

WHAT'S NEW AND EXCITING IN ARTHROGRYPOSIS

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PLAN OF TALK

- **Definitions**
- **Fetal akinesia sequence**
- **Many specific types – over 400**
- **Ways to categorize**
- **New findings**
- **Potential therapies**

- **Arthro = joint**
 - **gry = curved**
 - **posis = a condition**

(Multiple congenital contractures)

ARTHROGRYPOSIS

**Congenital nonprogressive
limitation of movement of
two or more joints in
different body
areas**

CONGENITAL CONTRACTURES IN THE NEWBORN

- Clubfoot.....1/500
- Congenital dislocated hips.....1/200–1/500
- Multiple congenital contractures....1/3000
- All congenital contractures...1/100– 1/250

ARTHROGRYPOSIS (MCC) PREVALENCE

Seattle/Washington (JGH)	1970s	1/3,000
BC (JGH)	1980s	1/3,000
Helsinki (Laiten et al)	1966	1/3,337
Western Australia (Silbert et al)	1998	1/12,037
Sweden (Darin et al)	2002	1/5,058
Finland (Pakkasjarvi et al)	2006	1/4,206
Alberta (-TOP) (Lowry et al)	2010	1/8,713

1/3,000 – 1/12,000

(1/4,000 – more common than most common congenital anomalies)

**Arthrogryposis is a sign,
not a diagnosis!**

**The challenge is to make a
specific diagnosis –
if possible!**

1970s

FETAL AKINESIA

Fetus not moving

FETAL AKINESIA SEQUENCE

PENA SHOKIER PHENOTYPE

- Intrauterine growth retardation
- Congenital contractures of the limbs
- Hypoplastic lungs
- Short umbilical cord
- Polyhydramnios – short gut
- Craniofacial anomalies
 - Micrognathia +/- small mouth
 - +/- cleft palate
 - High bridge of nose
 - Depressed tip of nose

IDENTIFIABLE FAMILIAL FORMS OF PENA SHOKEIR PHENOTYPE/FETAL AKINESIA SEQUENCE

Name Designation	Chromosome Location	Gene
1. Classic Pena Shokeir syndrome	—	—
2. Lower Motor Neuron Disorder with generalized decrease in anterior horn cells (Chen type)	— 9q34	— GLE mRNA export
3. Lethal Congenital Contractures Syndrome Type I (LCCS-1)	12q13	medicac
4. Lethal Congenital Contracture Syndrome Type II (LCCS-2)	19q13	ERBB3
5. Lethal Congenital Contracture Syndrome Type (LCCS-3)	5q	P1P5K1C
6. Lethal Lower Motor Neuron Deficiency with degeneration	—	—
7. Families with apparent increase in monozygotic twinning	—	—
8. Normal <i>in utero</i> growth, macrocephaly and PSP (Lammer type)	—	—
9. Absence of pyramidal cells, immature development, adducted thumbs, kyphoscoliosis and severe pulmonary hypoplasia (Biscegli type)	— — —	— — —
10. dysgenesis and degeneration, seizures, trisumus, endocrine hyperplasia, and abdominal wall herniation (Erdl type)	— —	— —
11. Skeletal muscle maturation defect	—	—
12. Pyramidal tract degeneration	—	—
13. <i>In utero</i> seizures, scoliosis, together with cerebral and cerebellar hypoplasia in males (Persutte type)	— —	— —
14. Microphthalmia, microtia, and normal birth size (Thomas type)	—	—
15. Olivo-ponto-cerebellar hypoplasia	—	—
16. Failure to myelinate peripheral nerves	—	—
17. Holoprosencephaly with hypokinesia and congenital contractures in an X-linked recessive pattern of inheritance	—	—
18. Hydranencephaly, calcification of basal ganglion and proliferative vasculopathy (Fowler type)	—	—
19. Calcification of leptomeninges, the surface of cerebral convolutions, neurons, muscles, and vessels (Illum type)	—	—
20. Familial intrauterine anoxia and/or ischemia	—	—

- **Lack of normal mechanical forces *in utero* may lead to deformations at birth**
- **“Use” is essential for normal development**

WHAT IS NECESSARY TO MOVE?

