XGS - AHDC1 - Update

Richard Gibbs AC Ph.D.,

Baylor College of Medicine – Human Genome Sequencing Center

DISCLOSURES:

- Honorary advisor to Geneial,
- BCM is a joint owner of Baylor Genetics Laboratories (BGL)
- BCM owns stock in Codified Genomics

Thanks

- Emily, Monica, XGS Society,
- Families for sharing your day,
- Jianhong Hu,
- Scientific colleagues:
  - Jennifer Posey, M.D., Ph.D.
  - Davut Pehlivan, M.D.
  - Claudio Cinquemanni, CureRare,
  - Adam Hansen, Ph.D.
  - Anthony Oro, M.D.
  - Bo Yuan, Ph.D.,
  - James Lupski, M.D., Ph.D.
  - David Murdock, M.D., Ph.D.

Baylor College of Medicine Research on XGS and AHDC1

HGSC™
HUMAN GENOME SEQUENCING CENTER

Past -Lab
Yunyun Jiang
Shoudong Li
Michael Khayat
Varuna Chander
*Adam Hansen

Present - Lab
Harsha Doddapaneni
Heer Mehta
Bo Yuan
Eric Venner
Aniko Sabo

Jianhong Hu*
Mullai Murugan

Moez Dawood

Clinical Genetics (M.D.)
David Murdoch
Michael Wangler
*Jennifer Posey
James Lupski
*Davut Pehlivan

*Presenting today
** Supported by
Xia-Gibbs Society

The XGS Registry – May 2024, More from Jianhong later today

- First step to understanding XGS basics and to accessing individuals and families,
- Began in 2014
- 503 XGS individual, worldwide
- 179 in the Registry
- Updates from Geneial (Adam Hansen)

Jianhong Hu

Mullai Murugan

Xia-Gibbs Syndrome Groups

- XGS Society (Australia, USA)

