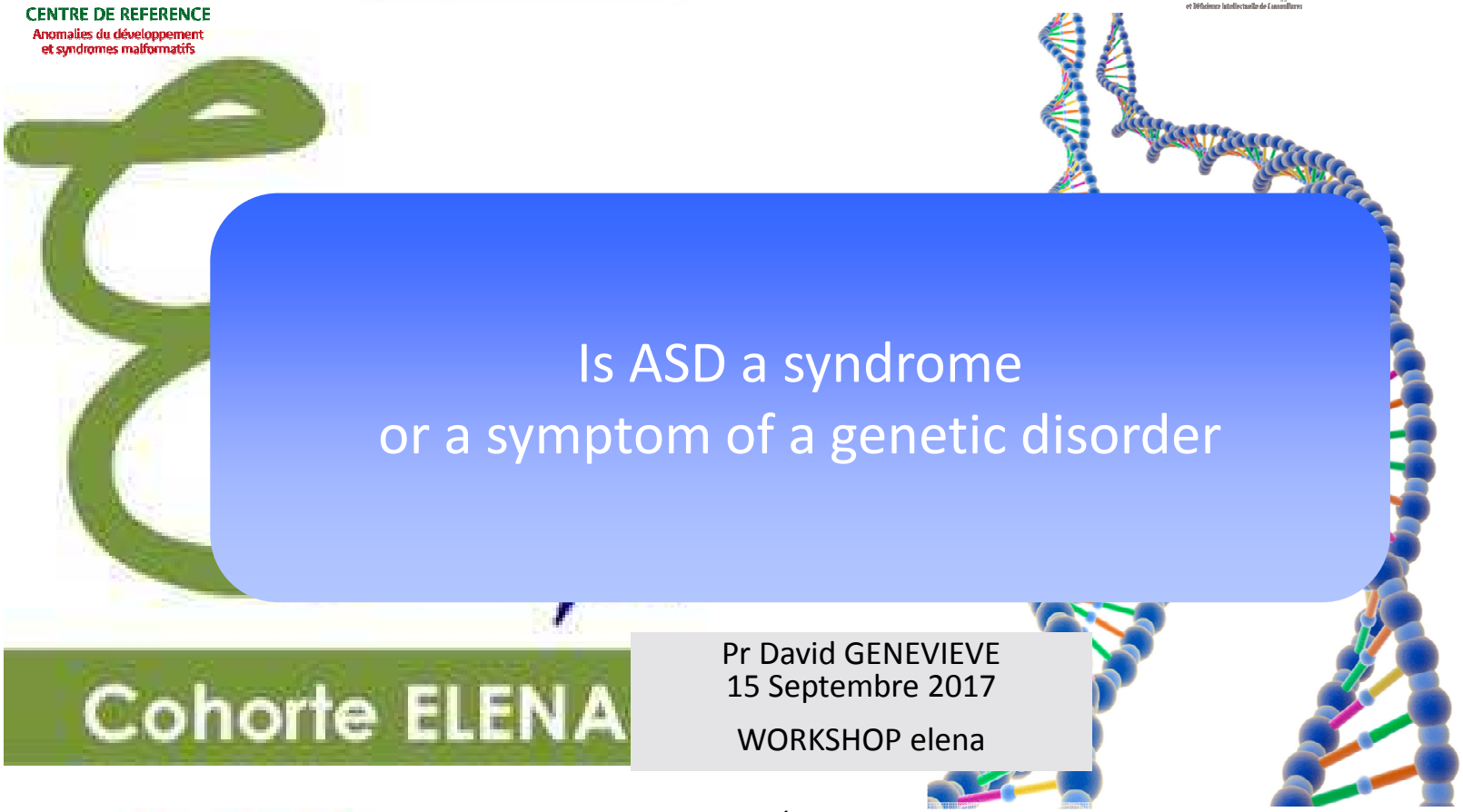
CENTRE DE REFERENCE
Anomalies du développement
et syndromes malformatifs

AFGC
Association Francophone de Génétique Clinique

Inserm
Institut national
de la santé et de la recherche médicale

AnDDI-Rares

MONTPELLIER
CHU
CENTRE HOSPITALIER UNIVERSITAIRE



Is ASD a syndrome or a symptom of a genetic disorder

Cohorte ELENA

Pr David GENEVIEVE
15 Septembre 2017

WORKSHOP elena

Unité Inserm U1183
Département de Génétique médicale
Hôpital Arnaud de Villeneuve,
CHRU Montpellier

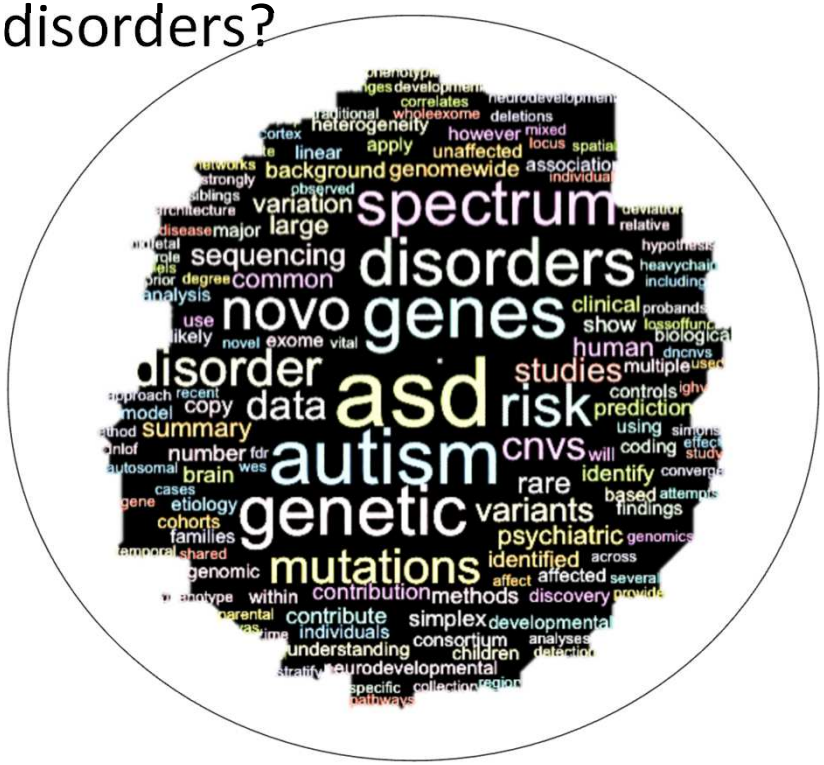
IRMB
FOR REGENERATIVE MEDICINE & BIOTHERAPY

UNIVERSITÉ DE MONTPELLIER

Aetiology of ASD ?

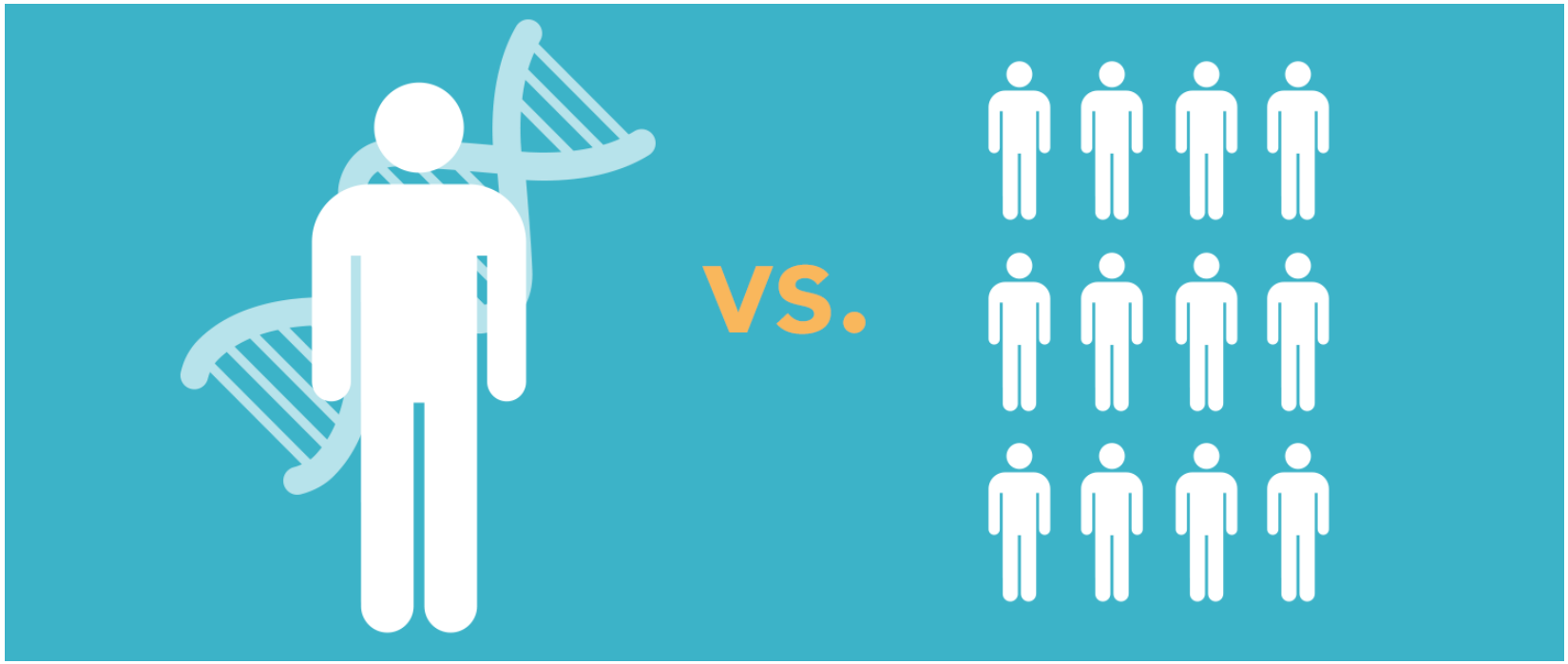
- Does ASD is an environmental disorder?
- Does ASD is a genetic disorder ?
- Does ASD is a feature of several genetic disorders?

- Why having an answer?
  - What is the goal ?



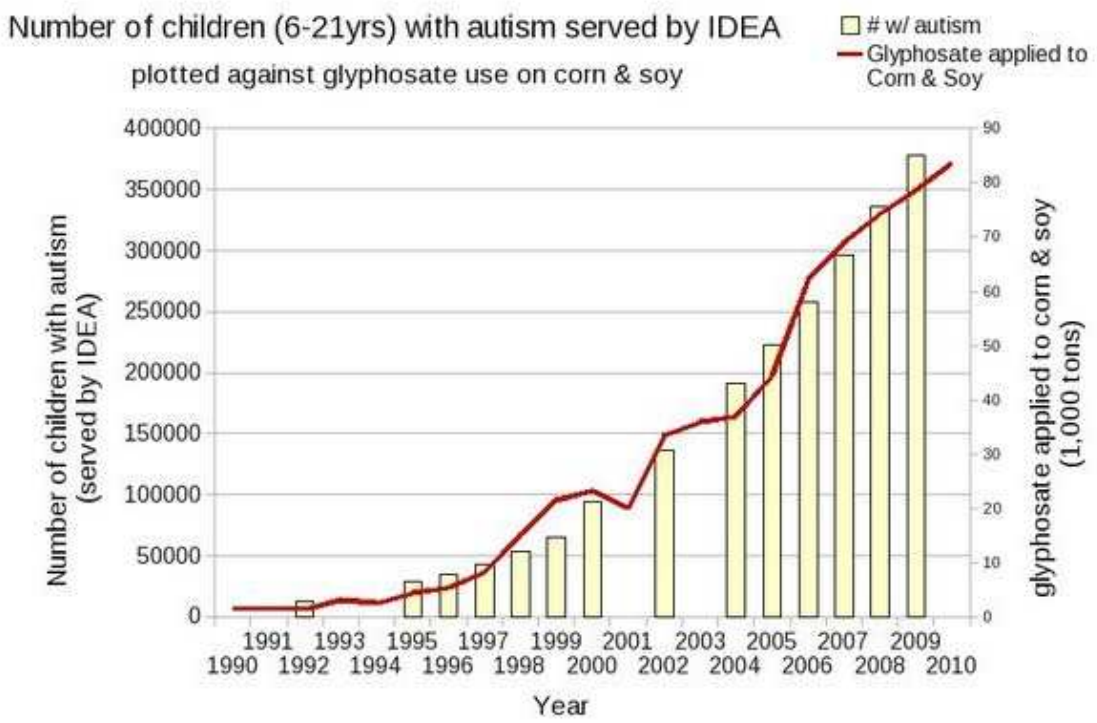
Why an exact aetiology ?

- A precise diagnostic to propose a precise counselling and a precise care (treatment?)



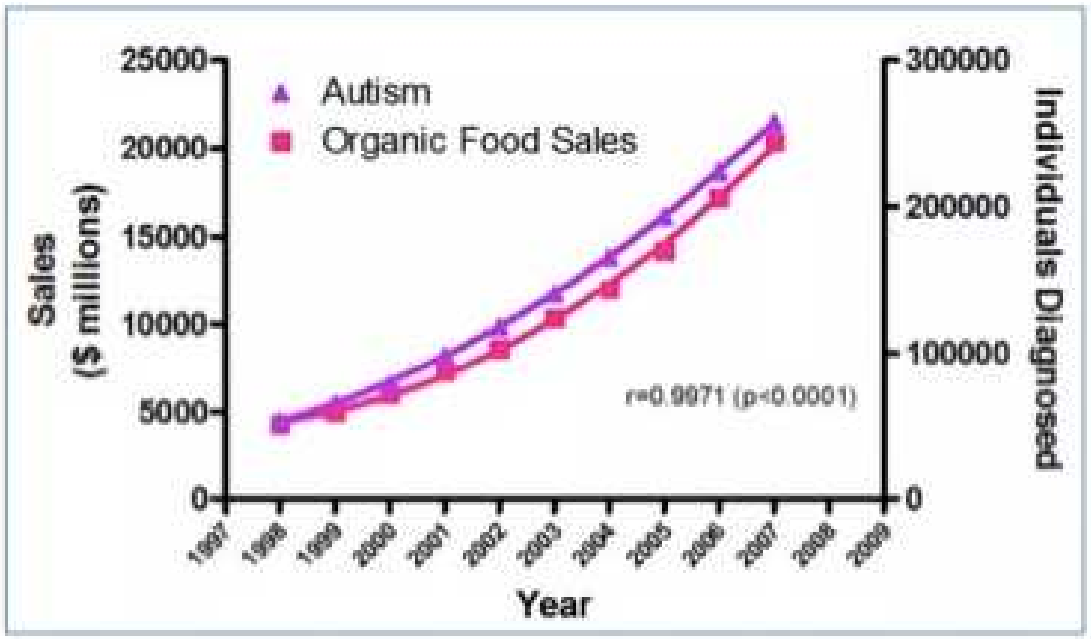
Aetiology of ASD ?

- What lead to the increase of the incidence of ASD ?
  - Environment ? Toxics?



Aetiology of ASD ?

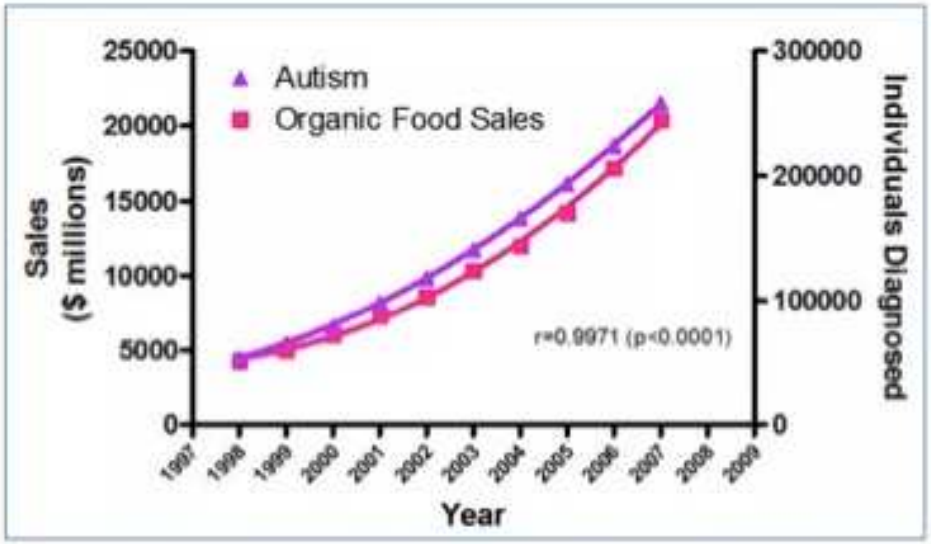
- What lead to the increase of the incidence of ASD ?
  - Environment ? Toxics?