- **Central nervous system (CNS) intact and upper motor neurons working**
- **Spinal cord (in spinal canal)**
- **Anterior horn cell (motor neuron)**
- **Axon from AHC with myelin coat**
- **End plate between nerve and muscle**
- **Muscle**
- **Tendons**
- **Joints between bones moveable**

- **Over 400 specific conditions with arthrogryposis (multiple congenital joint contractures)**
- **Many have a genetic (hereditary) basis**
- **In fact, over 120 specific genes have been identified in specific conditions**
- **Need to know basic problem/pathway to identify appropriate therapy**

WHY MAKING A SPECIFIC DIAGNOSIS IS REALLY IMPORTANT

- 1. Natural history - what will happen over time?**
- 2. Recurrence risk – will this happen again in our family?**
- 3. What is the best therapy?**

See your friendly medical geneticist and ask lots of questions

HOW APPROACH CATEGORIZING ARTHROGRYPOSIS

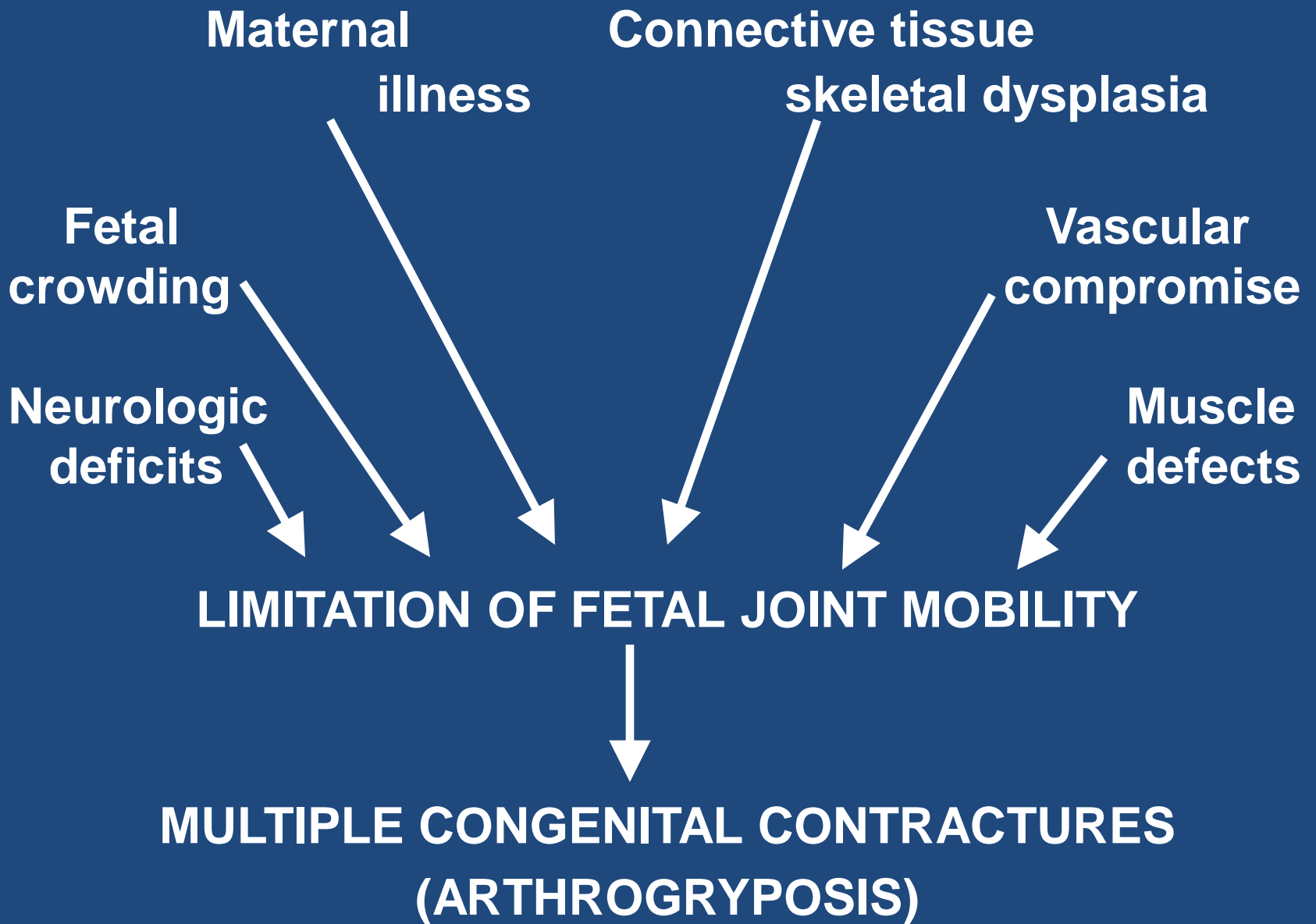
- **Body area involved**
- **What caused the decreased movement**
- **What's not working**

