Phenotypic characterization: Refining the denominator

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Phenotype: a medical genetics viewpoint

- For even the strongest variant, nearly all phenotypes exhibit variation in expressivity
- For nearly all phenotypes, heterogeneity of etiology is the rule
- Informed, rigorous, iterative phenotyping yields best data

For all these reasons and more, phenotyping is difficult!

*Box 1: Research strategies using rare, low frequency variants and structural variants**

3 - Using targeted sequencing judiciously, focusing on people with extreme or unusual phenotypes

5 - Focusing discovery efforts on well-phenotyped groups, accessible families with large sibships, and families that allow return to family members for iterative phenotyping

* Manolio et al., Nature, 2009

Centers for Mendelian Genomics

Goal: Identify all genes with high penetrance variants to produce a map of genotype/phenotype relationships for all genes in the genome – "integrative, whole organism phenotypes"

Strategy:

- Recruit well-phenotyped probands and families or cohorts from around the world
- Perform WES or WGS on relevant family members
- Use family relationships, allele frequency data, functional predictions, model organism results and functional studies to identify the responsible genes and variants

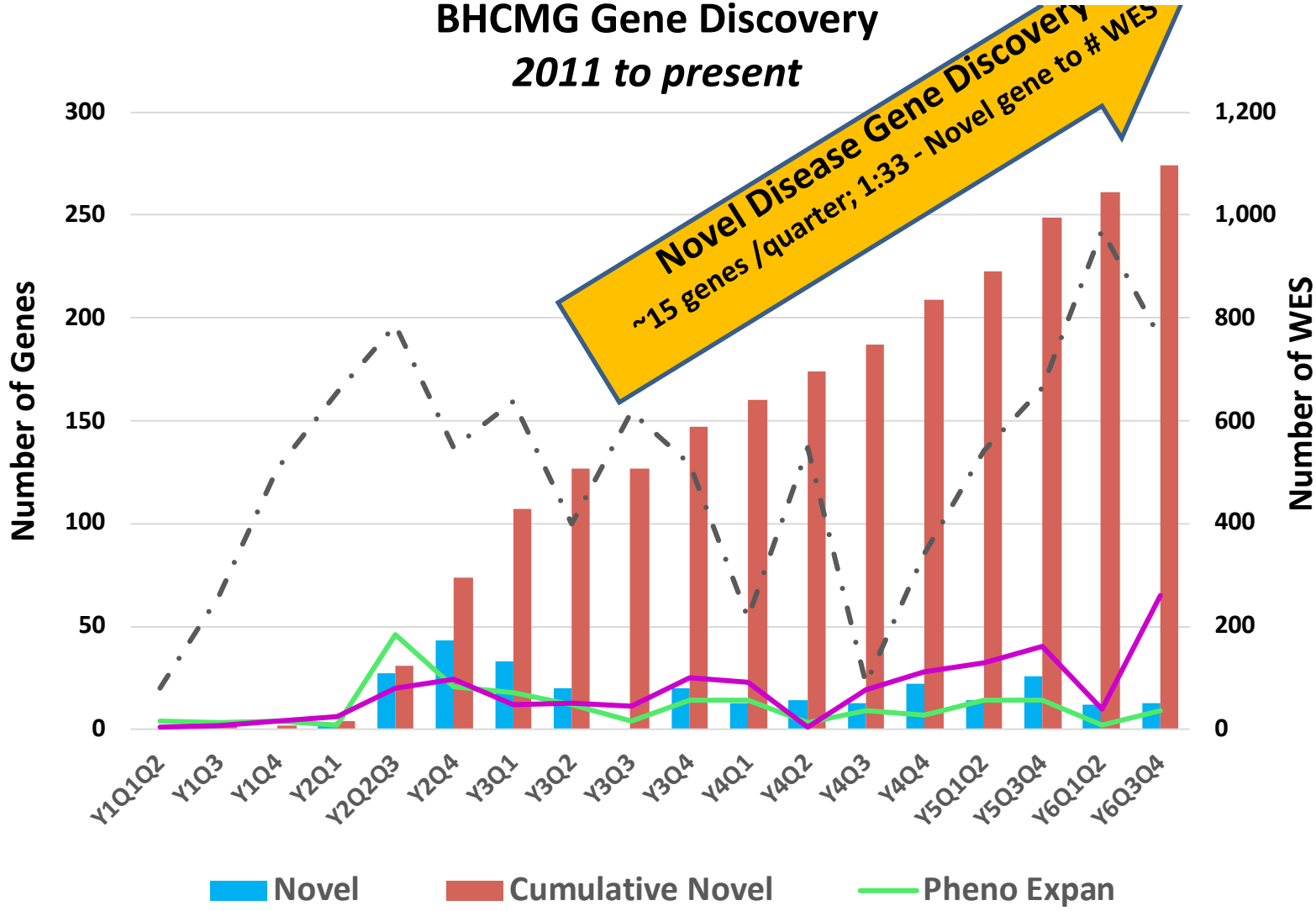
Baylor College of Medicine · BROAD INSTITUTE · JOHNS HOPKINS MEDICINE · UNIVERSITY of WASHINGTON · Yale SCHOOL OF MEDICINE

