Rapid Identification and Validation of Human Craniofacial Development Genes

FaceBase

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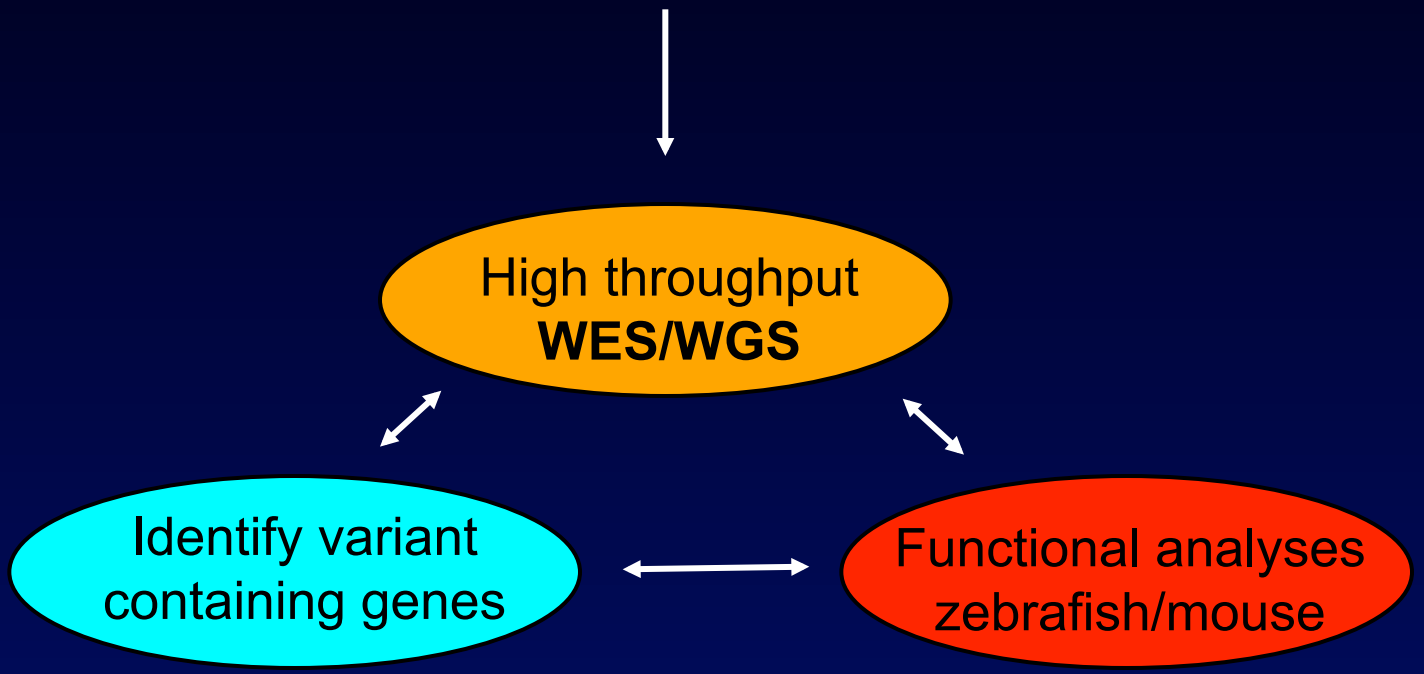
Genomic sequencing is transformative!

- The cost of WES/WGS continues to fall
- Only a small fraction of genes have assigned human phenotypes
- Monogenic disease genes may contribute to common disease phenotypes
- Integration of *clinical and research* efforts across FaceBase
- Raison d'etre: Application of WES/WGS to carefully selected cases of monogenic disease can reveal new underlying genetic etiologies and therapeutic pathways

Discovering Human Birth Defect Genes

Identify genes in patients with craniofacial developmental defects *and* bioinformatically tractable monogenic inheritance



Rapid Craniofacial Gene Discovery: Specific Aims

1. Ascertain and recruit patients with a wide range of craniofacial dysmorphoses of likely monogenic etiology.

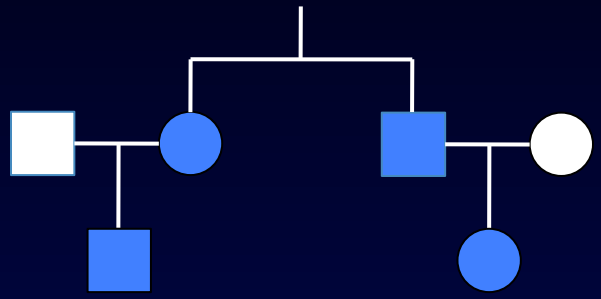
2. Rapid identification of genes regulating human craniofacial development (WES, WGS and seq. analysis).