APPROACH TO MULTIPLE CONGENITAL CONTRACTURES - CLINICAL

- **Mainly limbs**
- **Limbs and other body areas**
- **Limbs and CNS/lethal**

OCCURRENCE OF ARTHROGRYPOSIS

- ~ 1/3000 – 5000....live births
- 1/3.....Amyoplasia
- 1-3.....Heterogeneous group
of disorders
- 1/3.....CNS not functioning,
often – lethal



SPECIFIC RELATIVELY FREQUENT CATEGORIES OF ARTHROGRYPOSIS

- **Amyoplasia**
- **Lower limb only**
- **Boney anomalies**
- **Distal arthrogyposes**
- **Pterygium syndromes**
- **X-linked**
- **CNS dysfunction**

AMYOPLASIA

- A – no
 - myo – muscle
 - plasia – growth

(Using US or MRI it is possible to establish how much muscle tissue is present – so you know what there is to work with)

- **1980 – recognized Amyoplasia as a specific form of arthrogryposis (multiple congenital contractures)**
- **135 of 350 individuals with arthrogryposis in large survey**
- **It is what the orthopedist called “classical arthrogryposis”**

1980 – AMYOPLASIA CHARACTERIZED BY

- Typical involvement and usually of all 4 limbs
- Severe equinovarus deformity of feet, internally rotated shoulders, extended elbows, flexed wrists, contractures of fingers – typical positioning
- Absent muscle with fatty – fibrous replacement
- Deep dimples over joints
- Surprisingly good response to early physical therapy
- Normal intelligence
- No recurrence risk

(IT WAS/IS A CLINICAL DIAGNOSIS)

OVER THE LAST 30 YEARS

- Now over 540 cases
- Trunk and face mostly spared
- IUGR with decreased muscle mass – at or below 3rd centile for gestation as well short for family later in life
- Excess of one of MZ twins (9% in all subtypes)
- Vascular compromise/disruption
 - Abdominal wall, bowel atresia – 12%
 - “Smushed”/lost digits – 12%
 - Mid facial “stork mark” – most
- Affected limbs are slightly under grown

EXCESS OF MZ TWINS

- **9% of all individual among the Amyoplasia subtypes is a MZ twin as compared to 1/300 live births (1/150 individuals – 0.6%) in general population (12x increase)!**
- **2% Amyoplasia patients who had early ultrasound also report a “vanished” twin (e.g., a twin was recognized, then lost)**
- **70% of all MZ twins share a placenta making them susceptible to vascular compromise**

DEMOGRAPHICS

- **Incidence of Amyoplasia – 1/10,000 live births**
- **Sporadic**
- **Sex ratio overall equal**
 - **BUT excess of females with upper limb only and gastroschisis**
 - **Excess of males with lower limbs only, bowel atresia, and among severe and hyperextended**

AMYOPLASIA NATURAL HISTORY

- 1% died in the first year
(prematurity, post-surgery,
respiratory, etc.)
- 30% - 40% have feeding problems
early – most outgrow
- 5% have trismus and facial
asymmetry
- 4% early breathing problems –
usually resolve
- 3 – 4 month window of “catch up”

