Further Delineation of 1p36 Deletion Syndrome in Adolescents and Adults

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Purpose

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- To begin to describe the natural progression of 1p36 deletion syndrome
- To further additional research opportunities for 1p36 deletion syndrome and address families' and clinicians' questions about the syndrome.

Background

Background[1-4]

- Most common terminal deletion syndrome
- Incidence :1/5,000 – 1/10,000
- About 95% of deletions are de novo
- First reported in 1981, first "true" case reported in 1993
- Common facial characteristics:
  - Straight eyebrows, deep-set eyes, pointed chin, flat nasal bride, long philtrum, etc.

Common Characteristics[1-6]

- Central Nervous System
  - 50% - 79% seizures
  - Brain malformations
  - Hypotonia, spasticity, contractures
- Cardiovascular
  - 17% - 31% cardiomyopathy
  - CHD
- GU
  - Renal anomalies

Common Characteristics[1-6]

- Vision
  - 30% - 67% strabismus
  - Myopia and hypermetropia
- Hearing
  - Up to 2/3 with hearing loss
- GI
  - 60% - 70% gastroesophogeal reflux in infancy
  - Constipation, diarrhea, general discomfort, and ulcers

Common Characteristics[1-8]

- Speech and Communication
  - Delays in speech development; almost universal
- Feeding and Toileting
  - 47% - 77% of infants have difficulty feeding
- Mobility
  - Usually delayed
  - May achieve independent walking or be wheelchair dependent
- Behavioral
  - Ranges from happy temperament to autistic-like features

Additional Features

- Physical Development[2,7]
  - Case reports of precocious puberty and delays in puberty
- Cancer[9-11]
  - Few case reports on neuroblastoma in children with 1p36 deletion syndrome
  - Tumor suppressor genes located on the 1p36 region

Methods

Participants

- Primary caregivers of adolescents and adults with 1p36 deletion syndrome aged 12 or older
- Must have a confirmed diagnosis of 1p36 deletion syndrome
- English as primary language
- Recruited through three online support groups and cohort of CCHMC patients
  - 1p36 Deletion Support and Awareness
  - UNIQUE
  - Chromosome Disorder Outreach, Inc.

Survey Development

- Cross-sectional descriptive survey
- 133 item questionnaire
  - 72 close-ended questions
  - 61 open-ended questions
- Developed based on literature review and anticipated medical problems
- Administered electronically through REDCap® and via mail

Survey Measures

- 12 sections of questions
  - Demographic
  - Medical history
  - Central nervous system
  - Hearing and vision
  - Cardiovascular
  - Physical abnormality
  - Cancer
  - Puberty
  - Mobility
  - Feeding and toileting
  - Speech and communication
  - Behavioral

Results

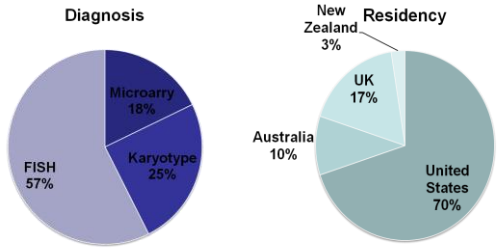
Responses

- 50 surveys attempted completion
- 38 filled out to completion
  - 28 females
  - 10 males
- 12 incomplete
  - 7 left blank
  - 1 did not meet age requirement
  - 2 filled out all but behavioral section; included in analysis
- 40 surveys included in analysis

Demographics: Males and Females

- Female ages ranged 12 – 46 years old
  - Mean: 19.7 years old
- Male ages ranged from 13 – 34 years old
  - Mean: 19.2 years old
- No statistical significance was found between the ages of males and females (chi sqaure, p=0.8738)

Demographics: Diagnosis and Residency



Medical History: GI and Renal Problems

	Males (n=11)	Females (n=29)	Total (n=40)
Constipation	27% (3)	45% (13)	40% (16)
Diarrhea	27% (3)	24% (7)	25% (10)
Kidney Infections	27% (3)	21% (6 out of 28)	23% (9 out of 39)
GE Reflux	27% (3)	17% (5)	20% (8)
Abdominal Pain	9% (1)	24% (7)	20% (8)
Ulcers	9% (1)	3% (1)	5% (2)

