2nd Annual

CHARGE Syndrome

Professional Day

July 28, 2011
Rosen Shingle Creek
Orlando, Florida

PROFESSIONAL DAY PROGRAM AND HANDOUTS

The CHARGE Syndrome Foundation, Inc.
www.chargesyndrome.org

Thursday, July 28th, 2011

8:00 - 9:00	**Professional Day Registration at registration desk in Transportation Lobby *(between hotel lobby and conference center)***
8:00 - 9:00	**Continental Breakfast in Wekiwa # 6**
8:00 - 9:00	**Poster Set up in Wekiwa # 5**
9:00 - 9:15	**Welcome and Opening Remarks in Wekiwa 3&4**
9:15 - 9:40	**Molecular Studies to uncover the Cellular Functions of CHD7 – Peter Scacheri**
9:40 - 10:05	**Phenotypes in Drosophila Model of CHARGE Syndrome – Daniel Marenda**
10:05 - 10:30	**Advances in Understanding CHD7 through Use of Genetically Engineered Mice – Donna Martin, E. Hurd, W. Layman, Y. Raphael**
10:30 – 11:00	**Break**
11:00 – 11:25	**CHD7 Mutations & CHARGE Syndrome: Clinical & Diagnostic Implications of an Expanding Phenotype – Conny van Ravenswaaij-Arts, J. Bergman, N. Janssen, L. Hoesfloot, M. Jongmans, R. Hofstra**
11:25 – 11:50	**National Cochlear Implantation Studies with Children Who Experience Deafblindness: Results For Participants With CHARGE Syndrome – Susan Bashinsky**
11:50 – 12:15	**The Child's Voice (Case Study: Interview with a 9 Year old) – Eva Seljestad, Wenche Anderson**
12:15 – 1:15	**Lunch in Wekiwa #6**
1:15 – 2:30	**Poster Presentations in Wekiwa # 5** **CHARGE Syndrome and the Neurophysiological Benefits of Tai Chi – Maria Alejandra Ramirez, Tim Hartshorne, Sharon Barrey Grassic** **Sign Chi – Sharon Barrey Grassick** **Temperment & Goodness of Fit – Stephanie Budde, Tim Hartshorne** **Victory and Fragrance – Yun Hua (Stella) Chang** **Technology for Learning and Fun; Using Assistive Technology in the Home and in the Classroom – Holly Cooper** **Effects of Self-Directed Teaching Program on the Verbal Behavior of Parents Preparing for a Psychiatric Appointment for their Child with CHARGE Syndrome – Lauri S Denno** **Feeling Good – Gail Deuce** **Activities of SENSE – Gail Deuce** **Activities of the CHARGE Family Support Group and SENSE – Simon Howard, Gail Deuce** **Congenital Heart Defects Due to CHD&-mutations – Nicole Jansse, Livia Kapsuta, Gideon J. du Marchie Servaas, Lies H. Hoefsloot, Mieke (WS) Kerstjens, Conny M.A. van Ravenswaaij-Arts,** **CHARGE Syndrome in German Speaking Countries – Claudia Junghaus, Ursula Horsch, Andrea Scheels** **Components of Educational Evaluations for Children with CHARGE Syndrome – Martha Majors, Christopher Underwood** **CHARGE Families in the Know Read….. – Kathy Mcnulty, Lori Swanson** **Adolescent Development in CHARGE: Six Cases – Tasha Nacarato, Tim Hartshorne, Kasee Stratton** **Understanding Sleep Apmea in Children with CHARGE Syndrome – Carrie Lee Trider, Kim Blake** **Experience of Siblings of Individuals with CHARGE – Rachel Vert**
2:30 – 2:55	**Problems with Self-Regulation & Behavior in CHARGE Syndrome – Tim Hartshorne**
2:55 – 3:20	**Identifying the "P" in CHARGE: Pain and the Relationship of Pain to Challenging Behavior – Kasee Stratton**
3:20 – 3:45	**Navigating the NIH – Tiina Urv**
3:45 – 4:10	**Break**
4:10 – 4:35	**CHARGE Syndrome: Quality of Life in Adolescence & Adulthood (study) – Nancy Salem Hartshorne, Kim Blake, J MacCuspie, T Nacarato**
4:35 – 5:00	**So Many Ways to Have a Conversation – Martha Majors**
5:00 – 5:25	**The Potential of Diversity – Andrea Scheele, Ursula Horsch**
5:25 – 5:30	**Concluding Remarks**

Molecular Studies to Uncover the Cellular Functions of CHD7.

Thursday, 07/28/11
Platform #1: 9:15-9:40
Wekiwa 3 & 4

Peter C. Scacheri, PhD
Assistant Professor
Department of Genetics
Case Western Reserve University

Presenter Information:

Peter Scacheri graduated with a BS in Biology from Gettysburg College and earned his Ph.D. in Biochemistry and Molecular Genetics from the University of Pittsburgh. His graduate work was focused on the genetics of muscular dystrophy. His postdoctoral fellowship was at the National Human Genome Research Institute at the National Institutes of Health, where he studied a type of cancer that affects the endocrine organs. Dr. Scacheri is currently an Assistant Professor in the Department of Genetics at Case Western Reserve University School of Medicine. The Scacheri lab uses cutting edge genomics to investigate the function of the CHD7 protein and its role in CHARGE syndrome. Dr. Scacheri's research on CHARGE syndrome is supported by an R01 grant awarded from the National Institute of Child Health and Human Development.

Presentation Abstract:

It is known that DNA mutations in the CHD7 gene cause CHARGE syndrome, but how? My lab has been addressing this question by investigating the function of CHD7 in both normal and CHD7 mutant cells from humans, mice, and zebrafish. Our research indicates that CHD7 functions in the cell nucleus to fine-tune the expression of genes that control the development of organs that are affected in CHARGE syndrome. In addition CHD7 activates genes that encode components of the protein manufacturing machinery of all living cells. These findings suggest that the multiple anomalies in CHARGE syndrome are due to the combined effects of altered gene expression and reduced protein synthesis.

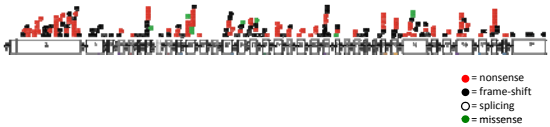
Molecular studies to uncover the cellular functions of CHD7.

Peter C. Scacheri, PhD
Department of Genetics
Case Western Reserve University
Cleveland, OH

Outline

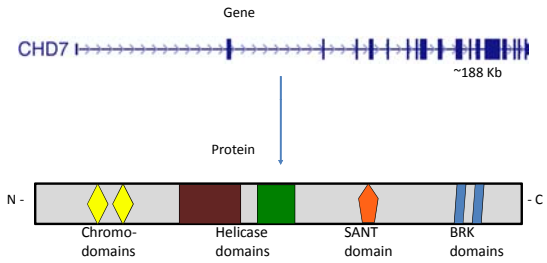
- Overview of the cellular functions of CHD7
  - Regulator of genes that orchestrate development
  - Regulator of protein synthesis.
- Zebrafish model of CHARGE syndrome
- Overview of high-throughput sequencing of CHD7 to identify mutations in patient cohorts
- Where we are headed

Mutations in *CHD7* (chromodomain helicase DNA-binding protein 7) cause CHARGE syndrome

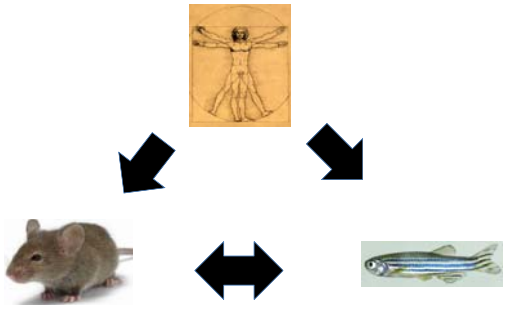


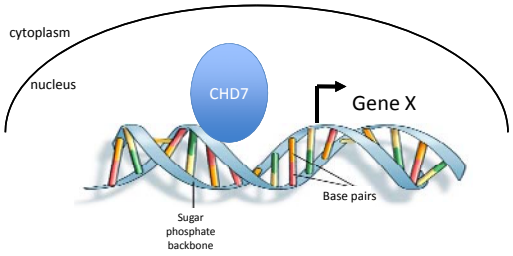
- Mutations in 58-71% of patients
- Arise spontaneously
- Mostly protein truncation mutations (Loss-of-function)
- Haploinsufficiency (one-half the amount of CHD7 protein is made, but half isn't enough for normal development)

What does CHD7 do?



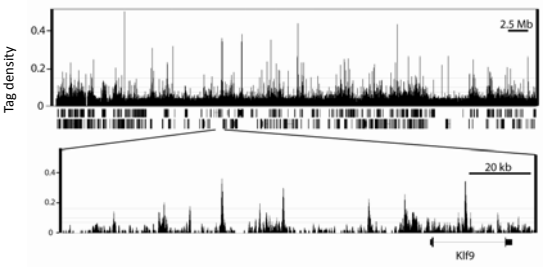
Model Systems for studying CHD7 function





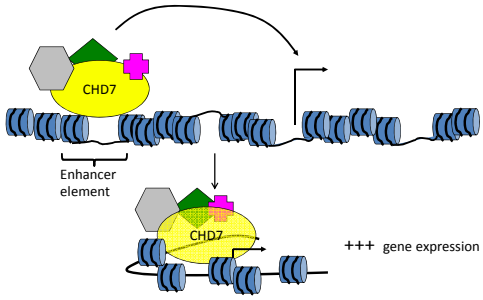
ChIP-seq – A method to find the sites on DNA where CHD7 binds

CHD7 ChIP-seq (embryonic stem (ES) cells)



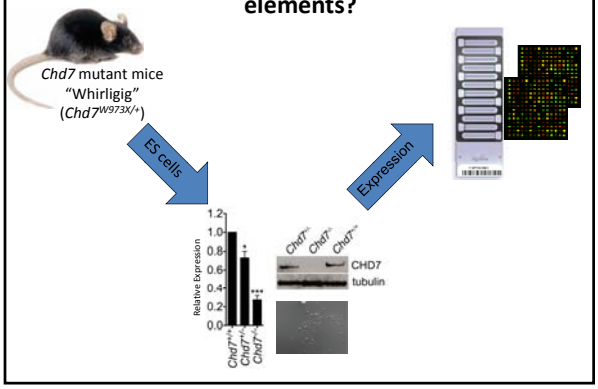
> 20,000 CHD7 binding sites across the genome

CHD7 binding sites are gene enhancer elements

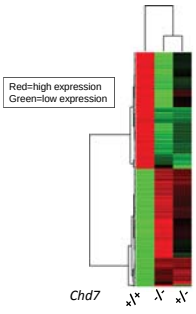


WHAT ARE THESE GENES?
WHICH CELL TYPE AND WHICH STAGE OF DEVELOPMENT ARE THESE GENES AFFECTED?

Is there a regulatory role for CHD7 at enhancer elements?

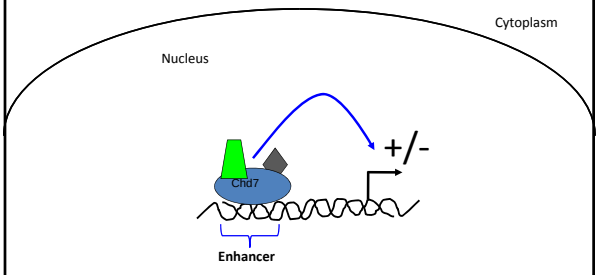


CHD7 Mutations Cause Changes in Gene Expression

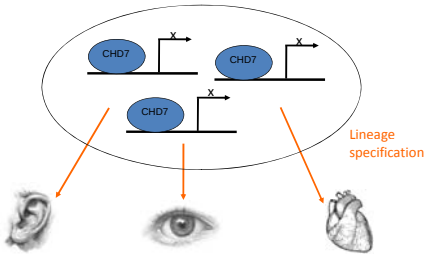


- CHD7 binds to thousands of genes
- Only about 10% have altered expression in ES cells
- We think most CHD7 target genes probably change later in development in the eyes, ears, heart, and other tissues affected in CHARGE syndrome

CHD7 as a regulator of tissue-specific genes

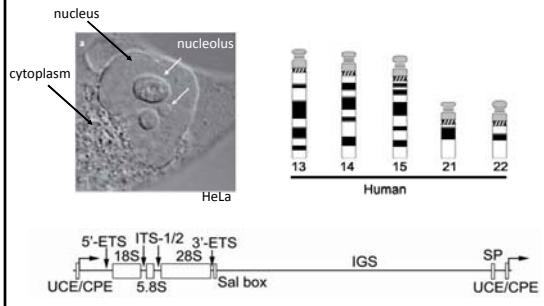


Working Model



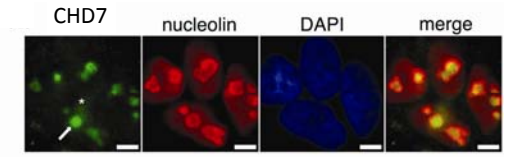
Misexpression of lineage specific genes during embryonic development, due to haploinsufficiency of CHD7, leads to CHARGE syndrome.

The Nucleolus and Ribosomal RNA



EST = external transcribed spacer	SP = spacer promoter
ITS = internal transcribed spacer	UCE = upstream control element
IGS = intergenic spacer	CPE = core promoter element

CHD7 is also located in the cell nucleolus

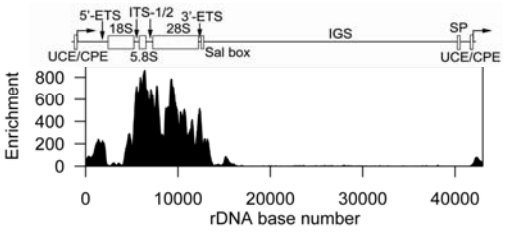


Gabe Zentner

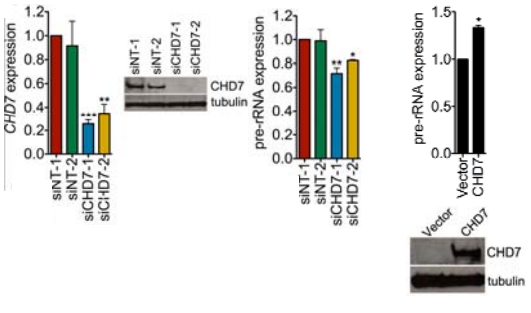
Ribosomal RNA (rRNA)

- rRNA accounts for 60-80% of all RNA in the cell
- rRNA makes proteins and helps cells grow and divide
- Problems with rRNA synthesis kills cells or slows their growth
- Human diseases due to problems with rRNA:
  - Treacher Collins syndrome
  - Diamond-Blackfan anemia
  - Cancer

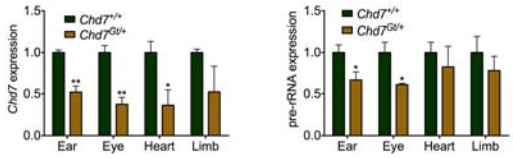
CHD7 binds to ribosomal RNA genes



CHD7 Helps Make Ribosomal RNA



Mutations in the *Chd7* gene in CHARGE mouse models reduce rRNA levels



Problems with rRNA production can cause genetic diseases

Diamond-Blackfan anemia

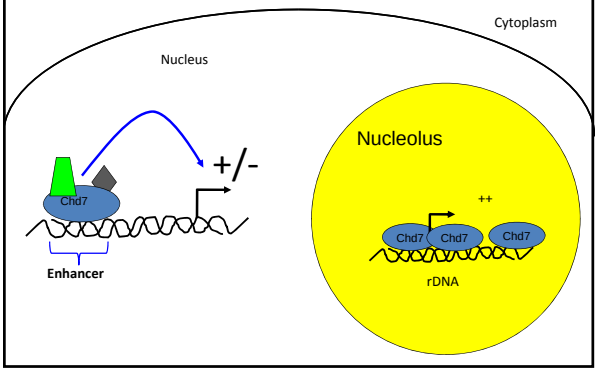
- Mutations in RPS19, and other ribosomal genes
- Mostly sporadic dominant
- Likely haploinsufficiency
- Red blood cell aplasia, craniofacial, thumb, cardiac and urogenital abnormalities

Treacher Collins syndrome

- Mutations in TCOF1, encoding nucleolar treacle
- Autosomal Dominant
- Haploinsufficiency
- craniofacial abnormalities, including coloboma of the lid, micrognathia, microtia and other ear deformities. Conductive hearing loss, cleft palate

CHARGE Syndrome

Summary: Two functions for CHD7



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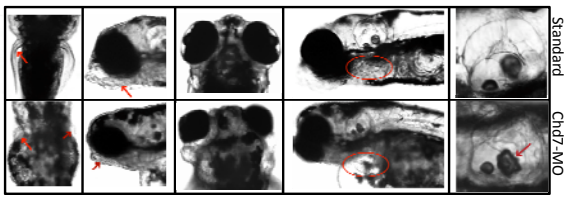
Zebrafish: A powerful model system

- Zebrafish is a vertebrate that shares the majority of genes with mammals, including CHD7
- Developmental processes are highly conserved between zebrafish and mammals
- Transparent embryogenesis that is also very rapid
  - Egg to embryo within 24 hours
- Targeted gene knockdown is feasible and straightforward (Morpholino (MO) technology)
- Low cost

Stephanie Balow

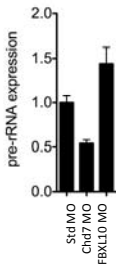
Chd7-MO phenotypes

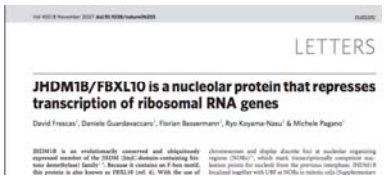
(Highly Dose Dependent)



Pectoral Fin Defects | Jawless | Ocular Edema, Lens Defects | Cardiac edema, Weak heartbeat | Deformed otoliths

Effects on rRNA biogenesis in zebrafish

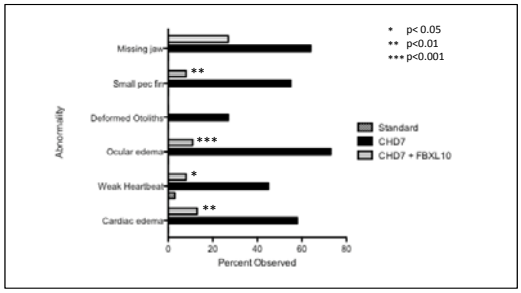


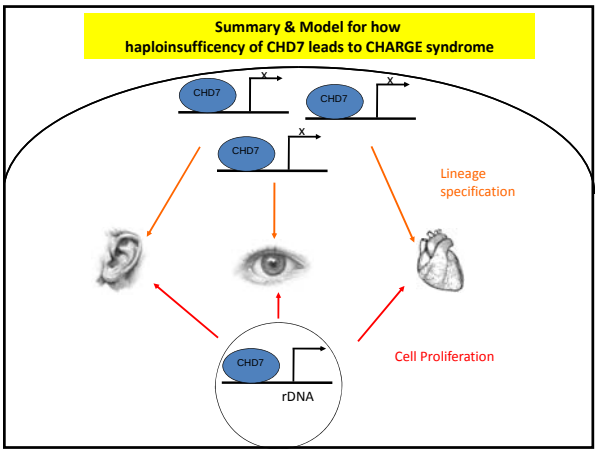


LETTERS

JHDM1B/FBXL10 is a nucleolar protein that represses transcription of ribosomal RNA genes

Rescue of CHARGE phenotype





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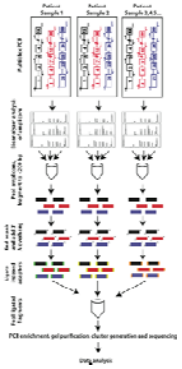
CHD7 gene sequence analysis that is fast and cheap

Illumina Genome Analyzer

- CHD7 gene is big, mutation analysis is expensive through commercial labs.
- CHARGE syndrome shares clinical overlap with Kallmann syndrome, T-cell immunodeficiency, idiopathic scoliosis, and DiGeorge syndrome.
- Allows for testing in large patient cohorts

Cindy Bartels

Strategy



It works!

- We pooled ~50 patients with known mutations in CHD7 and ran them through our analysis. We were "blinded" to the location of the CHD7 mutation in all patients. Virtually all CHD7 mutations were detected!
- Also tested 80 patients with isolated coloboma.
- Major reduction in costs.

Summary

- CHD7 binds to thousands of gene enhancer elements
  - These enhancers regulate the genes that specify the tissues & organs that are affected in CHARGE syndrome.
- CHD7 controls the genes that are responsible for synthesizing proteins.
- The gene targets of CHD7 are dysregulated in other congenital disorders that show clinical overlap with CHARGE syndrome.
- CHD7 mutations can be identified in large patient cohorts relatively quickly and at low cost

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Where we are headed & what we need

- Clinical Samples (blood and skin biopsies)
  - CHD7 mutation screening
  - Generation of induced pluripotent stem cells (iPS cells).
    - Further molecular understanding of human CHD7.
- Additional Government funding for research

Acknowledgments

Scacheri Lab
Cindy Bartels, MS
Batool Akhtar-Zaidi
Michael Schnetz*
Gabe Zentner
Stephanie Balow
Olivia Corradin
Deb Schelling
Alina Saiakhova
Pavel Manaenkov*
Dheepa Balasubramanian, PhD
Lain Pierce, PhD*
*former member

CWRU
Paul Tesar, PhD
Tom LaFramboise, PhD
John Wang, PhD
Xiaodong Zhang, PhD
Maria Hatzoglou, PhD
Peter Harte, PhD

University of Michigan
Donna Martin, MD, PhD

Funding:
NICHD & NHGRI

Publications/Resources

- Review Article on CHARGE syndrome
  - http://www.ncbi.nlm.nih.gov/pubmed/20186815
- CHD7 as an enhancer binding protein
  - http://www.ncbi.nlm.nih.gov/pubmed/20657823
- CHD7 as a regulator of ribosomal genes
  - http://www.ncbi.nlm.nih.gov/pubmed/21355038

Phenotypes in a Drosophila model of CHARGE syndrome

Thursday, 07/28/11
Platform #2: 9:40-10:05
Wekiwa 3 & 4

Daniel R. Marenda
Ph.D., Assistant Professor, Drexel University, Philadelphia PA

Presenter Information:

Dr. Marenda is an Assistant Professor in the department of Biology at Drexel University in Philadelphia.

