Per quanto concerne i moderatori, relatori, formatori, tutor, docenti è richiesta dall'Accordo Stato-Regioni vigente apposita dichiarazione esplicita dell'interessato, di trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali relativi agli ultimi due anni dalla data dell'evento.
La documentazione deve essere disponibile presso il Provider e conservata per almeno 5 anni.

Dichiarazione sul Conflitto di Interessi

Il sottoscritto_____DAVIDE VECCHIO_____ in qualità di:

□ moderatore X docente □ relatore □ tutor

dell'evento "INDIVIDUAZIONE DEI DISTURBI DEL NEUROSVILUPPO 0-3 ANNI"

da tenersi per conto di **Biomedia srl Provider n. 148,**

ai sensi dell'Accordo Stato-Regione in materia di formazione continua nel settore "Salute" (Formazione ECM) vigente,

Dichiara

X che negli ultimi due anni NON ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

□ che negli ultimi due anni ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario (indicare quali):

_____ _____
_____ _____
_____ _____
_____ _____

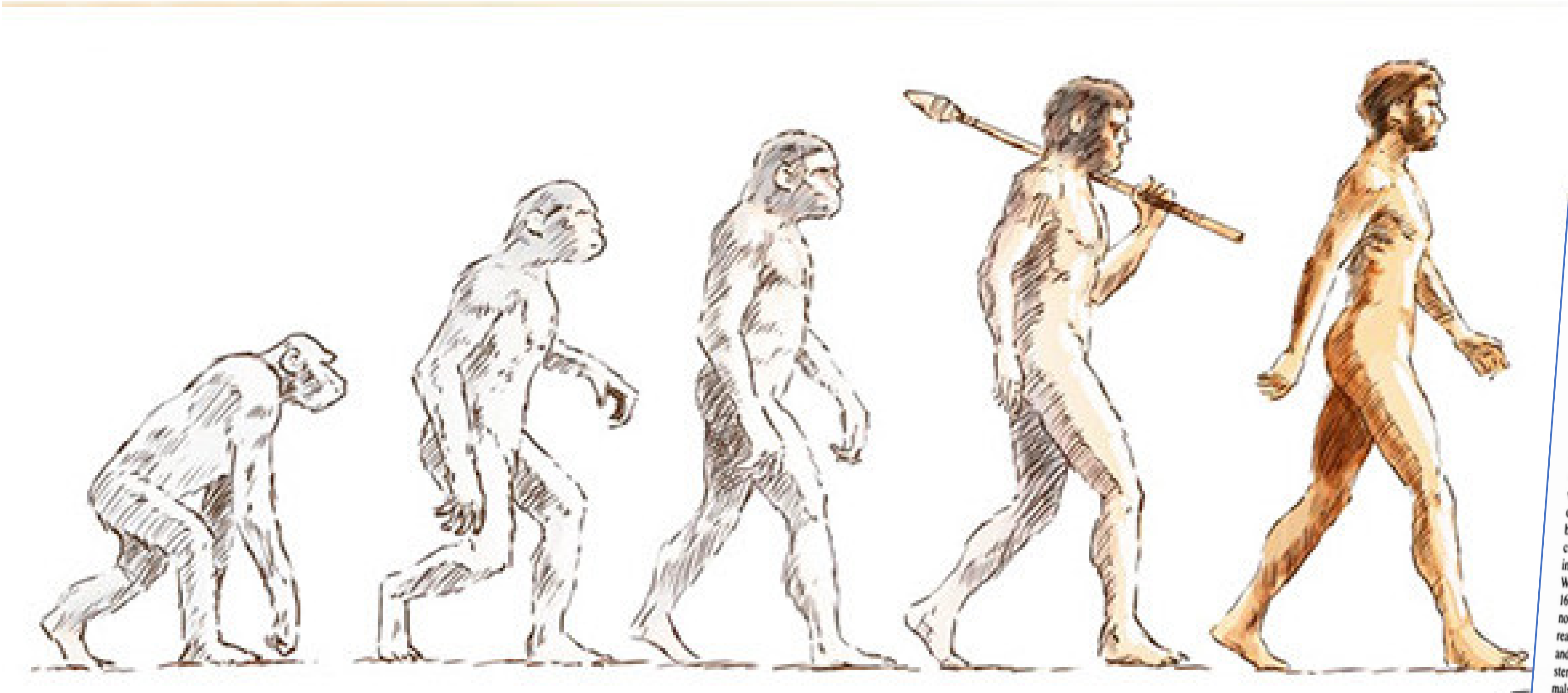
Il neurosviluppo: origini e basi etiopatogenetiche dei disturbi correlati

Davide Vecchio

Consigliere junior Società Italiana di Pediatria

Roma, 3 Febbraio 2021

Where does human neurodevelopment come from?



10 June 1977, Volume 196, Number 4295 **SCIENCE**

Evolution and Tinkering

François Jacob

Some of the 16th-century books devoted to zoology and botany are illustrated by superb drawings of the various animals that populate the earth. Certain contain detailed descriptions of such creatures as dogs with fish heads, men with chicken legs, or even women without heads. The notion of monsters that blend the characteristics of different species is not itself surprising: everyone has imagined or sketched such hybrids. What is disconcerting today is that in the 16th century these creatures belonged, not to the world of fantasies, but to the real world. Many people had seen them and described them in detail. The monsters walked alongside the familiar animals of everyday life. They were within the limits of the possible.

The interest in these monsters is that they show how a culture handles the possible and marks its limits. It is a requirement of the human brain to put order in the universe. It seems fair to say that all cultures have more or less succeeded in providing their members with a unified and coherent view of the world and of the forces that run it. One may disagree with the explanatory systems offered by myths or magic, but one cannot deny them unity and coherence. In fact, they are often charged with too much unity and coherence because of their capacity to explain anything by the same simple argument. Actually, despite their differences, whether mythic, magic, or scientific, all explanatory systems operate on a common principle. In the words of

terest. To produce a valuable observation, one has first to have an idea of what to observe, a preconception of what is possible. Scientific advances often come from uncovering a hitherto unseen aspect of things as a result, not so much of using some new instrument, but rather of looking at objects from a different angle. This look is necessarily guided by a certain idea of what the so-called reality might be. It always involves a certain conception about the unknown, that is, about what lies beyond that which one has logical or experimental reasons to believe. In the words of Peter Medawar, scientific investigation begins by the "invention of a possible world or of a tiny fraction of that world" (2). So also begins mythical thought. But it stops there. Having constructed what it considers as the only possible world, it easily fits reality into its scheme. For scientific thought, instead, imagination is only a part of the game. At every step, it has to meet with experimentation and criticism. The best world is the one that exists and has proven to work already for a long time. Science attempts to confront the possible with the actual.

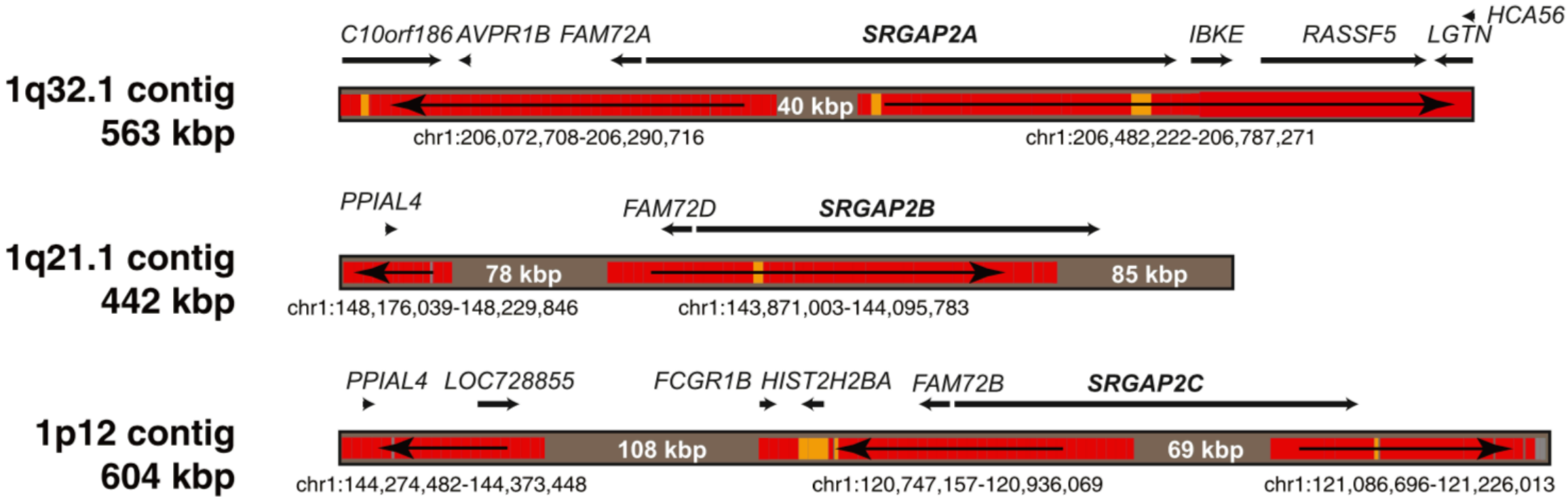
The price to be paid for this outlook, however, turned out to be high. It was, and is perhaps more than ever, renouncing a unified world view. This results

«Natural selection works like a tinkerer.. A tinkerer who does not know exactly what he is going to produce but uses whatever he finds around him.. A tinkerer who uses everything at his disposal to produce some kind of workable object»