CMGs: current progress (6yrs)

- Start date 1 Dec 2011

		Total	Novel	Known
Gene discovery	Tier 1	2197	1251	946 (~50% Pheno Exp)
	Tier 2	1000	933	67

- 437 publications
- 5250 unique authors
- 74 countries

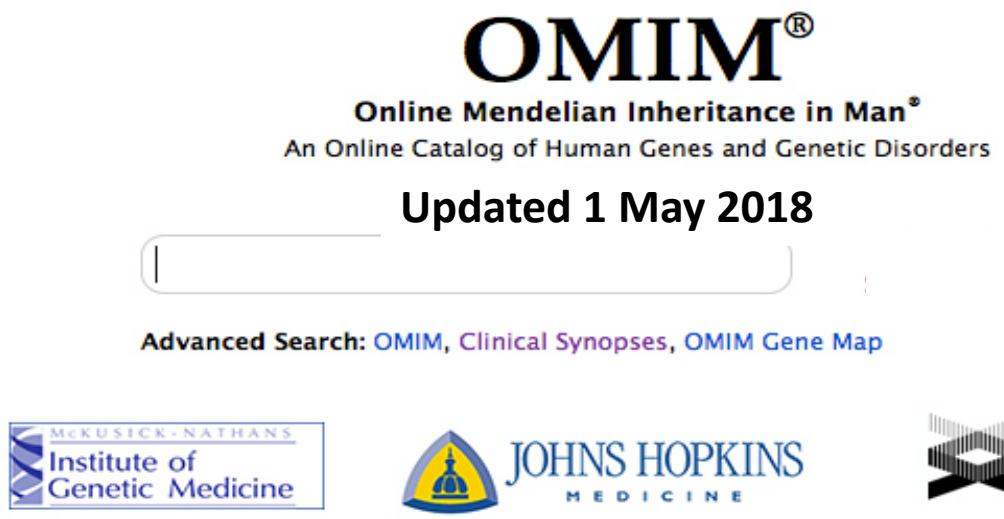


Data directly from submitted quarterly reports

Shalini N Janghani
Donna M. Muzny
Corinne Boehm

Mendelian disease: current scorecard

OMIM.org