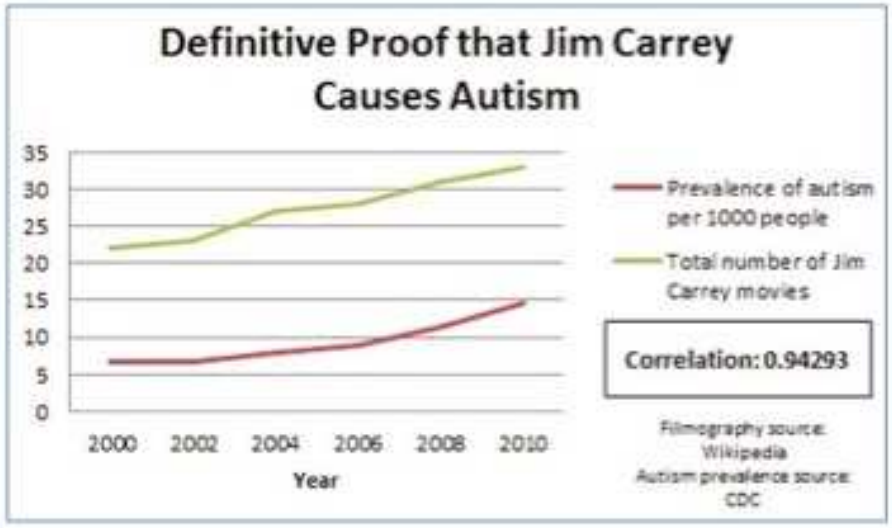
Rates of autism correlate *perfectly* with sales of organic foods

Aetiology of ASD ?

- What lead to the increase of the incidence of ASD ?
  - Environment ? Toxics?



Rates of autism correlate *perfectly* with sales of organic foods

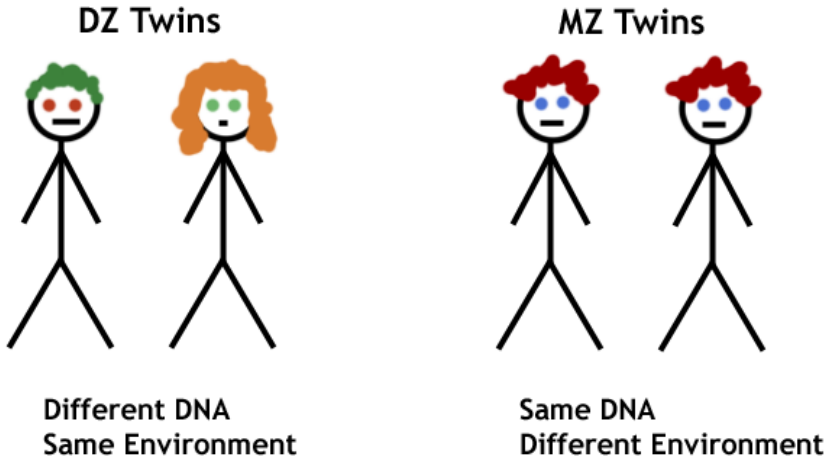


As well as the number of Jim Carrey movies

How to reach the precise aetiology ?

Genetic could help in ASD?

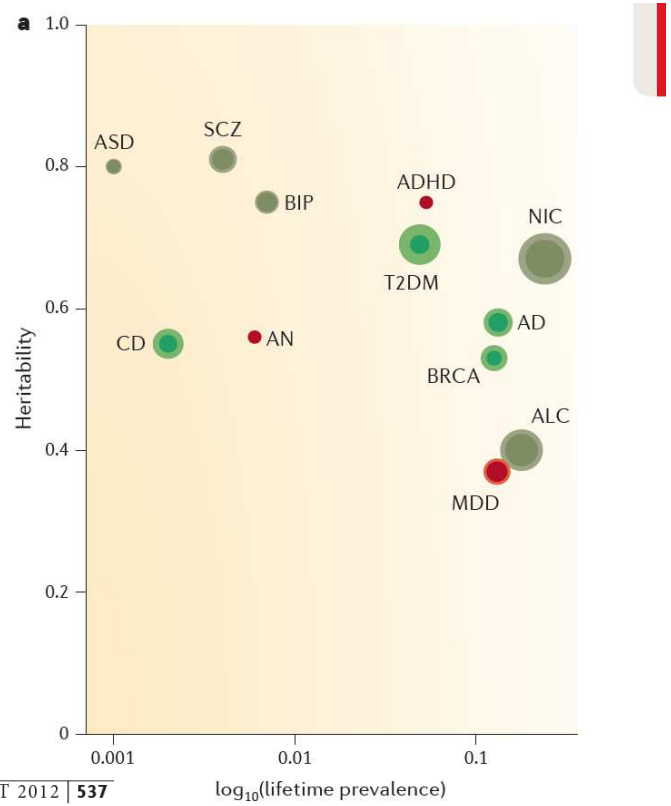
- Heritability in ASD around 80%



DISEASE MECHANISMS

Genetic architectures of psychiatric disorders: the emerging picture and its implications

Patrick F. Sullivan[1], Mark J. Daly[2] and Michael O'Donovan[3]



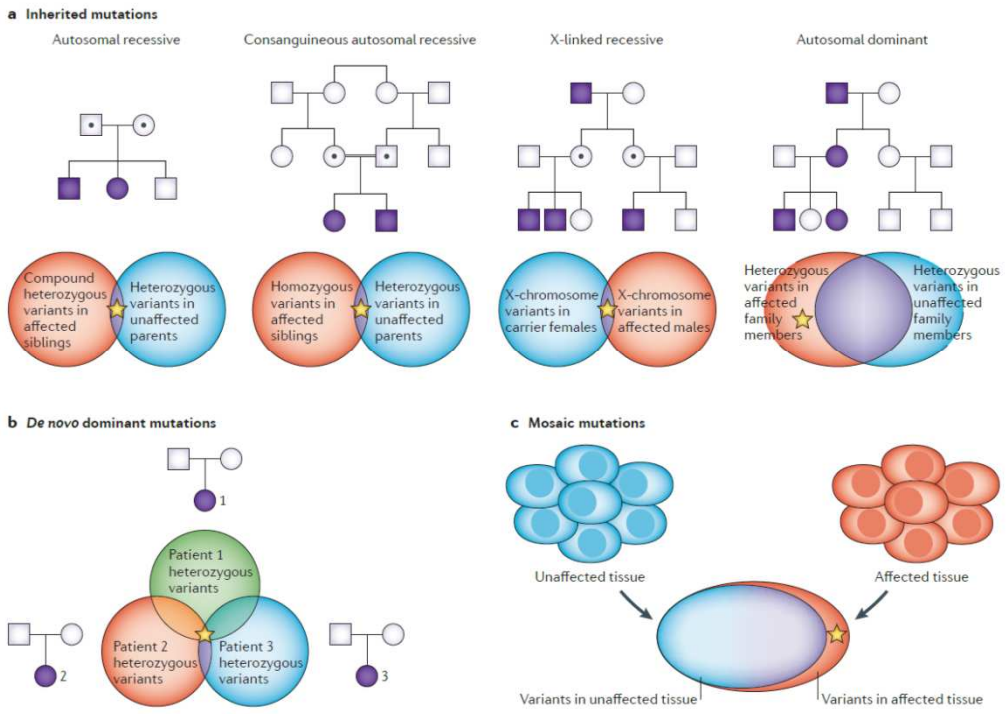
Concepts in genetics

- Heredity (different from heritability)
  - Several mode of inheritance are observed
  - No familial history doesn't means no Mendelian disorders

TRANSLATIONAL GENETICS

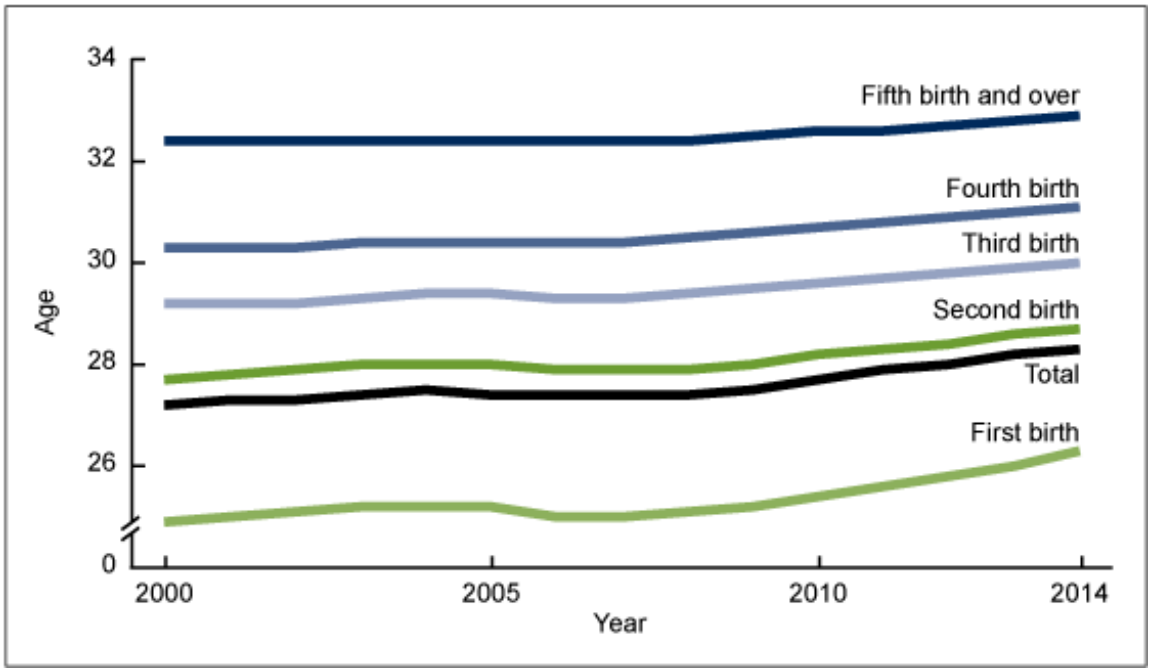
Rare-disease genetics in the era of next-generation sequencing: discovery to translation

Kym M. Boycott, Megan R. Vanstone, Dennis E. Bulman and Alex E. MacKenzie



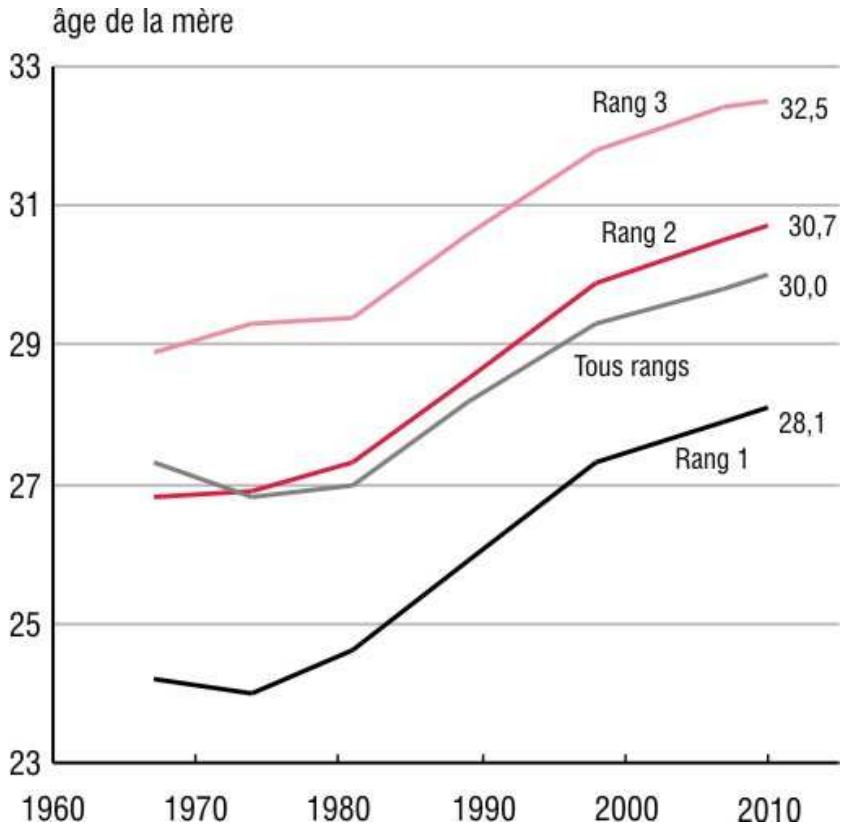
Increased maternal and paternal age ?

CDC
Centers for Disease Control and Prevention



USA

Insee Institut national de la statistique et des études économiques
Mesurer pour comprendre



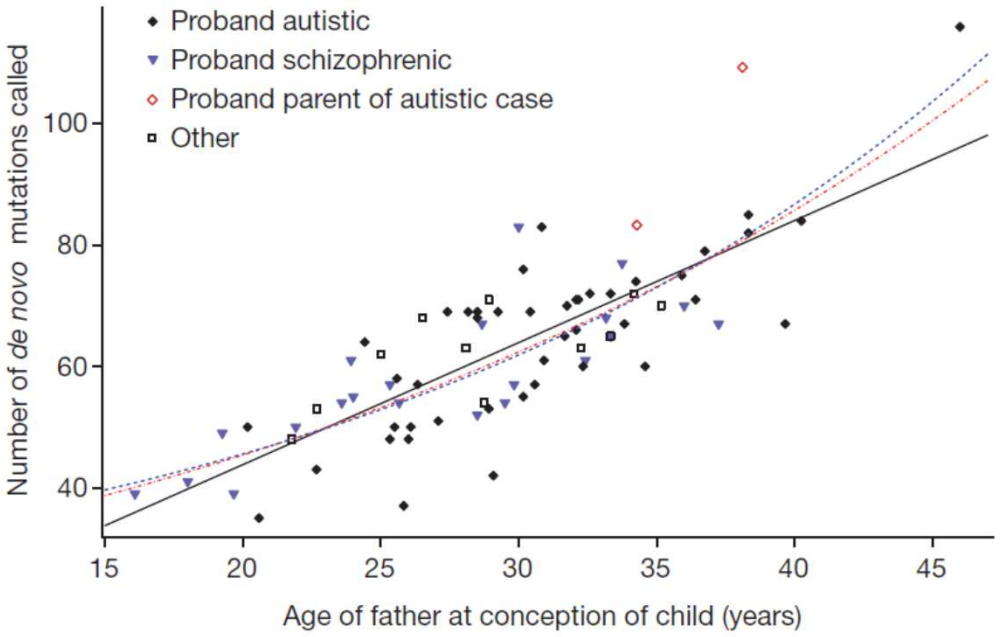
France

Increased maternal and paternal age ?