F. Jacob. Evolution is a tinkerer.
in Science 10 June 1977 vol. 196, no. 4295

Evolution of Human-Specific Neural *SRGAP2* Genes by Incomplete Segmental Duplication

Megan Y. Dennis[8], Xander Nuttle[8], Peter H. Sudmant, Francesca Antonacci, Tina A. Graves, Mikhail Nefedov, Jill A. Rosenfeld, Saba Sajjadian, Maika Malig, Holland Kotkiewicz, Cynthia J. Curry, Susan Shafer, Lisa G. Shaffer, Pieter J. de Jong, Richard K. Wilson, Evan E. Eichler

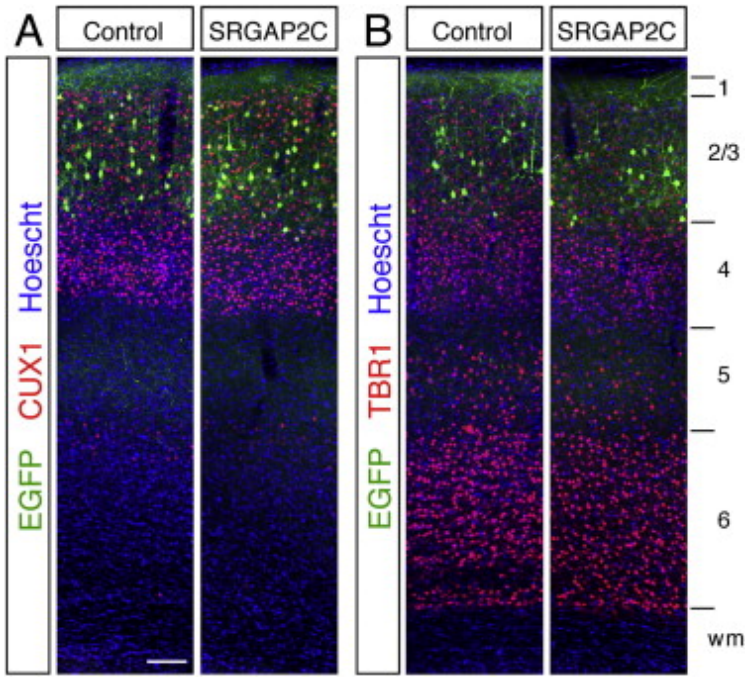


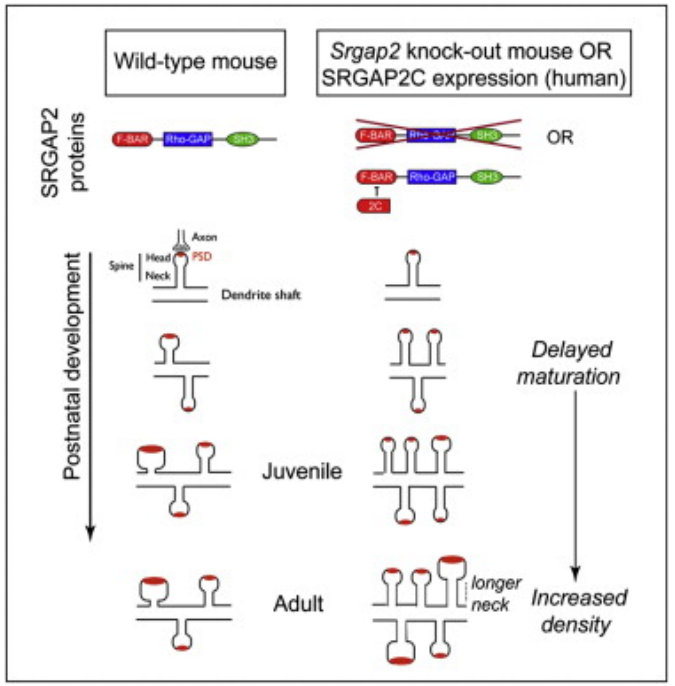
Cell 2012 149, 912-922DOI: (10.1016/j.cell.2012.03.033)

Inhibition of SRGAP2 Function by Its Human-Specific Paralogs Induces Neoteny during Spine Maturation

Cécile Charrier[7], Kaumudi Joshi[7], Jaeda Coutinho-Budd, Ji-Eun Kim, Nelle Lambert, Jacqueline de Marchena[8], Wei-Lin Jin, Pierre Vanderhaeghen, Anirvan Ghosh, Takayuki Sassa[9], Franck Polleux

Cell 2012 149, 912-922DOI: (10.1016/j.cell.2012.03.033)



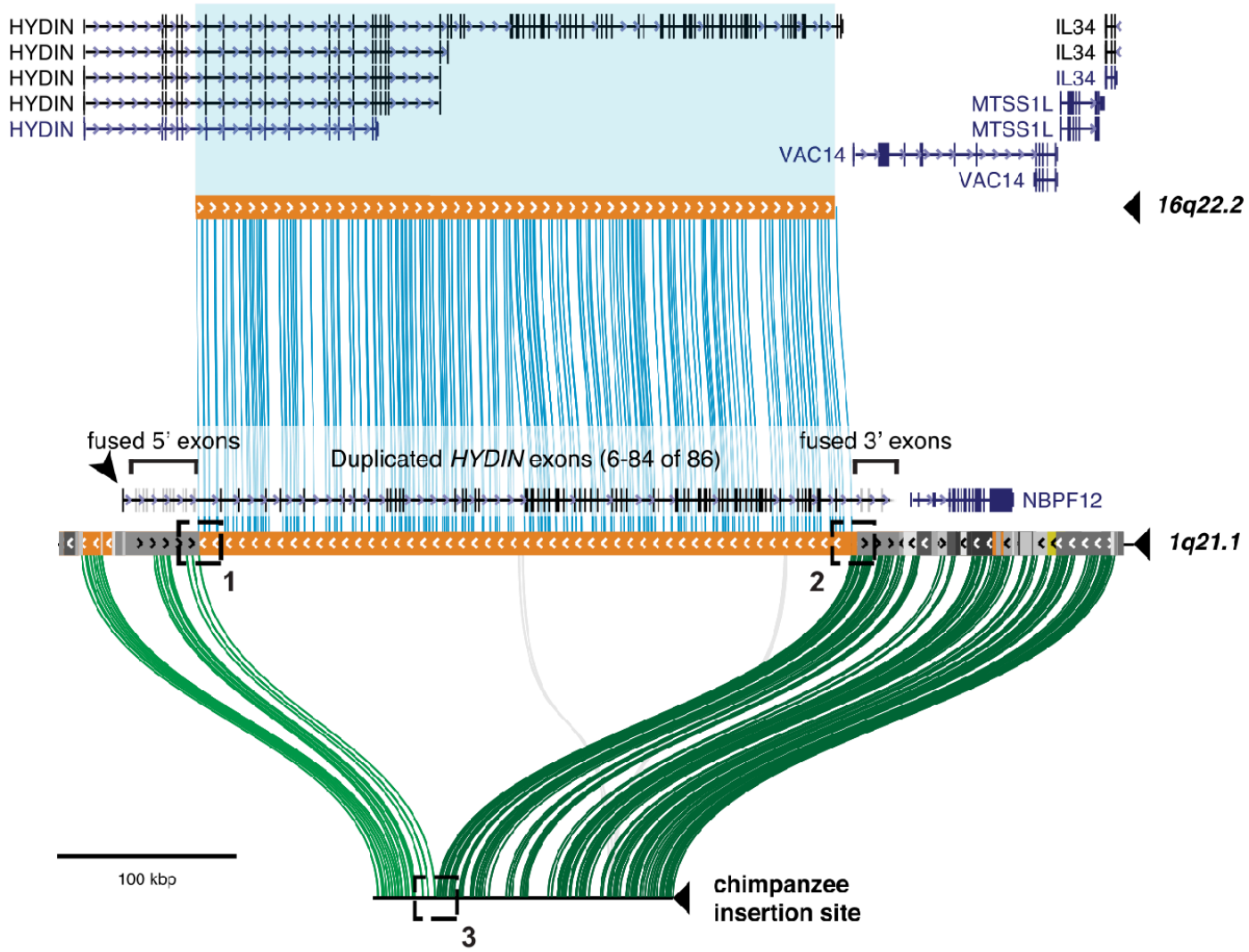


"Novelties come from previously unseen association of old material.
To create is to recombine"

F. Jacob. Evolution is a tinkerer.
in Science 10 June 1977 vol. 196, no. 4295

RESEARCH Open Access

The birth of a human-specific neural gene by incomplete duplication and gene fusion



HYDIN2 was generated by the juxtaposition of multiple segmental duplications culminating with the partial duplication of *HYDIN* ~3.2 mya.