3. Rapid expression and functional analysis of human candidate genes (zebrafish > mouse).

Bioinformatically solvable genetic paradigms

Dominant

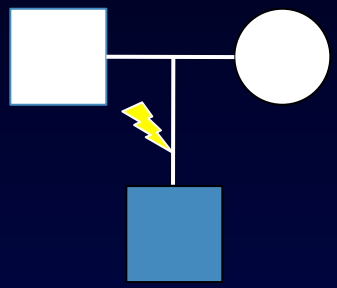
Transmitted mutations



~50 variants transmitted, solve statistically

Dominant

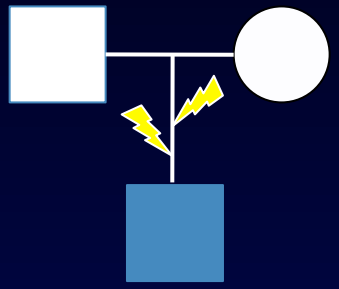
De novo mutations



0-3 mutations

Recessive

Rare cpd het. and homo. mutations



3-5 cpd het or 1-2 homo mutations

Assumptions

- Monogenic inheritance
- Complete penetrance
- Limit to protein coding mutations, splice site mutations, structural variants

FaceBase Craniofacial Gene Discovery Program

- Starting from the CLARITY Challenge, 2012
- Clinical, Bioinformatics and Experimental faculty work interactively on cases

- 37 cases ascertained ➔ propose to accept ~100 (~250 WES/WGS)
- Expand monogenic case referrals for WES/WGS
- Develop new statistical, computational methods, crowd sourcing, experimental validation platform

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Genome Analysis Case Selection Process

1. Does the case present an opportunity for an important clinical or biological discovery?

2. Is the case potentially statistically solvable?

3. What would be important biological considerations?

4. Do we have a follow up strategy?

Assign: Clinical, Genome Analysis, Bioinformatics and Biologist Team Members to each case

Patients with craniofacial defects: genes identified to date

- *SPECC1L* Oblique facial clefting (mouse, fly)
  AJHG 89, 44-55, 2011; *Plast Reconstr Surg.* 134, 748, 2014.
- *CAPZB* Pierre Robin Syndrome (mouse, fish)
  HMG 25, 1255, 2016.
- *RSPRY1* Progressive skeletal dysplasia – facial dysmorphism (mouse)
  AJHG 97, 608, 2015.
- *PIEZO2* Arthrogryposis, characteristic facies, cleft palate (fish)
  PNAS 110, 4667-72, 2013
- *ZEB2* Mowat-Wilson Syndrome - Mandibular prognathism (mouse)
- *ATG4C* Cleft palate (fish)
- *MAP3K7 (TAK1)* Facial dysmorphosis (variable phenotype)
- *FBN1* Atypical Marfanoid syndrome (micrognathia, brachycephaly, +)

FaceBase Project Milestones

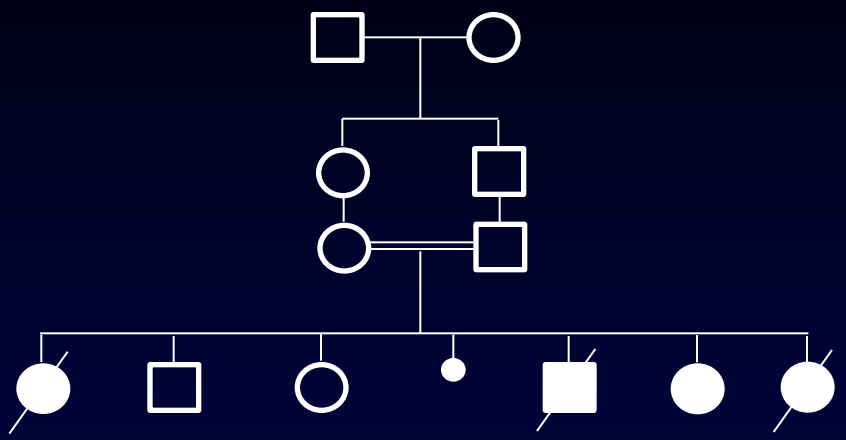
Goal:	To solve ~25 cases
Assume:	~25% success rate
Therefore:	Accept and sequence about 100 cases
Trio assumption:	Consent and sequence ~250 individuals
Models / fxnal expts / causality:	As needed

