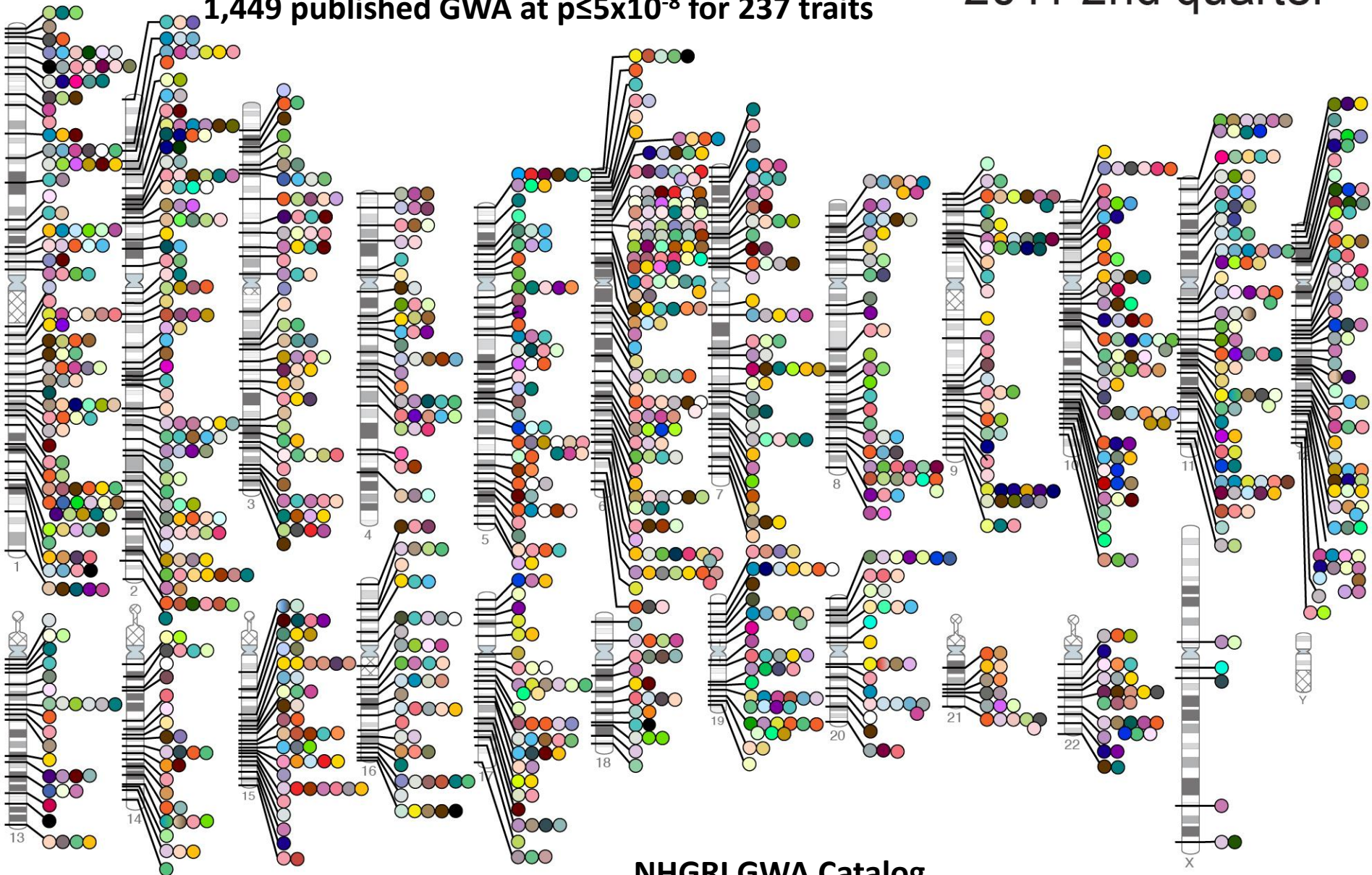
Frontiers in Personalized Medicine

- PW-GW-AS
- DNA sequencing
- Reverse human genetics

Published Genome-Wide Associations through 06/2011,
1,449 published GWA at $p \leq 5 \times 10^{-8}$ for 237 traits