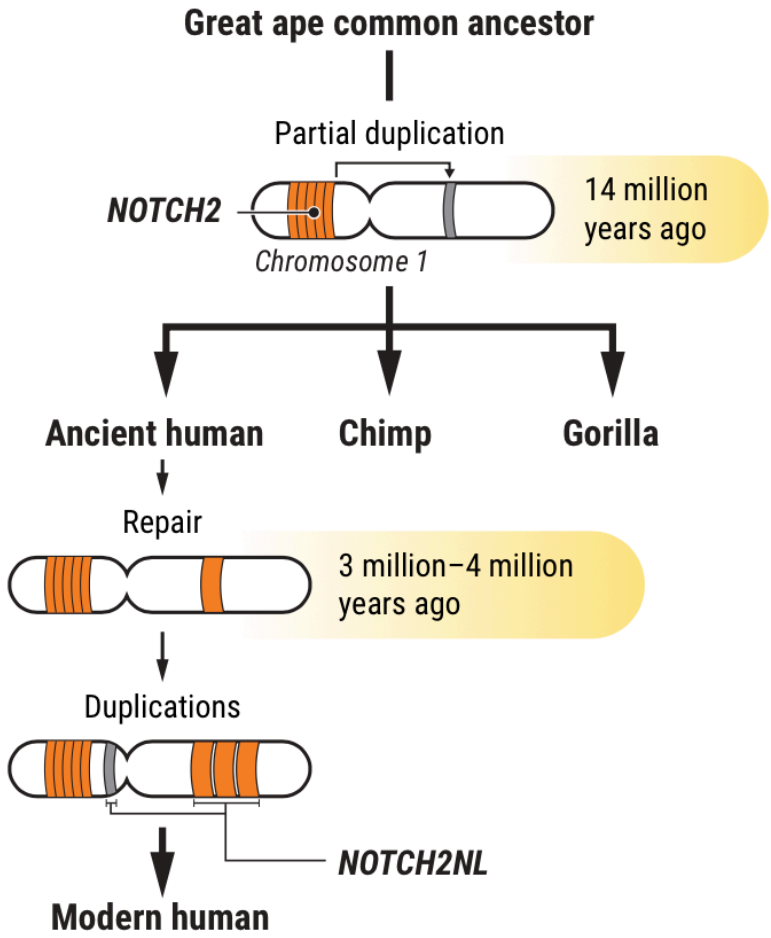
We identify a new promoter that "rescued" the truncated gene duplicate and drives a neuronal pattern of expression.

We show that the reciprocal macro/microcephaly phenotypes associated with chromosome 1q21 rearrangements can occur without *HYDIN2* copy number changes.

Dougherty *et al. Genome Biology* (2017) 18:49
DOI 10.1186/s13059-017-1163-9

Trio of genes supercharged human brain evolution

By **Elizabeth Pennisi** | May. 31, 2018 , 12:00 PM

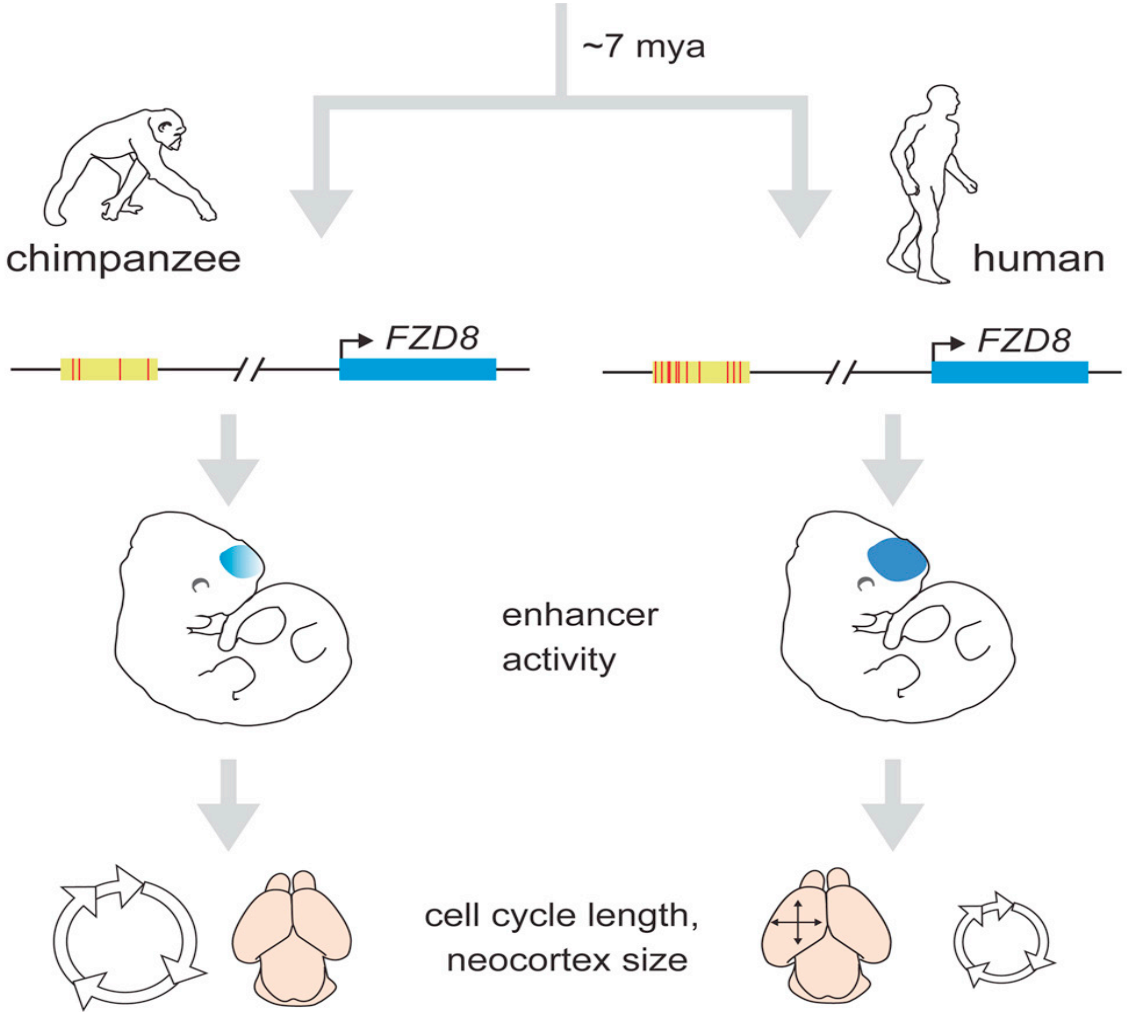


(GRAPHIC) V. ALTOUNIAN/*SCIENCE*; (DATA) FIDDES *ET AL.*, *CELL* 173, 1, (2018)

Human-Chimpanzee Differences in a *FZD8* Enhancer Alter Cell-Cycle Dynamics in the Developing Neocortex

J. Lomax Boyd, Stephanie L. Skove, Jeremy P. Rouanet, Louis-Jan Pilaz, Tristan Bepler, Raluca Gordân, Gregory A. Wray, Debra L. Silver

Published Online: February 19, 2015



This study reports the discovery of a human-accelerated enhancer of *FZD8* functioning in brain development.

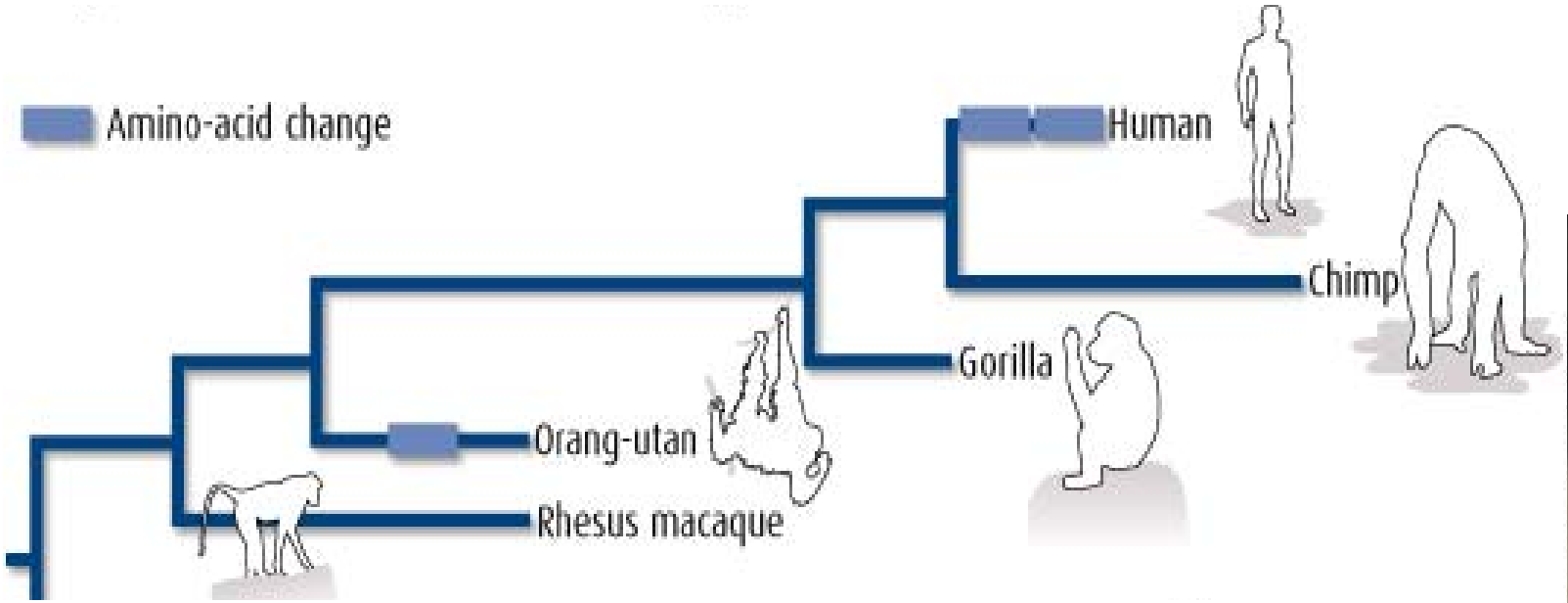
Boyd et al. demonstrate species-specific activity differences and show that the human enhancer promotes a faster progenitor cell cycle and increased neocortical size.