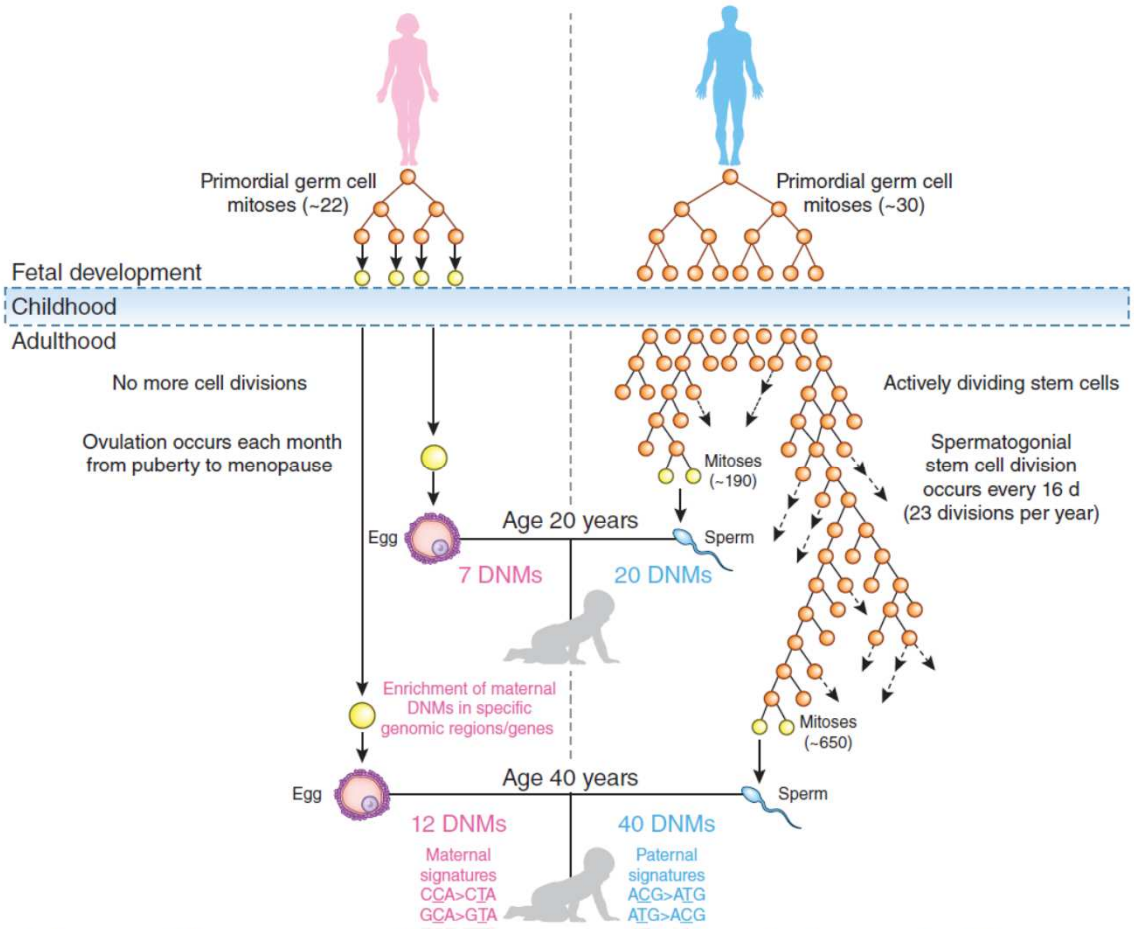
Rate of *de novo* mutations and the importance of father's age to disease risk

Augustine Kong[1], Michael L. Frigge[1], Gisli Masson[1], Soren Besenbacher[1,2], Patrick Sulem[1], Gisli Magnusson[1], Sigurjon A. Gudjonsson[1], Asgeir Sigurdsson[1], Aslaug Jonasdottir[1], Adalbjorg Jonasdottir[1], Wendy S. W. Wong[3], Gunnar Sigurdsson[1], G. Bragi Walters[1], Stacy Steinberg[1], Hannes Helgason[1], Gudmar Thorleifsson[1], Daniel F. Gudbjartsson[1], Agnar Helgason[1,4], Olafur Th. Magnusson[1], Unnur Thorsteinsdottir[1,5] & Kari Stefansson[1,5]

23 AUGUST 2012 | VOL 488 | NATURE | 471



NATURE GENETICS | VOLUME 48 | NUMBER 8 | AUGUST 2016



Decoding germline *de novo* point mutations

Does *de novo* mutation due to increase paternal age is responsible for the increasing of the prevalence of ASD ?

Exome sequencing in sporadic autism spectrum disorders identifies severe *de novo* mutations

Brian J O'Roak[1], Pelagia Deriziotis[2], Choli Lee[1], Laura Vives[1], Jerrod J Schwartz[1], Santhosh Girirajan[1], Emre Karakoc[1], Alexandra P MacKenzie[1], Sarah B Ng[1], Carl Baker[1], Mark J Rieder[1], Deborah A Nickerson[1], Raphael Bernier[3], Simon E Fisher[2,4], Jay Shendure[1] & Evan E Eichler[1,5]

nature genetics

Frequency and Complexity of De Novo Structural Mutation in Autism

The American Journal of Human Genetics *98*, 1–13, April 7, 2016

William M. Brandler,[1,2,3,12] Danny Antaki,[1,2,3,4,12] Madhusudan Gujral,[1,2,3,12] Amina Noor,[1,2,3] Gabriel Rosanio,[1,2,3] Timothy R. Chapman,[1,2,3] Daniel J. Barrera,[1,2,3] Guan Ning Lin,[2] Dheeraj Malhotra,[1,2,3] Amanda C. Watts,[4] Lawrence C. Wong,[5] Jasper A. Estabillo,[5] Therese E. Gadomski,[1,2,3] Oanh Hong,[1,2,3] Karin V. Fuentes Fajardo,[1,2,3] Abhishek Bhandari,[1,2,3] Renius Owen,[6] Michael Baughn,[4] Jeffrey Yuan,[4] Terry Solomon,[4] Alexandra G. Moyzis,[4] Michelle S. Maile,[1,2,3] Stephan J. Sanders,[7] Gail E. Reiner,[8] Keith K. Vaux,[8] Charles M. Strom,[6] Kang Zhang,[9] Alysson R. Muotri,[3] Natacha Akshoomoff,[5] Suzanne M. Leal,[10] Karen Pierce,[11] Eric Courchesne,[11] Lilia M. Iakoucheva,[2] Christina Corsello,[5] and Jonathan Sebat[1,2,3,*]

71 patients ASD, non affected siblings, parents)

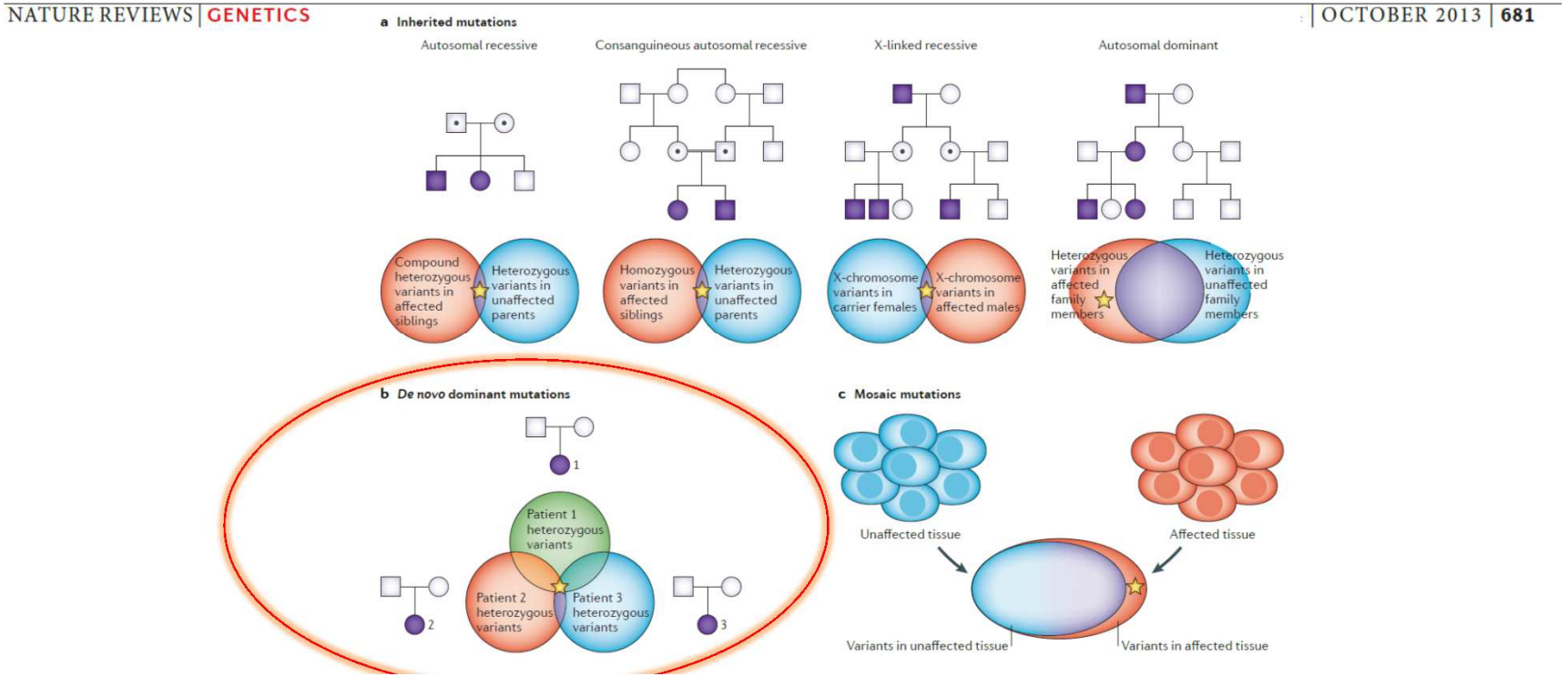
De novo mutations are frequent in ASD

- De novo mutations seems frequent in ASD (and ID)
- Could Explain
  - absence of familial history
  - Increased incidence of ASD

TRANSLATIONAL GENETICS

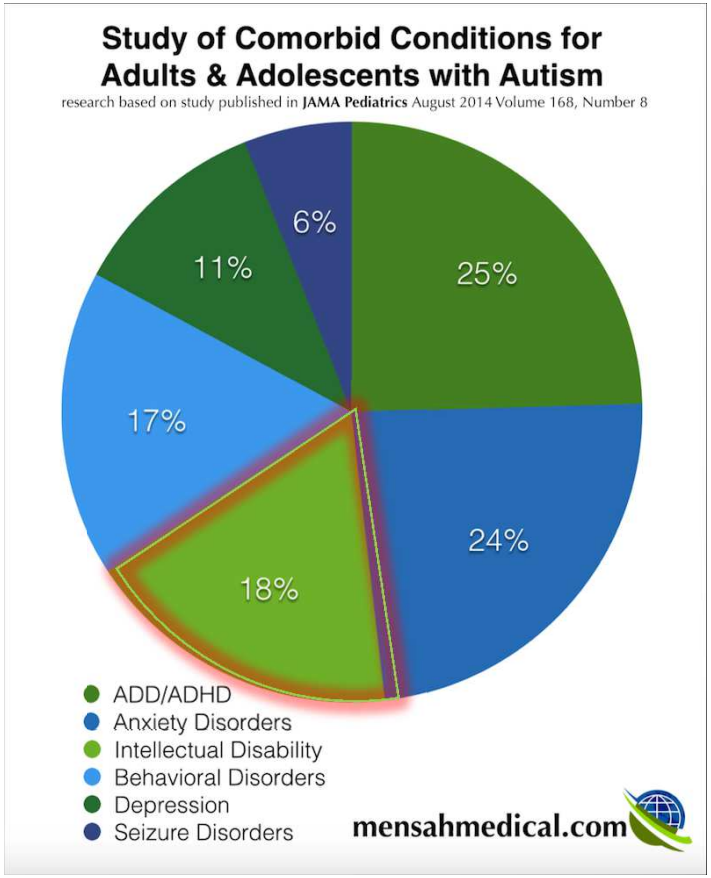
Rare-disease genetics in the era of next-generation sequencing: discovery to translation

Kym M. Boycott, Megan R. Vanstone, Dennis E. Bulman and Alex E. MacKenzie



Does ASD is a disease or feature of genetic disorders ?

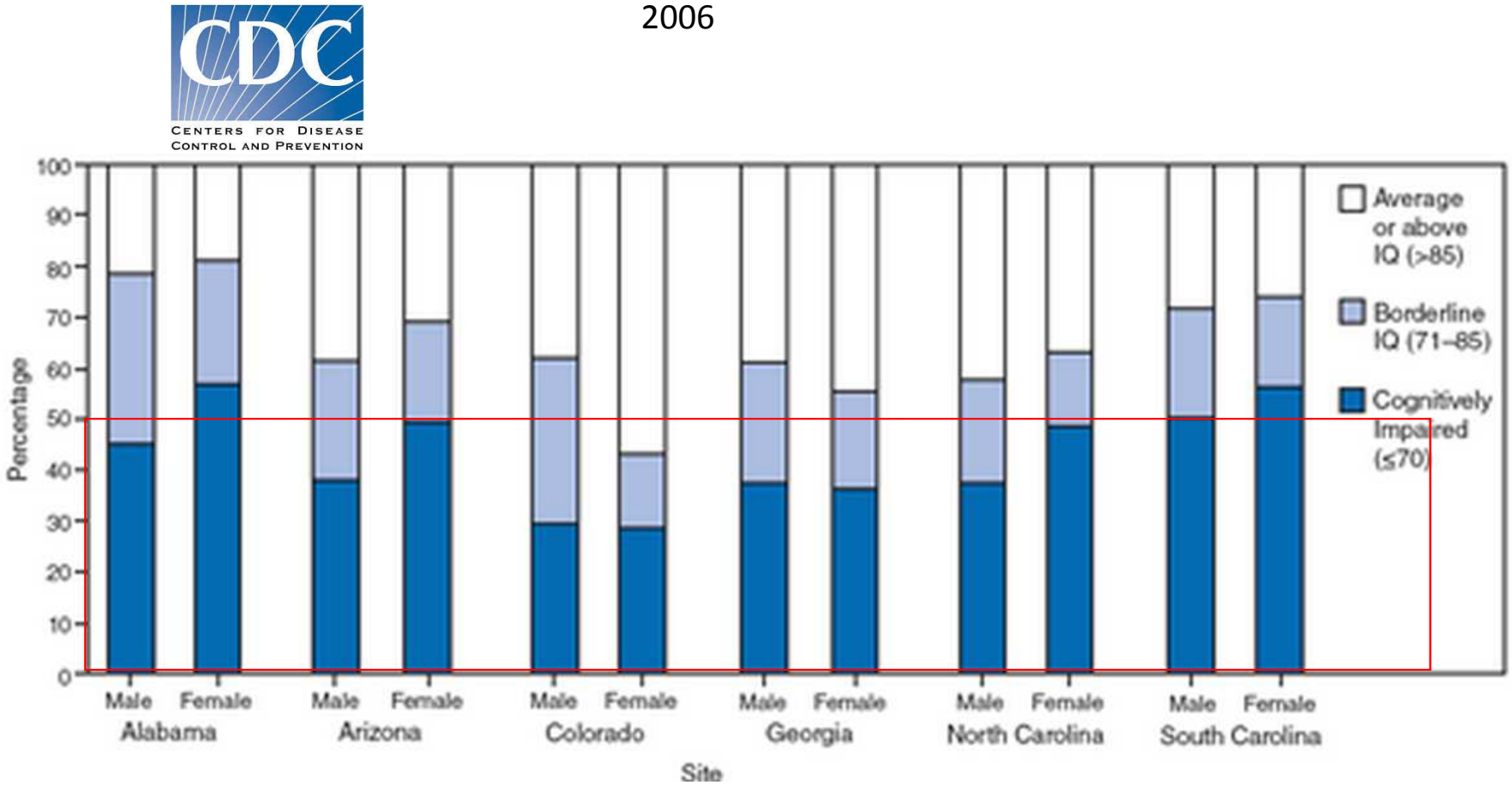
- ASD observed in an isolated or in a syndromic form
  - ID is a comorbidity ?