AMYOPLASIA NATURAL HISTORY – 2

- Osteoporosis = prone to fractures – often iatrogenic at or after birth
- Molding of bone/joint which occurs with *in utero* movement is missing – joint surfaces not rounded
- Contractures “try” to return to original position – need night splints
- 15% develop mild scoliosis over time
- 75% missed prenatally in spite of prenatal ultrasound(s)

AMYOPLASIA NATURAL HISTORY – 3

- **Babies are alert, interactive, and assertive**
- **All individuals with Amyoplasia have developmental delay because of limb involvement**
- **3% of individuals with Amyoplasia have true intellectual disability**
- **97% of individuals with Amyoplasia appear to be normal or high intelligence**
- **Most families say that affected individuals are smarter than average**

AMYOPLASIA NATURAL HISTORY – 4

- 10% had been adopted (often from other countries)
- 60% had good family history information and in those
 - 3% had a history of clubfoot or dislocated hips
 - 1% had a history of someone with vascular compromise or thrombophilia
- No confirmed recurrence either to parents or affected individual when they grow up
- 26 affected individuals have 40 children (none affected)

AMYOPLASIA NATURAL HISTORY – 5

- **Affected individuals have IUGR (average at 3rd centile) at birth for gestation, but normal 50% OFC, length is often hard to measure**
- **Short stature – are at the 3 – 5 centile for family height later in childhood**
- **Continues to be under weight for age (were IUGR) probably because they have less muscle and bone density**

AMYOPLASIA FUNCTIONAL OUTCOME

- 38 children (0 – 16 years) (20F, 18M)
- 84% symmetric 4 limb involvement
- All had OT, PT, multiple casts & splints
- 5.7 orthopedic procedures/child
- 85% ambulatory by 5 years
- Relatively independent in daily living
- 20% excellent response
- Growth at 5th – 10th centile

AMYOPLASIA OUTCOMES (Sweden, Seattle Clinic)

- **Community ambulator** **40%**
- **Home ambulator** **45%**
- **Dependent** **15%**

SO DOUBT THE DIAGNOSIS OF AMYOPLASIA IF:

- Normal birth weight – should be IUGR (among MZ twins affected twin is 8 oz – 2 pounds less than unaffected MZ twin)
- Markedly asymmetric
- No equinovarus deformity of the feet
- No “policeman tip” position of the arms
- No nevus flammeus “stork mark” of midface
- No dimples over affected joints
- No obvious decrease of muscle mass in affected limb
- No shortening of affected limbs
- Normal flexion creases if hands are involved

LOWER LIMBS ONLY ARTHROGRYPOSIS

- **Amyoplasia lower limbs only**
- **Angulation of long bone Syndrome**
- **Fuhrmann Syndrome**
- **Genitopatellar Syndrome**
- **Kuskokwim Syndrome**
- **Lower limb AD (Fleury type)**
- **Lower limb AR (Ray/Sarralde)**
- **Lower limb X-linked, caudal dysplasia (Zori)**
- **Meningomyelocele/spina bifida/spinal dysraphism**
- **Prenatal early amniocentesis or CVS**
- **NEED CAREFUL DIFFERENTIAL DIAGNOSIS**

BONY ANOMALIES SEEN WITH OR CONFUSED WITH ARTHROGRYPOSIS

- **Chondrodysplasias** - **dwarfing conditions**
- **Symphalangism** - **fusion of phalanges**
- **Coalition** - **fusion of carpals or tarsals**
- **Synostosis** - **fusion of sutures or between other bones**

“DISTAL” ARTHROGRYPOSIS

- **Characteristic hand anomaly**
- **Primarily “distal” involvement**
- **Usually both hands and feet**
- **No non-orthopedic anomalies**
- **Usually quite responsive to therapy**
- **Autosomal dominant inheritance**