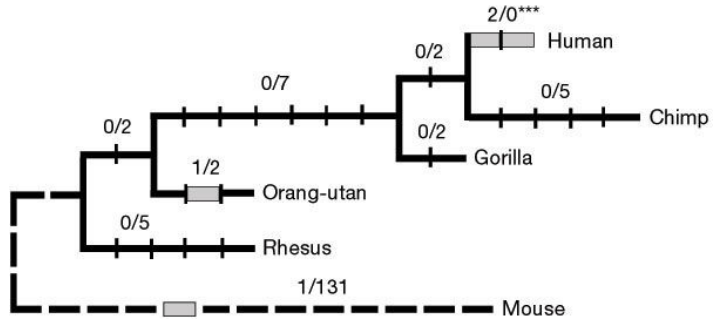
Enhancer sequence changes may contribute to unique features of the human brain.

Current Biology 2015 25, 772-779DOI: (10.1016/j.cub.2015.01.041)

Molecular evolution of *FOXP2*, a gene involved in speech and language

Wolfgang Enard, Molly Przeworski, Simon E. Fisher, Cecilia S. L. Lai, Victor Wiebe, Takashi Kitano, Anthony P. Monaco & Svante Pääbo ✉





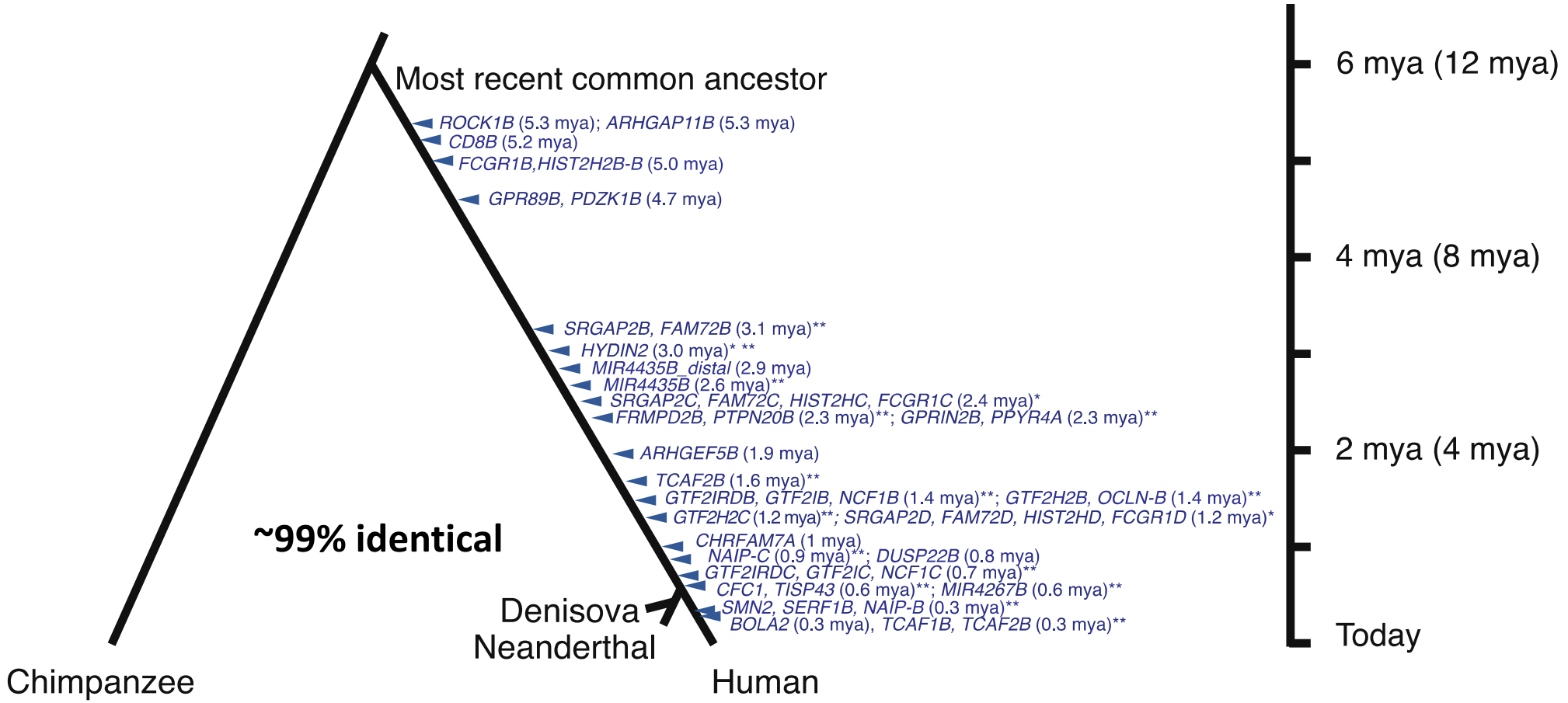
Silent and replacement nucleotide substitutions mapped on the phylogeny of primates

Nature **volume 418**, pages 869–872 (22 August 2002)
doi:10.1038/nature01025

Nat Ecol Evol. 2017;1(3):69. doi: 10.1038/s41559-016-0069. Epub 2017 Feb 17.

The evolution and population diversity of human-specific segmental duplications.

Dennis MY[1,2], Harshman L[2], Nelson BJ[2], Penn O[2], Cantsilieris S[2], Huddleston J[2,3], Antonacci F[4], Penewit K[2], Denman L[2], Raja A[2,3], Baker C[2], Mark K[2], Malig M[2], Janke N[2], Espinoza C[2], Stessman HAF[2], Nuttle X[2], Hoekzema K[2], Lindsay-Graves TA[5], Wilson RK[5], Eichler EE[2,3].

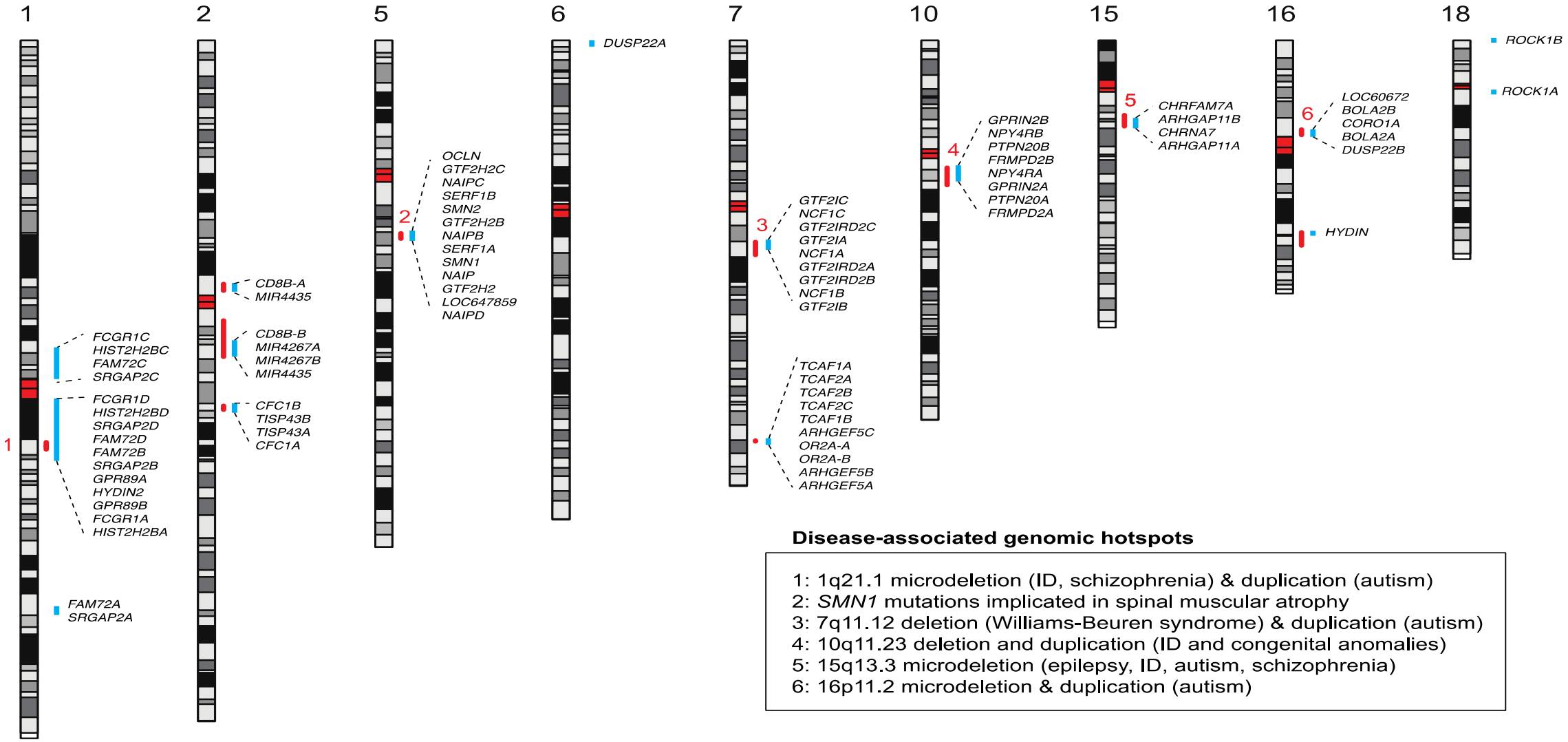


Human-specific duplications create new genes and features unique to the human genome

Nat Ecol Evol. 2017;1(3):69. doi: 10.1038/s41559-016-0069. Epub 2017 Feb 17.

The evolution and population diversity of human-specific segmental duplications.