Stratification into ASD patients +/- ID

- Co-existence of ID and ASD

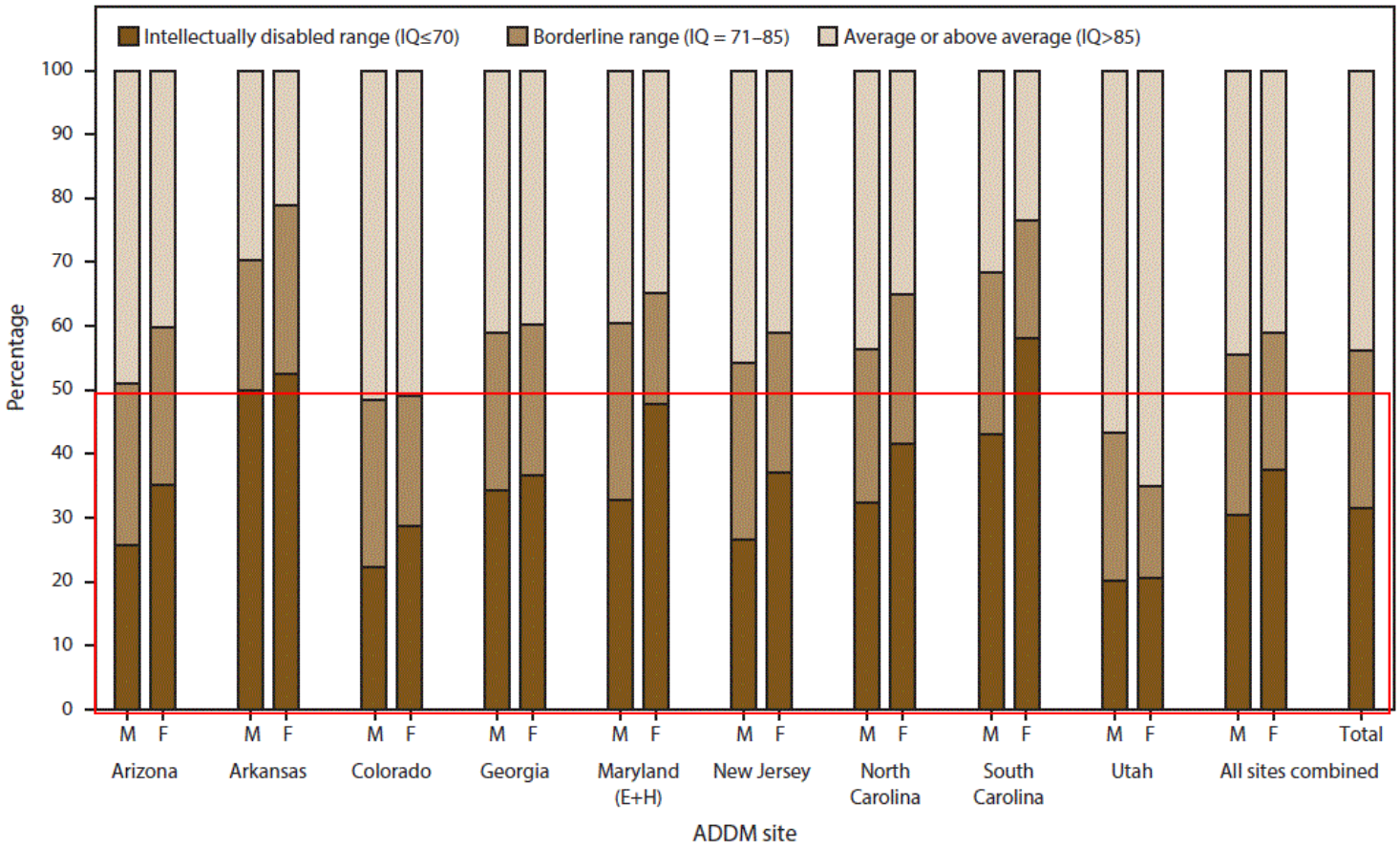
2006



Stratification into ASD patients

- Co-existence of ID and ASD 2012

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION



Focus on genetic of ID

Does Mendelian disorders are frequent in ID ?

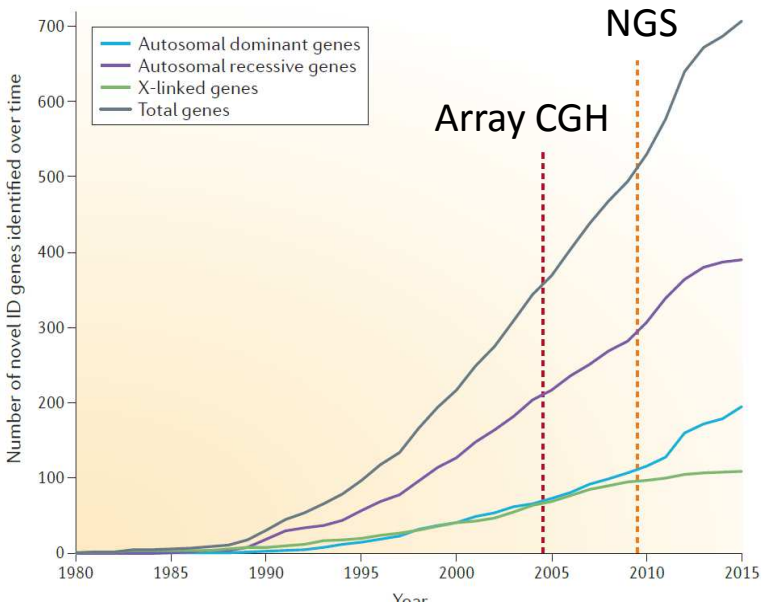
APPLICATIONS OF NEXT-GENERATION SEQUENCING

Genetic studies in intellectual disability and related disorders

Lisenka E. L. M. Vissers[1], Christian Gilissen[1] and Joris A. Veltman[1,2]

NATURE REVIEWS | GENETICS

VOLUME 17 | JANUARY 2016



Does Mendelian disorders are frequent in ID ?

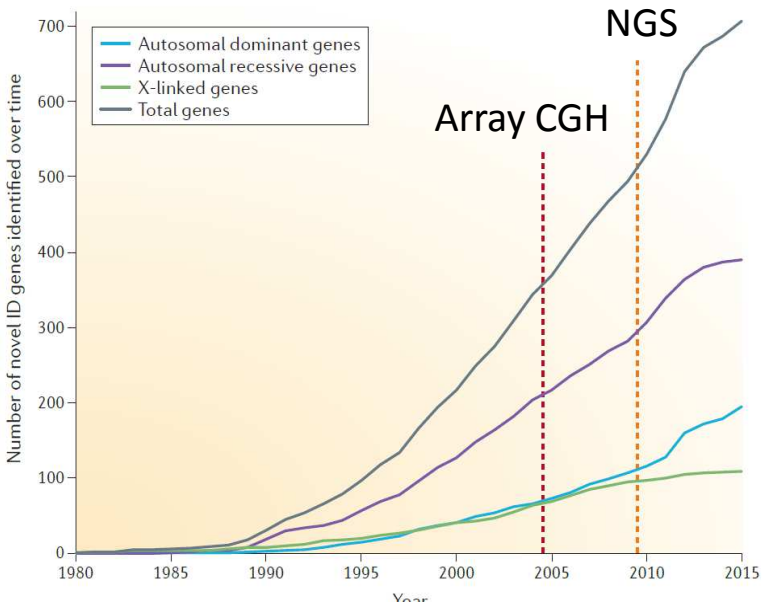
APPLICATIONS OF NEXT-GENERATION SEQUENCING

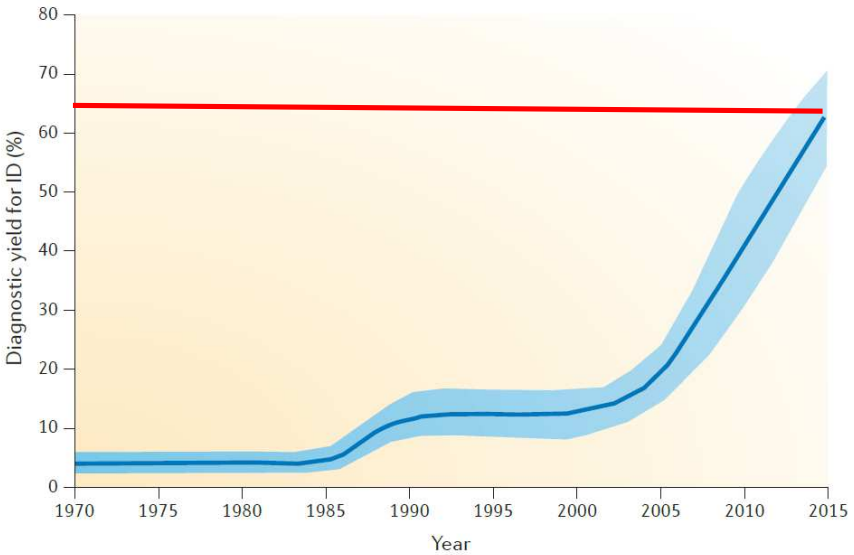
Genetic studies in intellectual disability and related disorders

Lisenka E. L. M. Vissers[1], Christian Gilissen[1] and Joris A. Veltman[1,2]

NATURE REVIEWS | GENETICS

VOLUME 17 | JANUARY 2016





A link between the genetic of ID and ASD ?

APPLICATIONS OF NEXT-GENERATION SEQUENCING

NATURE REVIEWS | GENETICS VOLUME 17 | JANUARY 2016

Genetic studies in intellectual disability and related disorders

Lisenka E. L. M. Vissers[1], Christian Gilissen[1] and Joris A. Veltman[1,2]

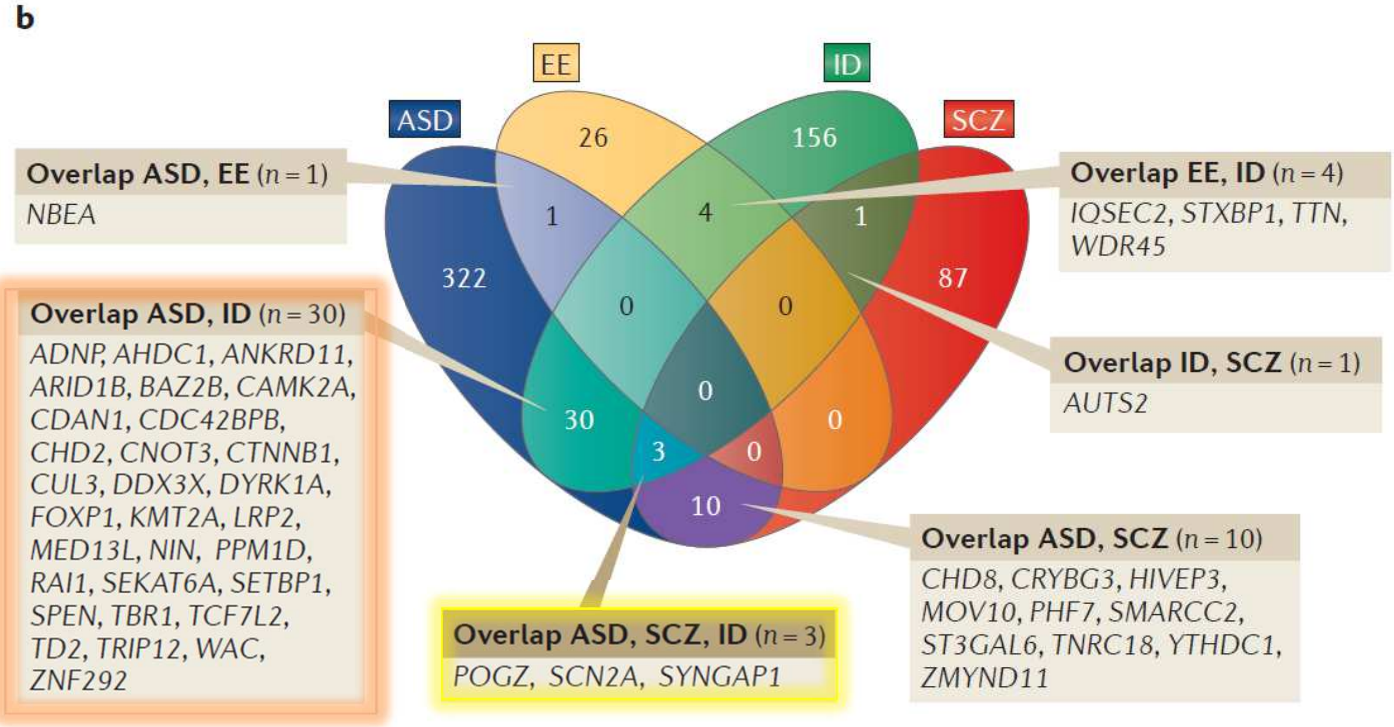
Does ASD as well as ID are features of genetic disorders ?

APPLICATIONS OF NEXT-GENERATION SEQUENCING

NATURE REVIEWS | GENETICS VOLUME 17 | JANUARY 2016

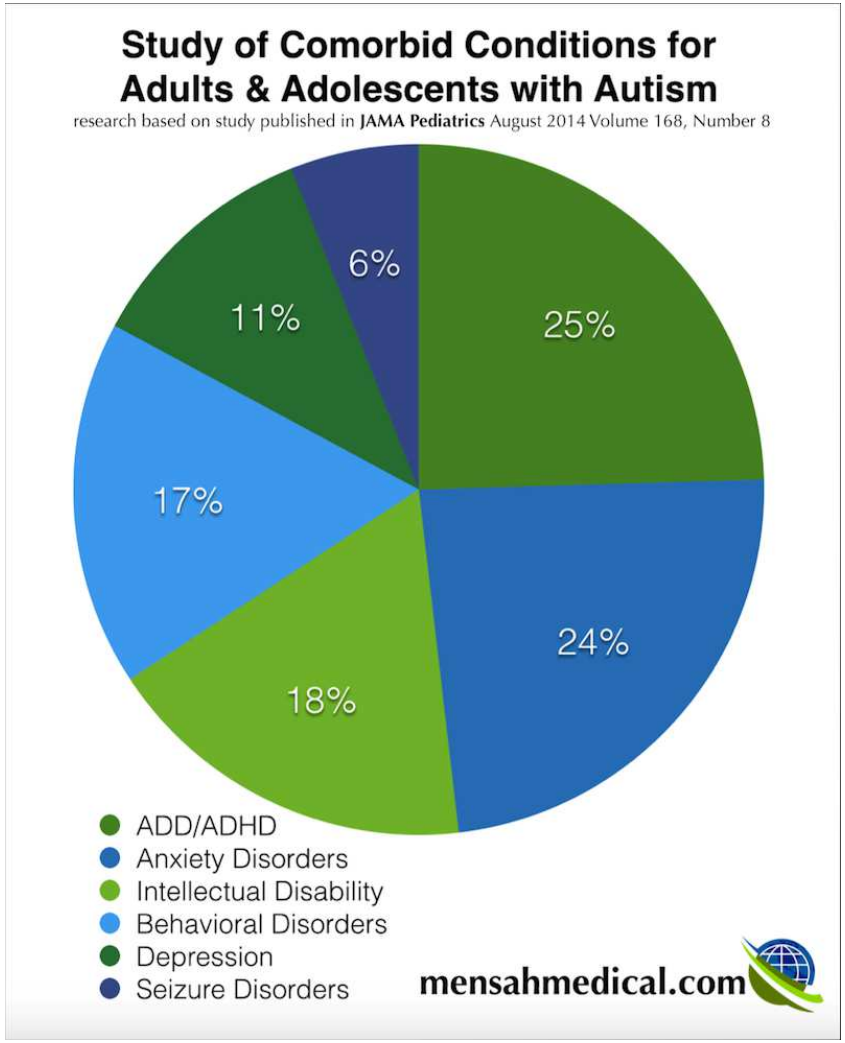
Genetic studies in intellectual disability and related disorders

Lisenka E. L. M. Vissers[1], Christian Gilissen[1] and Joris A. Veltman[1,2]



Concept of features Vs co-morbidities

ID is a comorbidity or a feature?



