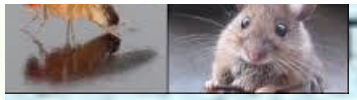
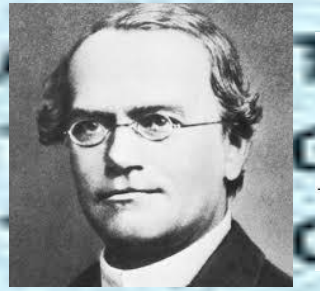
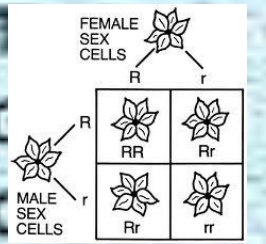
Xia- Gibbs Syndrome: June 2022 Update

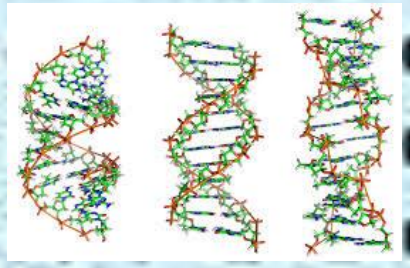
Richard Gibbs AC Ph.D.,

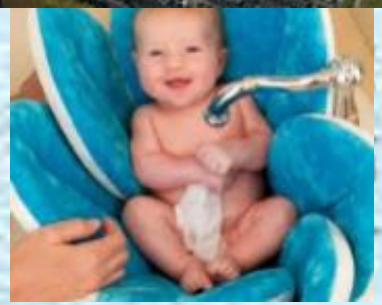
Baylor College of Medicine - Human Genome Sequencing Center









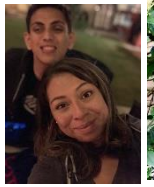


NO CONFLICTS OF INTEREST TO DECLARE

- Thank you: XGS families,
- XGS Society and Advisors,
- Lab members, past and present
  Varuna Chander, Jianhong Hu
  Michael Khayat, Shoudong Li;
  Moez Dawood, Adam Hansen,
  Aniko Sabo, Mullai Murugan
  He Li, George Weissenberger,
  Helen Shen
- Colleagues
- Funding
  - XGS-Society
  - Private Donation


Monica Pendleton


Arika Estep


Jeanine Garcia


Molly Nelson


Greg Wilkinson


Emily Wilkinson


Catherine Brownstein


Wendy Chung


Megan Odgers


Jianhong Hu


Varuna Chander


Michael Khayat


He Li


Moez Dawood


Mullai Murugan


Adam Hansen


Shoudong Li


Jennifer Posey


James Lupski


David Murdock


Michael Wangler

Talk Outline

1: The approach to XGS Research,

2: The XGS Registry,

3: The Clinical Spectrum,

4: The Molecular Spectrum

5: Cellular Studies

6: Case reports, ‘outliers’ and mild cases,

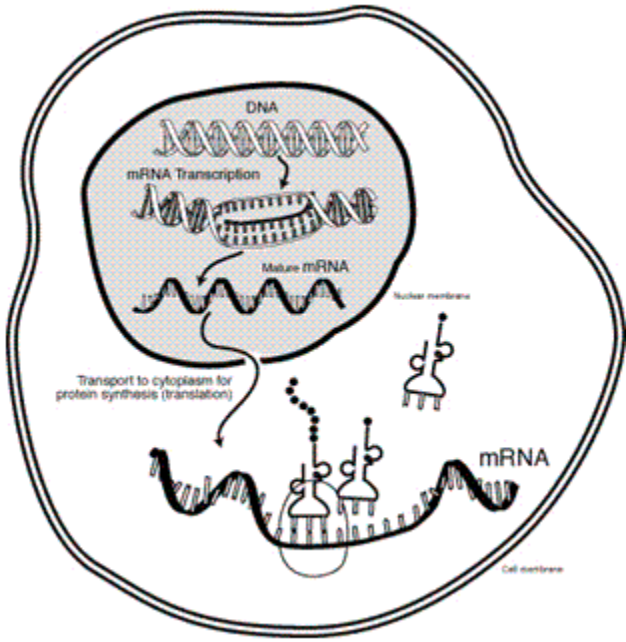
7: Studies in other laboratories,

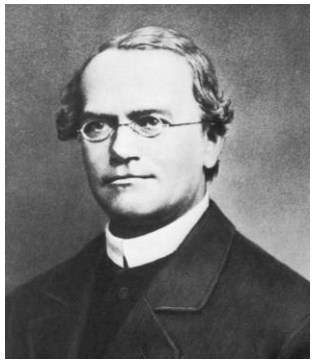
8: XGS Awareness in the Research community,

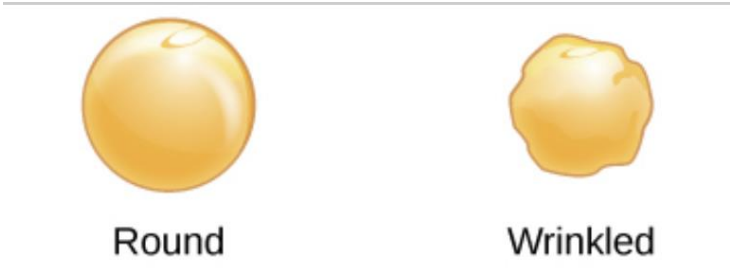
9: Pathway ahead.

Approach to XGS Research,

- Long term goal is a cure for XGS (or full amelioration),
- Steps are describe, then understand - then cure,
- Today is about the first two elements,
- The power of genetics,



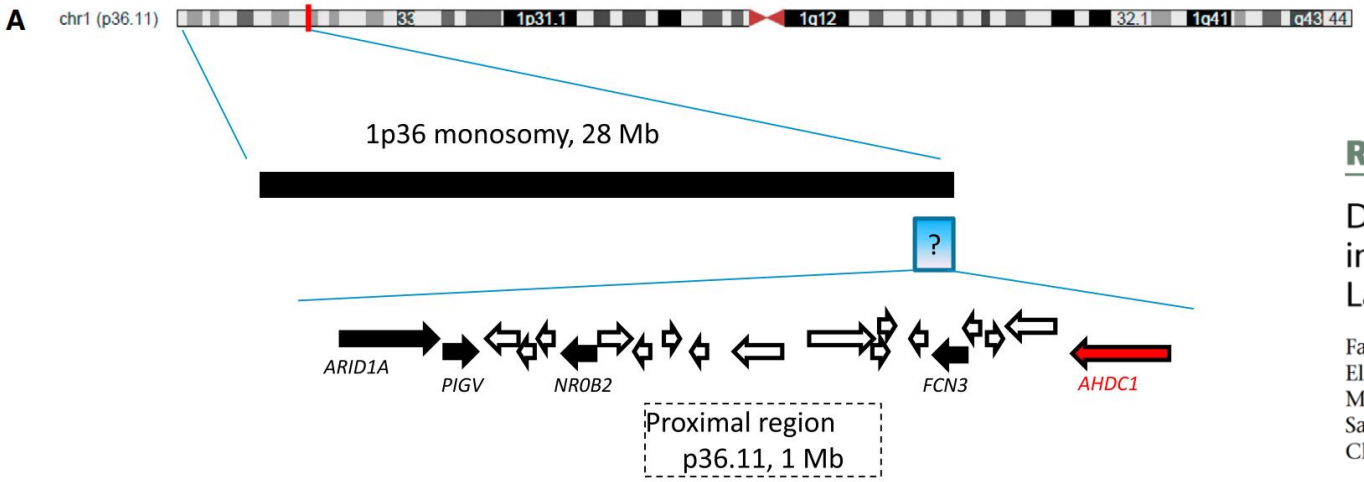


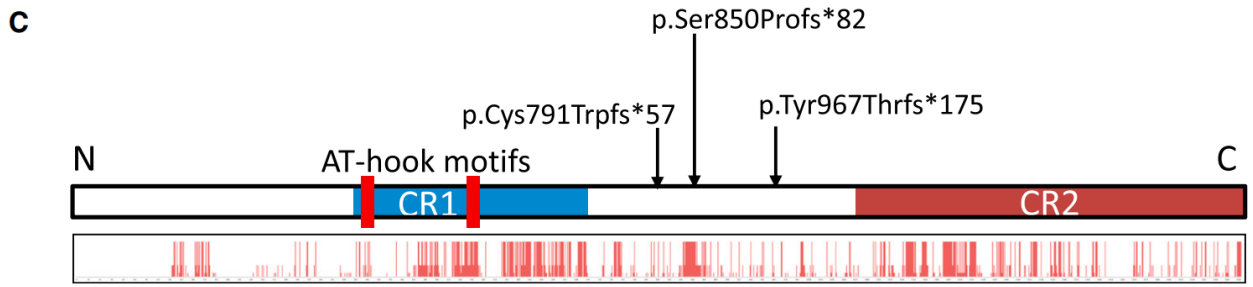


FUNCTION

Gregor Mendel = 1860's – still relevant today

XGS: 4 individuals with ‘nonsense’ mutations in AHDC1, (2013 - published 2014, confirmed 2015)





What does AHDC1 do?

- Cellular distribution?
- Timing and place of expression?
- What kind of mutations disrupt the gene?

REPORT

De Novo Truncating Mutations in *AHDC1* in Individuals with Syndromic Expressive Language Delay, Hypotonia, and Sleep Apnea

Fan Xia,[1] Matthew N. Bainbridge,[2] Tiong Yang Tan,[3,4] Michael F. Wangler,[1,5] Angela E. Scheuerle,[6] Elaine H. Zackai,[7] Margaret H. Harr,[7] V. Reid Sutton,[1,5] Roopa L. Nalam,[2,8] Wenmiao Zhu,[1] Margot Nash,[3] Monique M. Ryan,[3] Joy Yaplito-Lee,[3] Jill V. Hunter,[5] Matthew A. Deardorff,[7] Samantha J. Penney,[1] Arthur L. Beaudet,[1] Sharon E. Plon,[1,5] Eric A. Boerwinkle,[2,9] James R. Lupski,[1,5] Christine M. Eng,[1] Donna M. Muzny,[2] Yaping Yang,[1] and Richard A. Gibbs[1,2,*]