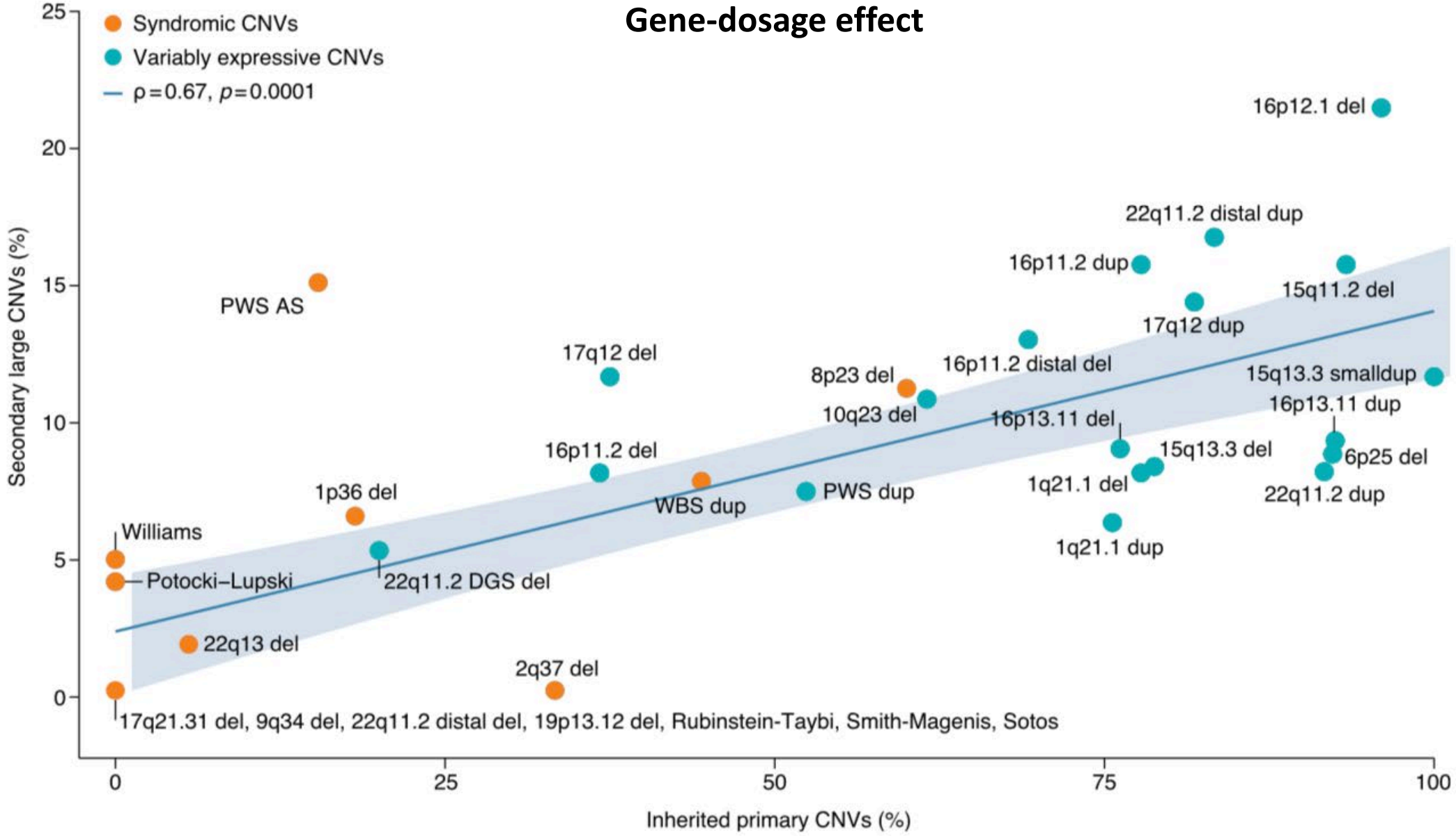
Dennis MY[1,2], Harshman L[2], Nelson BJ[2], Penn O[2], Cantsilieris S[2], Huddleston J[2,3], Antonacci F[4], Penewit K[2], Denman L[2], Raja A[2,3], Baker C[2], Mark K[2], Malig M[2], Janke N[2], Espinoza C[2], Stessman HAF[2], Nuttle X[2], Hoekzema K[2], Lindsay-Graves TA[5], Wilson RK[5], Eichler EE[2,3].



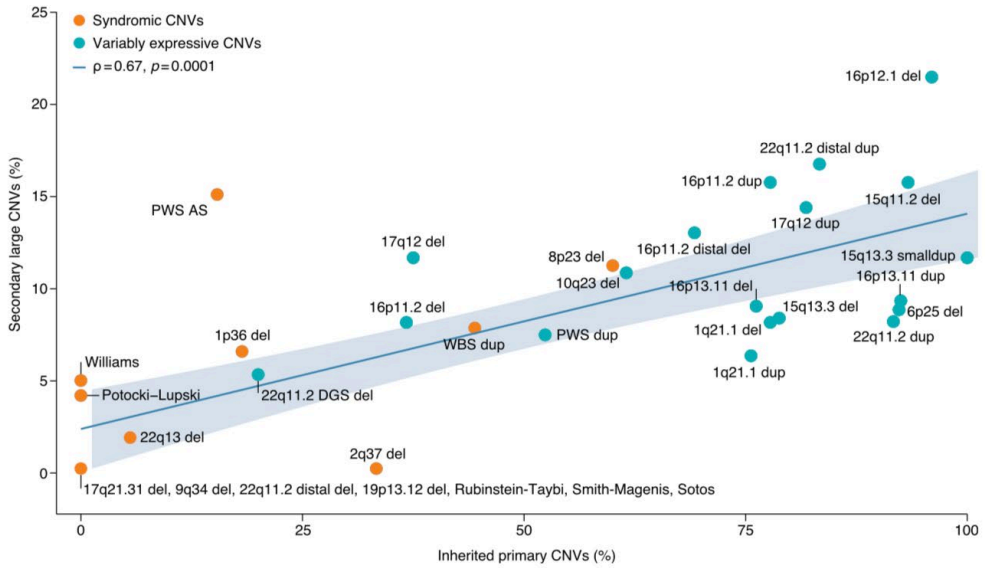
Disease-associated genomic hotspots

1: 1q21.1 microdeletion (ID, schizophrenia) & duplication (autism)
2: *SMN1* mutations implicated in spinal muscular atrophy
3: 7q11.12 deletion (Williams-Beuren syndrome) & duplication (autism)
4: 10q11.23 deletion and duplication (ID and congenital anomalies)
5: 15q13.3 microdeletion (epilepsy, ID, autism, schizophrenia)
6: 16p11.2 microdeletion & duplication (autism)

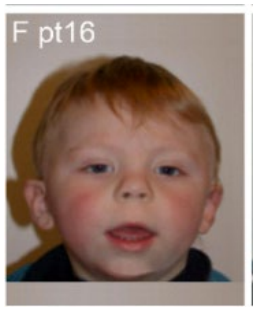
Recurrent *de novo* segmental aneuploidies
&
Gene-dosage effect



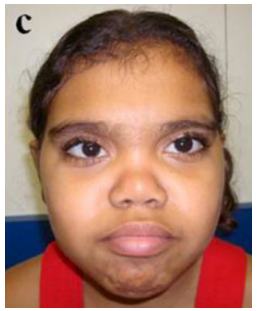
Recurrent *de novo* segmental aneuploidies