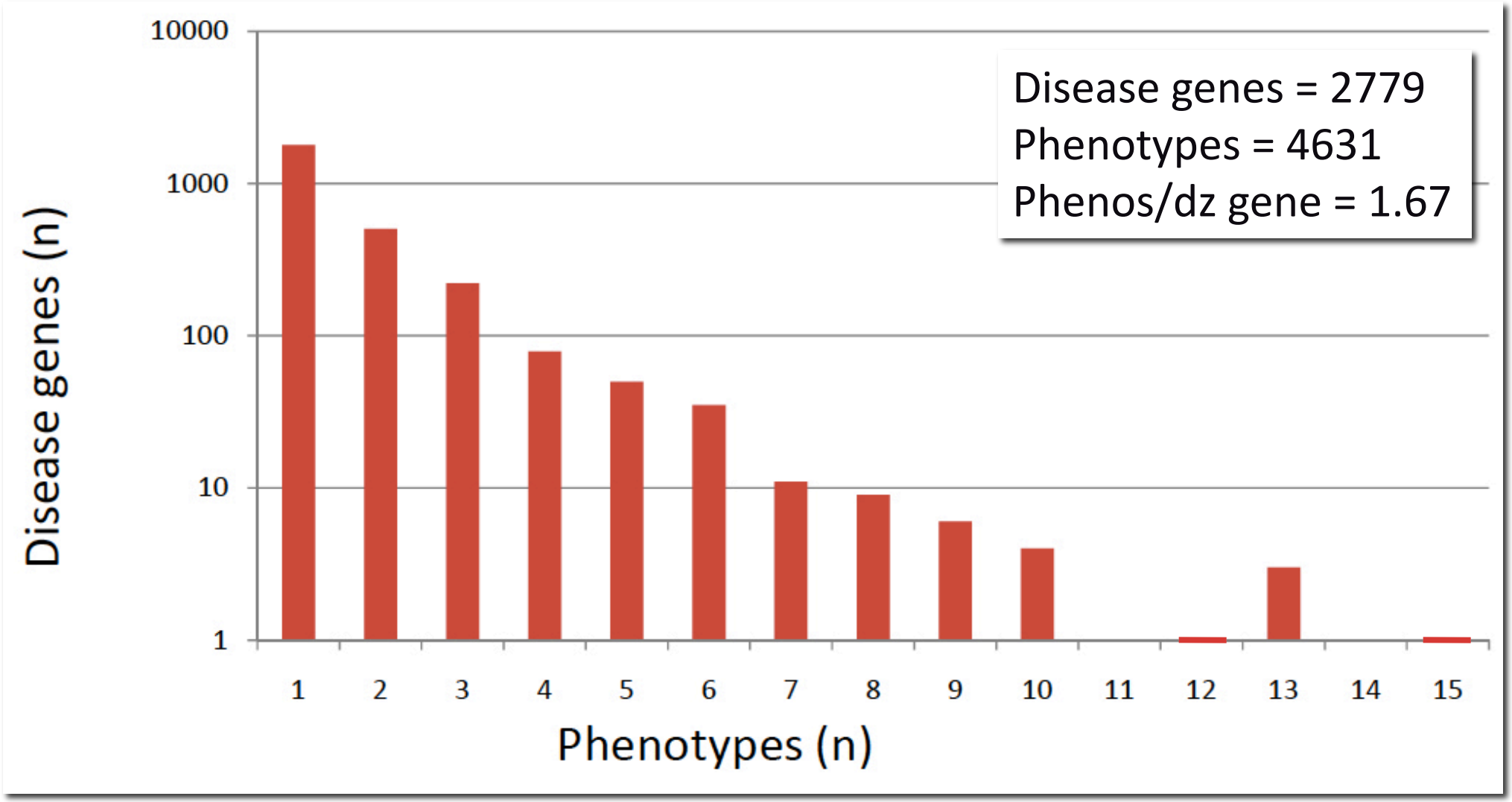
- Mendelian phenotypes ~8,500
- Genes with phenotypes ~3,894 (~19% of total)
- Explained phenotypes ~6,187
- Unexplained phenotypes ~2,500

~300 new phenotypes/yr

Some lessons learned

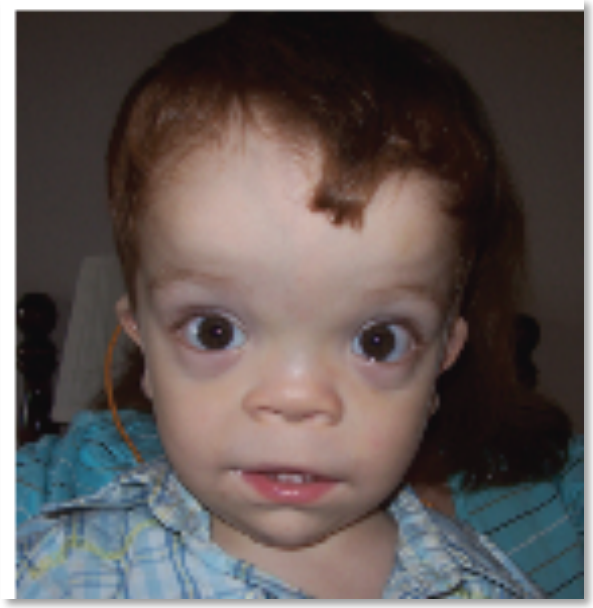
- Heterogeneity extensive
  - Allelic often with different phenotypes
  - Locus
- Atypical phenotypes - Multi-Mendels
- Genome/epigenome interactions
- Penetrance

