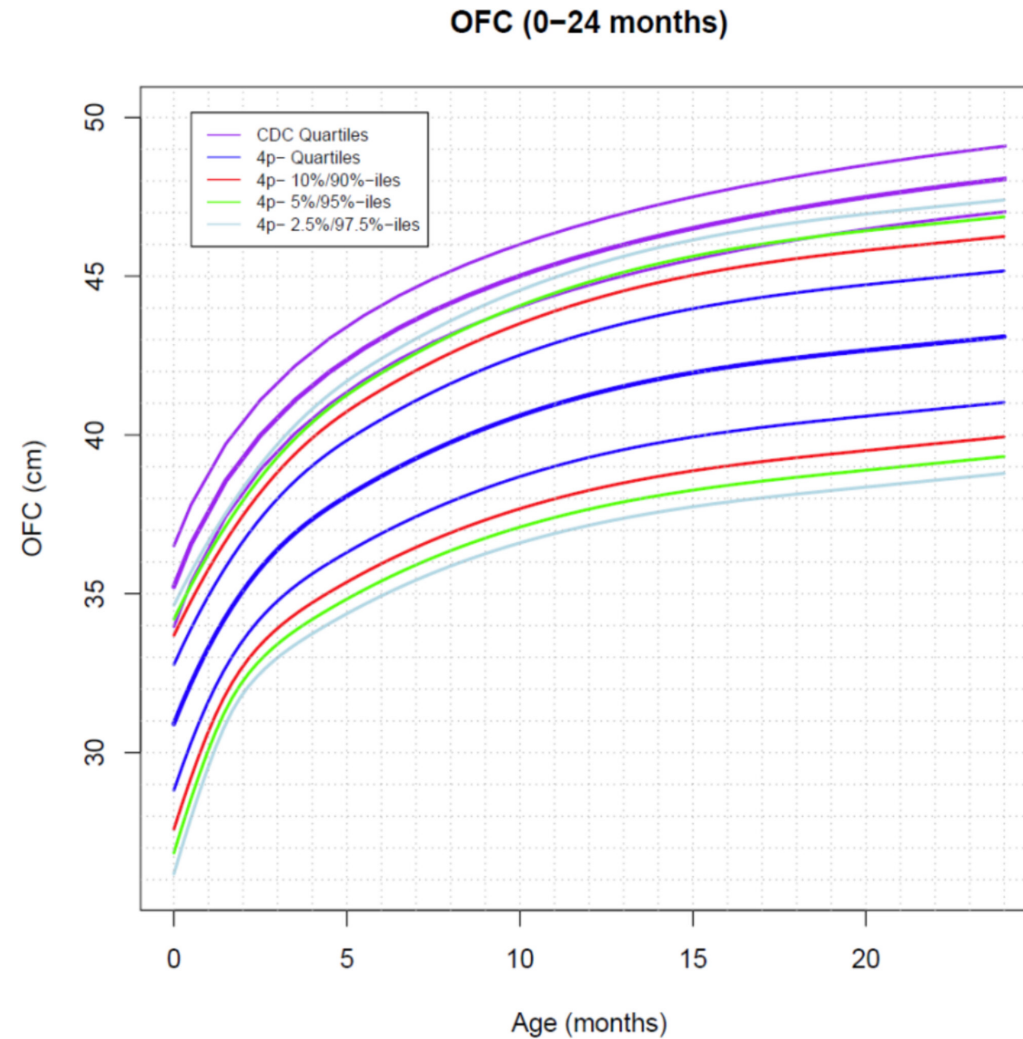
Length (0-24 months)



Length (2+ years)



# Extended Growth Curves for the Wolf-Hirschhorn Syndrome (4p-)



Grazie alle famiglie ed ai giovani adulti che  
abbiamo incontrato in questo periodo.