COLD SPRING HARBOR Molecular Case Studies

RESEARCH REPORT

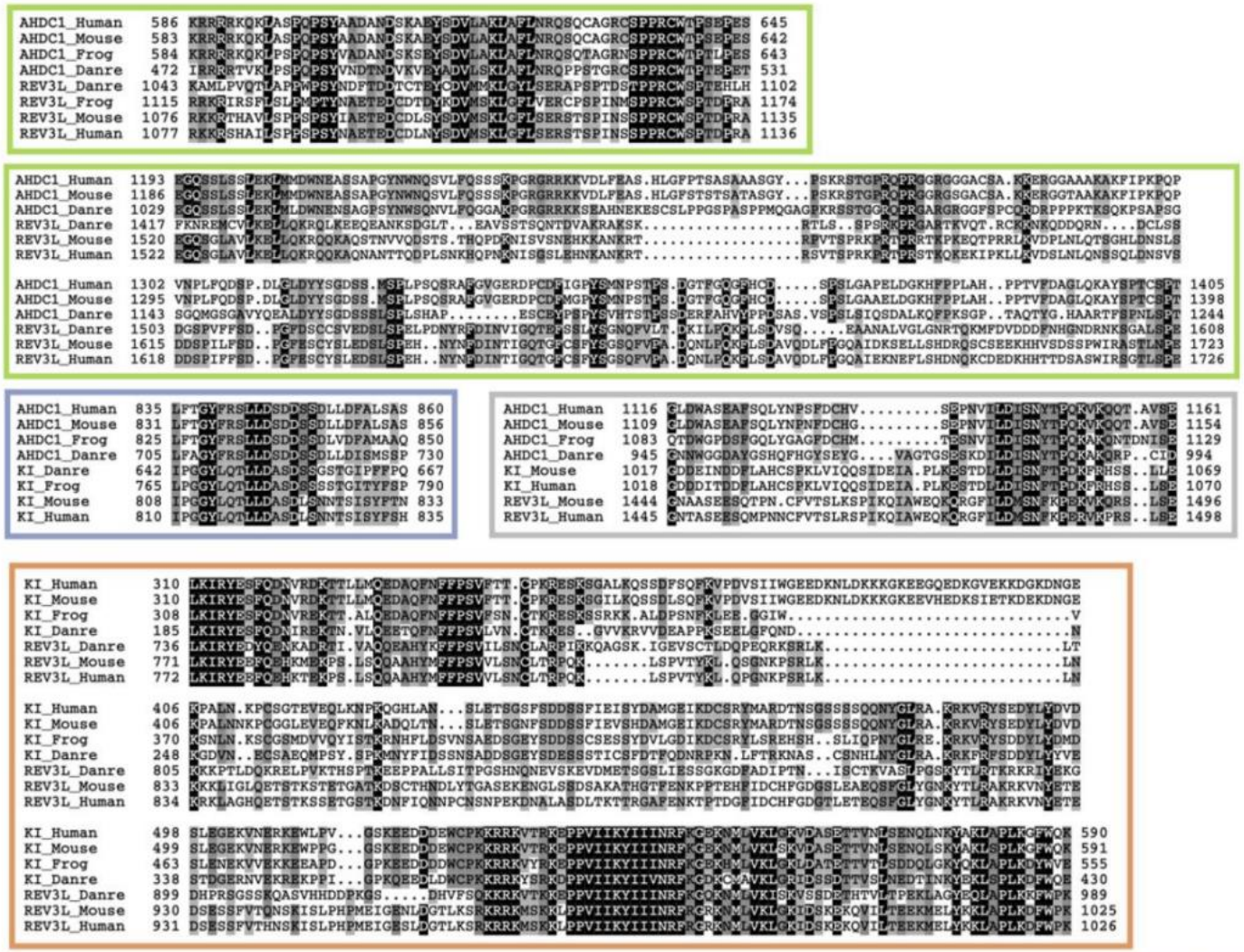
De novo truncating variants in the *AHDC1* gene encoding the AT-hook DNA-binding motif-containing protein 1 are associated with intellectual disability and developmental delay

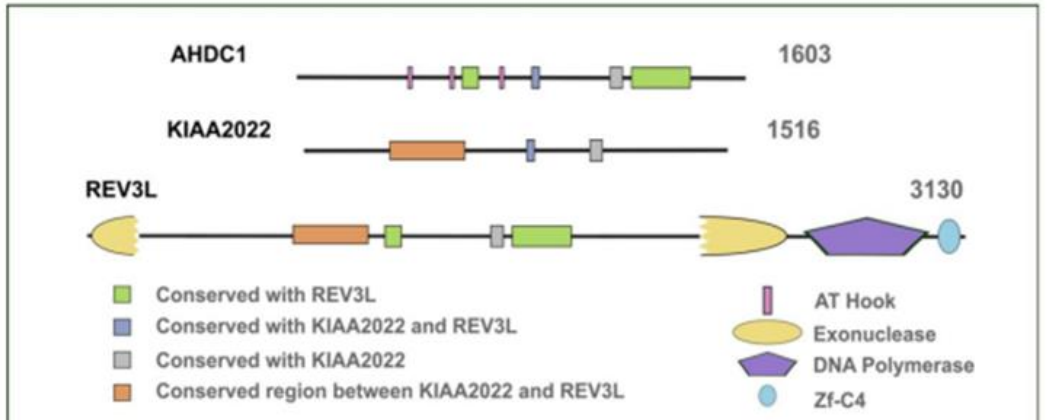
Hui Yang,[1] Ganka Douglas,[1] Kristin G. Monaghan,[1] Kyle Retterer,[1] Megan T. Cho,[1] Luis F. Escobar,[2] Megan E. Tucker,[2] Joan Stoler,[3] Lance H. Rodan,[3] Diane Stein,[4] Warren Marks,[5] Gregory M. Enns,[6] Julia Platt,[6] Rachel Cox,[6] Patricia G. Wheeler,[7] Carrie Crain,[7] Amy Calhoun,[8] Rebecca Tryon,[8] Gabriele Richard,[1] Patrik Vitazka,[1] and Wendy K. Chung[9]

What we know about the protein from computers.

1: Strong conservation in vertebrates

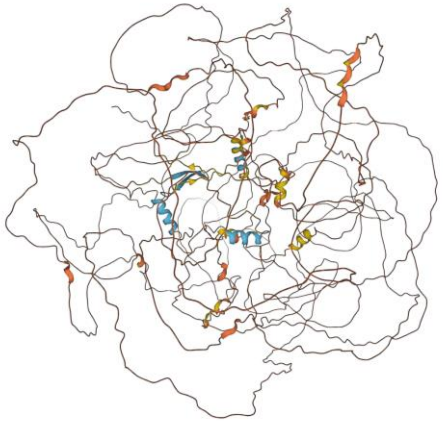
2: Less across evolutionary tree,





2: Some key motifs:

- ‘AT-hooks’ short motifs that bind AT rich DNA/RNA;
- REV3L/exonuclease/DNA polymerase homologies;
- KIAA2022 is a neurological disease gene;
- Zf-C4 region is usually a nuclear receptor binding function;
- In aggregate, these imply a role in DNA replication and/or chromatin state maintenance;



3: 3D structure (inferred) not new insights

The XGS Registry,

Jianhong Hu

Mullai Murugan

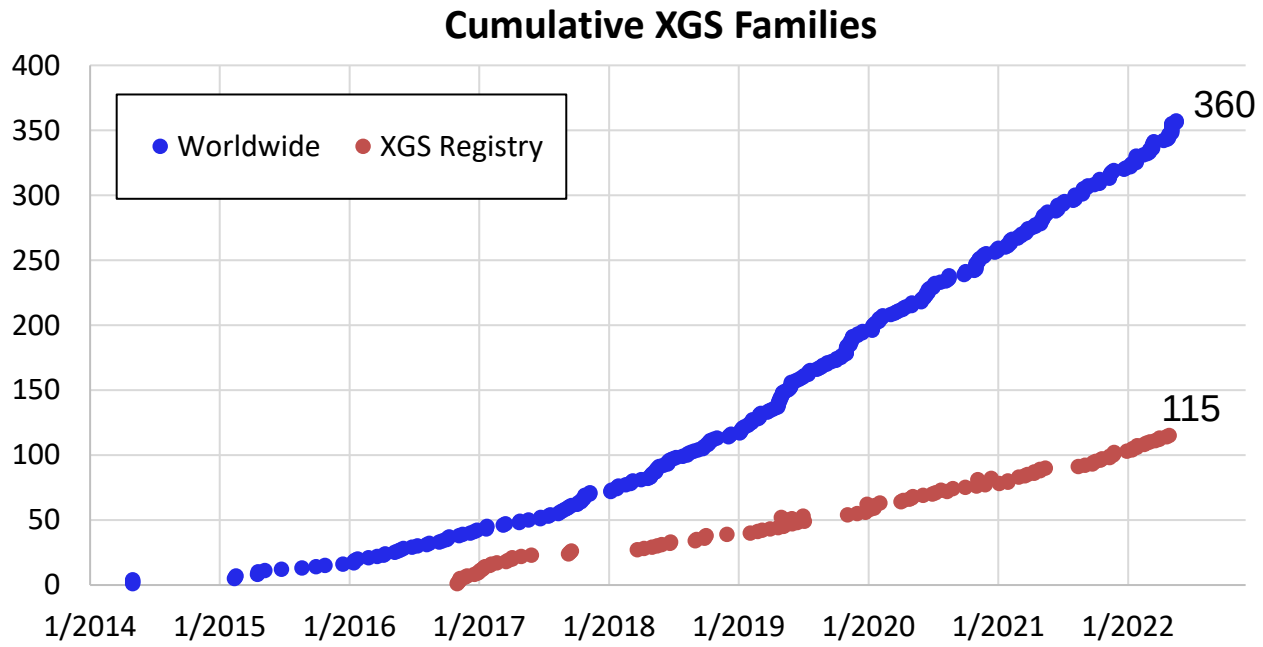
First step to understanding XGS basics and to accessing individuals and families,