2011 2nd quarter

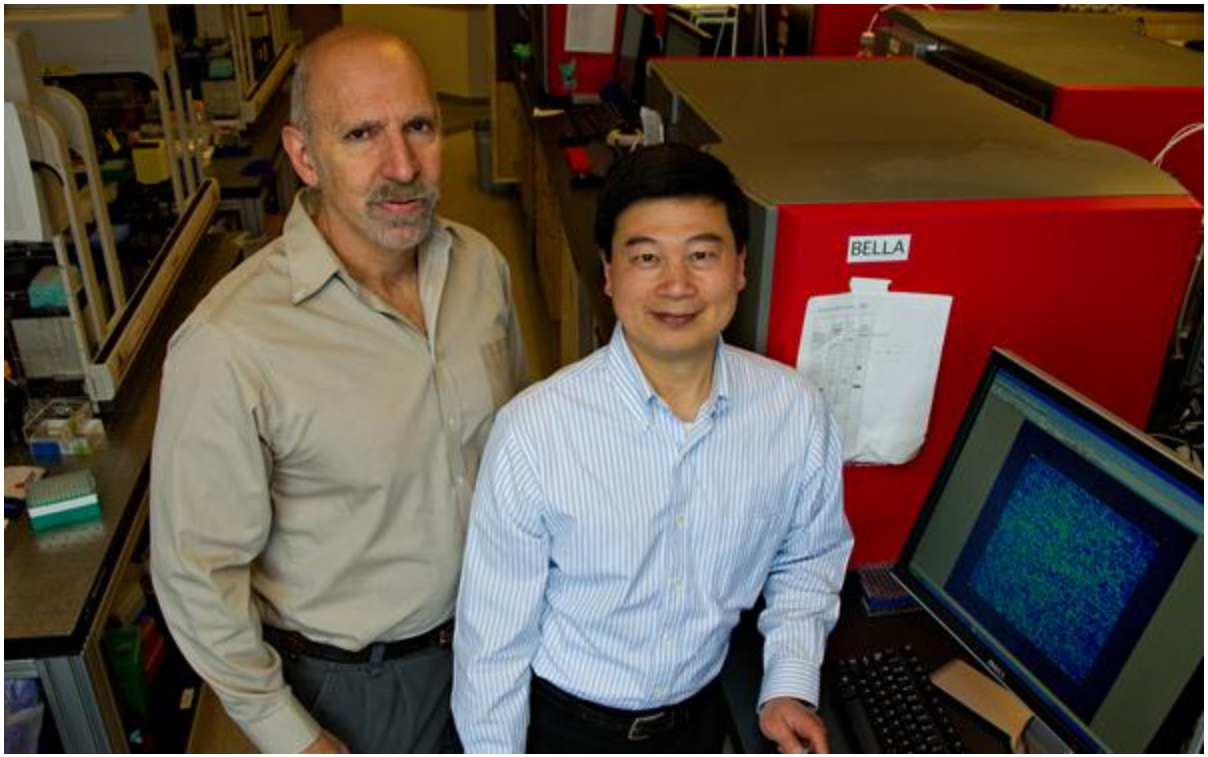


NHGRI GWA Catalog
www.genome.gov/GWAStudies

GWAS examples

Date Added to Catalog (since 11/25/08)	First Author/Date/ Journal/Study	Disease/Trait	Initial Sample Size	Replication Sample Size	Region	Reported Gene(s)	Mapped Gene(s)	Strongest SNP-Risk Allele	
05/25/12	Taal HR April 15, 2012 *Nat Genet* Common variants at 12q15 and 12q24 are associated with infant head circumference.	Head circumference (infant)	10,768 European ancestry infants	8,321 European ancestry infants	12q14.3 12q24.31 17q21.31	*HMGA2* *SBNO1* *CRHR1, MAPT*	HMGA2 SBNO1 C17orf69 - CRHR1	rs1042725-T rs7980687-A rs11655470-T	UTI intr int
05/25/12	Bhatnagar R April 12, 2012 *Oral Oncol* Genome-wide disease association study in chewing tobacco associated oral cancers.	Oral cancers (chewing tobacco related)	55 South Asian ancestry cases, 92 South Asian ancestry controls	NR	NS	*NS*	NS	NS	NS
05/25/12	Jylhava J April 12, 2012 *PLoS One* A genome-wide association study identifies UGT1A1 as a regulator of serum cell-free DNA in young adults: The Cardiovascular Risk in Young Finns Study.	Circulating cell-free DNA	1,841 individuals	NR	2q37.1	*UGT1A1*	UGT1A10; UGT1A8; UGT1A7; UGT1A6; UGT1A5; UGT1A9; UGT1A4; UGT1A1; UGT1A3	rs6742078-T	intr
05/25/12	Burri A April 11, 2012 *PLoS One* A genome-wide association study of female sexual dysfunction.	Sexual dysfunction (female)	1,104 European ancestry twins	NR	6q14.3 10p11.22 22q12.3	*Intergenic* *EPC1* *PVALB*	RPL7P27 - HTR1E EPC1 PVALB	rs13202860-A rs2370759-G rs4820255-C	int intr intr

UCSF Kaiser-Permanente
N. Risch and P. Y. Kwok



UCSF Kaiser-Permanente

- 100,000 patients
- Genotype and telomere lengths
- ***many*** health traits

23andme

research surveys

23andWe begins with you. Learn about yourself while contributing to research.

Related topics: About 23andWe, Research Initiatives, 23andWe FAQ

Featured Research Survey:

Reading the Mind in the Eyes

About this survey | May 2012

This test is a measure of adult "mentalising", the ability to sense other people's emotions based on their facial expressions, and is believed to be an important component of empathy. Find out how you score!

start survey

Click on a survey to get started or to view your results

Your Health Profile

Help us personalize your 23andMe experience by taking 3-5 minutes to answer a few questions about yourself.

Published: June 2011

resume survey

Longevity

About this survey | Published: December 2009

resume survey

Physical Features

About this survey | Published: July 2010

start survey

Headaches

About this survey | Published: October 2009

start survey

Caffeine Usage

About this survey | Published: March 2011

start survey

PLoS Genet. 2010 Jun 24;6(6):e1000993.

Web-based, participant-driven studies yield novel genetic associations for common traits.