- UK Group

- Italy

- Germany

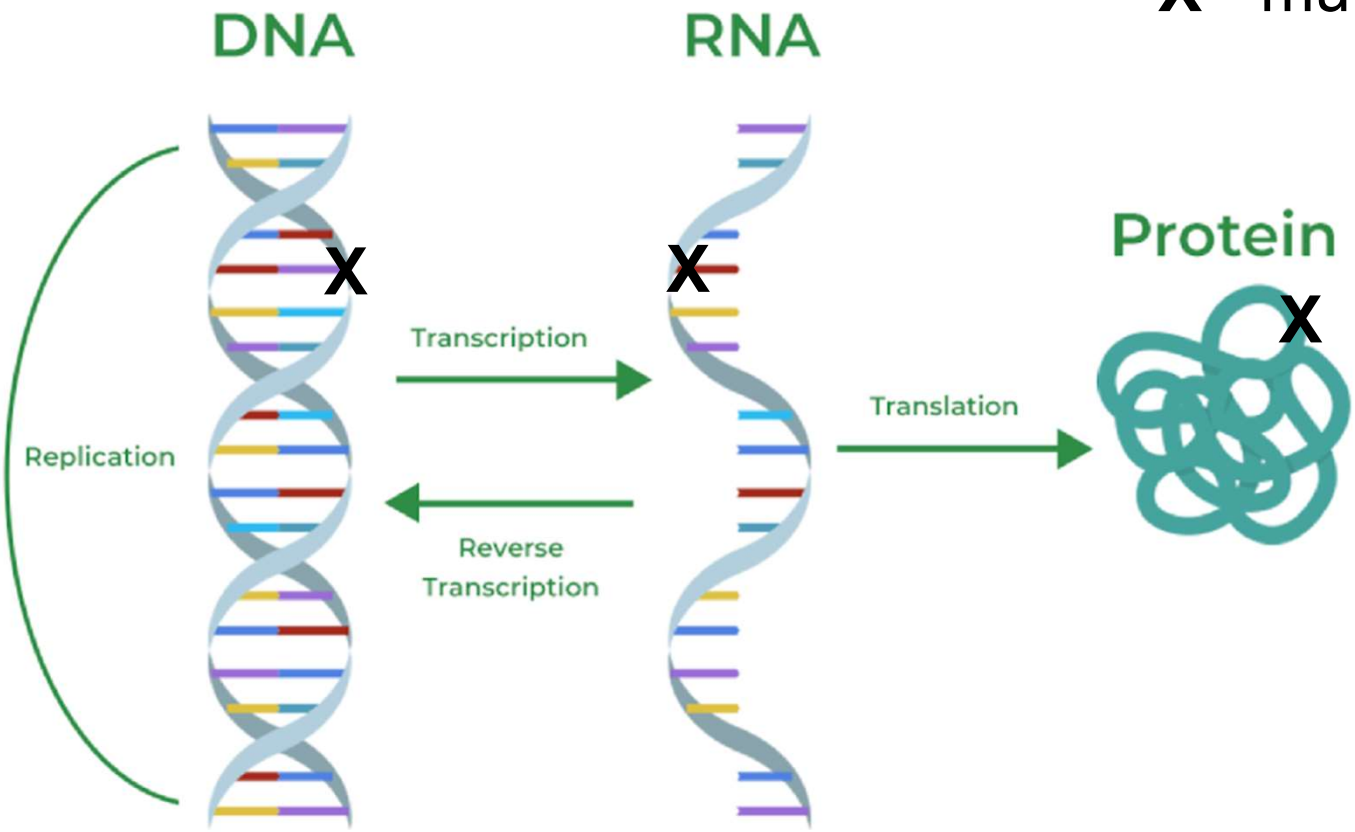
Xia-Gibbs Syndrome

Questions:

- What does the protein do?
- What about other mutations?
- Is the disorder:
  - ‘gain of function’ (ie ‘bad’ version causes XGS)?
  - or ‘haploinsufficient’ (ie absence of enough good AHDC1 causes XGS)?

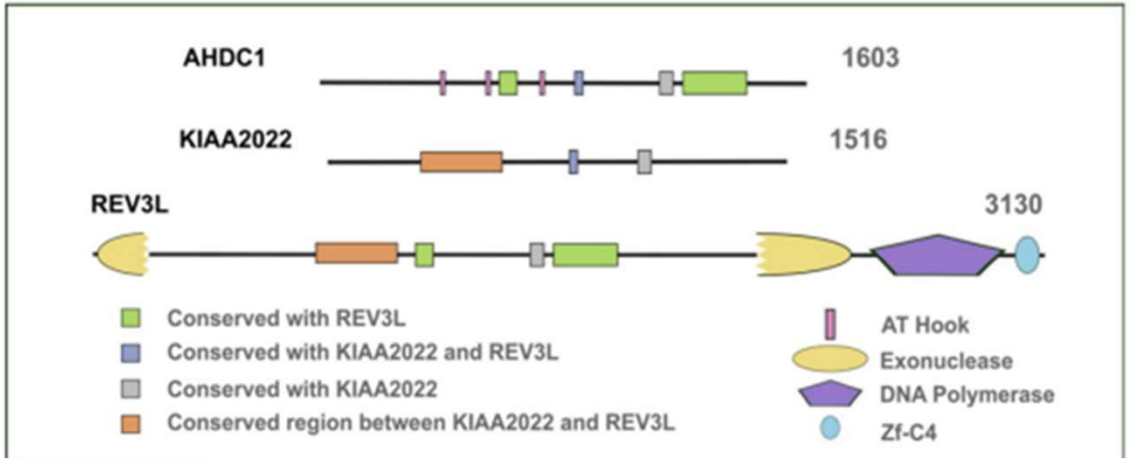
Quick Genetics Lesson:Genes in DNA-> Protein