Presentation Abstract:

In the study of human disease, animal models (called model organisms) often act as surrogates for patients when (as if often the case) experimentation on humans is unfeasitble or unethical. One of these model organisms, the fruit fly Drosophila melanogaster, has been a powerhouse in the understanding of human disease. Using this powerful system, my lab inactivated the Drosophila equivalent of the Chd7 gene in the fly (a gene called kismet), and discovered that kismet was required in the muscle cells of the fly for posture and coordinated movement, and in the fly brain for memory. We also found that kismet is required for the maintenance and growth of axons (structures in brain cells that function similarly to telephone wires, bringing information from one part of the brain to another). By better understanding some of the basic functions of kismet, our hope is that we can shed light on similar functions of CHD7 in humans, and eventually help give all of the researchers working on CHARGE syndrome the information they need to develop a therapeutic intervention for patients with CHARGE."

Phenotypes in a Drosophila Model of CHARGE Syndrome

Daniel R. Marenda, Ph.D.
Assistant Professor

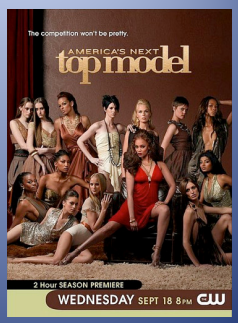
http://www.gpoaccess.gov/usbudget/index.html

First things First:

$$$$ Average 2000-2009

2.149 Trillion income
National Debt (2010): ~12.4 trillion
371.4 billion in interest (~17.3%)
~26.2 billion to NIH (~1.2%)
~4.9 billion to NSF (.22%)
~446.3 billion to DOD (~20.8%)
~109.9 MILLION to NEA (.005%)

Model Organisms:



- Because models are JUST LIKE everybody else…..
- Right???

Why use model systems?

Model Organisms:

- Model organisms are widely used to explore potential causes and treatments for human disease when experimentation on humans would be unfeasible or unethical.

Mice

Yeast

Zebrafish

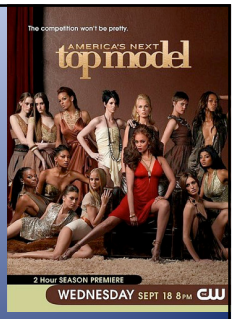
Xenopus

Worms

Plants

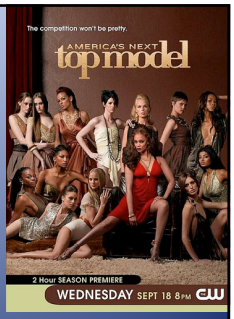
FLIES

Model Organisms:



- The expectation that discoveries made in the organism model will provide insight into the workings of other organisms.

Model Organisms:

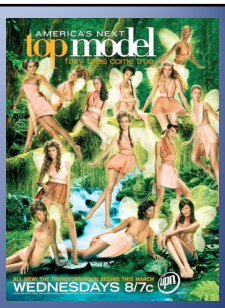


- The expectation that discoveries made in the organism model will provide insight into the workings of other organisms.
- WHY?

Model Organisms:

- This strategy is made possible by the common descent of all living organisms, and the conservation of metabolic and developmental pathways and genetic material over the course of evolution

Model Organisms:



- This strategy is made possible by the common descent of all living organisms, and the conservation of metabolic and developmental pathways and genetic material over the course of evolution

Indeed, flies are like little people with wings

What about the Public Good?

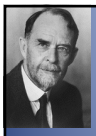
The laws of Heredity

Gregor Mendel

The common garden pea

Mendel did his pioneering work from 1856 to 1865 and his results were published in one paper (reports) in 1866.

X-linked inheritance
Gene linkage



Drosophila

Thomas Hunt Morgan:
Nobel Prize in Medicine or Physiology 1933

"for his discoveries concerning the role played by the chromosome in heredity"

(1) At the time it was generally assumed that chromosomes could not be the carriers of the genetic information.

d be

Neuron
Report

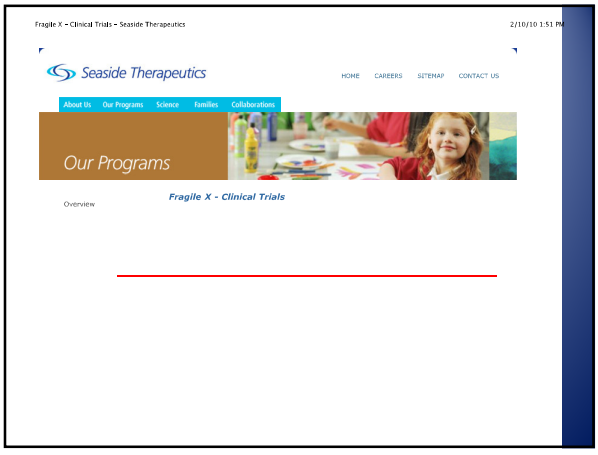
Correction of Fragile X Syndrome in Mice

Gül Dölen,[1,2] Emily Osterweil,[1] B.S. Shankaranarayana Rao,[3] Gordon B. Smith,[1] Benjamin D. Auerbach,[1] Sumantra Chattarji,[4] and Mark F. Bear[1,*]
[1]Howard Hughes Medical Institute, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[2]Department of Neuroscience, Brown Medical School and the Division of Biology and Medicine, Providence, RI 02912, USA
[3]Department of Neurophysiology, National Institute of Mental Health and Neuroscience, Bangalore 560 002, India
[4]National Center for Biological Sciences, Tata Institute of Fundamental Research, Bangalore 560 002, India
*Correspondence: mbear@mit.edu
DOI 10.1016/j.neuron.2007.12.001

Most common form of inherited mental retardation

Most common form of autism

Researchers used mice to decrease glutamate receptor expression in Fragile X mice, and "cured" the disease



Neuron, Vol. 45, 753–764, March 3, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.01.038

Pharmacological Rescue of Synaptic Plasticity, Courtship Behavior, and Mushroom Body Defects in a *Drosophila* Model of Fragile X Syndrome

Sean M.J. McBride,[1,6,*] Catherine H. Choi,[4,5] Yan Wang,[3] David Liebelt,[1] Evan Braunstein,[1] David Ferreiro,[1] Amita Sehgal,[4] Kathleen K. Siwicki,[7] Thomas C. Dockendorff,[2] Hanh T. Nguyen,[2] Thomas V. McDonald,[3] and Thomas A. Jongens[4,*]
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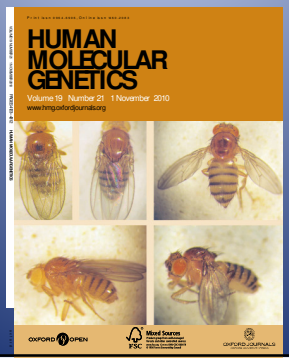
PS: They did it in flies first.

Developing a model of CHARGE Syndrome in Flies.

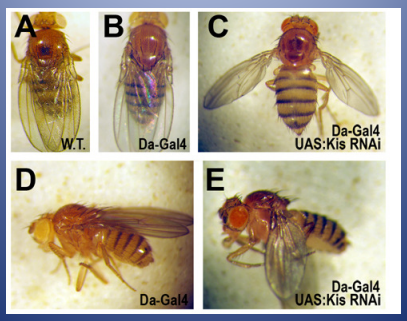


KISMET: Fate; Fortune Homolog of CHD7

PROTEIN DOMAINS
- Chromo-domain: chromatin remodeling and manipulation
- SNF2/ATPase domain: similar to chromatin remodeling proteins
- BRK domain: found only in metazoans. Function is unclear

CELLULAR FUNCTIONS
- Member of the trithorax group of transcriptional activators
- Proposed to facilitate an early step in transcriptional elongation
- Regulator of circadian rhythm
- Involved in hedgehog pathway, Ras, Notch (eyes, wings)

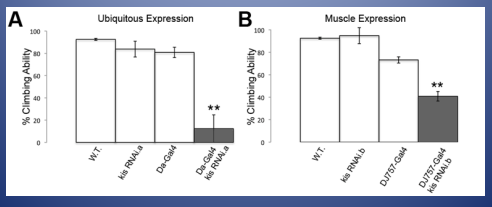
Kismet Knockdown flies have abnormal posture



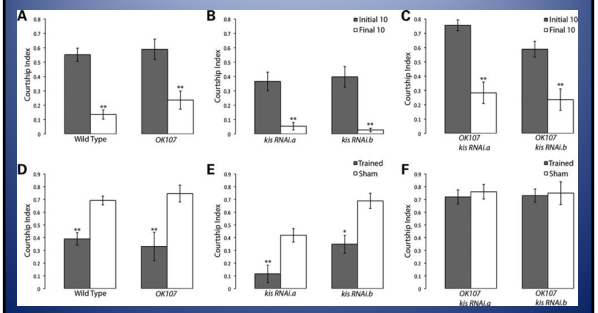
Motor function: Climbing Assay

- Negative Geotaxis behavior of flies
- Ability to climb predetermined length in a given time.
- Predicts:
  - Functioning of nervous system
  - Reflex behavior
  - Spatial awareness

Kismet Knockdown flies have defective motor reflex function.



Kismet knockdown flies have defective immediate recall memory



Kismet knockdown flies have defective axon pruning in learning and memory neurons

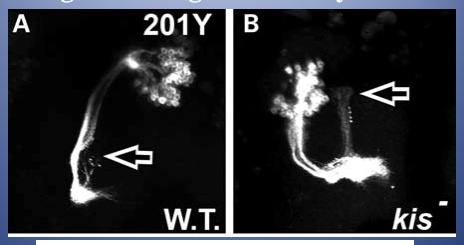
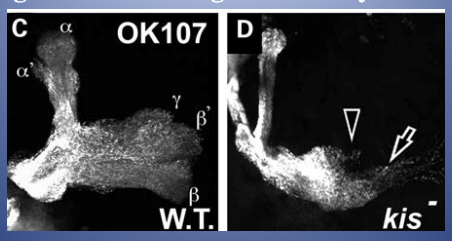


Table 2. Neuronal defects observed in *kismet* MARCM mutants

Neuron	Gal4-line	*n*	Defects observed	%	*P*-value
γ neurons, MB control (pupal)	201Y	8	Unpruned axons	0%	—
kis mutant (pupal)		10	Unpruned axons	40%	<0.05

Kismet knockdown flies have defective axon migration in learning and memory neurons



α, β, γ neurons, MB	OK107				
Control (adult)		9	Lobe structure	0%	—
			Cell migration	0%	—
			Axon migration	11%	—
kis mutant (adult)		11	Lobe structure	55%	<0.05
			Cell migration	36%	<0.05
			Axon migration	55%	<0.05

By better understanding some of the basic functions of kismet, our hope is that we can shed light on similar functions of CHD7 in humans, and eventually help give all of the researchers working on CHARGE syndrome the information they need to develop a therapeutic intervention for patients with CHARGE.

=

Drexel UNIVERSITY

- David Melicharek
- Sukhdeep Singh
- Laura Ramirez
- Rhea Thompson
- Sarah Michelson
- Guovanna and Sylvia Shoukri

- Ginnene DiStefano
- Siddhita Mhatre
- Mitch D'Rozario
- Brie Paddock
- Rupa Ghosh
- Shanthi Bradley

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Advances in Understanding CHD7 through Use of Genetically Engineered Mice

Thursday, 07/28/11
Platform #3: 10:05-10:30
Wekiwas 3 & 4

Donna Martin, MD, PhD,
Elizabeth A. Hurd, PhD,
Wanda S. Layman, PhD,
Yehoash Raphael, PhD
The University of Michigan

Presenter Information:

Donna M. Martin is a Physician-Scientist and Associate Professor at The University of Michigan Medical School in the Departments of Pediatrics and Human Genetics. Her expertise is in Medical Genetics of developmental disorders including CHARGE syndrome.
Elizabeth A. Hurd is a Senior Research Associate working in Dr. Martin's laboratory. Dr. Hurd generated *Chd7* mutant mice and is analyzing them for inner ear defects and hearing abilities.
Wanda S. Layman is a recent PhD graduate of the Department of Human Genetics at The University of Michigan. She worked in Dr. Martin's laboratory and generated all of the data on endocrine and olfactory systems in *Chd7* mutant mice.
Yehoash Raphael is Professor of Otolaryngology at The University of Michigan. He specializes in studies of the inner ear, with a special focus on CHARGE syndrome.

Presentation Abstract:

CHD7, the gene mutated in human CHARGE Syndrome, encodes a chromodomain DNA-binding protein that is highly expressed in specific tissues of the developing embryo. Our laboratory has generated and analyzed several different strains of mice with mutations in the mouse *Chd7* gene, with the goal of exploring the underlying mechanisms by which CHD7 regulates organ growth and development. We will discuss recent findings and roles for CHD7 in the development of several organs and tissues, including neurons that influence hearing, balance, and olfaction.

Advances in Understanding CHD7 through Use of Genetically Engineered Mice

CHARGE Syndrome Conference
July 28-31, 2011

Donna M. Martin, MD, PhD
Elizabeth A. Hurd, PhD
Wanda S. Layman, PhD
Yehoash Raphael, PhD

Departments of Pediatrics, Human Genetics, and Otolaryngology

The University of Michigan

Outline

- *Chd7* deficient mice
  - ENU mutants
  - Gene trapped allele
  - Conditional (flox) allele
- Organ system-specific defects
  - Olfactory
  - Endocrine
  - Inner ear

Mouse models of CHARGE Syndrome

- ENU-derived mutants (10 alleles) with single base pair heterozygous loss of function mutations in *Chd7*
- *Chd7*$^{Gt/+}$ gene trapped loss of function allele
- Phenotypes of *Chd7* heterozygous mutant mice are consistent with those observed in CHARGE patients

Hurd et al., *Mammalian Genome*, 2007; Bosman et al., *Human Mol Gen 2005*

First report of *Chd7* mutant mice

Human Molecular Genetics, 2005, Vol. 14, No. 22 3463–3476
doi:10.1093/hmg/ddi375
Advance Access published on October 3, 2005

Multiple mutations in mouse *Chd7* provide models for CHARGE syndrome

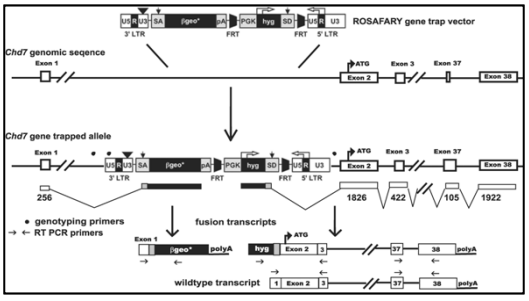
Erika A. Bosman†, Andrew C. Penn†, John C. Ambrose†, Ross Kettleborough, Derek L. Stemple and Karen P. Steel*

Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK

Table 1. Mutations identified in nine *Chd7* mutant mouse lines

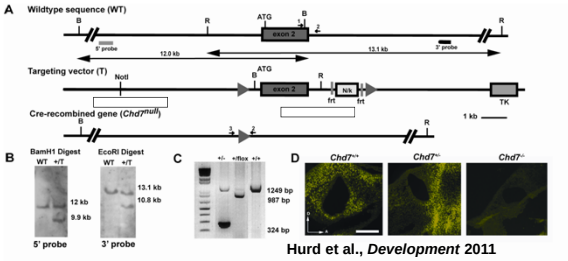
Mutant	DNA mutation	Exon	Protein consequence
Edy	307C→T	2	Q103X
Todo	IVS3 + 2T→C	3	Donor splice site—(H549X)
Whi	2918G→A	11	W973X
Lda	3195T→A	13	Y1066X
Obt	3945T→A	16	Y1315X
Cyen	4286T→A	18	L1429X
Mt	IVS22-2A→G	22	Acceptor splice site—(V1688X)
Dz	5536G→T	27	E1846X
Flo	IVS27 + 2T→C	27	Donor splice site—(S1864X)

Chd7$^{Gt/+}$ mice are a model for CHARGE



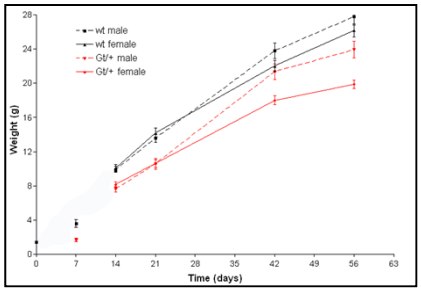
Hurd et al., *Mammalian Genome*, 2007

Generation of a *Chd7*^{flox} allele



Hurd et al., *Development* 2011

Chd7$^{Gt/+}$ mutants have postnatal growth delays and circling



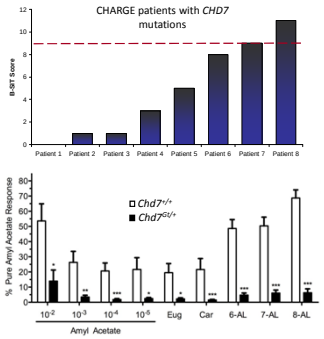
Hurd et al., ***Mammalian Genome*, 2007**

Outline

- *Chd7* deficient mice
  - ENU mutants
  - Gene trapped allele
  - Conditional (flox) allele
- Organ system-specific defects
  - Olfactory
  - Endocrine
  - Inner ear

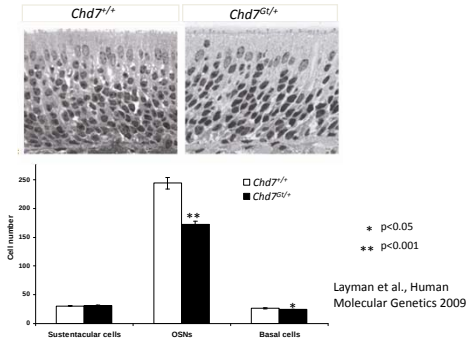
Olfaction and CHARGE syndrome

- Olfactory bulb defects (33/33) and olfactory impairment (18/19) are common features of CHARGE
- *Chd7* is expressed in olfactory epithelium and olfactory bulb in humans and mice



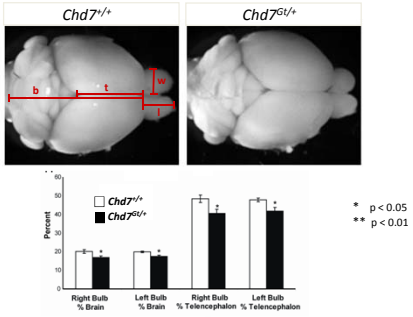
Layman et al., Human Molecular Genetics 2009

Olfactory sensory neurons are reduced in *Chd7*$^{Gt/+}$ mice



Layman et al., Human Molecular Genetics 2009

Chd7$^{Gt/+}$ mice have olfactory bulb hypoplasia



Layman et al., Human Molecular Genetics 2009

Conclusions (olfactory)

- *Chd7*$^{Gt/+}$ mice have olfactory defects similar to human CHARGE individuals
- Olfactory sensory neurons are reduced in *Chd7*$^{Gt/+}$ mice
- Cellular proliferation is reduced in *Chd7*$^{Gt/+}$ olfactory epithelium

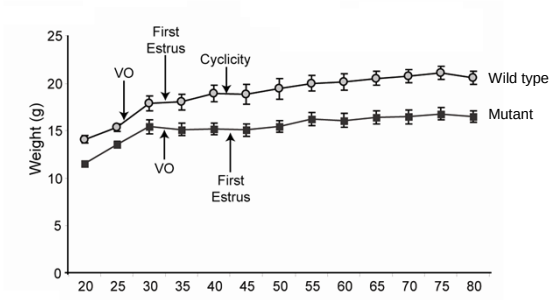
Outline

- *Chd7* deficient mice
  - ENU mutants
  - Gene trapped allele
  - Conditional (flox) allele
- Organ system-specific defects
  - Olfactory
  - Endocrine
  - Inner ear

Endocrine dysfunction and CHARGE

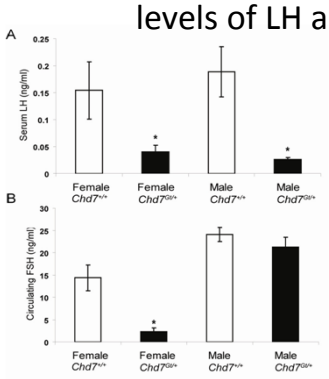
- 81% of males and 93% of females with CHARGE have LH and FSH are deficient
- Genital hypoplasia including cryptorchidism and micropenis occurs in 62% of CHARGE individuals with confirmed *CHD7* mutations
  - Females often have hypoplastic labia
- Anosmia and hyposmia can predict idiopathic hypogonadotropic hypogonadism in CHARGE individuals (Bergman et al., 2010)