Concept of features Vs co-morbidities

- Penetrance of features, including ASD, in X fragile syndrome

Co-Occurring Conditions Associated With *FMR1* Gene Variations: Findings From a National Parent Survey

Donald B. Bailey Jr,* Melissa Raspa, Murrey Olmsted, and David B. Holiday
American Journal of Medical Genetics Part A 146A:2060–2069 (2008)

TABLE III. Frequency of Reported Developmental Delay and Other Conditions for Premutation Males Compared With a Sample of Normal Males Matched on Age and Family Income

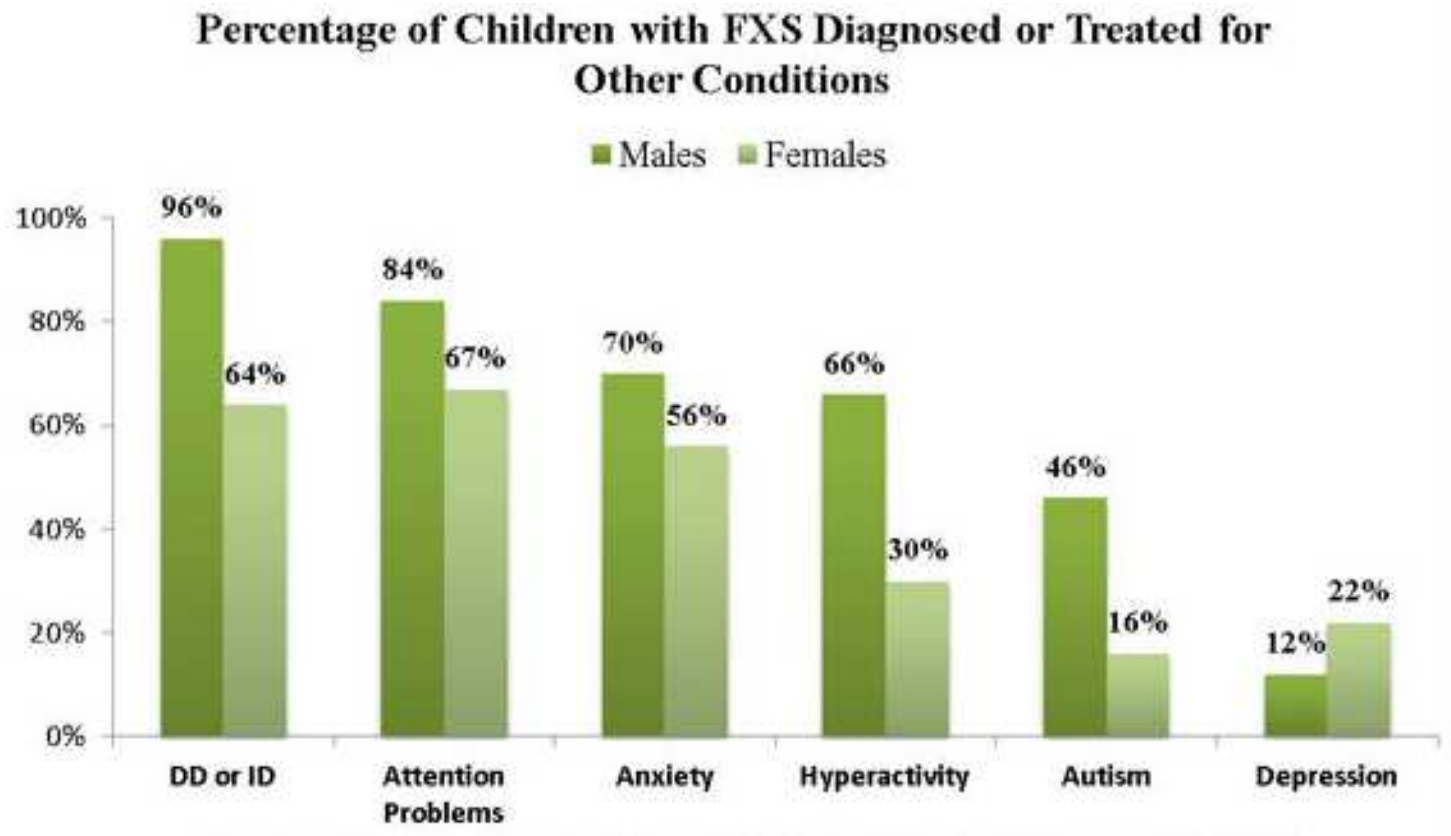
Condition	Premutation males (n = 57)	Non-FX males (n = 57)
Developmental delay	33.0***	1.8
Attention problems	41.1*	21.4
Hyperactivity	28.1	14.0
Aggressiveness	19.3*	5.3
Self-injury	8.9	1.8
Autism	19.3*	5.3
Seizures	11.3**	1.2
Anxiety	33.3**	8.8
Depression	10.7	10.7

*$P < 0.05$
**$P < 0.01$
***$P < 0.001$

Developmental Delay (DD) or Intellectual Disability (ID): 96%
Attention Problems: 84%
Anxiety: 70%
Hyperactivity: 66%
Autism: 46%
Self-Injury: 41%
Aggressiveness: 38%
Obesity: 30% (near general population in USA)
Seizures: 18%
Depression: 12%

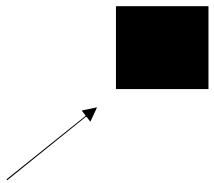
Penetrance of features in a precise diangosis = genetic disorder

- Penetrance of ASD in fragile-X syndrome
- Variability of the expression of features in a genetic disorder



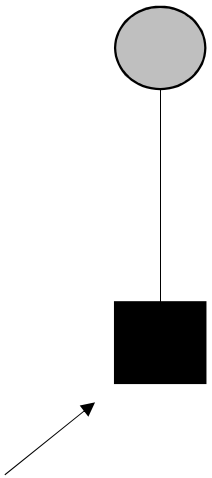
CDC
Centers for Disease Control and Prevention

Expanding features in Fragile X syndromes
Deciphering the genetic aetiologies = knowledge for patients



Fragile X syndrome

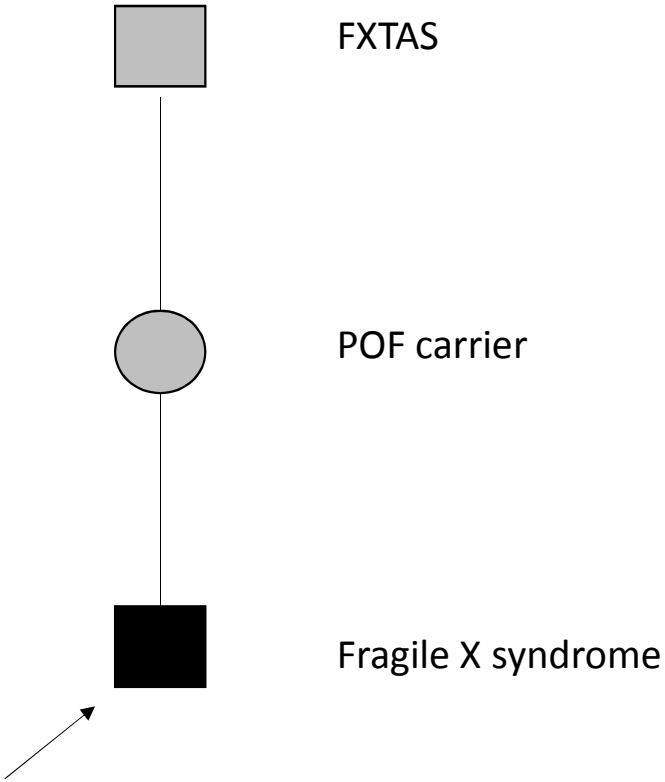
Expanding features in Fragile X syndromes
Deciphering the genetic aetiologies = knowledge for patients



Premature ovarian failure
preservation of fertility
pre implantatory
prenatal procedures

Fragile X syndrome

Expanding features in Fragile X syndromes
Deciphering the genetic aetiologies = knowledge for patients



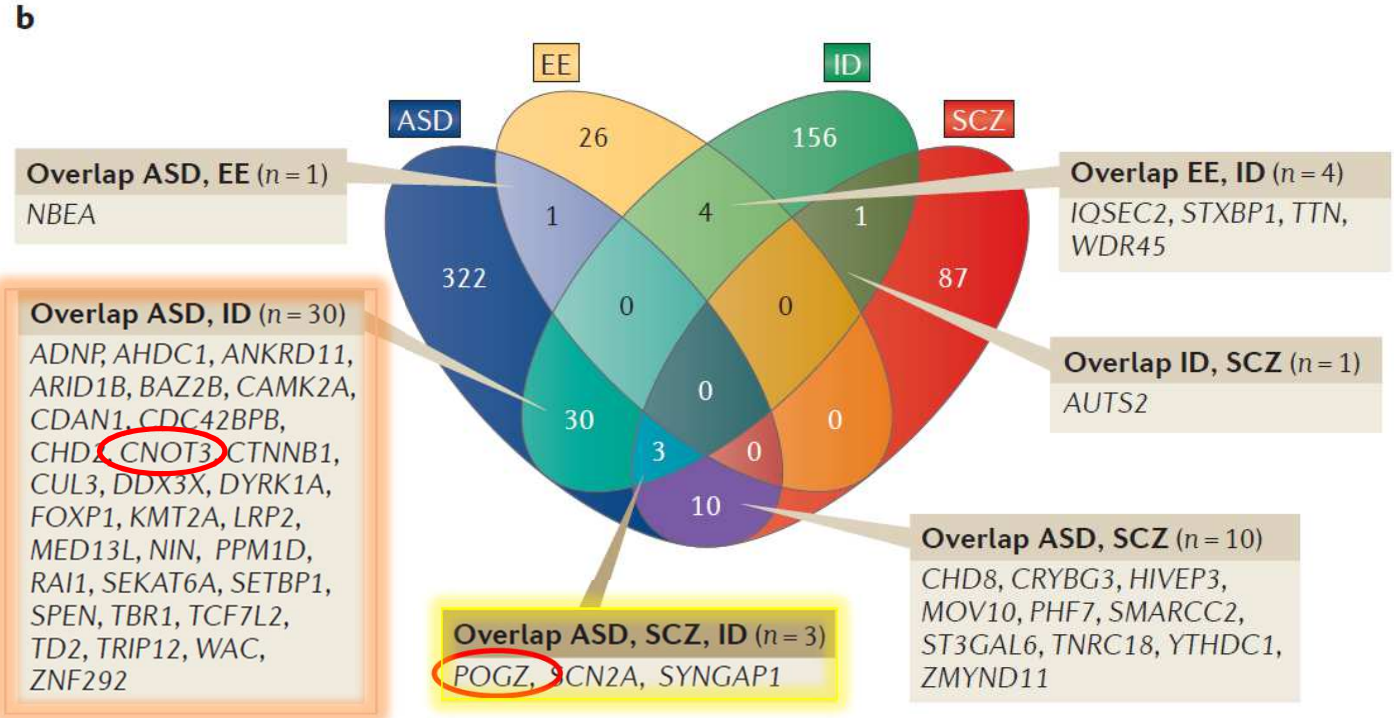
Does ASD is a feature of genetic disorders ? Examples

APPLICATIONS OF NEXT-GENERATION SEQUENCING

NATURE REVIEWS | GENETICS VOLUME 17 | JANUARY 2016

Genetic studies in intellectual disability and related disorders

Lisenka E. L. M. Vissers[1], Christian Gilissen[1] and Joris A. Veltman[1,2]



Examples of variability of genetic disorders

- *POGZ – De Novo* mutation

	FR2
Mutation	c.2400dup (p.Lys801 Glnfs*7)
Age (years)	11
Gender	F
ID/DD	+
Speech or language delay	+
Motor delay	+
ASD	–
Microcephaly	–
Feeding problems	–
Vision problems	–
Obesity tendency	+

Disruption of *POGZ* Is Associated with Intellectual Disability and Autism Spectrum Disorders

Holly A.F. Stessman,[1,28] Marjolein H. Willemsen,[2,3,28,*] Michaela Fenckova,[2,3] Osnat Penn,[1] Alexander Hoischen,[2,3] Bo Xiong,[1] Tianyun Wang,[4] Kendra Hoekzema,[1] Laura Vives,[1] Ida Vogel,[5] Han G. Brunner,[2,3,6] Ineke van der Burgt,[2] Charlotte W. Ockeloen,[2] Janneke H. Schuurs-Hoeijmakers,[2] Jolien S. Klein Wassink-Ruiter,[7] Connie Stumpel,[6] Servi J.C. Stevens,[6] Hans S. Vles,[8] Carlo M. Marcelis,[2] Hans van Bokhoven,[2,3] Vincent Cantagrel,[9,10] Laurence Colleaux,[9,10] Michael Nicouleau,[9,10] Stanislas Lyonnet,[9,10,11] Raphael A. Bernier,[12] Jennifer Gerdts,[12] Bradley P. Coe,[1] Corrado Romano,[13] Antonino Alberti,[13] Lucia Grillo,[14] Carmela Scuderi,[15] Magnus Nordenskjöld,[16] Malin Kvarnung,[16] Hui Guo,[4] Kun Xia,[4] Amélie Piton,[17,18] Bénédicte Gerard,[18] David Genevieve,[19] Bruno Delobel,[20] Daphne Lehalle,[21] Laurence Perrin,[22] Fabienne Prieur,[23] Julien Thevenon,[21] Jozef Gecz,[24] Marie Shaw,[24] Rolph Pfundt,[2] Boris Keren,[25,26] Aurelia Jacquette,[25] Annette Schenck,[2,3] Evan E. Eichler,[1,27,29,*] and Tjitske Kleefstra[2,3,29]

The American Journal of Human Genetics *98*, 541–552, March 3, 2016

Examples of variability of genetic disorders

- *POGZ*

Mutation	Asn882Lysfs*14 de novo
Age (years)	13
Gender	F
ID/DD	+
Speech or language delay	+
Motor delay	+
ASD	+
Microcephaly	-
Feeding problems	-
Vision problems	+
Obesity tendency	-

Examples of variability of genetic disorders

- *CNOT3*
  - De novo NM_014516.3:c.439G>A, p.(Glu147Lys)

Severe ID
    Walk 30 months
    no language
Seizures
ASD
Short stature
Relative macrocephaly

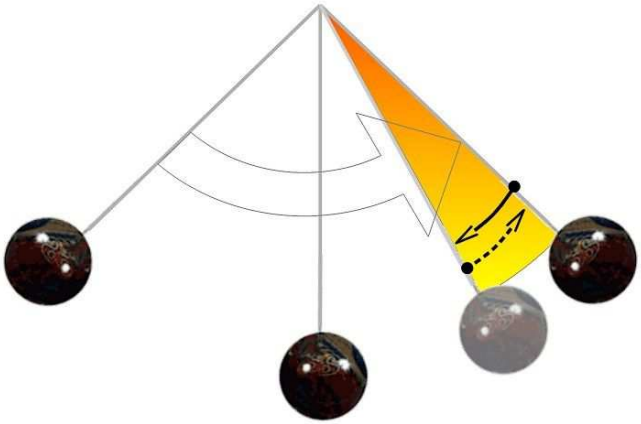
Examples of variability of genetic disorders

- *CNOT3*
  - De novo NM_014516.3:c.1537_1540delAGTG, p.(Ser513Metfs*27)

Learning difficulties
ASD

No Seizures
Normal growth parameters

Mendelian is not All



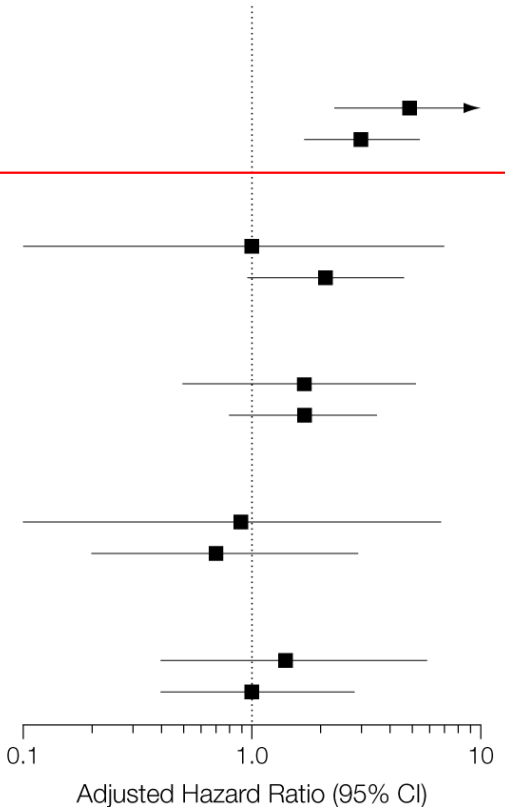
Environment and ASD

Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism

Jakob Christensen, PhD, Therese Koops Grønborg, MSc, Merete Juul Sørensen, PhD, Diana Schendel, PhD, Erik Thorlund Parner, PhD, Lars Henning Pedersen, PhD, and Mogens Vestergaard, PhD

JAMA. 2013 April 24; 309(16): 1696–1703.