Cases evaluated:	37
Cases accepted:	22
Cases rejected:	4
Cases deferred:	11

Cases consented:	10 prior + 8 (6 as trios)
DNAs drawn:	10 prior + 5 trios (2 pt. only)
Genomic DNA seq:	10 prior +2 completed
Models / fxn / 2nd hits:	9

Face Base Case # 009: *ISLR2*

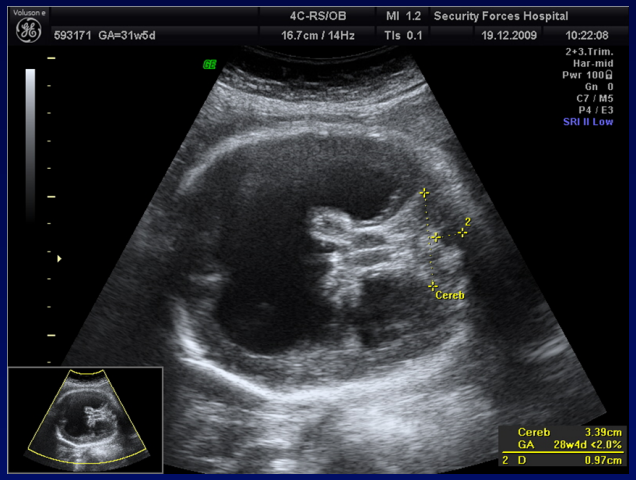
Case: 0 y/o, Female

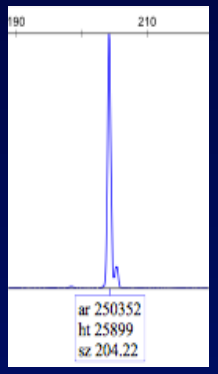


Notable Symptoms:

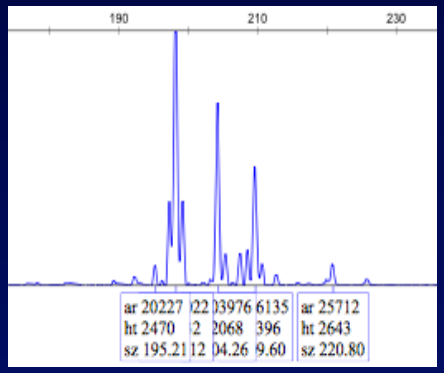
- Large intestine (Hirschsprung's Disease)
- Hydrocephalus

- The patient has a frame shift deletion in ***ISLR2***.