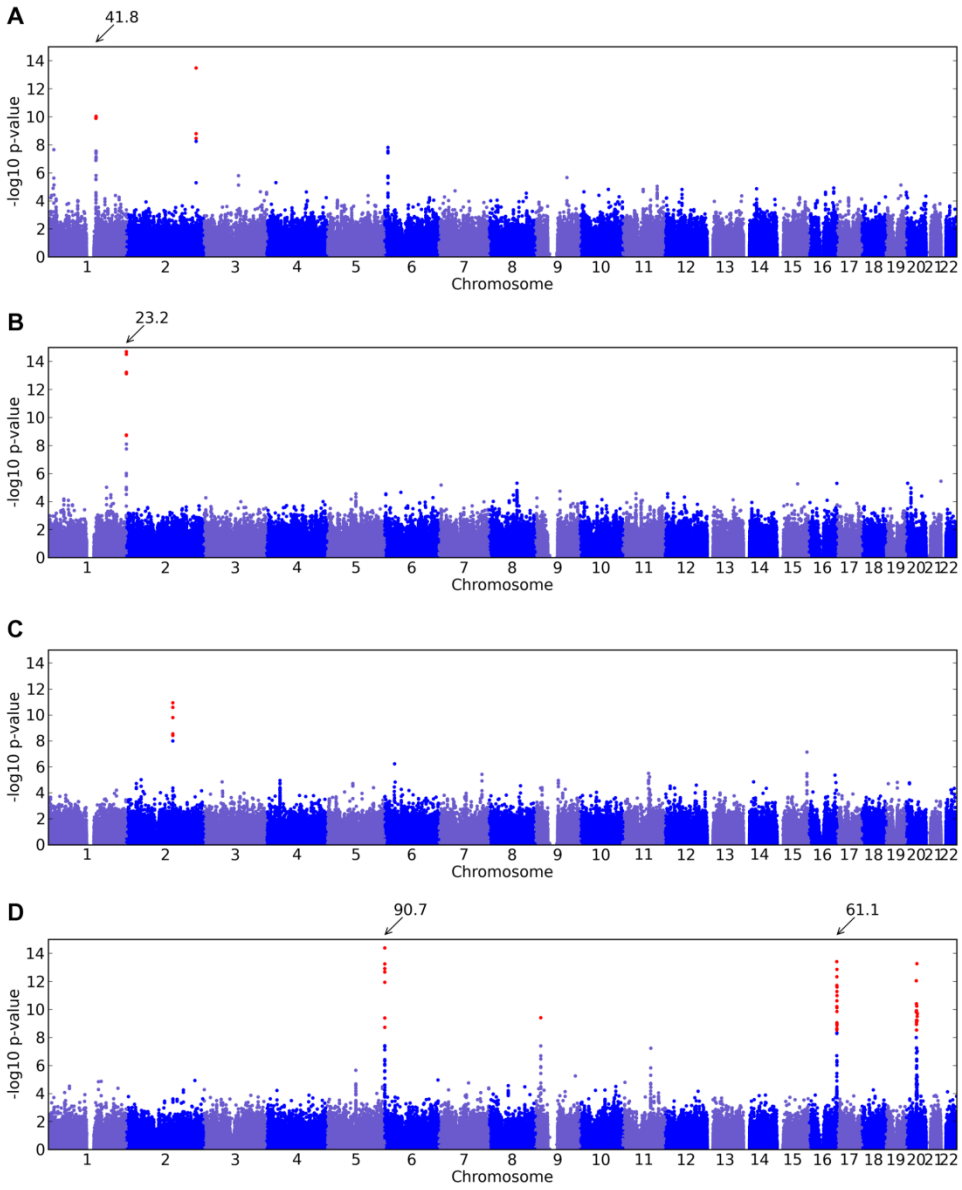
Eriksson N, Macpherson JM, Tung JY, Hon LS, Naughton B, Saxonov S, Avey L, Wojcicki A, Pe'er I, Mountain J.

23andMe, Mountain View, California, United States of America. nick@23andme.com

Phenotype	Size	Top hit	# Loci	Loci
Eye color, blue to brown	4402	>300	6	OCA2, SLC24A4, IRF4, SLC45A2, TYR, (TYRP1)
Freckles	4405	90.68	5	*IRF4*, MC1R, ASIP, **BNC2**, (TYR)
Hair color, blond to brown	3044	87.07	5	OCA2, IRF4, SLC45A2, SLC24A4, MC1R
Red hair	4422	86.28	2	MC1R, ASIP
Eye color, green/blue	2826	51.52	3	OCA2, SLC24A4, TYR
Hair curl	5385	41.80	3	TCHH, **WNT10A**, (**OFCC1**)
Asparagus anosmia	4742	23.18	1	**OR2M7**
Photic sneeze reflex	5390	10.93	2	**2q22.3**, (**NR2F2**)
Footedness	3079	6.75	0	
Attached earlobes	3915	6.59	0	
Morningness	4264	6.50	0	
Braces	4011	6.45	0	
Optimism	3936	6.29	0	
Astigmatism	7701	6.17	0	
Prefer sweet snacks	3100	6.07	0	
Wisdom teeth	3983	5.89	0	
Cavities	5366	5.81	0	
Glasses	5386	5.76	0	
Ocular dominance	3126	5.70	0	
Hand-clasp	5256	5.66	0	
Motion sickness	2987	5.55	0	
Handedness	4268	5.30	0	

Loci are called significant if they contain a SNP with $-\log_{10}$ p-value over 8.4 and suggestively significant if they have one between 7.1 and 8.4. Loci that were not previously associated with the given trait are in bold, those where we report a remapping of a previous hit are in italics, and suggestively significant loci are in parentheses. Size refers to the total number of individuals in the study. The ''top hit'' refers to the largest $-\log_{10}$ p-value for the given trait. The genomic control inflation factor, λ, [59] was between 1.0 and 1.02 for all studies. For more details, including λ, numbers of cases and controls, and covariates used in the analyses, see Supplementary Table 1 of Text S6.

doi:10.1371/journal.pgen.1000993.t001



Hair Curl

Asparagus smell

Photic sneeze

freckling

Research Discoveries at 23andme

Getting Attached to Earlobe Genetics

✔ **Thanks!** You took a survey that fueled this discovery.

view discovery

Understanding the Genetics of Freckling

● **Thank you for taking the survey in time for our first publication!** You are a Research Pioneer.

view discovery

Combing Through the Science of Hair Curl

● **Thank you for taking the survey in time for our first publication!** You are a Research Pioneer.

view discovery

Blonde on Blonder

✔ **Thanks!** You took a survey that fueled this discovery.

view discovery

Are We There Yet? Clues to Motion Sickness

✔ **Thanks!** You took a survey that fueled this discovery.

view discovery

Don't It Make Your Brown Eyes Blue

✔ **Thanks!** You took a survey that fueled this discovery.

view discovery

Genes and Geography

✔ **Thanks!** You took a survey that fueled this discovery.

view discovery

The ACHOO Syndrome

● **Thank you for taking the survey in time for our first publication!** You are a Research Pioneer.

view discovery

Eeny, Meeny, Miny, Moe, What's Your Biggest Toe?