	No. Unexposed	No. Exposed	Adjusted Hazard Ratio (95% CI)
Valproate			
Total	655 107	388	
Childhood autism	2058	7	4.9 (2.3-10.3)
Autism spectrum disorder	5423	12	3.0 (1.7-5.4)
Oxcarbazepine			
Total	655 205	321	
Childhood autism	2064	1	1.0 (0.1-6.9)
Autism spectrum disorder	5427	7	2.1 (0.96-4.6)
Lamotrigine			
Total	654 747	647	
Childhood autism	2062	4	1.7 (0.5-5.2)
Autism spectrum disorder	5426	8	1.7 (0.8-3.5)
Clonazepam			
Total	655 233	269	
Childhood autism	2063	2	0.9 (0.1-6.7)
Autism spectrum disorder	5431	3	0.7 (0.2-2.9)
Carbamazepine			
Total	655 153	386	
Childhood autism	2065	2	1.4 (0.4-5.8)
Autism spectrum disorder	5433	4	1.0 (0.4-2.8)

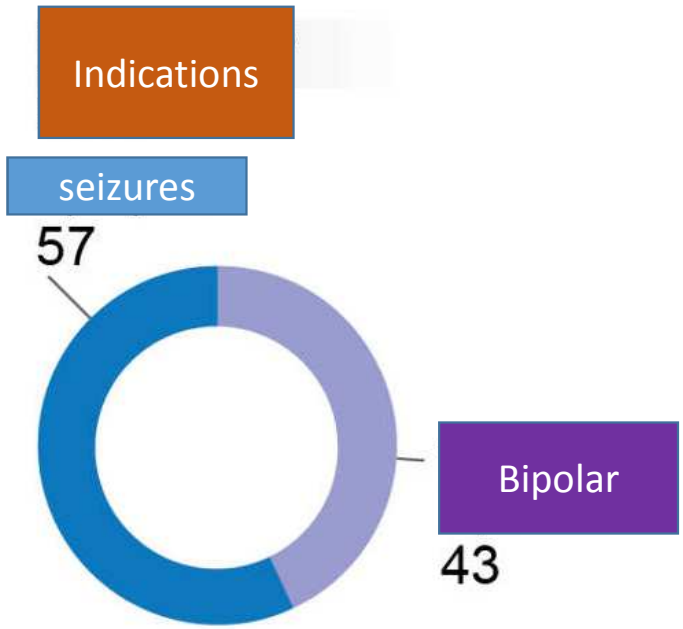


ASD and valproic acid

In France 2007-2015

15 000 pregnancy with in utero exposition to valproic acid

1,9/1000 pregnancy



2017

VALPROATE*+ GROSSESSE = DANGER

Ne pas utiliser chez les filles, adolescentes, femmes en âge de procréer ou enceintes, sauf en cas d'échec des autres traitements

[*] Le nom de la spécialité concernée (Dépakine, Micropakine, Dépamide, Dépakote, génériques) sera indiqué à cet endroit.

Conclusions (for now)

- We need to decipher using exome or genome the ASD “feature” in an attempt to
  - Have a precision diagnostic = genotype = Mendelian disorder
  - Propose a genetic counselling
    - Recurrence or not
  - Adapt the cure and the prevention of the features (phenotype) based on
    - the knowledge of the genetic disease,
    - the penetrance of the associated features
    - and the age of apparition of these features
  - Avoid exposition to known exogenous factors (valproic acid for instance)


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
рахмат
Баярлалаа
спасибо
gracias
merci
obrigado
bedankt
dziękuję
sukriya
kop khun krap
go raibh maith agat
mochchakkeram
tapadh leat
arigatô
dakujem
takk
grazie
terima kasih
감사합니다
ありがとう
ευχαριστώ
мерси
хвала
dank je
hvala
mauruuru
sagolun
taiku
faafetai lava
kiitos
dankie
dhanyavad
nandri
nanni
bayarlalaa
gràçie
enkosi
sobodi
dekuji
mèsi
koszonom
chnorakaloutioun
grafias ago
gràcies
sulpay
akun
dankon
aciu
vinaka
спасибі
blagodaram
mersi
kia ora
barka
welalin
tack
spas
misaotra
matondo
paldies
grazzi
mahalo
asante
manana
obrigada
tenki
murakoze
chokrane
djiere dieuf
fau
дякую
mamnun
trugarez
shukriya
merce
dhanyavadagalu
diolch
rahmet
tanemirt
xiexie
najis tuke
kam sah hamnida
didi madloba
rahmat

Deciphering ASD on other features

IMMEDIATE COMMUNICATION

Targeted sequencing and functional analysis reveal brain-size-related genes and their networks in autism spectrum disorders

Molecular Psychiatry (2017) 22, 1282–1290

Jinchen Li[1,8], Lin Wang[1,8], Hui Guo[1], Leisheng Shi[2], Kun Zhang[2], Meina Tang[1], Shanshan Hu[2], Shanshan Dong[1], Yanling Liu[1], Tianyun Wang[1], Ping Yu[2], Xin He[3], Zhengmao Hu[1], Jinping Zhao[4], Chunyu Liu[1,5], Zhong Sheng Sun[2,6] and Kun Xia[1,7]

536 patients with ASD > 294 genes tested (genes supposed to be involved in brain size) > 22 patients with mutations

Deciphering ASD on other features

IMMEDIATE COMMUNICATION

Targeted sequencing and functional analysis reveal brain-size-related genes and their networks in autism spectrum disorders

Jinchen Li[1,8], Lin Wang[1,8], Hui Guo[1], Leisheng Shi[2], Kun Zhang[2], Meina Tang[1], Shanshan Hu[2], Shanshan Dong[1], Yanling Liu[1], Tianyun Wang[1], Ping Yu[2], Xin He[3], Zhengmao Hu[1], Jinping Zhao[4], Chunyu Liu[1,5], Zhong Sheng Sun[2,6] and Kun Xia[1,7]

Molecular Psychiatry (2017) 22, 1282–1290

536 patients with ASD > 294 genes tested (genes supposed to be involved in brain size) > 22 patients with mutations = 4%

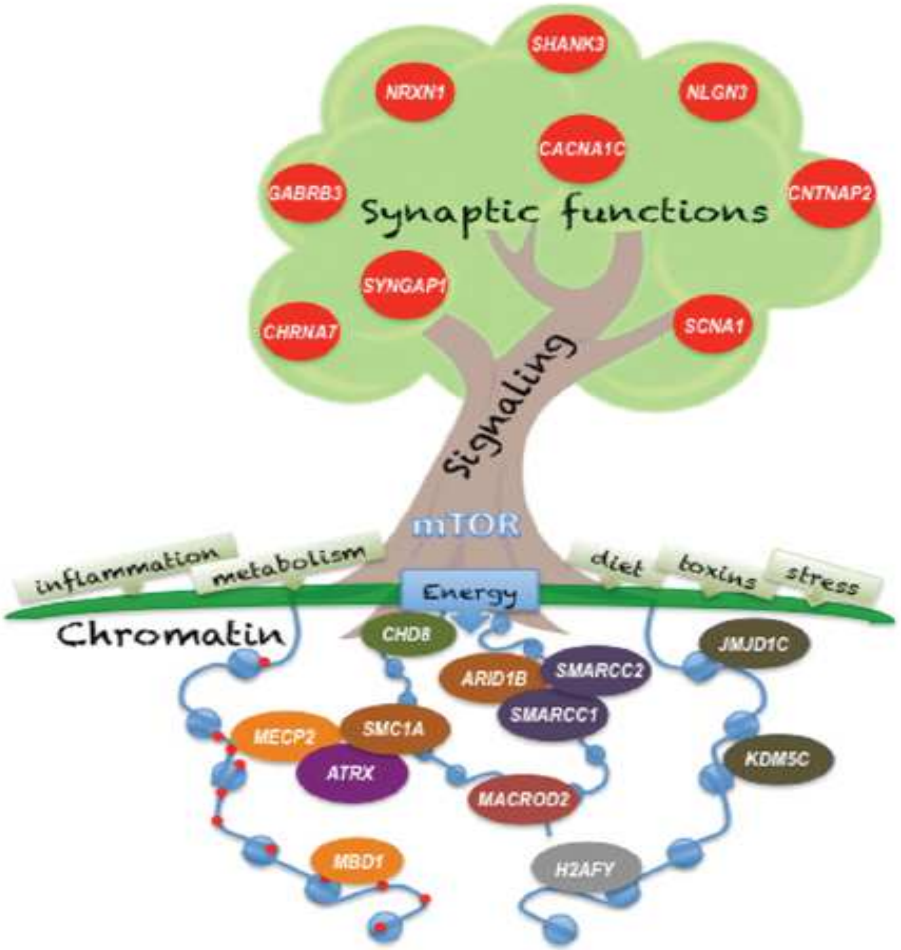
Chr.	Position	Ref	Alt	Gene symbol	GenBank No.	Effect	Nucleotide change	AA. alteration	DNMs in SSC or ASC	PH (percentile)	RVIS (percentile)
DNMs											
chr14	21862265[a]	–	T	*CHD8*	NM_001170629	Frameshift	c.5688dupA	p.R1897fs	7 LoF, 2 Dmis	0.637 (10.3%)	−2.337 (1.2%)
chr14	21862296	AG	–			Frameshift	c.5657delAG	p.T1886fs			
chr21	38853069[a]	G	T	*DYRK1A*	NM_001396	Stop-gain	c.457G>T	p.E153X	4 LoF	0.658 (9.6%)	−0.422 (25.6%)
chrX	153296471[b]	G	A	*MECP2*	NM_001110792	Stop-gain	c.844C>T	p.R282X	1 Dmis	0.359 (24.3%)	−0.885 (10.5%)
chr11	64457918	–	G	*NRXN2*	NM_015080	Frameshift	c.808dupG	p.A270fs	–	0.197 (43.7%)	−2.164 (1.4%)
chr1	151402109[a]	G	A	*POGZ*	NM_207171	Stop-gain	c.379C>T	p.Q127X	3 LoF	0.192 (44.5%)	−1.527 (3.4%)
chr2	166179813[a]	C	T	*SCN2A*	NM_001040143	Stop-gain	c.1819C>T	p.R607X	4 LoF, 7 Dmis	0.566 (12.7%)	−1.990 (1.8%)
chr2	166170189[a]	C	T			Missense	c.1094C>T	p.T365M			
chr9	3248164	TA	–	*RFX3*	NM_001282116	Frameshift	c.1835delTA	p.L612fs	–	0.934 (2.5%)	−0.799 (12.5%)
chr4	114275103[b]	G	C	*ANK2*	NM_001148	Missense	c.5329G>C	p.V1777L	4 LoF, 4 Dmis	0.953 (2.0%)	−3.329 (0.4%)
chr8	1877564	G	A	*ARHGEF10*	NM_014629	Missense	c.3034G>A	p.A1012T	1 Dmis	0.192 (44.6%)	−1.016 (8.1%)
chr9	136913560	C	T	*BRD3*	NM_007371	Missense	c.731G>A	p.R244Q	–	0.437 (18.8%)	−0.705 (14.8%)
chr15	49048380	T	C	*CEP152*	NM_001194998	Missense	c.3065 A>G	p.Q1022R	–	0.139 (57.8%)	0.972 (90.2%)
chr1	240072174	A	T	*CHRM3*	NM_000740	Missense	c.1423 A>T	p.I475F	1 Dmis	0.177 (47.5%)	−0.136 (43.8%)
chr1	53676893	T	C	*CPT2*	NM_000098	Missense	c.1547 T>C	p.F516S	–	0.115 (66.5%)	0.514 (80.3%)
chr5	127702120	T	G	*FBN2*	NM_001999	Missense	c.2252 A>C	p.E751A	–	0.625 (10.7%)	−1.868 (2.0%)
chr12	52635307	A	G	*KRT7*	NM_005556	Missense	c.745 A>G	p.M249V	–	0.250 (35.4%)	1.067 (91.7%)
chr18	48241495	G	A	*MAPK4*	NM_001292040	Missense	c.593G>A	p.R198Q	–	0.136 (58.7%)	−0.511 (21.7%)
chr16	14340619	C	T	*MKL2*	NM_014048	Missense	c.1502C>T	p.S501F	–	0.316 (27.9%)	−1.549 (3.3%)
chr22	36697021	C	T	*MYH9*	NM_002473	Missense	c.2714G>A	p.R905H	1 Dmis	0.259 (34.3%)	−1.994 (1.7%)
chr9	134396829	C	T	*POMT1*	NM_001136114	Missense	c.1444C>T	p.R482W	–	0.134 (59.6%)	−0.301 (32.3%)
chr9	71849443	T	C	*TJP2*	NM_001170415	Missense	c.1772 T>C	p.L591S	–	0.302 (29.1%)	1.459 (95.2%)
Hemizygous variations											
chrX	76814250	C	T	*ATRX*	NM_138270	Missense	c.6280G>A	p.V2094I	–	NA	−0.926 (9.8%)
chrX	18622983	C	A	*CDKL5*	NM_003159	Missense	c.1939C>A	p.P647T	–	0.432 (19.1%)	−0.667 (15.9%)
chrX	153594754	C	T	*FLNA*	NM_001110556	Missense	c.1150G>A	p.V384M	–	0.752 (7.1%)	−3.240 (0.4%)
chrX	13771497	G	C	*OFD1*	NM_003611	Missense	c.1066G>C	p.E356Q	1 LoF, 1 Dmis	0.106 (70.4%)	−0.176 (40.6%)
chrX	153694155	A	T	*PLXNA3*	NM_017514	Stop-gain	c.2497 A>T	p.K833X	1 LoF	0.114 (66.9%)	−2.494 (0.9%)
chrX	153698849	C	T			Missense	c.5051C>T	p.S1684L			
chrX	154493543	G	A	*RAB39B*	NM_171998	Missense	c.31C>T	p.L11F	–	0.432 (19.1%)	0.013 (54.6%)
chrX	152959387	C	A	*SLC6A8*	NM_001142805	Missense	c.C1139A	p.P380Q	1 LoF	0.415 (20.2%)	−0.737 (13.9%)

Epigenetics or mutations in genes controlling epigenetics ?

LaSalle JM. Autism genes keep turning up chromatin. OA Autism 2013 Jun 19;1(2):14.