Began in 2014 using RedCap for secure data management,

Developed a full consent model,

Somewhat – ‘clunky’ – functional improvements in 2021,

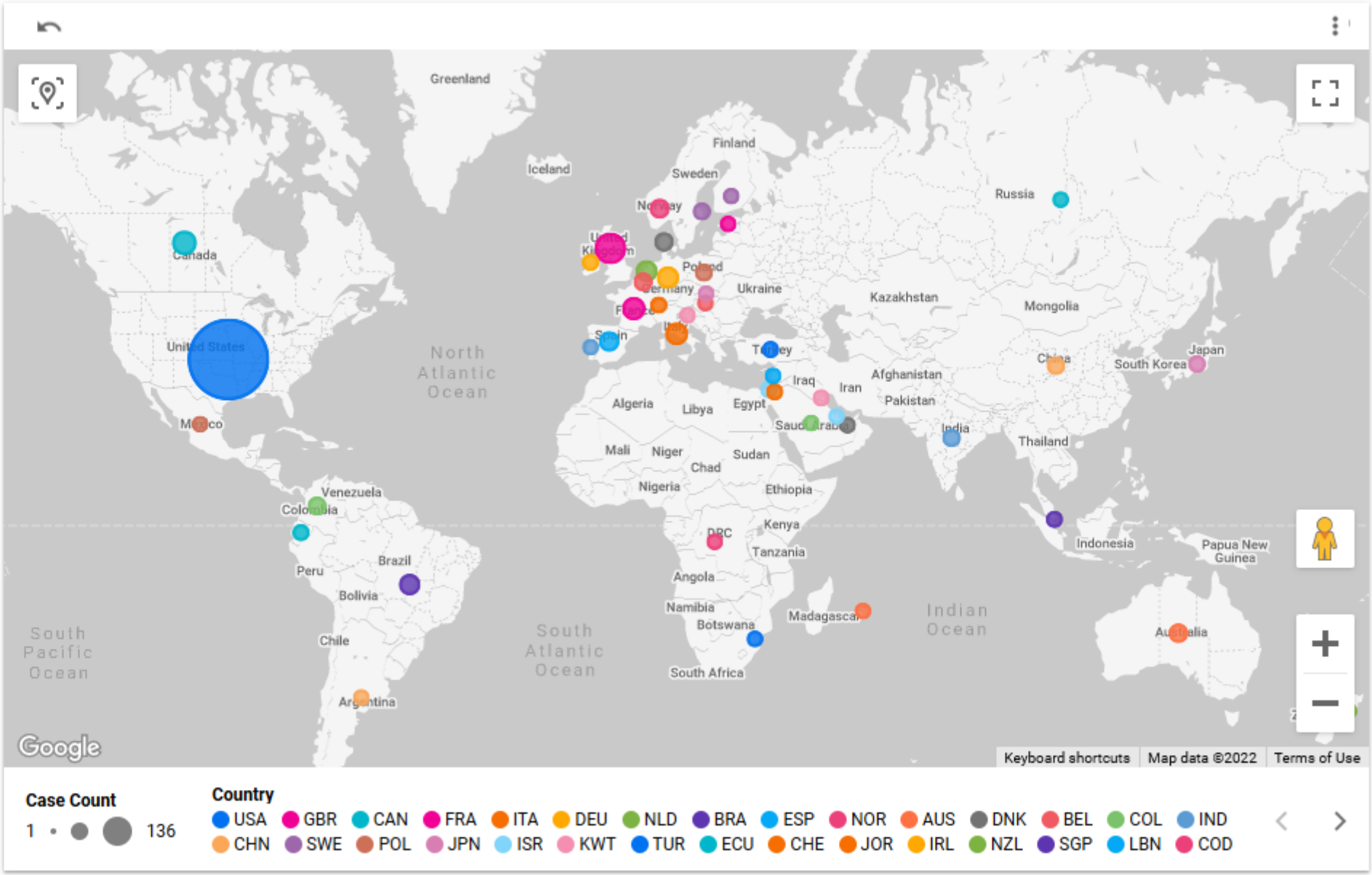
Long term goal – to be a centralized resource for XGS information and to facilitate XGS research,



XGS Worldwide Location

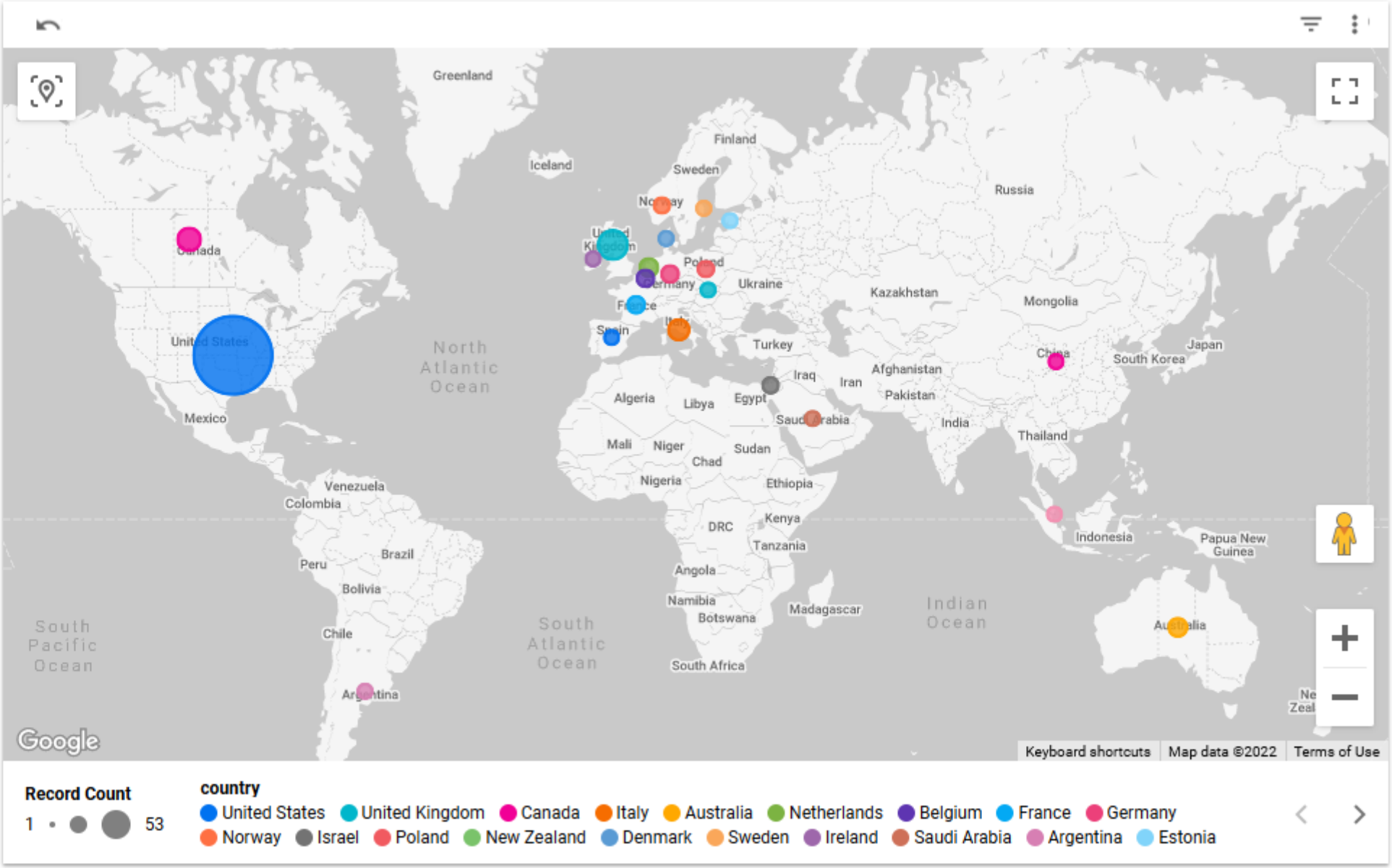
	Country	Case Count...
1.	USA	136
2.	GBR	32
3.	CAN	18
4.	FRA	15
5.	ITA	14
6.	DEU	13
7.	NLD	12
8.	BRA	11
9.	ESP	9
10.	NOR	8
11.	AUS	7
12.	DNK	7
13.	BEL	6
14.	COL	6
15.	IND	5
16.	CHN	5
17.	SWE	4
18.	POL	4
19.	JPN	3
20.	ISR	3
21.	KWT	2

1 - 44 / 44



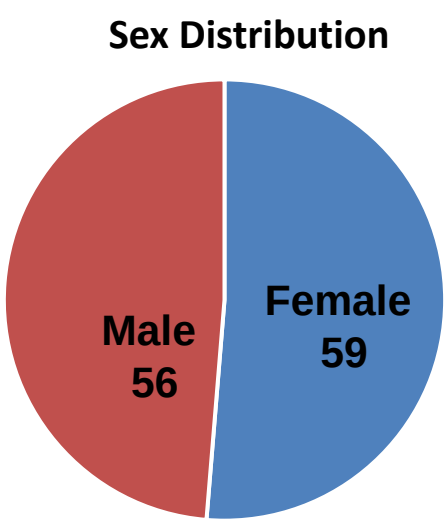
XGS Registry Location

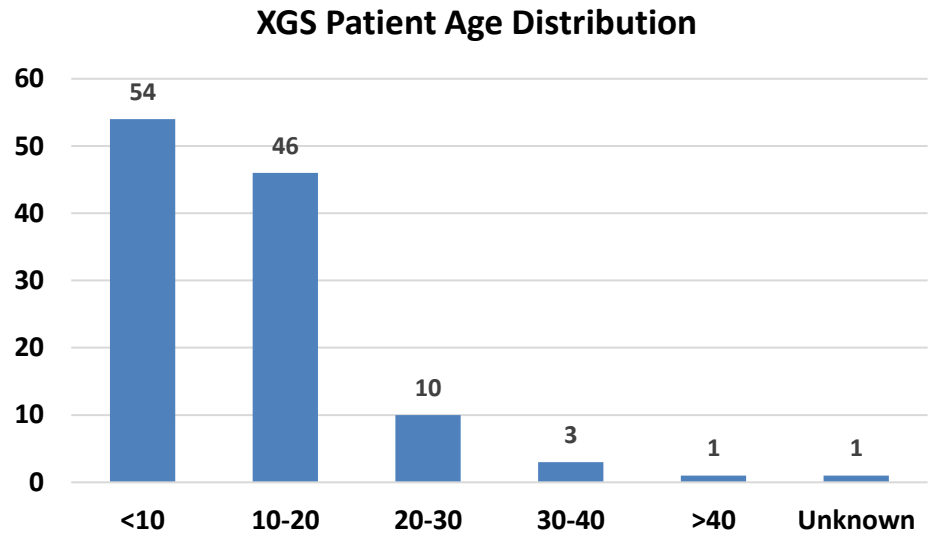
	country	Record ...
1.	United States	53
2.	United Kingd...	13
3.	Canada	8
4.	Italy	6
5.	Australia	4
6.	Netherlands	4
7.	Belgium	3
8.	France	3
9.	Germany	3
10	Norway	2
11	Israel	2
12	Poland	2
13	New Zealand	2
14	Denmark	1
15	Sweden	1
16	Ireland	1
17	Saudi Arabia	1
18	Argentina	1
19	Estonia	1
20	Singapore	1
21	Spain	1
22	Slovakia	1
23	China	1



The XGS Registry Dashboard:

Mining and reporting data is currently manual and somewhat limited:



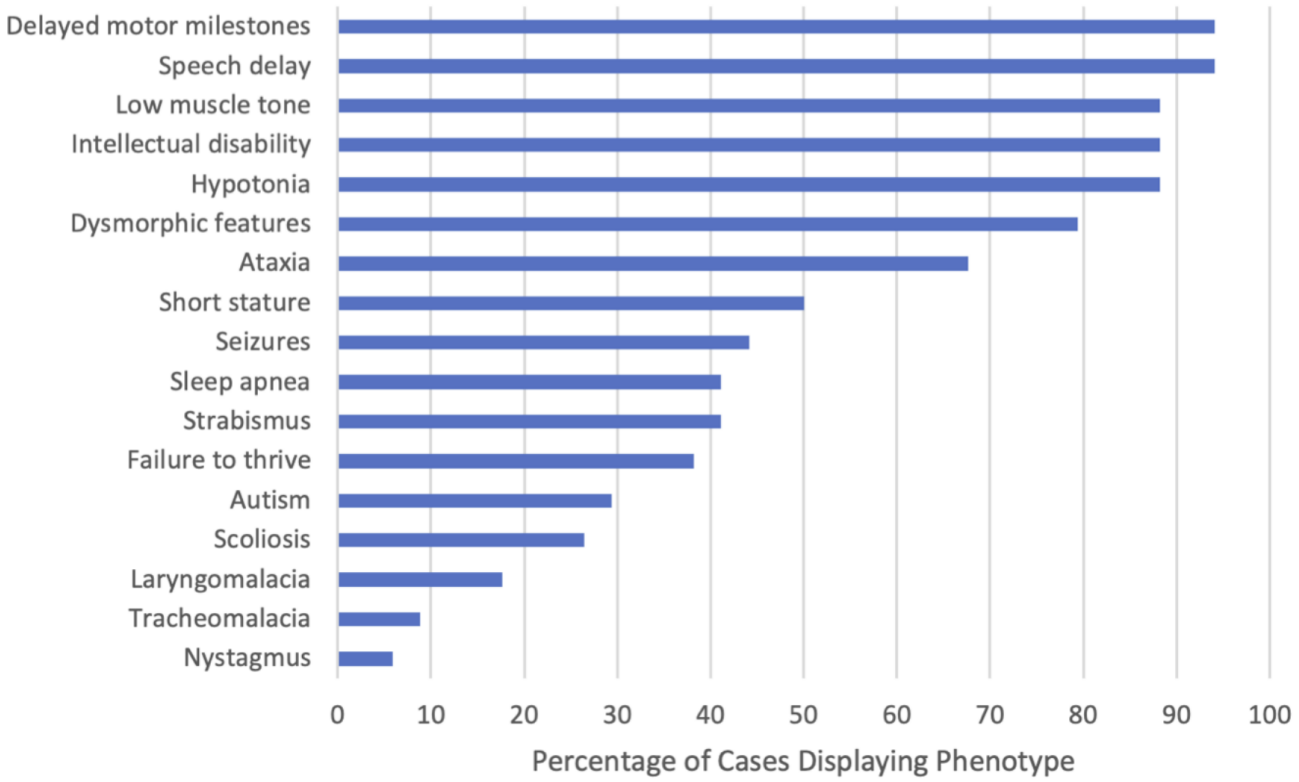


Geneial

Adam Hansen

- Contracted to build ‘back end’ for BCM by end of summer, 2022,
- Planning for patient-facing build – end of 2022?
- Then transfer to XGS Society,

Using the Registry: Defining the XGS Clinical Spectrum



Core versus additional clinical features,

Received: 30 November 2017 | Revised: 11 March 2018 | Accepted: 12 March 2018
DOI: 10.1002/ajmg.a.38699

ORIGINAL ARTICLE

WILEY American Journal of medical genetics Part A

The phenotypic spectrum of Xia-Gibbs syndrome

Yunyun Jiang[1,2] | Michael F. Wangler[2,3] | Amy L. McGuire[4] | James R. Lupski[1,2,3,5] | Jennifer E. Posey[2] | Michael M. Khayat[1,2] | David R. Murdock[1,2] | Luis Sanchez-Pulido[6] | Chris P. Ponting[6] | Fan Xia[2] | Jill V. Hunter[3] | Qingchang Meng[1,2] | Mullai Murugan[1,2] | Richard A. Gibbs[1,2]

COLD SPRING HARBOR Molecular Case Studies

RESEARCH REPORT

Xia–Gibbs syndrome in adulthood: a case report with insight into the natural history of the condition

David R. Murdock,[1,2] Yunyun Jiang,[1,2] Michael Wangler,[2,3] Michael M. Khayat,[1,2] Aniko Sabo,[1,2] Jane Juusola,[4] Kirsty McWalter,[4] Krista Sondergaard Schatz,[5] Meral Gunay-Aygun,[5] and Richard A. Gibbs[1,2]

Received: 7 September 2020 | Revised: 1 February 2021 | Accepted: 14 February 2021
DOI: 10.1002/humu.24190

RESEARCH ARTICLE

Human Mutation HGVS WILEY

Phenotypic and protein localization heterogeneity associated with *AHDC1* pathogenic protein-truncating alleles in Xia–Gibbs syndrome

Michael M. Khayat[1,2] | He Li[1] | Varuna Chander[1,2] | Jianhong Hu[1] | Adam W. Hansen[1,2] | Shoudong Li[1] | Josh Traynelis[1] | Hua Shen[1] | George Weissenberger[1] | Fabio Stossi[3,4] | Hannah L. Johnson[3] | James R. Lupski[1,2,5,6] | Jennifer E. Posey[2] | Aniko Sabo[1] | Qingchang Meng[1] | David R. Murdock[1,2] | Michael Wangler[2,5] | Richard A. Gibbs[1,2]

Additional Clinical Features from the Literature:

- Skin conditions (loose, atypical aplasia cutis),
- Lipoma
- Craniosynestosis,
- Bicuspid aortic valve

- **ALL LOW FREQUENCY, NOT VERIFIED AS PART OF XGS**

Received: 10 November 2017 | Revised: 31 May 2018 | Accepted: 4 June 2018
DOI: 10.1002/ajmg.a.40380

WILEY AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE

Variable Clinical Manifestations of Xia-Gibbs syndrome: Findings of Consecutively Identified Cases at a Single Children's Hospital

Alyssa L. Ritter[1] | Carey McDougall[1] | Cara Skraban[1,2] | Livija Medne[1] | Emma C. Bedoukian[1] | Stephanie B. Asher[1] | Jorune Balciuniene[3] | Colleen D. Campbell[3] | Samuel W. Baker[3] | Elizabeth H. Denenberg[3] | Sarah Mazzola[1] | Sarah K. Fiordaliso[1] | Ian D. Krantz[1,2] | Paige Kaplan[1,2] | Lynne Ierardi-Curto[1,2] | Avni B. Santani[3,4] | Elaine H. Zackai[1,2] | Kosuke Izumi[1,2,3]

European Journal of Medical Genetics 63 (2020) 103637

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Extending the phenotype of Xia-Gibbs syndrome in a two-year-old patient with craniosynostosis with a novel de novo *AHDC1* missense mutation

Evren Gumus

Department of Medical Genetics, Faculty of Medicine, University of Harran, Sanliurfa, 63000, Turkey

Received: 29 September 2020 | Revised: 17 December 2020 | Accepted: 26 December 2020
DOI: 10.1111/pde.14515

Pediatric Dermatology WILEY

BRIEF REPORT

Atypical aplasia cutis in association with Xia Gibbs syndrome

Carter Ellis BS[1]
Gurpur Shashidhar Pai MD[2]
Lara Wine Lee MD, PhD[3]

[1]*College of Medicine, Medical University of South Carolina, Charleston, SC, USA*
[2]*Department of Genetics, Medical University of South Carolina, Charleston, SC, USA*
[3]*Department of Dermatology and Dermatologic Surgery and Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA*

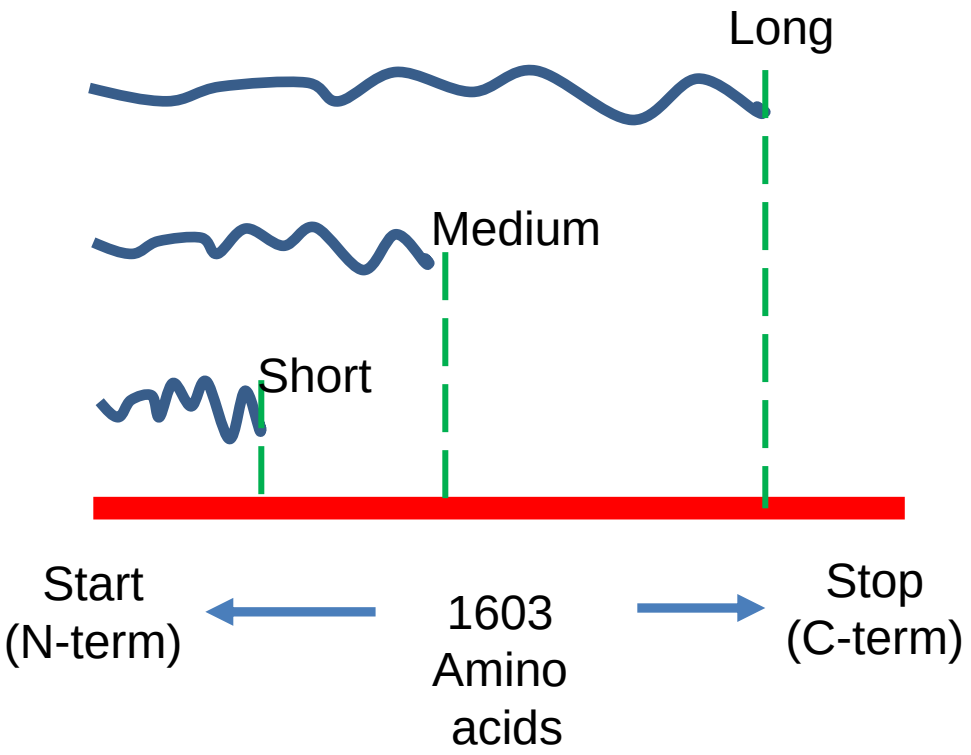
Abstract

tube dysfunction requiring bilateral myringotomy and tube place-

Using the Registry: Defining the XGS Molecular Spectrum – nonsense mutations

First observations were ‘nonsense’ mutations:

Are all nonsense the same?