*Allelic heterogeneity and the Phenotype/Gene relationship**



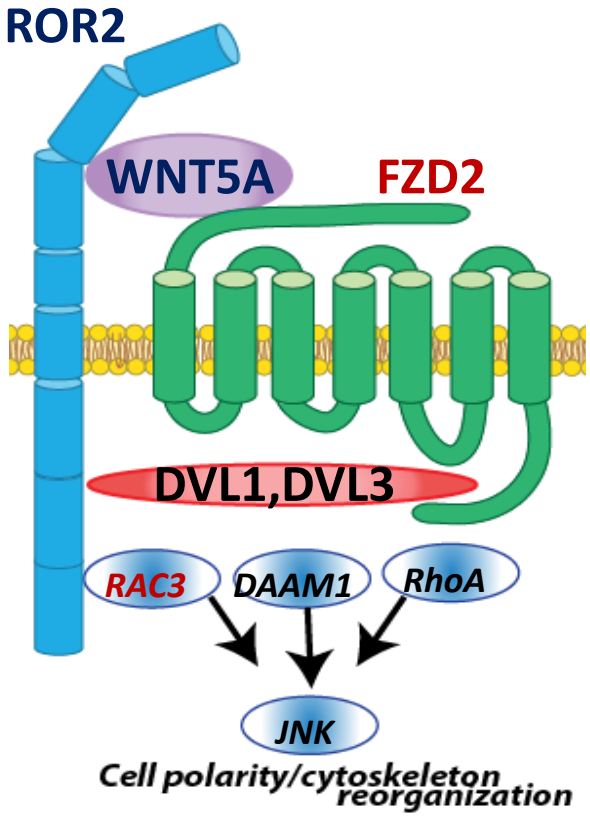
* OMIM

Locus heterogeneity: Robinow syndrome and the Wnt-PCP pathway (Lupski et al.)



BHCMG
Internal Robinow database

Robinow Gene	Contribution
ROR2-recessive	3/34: 9%
WNT5A	1/34: 3%
DVL1	**9/34: 26%**
DVL3	**6/34: 18%**
FZD2	**5/34: 15%**
Gene in differential	**4/34: 12%**



	Gene	Role in PCP pathway	Clinical evidence
Robinow-associated genes	*WNT5A*	Noncanonical Wnt ligand	Person *et al. Dev Dyn*. (2010)
	ROR2	Co-receptor for WNT5A ligand	Afzal *et al. Nat. Genet*. (2000)
	DVL1	Mediates canonical & noncanonical signals	White *et al. Am J Hum Genet.* (2015)
	DVL3	Mediates canonical & noncanonical signals	White *et al. Am J Hum Genet*. (2016)
	FZD2	Co-receptor for WNT5A ligand	5 families (current)
	RAC3	Downstream GTPase effector	1 *de novo* variant identified

Multi-Mendels

Recognition informs diagnosis, treatment, recurrence risk

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

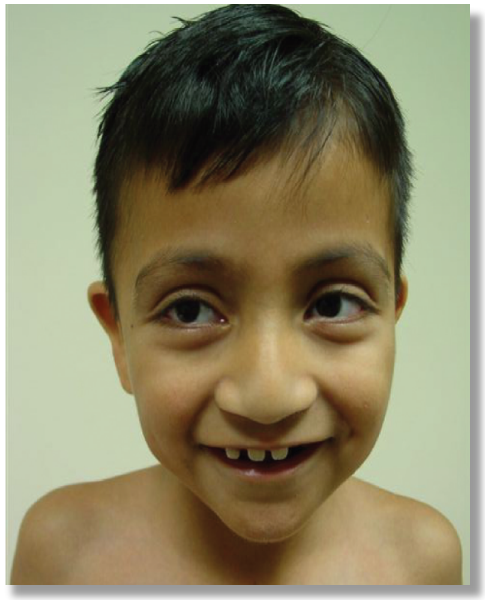
Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation

Jennifer E. Posey, M.D., Ph.D., Tamar Harel, M.D., Ph.D., Pengfei Liu, Ph.D., Jill A. Rosenfeld, M.S., Regis A. James, Ph.D., Zeynep H. Coban Akdemir, Ph.D., Magdalena Walkiewicz, Ph.D., Weimin Bi, Ph.D., Rui Xiao, Ph.D., Yan Ding, M.D., Fan Xia, Ph.D., Arthur L. Beaudet, M.D., Donna M. Muzny, M.S., Richard A. Gibbs, Ph.D., Eric Boerwinkle, Ph.D., Christine M. Eng, M.D., V. Reid Sutton, M.D., Chad A. Shaw, Ph.D., Sharon E. Plon, M.D., Ph.D., Yaping Yang, Ph.D., and James R. Lupski, M.D., Ph.D., D.Sc.

2017

Jennifer Posey

Epigenome Patterns in Kabuki Syndrome *



- Kabuki syndrome
  - ID, growth retardation, dysmorphic features
  - *KMT2D* (~65%), *KDM6A* (4%)
- Sequencing in 27 KS probands
  - 12 with variants in *KMT2D*
  - 6 with likely pathologic variants in other genes incl. *KMT2A*, *HCFC1*, *ZBTB24*, *KMT2B*, *DNMT3B*