Chd7$^{Gt/+}$ female mice have delayed puberty



Layman et al., Human Molecular Genetics 2011

Chd7$^{Gt/+}$ mice have decreased levels of LH and FSH

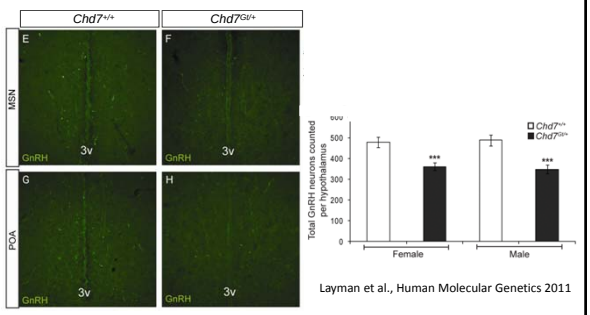


Chd7$^{Gt/+}$ females and males have reduced LH

Chd7$^{Gt/+}$ females have reduced FSH

Layman et al.,
Human Molecular Genetics 2011

GnRH neurons are reduced in *Chd7*$^{Gt/+}$ mice



Layman et al., Human Molecular Genetics 2011

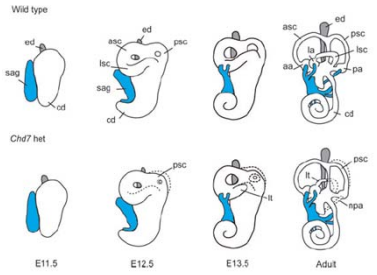
Conclusions part II (endocrine)

- *Chd7*$^{Gt/+}$ mice have pubertal defects and decreased LH, FSH similar to human CHARGE individuals
- GnRH neurons are reduced in *Chd7*$^{Gt/+}$ embryos and adults
- Cellular proliferation is reduced in the olfactory epithelium of *Chd7*$^{Gt/+}$ embryos
- Reduced CHD7 dosage lowers expression of *Bmp4*, *Fgfr1*, *Otx2*, *GnRH1*, and *GnRHR*

Outline

- Chromatin remodeling proteins
  - Classification and roles in human disease
  - CHD7 and CHARGE Syndrome
- Organ system-specific defects
  - Olfactory
  - Endocrine
  - Inner ear

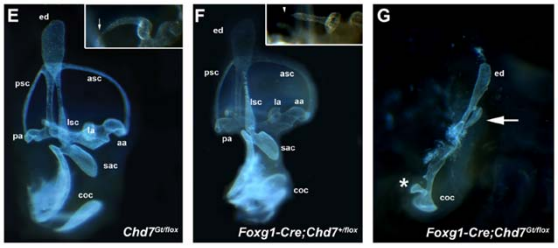
Chd7$^{Gt/+}$ mice have defects in inner ear morphogenesis



Elizabeth Hurd

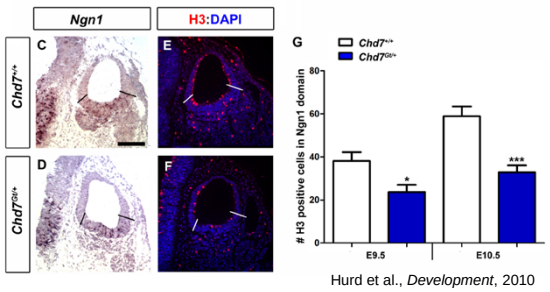
Layman et al, *Clin Gen* 2010; Hurd et al, *Mamm Gen* 2007; Bosman et al, *HMG*, 2005; Adams et al, *JCN* 2008

FoxG1cre-Chd7 conditional mutants have severe semicircular canal and cochlear defects



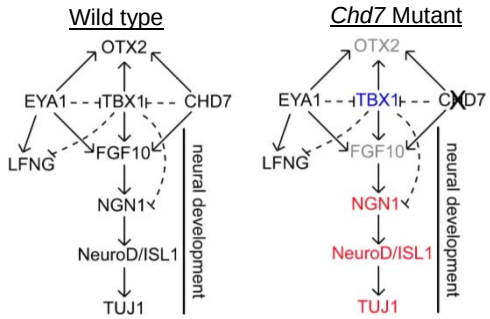
Hurd et al., *Development*, 2010

Chd7 mutants have reduced proliferation in the neurogenic domain



Hurd et al., *Development*, 2010

Model for CHD7 Developmental Gene Regulation in Inner Ear



Hurd et al., *Development*, 2010

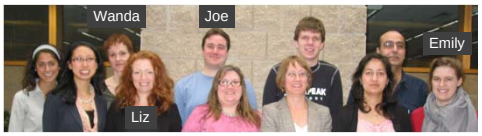
Conclusions part III (inner ear)

- *Chd7*$^{Gt/+}$ mice have inner ear defects and hearing loss similar to human CHARGE individuals
- Inner ear neuroblast proliferation is sensitive to CHD7 dosage
- CHD7 likely acts upstream of proneural genes to regulate inner ear neurogenesis

Take-home points

- CHD7 deficiency affects development of multiple similar tissues in humans and mice
- Neurogenesis in the olfactory epithelium and inner ear requires appropriate CHD7 dosage
- Mouse mutants are a powerful tool for exploring CHD7 function during development and beyond

Acknowledgements



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Yehoash Raphael
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Transgenic Animal Model Core
Thom Saunders
Sally Camper

CHD7 Mutations and CHARGE Syndrome: Clinical and Diagnostic Implications of an Expanding Phenotype

Thursday, 07/28/11
Platform #4: 11:00-11:25
Wekiwa 3 & 4

Prof. Conny van Ravenswaaij-Arts
Dept. of Genetics, University Medical Centre Groningen, Groningen, The Netherlands

Presenter Information:

Conny van Ravenswaaij studied medicine at the University of Leiden. In 1997 she was registered as a clinical geneticist. Her main interest has always been children with multiple congenital anomalies. Her group discovered the CHD7 gene as major cause of CHARGE syndrome in 2004. In 2006 she changed affiliation to the University Medical Centre Groningen, where she continued her multi-disciplinary outpatient clinic for CHARGE syndrome. She supervises studies in CHARGE syndrome, focusing on clinical variability and phenotype-genotype correlations, puberty development and smell, the role of CHD7 in heart development, Cochlear Implants and other aspects of CHARGE syndrome.

Presentation Abstract:

CHARGE syndrome is a highly variable syndrome of which the phenotypic spectrum could only be revealed after the identification of the *CHD7*-gene. We evaluated the clinical features in our cohort of 280 *CHD7*-positive patients and compared these with previously reported patients with CHARGE syndrome but unknown *CHD7* status. Interestingly, 14% of the *CHD7* positive patients could not be clinically diagnosed as having CHARGE syndrome based on the Blake criteria. This was most obvious in familial CHARGE syndrome; only 62% of familial cases could be diagnosed as CHARGE syndrome on clinical features alone.
The expanding phenotype has several clinical implications and updated recommendations for surveillance based on the phenotypic spectrum and on our experience in a multidisciplinary clinic for CHARGE syndrome will be given. Finally, guidelines for *CHD7* analysis will be proposed.

REVIEW

CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype

J E H Bergman,[1] N Janssen,[1] L H Hoefsloot,[2] M C J Jongmans,[2] R M W Hofstra,[1] C M A van Ravenswaaij-Arts[1]

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ABSTRACT

Background CHARGE syndrome is a highly variable, multiple congenital anomaly syndrome, of which the complete phenotypic spectrum was only revealed after identification of the causative gene in 2004. CHARGE is an acronym for ocular coloboma, congenital heart defects, choanal atresia, retardation of growth and development, genital hypoplasia, and ear anomalies associated with deafness. This typical combination of clinical features is caused by autosomal dominant mutations in the *CHD7* gene.

Objective To explore the emerging phenotypic spectrum of *CHD7* mutations, with a special focus on the mild end of the spectrum.

Methods We evaluated the clinical characteristics in our own cohort of 280 *CHD7* positive patients and in previously reported patients with *CHD7* mutations and compared these with previously reported patients with CHARGE syndrome but an unknown *CHD7* status. We then further explored the mild end of the phenotypic spectrum of *CHD7* mutations.

Results We discuss that CHARGE syndrome is primarily a clinical diagnosis. In addition, we propose guidelines for *CHD7* analysis and indicate when evaluation of the semicircular canals is helpful in the diagnostic process. Finally, we give updated recommendations for clinical surveillance of patients with a *CHD7* mutation, based on our exploration of the phenotypic spectrum and on our experience in a multidisciplinary outpatient clinic for CHARGE syndrome.

Conclusion CHARGE syndrome is an extremely variable clinical syndrome. *CHD7* analysis can be helpful in the diagnostic process, but the phenotype cannot be predicted from the genotype.

INTRODUCTION

The first patients with what later became known as CHARGE syndrome (OMIM 214800) were described in 1961.[1 2] In 1979, two independent clinicians recognised that coloboma, choanal atresia, and congenital heart defects clustered together in several patients.[3 4] The acronym CHARGE dates from 1981 and summarises some of the cardinal features: ocular coloboma, congenital heart defects, choanal atresia, retardation of growth and/or development, genital anomalies, and ear anomalies associated with deafness.[5] In 2004, mutations in the *CHD7* gene were identified as the major cause and 'CHARGE association' was changed to 'CHARGE syndrome'.[6] CHARGE syndrome occurs in approximately 1 in 10 000 newborns.[7] The inheritance pattern is autosomal dominant with variable expressivity. Almost all mutations occur de novo, but parent-to-child transmission has occasionally been reported.[8] In this review, we explore the phenotypic spectrum of *CHD7* mutations with special focus on the mild end of the spectrum. In the light of this expanding phenotype, we discuss whether CHARGE syndrome is a clinical or a molecular diagnosis, we propose guidelines for *CHD7* analysis, and give updated recommendations for the clinical surveillance of *CHD7* positive patients.

BACKGROUND

Clinical diagnosis

Before discovery of the causative gene, CHARGE syndrome was a clinical diagnosis (clinical features summarised in figure 1). Pagon was the first to introduce diagnostic criteria for CHARGE syndrome in 1981,[5] but these criteria are no longer in use. At present, the clinical criteria by Blake *et al* and Verloes are used in conjunction (table 1).[9 10]

The Blake criteria[9] were slightly adjusted by a consortium and last updated in 2009.[11] These criteria encompass four major and seven minor criteria. The four major criteria are coloboma, choanal atresia, cranial nerve dysfunction, and abnormalities of the inner, middle, or external ear. At least four major, or three major and three minor, criteria must be present in order to diagnose CHARGE syndrome. In 2005, Verloes proposed renewed criteria.[10] He included semicircular canal defects as a major criterion, as these defects were shown to be a very specific and consistent feature in CHARGE syndrome.[12] Verloes also anticipated broadening of the phenotypic spectrum and reduced the number of features necessary for a diagnosis of CHARGE (to only three major, or two major and two minor, criteria) and he made his criteria less age and sex dependent. A common feature of both sets of criteria is that either coloboma or choanal atresia (which can sometimes be replaced by cleft palate, table 1[13]) must be present in order to diagnose CHARGE syndrome.

Molecular diagnosis

Nowadays, CHARGE syndrome can also be diagnosed by a molecular genetic test. The *CHD7* gene, mutated in the majority of patients with CHARGE syndrome, consists of 37 coding exons and one non-coding exon.[6] The gene encodes for a 2997 amino acid long protein that belongs to the Chromodomain Helicase DNA binding (CHD) family.[14] CHD7 can form complexes with different proteins,

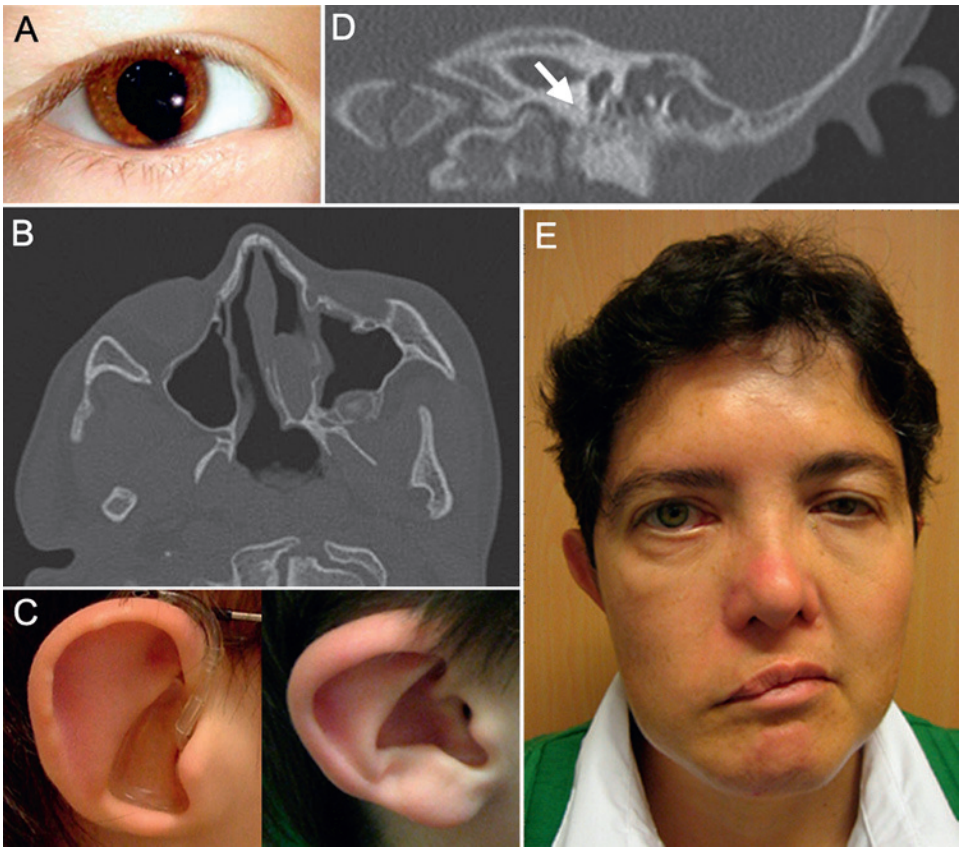

Figure 1 Overview of features occurring in CHARGE syndrome (frequencies are shown in table 2). **Major features** Coloboma of the iris (A) and/or retina, with or without microphthalmia, often only visible by funduscopy. Choanal atresia (B, unilateral) or stenosis. Characteristic ear anomaly (C): cup shaped ear with triangular conchae and small/absent ear lobes. Middle or inner ear malformations may be present as well. Semicircular canal hypoplasia or aplasia (D arrow, semicircular canal aplasia of the left ear on a coronal CT scan). Cranial nerve dysfunction: oculomotor dysfunction (III/VI), less powerful chewing (V), facial palsy (VII) (E, right sided), hearing loss/vestibular problems (VIII), swallowing and feeding problems (IX/X). **Minor features/occasional findings** Hypothalamo-hypophyseal dysfunction: gonadotropin deficiency (hypogonadotropic hypogonadism), growth hormone deficiency. Other congenital anomalies: cleft lip/palate, congenital heart defects, tracheo-oesophageal anomalies, kidney anomalies, brain anomalies (including olfactory bulb hypoplasia), lacrimal duct atresia. Developmental delay: delayed motor development and/or cognitive delay. Characteristic face: broad forehead, square face, facial asymmetry. Other features: behavioural problems, sleep disturbance, scoliosis, respiratory aspiration, gastro-oesophageal reflux, postoperative complications, sudden death, obstructive sleep apnoea, enuresis nocturna, hockey stick palmar crease, webbed neck/sloping shoulders. **Rare features** Immune deficiency, limb anomalies, epilepsy, oligodontia, anal atresia. Informed consent was obtained for publication of the photographs.

thereby ensuring specific binding to different enhancer regions leading to time and tissue specific regulation of gene expression.[15] One example is the association of CHD7 with PBAF (polybromo- and BRG1-associated factor containing complex) that is essential for neural crest gene expression and cell migration.[16] This is in line with previous assumptions that many of the congenital defects seen in CHARGE syndrome may be neural crest related.[17] CHD7 was also shown to associate with rDNA and was therefore suggested to play a role as positive regulator of rRNA synthesis.[18]

Haploinsufficiency of the *CHD7* gene leads to CHARGE syndrome and, as expected, most patients are found to have truncating *CHD7* mutations.[19–24] Missense mutations occur in a minority of patients and partial or full deletions of the *CHD7* gene are rare events.[6 19 23 25–31] Most *CHD7* mutations occur de novo. There are no mutational hotspots and recurrent mutations are rare.[20] No clear genotype–phenotype correlation exists, although it seems that missense mutations in general are associated with a milder phenotype.[20]

CHD7 analysis detects mutations in more than 90% of patients fulfilling the clinical criteria for CHARGE syndrome. The lack of mutation detection in the remaining 5–10% of patients suggests genetic heterogeneity. The *SEMA3E* gene was proposed as

Table 1 Clinical criteria for CHARGE syndrome

	Major criteria	Minor criteria	Inclusion rule
Blake* [9]	1. Coloboma, microphthalmia 2. Choanal atresia or stenosis† 3. Characteristic external ear anomaly, middle/inner ear malformations, mixed deafness 4. Cranial nerve dysfunction	1. Cardiovascular malformations 2. Tracheo-oesophageal defects 3. Genital hypoplasia or delayed pubertal development 4. Cleft lip and/or palate 5. Developmental delay 6. Growth retardation 7. Characteristic face	Typical CHARGE: 4 major *or* 3 major + 3 minor
Verloes[10]	1. Ocular coloboma 2. Choanal atresia 3. Hypoplastic semicircular canals	1. Heart or oesophagus malformation 2. Malformation of the middle or external ear 3. Rhombencephalic dysfunction including sensorineural deafness 4. Hypothalamo-hypophyseal dysfunction (gonadotropin or growth hormone deficiency) 5. Mental retardation	Typical CHARGE: 3 major *or* 2 major + 2 minor Partial CHARGE: 2 major + 1 minor Atypical CHARGE: 2 major + 0 minor *or* 1 major + 3 minor

*Updated by a consortium in 2006 and 2009.[11]
†Cleft palate can be substituted for choanal atresia, since these anomalies rarely occur together.[13]

a candidate gene, but it seems to play a minor role as only two *SEMA3E* alterations have been described in patients with CHARGE syndrome.[32] Besides genetic heterogeneity, it is also possible that mutations in intronic regions, 5′ or 3′ untranslated regions, or in regulatory elements of *CHD7* underlie the *CHD7* negative cases. Phenocopies of CHARGE or CHARGE-like syndrome can be due to teratogen exposure (eg, thalidomide, retinoic acid, maternal diabetes) or chromosomal aberrations.[8]

PHENOTYPIC SPECTRUM OF PATIENTS WITH A MUTATION IN THE *CHD7* GENE

Phenotypic spectrum in our *CHD7* positive cohort compared to two other cohorts

Our *CHD7* positive cohort consists of patients who had *CHD7* analysis done in Nijmegen in the Netherlands. In Nijmegen, *CHD7* analysis was performed in 863 patients suspected of CHARGE syndrome and 360 *CHD7* mutations were found (360/863=42%). The mutations were scattered throughout the entire coding region and splice sites of the *CHD7* gene. One third of the mutations were found in exons 2, 3, 30, and 31 (34% of mutations, 33% of genomic size). However, exons 8, 12, 26, 30, and 36 showed a remarkably high number of mutations relative to their genomic size (19% of mutations, 9% genomic size). No mutations were found in exons 6, 7, 20, and 28, but these comprise only 3% of the coding genome of *CHD7*. Apart from the high number of mutations in exon 2 (the largest exon), our results do not agree with a previous report (n=91).[33] Most mutations were nonsense (38%) or frameshift mutations (32%). Missense mutations and splice site mutations occurred in 13% and 17%, respectively, and deletions were rarely present (<1%). The phenotypic spectrum of the missense mutations was more variable and on average milder when compared to the truncating mutations.

In table 2 we present an overview of the clinical features of 280 of our *CHD7* positive patients, the *CHD7* positive cohort reported in the literature (reviewed by Zentner et al, n=254[24]), and a cohort of patients clinically diagnosed with CHARGE syndrome, but of whom the *CHD7* status is unknown (n=124[7 34]). We only included 280 of our 360 *CHD7* positive patients, because clinical data were lacking in the other 80 patients. The phenotypes of 64 of the 280 patients have been published previously (table 2).[20 26 35–40]

The clinical features of the *CHD7* positive patients, previously reported or presented here, are rarely completely known. When calculating the percentage of patients who exhibit a certain feature, the incompleteness of the clinical data will have a major effect on the accuracy of the percentage. In order to compensate for this inaccuracy, we also calculated the frequency range. The minimum frequency is defined as the number of patients with

Table 2 Clinical features of patients with a *CHD7* mutation compared to clinically diagnosed patients with CHARGE syndrome

Feature	Our *CHD7* positive cohort (n=280)	*CHD7* positive cohort from the literature (n=254)*	CHARGE patients before *CHD7* discovery (n=124)†
External ear anomaly	224/231‡	214/235	74/77
	97% (80–98%)§	91%	96%
Cranial nerve dysfunction (VII, VIII and others)	173/174	?	107/124
	99% (62–100%)		86%
Semicircular canal anomaly	110/117	94/96	12/12
	94% (39–98%)	98%	100%
Coloboma	189/234	190/253	96/124
	81% (68–84%)	75%	77%
Choanal atresia	99/179	95/247	76/124
	55% (35–71%)	38%	61%
Cleft lip and/or palate	79/163	79/242	22/124
	48% (28–70%)	33%	18%¶
Feeding difficulties necessitating tube feeding	90/110	?	40/47
	82% (32–93%)		85%
Facial palsy	80/121	72/187	17/47
	66% (29–85%)	39%	36%
Anosmia on formal smell testing	24/30	?	?
	80%		
Genital hypoplasia	118/145	116/187	45/124
	81% (42–90%)	62%	36%¶
Congenital heart defect	191/252	193/250	105/124
	76% (68–78%)	77%	85%¶
Tracheo-oesophageal anomaly	42/146	35/185	22/124
	29% (15–63%)	19%	18%
Developmental delay	Delayed motor milestones 147/149 99% (53–99%) Intellectual disability 108/134 74% (39–91%)	Developmental delay 107/141 76%	Developmental delay 47/47 100%
Growth retardation	35/94	101/141	80/124
	37% (13–79%)	72%	65%

**CHD7* positive cohort from the literature as reviewed by Zentner *et al* in 2010.[24] This cohort partially overlaps with our *CHD7* positive cohort because the phenotypes of 64 of our patients were published previously.[20 26 35–40]

†Cohort of patients with clinically diagnosed CHARGE syndrome reported by Tellier *et al* in 1998 and Issekutz *et al* in 2005, before *CHD7* analysis was possible.[7 34]

‡Frequencies are represented as the number of patients with a particular feature/the total number of patients that were tested for that particular feature.