Central Nervous System

	Males (n=11)	Females (n=29)	Total (n=40)
Hx of seizures	64% (7)	83% (24)	78% (31)
Currently HAS seizures	43% (3 out of 7)	42% (10 out of 24)	42% (out of 31)
Currently DOES NOT have seizures	57% (4 out of 7)	58% (14 out of 24)	58% (out of 31)
Currently hypotonic	55% (6)	69% (20)	65% (26)
Currently spastic	36% (4)	52% (15)	48% (19)
Hx of contractures	25% (2 out of 8)	31% (8 out of 26)	29% (10 out of 34)
Brain anomaly	27% (3)	14% (4)	18% (7)

Hearing Problems

	Males (n=11)	Females (n=29)	Total (n=40)
No HL	45% (5)	59% (17)	55% (22)
Conductive	18% (2)	13% (5)	18% (7)
Sensorineural	9% (1)	14% (4)	13% (5)
Mixed	18% (2)	7% (2)	8% (3)
Other	9% (1)	4% (1)	8% (3)

Vision Problems

	Males (n=11)	Females (n=29)	Total (n=40)
Myopia	55% (6)	31% (9)	38% (15)
Strabismus	27% (3)	38% (11)	35% (14)
Hypermetropia	9% (1)	10% (3)	10% (4)
Other	0% (0)	31% (9)	23% (9)
No vision problems	27% (3)	17% (5)	20% (7)

Congenital Heart Defects

	Males (n=6)	Females (n=14)	Total (n=20)
VSD	2	5	7
PDA	1	4	5
Murmur	1	3	4
Ebstein's anomaly	0	2	2
PFO	0	1	1
ASD	1	0	1
Narrow aortic arch	1	0	1
Bicuspid aortic valve	1	0	1
Tricuspid aortic valve	0	1	1
Tetralogy of Fallot	0	1	1
Transient myocardial dysfunction	0	1	1

Acquired/Persistent Cardiovascular Disease

	Males (n=3)	Females (n=4)	Total (n=7)
Cardiomyopathy	2	1	3
Dialated aortic and pulmonary root	0	1	1
LVNC and CHF	0	1	1
Unspecified	1	1	2

Unspecified: "new hole in heart" and "left ventricle"

Physical Development

Tanner Stage	Males (n=11)	Females (n=28)	Total (n=39)
II	9% (1)	0	
III	0	11% (3)	8% (3)
IV	0	21% (6)	15% (6)
V	73% (8)	64% (18)	67% (26)
None	9% (1)	0	3% (1)
Onset of Menses	N/A	11.3 years old	
Atypical Development	55% (6)	17% (5)	28% (11)

Cancer/Tumors

- 0 out of 40 respondents reported a tumor or cancer diagnoses among the surveyed population
- However, this does not establish low risk for developing cancer
- Primary care physicians should be aware of a potentially increased risk

Ability to Achieve Independent Mobility

	Males (n=11)	Females (n=29)	Total (n=40)
Sit	91% (10)	100% (29)	98% (39)
Walk	82% (9)	79% (23)	80% (32)
Crawl	9% (1)	17% (5)	15% (6)
"Bottom-Shuffle"	9% (1)	17% (5)	15% (6)
Crawl and "bottom-shuffle"	27% (3)	14% (4)	18% (7)
No wheelchair assistance	64% (7)	62% (18)	63% (25)
Used wheelchair	18% (2)	34% (10)	30% (12)

Ability to Feed Independently

	Males (n=11)	Females (n=29)	Total (n=40)
Never needed tube	73% (8)	79% (23)	78% (31)
Ever needed G-tube	27% (3)	17% (5)	20% (8)
Ever needed NG-tube	0	3% (1)	3% (1)
Currently no tube	81% (9)	90% (26)	88% (35)
Currently G-tube	18% (2)	7% (2)	10% (4)
Majority of nutrition orally	91% (10)	97% (28)	95% (38)
Hold cup or spoon	10 out of 10	28 out of 28	
Feed themselves	90% (9 out of 10)	85% (23 out of 27)	86% (32 out of 37)