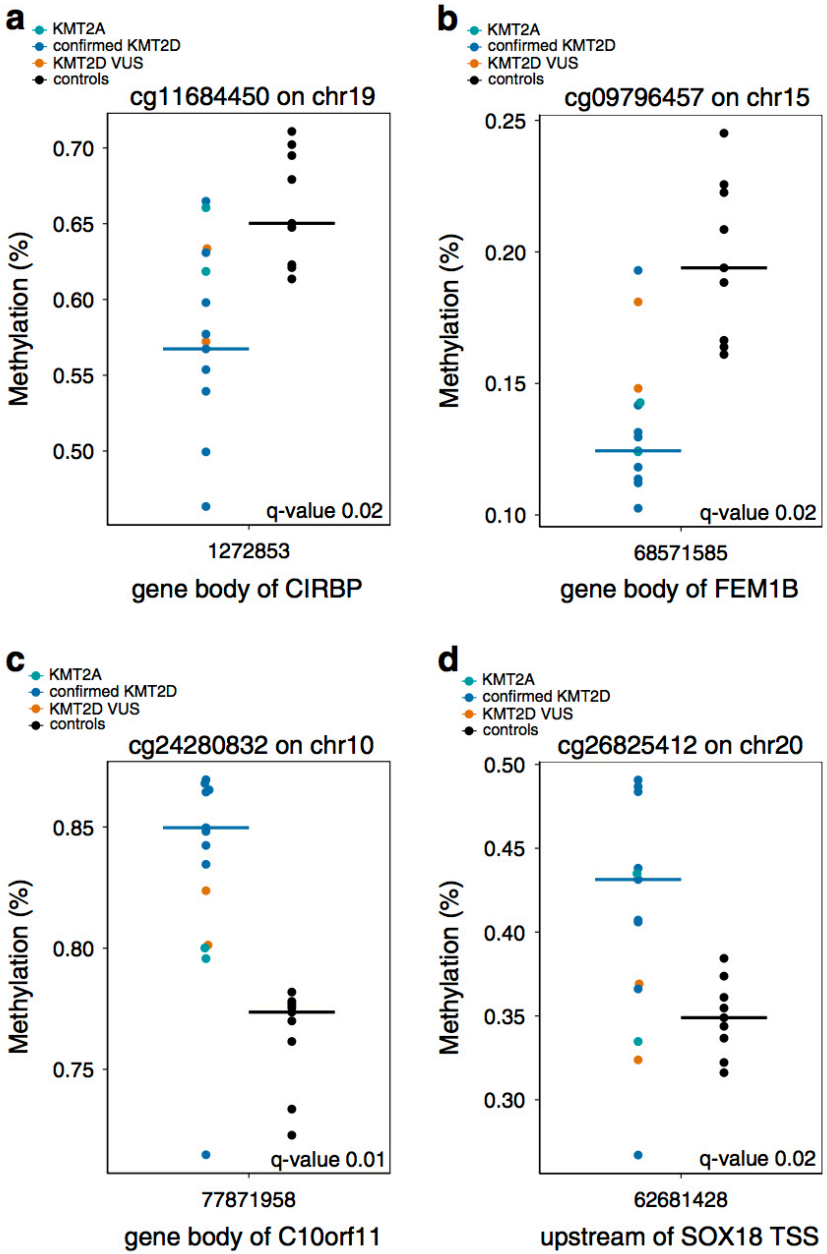
* Sobreira, ….Bjornsson, EJHG, 2017

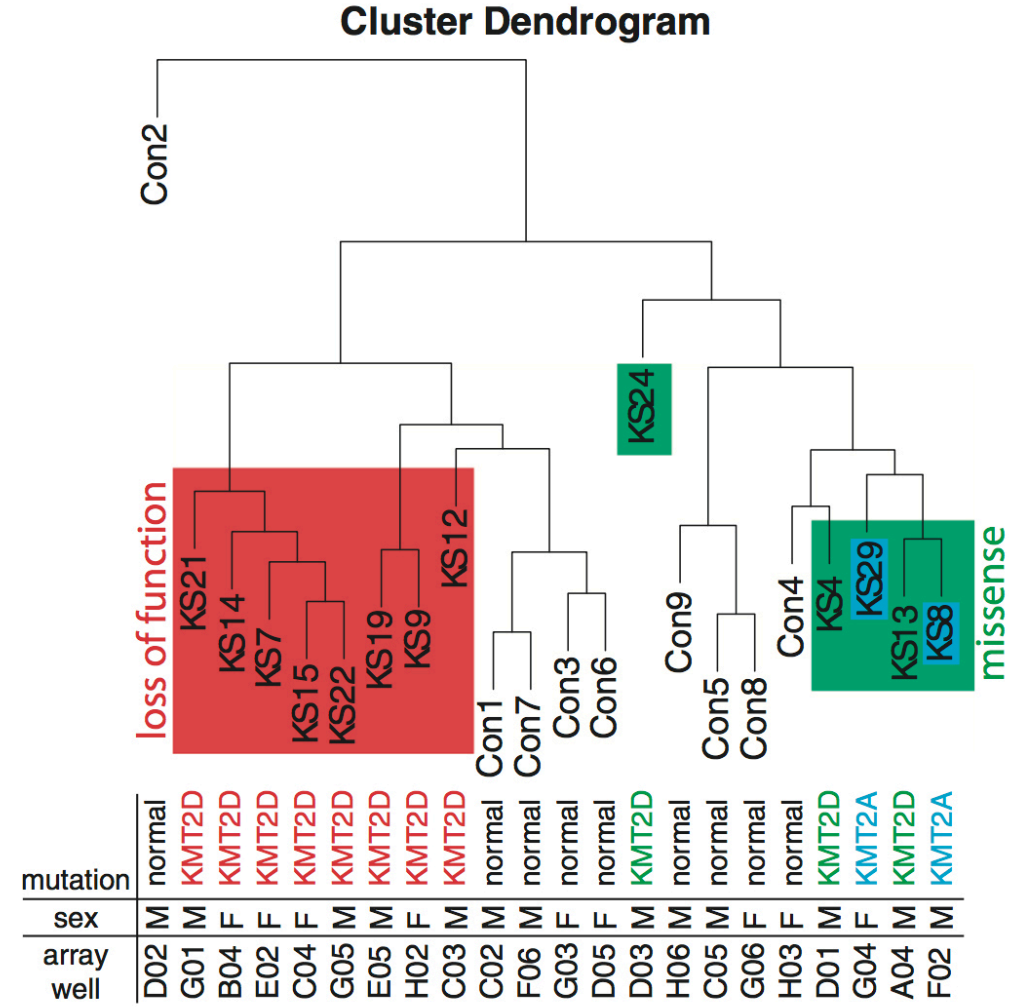
*How do histone alterations produce disease in KS? **

- Examine DNA methylation patterns in 9 KS probands and 9 age, sex matched controls to identify differentially methylated regions (DMRs)
- Whole blood DNA samples
- Infinium HumanMethylation 450 Bead Chip

* Sobreira, ….Bjornsson, EJHG, 2017

*DNA methylation patterns in KS? **





* Sobreira, ….Bjornsson, EJHG, 2017