§The range of percentages presented between brackets was calculated as: (positive/total)×100%−(positive+unknown/total)×100% (for further explanation see text).

¶Outside the frequency range of patients with a *CHD7* mutation.

a particular feature divided by the total number of patients in the cohort. The maximum frequency is defined as the number of patients with a particular feature plus patients for whom it is unknown whether they have the feature, divided by the total number of patients in the cohort.

Four features are almost always present in patients with a *CHD7* mutation: external ear anomalies, cranial nerve dysfunction, semicircular canal hypoplasia, and delayed attainment of motor milestones (table 2). The characteristic external ear anomaly consists of triangular conchae or cup shaped ears (figure 1) and occurs in more than 90% of patients with a *CHD7* mutation. The second feature, cranial nerve dysfunction, is present in more than 95% of patients. The seventh and eighth cranial nerves are most often affected, leading to facial palsy and sensorineural hearing loss, respectively. Dysfunction of other cranial nerves can also occur. The third feature, semicircular canal hypoplasia, is not always assessed, but when investigated it is found to be present in over 90% of patients. The high frequency of semicircular canal hypoplasia is reflected in the delayed attainment of motor milestones (often scored as developmental delay in previous papers), that is almost universally present in patients with CHARGE syndrome. A delay in speech development is also common in these patients who suffer from multiple sensory impairment (eg, blindness and/or deafness).[41 42] In our cohort, approximately 75% of patients had intellectual disability, indicating that one quarter had a normal intelligence.

Two features seem to occur more frequently since *CHD7* analysis has become available as a diagnostic tool in CHARGE syndrome (table 2). These are cleft lip and/or palate and genital hypoplasia; in the study by Tellier *et al*,[34] the percentages of these two features were below our frequency range. The most likely explanation is that in the past, patients with cleft palate, and thus often without choanal atresia, were not recognised as having CHARGE syndrome. Mutation analysis enables a diagnosis in these clinically less typical patients. The higher prevalence of genital hypoplasia in patients with a *CHD7* mutation can be explained by a higher mean age in the patients for whom molecular studies have been performed, but it may also be due to an increased awareness that genital hypoplasia is a frequent feature in patients with a *CHD7* mutation.

One feature seems to occur less frequently since *CHD7* analysis became available: congenital heart defects were present in 76% of *CHD7* positive patients and in 85% of patients with a clinical diagnosis of CHARGE syndrome. The most likely explanation is that the clinical diagnosis was more readily made in hospitalised children with a heart defect and that, like children with cleft palate, children without a heart defect were more likely to remain unrecognised as having CHARGE syndrome before *CHD7* analysis.

Exploration of the mild end of the phenotypic spectrum of *CHD7* mutations

Patients with a typical presentation of CHARGE syndrome are easily clinically recognised, but those who are mildly affected can be missed, as the mild end of the CHARGE spectrum is only recently starting to emerge. Several studies have shown that an increasing number of patients with a *CHD7* mutation do not fulfil the clinical criteria, as they do not have coloboma or choanal atresia or cleft palate.[20] Exploration of the mild end of the CHARGE spectrum can be undertaken in four ways: by studying familial CHARGE syndrome; by evaluating very mildly affected patients who are picked up with *CHD7* analysis; by performing *CHD7* analysis in cohorts of patients with only one CHARGE feature; and finally by studying syndromes that show clinical overlap with CHARGE syndrome (eg, 22q11 deletion syndrome and Kallmann syndrome).

Familial CHARGE syndrome

Very mildly affected patients with CHARGE syndrome can be identified by studying familial CHARGE syndrome. In the literature, only 16 families have been described with recurrence of molecularly confirmed CHARGE syndrome.[20 21 23 37 43–45] These families include seven sib-pairs, three monozygotic twin-pairs, and six two-generation families. In this review, we describe another two-generation family from our *CHD7* positive cohort, making a total of 17 families (table 3).

Table 3 Familial CHARGE syndrome

Reference		Fulfilling clinical criteria			Segregation
Sib-pairs	***CHD7* mutation**	**Sib 1**	**Sib 2**		
1. Wincent[23]	c.4015C→T; p.R1339X	+ (case 11a)	+ (case11b)		Father no mutation
2. Pauli[44]	c.7302dupA	+ (girl)	+ (boy)		Germline mosaicism in father
3. Lalani[21]	p.W2332X	+ (died)	– (case CHA76)		Parents no mutation
4. Jongmans[37]	c.2442+5G→C	– (case 1)	+ (case 2)		Mother no mutation
5. Jongmans[37]	c.2520G→A; p.W840X	+ (case 3)	+ (case 4)		Somatic mosaicism in father
6. Jongmans[37]	c.1610G→A; p.W537X	+ (case 5)	+ (case 6)		Parents no mutation
7. Jongmans[20]	c.5982G→A; p.W1994X	+ (case 29)	+ (case 30)		Somatic mosaicism in mother
Monozygotic twins		**Twin 1**	**Twin 2**		
1. Wincent[23]	c.5428C→T; p.R1810X	+ (case 13a)	+ (case 13b)		De novo
2. Lalani[21]	p.E1271X	+ (case A)	+ (case B)		Unknown
3. Jongmans[20]	c.5752_5753dupA; p.T1918fs	+ (case 26)	– (case 27)		Parents were not tested
Parent–child		**Child 1**	**Child 2**	**Parent**	
1. Vuorela[45]	c.4795C→T; p.Q1599X	+ (case 1)	+ (case 2)	– (case 3)	De novo in father*
2. Delahaye[43]	c.2501C→T; p.S834F	+ (case A III-2)	+ (case A III-3)	– (case A II-2)	De novo in mother
3. Delahaye[43]	c.469C→T; p.R157X	+ (B III-1)	+ (B III-3)	– (B II-2)	De novo in father
4. Lalani[21]	p.R2319S	– (case CHA166)		–	Unknown
5. Jongmans[37]	c.6322G→A; p.G2108R	– (case 7)		– (case 8)	De novo in mother*
6. Jongmans[37]	c.6322G→A; p.G2108R	– (case 9)	+ (case 10)	– (case 11)	De novo in mother
7. This study	c.7769del	–	–	–	Unknown
Total clinical criteria positive		**Children 24/32**		**Parents 0/7**	

+, Fulfilling the criteria; –, not fulfilling the clinical criteria of Blake *et al* and/or Verloes.[9 10]
*Somatic mosaicism was excluded (the *CHD7* mutation was present in both peripheral blood lymphocytes and buccal cells).

Of the 39 *CHD7* positive individuals, only 24 (62%) fulfilled the clinical criteria for CHARGE syndrome as defined by either Blake *et al*[9] or Verloes.[10] Atypical CHARGE patients are most frequently seen in the two-generation families. Often, the mildly affected individuals were recognised only after a *CHD7* mutation was found in a more severely affected family member. The most mildly affected patients described in the literature had dysmorphic ears and balance disturbance as the only manifestations of CHARGE syndrome. Somatic mosaicism was considered unlikely in two of the very mildly affected parents, because the *CHD7* mutation was found in different tissues.[37 45] The monozygotic twin pairs showed strikingly discordant features and underscore the great intra-familial variability seen in CHARGE syndrome.[20 21 23] This variability might be explained by differential epigenetic regulation or fluctuating embryonic CHD7 levels in relation to a time and tissue dependent critical threshold during embryonic development.

Mildly affected patients from our *CHD7* positive cohort

The most widely used criteria are those of Blake *et al*[9] and Lalani *et al*.[11] Interestingly, 18 out of the 131 (14%) *CHD7* positive patients that could be scored for these criteria had only one or two major Blake features and thus could not be clinically diagnosed as having CHARGE syndrome. Based on the presence of none, or only one major Verloes feature, as many as 17% (22/124 patients) could not be clinically diagnosed with CHARGE syndrome using the Verloes criteria. The phenotypes of the three most mildly affected (previously unpublished) patients are presented below.

The first patient had abnormal external ears and a congenital heart defect, but no other features of CHARGE syndrome. She had normal semicircular canals, no cranial nerve dysfunction, and a normal pubertal development. She had a de novo pathogenic missense mutation in the *CHD7* gene that had not been described before (c.4406A→G, p.Y1469C in exon 19).

The second patient had mild semicircular canal anomalies and a mild hearing loss. His external ears were normal. He was only recognised as having CHARGE syndrome after a *CHD7* splice site mutation was found in his more severely affected children (table 3, two-generation family from this study).

The third patient was diagnosed with Kallmann syndrome and had sensorineural hearing loss. After a de novo pathogenic missense mutation in the *CHD7* gene (c.6322G→A, p.G2108R in exon 31) was identified, a CT scan of his temporal bone was re-evaluated and semicircular canal hypoplasia was seen. He had normal external ears.

CHD7 analysis in cohorts of patients with only one CHARGE feature

Some authors have undertaken *CHD7* screening in patients with only one CHARGE syndrome feature—for example, cleft lip and/or palate,[46] congenital heart disease,[47] or scoliosis.[48] These studies did not identify pathogenic *CHD7* mutations. The general impression is that in the absence of other CHARGE features, the chance of finding a *CHD7* mutation is very low.

Studies in syndromes that overlap with CHARGE syndrome

Thus far, two clinically overlapping syndromes have been studied in relation to *CHD7* mutations: velocardiofacial syndrome (VCFS), and Kallmann syndrome.

Velocardiofacial or 22q11 deletion syndrome shares many features with CHARGE syndrome, including congenital heart defects, cleft palate, developmental delay, renal anomalies, growth retardation, ear anomalies, hearing loss, hypoglycaemia, and lymphopenia.[49] In particular, thymus aplasia and hypoparathyroidism are increasingly recognised in CHARGE syndrome and mark the clinical overlap with the DiGeorge phenotype of 22q11 deletions.[50 51] In approximately 85% of VCFS patients, a common 3 Mb heterozygous deletion of 22q11.2 is present, resulting in *TBX1* haploinsufficiency. Mutations in the *TBX1* gene are present in a minority of VCFS patients. Array comparative genomic hybridisation (CGH) in a cohort of VCFS patients without 22q11 deletion or *TBX1* mutation revealed one heterozygous deletion encompassing the *CHD7* gene in a patient with features typical of VCFS.[52] This patient had a learning difficulty with speech delay, severe feeding difficulties, a congenital heart defect (interruption of the aortic arch, coarctation of the aorta, bicuspid aortic valve, ventricular and atrial septal defect), long slender fingers, and low set, over-folded ear helices. The patient did not have coloboma, choanal atresia or cleft palate, but did have typical CHARGE ears with triangular conchae. To our knowledge, *CHD7* sequence analysis has not yet been performed in a cohort of VCFS patients without deletion or mutation of *TBX1*. In figure 2 we illustrate how difficult it can be to distinguish between CHARGE syndrome and 22q11 deletion syndrome. The phenotypic similarity between VCFS and

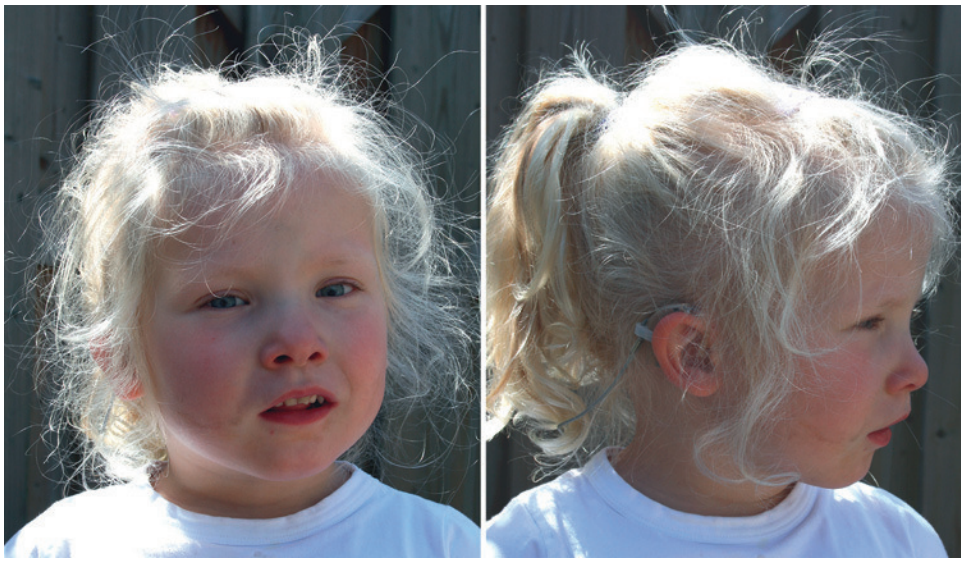

Figure 2 Patient with typical CHARGE syndrome and a 22q11 deletion. This 3½-year-old girl presented with retinal and iris coloboma, unilateral choanal stenosis, abnormal semicircular canals, mixed hearing loss, pulmonary valve stenosis, and simple ears. Clinically she has typical CHARGE syndrome, but neither a *CHD7* mutation nor a deletion could be detected by sequence analysis and multiplex ligation dependent probe amplification (MLPA).[26] Subsequently, array comparative genomic hybridisation (CGH) was performed (Agilent 180 K custom HD-DGH microarray) and revealed a de novo 3 Mb 22q11.2 loss, suggestive for the typical DiGeorge/velocardiofacial syndrome deletion. Informed consent was obtained for publication of the photographs.

CHARGE syndrome is also apparent in mice with haploinsufficiency of *Tbx1* and *Chd7*.[52] Both genes are required in pharyngeal ectoderm for fourth pharyngeal artery development. In addition, both genes are important in development of the thymus and semicircular canals. The *Tbx1* and *Chd7* genes were shown to interact in mice, but a direct regulatory effect of Chd7 on *Tbx1* expression could not be demonstrated.[52]

Kallmann syndrome usually presents as the combination of hypogonadotropic hypogonadism (HH) and anosmia. Both features also occur in the majority of patients with CHARGE syndrome.[53–56] Other features that can be present in both syndromes are hearing loss, cleft lip/palate, and renal malformations. Two studies have been performed in which patients with normosmic HH or Kallmann syndrome were screened for *CHD7* mutations. *CHD7* mutations were reported in seven out of 197 patients with normosmic HH or Kallmann syndrome,[57] and in three out of 36 patients with Kallmann syndrome (confirmed by a smell test), but in none of 20 patients with normosmic HH.[58] The second study showed that after thorough clinical examination of the *CHD7* positive Kallmann patients, other CHARGE features were universally present. The authors concluded that these patients represent the mild end of the CHARGE phenotypic spectrum, as we also demonstrated in our patient who was referred with Kallmann syndrome (see the section 'Mildly affected patients from our *CHD7* positive cohort').

CHD7 AND CHARGE SYNDROME: THE CLINICAL IMPLICATIONS

Based on the studies conducted after the identification of *CHD7* and summarised above, we discuss whether CHARGE syndrome is a clinical or molecular diagnosis, propose a new guideline for *CHD7* analysis, and give recommendations for clinical surveillance of *CHD7* positive patients.

CHARGE syndrome, a clinical or molecular diagnosis?

In our opinion, CHARGE syndrome is primarily a clinical diagnosis. If patients fulfil the clinical criteria of Blake or Verloes, and chromosomal aberrations and teratogenic exposure effects fully explaining the clinical features have been ruled out, then they have CHARGE syndrome, irrespective of the results of *CHD7* analysis. On the other hand, patients who do not completely fulfil the clinical criteria should not be excluded from *CHD7* analysis. If a mutation is found in these patients, clinical follow-up and genetic counselling should be performed as in clinically diagnosed patients with CHARGE syndrome.

Guideline for *CHD7* analysis

Considering the broad phenotypic spectrum, it is evident that *CHD7* analysis should not be restricted to patients fulfilling the clinical criteria for CHARGE syndrome. Coloboma and choanal atresia (or cleft palate) are not always present in CHARGE syndrome. Therefore patients with other CHARGE features, but without those cardinal features, should not be excluded from *CHD7* analysis. When a patient is suspected of CHARGE syndrome, the external ears, cranial nerve function, and semicircular canals should be thoroughly examined, as these features occur in the great majority of patients with a *CHD7* mutation (table 2).

We propose a guideline for *CHD7* analysis in figure 3. In our experience, imaging of the semicircular canals is not an easy

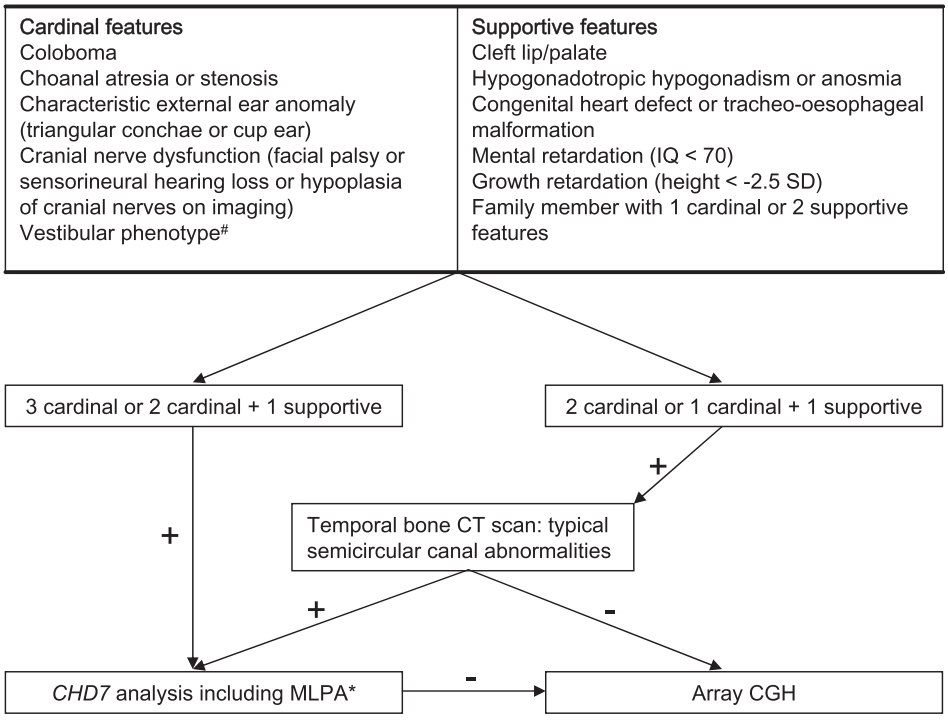

Figure 3 Guideline for *CHD7* analysis in patients suspected of CHARGE syndrome. CGH, comparative genomic hybridisation; MLPA, multiplex ligation dependent probe amplification.

#A convincing history of vestibular problems (e.g., five-point crawl) or abnormal vestibular test or semicircular canal hypoplasia

*If clinical presentation is very atypical, it is recommended to perform array CGH first

Patients with velocardiofacial syndrome, but without a mutation or deletion of the *TBX1* gene, are also good candidates for *CHD7* analysis

routine in daily clinical practice, especially in children in whom sedation can be complicated (see 'Clinical surveillance' and table 4). Therefore, in our guideline we have indicated when imaging of the semicircular canals is needed to support the decision for *CHD7* analysis. We based our guideline on the clinical features that were present in our *CHD7* positive patients (n=280). When applying our guideline, *CHD7* analysis would not have been recommended in one of our patients. This patient is the first one described in the section 'Mildly affected patients from our *CHD7* positive cohort' and is extremely mildly affected. A prospective study is needed to evaluate the usefulness of this guideline in clinical practice.

Clinical surveillance of patients with a *CHD7* mutation or typical CHARGE syndrome

Ideally, follow-up of patients with a *CHD7* mutation or typical CHARGE syndrome should be done by an expert multidisciplinary team, because this approach will ensure optimal treatment of this very complex patient group. In the Netherlands, several specialities are involved in the CHARGE outpatient clinic of the University Medical Centre Groningen: clinical genetics, paediatric endocrinology, ear nose throat (ENT), speech and occupational therapy, ophthalmology, child and youth psychiatry, social paediatrics, gynaecology, endocrinology, paediatric cardiology, neuroradiology, and dentistry. In table 4, we show updated recommendations for clinical surveillance of patients with a *CHD7* mutation based on the experiences of our CHARGE outpatient clinic, on the clinical features in our *CHD7* positive cohort (table 2), and on a literature review.

An ultrasound of the heart and kidneys should be done in all patients, because mild congenital anomalies can remain undetected until adulthood, but may have therapeutic consequences (eg, early treatment of urinary tract infections in case of renal anomalies).