✔ **Thanks!** You took a survey that fueled this discovery.

view discovery

Frontiers in Personalized Medicine

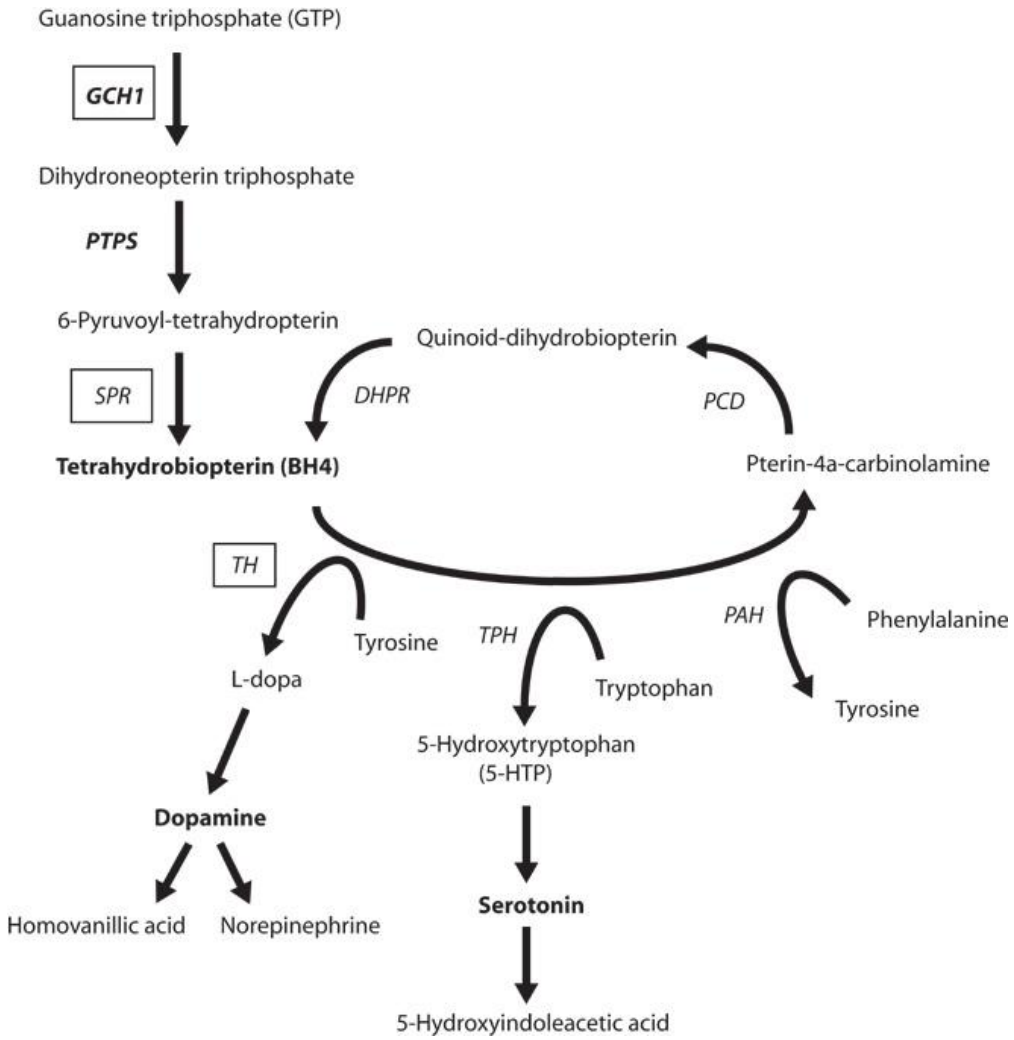
- PW-GW-AS
- DNA sequencing
- Reverse human genetics

Dopa (3,4-dihydroxyphenylalanine)–responsive dystonia (DRD).

- hereditary dystonia with marked diurnal variation.
- begins in childhood.
- associated with mutations in genes encoding guanosine 5’-triphosphate (GTP) cyclohydrolase (*GCH1*), tyrosine hydroxylase (*TH*), and sepiapterin reductase (*SPR*).

Bainbridge, M.N. et al. Whole-genome sequencing for optimized patient management. Sci. Transl. Med. 3, 87re3 (2011).

Fig. 1 Metabolic pathways of neurotransmitter production.



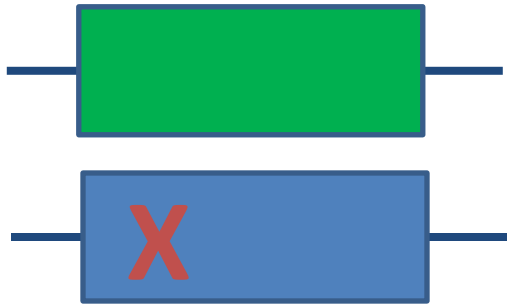
Bainbridge M N et al. Sci Transl Med 2011;3:87re3-87re3

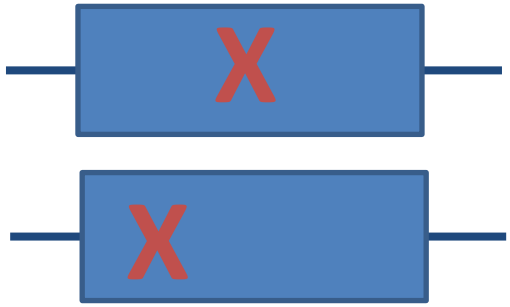
Clinical history

- fraternal twin pair.
- diagnosed with DRD at age 5.
- L-dopa was found to alleviate the clinical symptoms of dystonia in one twin.
- no identified deleterious variants in the *TH* or *GCH1* genes.
- Sequencing of the *SPR* gene was not available.
- high-throughput sequencing used to interrogate the whole genomes of the male and female twins.