CLASSIFICATION OF DISTAL AMCs

Hall		Bamshad	Gene
I	Distal	1A	TPM2
IIA	Gordon	3	
IIB	Ophthalmoplegia	5	
IIC	Clefting	(10)	
IID	Scoliosis	4	
IIE	Trismus + Unusual Hand	7B	
	Freeman-Sheldon Syndrome	2	MYH3
	Sheldon-Hall	2B	TNNT3, TNN12
	Sheldon-Hall Look Alike	2C	MYH3
	Deafness	6	11q25
	Trismus Pseudocamptodactyly	7A	MYH8
	AD, Multiple Pterygium	8	
	Contractural Arachnodactyly	9	FBN2
	Absent Teeth	(11)	
	Chitayat, AR	(12)	
	X-linked	(13)	
	Stavit, S. African, Naguib	(14)	
	Moore-Weaver Distal	(15)	
	MR, DD, Wipe Out (Bad Brain)	(16)	

DISTAL ARTHROGRYPOSES

- **Often related to “fast twitch” muscle defect**
- **8 different genes identified so far**
- **Autosomal dominant with variable expression**
- **Sometimes with facial involvement**

PTERYGIUM = A “wing-like” structure

**A web across body
joint**

A triangular membrane

PTERYGIUM SYNDROMES

TYPE	INHERITANCE	DISTINGUISHING FEATURES
Popliteal pterygium	AD	Clefts, lip pits normal nail
Antecubital pterygium	AD	Only elbows involved
Mutiple pterygium (Escobar type)	AR	Cervical vertebral anomalies, hands involved, chin- sternum pterygium, facies
Lethal mutiple pterygium	AR	Extensive contractures, hypertelorism, chin-sternum pterygium, small chest
Lethal popliteal pterygium (Bartoscas Papas)	AR	Facial cleft, syndactyly (hands and feet), genital anomaly
Pterygium and ectodermal dysplasia	AR	Fine sparse hair, nail anomalies (hands and feet)
Pterygium and malignant hyperthermia	AR	Torticollis, scoliosis, MH

MYASTHENIA SYNDROMES

- **Myasthenia gravis**
- **Maternal myasthenia**
- **Congenital myasthenia**
- **Maternal antibodies against paternally inherited genes**
- **Genes for neuroreceptors**

MYASTHENIA GRAVIS

- **Autoimmune disorder – antibodies against own neuroreceptors**
- **May cross the placenta and effect embryonic/fetus neurotransmission**

MULTIPLE PTERYGIUM – ESCOBAR TYPE

- **1990s** Maternal antibodies against embryonic neurotransmitters lead to increasing contractures with each pregnancy (like Rh disease)
- **2000** Genes for embryonic and adult receptors identified

MULTIPLE PTERYGIUM – ESCOBAR TYPE

- **2006** Both lethal Multiple pterygium syndrome and Escobar types found to be due to mutations in the subunits of the embryonic ACh receptor (adult receptor “just fine”) Mice with mutation responded to Tensilon
- **2010** Patients with Escobar type respond to Mestinon

X-LINKED DISORDERS

- **Primarily affect males**
- **1/3 new mutation, 1/3 mother carrier, 1/3 arise in maternal grandfather**
- **Present research project to find X-linked disorders**

X-LINKED DISORDERS

p

- 22 Aicardi syndrome – AIC
- 21.3 Proud syndrome (agenesis corpus callosum, seizures, MR) – ARX
- 11.4 FG (4) – CNS/CASK syndrome (microcephaly, cerebellar hypoplasia) – CASK
- 11.23 Conradi-Hunerman – EBP
- 11.23 TARP (talipes equinovarus, Robin sequence, Cardiac defect) – RBM10
- 11.22 Aarskog syndrome – FGD1