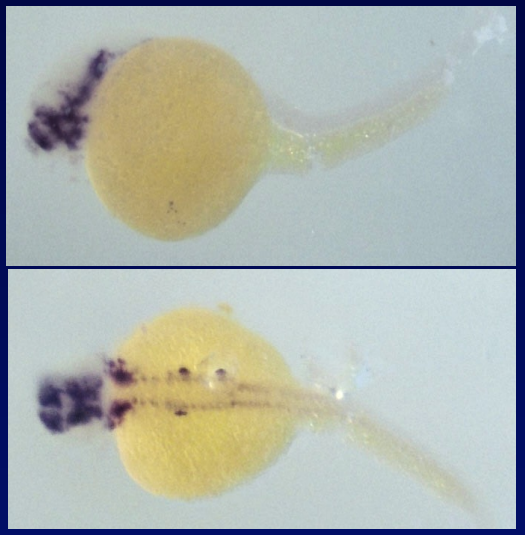




WT



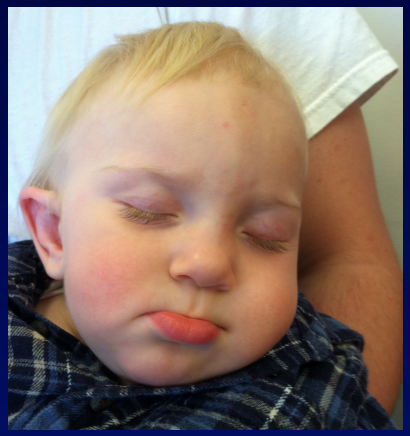
Mutant

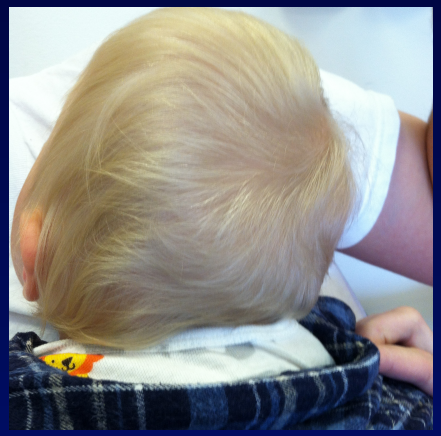


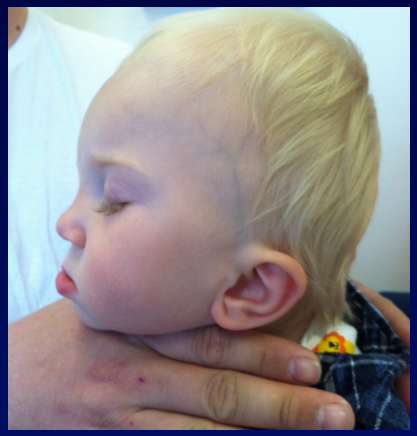
FB Case # 027: Asymmetric skull

Joan Stoler, Catherine Nowak and colleagues

- Asymmetric skull configuration w/ fusion of R sphenofrontal suture, accessory R parietal suture; absent R squamosal suture.
- Congenital plagiocephaly, brachcephaly, torticollis, mandibular prognathism
- C-spine vertebral fusions
- Metopic and occipital prominence, mild prognathia
- Bony ridging of frontal bones in midline – nl. variant vs. 2° to prematurely fused metopic suture.
- Other: anklyglossia, hearing loss



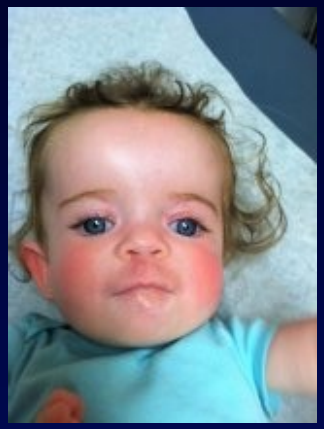


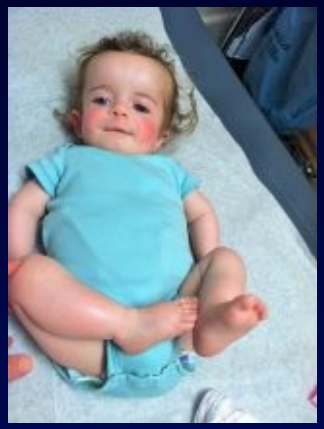


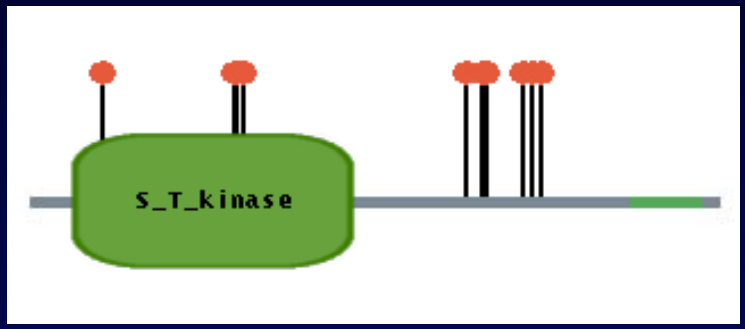
FB Case # 031: Macrocephaly

Catherine Nowak. M.D. and colleagues

- 3 yo female, dysmorphosis, relative macrocephaly, frontal bossing
- Small stature, hypotonia, hypermobility, cardiac valve prolapse, global developmental delay.
- Microarray with 7p21.2 deletion (mat). Russel-Silver panel neg.
- Previous Studies: brain MRI with mega cisterna magna.