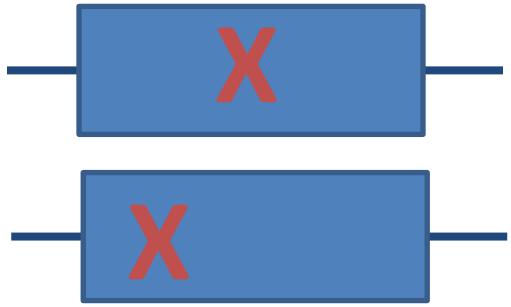
Mother

Father





Affected

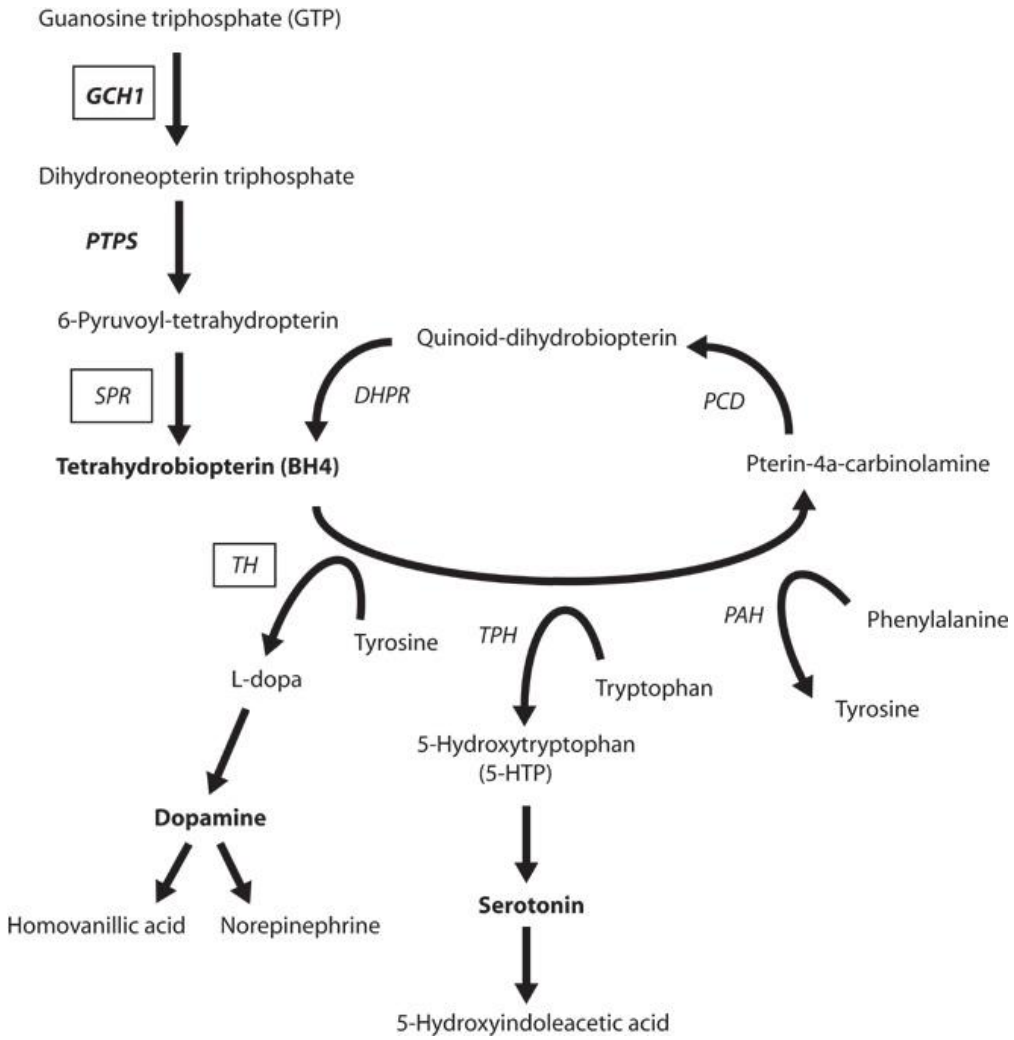


Affected

Results

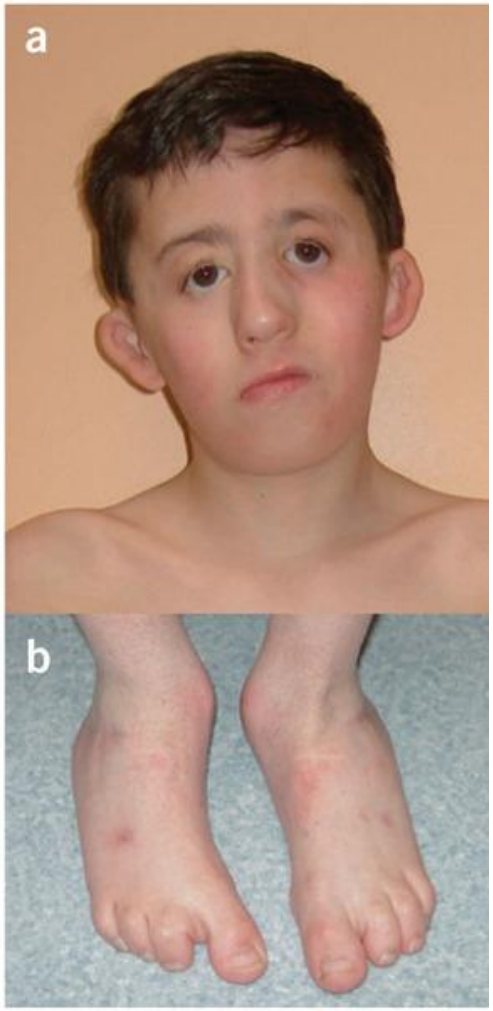
- Three genes found with rare compound heterozygous mutations.
  - *ZNF544* encodes a computationally predicted zinc finger protein with no known function or targets
  - *C2orf16.*
  - *SPR* encoding sepiapterin reductase.
- *SPR* mutations seen in two previous families with DRD.
- recommended treatment of DRD caused by SPR mutations is with both the dopamine precursor L-dopa, which the twins were already prescribed, and the serotonin precursor 5-hydroxytryptophan (5-HTP), which the twins were not receiving.
- The male DRD patient reported improved focus in school, as well as improved coordination in athletics. Further, the male showed reduced drooling and hand tremor, and objective evidence for the latter was provided by serial handwriting samples.
- The female twin reported reduced frequency of laryngeal spasms, improved sleep and focus, and improved tolerance for exercise and was able to resume participation in sports after a 14-month absence. In the female DRD patient, there were also reduced choreiform movements of the tongue by objective physical examination.

Fig. 1 Metabolic pathways of neurotransmitter production.