Table 1 Chromatin genes implicated in autism spectrum disorders

Gene name	Aliases	Human chromosome location	Human disease	Protein function
MECP2	Methyl CpG-binding protein 2, *ARBP*	Xq28	Rett syndrome, autism (rare mutation or aberrant methylation)	Binds mCpG, repression, chromatin dynamics
ATRX	*RAD54, XH2*	Xq21.1	Thalassaemia, intellectual disabilities	SWI/SNF chromatin remodelling, ATPase/helicase domain
H2AFY	*MACROH2A1.1*	5q31.1	Autism (association)	Histone H2 variant, X chromosome inactivation
SMC1A	Cohesin, *CDLS2*	Xp11.22	Cornelia de Lange syndrome	Chromosome cohesion
MACROD2		20p12.1	Autism (association)	O-acetyl-ADP-ribose deacetylase, binds this metabolite from histone deacetylation
KDM5C	*JARID1C, SMCX*	Xp11.22	ASD, ID (rare mutations)	Histone demethylase of H3K4, gene repression
MBD1	*CXXC3*	18q21	Autism (rare mutations), also rare variants in related genes *MBD4, MBD5*	Binds mCpG, links mCpG to H3K9me3
ARID1B	*BAF250B*	6p25.3	Coffin-Siris syndrome, mental retardation autosomal dominant type 12 (*MRD12*), autism (rare)	Component of SWI/SNF chromatin remodelling complex, AT-rich binding domain
SMARCC1	*BAF155*	3p31.21	Autism (rare mutation)	Component of SWI/SNF chromatin remodelling complex and neuronal BAF complex (nBAF)
SMARCC2	*BAF170*	12q13.2	Autism (rare mutation)	Component of SWI/SNF chromatin remodelling complex and nBAF
JMJD1C	*TRIP8*	10q21.3	Autism (rare mutation, translocation, abnormal methylation)	Histone demethylase for H3K9, hormone-dependent transcriptional activation
CHD8	*AUTS18*	14q11.2	Autism (rare mutation), also rare autism variants in family members *CHD1, CHD3, CHD7*)	ATP-dependent chromatin helicase, negative regulator of Wnt signalling pathway by regulating beta-catenin (*CTNNB1*)



Constant progression of Knowledge

Review

Intellectual disability and autism spectrum disorders: Causal genes and molecular mechanisms

Anand K. Srivastava, Charles E. Schwartz*

Neuroscience and Biobehavioral Reviews 46 (2014) 161–174

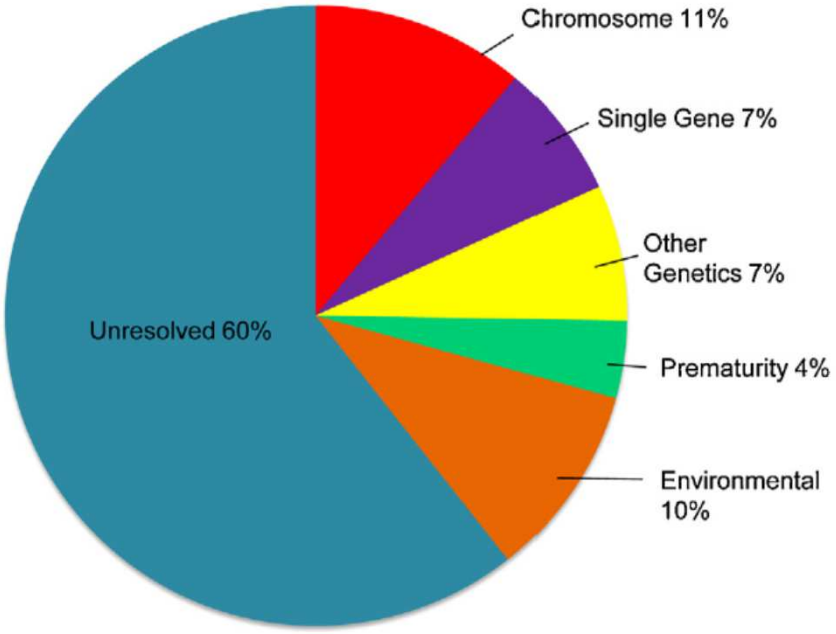


Fig. 1. Etiological causes of intellectual disability. Percentages are based on the evaluation of 15,484 individuals seen by the Greenwood Genetic Center.

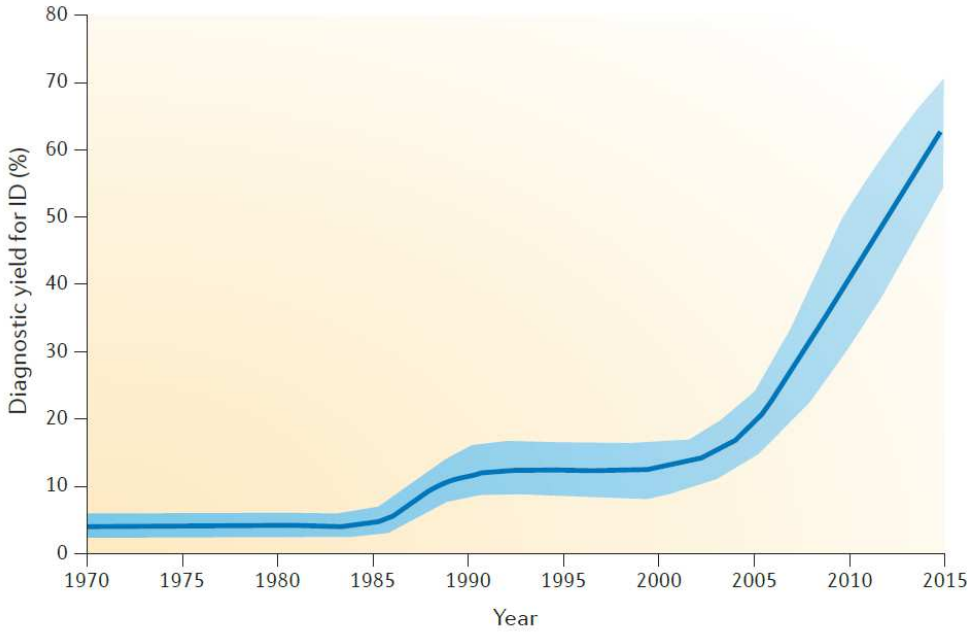
APPLICATIONS OF NEXT-GENERATION SEQUENCING

Genetic studies in intellectual disability and related disorders

Lisenka E. L. M. Vissers[1], Christian Gilissen[1] and Joris A. Veltman[1,2]

NATURE REVIEWS | GENETICS

VOLUME 17 | JANUARY 2016 |



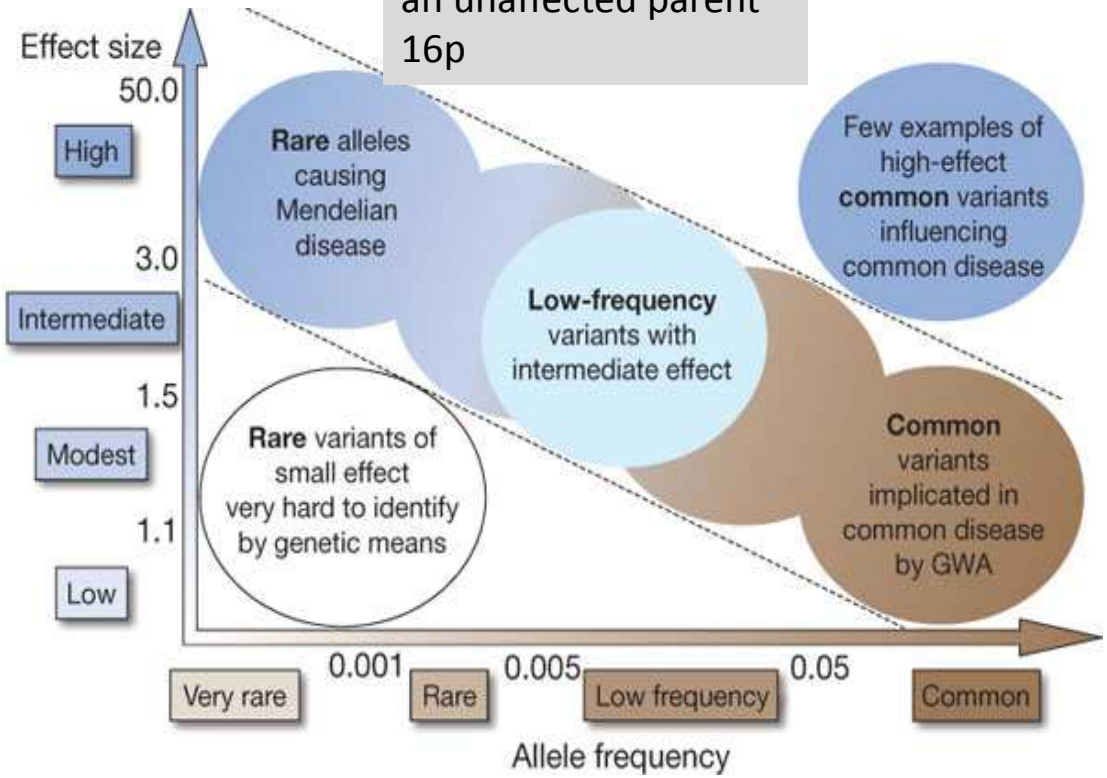
Concepts in genetics

Effect of genetic variants

Rare variant with strong effect vs frequent variant without or only weak effect

Mendelian disorders
Penetrant variant
- Mutation
- CNV
  - 22q13 (SHANK3)
  - 22q11,2

Predisposition variant
Often inherited from an unaffected parent
16p



Frequent variant
Weak effect
- SNP from GWAS

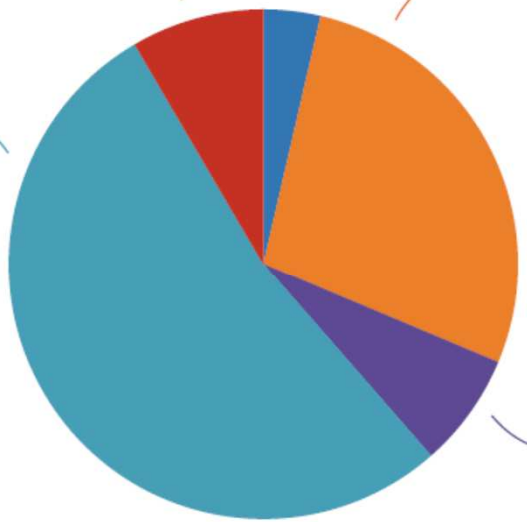
CNV in ASD (and ID)

Convergence of Genes and Cellular Pathways Dysregulated in Autism Spectrum Disorders

2446 patients

The American Journal of Human Genetics *94*, 1–18, May 1, 2014

A



Chromosomal abnormalities
Unbalanced translocation (n=2, 1 dn, 1 inh)
Terminal 1q duplication syndrome (n=1, dn)
Ring chromosome 8 syndrome (n=1, dn)
Down syndrome (n=1, dn)
XYY syndrome (n=2, 2 dn)

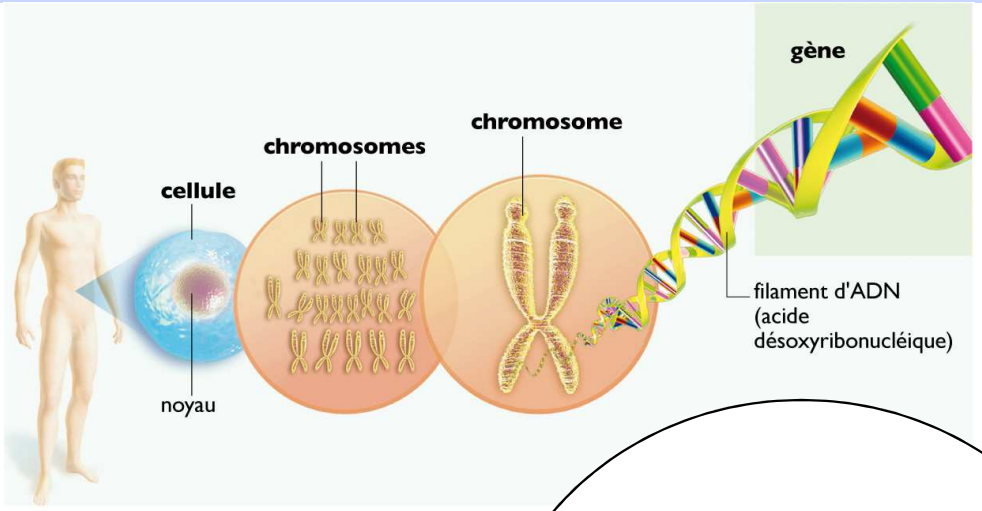
Genomic disorders, recurrent breakpoints
1q21.1 deletion syndrome (n=1, dn)
1q21.1 duplication syndrome (n=4, 3 dn, 1 inh)
Williams syndrome (7q11.23 deletion) (n=1, dn)
10q11.21-q11.23 deletion (n=2, 1 dn, 1 inh)
15q11-q13 duplication syndrome (n=7, 5 dn, 2 inh; origin: 6 mat, 1 pat)
15q13.3 deletion syndrome (n=4, 1 dn, 3 inh)
Distal 15q25 deletion syndrome (n=1, inh)
16p13.11 deletion syndrome (n=3, 3 inh)
16p11.2 deletion syndrome (n=5, 4 dn, 1 inh)
16p11.2 duplication syndrome (n=4, 2 dn, 2 inh)
Smith-Magenis syndrome (17p11.2 deletion) (n=2, 2 dn)
17q12 duplication syndrome (n=1, inh)
22q11 deletion syndrome (DiGeorge syndrome) (n=2, 2 dn)
22q11 duplication syndrome (n=5, 2 dn, 3 inh)
Xq28 duplication including *GDI1* (n=2, 1 dn, 1 XL mat)

Rare, large, de novo CNV (n=3, 1.6-4.5 Mb)

CNV disrupting ASD and/or ID genes
NRXN1 exonic deletion (n=8, 4 dn, 4 inh)
NRXN1 intragenic duplication (n=1, dn)
HDAC4 exonic deletion (n=1, inh)
SYNGAP1 exonic deletion (n=1, dn)
ARID1B exonic deletion (n=1, dn)
SHANK2 exonic deletion (n=3, 3 dn)
CHD2 exonic deletion (n=1, dn)
SHANK3 exonic deletion (n=1, dn)
PTCHD1 exonic deletion (n=1, XL mat)
IL1RAPL1 intragenic duplication (n=1, XL mat)
DMD exonic deletion (n=2, XL mat)
DMD exonic duplication (n=1, XL mat)
CASK partial duplication (n=1, XL mat)

Genomic disorders, nonrecurrent breakpoints
Terminal 9p deletion (n=1, dn)
Kleefstra syndrome (9q34.3 deletion) (n=1, dn)
Jacobsen syndrome (11q deletion) (n=1, dn)
Phelan-McDermid syndrome (22q13 deletion) (n=3, 3 dn)

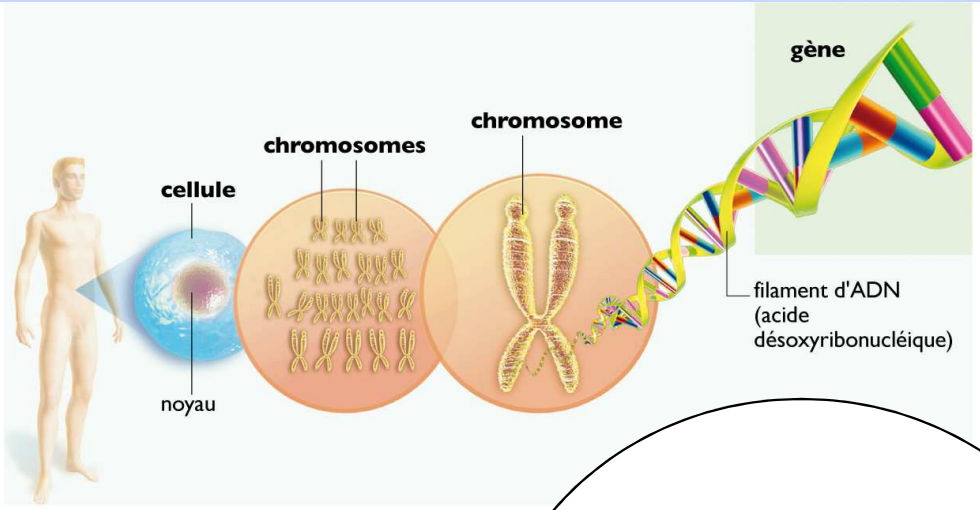
Emerging Knowledge

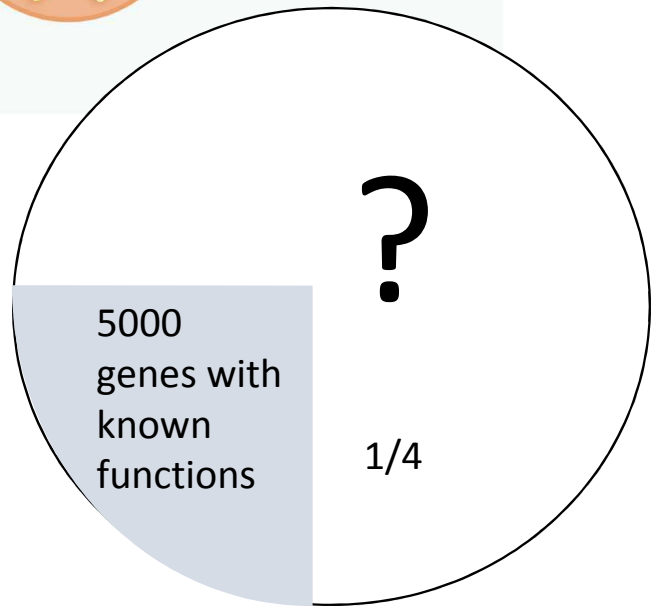


- Genetic information in DNA
  - 46 (2x23) ADN molecules (chromosomes)
  - 2x20 000 genes