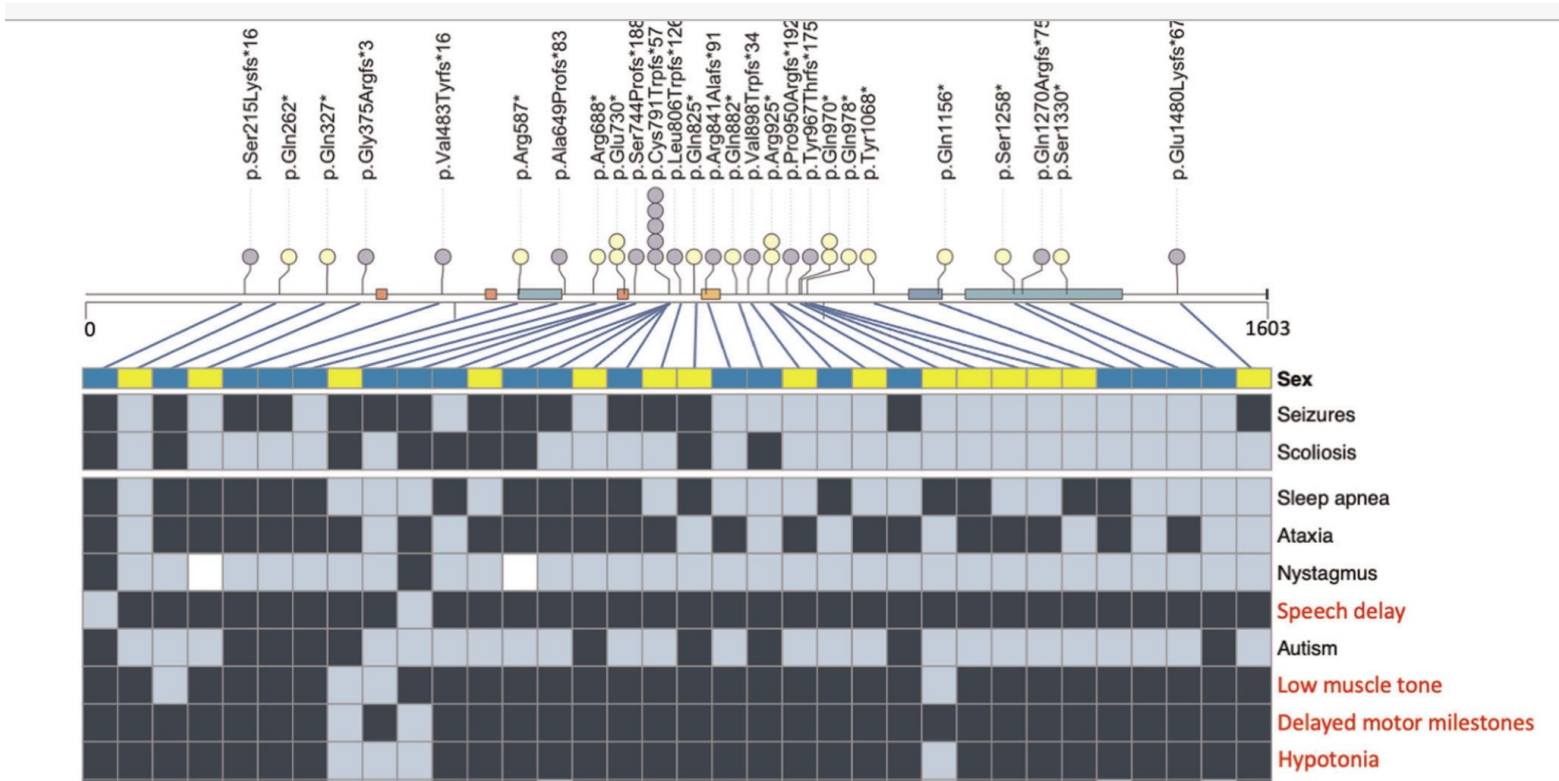
Not the same!

‘Short’: ⇧ seizure, scoliosis

Michael Khayat

Jianhong Hu

He Li



Using the Registry: Defining the XGS Molecular Spectrum – missense mutations

- First tentative diagnosis in 2018 by Dr. Gail Herman,
- Skeptical – no orthogonal data to verify,
- Gumus reported one individual in 2020,
- Important question as it informed the question of disease mechanism,

European Journal of Medical Genetics 63 (2020) 103637

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Extending the phenotype of Xia-Gibbs syndrome in a two-year-old patient with craniosynostosis with a novel de novo *AHDC1* missense mutation

Evren Gumus

Department of Medical Genetics, Faculty of Medicine, University of Harran, Sanliurfa, 63000, Turkey

- By 2021 there were 10 missense individuals reported
- (almost) all were *de novo* events,

HGG Advances

ARTICLE

AHDC1 missense mutations in Xia-Gibbs syndrome

Michael M. Khayat,[1,2,14] Jianhong Hu,[1,14] Yunyun Jiang,[1,14] He Li,[1] Varuna Chander,[1,2] Moez Dawood,[1,2,3] Adam W. Hansen,[1,2] Shoudong Li,[1] Jennifer Friedman,[4] Laura Cross,[5] Emilia K. Bijlsma,[6] Claudia A.L. Ruivenkamp,[6] Francis H. Sansbury,[7] Jeffrey W. Innis,[8] Jessica Omark O'Shea,[9] Qingchang Meng,[1] Jill A. Rosenfeld,[2] Kirsty McWalter,[10] Michael F. Wangler,[2,11] James R. Lupski,[1,2,12,13] Jennifer E. Posey,[2] David Murdock,[1,2] and Richard A. Gibbs[1,2,*]

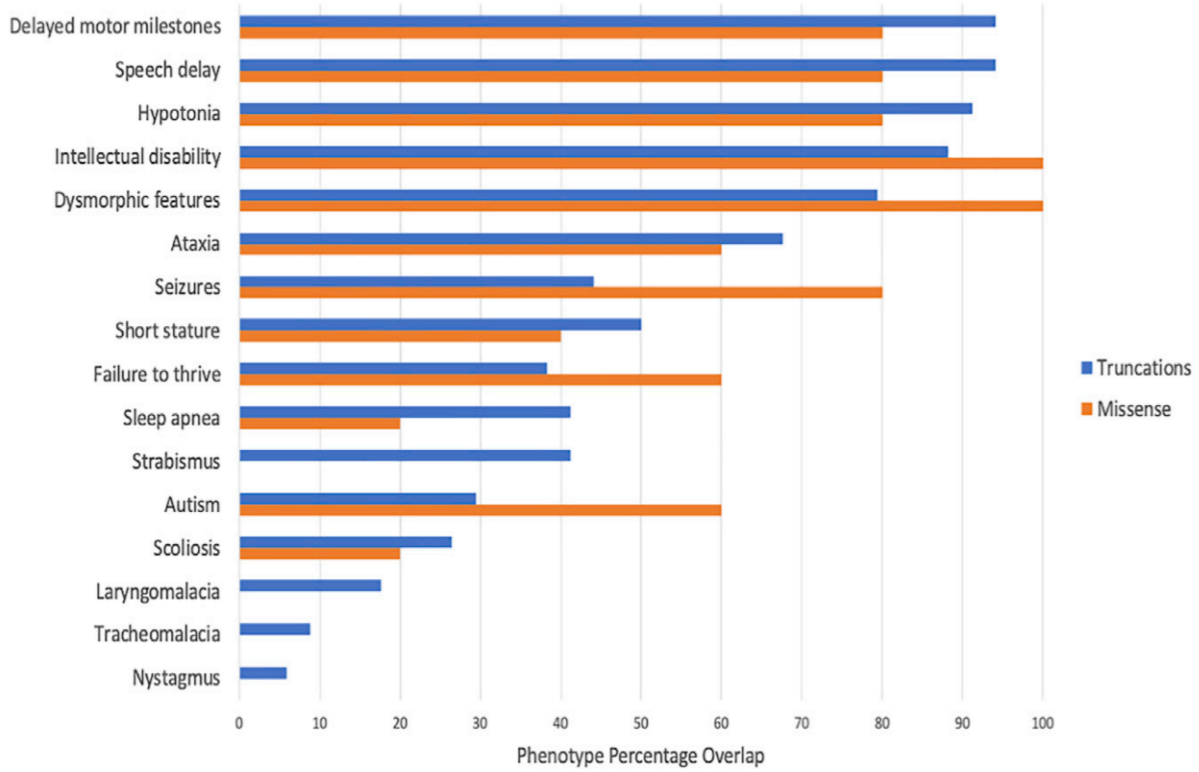
Michael Khayat

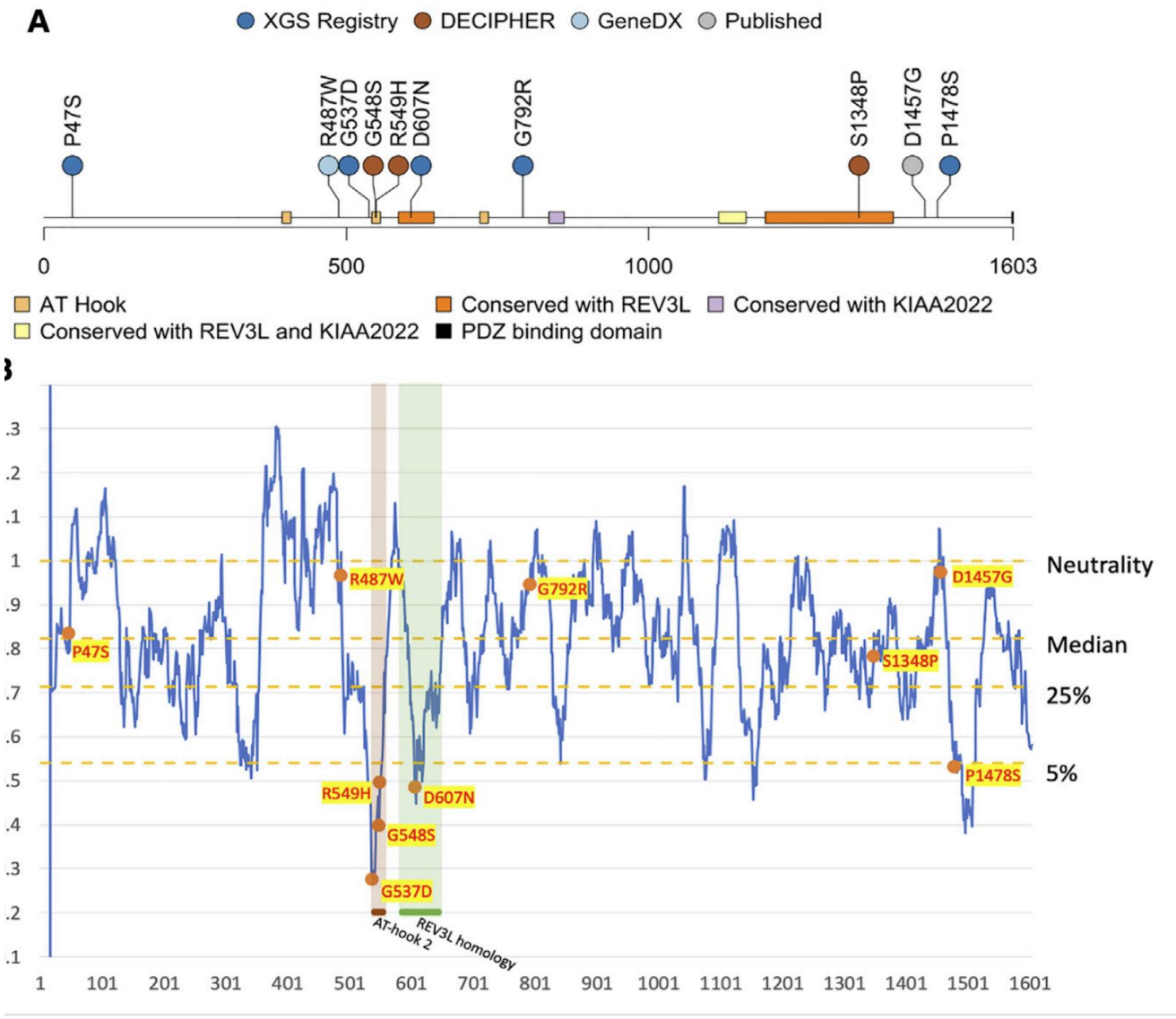
Jianhong Hu

Using the Registry: Defining the XGS Molecular Spectrum – missense mutations

Conclusion:

- SOME missense cause XGS
- Clusters = functionally important parts of the protein,
- Increase risk of seizure?