Bainbridge M N et al. Sci Transl Med 2011;3:87re3-87re3

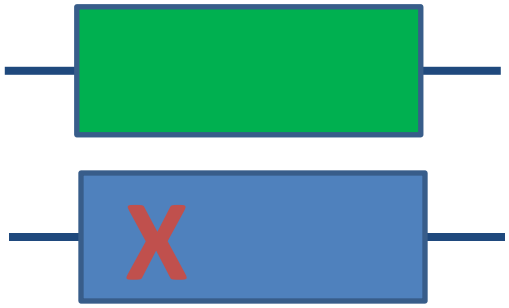
Miller Syndrome

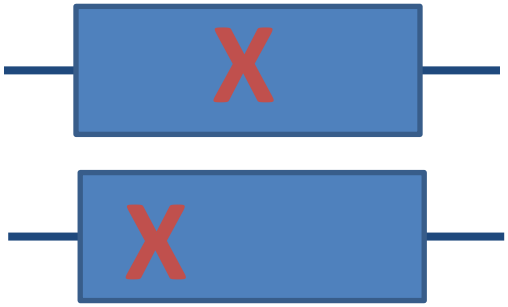


Ng, S.B. et al. Exome sequencing identifies the cause of a Mendelian disorder. Nat. Genet. 42, 30–35 (2010).