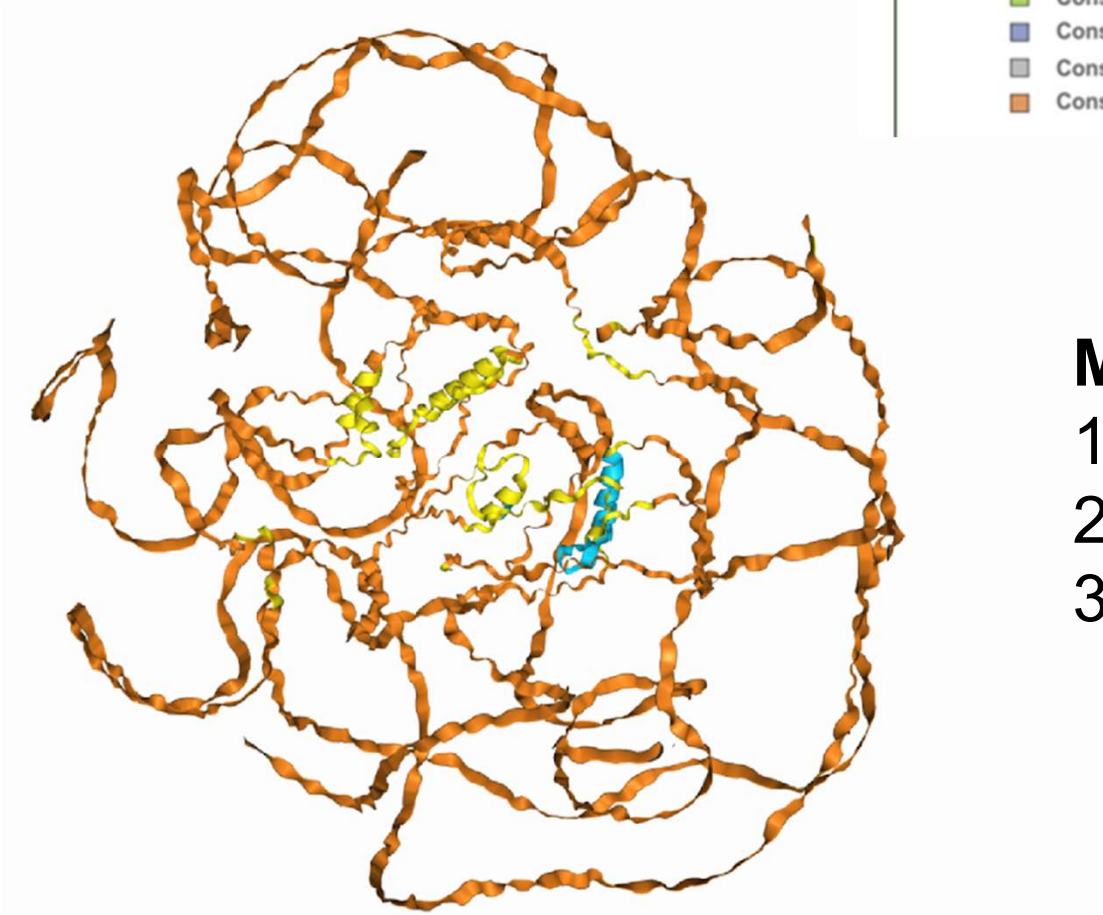
X - mutation



AHDC1:

Mostly ‘intrinsically disordered’,





Mutations:

1: Mostly ‘truncation’

2: Some amino acid changes

3: Some deletions

AHDC1

Effect of Mutation Length:

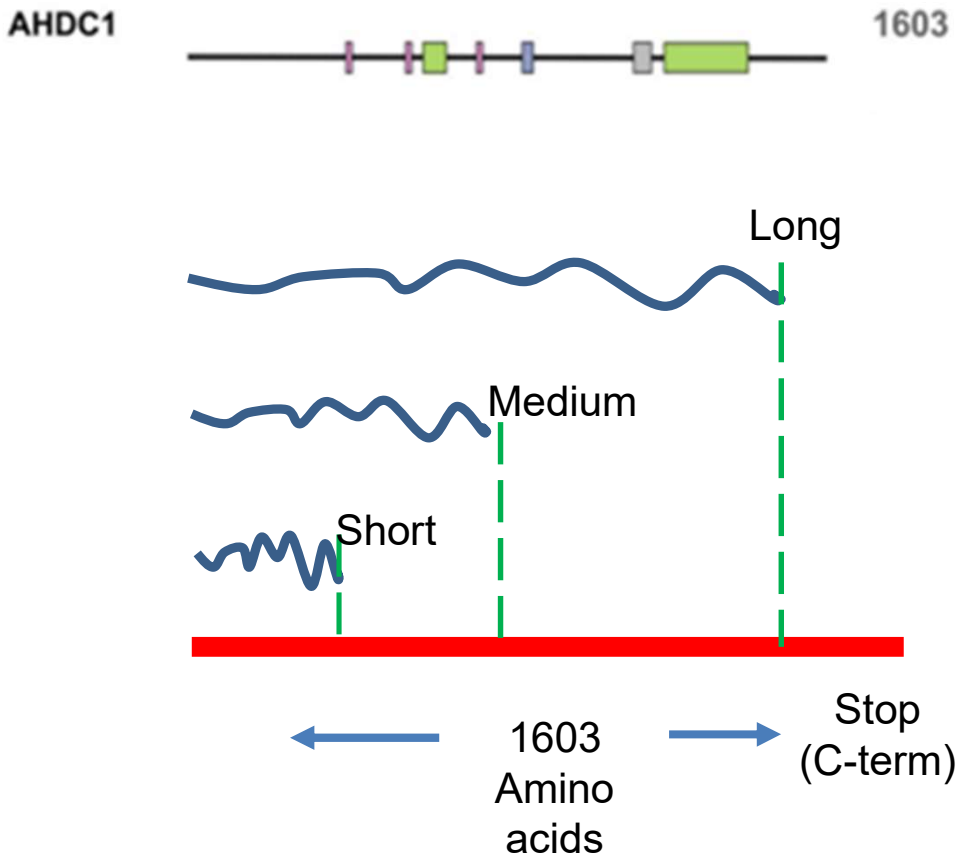
1: Short may = ‘mild’

2: Medium may = severe

3: Long may = variable

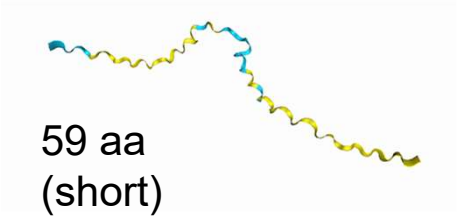
Exceptions:

1: Same mutation, different outcome,



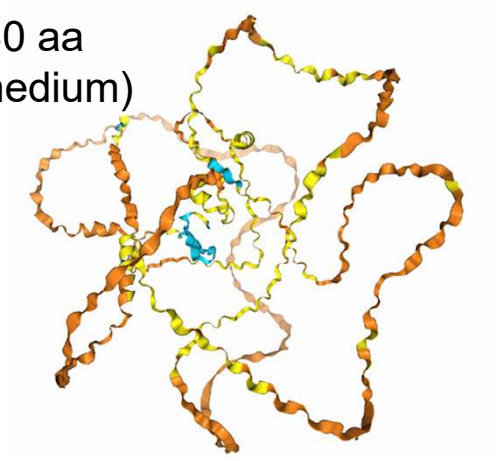
AHDC1 Truncations (alphafold 3):

not informative

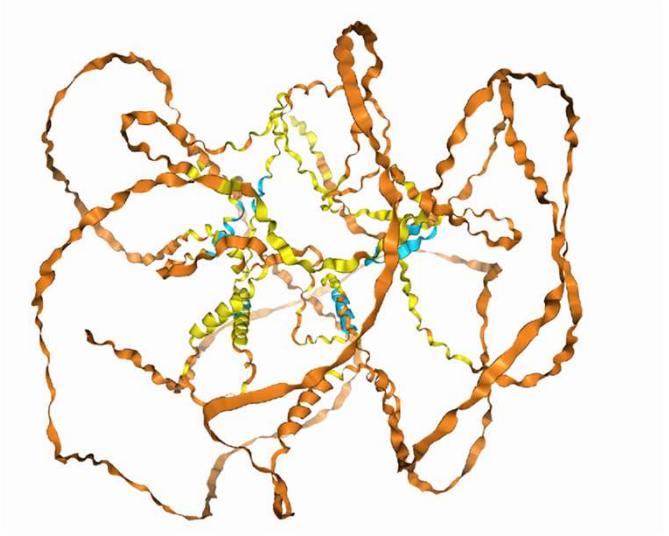


59 aa
(short)

540 aa
(medium)



968 aa
(long)



AHDC1: Mechanism

1: Some amino acid changes do cause XGS – but not all

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,*]