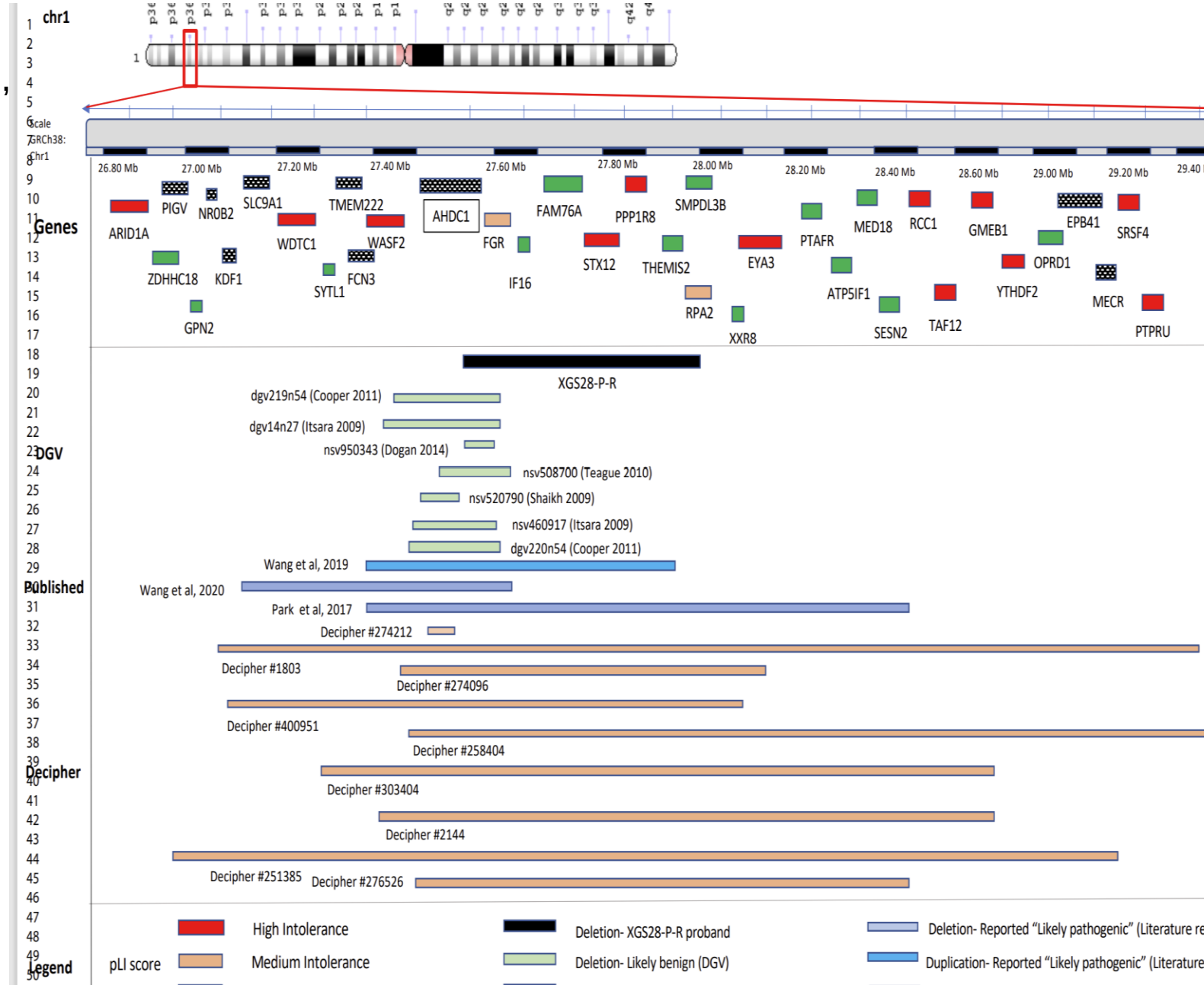




Using the Registry: Defining the XGS Molecular Spectrum – contiguous deletions

- Diagnostic labs have started reporting large deletions as having XGS,
- Usually several genes involved,
- Important question for the loss vs gain of function question,
- Identified a key individual with smallest know contiguous deletion.

Varuna Chander



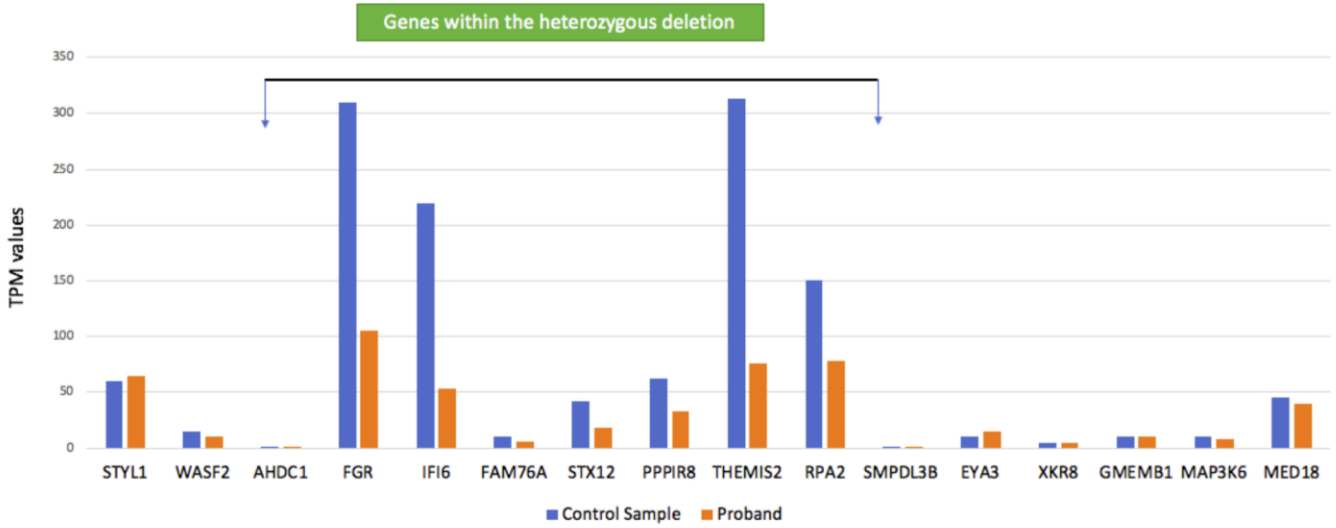
Using the Registry: Defining the XGS Molecular Spectrum – contiguous deletions

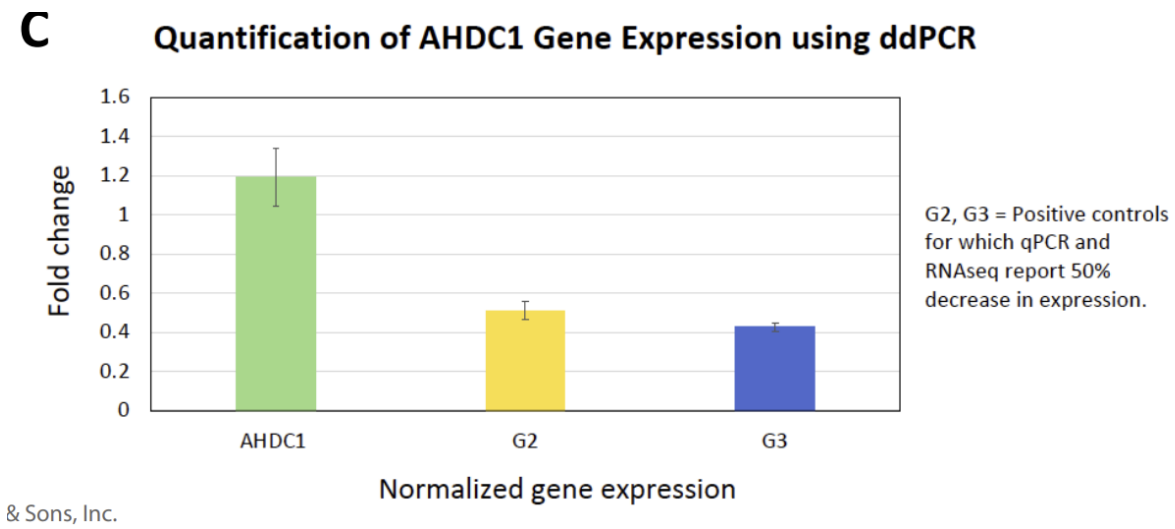
Unexpected finding:

- Even with 1 copy of AHDC1 there are ‘normal’ expression levels!
- Confirmed using very sensitive methods,
- Shows some unusual regulatory mechanism,
- Possible RNA regulatory circuit?

Varuna Chander

Submitted for publication





& Sons, Inc.

Using the Registry: Summary of Mutation Data

- Position of ‘nonsense’ mutation matters - gives some difference in clinical features,
- Missense (single letter change) mutations can cause XGS,
- Reports of contiguous deletions causing XGS **BUT**
- Varuna’s studies show that contiguous deletion conclusions might be erroneous

$\Rightarrow$ Supports ‘gain of function’ mechanism,

$\Rightarrow$ Good news for directing therapeutics.

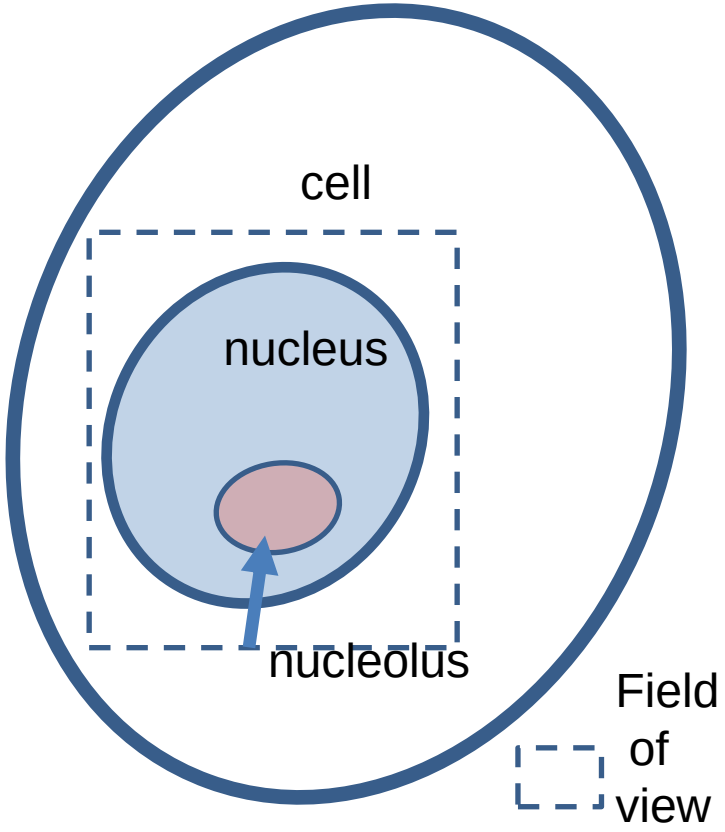
AHDC1 Laboratory Studies:

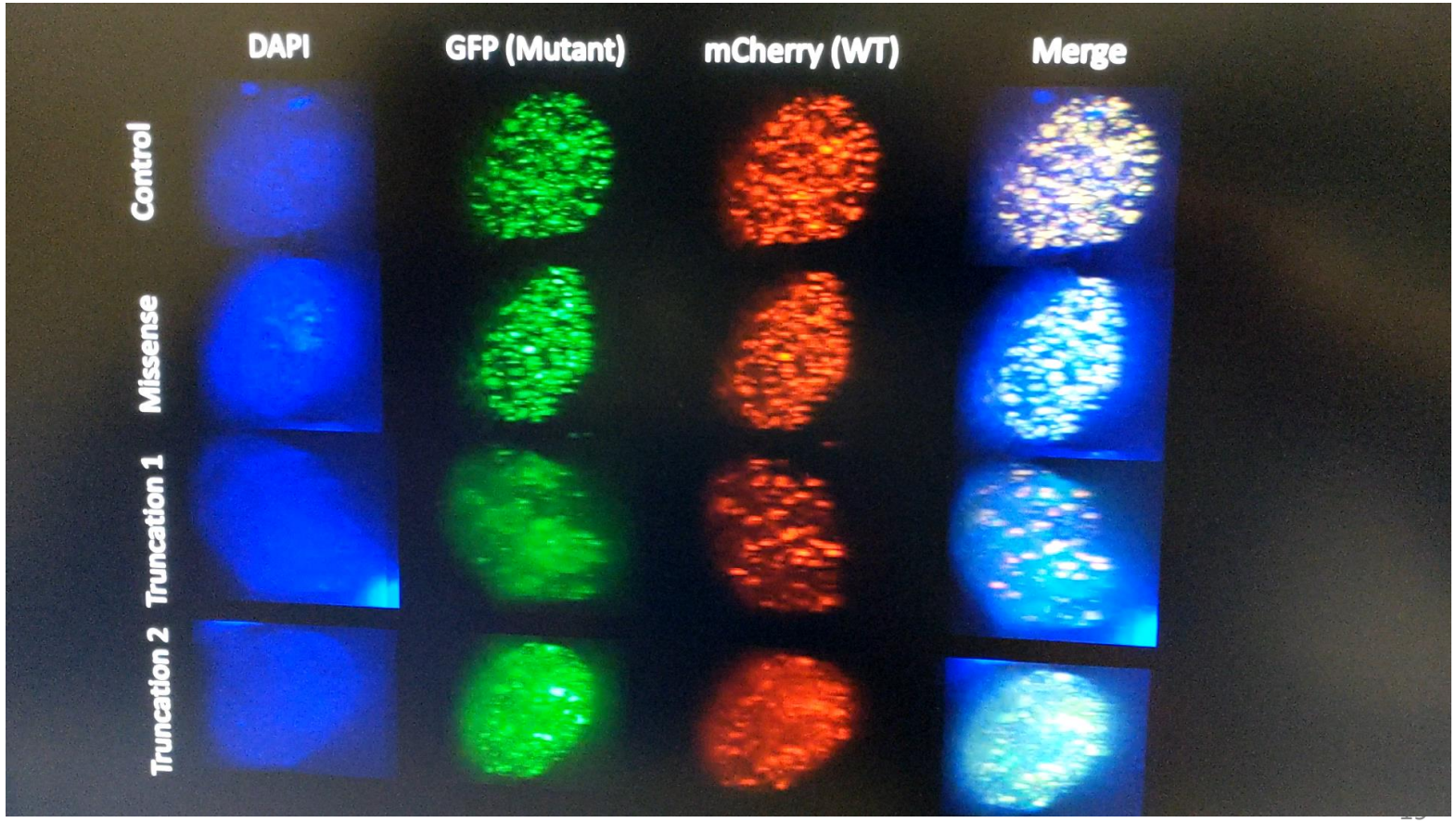
1: Making the protein in the laboratory unsuccessful, (bacteria, insect cells)

2: Inducible mammalian cell models – underway,

3: Successful transient mammalian cell models,

Michael Khayat

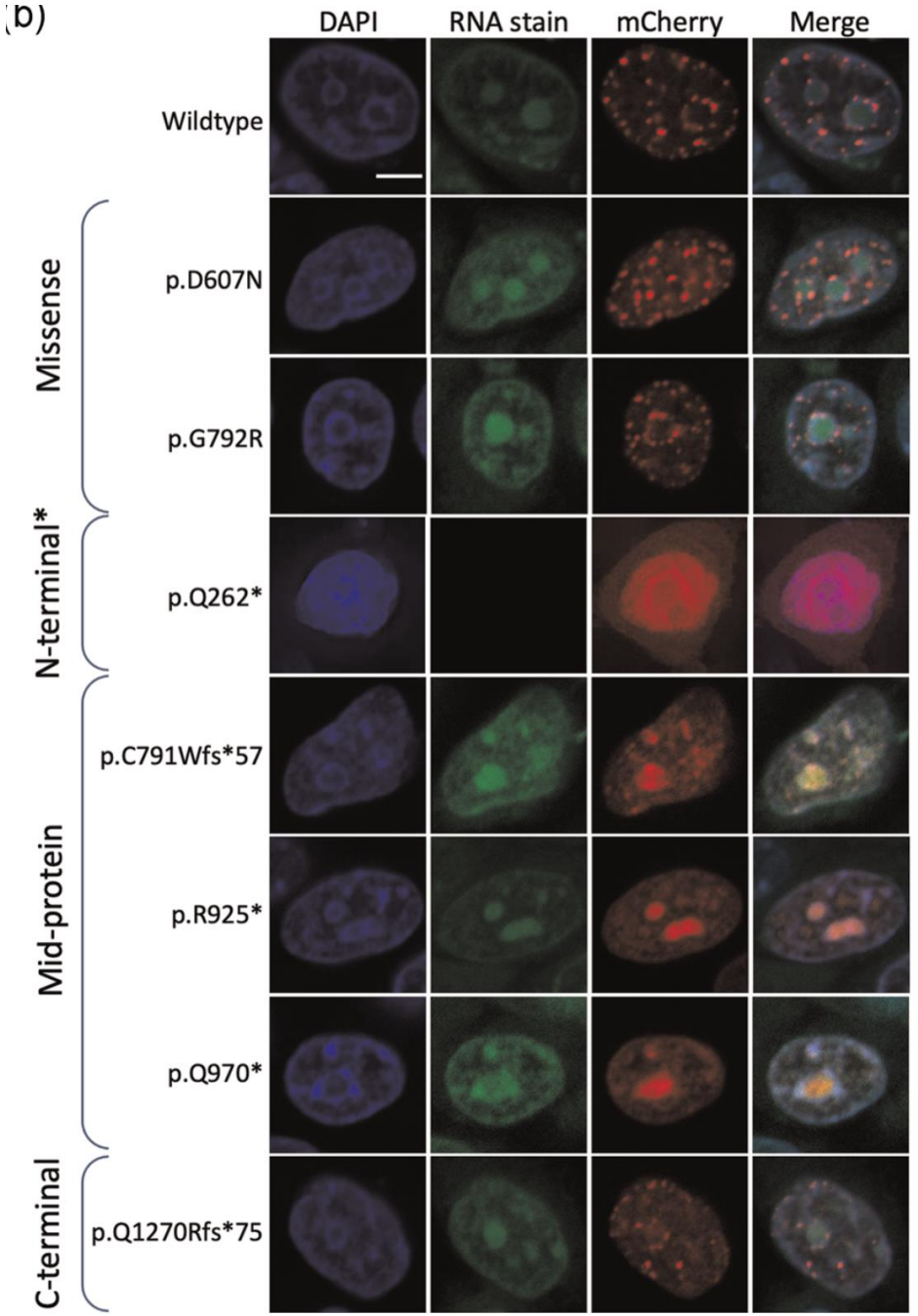




AHDC1 Laboratory Studies:

- Different length truncations,
- Mixtures of mutated and ‘normal’ genes
- Revealed different effects of different length proteins
- Short = minimal effect
- Medium = maximum effect
- Long = middle effect.

Michael Khayat



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DOI: 10.1002/humu.24190

RESEARCH ARTICLE

Human Mutation HGVS HUMAN GENOME VARIATION SOCIETY WILEY

Phenotypic and protein localization heterogeneity associated with *AHDC1* pathogenic protein-truncating alleles in Xia–Gibbs syndrome

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Summary So Far:

Mutation patterns suggest a ‘gain of function’ model,

AHDC1 mutations lead to altered distribution of the protein in the cell nucleus, but do perturb the distribution of the normal forms,

The length of the mutated protein matters – and reveals that some forms accrue around the nucleolus, the site of assembly of ribosomes in the cell,

Interestingly the ‘short forms’ gave a distinctive pattern not involving the nucleolus……

Some ‘Mild XGS’ Individuals:

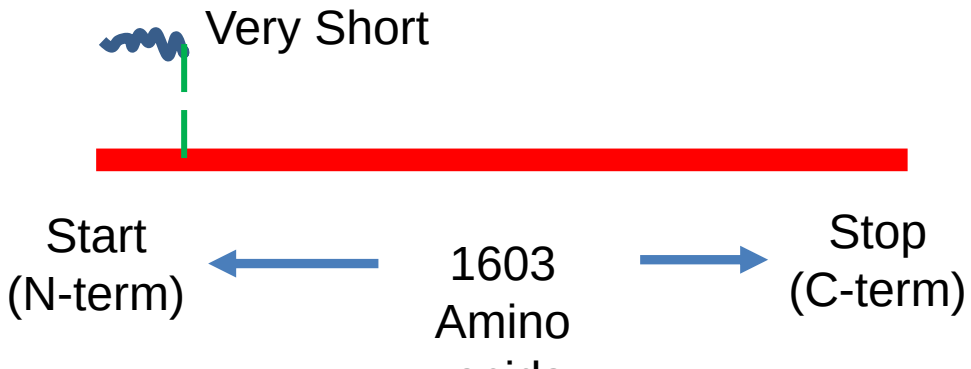
Anecdotal reports of ‘mild’ cases,

We now know of 4 individuals clearly classed as ‘mild,

One is transmitted! (Caveat – mosaicism not eliminated),

All have very short proteins!