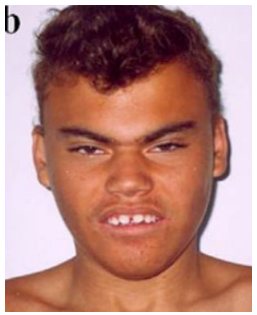


Potocki – Lupski S.
Dup 17p11.2

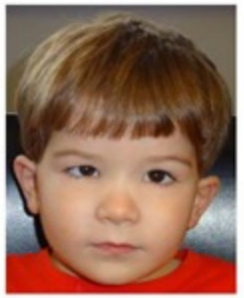


Smith – Magenis S.
Del 17p11.2

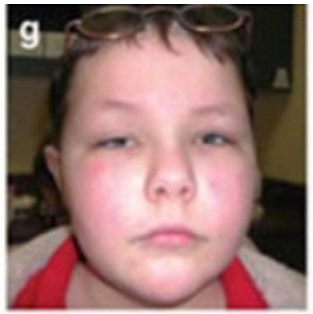




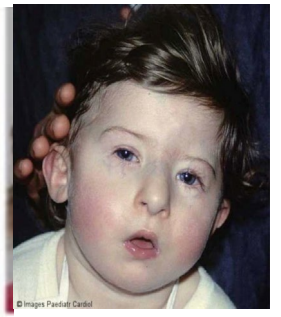
7q11.23 Syn.
Duplication

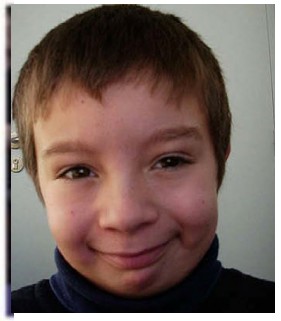


Williams-Beuren
Del. 7q11.23

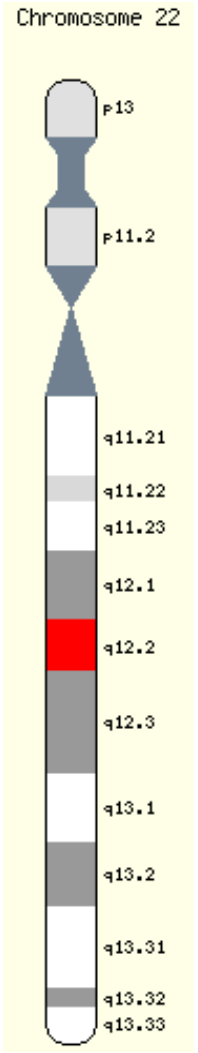


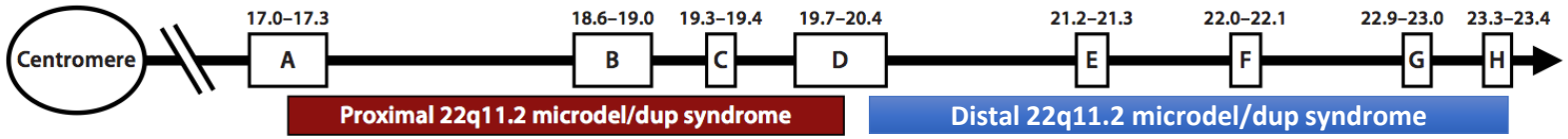
DiGiorge S.
Del. 22q11.2

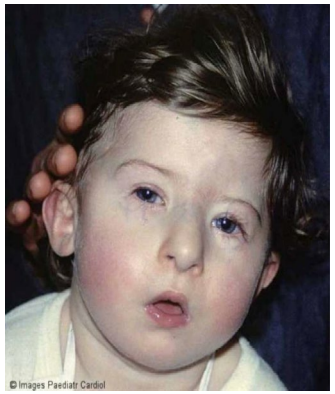


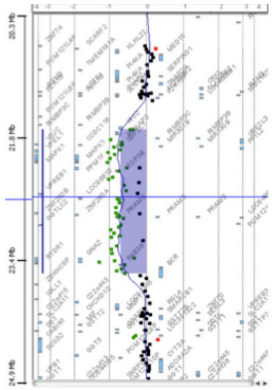


The 22q11.2 region

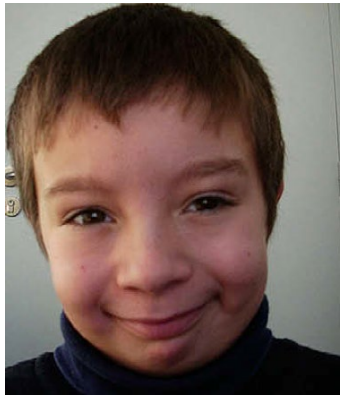


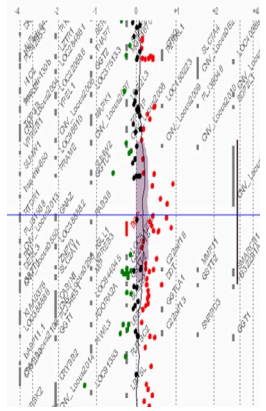




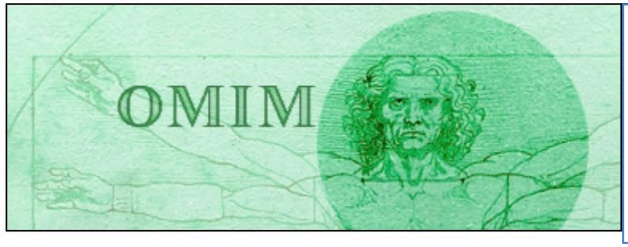


DiGeorge Syndrome
[OMIM 192430]





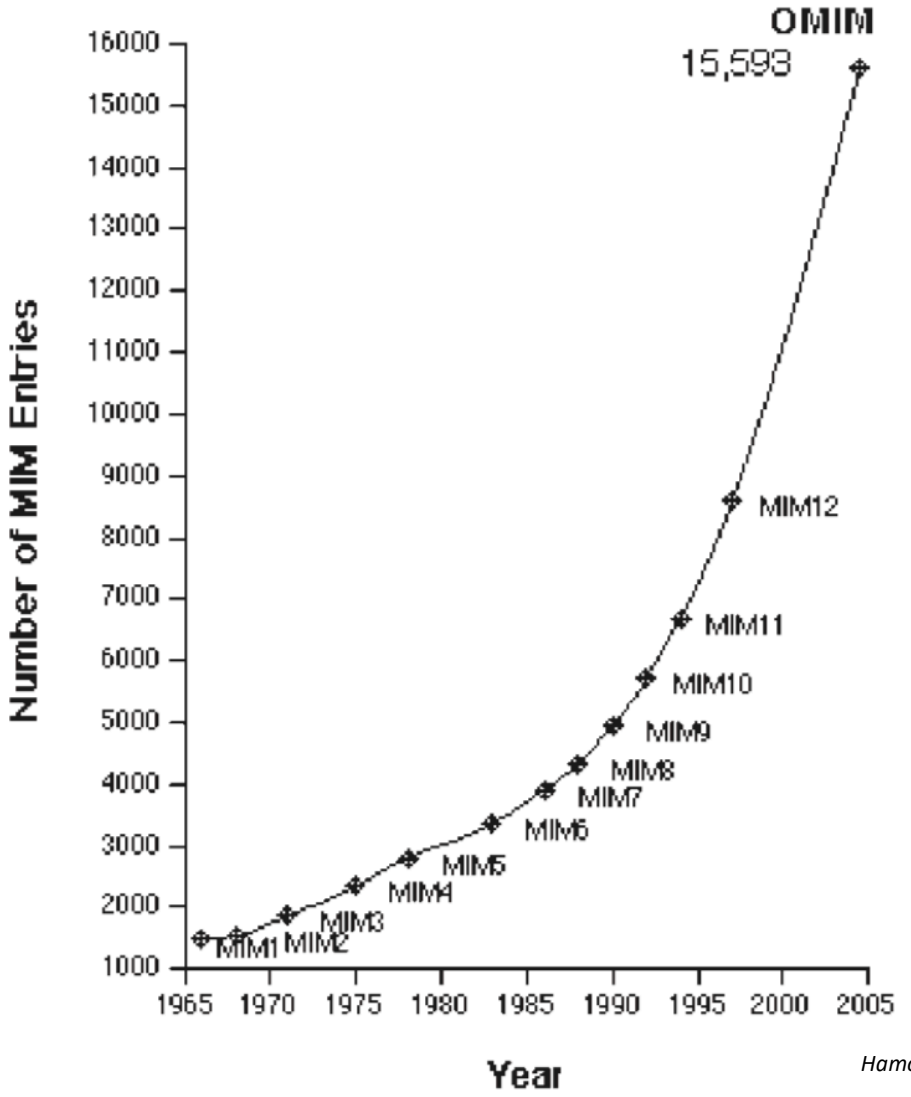
22q11.2 proximal
microduplication Syndrome
[OMIM 608363]



Nucleic Acids Res. 2006; 34(2): 445–450.
PMCID: PMC1356528
Published online 2006 Jan 26. doi: 10.1093/nar/gkj456

BAC to the future! or oligonucleotides: a perspective for micro array comparative genomic hybridization (array CGH)

Bauke Ylstra,* Paul van den IJssel, Beatriz Carvalho, Ruud H. Brakenhoff,[1] and Gerrit A. Meijer



OMIM Update List

Updates since the database was placed on the web in December 1995

2019	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
New	47	35	35	37	42	39	35	41	49	47	7
Updated	358	382	363	388	621	512	412	604	617	511	137

2018	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
New	37	35	29	26	50	45	27	35	33	36	46	49
Updated	545	463	455	374	329	401	358	404	520	330	384	221

2017	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
New	53	53	44	44	46	46	46	61	51	48	41	34
Updated	346	409	350	445	487	429	409	540	334	456	387	361

2016	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
New	57	60	50	51	43	46	47	48	42	42	54	50
Updated	405	497	575	508	687	735	957	1100	947	1054	300	370