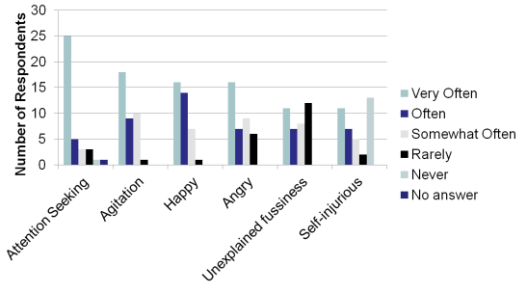
Toileting

	Males (n=11)	Females (n=29)	Total (n=40)
Stool and urine	45% (5)	41% (12)	43% (17)
Urine only	9% (1)	7% (2)	8% (3)
Not toilet trained	45% (5)	48% (14)	48% (19)
Accidents	33% (2 out of 6)	43% (6 out of 14)	40% (8 out of 20)

Speech and Communication

	Males (n=11)	Females (n=28)	Total (n=39)
Verbal	37% (4)	46% (13)	44% (17)
10 words or less	0	8% (1 out of 13)	6% (1 out of 17)
11-50 words	25% (1 out of 4)	8% (1 out of 13)	12% (2 out of 17)
51-100 words	0	15% (2 out of 13)	12% (2 out of 17)
Over 100 words	75% (3 out of 4)	69% (9 out of 13)	71% (12 out of 17)
Speak sentences	3 out of 4	13 out of 13	
Imitate sounds	73% (8)	79% (22)	77% (30)
Exclusive use of sign language	55% (6)	30% (8 out of 27)	37% (14 out of 37)
Specific Speech problem	36% (4)	43% (12)	41% (16)

Behavioral



Implications/Conclusions

Implications and Conclusions

- Corroborated some of same existing data
  - Seizures are a prominent medical problem and can persist into adulthood
  - Vision problems also are very common
- Elucidated new medical problems
  - Hypotonia may persist into adulthood
  - Acquired cardiovascular manifestations

Implications and Conclusions

- Many individuals are mobile
- Most individuals are able to feed themselves
- Verbal and non-verbal communication occur frequently
- Some behavioral concerns still exist

Implications and Conclusions

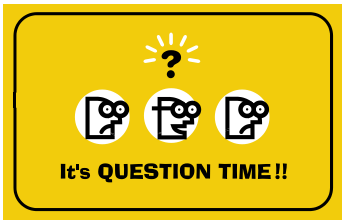
- Proper medical care and support (therapies, etc.) is imperative
- Individuals appear to make significant developmental progress
- Ability to achieve a level of independence not previously documented

Future Research

Future Research

- Continuing to characterize 1p36 deletion syndrome in adolescents and adults
- Evaluating 1p36 deletion syndrome and obesity in adulthood
- Formal speech evaluations

Questions?



Thank you!!!!!

References

1) Gajecka M, Mackay KL, Shaffer, LG. 2007. *Monosomy 1p36 deletion syndrome*. Am J Med Genet Part C Semin Med Genet 145C:346-356.
2) Shapira, SK, et al. *Chromosome 1p36 deletions: the clinical phenotype and molecular characterization of a common newly delineated syndrome.* Am J Hum Genet, 1997. 61(3):642-50.
3) Heilstedt, HA, et al. *Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome.* Am J Hum Genet, 2003. 72(5): 1200-12.
4) 1p36 Deletion Syndrome. GeneReviews. http://www.ncbi.nlm.nih.gov/books/NBK1191/
5) UNIQUE. *1p36 Deletion Syndrome*. 2011, UNIQUE.
6) Battaglia, A, et al., *Further Delineation of Deletion 1p36 Syndrome in 60 Patients: A Recognizable Phenotype and Common Cause of Developmental Delay and Mental Retardation.* Pediatrics, 2008. 121(2):404-410.
7) Knight-Jones, E, et al. *Neurodevelopmental profile of a new dysmorphic syndrome associated with submicroscopic partial deletion of 1p36.3.* Dev Med Child Neurol, 2000. 42(3):201-6.
8) D'Angelo, CS, et al. *Extending the phenotype of monosomy 1p36 sundrome and mapping of a critical region for obesity and hyperphagia.* Am J Med Genet A, 2010. 152A(1):102-10
9) White, PS, et al. *A region of consistent deletion in neuroblastoma maps within human chromsome 1p36.2-36.3*. Proc Natl Acad Sci USA, 1995. 92(12)5520-4
10) Biegel, JA, et al. *Constitutional 1p36 deletion in a child with neuroblastoma*. Am J Hum Genet, 1993. 52(1):176-82.
11) Laureys, G, et al. *Constitutional translocation t(1;17)(p36;q12-21) in a patient with neuroblastoma.* Genes Chromosomes Cancer, 1990. 2(3):252-4.