Table 4 Clinical surveillance of patients with a *CHD7* mutation

Evaluation	Tests	Treatment/advice	Be aware of
Ophthalmology	Full ophthalmological examination including funduscopy	Tinted spectacles for photophobia (iris coloboma) Artificial tears in case of facial palsy Correction of refraction errors	Retinal detachment (in case of retinal coloboma)
ENT, audiology, occupational/speech therapy, gastroenterology	Multidisciplinary evaluation: Assess patency of choanae (CT scan or nasal endoscopy) Evaluation for cleft palate and tracheo-oesophageal anomalies Audiometry (BAER), tympanometry Temporal bone CT scan (pathology of middle ear, inner ear, cranial nerves, semicircular canals, aberrant course of blood vessels or cranial nerves) Cranial nerve function tests Swallowing studies, pH monitoring, reflux scan in case of feeding/swallowing difficulties University of Pennsylvania Smell Identification Test	Surgical correction of choanal atresia Hearing aids, ventilation tubes Sign language and speech training GORD: Nissen fundoplication, antispasmodics Gastrostomy/tracheotomy in case of severe swallowing problems Surgery of tracheo-oesophageal abnormalities Advice concerning anosmia	Respiratory aspiration (recurrent pneumonias) Aberrant course of blood vessels or cranial nerves when surgery for cochlear implants Obstructive sleep apnoea
Paediatrics/endocrinology	Renal ultrasound, voiding cysto-urethrogram in case of urinary infections Immunological studies in case of recurrent infections or suspected hypocalcaemia Follow-up of growth and development (growth hormone stimulation test if indicated) Monitor cryptorchidism Gonadotropin levels (age 6–8 weeks) and follow-up of pubertal development DEXA scan (when suspected for osteoporosis) Monitor for scoliosis	Early treatment of bladder infections (especially in case of unilateral renal agenesis or vesico-urethral reflux) Growth hormone treatment if growth hormone deficiency is present Orchidopexy when indicated Gonadotropin treatment in case of hypogonadotropic hypogonadism Corset or surgery when severe progressive scoliosis is present	
Cardiology	Cardiac evaluation including ultrasound	Cardiac surgery and/or antibiotic prophylaxis	
Anaesthesiology	Extensive preoperative assessment	Combine surgical procedures whenever possible Longer surveillance after surgery	Postoperative complications (due to aspiration/cranial nerve dysfunction) Problems with intubation
Neurology	Cerebral MRI scan (including visualisation of olfactory bulbs, and inner ear if no temporal bone CT scan has been performed) EEG (only when clinically seizures are observed)	Anticonvulsants if overt epilepsy seen	
Behaviour, developmental and educational services	Extensive multidisciplinary evaluation of developmental and sensory impairments and behavioural problems Use formal tests in order to screen for autism spectrum, obsessive compulsive disorders and ADHD Perform IQ tests regularly	Integrated individualised therapy with special attention for optimising communication	
Physiotherapy	Assessment of balance problems, motor delay, visiospatial coordination, and hypotonia	Therapy for hypotonia and devices to overcome balance impairment	
Genetics	*CHD7* analysis (when no *CHD7* mutation or deletion is found, perform array CGH)	Genetic counselling, options for prenatal diagnosis	Intra-familial variability in CHARGE syndrome

ADHD, attention deficit hyperactivity disorder; BAER, brain stem auditory evoked response; CGH, comparative genomic hybridisation; DEXA, dual energy x-ray absorptiometry; EEG, electroencephalogram; ENT, ear nose throat; GORD, gastro-oesophageal reflux disease.

Cranial nerve investigation is important. Dysfunction of the seventh, ninth, and 10th cranial nerve can lead to severe feeding and swallowing problems, can result in respiratory aspiration and postoperative complications, and might be involved in sudden death.[59–62]

HH should be diagnosed at an early stage, because patients are at risk for osteoporosis if hormone replacement therapy is not started in time. We recently demonstrated that anosmia and HH are 100% correlated in CHARGE syndrome and we proposed smell testing as a predictive test for HH.[63]

Last, but not least, an individualised educational programme is needed in order to stimulate fully the intellectual potential of a child with CHARGE syndrome and to manage behavioural problems.[64–68] Clinicians should be aware that semicircular canal hypoplasia, a very frequent feature in CHARGE syndrome, causes balance problems and therefore a delay in motor development. This motor retardation may erroneously lead to the suspicion of intellectual disability, although approximately 25% of patients have a normal intelligence.

In addition, identifying a *CHD7* mutation gives further tools for genetic counselling of both the parents and the patients themselves. When the *CHD7* mutation has occurred de novo in the index patient, the recurrence risk for the parents is 2–3% because both germline and somatic mosaicism have been described in CHARGE syndrome.[20 37 44] Patients themselves, when fertile with or without appropriate hormone replacement therapy, have a 50% chance of transmitting the *CHD7* mutation to their offspring. The severity of CHARGE syndrome in offspring cannot be predicted, because intra-familial variability is large. Prenatal diagnosis, either by molecular analysis or ultrasound, and pre-implantation genetic diagnosis, when appropriate, should be discussed with parents and patients.

CONCLUSIONS

CHARGE syndrome is extremely variable, an observation that has been strongly underscored since the discovery of the *CHD7* gene. The phenotype cannot be predicted from the genotype, as exemplified by intra-familial variability. CHARGE syndrome remains primarily a clinical diagnosis, but molecular testing can confirm the diagnosis in mildly affected patients. Guidelines for *CHD7* analysis in individuals suspected of having CHARGE syndrome are proposed in figure 3. In addition, updated guidelines for the surveillance of patients with a *CHD7* mutation or typical CHARGE syndrome are presented in table 4.

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Contributors All authors have substantially contributed to the manuscript and will take public responsibility. There is no one else who fulfils the authorship criteria who has not been included as an author.

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REFERENCES

1. **Angelman H.** Syndrome of coloboma with multiple congenital abnormalities in infancy. *Br Med J* 1961;**1**:1212–14.
2. **Edwards JH,** Finlay HVL, Young RB. Coloboma with multiple congenital anomalies. *Br Med J* 1961;**2**:586–7.
3. **Hall BD.** Choanal atresia and associated multiple anomalies. *J Pediatr* 1979;**95**:395–8.
4. **Hittner HM,** Hirsch NJ, Kreh GM, Rudolph AJ. Colobomatous microphthalmia, heart disease, hearing loss, and mental retardation—a syndrome. *J Pediatr Ophthalmol Strabismus* 1979;**16**:122–8.
5. **Pagon RA,** Graham JM Jr, Zonana J, Yong SL. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981;**99**:223–7.
6. **Vissers LE,** van Ravenswaaij CM, Admiraal R, Hurst JA, De Vries BB, Janssen IM, van der Vliet WA, Huys EH, de Jong PJ, Hamel BC, Schoenmakers EF, Brunner HG, Veltman JA, van Kessel AG. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet* 2004;**36**:955–7.
7. **Issekutz KA,** Graham JM Jr, Prasad C, Smith IM, Blake KD. An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. *Am J Med Genet A* 2005;**133**:309–17.
8. **Sanlaville D,** Verloes A. CHARGE syndrome: an update. *Eur J Hum Genet* 2007;**15**:389–99.
9. **Blake KD,** Davenport SL, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM Jr. CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr (Phila)* 1998;**37**:159–73.
10. **Verloes A.** Updated diagnostic criteria for CHARGE syndrome: a proposal. *Am J Med Genet A* 2005;**133**:306–8.
11. **Lalani SR,** Hefner MA, Belmont JW, Davenport SLH. CHARGE Syndrome. GeneReviews 2009. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=charge (accessed Nov 2010).
12. **Admiraal RJ,** Joosten FB, Huygen PL. Temporal bone CT findings in the CHARGE association. *Int J Pediatr Otorhinolaryngol* 1998;**45**:151–62.
13. **Blake KD,** Prasad C. CHARGE syndrome. *Orphanet J Rare Dis* 2006;**1**:34.
14. **Woodage T,** Basrai MA, Baxevanis AD, Hieter P, Collins FS. Characterization of the CHD family of proteins. *Proc Natl Acad Sci U S A* 1997;**94**:11472–7.
15. **Layman WS,** Hurd EA, Martin DM. Chromodomain proteins in development: lessons from CHARGE syndrome. *Clin Genet* 2010;**78**:11–20.
16. **Bajpai R,** Chen DA, Rada-Iglesias A, Zhang J, Xiong Y, Helms J, Chang CP, Zhao Y, Swigut T, Wysocka J. CHD7 cooperates with PBAF to control multipotent neural crest formation. *Nature* 2010;**463**:958–62.
17. **Siebert JR,** Graham JM Jr, MacDonald C. Pathologic features of the CHARGE association: support for involvement of the neural crest. *Teratology* 1985;**31**:331–6.
18. **Zentner GE,** Hurd EA, Schnetz MP, Handoko L, Wang C, Wang Z, Wei C, Tesar PJ, Hatzoglou M, Martin DM, Scacheri PC. CHD7 functions in the nucleolus as a positive regulator of ribosomal RNA biogenesis. *Hum Mol Genet* 2010;**19**:3491–501.
19. **Aramaki M,** Udaka T, Kosaki R, Makita Y, Okamoto N, Yoshihashi H, Oki H, Nanao K, Moriyama N, Oku S, Hasegawa T, Takahashi T, Fukushima Y, Kawame H, Kosaki K. Phenotypic spectrum of CHARGE syndrome with CHD7 mutations. *J Pediatr* 2006;**148**:410–14.
20. **Jongmans MC,** Admiraal RJ, van der Donk KP, Vissers LE, Baas AF, Kapusta L, van Hagen JM, Donnai D, de Ravel TJ, Veltman JA, Geurts van Kessel A, De Vries BB, Brunner HG, Hoefsloot LH, van Ravenswaaij CM. CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. *J Med Genet* 2006;**43**:306–14.
21. **Lalani SR,** Safiullah AM, Fernbach SD, Harutyunyan KG, Thaller C, Peterson LE, McPherson JD, Gibbs RA, White LD, Hefner M, Davenport SL, Graham JM, Bacino CA, Glass NL, Towbin JA, Craigen WJ, Neish SR, Lin AE, Belmont JW. Spectrum of CHD7 mutations in 110 individuals with CHARGE syndrome and genotype-phenotype correlation. *Am J Hum Genet* 2006;**78**:303–14.
22. **Lee YW,** Kim SC, Shin YL, Kim JW, Hong HS, Lee YK, Ki CS. Clinical and genetic analysis of the CHD7 gene in Korean patients with CHARGE syndrome. *Clin Genet* 2009;**75**:290–3.
23. **Wincent J,** Holmberg E, Stromland K, Soller M, Mirzaei L, Djureinovic T, Robinson KL, Anderlid BM, Schoumans J. CHD7 mutation spectrum in 28 Swedish patients diagnosed with CHARGE syndrome. *Clin Genet* 2008;**74**:31–8.
24. **Zentner GE,** Layman WS, Martin DM, Scacheri PC. Molecular and phenotypic aspects of CHD7 mutation in CHARGE syndrome. *Am J Med Genet A* 2010;**152A**:674–86.
25. **Arrington CB,** Cowley BC, Nightingale DR, Zhou H, Brothman AR, Viskochil DH. Interstitial deletion 8q11.2-q13 with congenital anomalies of CHARGE association. *Am J Med Genet A* 2005;**133**:326–30.
26. **Bergman JE,** de Wijs I, Jongmans MC, Admiraal RJ, Hoefsloot LH, Ravenswaaij-Arts CM. Exon copy number alterations of the CHD7 gene are not a major cause of CHARGE and CHARGE-like syndrome. *Eur J Med Genet* 2008;**51**:417–25.
27. **Hurst JA,** Meinecke P, Baraitser M. Balanced t(6;8)(6p8p;6q8q) and the CHARGE association. *J Med Genet* 1991;**28**:54–5.
28. **Johnson D,** Morrison N, Grant L, Turner T, Fantes J, Connor JM, Murday V. Confirmation of CHD7 as a cause of CHARGE association identified by mapping a balanced chromosome translocation in affected monozygotic twins. *J Med Genet* 2006;**43**:280–4.
29. **Udaka T,** Okamoto N, Aramaki M, Torii C, Kosaki R, Hosokai N, Hayakawa T, Takahata N, Takahashi T, Kosaki K. An Alu retrotransposition-mediated deletion of CHD7 in a patient with CHARGE syndrome. *Am J Med Genet A* 2007;**143**:721–6.

30. **Vuorela P,** la-Mello S, Saloranta C, Penttinen M, Poyhonen M, Huoponen K, Borozdin W, Bausch B, Botzenhart EM, Wilhelm C, Kaariainen H, Kohlhase J. Molecular analysis of the CHD7 gene in CHARGE syndrome: identification of 22 novel mutations and evidence for a low contribution of large CHD7 deletions. *Genet Med* 2007;**9**:690—4.
31. **Wincent J,** Schulze A, Schoumans J. Detection of CHD7 deletions by MLPA in CHARGE syndrome patients with a less typical phenotype. *Eur J Med Genet* 2009;**52**:271—2.
32. **Lalani SR,** Safiullah AM, Molinari LM, Fernbach SD, Martin DM, Belmont JW. SEMA3E mutation in a patient with CHARGE syndrome. *J Med Genet* 2004;**41**:e94.
33. **Sanlaville D,** Audollent S, Goudefroye G, Amiel J, Abadie V, Baumann C, Dollfus H, Genevieve D, Thauvin C, Marlin S, Toutain A, Cruaud C, Etchevers HC, Weissenbach J, Munnich A, Attie-Bitach T, Lyonnet S. CHARGE syndrome: genotype-phenotype correlations and mutational hot-spots at the CHD7 locus. *Poster Presented as Part of the American Society of Human Genetics conference, New Orleans, Louisiana, USA*, 9—13 October 2006. Abstract no.1943.
34. **Tellier AL,** Cormier-Daire V, Abadie V, Amiel J, Sigaudy S, Bonnet D, Lonlay-Debeney P, Morrisseau-Durand MP, Hubert P, Michel JL, Jan D, Dollfus H, Baumann C, Labrune P, Lacombe D, Philip N, LeMerrer M, Briard ML, Munnich A, Lyonnet S. CHARGE syndrome: report of 47 cases and review. *Am J Med Genet* 1998;**76**:402—9.
35. **Bech AP,** op den Akker J, Matthijsse PR. Isolation of the left subclavian artery from the pulmonary artery in a patient with CHARGE association. *Congenit Anom (Kyoto)* 2010;**50**:200—2.
36. **Douglas AG,** Lam W. Extending the phenotypic spectrum of CHARGE syndrome: a case with preaxial polydactyly. *Clin Dysmorphol* 2009;**19**:33—4.
37. **Jongmans MC,** Hoefsloot LH, van der Donk KP, Admiraal RJ, Magee A, van de Laar I, Hendriks Y, Verheij JB, Walpole I, Brunner HG, van Ravenswaaij CM. Familial CHARGE syndrome and the CHD7 gene: a recurrent missense mutation, intrafamilial recurrence and variability. *Am J Med Genet A* 2008;**146**:43—50.
38. **Van de Laar I,** Dooijes D, Hoefsloot L, Simon M, Hoogeboom J, Devriendt K. Limb anomalies in patients with CHARGE syndrome: an expansion of the phenotype. *Am J Med Genet A* 2007;**143**:2712—15.
39. **Pedersen AM,** Skovby F. [Molecular diagnosis of CHARGE syndrom] (In Danish). *Ugeskr Laeger* 2007;**169**:402—6.
40. **Writzl K,** Cale CM, Pierce CM, Wilson LC, Hennekam RC. Immunological abnormalities in CHARGE syndrome. *Eur J Med Genet* 2007;**50**:338—45.
41. **Goldson E,** Smith AC, Stewart JM. The CHARGE association. How well can they do? *Am J Dis Child* 1986;**140**:918—21.
42. **Money J,** Norman BF. Pedagogical handicap associated with micropenis and other CHARGE syndrome anomalies of embryogenesis: four 46, XY cases reared as girls. *Am J Psychother* 1988;**42**:354—79.
43. **Delahaye A,** Sznajer Y, Lyonnet S, Elmaleh-Berges M, Delpierre I, Audollent S, Wiener-Vacher S, Mansbach AL, Amiel J, Baumann C, Bremond-Gignac D, Attie-Bitach T, Verloes A, Sanlaville D. Familial CHARGE syndrome because of CHD7 mutation: clinical intra- and interfamilial variability. *Clin Genet* 2007;**72**:112—21.
44. **Pauli S,** Pieper L, Haeberle J, Grzmil P, Burfeind P, Steckel M, Lenz U, Michelmann HW. Proven germline mosaicism in a father of two children with CHARGE syndrome. *Clin Genet* 2009;**75**:473—9.
45. **Vuorela PE,** Penttinen MT, Hietala MH, Laine JO, Huoponen KA, Kaariainen HA. A familial CHARGE syndrome with a CHD7 nonsense mutation and new clinical features. *Clin Dysmorphol* 2008;**17**:249—53.
46. **Felix TM,** Hanshaw BC, Mueller R, Bitoun P, Murray JC. CHD7 gene and non-syndromic cleft lip and palate. *Am J Med Genet A* 2006;**140**:2110—14.
47. **Qi Q,** Yi L, Yang C, Chen H, Shen L, Mo X, Hu Y, Wang Y. [Mutation analysis of the CHD7 gene in patients with congenital heart disease] (In Chinese). *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2008;**25**:637—41.
48. **Gao X,** Gordon D, Zhang D, Browne R, Helms C, Gillum J, Weber S, Devroy S, Swaney S, Dobbs M, Morcuende J, Sheffield V, Lovett M, Bowcock A, Herring J, Wise C. CHD7 gene polymorphisms are associated with susceptibility to idiopathic scoliosis. *Am J Hum Genet* 2007;**80**:957—65.
49. **Jyonouchi S,** McDonald-Mcginn DM, Bale S, Zackai EH, Sullivan KE. CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome and chromosome 22q11.2 deletion syndrome: a comparison of immunologic and nonimmunologic phenotypic features. *Pediatrics* 2009;**123**:e871—7.
50. **Inoue H,** Takada H, Kusuda T, Goto T, Ochiai M, Kinjo T, Muneuchi J, Takahata Y, Takahashi N, Morio T, Kosaki K, Hara T. Successful cord blood transplantation for a CHARGE syndrome with CHD7 mutation showing DiGeorge sequence including hypoparathyroidism. *Eur J Pediatr* 2010;**169**:839—44.
51. **Sanlaville D,** Etchevers HC, Gonzales M, Martinovic J, Clement-Ziza M, Delezoide AL, Aubry MC, Pelet A, Chemouny S, Cruaud C, Audollent S, Esculpavit C, Goudefroye G, Ozilou C, Fredouille C, Joye N, Morichon-Delvallez N, Dumez Y, Weissenbach J, Munnich A, Amiel J, Encha-Razavi F, Lyonnet S, Vekemans M, Attie-Bitach T. Phenotypic spectrum of CHARGE syndrome in fetuses with CHD7 truncating mutations correlates with expression during human development. *J Med Genet* 2006;**43**:211—17.
52. **Randall V,** McCue K, Roberts C, Kyriakopoulou V, Beddow S, Barrett AN, Vitelli F, Prescott K, Shaw-Smith C, Devriendt K, Bosman E, Steffes G, Steel KP, Simrick S, Basson MA, Illingworth E, Scambler PJ. Great vessel development requires biallelic expression of Chd7 and Tbx1 in pharyngeal ectoderm in mice. *J Clin Invest* 2009;**119**:3301—10.
53. **Asakura Y,** Toyota Y, Muroya K, Kurosawa K, Fujita K, Aida N, Kawame H, Kosaki K, Adachi M. Endocrine and radiological studies in patients with molecularly confirmed CHARGE syndrome. *J Clin Endocrinol Metab* 2008;**93**:920—4.
54. **Blustajn J,** Kirsch CF, Panigrahy A, Netchine I. Olfactory anomalies in CHARGE syndrome: imaging findings of a potential major diagnostic criterion. *Am J Neuroradiol* 2008;**29**:1266—9.
55. **Chalouhi C,** Faulcon P, Le Bihan C, Hertz-Pannier L, Bonfils P, Abadie V. Olfactory evaluation in children: application to the CHARGE syndrome. *Pediatrics* 2005;**116**: e81—8.
56. **Pinto G,** Abadie V, Mesnage R, Blustajn J, Cabrol S, Amiel J, Hertz-Pannier L, Bertrand AM, Lyonnet S, Rappaport R, Netchine I. CHARGE syndrome includes hypogonadotropic hypogonadism and abnormal olfactory bulb development. *J Clin Endocrinol Metab* 2005;**90**:5621—6.
57. **Kim HG,** Kurth I, Lan F, Meliciani I, Wenzel W, Eom SH, Kang GB, Rosenberger G, Tekin M, Ozata M, Bick DP, Sherins RJ, Walker SL, Shi Y, Gusella JF, Layman LC. Mutations in CHD7, encoding a chromatin-remodeling protein, cause idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. *Am J Hum Genet* 2008;**83**:511—19.
58. **Jongmans MC,** Ravenswaaij-Arts CM, Pitteloud N, Ogata T, Sato N, Claahsen-van der Grinten HL, van der Donk K, Seminara S, Bergman JE, Brunner HG, Crowley WF Jr, Hoefsloot LH. Claahsen-van der Grinten HL, van der Donk K, Seminara S, Bergman JE, Brunner HG, Crowley WF Jr, Hoefsloot LH. CHD7 mutations in patients initially diagnosed with Kallmann syndrome—the clinical overlap with CHARGE syndrome. *Clin Genet* 2009;**75**:65—71.
59. **Bergman JE,** Blake KD, Bakker MK.du Marchie Sarvaas GJ, Free RH, Ravenswaaij-Arts CM. Death in CHARGE syndrome after the neonatal period. *Clin Genet* 2010;**77**:232—40.
60. **Dobbelsteyn C,** Marche DM, Blake K, Rashid M. Early oral sensory experiences and feeding development in children with CHARGE syndrome: a report of five cases. *Dysphagia* 2005;**20**:89—100.
61. **Dobbelsteyn C,** Peacocke SD, Blake K, Crist W, Rashid M. Feeding difficulties in children with CHARGE syndrome: prevalence, risk factors, and prognosis. *Dysphagia* 2008;**23**:127—35.
62. **Sporik R,** Dinwiddie R, Wallis C. Lung involvement in the multisystem syndrome CHARGE association. *Eur Respir J* 1997;**10**:1354—5.
63. **Bergman JE,** Bocca G, Hoefsloot LH, Meiners LC, Ravenswaaij-Arts CM. Anosmia Predicts Hypogonadotropic Hypogonadism in CHARGE Syndrome. *J Pediatr* 2011;**158**:474—9.
64. **Brown D.** CHARGE syndrome "behaviors": challenges or adaptations? *Am J Med Genet A* 2005;**133A**:268—72.
65. **Hartshorne TS,** Hefner MA, Davenport SL. Behavior in CHARGE syndrome: introduction to the special topic. *Am J Med Genet A* 2005;**133A**:228—31.
66. **Hartshorne TS,** Grialou TL, Parker KR. Autistic-like behavior in CHARGE syndrome. *Am J Med Genet A* 2005;**133A**:257—61.
67. **Johansson M,** Gillberg C, Rastam M. Autism spectrum conditions in individuals with Möbius sequence, CHARGE syndrome and oculo-auriculo-vertebral spectrum: diagnostic aspects. *Res Dev Disabil* 2010;**31**:9—24.
68. **Souriau J,** Gimenes M, Blouin C, Benbrik I, Benbrik E, Churakowskyi A, Churakowskyi B. CHARGE syndrome: developmental and behavioral data. *Am J Med Genet A* 2005;**133A**:278—81.

CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype

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National Cochlear Implantation Studies with Children Who Experience Deaf-Blindness: Results for Participants with CHARGE Syndrome

Thursday, 07/28/11
Platform #5: 11:25-11:50
Wekiwa 3 & 4

Susan M. Bashinski, Ed.D.
East Carolina University

Presenter Information:

Dr. Susan M. Bashinski has been working in the field of special education for more than 35 years, teaching in public school Pre-K through high school programs, as well as at the university level. She has been recognized with several teaching awards. She is the author / co-author of numerous published research articles, chapters, and manuals associated with topics relevant to learners who experience low-incidence disabilities and / or deaf-blindness (DB). For the past six years, Dr. Bashinski has served as a Site Principal Investigator for two national research projects conducted with learners who experience DB and have received a cochlear implant. Dr. Bashinski has extensive experience providing professional development and technical assistance across the US and internationally, particularly in the areas of communication development, AAC, and nonsymbolic communication intervention strategies for learners with low-incidence disabilities, including CHARGE syndrome

Presentation Abstract:

Since October 2005, back-to-back national research studies have been underway with children who experience deaf-blindness and have received a cochlear implant. The second largest participant subgroup in these studies, by etiology, is children with CHARGE syndrome. This session will highlight results obtained with this subgroup of participants. Data for the entire subgroup of participants with CHARGE, as well as a comparison of skill gains and communication development for the CHARGE participant subgroup and the overall study group will be presented. Specific data regarding any relationship of age at implant, as well as duration of time in sound since implantation, to communication development for children with CHARGE will be discussed. Finally, the session will introduce the Language Environmental Analysis (LENA)—an emerging technology that measures a child's auditory environment (i.e., meaningful talk, distant talk, television, general noise, and silence) across a 16-hour period. LENA software, used to analyze the frequency of adult words spoken to a child, a child's vocalizations, and conversational turns will be described. One case study with a participant with CHARGE Syndrome, including LENA data, will be presented.

National Cochlear Implant Studies with Children with Deaf-Blindness: Results for Participants with CHARGE Syndrome

10th International CHARGE Syndrome Conference

July 2011

Susan M. Bashinski, Ed.D.

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2

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States Represented (26 + DC)

(States in blue include children with CHARGE)

Arizona	Maryland	Oklahoma
California	Massachusetts (Perkins)	Oregon
Delaware	Mississippi	Pennsylvania
Florida	Missouri	South Carolina
Georgia	Nebraska	Tennessee
Illinois	New Jersey	Texas
Indiana	New York	Virginia
Kansas	North Carolina	Washington
Kentucky	Ohio (CCHMC)	Washington DC

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Three Major Project Phases

- Research - *Today's focus*
- Research to Practice - *Intervention Strategies*
- Practice to Technical Assistance & Training – *Methods used to teach care providers*

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Outcomes
Participants will:

- learn aspects of cochlear implantation that appear to be positively correlated with communication skill gains by children with CHARGE
- gain knowledge regarding the range of outcomes achieved by children who have CHARGE Syndrome, following CI surgery
- learn about LENA technology and ways in which this data collection system can be used to guide intervention and language stimulation in the home

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2009 National Child Count for Children Who Are Deaf-Blind

- Overall 4,313 children have a moderate-severe, severe, or profound sensori-neural hearing loss
- States increased their identification of children with implants from 251 in 2005, to 581 in 2009
- An increased number of children are receiving bilateral implants
- 747 children have been identified as having CHARGE Syndrome, of which 72 have confirmed implants

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Outcomes of Project

- To collect data on the outcomes and related factors for children so parents / guardians can make more informed decisions about implantation, services, types of therapy for their children
- To identify factors correlated with more positive child outcomes, with the long-term objective of improved intervention and access to opportunities for language growth

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Research Studies

- **Study A** – What effect does age at implant and "time in sound" (hearing age) have on child outcomes?
- **Study B** – What are the differences in the care provider's verbal interactions before and after implant?
- **Study C** – What are the effects of individualized interventions carried out by care providers, post-implant, in natural environments? (In Progress)

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Research: Children Who Are Deaf-Blind With Cochlear Implants

- Participants' Status: How many children are participating?
- Demographics: Who are these children?

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Participant Demographics: Children with CHARGE

Status	Number of Assessments					Total
	0	1	2	3	4+	
Post CI Only	1	9	4	3	1	**18**
Pre CI Only		6		--	--	**6**
Pre-Post CI		--	2	2	1	**5**
TOTAL	**1**	**15**	**6**	**5**	**2**	**29**

• 3 children with bilateral implants

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Participant Demographics: Children with CHARGE

(n = 29)

Vision Impairment	Participants
Low Vision (<20/200)	38%
Legally Blind	28%
Light perception only	3%
Totally Blind	3%
Other	13%

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Participant Demographics: Children with CHARGE

(n = 29)

Additional Challenges

- 58.6% have physical challenges
- 58.6% have cognitive challenges
- 20.7% have behavior challenges
- 93.1% have complex health care needs

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Participant Demographics: Children with CHARGE

(n = 29)

Race/Ethnicity

- Black (6.9%)
- Latino (6.9%)
- White (82.8%)
- Mixed Race (3.4%)

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Participant Demographics: Children with CHARGE

Participants' Age at Implant (n = 23)

(Range = 11 months to 5 years 2 months)

12 months or younger = 6
13 - 24 months = 7
25 – 36 months = 8
37 – 48 months = 1
over 48 months = 1

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Participant Demographics: Children with CHARGE

Participants' "Time in Sound" / Hearing Age(as of most recent assessment) (n = 22)

(Range = 3 months to 6 years, 11 months)

12 months or less = 8
13 - 24 months = 4
25 – 36 months = 2
37 – 48 months = 1
over 48 months = 7

* A large number of young participants have little "time in sound."

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Participant Demographics: Children with CHARGE

Participants' Age
(as of most recent assessment) (n = 22)
(Range = 19 month to 8 years 3 months)

12 months or less	= 0
13 - 24 months	= 4
25 – 36 months	= 4
37 – 48 months	= 2
over 48 months	= 12

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Research Studies

- **Study A**: What effect does age at implant and "time in sound" (hearing age) have on outcomes for children with CHARGE Syndrome?
- n = 22
- Longitudinal design
- Outcomes: Taken from a battery of assessments

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Assessments

- A battery of assessments was selected that examined child behaviors across a variety of domains (birth to 60 months) & included small increments across items
- The Reynell-Zinkin Scales have been validated for children with low vision and blindness
- Assessments were repeated across time (depending on post-implant or pre-implant status; at least annually for post)

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Assessments Used In the Research/Intervention Project

- *Communication & Symbolic Behavior Scales Developmental Profile*
- *MacArthur-Bates Communicative Developmental Inventory (W&G or W&S)*
- *Reynell-Zinkin Scales-* 7 sub-scales
- *Infant-Toddler Meaningful Auditory Integration Scale or Meaningful Auditory Integration Scale*
- *Speech Intelligibility Measures*

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STUDY A: Example Data Analyses

Reynell – Zinkin Scales:

- Response to Sound
- Vocalization and Expressive Language

Other:

- Age at Implant
- "Time in Sound"
- Age at Assessment

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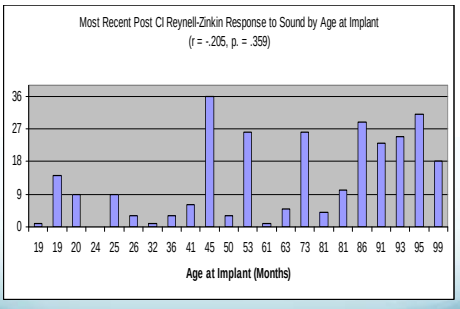
Data Analysis



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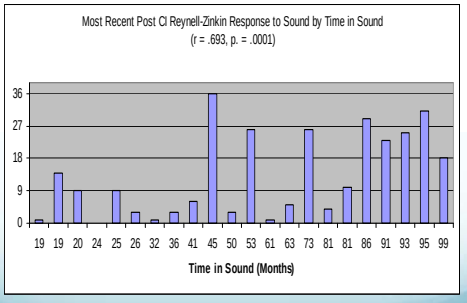

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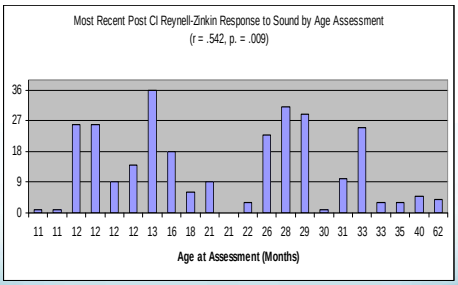

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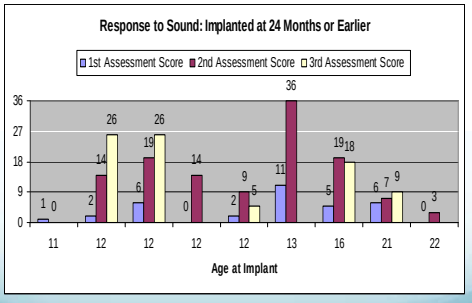

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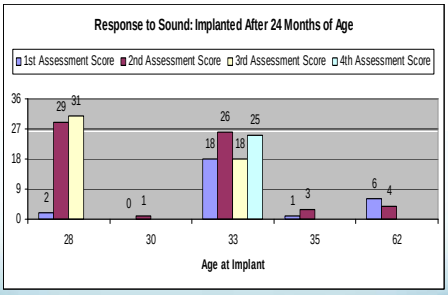

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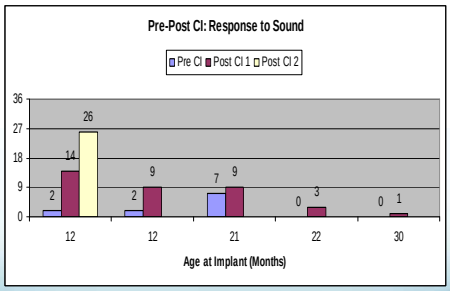


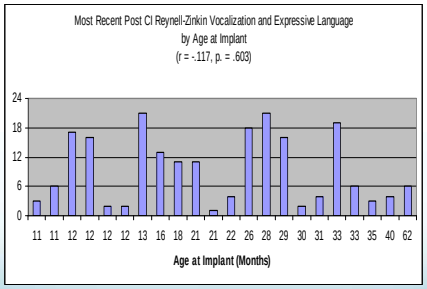
29

Reynell-Zinkin Response to Sound

- Weak relationship between age at implant and receptive language
- **Significant** *and* relationships between "time in sound" (hearing age) and age at assessment and receptive language
- Receptive language of children with CHARGE **DOES** improve significantly over time, post-implant
- Receptive language **DOES** improve significantly from pre- to post-implant

30

Data Analysis



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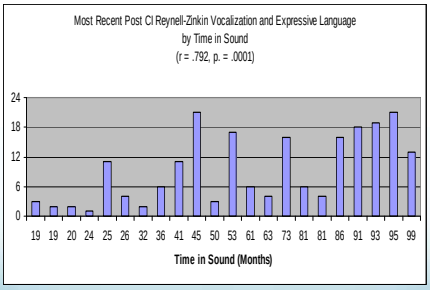

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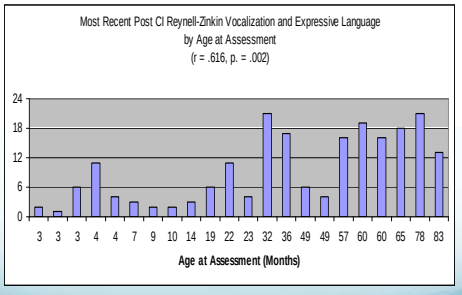

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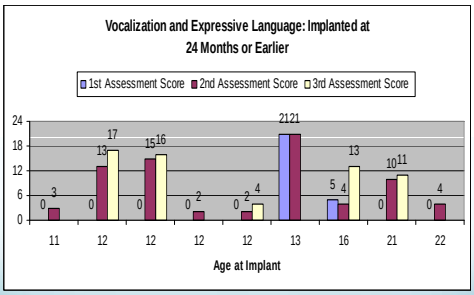

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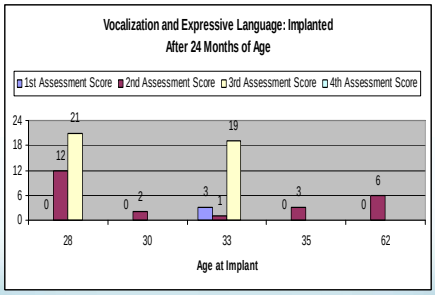

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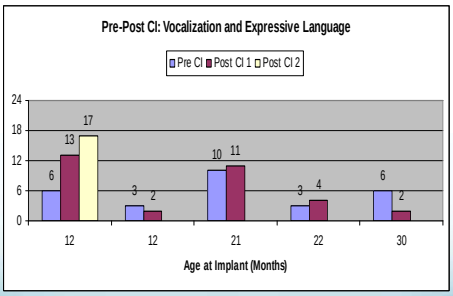

36

Reynell-Zinkin Vocalization and Expressive Language

- Little relationship between age at implant and expressive language
- **Significant** and strong relationships between "time in sound" (hearing age) and age at assessment and expressive language
- Expressive language of children with CHARGE **DOES** improve significantly over time, post-implant
- Expressive language **DOES** improve significantly from pre- to post-implant for *some but not all* children [to date]

37

Data for Post-Implant Children

(n = 22)

RECEPTIVE LANGUAGE		EXPRESSIVE LANGUAGE	
Response to sound	94.4%	Sound production	100%
Response to words and phrases	53.5%	One-word production/jargon	45.4%
Word identification (out of context)	45.4%	Meaningful words	45.4%
Simple directives	36.3%	Simple sentences	31.8%
Complex directives	31.8%	Complex sentences	18.2%

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Data for Pre-Post Implant Children

(n = 5)

RECEPTIVE LANGUAGE			EXPRESSIVE LANGUAGE		
	Pre-	Post-		Pre-	Post-
Response to sound	60%	100%	Sound production	11%	100%
Response to words and phrases	20%	60%	One-word production/jargon	0%	40%
Word identification (out of context)	0%	20%	Meaningful words	0%	40%
Simple directives	0%	20%	Simple sentences	0%	20%
Complex directives	0%	20%	Complex sentences	0%	0%

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Overall Findings to Date: Study A

- Participants in the study are a very diverse group
- With this diversity come complex relationships (rather than simple relationships between such variables as age and outcomes)

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Overall Findings to Date: Study A

- The participants (as a group) ***do*** experience improvements in receptive and expressive language over time, after receiving an implant
- Individual outcomes vary considerably

41

Study B – Care providers' talk to the child, after implantation (i.e., compared to pre-implant)

Use of the Language Environmental Analysis (LENA) to record:

- the auditory environment
- the adult's verbalizations
- the child's vocalizations
- the turns taken in conversation

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LENA Data

- Auditory Environment:
  - meaningful talk
  - distant talk
  - TV
  - noise
  - silence
- Adult Words
- Child Vocalizations

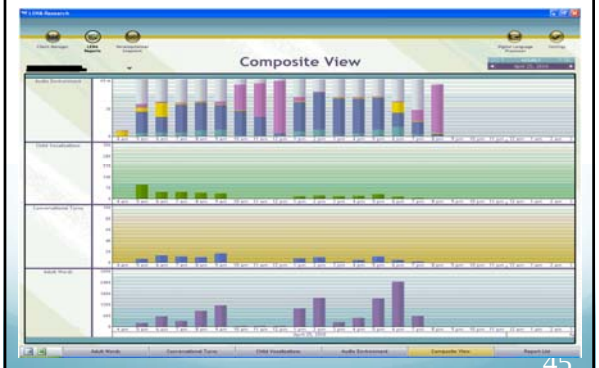
43

LENA Data

- Conversational Turns
- Estimated Mean Length of Utterance
- Estimated Developmental Age (in months)
- Standard Score
- Percentile

44

LENA Data



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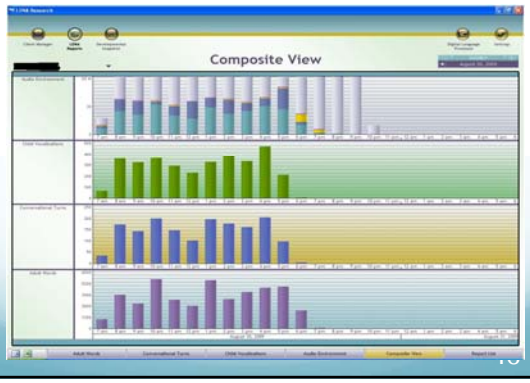
LENA Data



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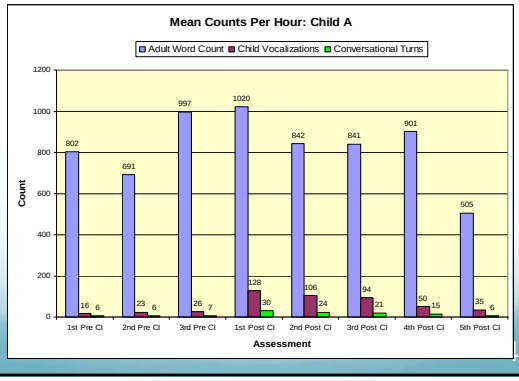

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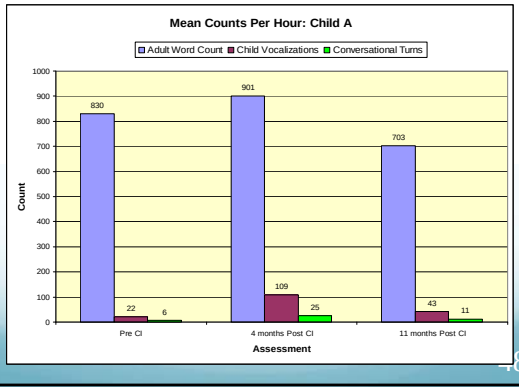

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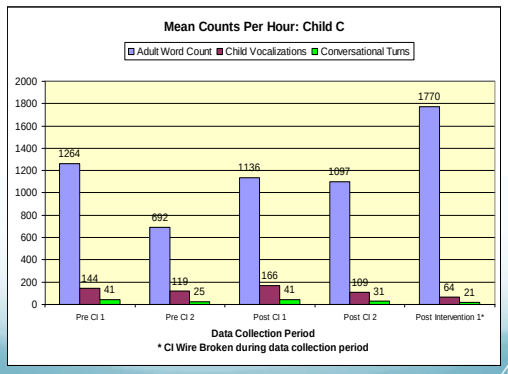

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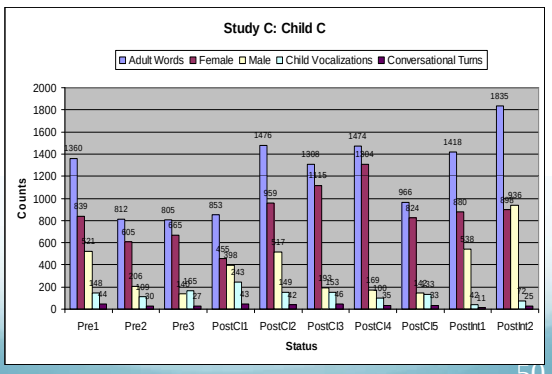

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Overall Findings to Date: Study B

- Small numbers of pre- / post-implant children and their parents have participated [to date]
- Significant variability seen in parents' interactions with their children
- Some initial increase in verbal interactions, by both parents, has been observed after CI surgery
- Parents' verbal interactions vary considerably over time

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Study C –Effects of individualized interventions, implemented by the care providers in natural environments, *after* CI surgery (In Progress)

[One participant with CHARGE]

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Overall Findings to Date: Study C

- Multiple child behaviors and care provider strategies are targeted in 12-16 sessions
- Repeated sessions, across time, are necessary for parent implementation [implications for TA]
- Three participants & their care providers have completed the intervention; four others are in progress
- Observed parent and child outcomes in maintenance and generalization conditions are encouraging

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Limitations To Progress

- Many participants did not have prelinguistic communication skills
- Many participants did not have skills of functional object use
- Auditory - Verbal programs were not individualized
- Many participants did not wear their implants consistently
- Many participants were not mapped frequently (and, possibly, accurately)

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Limitations To Progress

- Many children were "dropped" from Auditory - Verbal programs, due to lack of progress
- Parents reported not being taught effective strategies that could be used at home
- Frequent use (in therapy and in-home interactions) of toys / objects with "high" tactile and visual properties—but *not* sound
- Many children do not have the opportunity to frequently hear speech directed to them in close proximity

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Variability in Outcomes Indicates ….

- the need for individualized and adaptive approaches (Moeller, 2006)
- the need to integrate perception / receptive and production / expressive outcomes
- the need to incorporate more cognitive skills into intervention (Pisoni, et al., 2010)
- the need to do a better job of teaching parents how to implement strategies and embed them in caregiving, play, and family activities

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PLEASE visit our website:
www.kidsdbci.org

Family stories
Resources
Links

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Thanks so much for your attention!