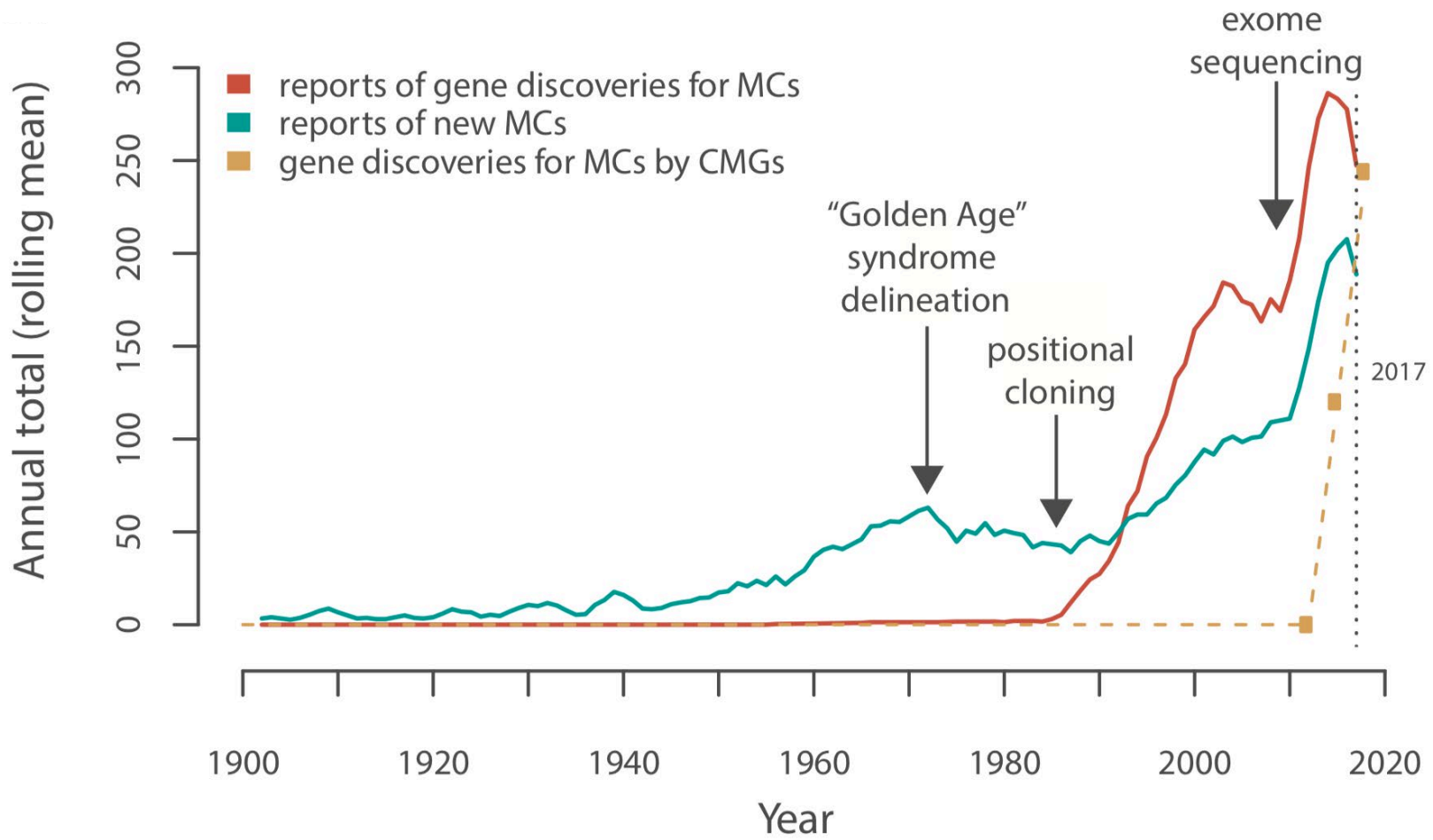
2015	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
New	52	46	43	54	56	52	54	42	50	45	40	58
Updated	593	698	618	552	614	598	666	699	476	386	395	388

2014	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
New	41	52	46	54	52	51	50	59	51	52	45	52
Updated	558	586	552	707	548	579	610	554	533	670	537	427

Hamosh, A., Scott, A. F., Amberger, J. S., Bocchini, C. A., & McKusick, V. A. (2005). Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic acids research, 33(suppl_1), D514-D517.

Mendelian Gene Discovery: Fast and Furious with No End in Sight

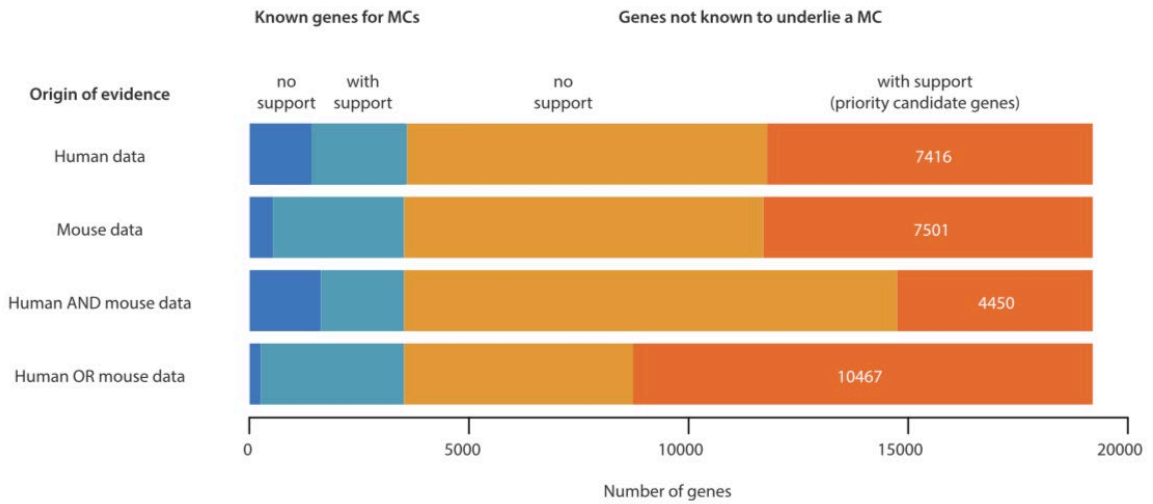
AJHG

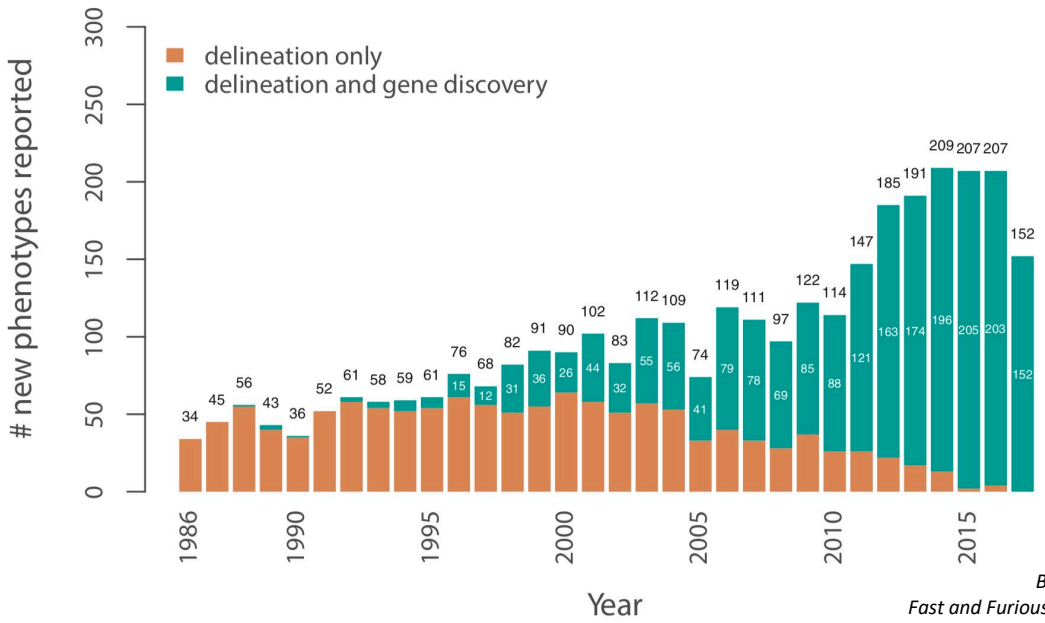


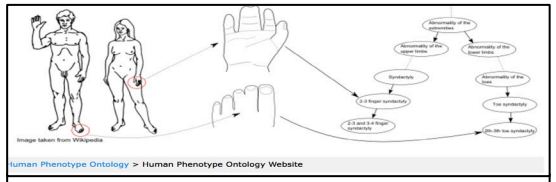
Bamshad, M. J., Nickerson, D. A., & Chong, J. X. (2019). Mendelian Gene Discovery: Fast and Furious with No End in Sight. The American Journal of Human Genetics, 105(3), 448-455.

Mendelian Gene Discovery: Fast and Furious with No End in Sight

AJHG







Known genes for MCs		Genes not known to underlie a MC	
no support	with support	no support	with support
1393	2180	8259	7416
533	2986	8174	7501
1623	1896	11225	4450
249	3270	5208	10467