*How do histone alterations produce disease in KS? **

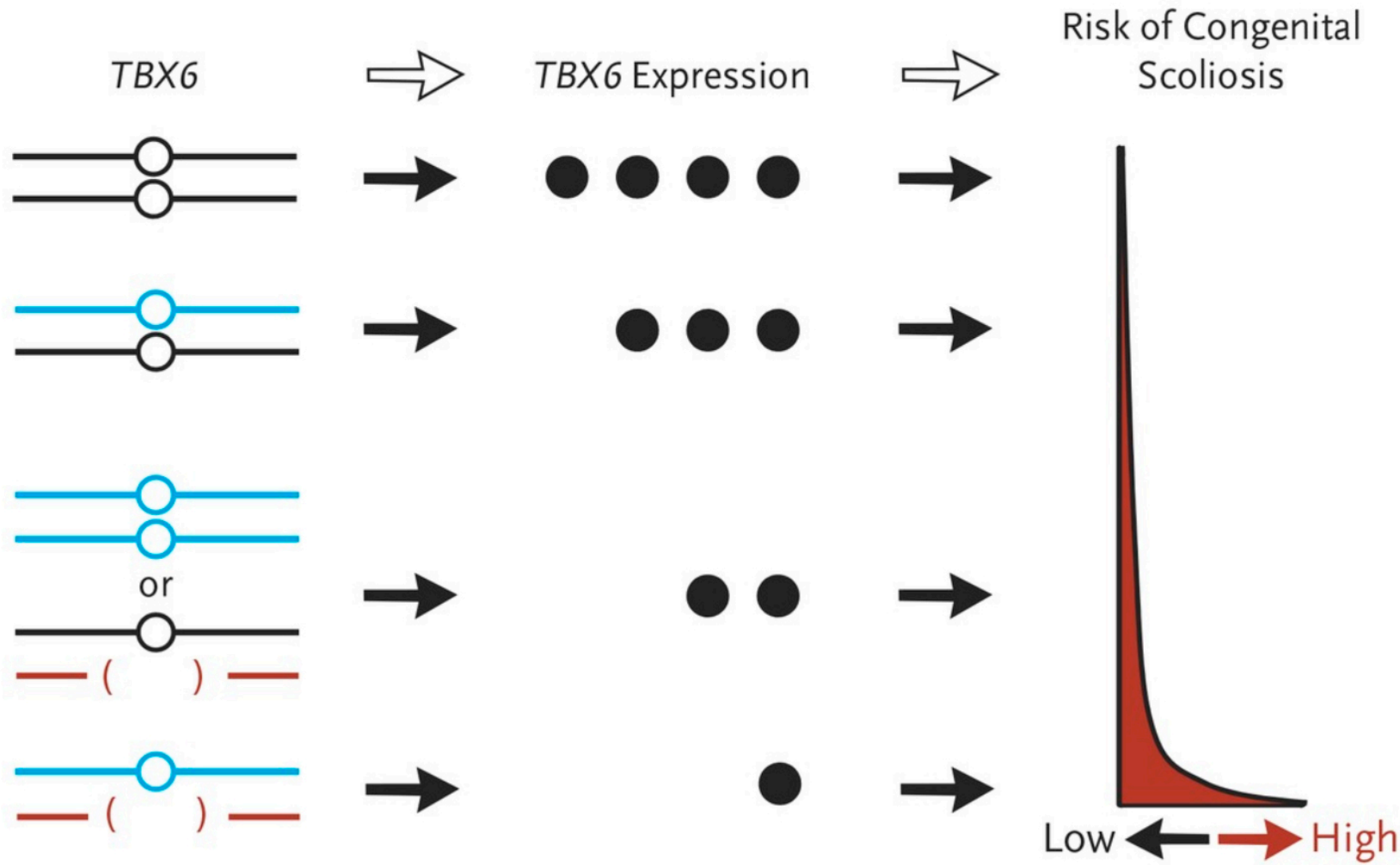
- Alterations in patterns of DNA methylation secondary to defects in genes encoding histone modifying enzymes
- Suggests “cross talk” between epigenome changes in histones and DNA methylation
- Patterns similar in KS secondary to KMT2D, KDM6A and to KMT2A (Wiedermann-Steiner) suggesting similar phenotype derives from similar epigenetic pattern
- Results point to a set of downstream genes that may be important for pathogenesis