Received: 2 May 2022 | Revised: 17 August 2022 | Accepted: 30 August 2022
DOI: 10.1002/humu.24461
RESEARCH ARTICLE
Human Mutation HGVS WILEY

2: Do large deletions cause XGS?
- We say 'no',
- Other evidence says 'maybe'

Long read sequencing and expression studies of *AHDC1* deletions in Xia-Gibbs syndrome reveal a novel genetic regulatory mechanism

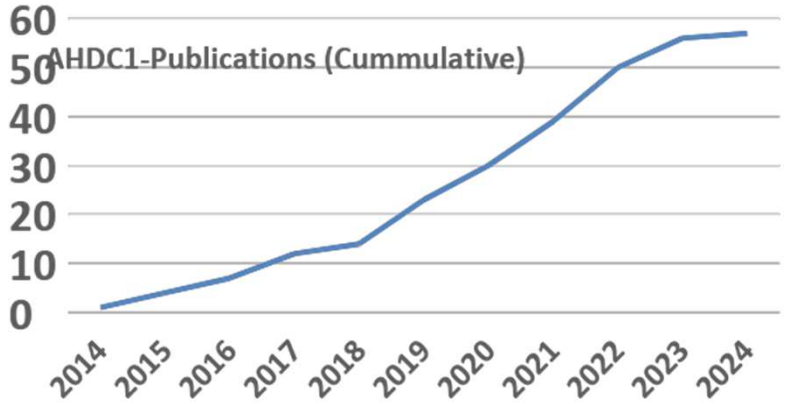
Varuna Chander[1,2] | Medhat Mahmoud[1,2] | Jianhong Hu[2] | Zain Dardas[2] | Christopher M. Grochowski[2] | Moez Dawood[1,2] | Michael M. Khayat[1,2] | He Li[1] | Shoudong Li[1] | Shalini Jhangiani[1] | Viktoriya Korchina[1] | Hua Shen[1] | George Weissenberger[1] | Qingchang Meng[1] | Marie-Claude Gingras[1,2] | Donna M. Muzny[1,2] | Harsha Doddapaneni[1] | Jennifer E. Posey[2] | James R. Lupski[1,2,3,4] | Aniko Sabo[1] | David R. Murdock[1,2] | Fritz J. Sedlazeck[1,2,5] | Richard A. Gibbs[1,2]

Conclude:

- Gain of Function' likely to operate
- Cannot exclude 'haploinsufficiency'
- Likely both mechanisms

Other Research on XGS and AHDC1?

Many countries now represented:
USA, China, India, Italy, Iran, Denmark,
Turkey, Brazil
Mostly clinical correlates:



‘Surprises’

1: Some cancer role for AHDC1

2: Possible RNA regulation circuit

3: Role in metabolism, obesity?

4: (unpublished) – ‘silenced’ AHDC1 leads to alteration of other genes in cultured cells,
– no ‘magic bullet’ yet (Silvana Bochicchio, Ph.D., unpublished)

Important developments:

1: Gibbin study (later today)
2: iPSCs

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&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 mesoderm factors act to stably pattern gene expression and lineage commitment remains unclear. Here we identify the protein Gibbin, encoded by the Xia–Gibbs AT-hook DNA-binding motif containing 1 (*AHDC1*) disease gene[7–9], as a key regulator

Anthony Oro

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Gene
journal homepage: www.elsevier.com/locate/gene

Methodological paper

Establishment of iPSC lines and zebrafish with loss-of-function *AHDC1* variants: Models for Xia-Gibbs syndrome

Laura Machado Lara Carvalho[a], Elisa Varella Branco[a], Raquel Delgado Sarafian[b], Gerson Shigeru Kobayashi[a], Fabiano Tófoli de Araújo[b], Lucas Santos Souza[a], Danielle de Paula Moreira[a], Gabriella Shih Ping Hsia[a], Eny Maria Goloni Bertollo[c], Cecília Barbosa Buck[d], Silvia Souza da Costa[a], Davi Mendes Fialho[a], Felipe Tadeu Galante Rocha de Vasconcelos[a], Luciano Abreu Brito[a], Luciana Elena de Souza Fraga Machado[a], Igor Cabreira Ramos[a], Lygia da Veiga Pereira[b], Celia Priszkulnik Koiffmann[a], Maria Rita dos Santos e Passos-Bueno[a], Tiago Antonio de Oliveira Mendes[e], Ana Cristina Victorino Krepischi[a], Carla Rosenberg[a,*]