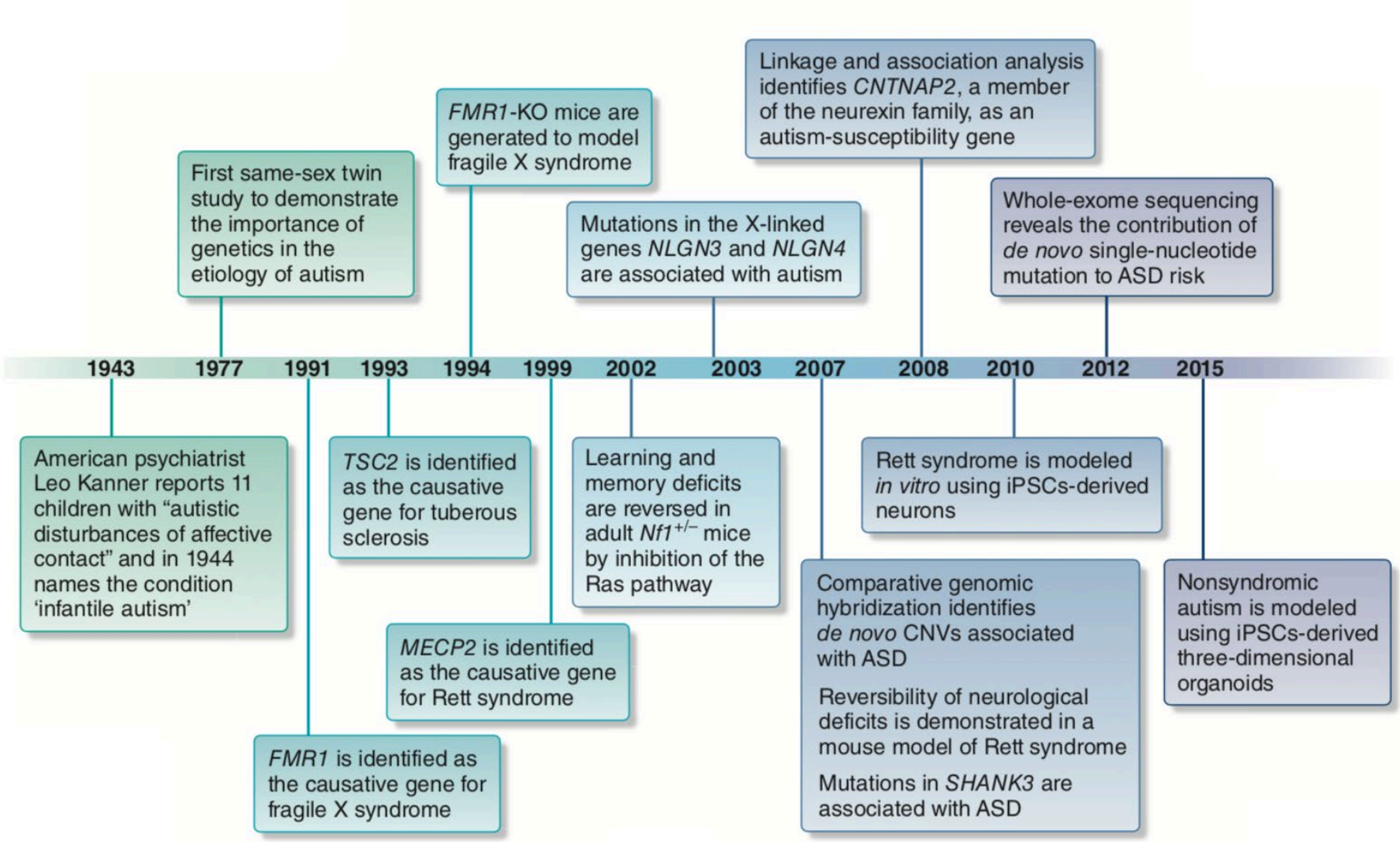
Bamshad, M. J., Nickerson, D. A., & Chong, J. X. (2019). Mendelian Gene Discovery: Fast and Furious with No End in Sight. The American Journal of Human Genetics, 105(3), 448-455.

Recurrent de novo mutations in neurodevelopmental disorders: properties and clinical implications

DNM class		Size	Description	Average number of DNMs* per genome
Copy number variant (CNV)		> 50 bp	Genomic deletions or duplications that can span both gene regions and noncoding, regulatory regions	0.05–0.16 [8, 23, 26]
Insertion/deletion (indel)		< 50 bp	Insertions or deletions of a small number of nucleotides that alter the reading frame of a protein are called frameshift mutations and typically result in a truncated peptide	2.6–9 [8, 23, 26, 27]
Single-nucleotide variant (SNV)		1 bp	Single base-pair change in the genome	45–89 [3, 7, 8, 23, 27, 28]
SNV subtype	Likely gene disrupting		Results in a truncated peptide, often referred to as stop-gain, stop-lost, or splice-altering mutations	
	Missense		Changes the amino acid sequence of a peptide but does not lead to peptide truncation	
	Synonymous		Mutations that do not alter peptide sequence or length but may alter regulatory regions or RNA processing	
	Noncoding		Changes that occur outside the protein-coding regions of the genome	
Mosaic SNV		1 bp	Single base-pair changes that occur in only a subset of cells in the human body, sometimes referred to as somatic mutations	0.05–22.2 [23, 27, 29–31]
Mosaic CNV		> 50 bp	Deletions or duplications that only occur in a subset of cells in the human body	$5e^{-4}$–$7.7e^{-3}$ [32, 35]

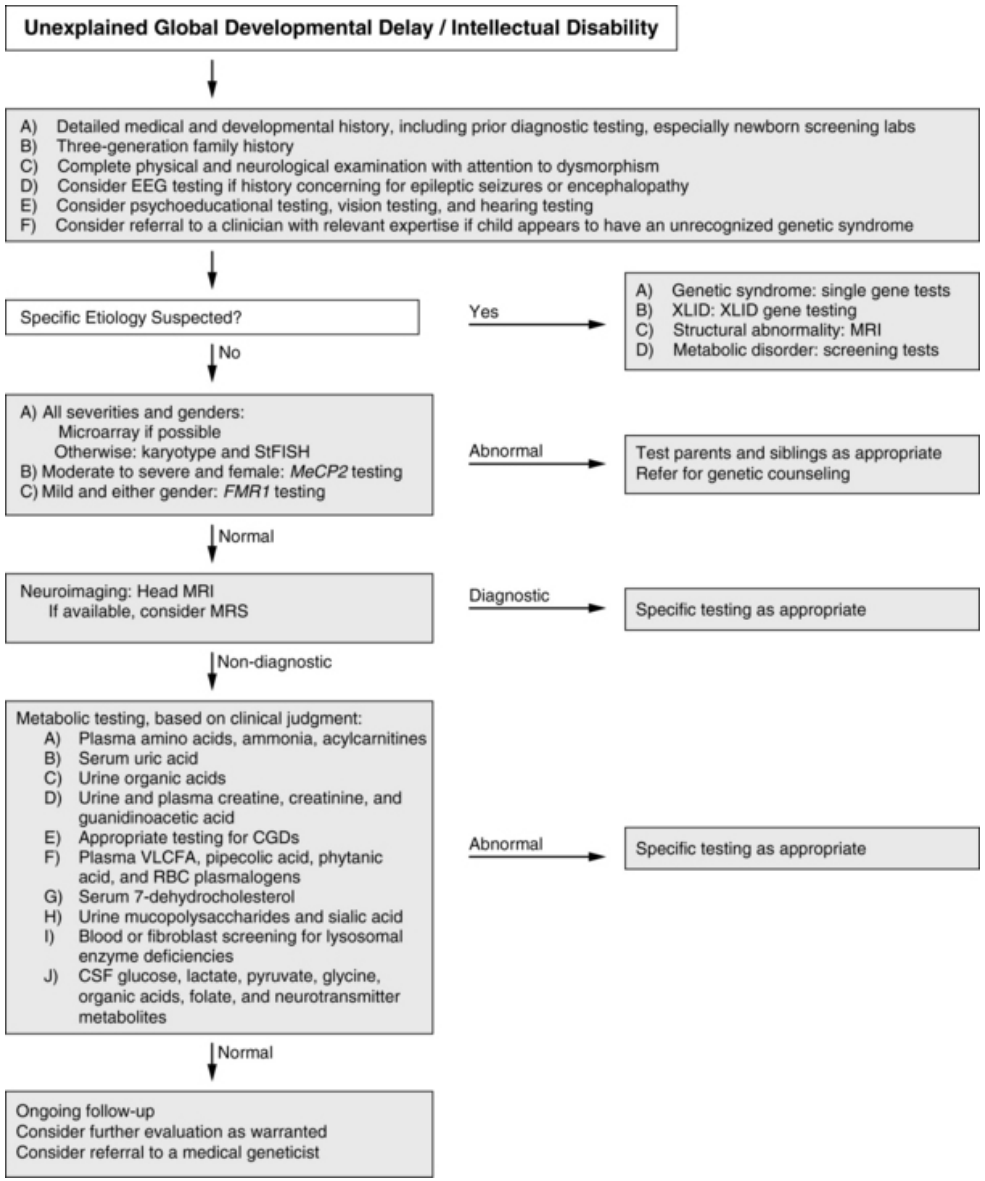
Wilfert, Amy B., et al. *Genome medicine* 9.1 (2017): 101.

Timeline of key discoveries in the history of NDD research



Sztainberg, Yehezkel, and Huda Y. Zoghbi. "Lessons learned from studying syndromic autism spectrum disorders." *Nature neuroscience* 19.11 (2016): 1408.

Comprehensive evaluation of the child with intellectual disability or global developmental delays



1st Tier: Non-Targeted screening to identify 54 (60%) treatable IEMs

Blood:
- ammonia, lactate
- plasma amino acids
- total homocysteine
- acylcarnitine profile
- copper, ceruloplasmin

Urine:
- organic acids
- purines & pyrimidines
- creatine metabolites
- oligosaccharides
- glycosaminoglycans

2nd Tier: Targeted testing to identify 35 (40%) treatable IEMs requiring 'specific testing'

- **according to patient's symptomatology patient (Table 4) & clinician's expertise**
- **utilization of textbooks & digital resources** (WebApp: www.treatable-ID.org)
- **consider the following biochemical / molecular analyses:**
  - whole blood manganese
  - plasma cholestanol
  - plasma 7-dehydroxy-cholesterol:cholesterol ratio
  - plasma pipecolic acid & urine AASA
  - plasma very long chain fatty acids
  - plasma vitamin B12 & folate
  - serum & CSF lactate:pyruvate ratio
  - enzyme activities (leucocytes): arylsulphatase A, biotinidase, glucocerebrosidase, fatty aldehyde dehydrogenase
  - urine deoxypyridonoline
  - CSF amino acids
  - CSF neurotransmitters
  - CSF: plasma glucose ratio
  - CoQ measurement fibcroblasts
  - molecular: *CA5A, NPC1, NPC2, SC4MOL, SLC18A2, SLC19A3, SLC30A10, SLC52A2, SLC52A3, PDHA1, DLAT, PDHX, SPR, TH*

Modified from: Moeschler, John B., and Michael Shevell. "Comprehensive evaluation of the child with intellectual disability or global developmental delays." Pediatrics 134.3 (2014): e903-e918.
AND
Miller, David T., et al. "Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies." The American Journal of Human Genetics 86.5 (2010): 749-764.