* Sobreira, ….Bjornsson, EJHG, 2017

TBX6 Null Variants and a Common Hypomorphic Allele in Congenital Scoliosis

Nan Wu, M.D., Xuan Ming, B.S., Jianqiu Xiao, Ph.D., Zhihong Wu, M.D., Xiaoli Chen, M.D., Ph.D., Marwan Shinawi, M.D., Yiping Shen, Ph.D., Guangju Yu, B.S., Jiaqi Liu, M.D., Hua Xie, M.D., Zoran S. Gucev, M.D., Ph.D., Sen Liu, M.D., et al.

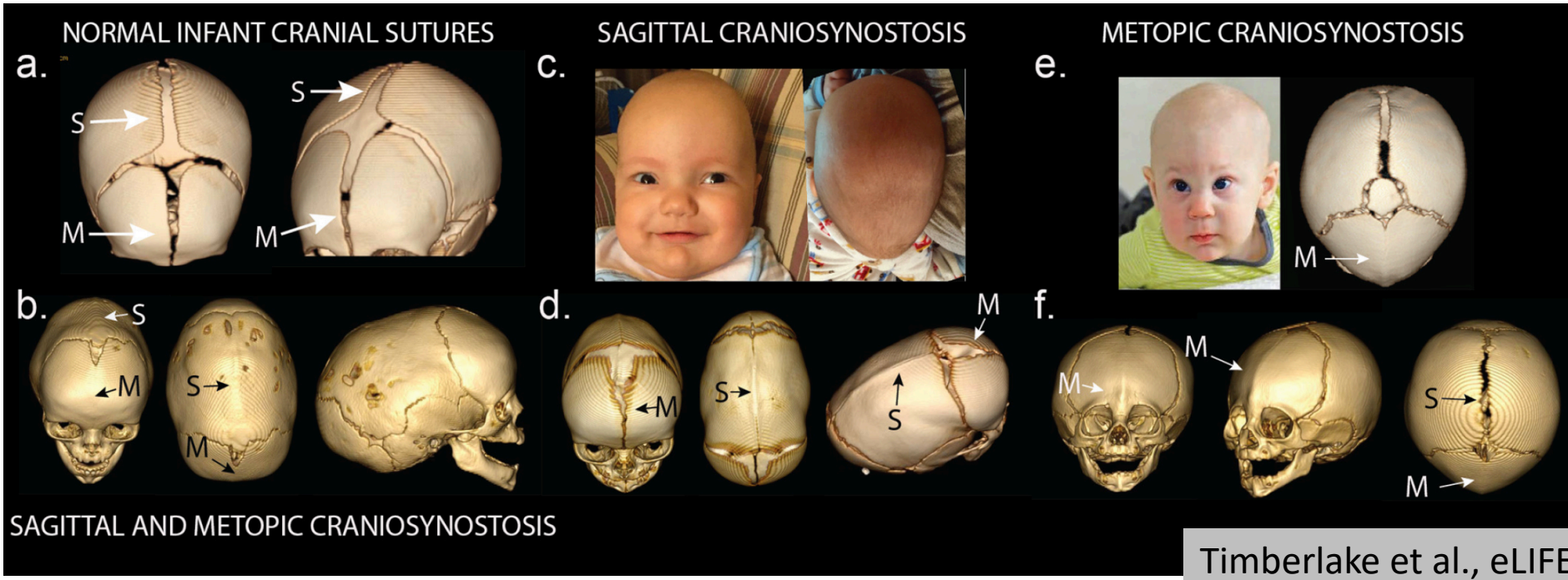
NEJM, 2015



Two locus inheritance of non-syndromic midline craniosynostosis via rare *SMAD6* and common *BMP2* alleles

Yale CMG

Andrew T Timberlake[1,2,3], Jungmin Choi[1,2], Samir Zaidi[1,2], Qiongshi Lu[4], Carol Nelson-Williams[1,2], Eric D Brooks[3], Kaya Bilguvar[1,5], Irina Tikhonova[5], Shrikant Mane[1,5], Jenny F Yang[3], Rajendra Sawh-Martinez[3], Sarah Persing[3], Elizabeth G Zellner[3], Erin Loring[1,2,5], Carolyn Chuang[3], Amy Galm[6], Peter W Hashim[3], Derek M Steinbacher[3], Michael L DiLuna[7], Charles C Duncan[7], Kevin A Pelphrey[8], Hongyu Zhao[4], John A Persing[3], Richard P Lifton[1,2,5,9*]

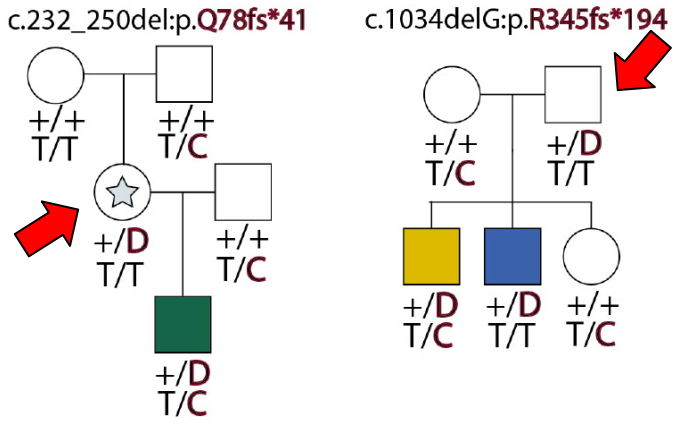


Timberlake et al., eLIFE, 2016

*Craniosynostosis: Two locus model**

- WES of a cohort of 191 (132 trios, 59 additional probands)
- 13 (7%) rare damaging de novo or transmitted variants in *SMAD6*