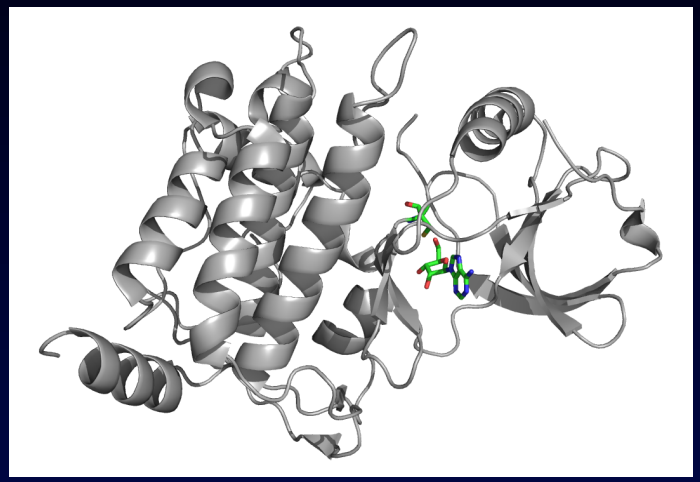




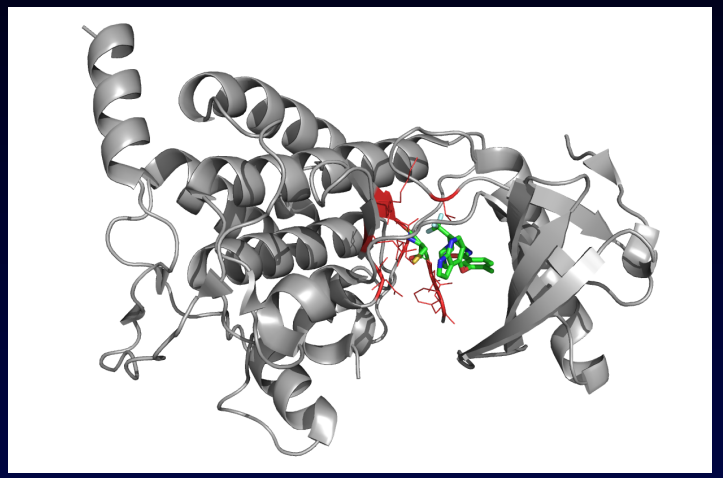
- WES (trio) ➔ *De novo* mutation in MAPK3K7, C174Y
- Located in Serine-Threonine Kinase domain
- Highly conserved, with C174Y= 0 counts in ExAC
- Aka: TGF-beta Activated Kinase 1, interacts with TAB1
- Matchmaker: 2 other ? similar cases

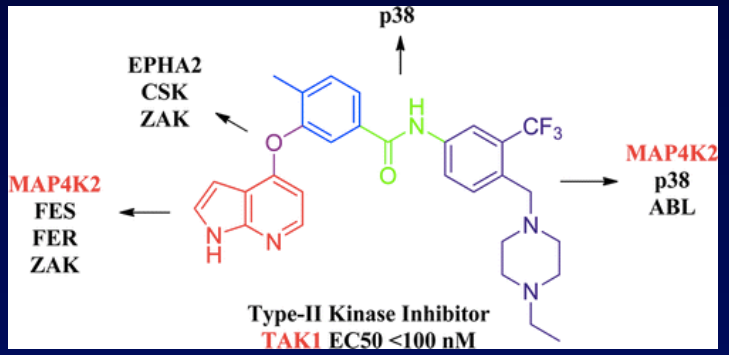
FB Case # 031 cont'd: MAP3K7 C174 resides in a ligand binding pocket