Susan M. Bashinski

bashinskis@ecu.edu

252.737.1705

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The Child`s voice

Thursday, 07/28/11
Platform #6: 11:50AM-12:15PM
Wekiwa 3 & 4

Wenche Andersen and Eva Seljestad
Skaadalen Resource Centre for the Deafblind

Presenter Information:

Wenche Andersen, Senior Adviser, Skaadalen Resource Centre for the Deafblind, Oslo, Norway

Eva Seljestad, Senior Adviser, Skaadalen Resource Centre for the Deafblind, Oslo, Norway

Presentation Abstract:

Comments on a conversation with a 9 year old girl with CHARGE syndrome. The combined hearing and vision loss makes it exhausting for the child to follow and participate in dynamic dialogues between hearing children. It is easy to underestimate this fact when a child in general, fulfills adequate demands for her age. She is talking, signing, reading and writing. Her cognitive capacity is good, but might not be properly evaluated because she often becomes overwhelmed with impressions from the environment. We focus upon challenges in social activities and communication. We also discuss how our counseling is influenced and enriched when we stop talking and start to listen.
(Case Study. Video)

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011

Problems with Self-Regulation and Behavior in CHARGE

Thursday, 07/28/11
Platform #7: 2:30-2:55
Wekiwa 3 & 4

Tim Hartshorne, Ph.D.
Central Michigan University

Presenter Information:

Tim Hartshorne is a professor of psychology, specialized in school psychology, at Central Michigan University. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. His particular interest is in understanding the challenging behavior exhibited by many individuals with CHARGE. He is the grant holder for DeafBlind Central: Michigan's Training and Resource Project.

Presentation Abstract:

The proposed CHARGE behavioral phenotype includes problems with self-regulation. This presentation explores the nature of self-regulation, its role in the behavioral challenges found with CHARGE, problems with the regulation of learning, behavior, emotions, and sensations, and how parents and teachers might use scaffolding to assist individuals with CHARGE to learn to self-regulate.

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011

Problems of self-regulation in the behavior of individuals with CHARGE syndrome

Tim Hartshorne
Central Michigan University

Two ends of the spectrum

- Totally regulated
- Completely dysregulated

Self-regulation Scale

I have a hard time paying attention and my mind tends to wander.

When I really need to pay attention I can focus my mind.

I can readily prioritize the things I need to get done in a day.

I become overwhelmed when faced with too many things to take care of.

I get upset a lot and cannot find any way to get rid of those feelings.

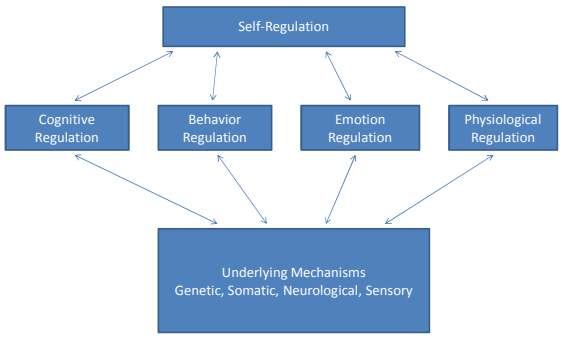
When I really need to control my feelings I can do it.

When there is nothing going on I have to create it.

When I am in a noisy crowd I have to find a way to leave.

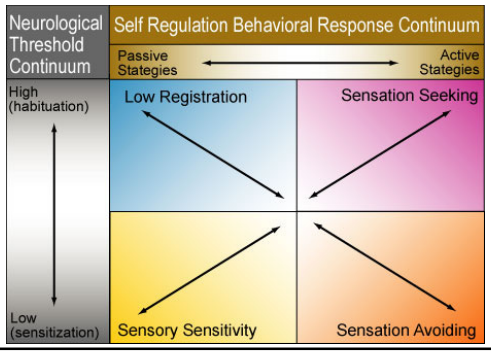
Self-Regulation

- Managing the threshold of arousal
- Processes of self-control
- Both suppresses and encourages; inhibits and promotes
- Supports homeostasis of the system
- Critical to development



Jude Nicholas and Tim Hartshorne, 2009

Dunn Conceptual Model



The extremes

- If a system cannot self-regulate, we have to provide external systems of regulation
- Too much regulation can stifle innovation
- Too little regulation can lead to chaos and abuse

Diagnoses in CHARGE

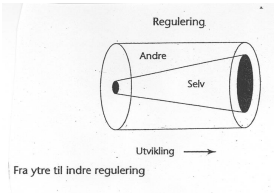
- OCD – a way to reduce stimulation and exercise control
- ADHD – a problem with regulating sensory stimulation and focusing on a problem
- Tic disorder – a stress response to lack of control over environment
- Autistic-like behavior – the failure of regulation strategies

Scaffolding

- The process of planning and organizing the activity of children so that they can execute a task that is beyond their current level of ability.

Scaffolding for self-regulation

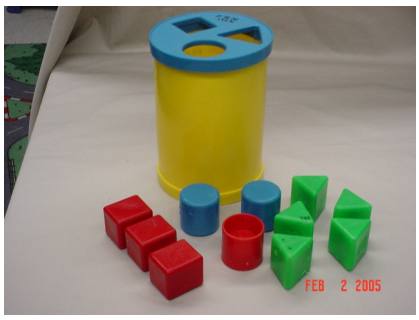
- Because self-regulation skills are hard for children with significant disabilities to develop
- We have to provide the external support for what will become an internal self-regulatory process



Components of Scaffolding

1. Identification of the problem to be solved
2. Focus activities on outcomes and goals
3. Frustration control
4. Reducing the complexity of the task
5. Marking critical relevant features
6. Modeling

The Shape Sorter



1. Problem Identification
2. Focus on outcomes
3. Frustration control
4. Reducing complexity
5. Marking features
6. Modeling

The four areas of self-regulation

- Define each area of self-regulation
- What is involved?
- Describe scaffolding strategies

Cognitive Regulation

- Motivated to think about a problem
- Being precise and accurate
- Comparing alternative choices
- Adapting prior learning to the problem

How learning changes

- Concrete reasoning
  - Objects and events available to the senses
- Rote learning and memorization
  - Alphabet
  - Multiplication table
  - Names of things
- Abstract reasoning
  - Ideas or concepts with no physical referents

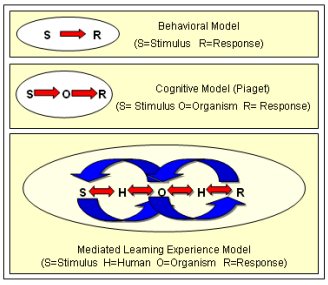
Executive Function

- Initiate – goal, planning, getting started
- Sustain – staying on task, moving toward goal
- Inhibit – avoiding getting side tracked
- Shift – changing directions when needed

These functions continue to develop into early adulthood and can be improved.

Cognitive Scaffolding

- Mediated Learning Experience



Example

1. Problem Identification
2. Focus on outcomes
3. Frustration control
4. Reducing complexity
5. Marking features
6. Modeling

•Motivated to think about a problem
•Being precise and accurate
•Comparing alternative choices
•Adapting prior learning to the problem

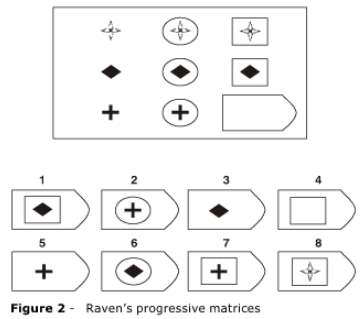


Figure 2 - Raven's progressive matrices

Behavior Regulation

- What is the purpose of the behavior?
- Is it consciously planned and intentional?
- Well regulated behavior is both intentional and goal directed.

The Self-Regulation of Behavior

- Too often we tell children what we do not want them to do, and not what we very much do want them to do

- Strategies for building self-regulation
  - Offering choices (shared control)
  - Rehearsing behavior options
  - Building communication
  - Delay of reinforcement
  - Embedding a positive context

Behavior Scaffolding

- Supporting what we want the child to do
- Positive Behavioral Supports
  - How does the social environment support positive behavior?
  - How does the physical environment support positive behavior?
  - What skills does the child possess for positive behavior?

Social Environment

- Social embeddedness
- Social skills
- Negative relational schemas
- Circle of Friends

Physical Environment

- Supporting what we want the child to do
- Responsive to sensory needs of the child
- Responsive to physical limitations
- Reducing complexity

Child's Behavior

- Supporting what we want the child to do
- Reading behavior as communication
- Understanding the purpose of behavior
- Functional Communication Training

1. Problem Identification
2. Focus on outcomes
3. Frustration control
4. Reducing complexity
5. Marking features
6. Modeling

Emotion Regulation

- What a person does to manage his or her emotional states
  - Regulate both negative and positive emotions
  - Decrease emotions or increase emotions
  - May be conscious or unconscious
  - May be internal or external
  - Are generally goal directed

Learning to regulate emotions

- "She didn't know what to do with her emotions"
  - Emotional expression
    (What does it look like to be angry, sad, etc.?)
  - Emotional intensity
    (How worried, sad or mad would you feel in this situation?")
  - Emotional self-efficacy
    (How could you make yourself feel better in this situation?)

Emotion Scaffolding

- Social referencing
- Attachment
- Talking about how you feel
- Soothing
- Positive face to face play
- Distraction
- Problem-solving
- Altering interpretations
- Suggesting better ways to respond
- Creating daily routines that make emotional demands predictable and manageable

1. Frustration control
2. Problem Identification
3. Focus on outcomes
4. Reducing complexity
5. Modeling
6. Marking features

Physiological Regulation

- Sensory
- Pain
- Fatigue
- Eating
- Sleeping
- Respiratory/Digestive/Temperature/Other systems

The Self-Regulation of Physical States

- Relaxation
- Tuning in to our bodies
- Bio-feedback – being aware of control
- Management of arousal
  - Timeout
  - Sensory room

Physiological Scaffolding

- Developmental Care
- Sensory Integration
- Physical responses
  - Hug
  - Squeeze
  - Touch
  - Rock
  - Tickle

Fun Chi

- Reduced stress
- Reduced anxiety
- Reduced depression
- Increased self-esteem
- Increased energy/focus/concentration
- Increased positive mood
- Better balance
- Improved sleep
- Improved immune system

1. Problem Identification
2. Focus on outcomes
3. Frustration control
4. Reducing complexity
5. Marking features
6. Modeling

Summary

- Children with CHARGE often have poorly regulated systems
- They will do better socially and academically if they can learn to self-regulate
- They can only develop self-regulation skills slowly unless they experience a lot of scaffolding from the adults in their lives

Thanks to my Lab

– Tasha Nacarato
– Maria Ramirez
– Rachel Vert
– Stephanie Budde
– Valerie Webber
– Kasee Stratton

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Identifying the 'P' in CHARGE: Pain & the Relationship of Pain to Challenging Behavior

Thursday, 07/28/11
Platform #8: 2:55-3:20
Wekiwa 3 & 4

Kasee Stratton, M.A.
Kennedy Krieger Institute: Pediatric Developmental Disorders Clinic at John Hopkins University School of Medicine
Central Michigan University

Presenter Information:

Kasee Stratton is a doctoral student at Central Michigan University. She received her Master of Arts in School Psychology in December of 2010. Currently she is completing her pre-doctoral internship in the Pediatric Developmental Disorders Clinic at the Kennedy Krieger Institute, a part of the John Hopkins University School of Medicine. She has been researching CHARGE syndrome, pain, and challenging behaviors for six years and has presented previously in Australia, New Zealand, Denmark, and at the 9th International CHARGE Syndrome Conference.

Presentation Abstract:

The research on pain in children with developmental disabilities is limited, including individuals with CHARGE. It has long been suspected that individuals with CHARGE have a high-threshold for pain. Our research, however, found that individuals with CHARGE experience considerable pain, including long term (chronic) pain. A relationship was found between challenging behavior (e.g. self injury) and an increase in pain intensity. A non-vocal pain measure will be discussed that was designed specifically for individuals with CHARGE to identify pain. Further, the relationship between pain and challenging behaviors will be described and intervention strategies will be suggested.

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011

Identifying the 'P' in CHARGE: Pain and the Relationship of Pain to Challenging Behavior

Kasee K. Stratton, M.A.
Kennedy Krieger Institute at John Hopkins University School of Medicine
Central Michigan University

CHARGE FAST PASS

- Pain in developmental disabilities
- CHARGE syndrome and pain
- Are we identifying pain?
- Challenging behaviors in CHARGE
- How pain is related to challenging behavior
- Reducing the pain experience

Pain in Developmental Disabilities

- "Higher" threshold for pain
  - Has been suggested in CHARGE (Davenport, 2002)
- No evidence
- Higher risk for experiencing more frequent pain
- Identifying Pain in CHARGE
  - Poor communication strategies

The 'P' in CHARGE

- Surgery (Stratton & Hartshorne, 2011)
  - 1 to 63 procedures
  - Average 13
  - Rated as painful experience
  - Average age of study 15 yrs. (Range of 7 months to 41.5 years)
- Procedures
- Doctor visits
- CHARGE related characteristics

Common Pain Experiences

Pain Experience	(N= 58*), n=	Percentage of Participants
Ear Infections	39	67.2
Sinus Infections	24	41.4
Gastroesophageal Reflux	24	41.4
Constipation	24	41.4
Surgery	23	39.7
Tactile Defensiveness	20	34.5
Migraine	14	24.1
Stoma Pain	12	20.7
Abdominal Migraine	11	19.0
Muscle Pain	11	19.0
Back Pain	8	13.8
Hip Pain	6	10.3
Jaw Pain	5	8.6
Pain During Sleep	5	8.6

Most Intense Pain and Average Duration

	Pain Intensity			Days per Year in Pain	
Characteristic	*M*	*SD*	Range	*M*	*SD*
Migraine	2.67	.87	2-4	13.50	13.51
Abdominal Migraine	2.45	1.10	1-4	97.47	128.95
Constipation	2.38	.80	1-4	52.25	58.38
Surgery Pain	2.34	.97	1-4	9.52	9.40
Chronic Recurrent Otitis Media	2.24	.99	0-4	22.88	32.18
Sinusitis	2.17	.82	1-4	35.13	41.51
Gastroesophageal Reflux	2.06	1.14	0-4	169.29	133.70
Breathing	2.00	1.03	1-4	108.67	131.82
Hip/Back Pain	1.86	.95	1-4	98.09	144.14
Muscle Pain	1.82	.87	1-3	95.70	136.07
Coughing	1.61	.80	1-3	66.48	99.42
Jaw Discomfort	1.56	.88	1-3	13.22	11.17
Difficulty Swallowing	1.50	.83	1-4	129.00	154.04

Migraines

- Trigeminal nerve (CN V)
  - Sensation and function to your jaws, face, tongue, sinus, palate, eyes, teeth, and lips.
  - Also has a role with chewing and swallowing
  - CN dysfunction in CHARGE

Blake, K.D., Hartshorne, T. S., Lawand, C., Dailor, A. N., & Thelin, J. W. (2008). Cranial nerve manifestations in CHARGE syndrome. *American Journal of Medical Genetics, 146A*, 585-592

Abdominal Migraine

- Typically children ages 5 to 9
- Linked to adult migraines
- Lasts 1 to 72 hours
- Acute stomach pain with
  - Nausea
  - Vomiting
  - Light sensitivity
  - Diarrhea
  - Loss of appetite

Constipation

- Painful bowel movements
- Dry or hard stool
- Nausea
- Cramps, abdominal pain

- Fecal impaction
  - Abdominal cramping
  - Rectum discomfort

Gastroesophageal Reflux

- Average of 170 days a year
- Heartburn
  - Involves a burning pain in the chest (under the breastbone)
  - Increased by bending, stooping, lying down, or eating
  - More frequent or worse at night
  - Relieved by antacids
- Nausea and vomiting
- Regurgitation of food
- Sore throat

Tactile Defensiveness

- textured materials or items
- "messy" things
- vibrating toys
- a hug or kiss
- certain clothing textures
- rough or bumpy bed sheets
- seams on socks
- tags on shirts
- light touch
- hands or face being dirty
- shoes and/or sandals
- wind blowing on bare skin
- bare feet touching grass or sand

Are we identifying pain?

- Are you able to determine when your child is experiencing pain?
  - 75% -Yes
  - Did not vary significantly by age of child

- Zero parents could identify chronic pain and no child could indicate chronic pain

Behaviors that Indicate Pain

- Vocal
  - Crying, moaning
- Social
  - Withdrawn, obstinate, difficult to distract, hard to console
- Facial
  - Frowns, mouth turned down, grinding teeth
- Activity
  - Less active, restless, disturbed sleep
- Body and Limb Movement
  - Rubbing area of pain, stiffens/spasms/seizures
- Physiological
  - Change in color, sharp intake of breath

Challenging Behaviors Indicate Pain

- Behavioral Challenges
- Self-Injurious Behavior (SIB)
- Dangerous Behaviors

- Aggressive, bites, hits head, throws objects, punches, pulls out g-tube

Why is it difficult to identify and measure pain in CHARGE?

- Limited or no communication strategies
  - Cannot use the gold-standard
- Possible social-communicative deficits
  - (Craig, 2006)
- Possible social referencing deficit
  - (Recchia 1997)

Measuring Pain

- Facial Reactions to Pain
  - Limited research
  - Facial palsy in CHARGE
- Rating Pain
  - Numerical ratings with pictures
  - Multidimensional pain tools

Measuring Pain

- Created a non-vocal, multidimensional pain scale
  - CHARGE Non-Vocal Pain Assessment (CNVPA)
- Developed from:
  - NCCPC-R (Breau et al., 1998)
  - PPP (Hunt, 2003)
  - Parent/caregiver input

#1 PAIN Assessment

→ **TODAY'S DATE:** _____

Who is completing this form?
- ❑ **MOTHER**
- ❑ **FATHER**
- ❑ **OTHER:** _____

DIRECTIONS:
Please complete the following rating after observations of your child for one day when you believe your child ***was experiencing pain***. For each item, circle the number that best describes your child's behavior during the pain episode.
If your child does not engage in a behavior when in pain OR is not capable of performing an action, score this item as *"not at all."*

	Not at all	A little	Quite a lot	A great deal
VOCAL				
Cries	0	1	2	3
Moans/groans/screams	0	1	2	3
SOCIAL				
Cheerful	3	2	1	0
Sociable/responsive	3	2	1	0
Not cooperative (cranky, irritable)	0	1	2	3
Obstinate (e.g. doesn't respond to directions)	0	1	2	3
Withdrawn or depressed	0	1	2	3
Hard to console or comfort	0	1	2	3
Difficult to distract	0	1	2	3
FACIAL				
Frowns/has furrowed brow/looks worried	0	1	2	3

What do we know about the CNVPA?

- Mean differences between no-pain and pain assessments were significantly different

Do parents find this pain assessment to be relevant to identify their child's pain (non-vocally)?

Relevance	*n*	Percentage of Participants
Extremely Relevant	14	24.6
Relevant	17	29.8
Somewhat Relevant	18	31.6
Not Relevant	8	14.0

Instrument may not be relevant because:

- Child can verbalize pain vocally (12)
- Never complains of pain and seems to tolerate it well
- I've already developed ways to identify pain for my child (3)
  - "After 24 years, I am in tune to my child's health"

PAIN AND BEHAVIOR

Does Pain Impact Behavior?

- Evidence that pain is associated with behavior problems in typical-developing children
  - De Lissovoy (1962) head banging and otitis media
  - Hart, Box, & Jenkins (1984) tantrums and upper respiratory infection
- Evidence that pain is associated with behavior problems in children with disabilities
  - O'Reilly (1997) self-injury and otitis media
  - Carr & Owen-DeSchryver (2007) sick days
  - Lekkas & Lentino (1978) constipation
  - Kennedy & Meyer (1996) allergies

Does Pain Impact Behavior?

- Aggressive behavior, destructive behavior, and self-injury (Kennedy & O'Reilly, 2006)
- Elevated pain → elevated self-injury (Symons & Danov, 2005)
- Attachment
- Adaptive Functioning
- Quality of life may be compromised (Oberlander & Symons, 2006)

Understanding Pain

- Unknown what children with CHARGE know about pain
  - How to predict when and how it will be resolved
  - Increase the intensity of the experience and also increase challenging behaviors
  - Individuals with CHARGE may need to be explicitly taught coping strategies to help identify pain and how to control these events in their lives

All Behavior is Communication!

Reducing the pain experience

- Mitigation
  - Analgesics
  - Bed rest
  - Dietary change
- Redesigning the environment
  - Reducing the demands
- Teaching coping skills
  - Self advocacy
  - Functional communication alternatives

Caution with Medications

Analgesic failure may be due to …

- Inappropriate drug or dose selection for type of pain
- Genetic factors inherent to capacity to metabolize medications
- Impact of use of multiple drugs with competition for metabolic and excretory pathways
- Neurological substrate underlying CHARGE

Presenter Information:

Kasee Stratton, M.A.
Central Michigan University
Doctoral Student in School Psychology

Kennedy Krieger Institute at John Hopkins University School of Medicine
Behavioral Psychology Intern

Contact Information:
strat1kk@cmich.edu

Navigating the NIH

Thursday, 07/28/11
Platform #9: 3:20-3:45
Wekiwa 3 & 4

Tiina K. Urv, Ph.D.
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)**
National Institutes of Health (NIH)

Presenter Information:

Tiina Urv, Ph.D., joined the Intellectual and Developmental Disabilities (IDD) Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH) as a program director in October 2006. Dr. Urv is a developmental disabilities specialist with a Ph.D. from Columbia University and over 25 years of experience working with individuals with intellectual disabilities in both clinical and research settings. Prior to joining the Branch, she was an assistant professor at University of Massachusetts Medical School's Eunice Kennedy Shriver Center and a research scientist at the New York State Institute for Basic Research in Developmental Disabilities. The focus of her work has been the behavioral aspect of aging and Alzheimer disease in adults with Down syndrome and developmental disabilities. Dr. Urv's work in the IDD Branch has focused on Newborn Screening of Rare Diseases and Fragile X syndrome (FXS).