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Stem Cell Research
journal homepage: www.elsevier.com/locate/scr

Lab Resource: Single Cell Line

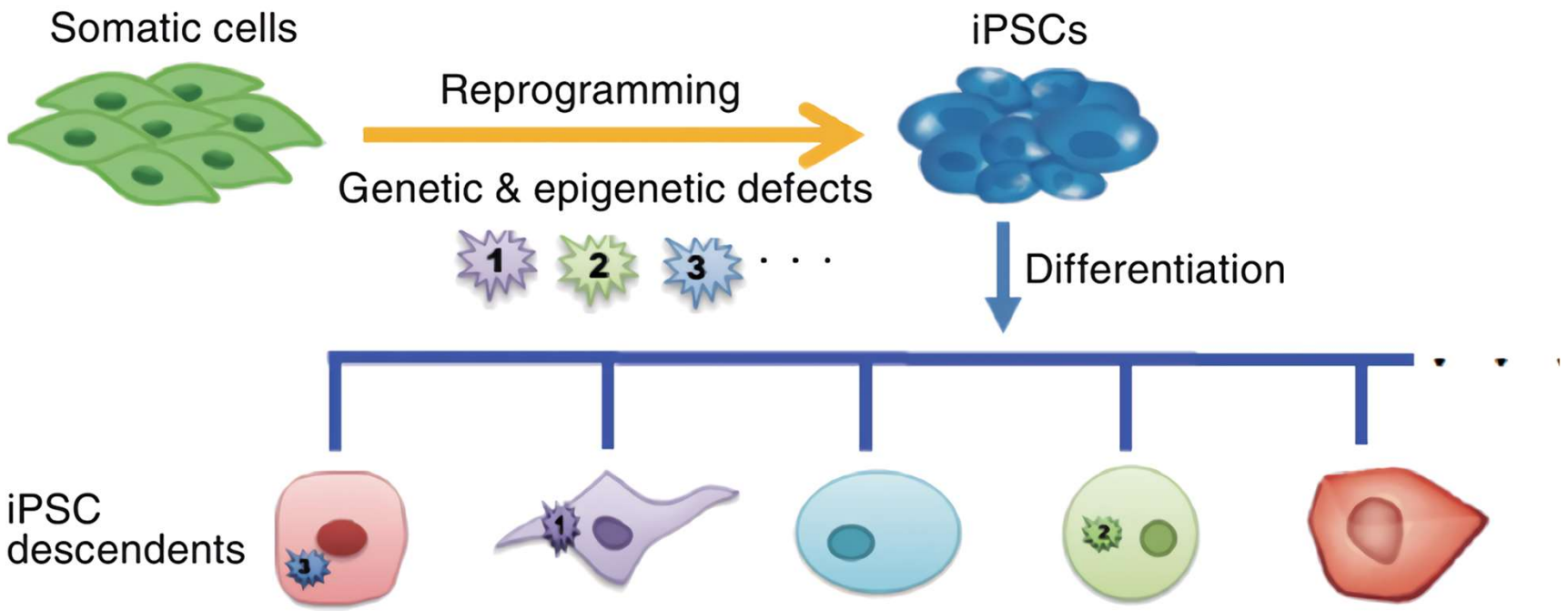
Generation of a human induced pluripotent stem cell line (FDCHi010-A) from a patient with Xia-Gibbs syndrome carrying *AHDC1* mutation (c.2062C > T)

Tingting Yin[a], Bingbing Wu[a], Ting Peng[b], Yunfei Liao[a], Shuangyun Jiao[a], Huijun Wang[a,*]

[a] Center for Molecular Medicine, Children's Hospital of Fudan University, Shanghai 201102, China
[b] Department of Neonatology, Children's Hospital of Fudan University, Shanghai 201102, China

iPSCs: induced pluripotent stem cells

- Contain all the DNA of the donor
- Made from blood samples
- a tool for studying each different mutation in a different cell type
- A full range of iPSCs will allow a range of AHDC1 studies



Questions?