pdb ID: 2eva; positions: 31-412 (out of 1-606); Domain: 36–291 Protein kinase



Binding site for adenosine
Also, for TAB1

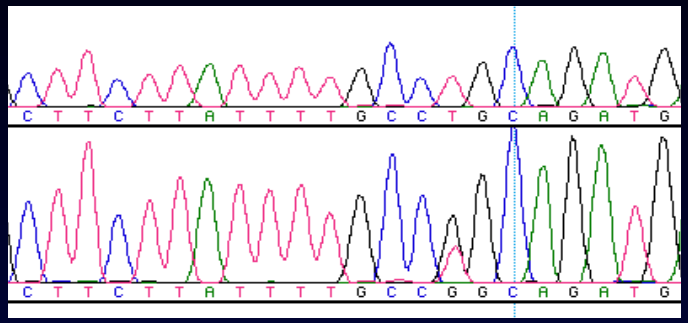




Binding site for Type II Inhibitors

FB Case # 037: Potential *FBN1* exon skipping mutation

intron 63 — exon 64



G

[C T] 11-13 N [C T] A G -

Furin cleavage site

FBN1 exon 64

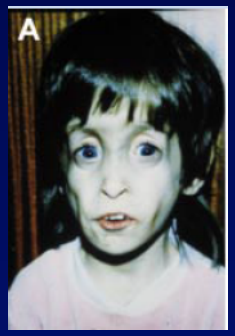
-5 -4 -3 -2 -1

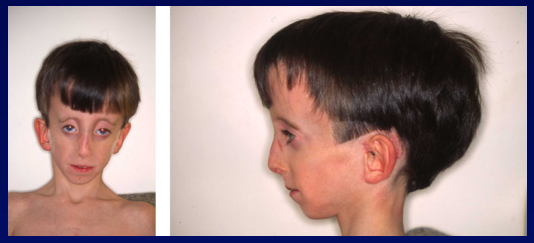
RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Marfan Syndrome With Neonatal Progeroid Syndrome-Like Lipodystrophy Associated With a Novel Frameshift Mutation at the 3′ Terminus of the *FBN1*-Gene

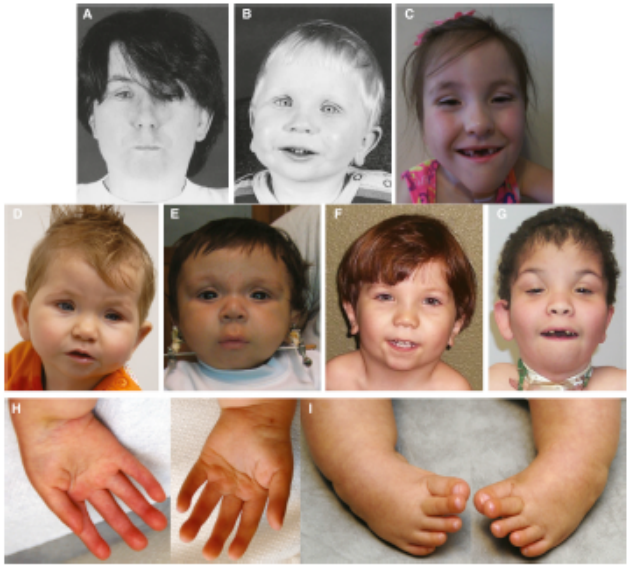
Luitgard M. Graul-Neumann,[1,2]* Tina Kienitz,[3] Peter N. Robinson,[2] Sevjidmaa Baasanjav,[2,4] Benjamin Karow,[2] Gabriele Gillessen-Kaesbach,[5] Raimund Fahsold,[6] Hartmut Schmidt,[3,7] Katrin Hoffmann,[2,8] and Eberhard Passarge[9]



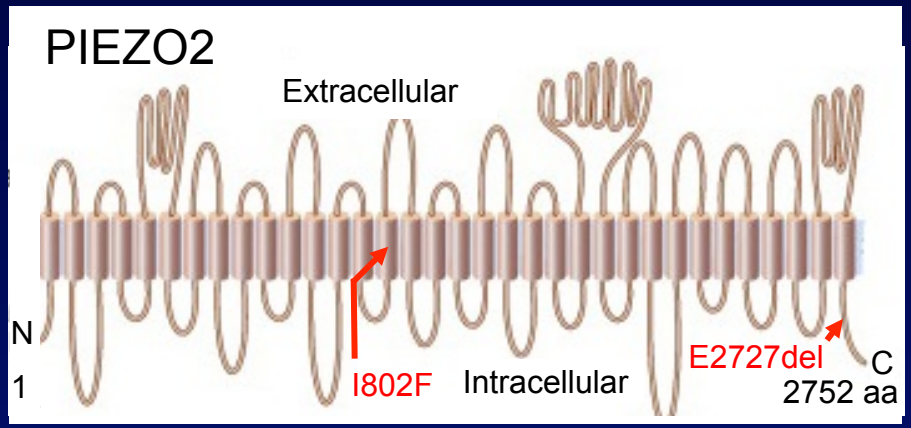


FB Case # 003: Distal Arthrogryposis Type 5

- Mechanically activated (MA) cation channel
- *PIEZO2* mutations in DA5 patients



Am. J. Hum. Genet. 94, 734-44, 2014



Acknowledgements – FaceBase Team

Clinical and Experimental Group

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Plus many other clinical and computational colleagues!

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