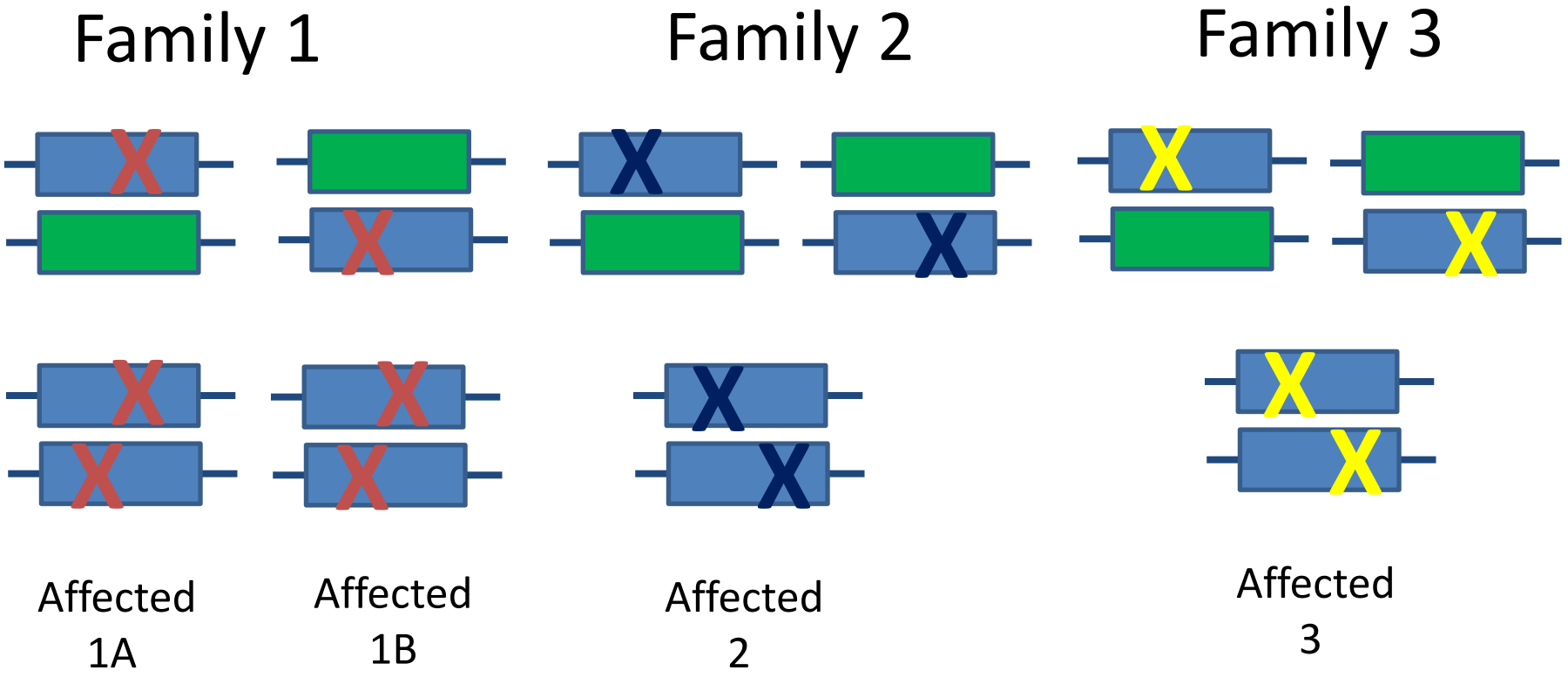
Mother

Father



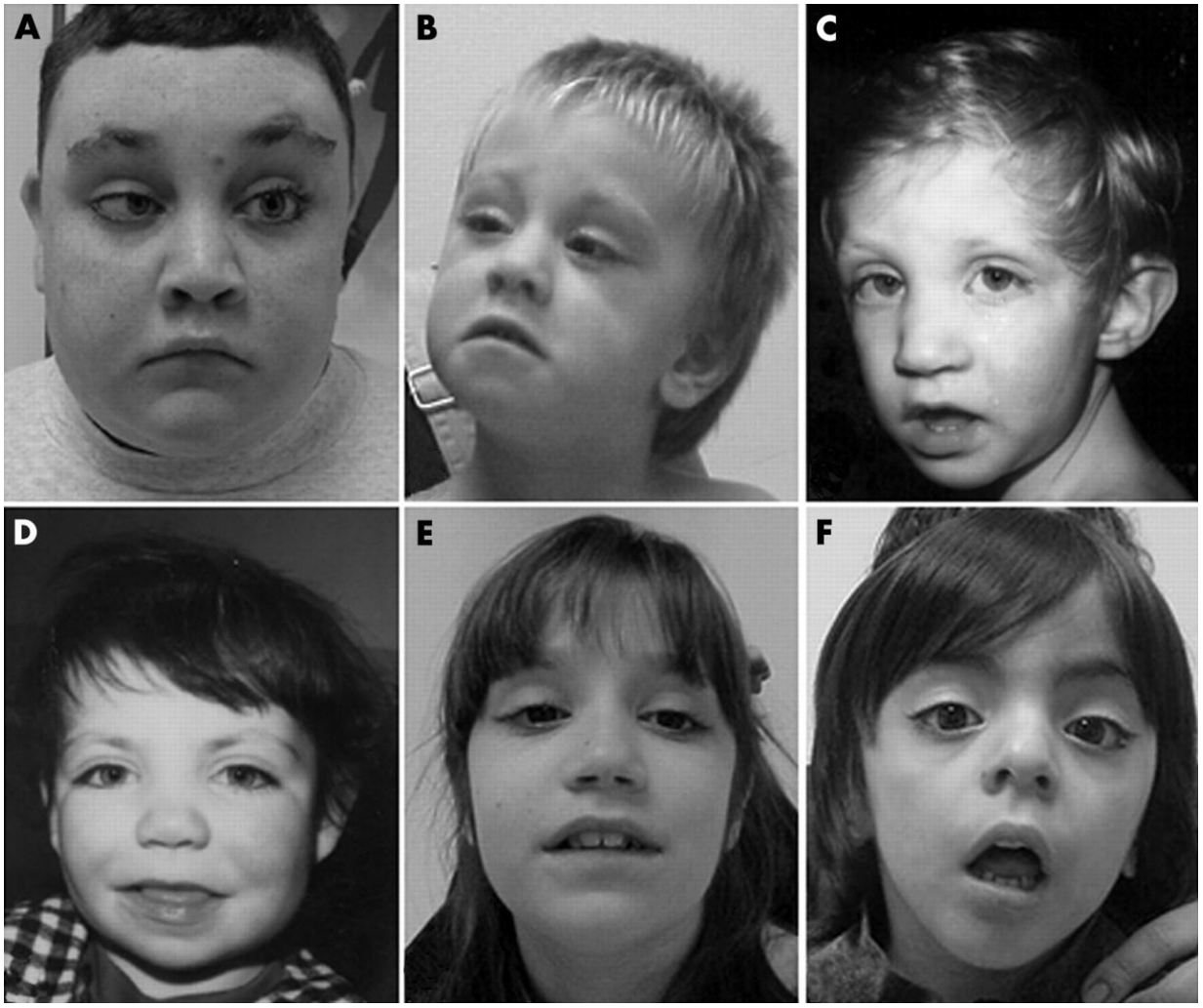


Affected


Family 1
Family 2
Family 3
Affected 1A
Affected 1B
Affected 2
Affected 3

- Non-synonymous and Rare (~450/person)
- Two variants in the same gene (30/person)
- Same gene in 1A and 1B = 9 genes
- Same gene in 1A, 1B, 2 and 3 = *DHODH*
- dihydroorotate dehydrogenase
- Validate by sequence gene in 3 more cases.

Kabuki Syndrome



Ng, S.B. *et al*. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. *Nat. Genet.* **42**, 790–793 (2010).

Kabuki syndrome

- Kabuki syndrome is a rare, multiple malformation disorder characterized by a distinctive facial appearance, cardiac anomalies, skeletal abnormalities, immunological defects and mild to moderate mental retardation.
- Six cases of parent-child transmission.
- Autosomal dominant disorder.

Mother

Father

Affected

Strategy

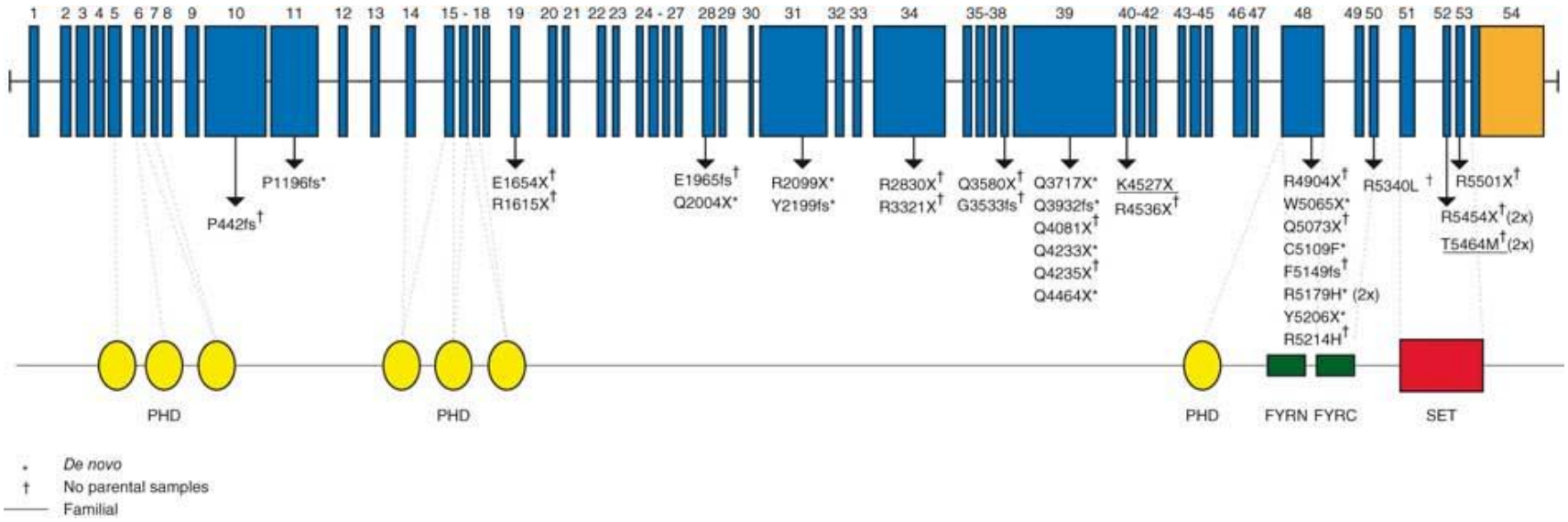
- Look for rare, loss-of-function protein coding changes in strongest patient
- See if find mutations in same gene in the second strongest patient, then third, then fourth, etc.
- After 4 patients, only one gene is common. MLL2
- Retrospectively, see that MLL2 has suggestive mutations in 5 more patients. Ultimately, 9/10 patients had mutations in MLL2.
- For validation, found 26/43 patients had mutations in MLL2. 0/190 controls had mutations.