Presentation Abstract:

Discussion of funding opportunities at the NIH for grants related to CHARGE syndrome.

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011

CHARGE Syndrome: Quality of Life in Adolescence and Adulthood

Thursday, 07/28/11
Platform #10: 4:10-4:35
Wekiwa 3 & 4

Nancy Salem-Hartshorne, Ph.D., Delta College
Kim Blake, M.D., Dalhousie University/IWK Health Center
Jillian McCuspie, Medical Student, Dalhousie University
Tasha Nacarato, Graduate Student, Central Michigan University

Presenter Information:

Dr. Salem-Hartshorne is an instructor at Delta College in Central Michigan. Her research has focused on developmental outcomes for individuals with CHARGE syndrome. She has a son, Jacob, aged 22, who has CHARGE syndrome.
Dr. Blake is a Pediatrician at IWK Health Center and Director of Undergraduate Education in Pediatrics at Dalhousie University in Nova Scotia. Her research focus is CHARGE syndrome, with a particular focus on adolescent and adult issues.
Jillian MacCuspie is a medical student at Dalhousie University. She has been research assistant to Dr. Blake for 3 years and her main interest is in pediatrics and disability.
Tasha Nacarato is a graduate student in School Psychology at Central Michigan University. She has been a research assistant to Dr. Hartshorne during the past two years in the area of CHARGE syndrome.

Presentation Abstract:
Very little is known about the quality of life of individuals with CHARGE syndrome during their adolescent and early adult years. Data was gathered both during the the previous CHARGE syndrome conference in Illinois, and over the phone and via mail. There were more than fifty respondents, most from the United States. Participants consisted of individuals aged 13 and up. Participants and their parents or guardians gave details, through interview and checklist, about their CHARGE features, developmental histories, medical and behavioral concerns, and independent abilities They also completed measures of general quality of life and health-related quality of life. Results will be presented and implications about findings will be discussed so that parents and professionals may have awareness of this information when working with individuals with CHARGE syndrome. Handouts will be available at the poster session.

So Many Ways to Have a Conversation

Thursday, 07/28/11
Platform #11: 4:35-5:00
Wekiwa 3 & 4

Martha Majors
Assistant Education Director
Deafblind Program
Perkins School for the Blind

Presenter Information:

Perkins School for the Blind developed a series of 3 webcasts related to CHARGE syndrome; Martha participated in these webcasts focusing on the educational implications for a child with CHARGE syndrome.

Presentation Abstract:

The develop of communication for children with CHARGE syndrome can be challenging for both the child and their team (families and educators). For most students receptive language is the area of strength; the use of expressive communication can be delayed and as a result there is a level of frustration that builds within the child. Current thinking includes the consistent use of total communication as well as assistive technology as a support. The best solutions come from a team approach where several disciplines come together to consider the strengths of the child that not only includes communication but use of vision, hearing, and physical presentation. In this way, the whole child is taken into consideration and outcomes can be more child specific and focused.

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011

Many Ways to Have a Conversation

Martha M. Majors
Assistant Education Director
Deafblind Program
Perkins School for the Blind

Conversation Format

- Case Study
  - Description of Sensory Loss
  - Developmental Level
  - Communication Matrix
    - Receptive
    - Expressive
  - Description of Total Communication
    - Receptive
    - Expressive

Conversation Conclusion

- Each child is an individual learner
- Each child develops a way to communicate
- Each child uses total communication in their own unique way
- Each child makes progress over time with consistent access to appropriate communication modes

The Potentials of Diversity. Results of a doctoral thesis referring early dialogues between children with CHARGE Syndrome and their parents

Thursday, 07/28/11
Platform #12: 5:00-5:25
Wekiwa 3 & 4

Andrea Scheele, Prof.
Dr. Ursula Horsch
University of Education Heidelberg, Germany

Presenter Information:

Ursula Horsch is Professor for the education of hard of hearing and deaf children and for Early Education at the University of Education in Heidelberg/Germany (since 1991). She is general and special education teacher and is working at the institute for special education since 1974. She finished her PhD at the University in Cologne in 1981. Her main areas are education of the hard of hearing under a dialogical point of view, research on the early and very early education with concentration on early dialogues between parents and their impaired and not impaired infants with a focus on "Bildung" within international and interdisciplinary research projects with partner Universities in Turku/Finland, Olsztyn/Poland and Listen and Talk Seattle/USA. She develops didactic dvds for computer based analysis of early dialogical interactions and has numerous publications referring early education and supports more than 20 doctoral studies, she has publications in research, book contributions as well as presentations in research at national and international conferences. *Contact: ursulahorsch@aol.com, website: www.ursula-horsch.de;* Andrea Scheele became teacher and early educationer for the deaf and the blind at the University of Education Heidelberg in Germany and is concentrating on pedagogic for the deafblind since 2002. In 2006 she became member of the research team of Prof. Dr. Horsch at the University of Education in Heidelberg and started her PhD study on early interactions between infants and toddlers with CHARGE Syndrome and their parents, which will be finished 2011. During that time she participated in many conferences on Deafblindness and had the chance to exchange and network with lots of people about Deafblindness and CHARGE Syndrome. In Germany she cooperates intensively with the CHARGE foundation of parents. *Contact: as@andrea-scheele.de, website: www.andrea-scheele.de*

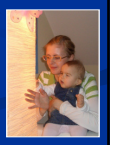
Presentation Abstract:

The study "*Early dialogues of children with CHARGE Syndrome and their parents*" is introduced and the most striking results are presented. Next to scientific results of early dialogues between children with CHARGE Syndrome and their parents in contrast to early dialogues of children without disabilities and their parents' selected screenshots from eminently interesting video sequences with different topics like gentle gestures are shown and discussed in the context of potentials of diversity and inclusion. In the presentation a short introduction into the methodology of the study is given and explained how more than 200 videos of children with CHARGE Syndrome and their parents were evaluated since 2006 and what they show. After that the scientific results which accentuate important elements in early dialogues like Motherese/Fatherese but also signs and gestures or touch, their correlations to each other and transition probabilities from one to the other and the effect of time are presented and discussed.

The Potentials of Diversity

Results of a doctoral thesis referring early dialogues between children with CHARGE Syndrome and their parents

2nd Professional Day
10th International CHARGE Syndrome Conference
July 28th 2011, 5 - 5.25
Orlando/FL



Andrea Scheele, Prof. Dr. Ursula Horsch
University of Education Heidelberg

Agenda

1. **A short insight into the PhD study**
2. **Let´s have a look at a dialogue**
3. **Most striking outcomes**
4. **Outlook and questions**

Agenda

1. **A short insight into the PhD study**
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A short insight into the PhD study

Aims

- Widespread collection, documentation and qualitative analysis of observable dialogic elements (Motherese/Fatherese, Dialogic Echo, vocalisation, eye and body contact),
- statements referring the development of the dialogical structure,
- reference to data and outcomes of children without disabilities and with different ones,
- evaluation of meaningful data and consequential impulses for early education,
- toehold for further research,
- calling attention to the topic of Deafblindness and CHARGE Syndrome.

A short insight into the PhD study

Method

- 25 Child-Parent-Pairs
- Congenitally Deafblind, 14 have CHARGE
- Monthly video recording (15 min./analysis: 4 min.)
- „Natural setting“
- Twelve months (+ more, some over 5 years)
- n=325 video recordings (February 2011)
- Analysis with software „Interact“ (Mangold) and statistical research instrument SAS
  - Macro: mean values, correlations, variance
  - Micro: transition probabilities, time series analysis, image recognition

A short insight into the PhD study

Analysis process

Agenda

1. A short insight into the PhD study
2. Let´s have a look at a dialogue
3. Most striking outcomes
4. Outlook and questions

Let´s have a look at a dialogue

Video

Jonas

(about 6 min)

Likes > Dislikes > Support > School

Let´s have a look at a dialogue

Let´s briefly talk about what you have just seen!

Agenda

1. A short insight into the PhD study
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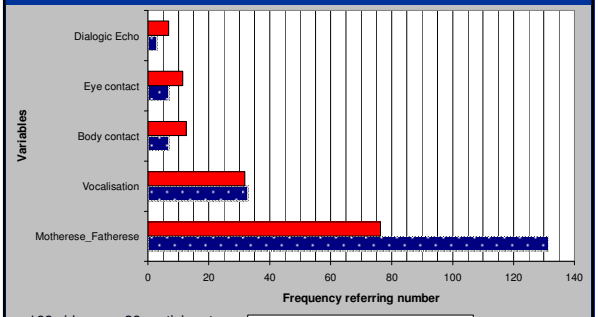
3. Most striking outcomes
4. Outlook and questions

Most striking outcomes

Mean values



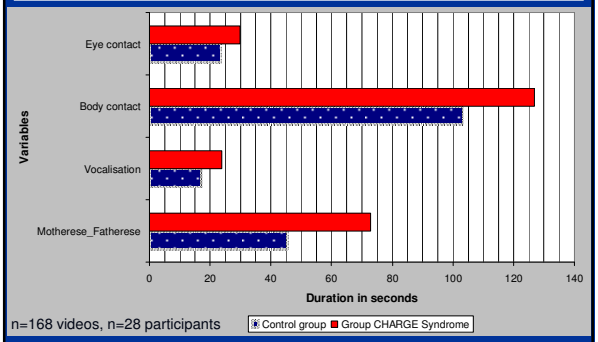
n=168 videos, n=28 participants

Most striking outcomes

Mean values

- Similarities over the groups in the tendency of the frequencies
- Varieties in the particular form, especially referring Motherese/Fatherese (! more rare used !)

→ More rare use of spoken language in the dialogues with a child with CHARGE?

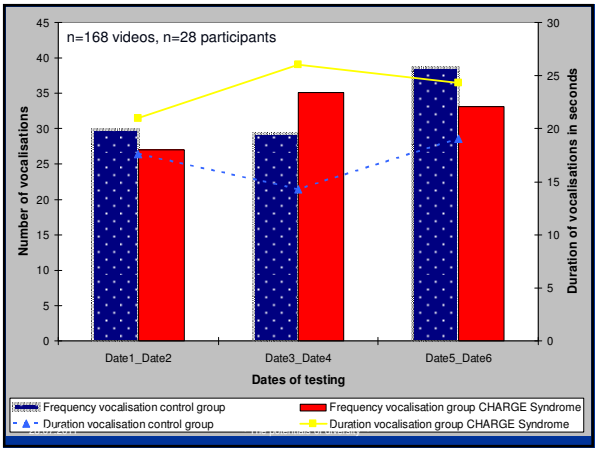


Most striking outcomes

Mean values

- Similarities over the groups in the tendency of the duration
- Varieties in the particular form, especially referring body contact and Motherese/Fatherese (! longer used !)

→ Duration makes the difference!



Most striking outcomes

Mean values

- Not just a differing development over the two groups, but actually a contrary development referring the vocalisation of the child.

(This is also true for eye contact.)

→ Increasing diversity with time

Most striking outcomes

Selected summarized outcomes

Most striking outcomes

Summar-ized

- Same elements!
- **CHARGE:**
  - eye & body contact; Dialogic echo
  - Children try to keep the dialogue going by the use of body contact and vocalisations, but parents especially answer on eye contact and the child offering non of the examined variables
  - Less correlations for Motherese/Fatherese and the variables of the child (and lower frequency)

Most striking outcomes

Summar-ized

- Less anticipation games (songs, finger games) ⇨ less negotiation-dialogues
- Sharing emotions ⇕ communication system ⇕ child's self-regulation

- Music and rhythm is a favourite! Is there a connection to this emotional aspect above?

Agenda

1. **A short insight into the PhD study**
2. **Let´s have a look at a dialogue**
3. **Most striking outcomes**
4. **Outlook and questions**

Outlook and questions

Outlook

- We could just highlight some of the outcomes of the study, but if you are interested in more (like the results of some of the other analysed areas), please feel free to contact us.
- We hope the research on CHARGE Syndrome goes on and we hope a connection between the outcomes and the practical work can be drawn, because we think that it´s most important to improve the current support system for families.

Thank you for your attendance!

We are looking forward to questions, comments, suggestions and an inspiring discussion.

Contact: ***ursulahorsch@aol.com*** and ***Andrea.Scheele@gmx.de*** or ***www.ursula-horsch.de*** and ***www.andrea-scheele.de***

Transcripts of the videos

Father (F) and son (S): 2 years and 6 months

F: Did you notice Mom? What are you doing now? Are you distracted? Yes? Are you distracted because Mom turned on the camera? Yes? Shall we put the picture away again? Yes? Well, let´s put the picture up. Of Mom and Dad. Look. Let´s put it there, the picture. Okay? Can you still see it? Yes? There is the picture. Well, up there. What is over there? Can you show me? That, over there. Hey! Is that the light over there? The picture? That´s what you want? Yes? Okay! Look out, I get it again. I get it again. Have a look, There it is. What do you see at the picture? A nose? Hey. And you see Mom, too. And an eye. Aha, aha. Hmm. Und now? Shall I put it back again? Look out, Dad puts it up once more. Look out. Do you still see it? There it is again. What? You want to have it again? But you just said, I shall put it up. Shall I get it again? Shall I show it once more to Jonas? Okay, look out. Let´s get it again. Is it a nice picture? Yes? Dad sees it, too. Dad. And Mom. And who else is on the picture? Mom, exactly. And Jonas? Is Jonas also at the picture? Can you show him to me? You are kidding around. Are you all done with… There it shall be put? Shall I put it up again? Yes? Okay. Okay. Let´s put it up. It´s away. What is over there? There? What is there? Tell it Dad. The light, exactly. And again the picture. But above, there above, there is the light. Did you see it? The light, exaxtly. Can you, can you also show your Dad´s nose? That´s the nose of Dad, yes. Super, you are doing so well, you are doing well.

Vater (V) und Sohn (S): 2 Jahre und 6 Monate

V: Hast du die Mama bemerkt? Was machst du jetzt? Bist du abgelenkt? Ja? Bist du abgelenkt, weil die Mama die Kamera angemacht hat? Ja? Wollen wir das Bild wieder wegstellen? Ja? So wir tun es wieder hoch das Bild. Von Mama und Papa. Schau her. Da tun wir es hin, das Bild. Okay? Siehst Du es noch? Ja? Da ist das Bild. Na, da oben. Was ist denn da oben? Kannst du es mir mal zeigen? Das da. Hey! Ist das da oben das Licht? Das Bild? Das willst du haben? Ja? Okay! Pass auf, ich hol es noch mal. Ich hol es noch mal. Schau her. Da ist es wieder. Was siehst du denn auf dem Bild? Eine Nase? Hey. Die Mama siehst du auch. Und ein Auge. Aha, aha. Hmm. Und nun? Soll ich es wieder hinstellen? Pass auf, genau, der Papa stellt es wieder hoch. Schau hier. Siehst du es noch? Da steht es wieder. Was denn? Willst du es schon wieder haben? Du hast doch grad gesagt, ich soll es hochstellen. Soll ich es noch mal holen? Soll ich es noch mal dem Jonas zeigen? Okay, pass auf. Holen wir es noch mal her. Ist das ist ein schönes Bild? Ja? Der Papa sieht es auch. Der Papa. Und die Mama. Wer ist denn noch auf dem Bild? Die Mama, genau. Und der Jonas? Ist der Jonas auch auf dem Bild? Schau mal zu dem Bild, schau` mal zu dem Bild. Ist der Jonas auch auf dem Bild? Kannst du ihn mir zeigen? Du machst einen Quatsch. Bist du schon fertig mit… Da soll es wieder hin? Soll ich es wieder hochstellen? Ja? Okay. Okay. Stellen wir es da hoch. Ist es weg. Was ist da oben? Da oben? Was ist da? Sag es mal dem Papa. Das Licht, genau. Und dann wieder das Bild. Da oben, da oben, da ist das Licht. Hast du es gesehen? Das Licht, genau. Kannst du, kannst Du auch mal bei Deinem Papa die Nase zeigen? Das ist die Nase vom Papa, ja. Super, machst du so prima, machst du ganz prima.

Father (F) and son (S): 5 years and 5 months
(cursive = addressed to another person)

F: Look. Now. Look at me.
S: Yes.
F: Now it´s your turn to turn a card around.
S: Yes.
F: One.
S: Yes.
F: Your turn. Turn around a card.
S: Yes.
F: Okay. Who is that? Put it back again.
S: Dora.
F: That is Dora. Now you have to find a second Dora. Where is the other Dora? There, you think?
S: Yes.
F: Oh. Who´s that? Put it down.
S: A Boots.
F: A Boots! Mmh. That doesn`t fit.
S: Yes.
F: Look. A Dora. And…
S: A Boots.
F: Okay. Let´s turn them around again. One for you.
S: Yes.
F: Okay. Turning around again. Now it´s daddys turn.
S: Yes.
F: Okay. Here was the Dora, there was the Boots.
S: Yes.
F: Okay, now it´s daddys turn.
S: Swiper.
F: A Swiper. Oh. Now we have had each of them. Super. And Backpack.
S: And backback.
F: Doesn´t fit.
S: Yes.
F: Do you still remember? Dora.
S: Dora.
F: Boots.
S: Boots.
F: Swiper.
S: Swiper.
F: Backpack.
S: Backpack.
F: Now it´s Jonas turn again. *That´s clever. I would have done the same.*
S: Swiper.
F: Put down.
S: Swiper.
F: Blimey! Jonas found it!
S: Yes.
F: Yes, super!
S: Yes.

F: Okay, now you may put them right here and then it´s your turn again. Because you found a pair.
S: Yes.
F: Now it´s Jonas turn again. How clever!
S: Dora.
F: A Dora. Where is the other Dora?
S: Dora!
F: Unbelievable! You found it again?
S: Yes.
F: Fantastic! Wow. Okay.
S: Yes.
F: Then it´s your turn again. You've again got a pair.
S: Yes.
F: Now look at me. It´s your turn again. You again.
S: Yes.
F: Boots.
S: Boots.
F: And where is the other Boots? That one? Mmh. Well, at least not that one.
S: There!
F: There or there?
S: There. Ohhh!!!
F: *Laughing.* Unbelievable. You found it?
S: Yes.
F: Oh. *He was sure that it is not this one. Mmh.* And now?
S: Backpack?
F: Backpack.
S: Yes.
F: And where is the other Backback?
S: Ahaaaaaaa!
F: Yes great! Super. Fantastic. You´ve all of them and I have nothing. Look, how many did you find? Please count them.
S: One. Two. Three. Four.
F: And how many has daddy?
S: Naught.
F: I have nothing. You found all of them on your own!
S: Yes.
F: Super!
S: Yes.
V: That was really great.

Vater (V) und Sohn (S): 5 Jahre und 5 Monate
(kursiv = richtet sich an eine andere Person)

V: Schau mal. Jetzt. Schau mich mal an.
S: Ja.
V: Jetzt darfst Du eine Karte umdrehen.
S: Ja.
V: Eine.
S: Ja.
V: Mach mal. Dreh mal eine Karte um.
S: Ja.
V: Okay. Wer ist das? Leg sie wieder hin.
S: Dora.
V: Das ist die Dora. Und jetzt musst Du noch eine zweite Dora finden. Wo ist die andere Dora? Da, denkst Du?
S: Ja.
V: Oh. Wer ist das? Leg es hin.
S: Ein Boots.
V: Ein Boots! Mmh. Passt nicht zusammen.
S: Ja.
V: Schau. Eine Dora. Und…
S: Ein Boots.
V: Okay. Drehen wir sie wieder um. Du auch eine.
S: Ja.
V: So. Wieder umdrehen. Jetzt ist der Papa dran.
S: Ja.
V: Okay. Hier war die Dora. Da war der Boots.
S: Ja.
V: Okay, jetzt ist der Papa dran.
S: Swiper.
V: Einen Swiper. Oh. Jetzt haben wir sie alle einmal gehabt. Super. Und Backback.
S: Und Backpack.
V: Passt auch nicht.
S: Ja.
V: Weißt Du noch? Dora.
S: Dora.
V: Boots.
S: Boots.
V: Swiper.
S: Swiper.
V: Backpack.
S: Backpack.
V: Jetzt ist der Jonas wieder dran. *Ist ja clever. Hätte ich auch gemacht.*
S: Swiper.
V: Leg hin.
S: Swiper.
V: Ich werd` verrückt! Der Jonas hat´s gefunden!
S: Ja.
V: Ja super!
S: Ja!

V: So, dann darfst Du die hier herlegen und dann darfst Du auch nochmal. Du hast ja ein Paar gefunden.
S: Ja.
V: Jetzt darf der Jonas noch einmal. Clever.
S: Dora.
V: Eine Dora. Wo ist die andere Dora?
S: Dora!
V: Das gibt´s doch nicht! Du hast es schon wieder gefunden?
S: Ja.
V: Ist ja klasse. Wow. Okay.
S: Ja.
V: Dann darfst Du nochmal. Hast du schon wieder ein Paar.
S: Ja.
V: Nun schau mich mal an. Jetzt darfst du noch einmal. Darfst du noch einmal.
S: Ja.
V: Boots.
S: Boots.
V: Und wo ist jetzt wohl der andere Boots? Der soll`s sein? Mmh. Zumindest ist es die nicht.
S: Da!
V: Da oder da?
S: Da. Ohhh!!
V: *Lachen.* Das gibt´s doch nicht! Du hast ihn gefunden?
S: Ja.
V: Ach. *Er war sich sicher, dass es die nicht ist. Mmh.* Und nun?
S: Backpack?
V: Backpack.
S: Ja.
V: Und wo ist der andere Backpack?
S: Ahaaaaaaa!
V: Ja klasse! Prima. Toll. Du hast sie alle und ich hab` nichts. Schau mal, wie viele hast Du gefunden? Zähl mal bitte.
S: Eins. Zwei. Drei. Vier.
V: Und wie viel hat der Papa?
S: Null.
V: Ich hab gar nichts. Du hast alle allein gefunden!
S: Ja.
V: Super!
S: Ja.
V: Das war ja mal klasse.