- *SMAD6* variants showed ~60% incomplete penetrance
- Previous GWAS identified common variant (allele frequency of 0.35) 345 kb downstream of BMP2

SMAD6/BMP2	Synostosis +	Synostosis -
SMAD6 +/BMP2 risk +	14	0
SMAD6 +/BMP2 risk -	3	13
SMAD6 -/BMP2 risk +	0	18



Timberlake et al., eLIFE, 2016

Phenotype risk scores identify patients with unrecognized Mendelian disease patterns

Lisa Bastarache,[1] Jacob J. Hughey,[1] Scott Hebbring,[2] Joy Marlo,[1] Wanke Zhao,[3] Wanting T. Ho,[3] Sara L. Van Driest,[4,5] Tracy L. McGregor,[5] Jonathan D. Mosley,[4] Quinn S. Wells,[4,6] Michael Temple,[1] Andrea H. Ramirez,[4] Robert Carroll,[1] Travis Osterman,[1,4] Todd Edwards,[4] Douglas Ruderfer,[4] Digna R. Velez Edwards,[7] Rizwan Hamid,[5] Joy Cogan,[5] Andrew Glazer,[4] Wei-Qi Wei,[1] QiPing Feng,[6] Murray Brilliant,[2] Zhizhuang J. Zhao,[3] Nancy J. Cox,[4] Dan M. Roden,[1,4,6] Joshua C. Denny[1,4]*

Science, 2018

- Phenotype risk scores (PheRSs) for > 1200 Mendelian traits from EHR
- Map back to ~21,000 genotyped individuals at Vanderbilt
- Identify associations with rare variants suggesting candidate responsible gene and variants

Thanks for your attention!

Acknowledgements:

CMGs and especially BHCMG colleagues