Table 2: Number of genes common in sequential analysis of phenotypically ranked individuals

Sequential analysis	1	+2	+3	+4	+5	+6	+7	+8	+9	+10
NS/SS/I	5,282	3,850	3,250	2,354	2,028	1,899	1,772	1,686	1,600	1,459
Not in dbSNP129 or 1000 Genomes	687	214	145	84	63	54	42	40	39	34
Not in control exomes	675	134	50	26	13	13	8	5	4	2
Not in either	467	89	34	18	9	8	4	4	3	1
Is loss-of-function (nonsense/frameshift indel)	25	1	1	1	0	0	0	0	0	0

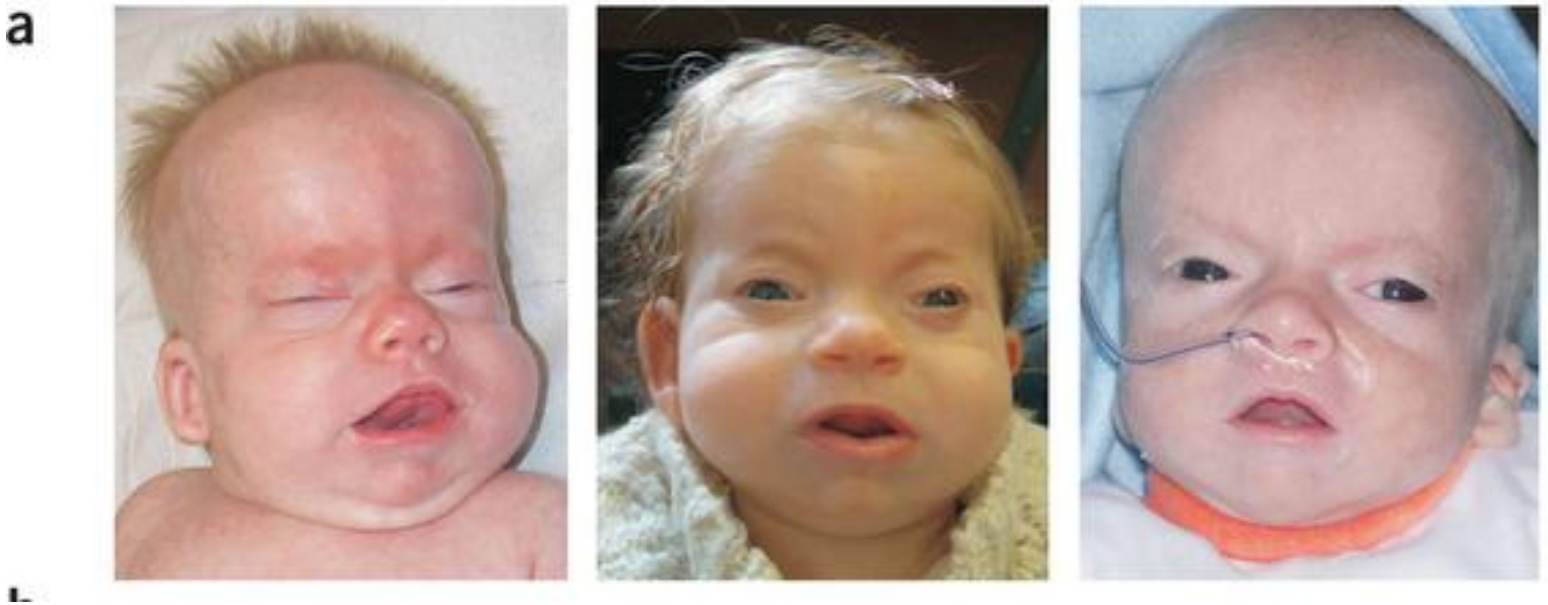
Variants were filtered as in **Table 1**. Exomes were added sequentially to the analysis by ranked phenotype; for example, column "+3" shows the number of genes at the intersection of the three top ranked cases (**Supplementary Fig. 1**). The gene with at least one NS/SS/I in all individuals is *MUC16*, which is very likely to be a false positive due to its extreme length (14,507 amino acids).

Genomic structure and allelic spectrum of *MLL2* mutations that cause Kabuki syndrome



The SET domain of MLL2 confers strong histone 3 lysine 4 methyltransferase activity and is important in the epigenetic control of active chromatin states.

Schinzel-Giedon syndrome



Hoischen, A. et al. De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. Nat. Genet. 42, 483–485 (2010).

Schinzel-Giedon syndrome

- Severe mental retardation, distinctive facial features, multiple congenital malformations (including skeletal abnormalities, genitourinary and renal malformations, and cardiac defects) and a higher-than-normal prevalence of tumors, notably neuroepithelial neoplasia.
- Sporadic, suggesting heterozygous *de novo* mutations in a single gene as the underlying mechanism.

Mother

Father

Affected

Strategy

- Look for rare, loss-of-function protein coding changes
- Only 1 gene shared in four patients – SETB1.
- In all cases, mutations occurred de novo in patients and were absent from parents.
- Validated in 8/9 additional patients.
- Gain-of-function effect or dominant-negative effect

Frontiers in Personalized Medicine

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- Reverse human genetics

Reverse Human Genetics

DRD sequencing: Results

- Three genes found with rare compound heterozygous mutations.
  - ***ZNF544* encodes a computationally predicted zinc finger protein with no known function or targets**
  - ***C2orf16.***
  - *SPR* encoding sepiapterin reductase.