q

- 11.3 Type I severe lethal UBE
 - 12-13 Ectodermal dysplasia/Ladda
 - 13.1 FG (1) syndrome (tall) – MED 12
 - 13.2 Wieacker syndrome (muscle atrophy, MR, oculomotor ataxia)
 - 13-22 Congenital fiber disproportion myopathy
 - 21-22 Spastic paraplegia (Goldblatt)
 - 21.3 Proud syndrome – ARX
 - 21.31 Miles Carpenter MR, camptodactyly, arachnodactyly, (DA 14)
 - 22.2 Simpson Golabi Behmel II – GFD 1
 - 22.3 FG syndrome
 - 22.2-28 Keipert syndrome – deafness, large mouth, hypertelorism, broad phalanges
 - 23 Lissencephaly – DCX
 - 23-27 Zori (lower limbs only, scoliosis)
Clasp thumb syndrome
 - 26 Pettigrew (MR, hypotonia, scoliosis, Dandy Walker, Basal ganglion calcification) – HPRT
 - 26.2 Simpson Golabi Behmel Type 1 – GPC3
 - 26.3 Hydrocephaly +/- VACTERL – Z1C3
 - 27.2 Perisylvian polymicrogyri syndrome, MR, seizures
 - 28 FG syndrome (2) – FLNA
Oto Palato Digital II syndrome – FLNA
MASA (adducted thumbs, MR, shuffling gate, aqueductal stenosis) – L1CAM
Myotubular myopathy – MTM1
Centronuclear myopathy – MTM1
- NAA10 syndrome (progeria, hypotonia, DD, cardiac arrhythmias) – NAA10

CNS DYSFUNCTION

- **Structural abnormalities (MRI, CAT scan, US)**
- **Structures look okay, but CNS not function normally**
- **Seizures, unresponsive, developmental delay, lack social response**

CHROMSOMAL DISORDERS

- Extra chromosome
- Missing or extra “chunks”
- Submicroscopic “chunks”
- CGH comparative genomic hybridization

WITH CGH ARRAY ANALYSIS CAN DIAGNOSE:

- **10% Multiple congenital anomalies**
- **10% Intellectual disability**
- **10% Behavioural problems**

VERY POWERFUL TECHNIQUE

POTENTIAL THERAPIES

1. **Standard – stretching**
 - a) **First 4 months particularly important**
 - b) **Prevent “return to original position”**
 - c) **Continuing stretching and splinting**
2. **Avoid “damage” and increased scarring**
3. **Specific cytokines**
4. **Stem cell/regenerative therapy**

SPINAL MUSCULAR ATROPHY

(Werdnig Hoffman syndrome)

- **Lacks anterior horn cell maintenance**
- **Once cells die, the attached muscle dies**
- **Tissues are interdependent – talk to each other**

STEM CELL RESEARCH – THE FUTURE

- **Lots of new work, each tissue goes through several different stages during development (embryo→fetus→newborn) and need several specific growth factors to differentiate**
- **AND a tissue must have cytokines/growth factors to stay differentiated**

Arthrogryposis is not a diagnosis
— **it is a sign, but the study of**
arthrogryposis does give
insight into the
importance of
embryonic/fetal
movement
— **and hold promise for therapy**

PARENT SUPPORT GROUPS

1. Information/Education
2. Support research
3. Guidelines for care
4. Social and sharing gatherings
5. Advocacy
6. Registry – biobank (privacy)
7. Ask questions, interact with professionals, how to keep record of your child

US NATIONAL INSTITUTES OF HEALTH

- **Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)**
- **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
- **National Institute of Neurological Disorders and Stroke**
- **Office of Rare Diseases**
- **MUSCULAR DYSTROPHY ASSOCIATION**
- **MARCH OF DIMES**
- **SHRINERS ORGANIZATIONS**

HOW TO GET MOVING

- Write to your congressional representatives about NIH
- Identify famous person/celebrity
- Spokesperson(s)
- Organize your messages
- Identify your advocacy activities
 - Awareness and education
 - More research
 - Funds for therapy
 - Other?

PERSONALIZED/HANDWRITTEN = 60 e-mails

Dear Senator _____,

My child has a form of arthrogryposis (multiple congenital contractures). One in 4,000 babies is born with arthrogryposis.

I do not understand why the NIH does not have and never has had an active program of research on this relatively common and highly disabling condition.

Most affected individuals can do well, be self-supporting and live independently if they receive an accurate diagnosis and appropriate therapy in a timely fashion.

Please do what you can to help my child.

Sincerely yours,

Attach photo