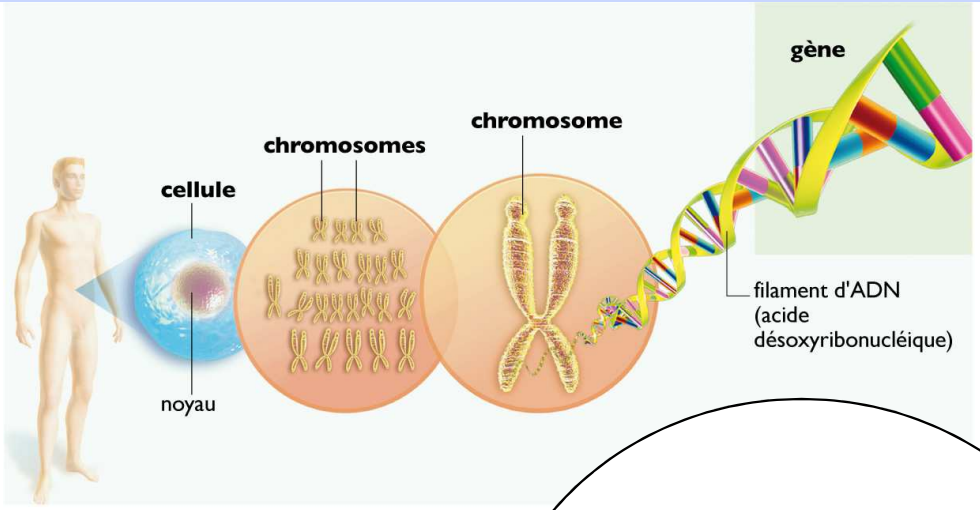
2X20 000 genes

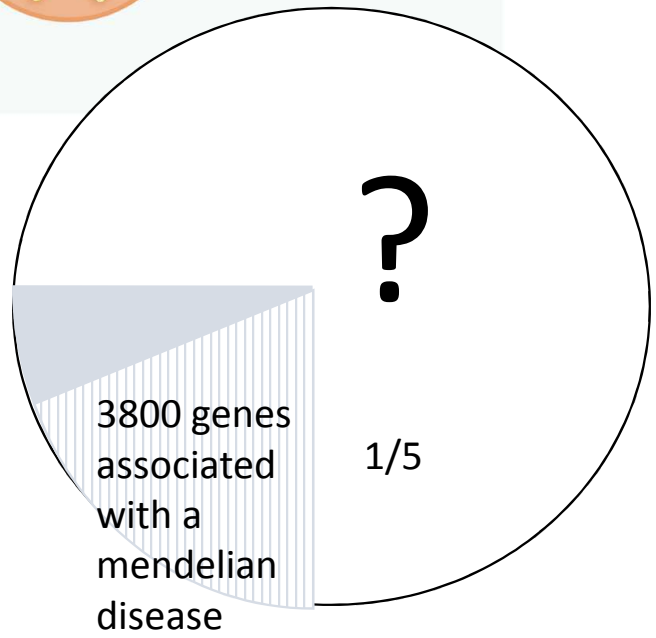
Emerging Knowledge



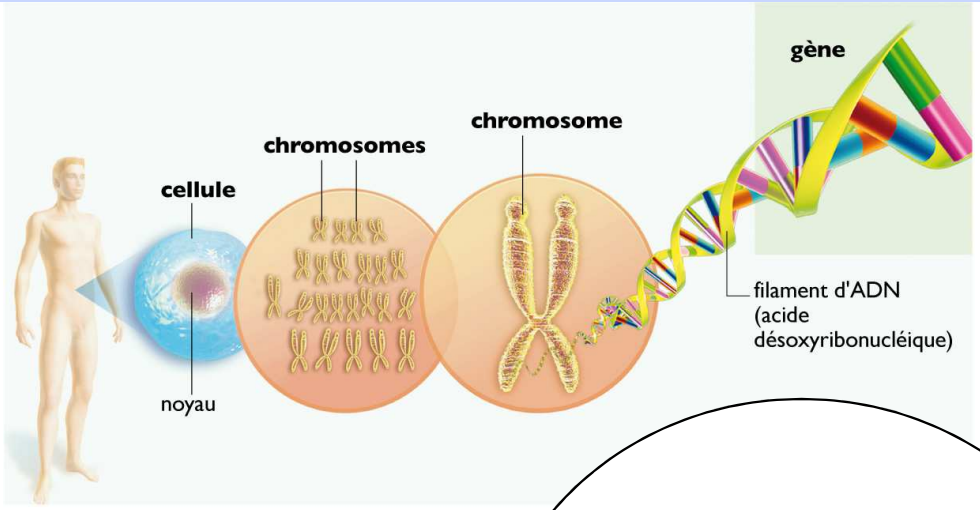


Emerging Knowledge





Emerging Knowledge

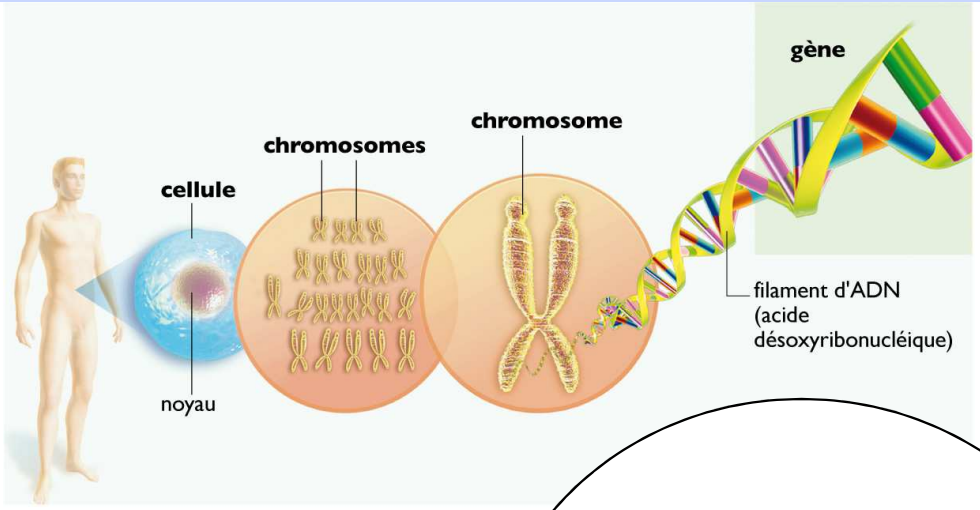


8000 genetic diseases

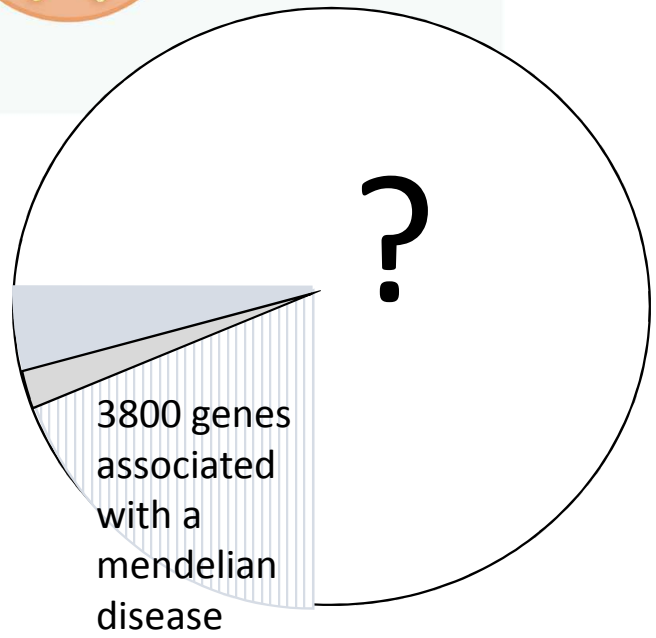
?

3800 genes associated with a mendelian disease

Emerging Knowledge



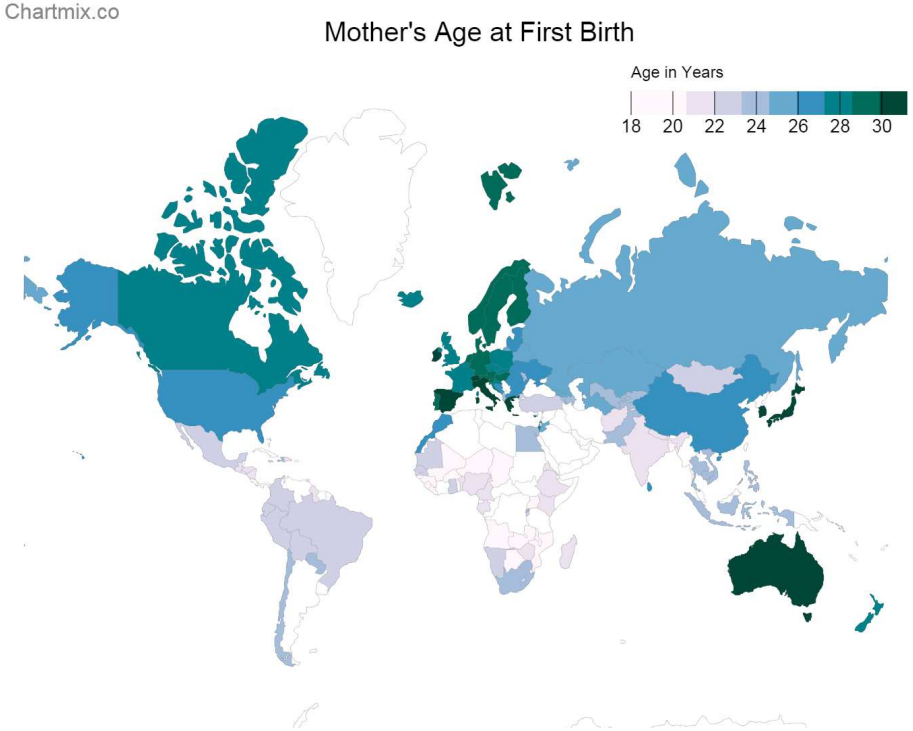
4 to 5
New diseases by week
60 new genes in ID in 2016

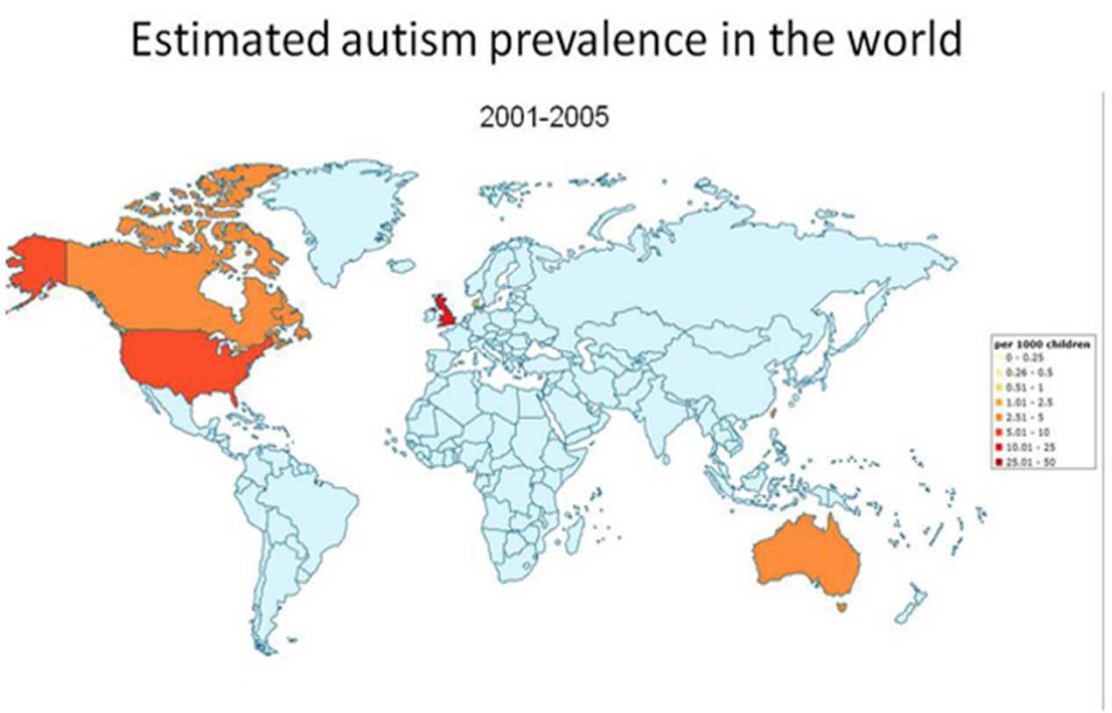


8000 genetic diseases

Increased maternal and paternal age and incidence of ASD?

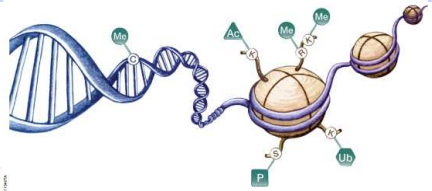
Chartmix.co





Complexe diseases

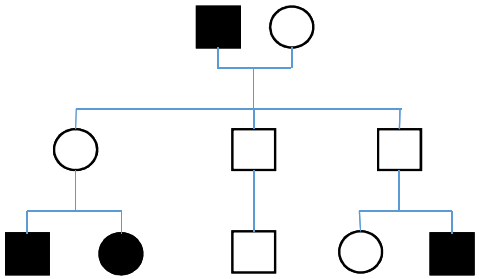
Multifactorial aetiology



epigenetic

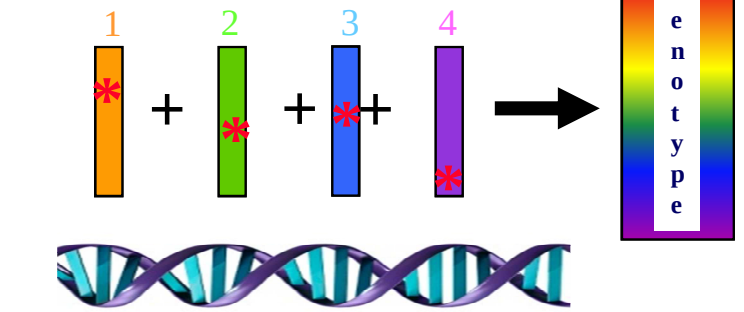
environment

Familial aggregation of cases



But not classical heredity

Genetic variant



The same gene is responsible for several disorders

One gene, many neuropsychiatric disorders: lessons from Mendelian diseases

Xiaolin Zhu[1], Anna C Need[1,2], Slavé Petrovski[1,3] & David B Goldstein[1]

NATURE NEUROSCIENCE VOLUME 17 | NUMBER 6 | JUNE 2014