Supports gain-of-function model,



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journal homepage: www.elsevier.com/locate/ejmg

Phenotypic heterogeneity and mosaicism in Xia-Gibbs syndrome: Five Danish patients with novel variants in *AHDC1*

Soren L. Faergeman [a,*], Anders B. Bojesen [a], Maria Rasmussen [c,d], Naja Becher [a], Lotte Andreasen [a], Brian N. Andersen [b], Emilie Erbs [c], Dorte L. Lildballe [c], Jens Erik K. Nielsen [e], Monica Zilmer [f], Trine Bjørg Hammer [f,k], Mikkel Ø. Andersen [g], Charlotte Brasch-Andersen [h], Christina R. Fagerberg [h], Niels O. Illum [i], Mette B. Thorup [j], Pernille A. Gregersen [a,b]

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[j] Department of Radiology, Aarhus University Hospital, Aarhus, Denmark

children

MDPI

Case Report

Focusing on Autism Spectrum Disorder in Xia–Gibbs Syndrome: Description of a Female with High Functioning Autism and Literature Review

Stefania Della Vecchia [1,2], Roberta Milone [1], Romina Cagiano [1], Sara Calderoni [1,2], Elisa Santocchi [1], Rosa Pasquariello [1], Roberta Battini [1,2,*] and Filippo Muratori [1,2]

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Other AHDC1 Laboratory Studies:

- Studied genes involved in early differentiation to skin,
- One of 50 important genes was AHDC1,
- AHDC1 renamed to Gibbin,
- Studied protein in segments,
- Gibbin connects to a lot of ‘early developmental’ genes,
- Gibbin controls a ‘gateway’ for this early pathway differentiation,
- Important insight into role of AHDC1 as an early differentiation determinant,

Nature May 2022, online

Article

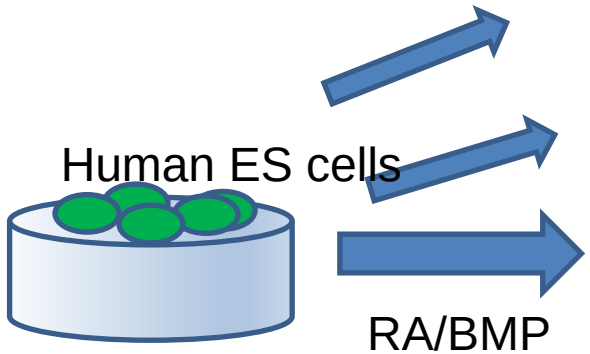
Gibbin mesodermal regulation patterns epithelial development

https://doi.org/10.1038/s41586-022-04727-9
Received: 31 December 2020
Accepted: 5 April 2022
Published online: 18 May 2022
Check for updates

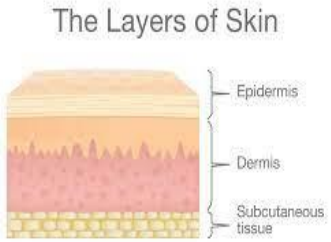
Ann Collier[1], Angela Liu[2], Jessica Torkelson[1], Jillian Pattison[1], Sadhana Gaddam[1], Hanson Zhen[1], Tiffany Patel[1], Kelly McCarthy[1], Hana Ghanim[2] & Anthony E. Oro[2]✉

Proper ectodermal patterning during human development requires previously identified transcription factors such as GATA3 and p63, as well as positional signalling from regional mesoderm[1–6]. However, the mechanism by which ectoderm and

Anthony Oro



Epithelial development



- Gibbin regulates process, via many other genes,
- Removal of Gibbin results in hypermethylation
- Removal of Gibbin very severely effects mice,

Implications of Gibbin Studies:

Article

Gibbin mesodermal regulation patterns epithelial development

https://doi.org/10.1038/s41586-022-04727-9
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Proper ectodermal patterning during human development requires previously identified transcription factors such as GATA3 and p63, as well as positional signalling from regional mesoderm[1–6]. However, the mechanism by which ectoderm and

- Clearly an early developmental role for the gene,
- Shared activity with MECP2, homoebox proteins,
- Involvement of methylation in early gene expression control,
- Wonderful news for the XGS community,
- Will prompt more methylation (epigenetic) studies,

Anthony Oro

Things to remember:

- Experiments are ‘knockouts’ – very severe mutations,
- No child is born with no copies of AHDC1!
- Only one report of prenatal XGS features – generally later developmental disorder
- Overall, good news for mechanism studies, not bad news for thoughts of therapy.

Other Unexplained AHDC1 Observations:

- Association with Kidney disease
- Association with Cancer
- Hibernation??

CLINICAL RESEARCH www.jasn.org

Exome-Based Rare-Variant Analyses in CKD

Sophia Cameron-Christie,[1] Charles J. Wolock,[2] Emily Groopman,[3] Slavé Petrovski,[1] Sitharthan Kamalakaran,[2] Gundula Povysil,[1,4] Dimitrios Vitsios,[1] Mengqi Zhang,[4,5] Jan Fleckner,[1] Ruth E. March,[6] Sahar Gelfman,[2] Maddalena Marasa,[3] Yifu Li,[3] Simone Sanna-Cherchi,[3] Krzysztof Kiryluk,[3] Andrew S. Allen,[4,5] Bengt C. Fellström,[7] Carolina Haefliger,[1] Adam Platt,[1] David B. Goldstein,[1,2,4] and Ali G. Gharavi[3,4]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

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DOI: 10.1111/cge.14038

ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

Whole genome sequencing identifies rare germline variants enriched in cancer related genes in first degree relatives of familial pancreatic cancer patients

Ming Tan[1,2,3] | Klaus Brusgaard[1,4] | Anne-Marie Gerdes[5] | Michael Bau Mortensen[1,3,6] | Sönke Detlefsen[1,3,7] | Ove B. Schaffalitzky de Muckadell[1,2,3] | Maiken Thyregod Joergensen[1,2,3]

cancer biology & therapy

Taylor & Francis

ISSN: 1538-4047 (Print) 1555-8576 (Online) Journal homepage: https://www.tandfonline.com/loi/kcbt20

LINC01133 promotes the progression of cervical cancer by sponging miR-4784 to up-regulate AHDC1

Yan Feng, Luyun Qu, Xiuli Wang & Chunyan Liu

Hibernation slows epigenetic aging in yellow-bellied marmots

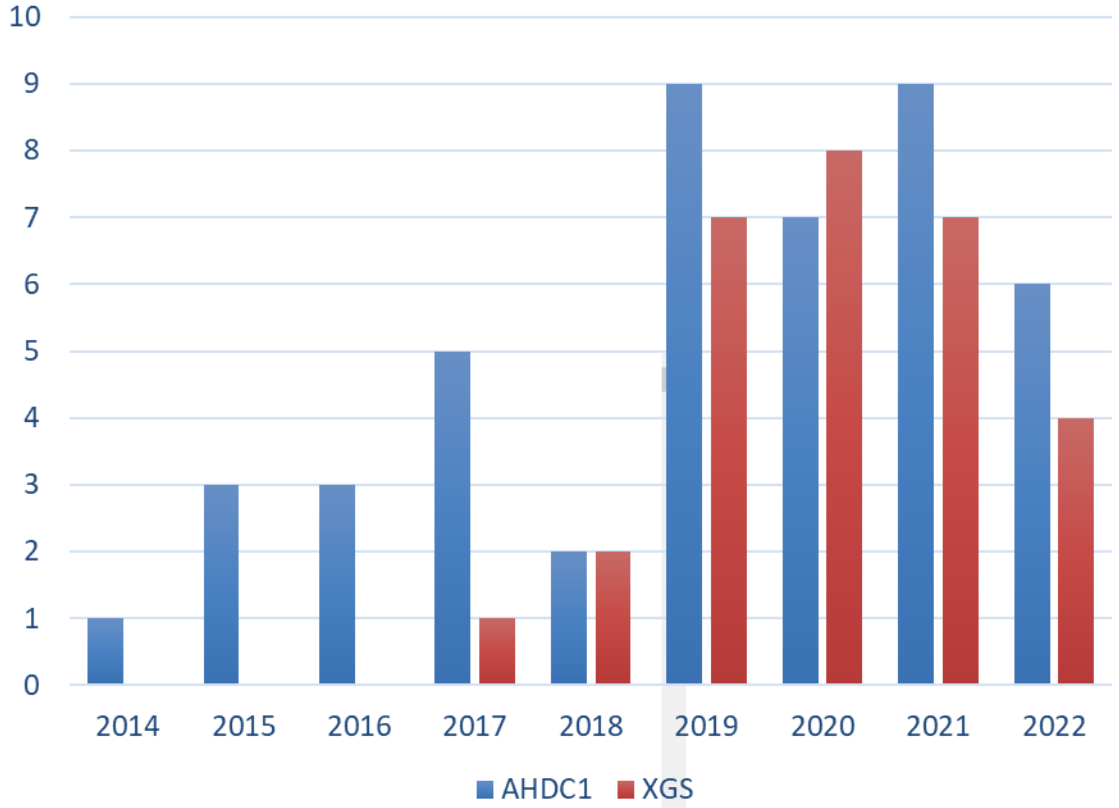
Gabriela M. Pinho[a,*], Julien G. A. Martin[b,*], Colin Farrell[c], Amin Haghani[d], Joseph A. Zoller[d], Joshua Zhang[d], Sagi Snir[e], Matteo Pellegrini[c], Robert K. Wayne[a], Daniel T. Blumstein[a,f,*] and Steve Horvath[d,g,*]

[a] Department of Ecology and Evolutionary Biology, University of California, 621 Young Drive South, Los Angeles, CA 90095–1606, USA

Awareness of AHDC1 in the Science Community:

- AHDC1/XGS publications increasing,
- Dr. Oro's studies will boost interest,
- Gene Reviews will impact clinical caregivers

- Papers on AHDC1 and XGS



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Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.

Xia-Gibbs Syndrome

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Estimated reading time: 24 minutes

Summary

Clinical characteristics. The main features of Xia-Gibbs syndrome (XGS), present in a majority of affected individuals, include delayed motor milestones, speech delay with severely limited or absent speech, moderate-to-severe cognitive impairment, hypotonia, structural brain anomalies, and nonspecific dysmorphic features. Other features may include sleep apnea, movement disorders (ataxia, tremors, and bradykinesias) that often become apparent in childhood or adolescence, short stature, seizures, eye anomalies, behavioral concerns, autism spectrum disorder, scoliosis, and laryngomalacia.

The Way Ahead:

1: The importance of the Registry,

2: Expanded genetic testing – more ‘mild’ individuals’?

3: Expanded behavioral and cognitive tests,

4: Expanded language studies,

5: More engagement of different laboratories, sharing,

6: More laboratory models: more from the mouse?

7: Will XGS be curable?

- Dr Oro’s studies show very early role for AHDC1/Gibbin,
- But XGS children do not report extensive prenatal issues,
- Open question - XGS mutations may be more mild than in laboratory knockouts,
- Neonatal intervention possible,
- Full understanding of the protein function is key to designing intervention,

Final thought: Some of the most difficult challenges like this have been met. Think of therapy for Spinal Muscular Atrophy (SMA) and related advances in Huntingtons Corea and Duchenne’s Muscular Dystrophy. Optimism and persistence is key.

- Discussion