The familial risk of Tourette syndrome and OCD

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Objectives

- To compare the heritability of Tourette syndrome (TS) and OCD.
- To know the different techniques and studies used to assess the genetic risk.
- To discuss how to communicate this risk to patients and what the clinical implications are.

Parents frequently ask…

Are Tourette syndrome and OCD genetic diseases?

Why does my child have several mental health disorders?

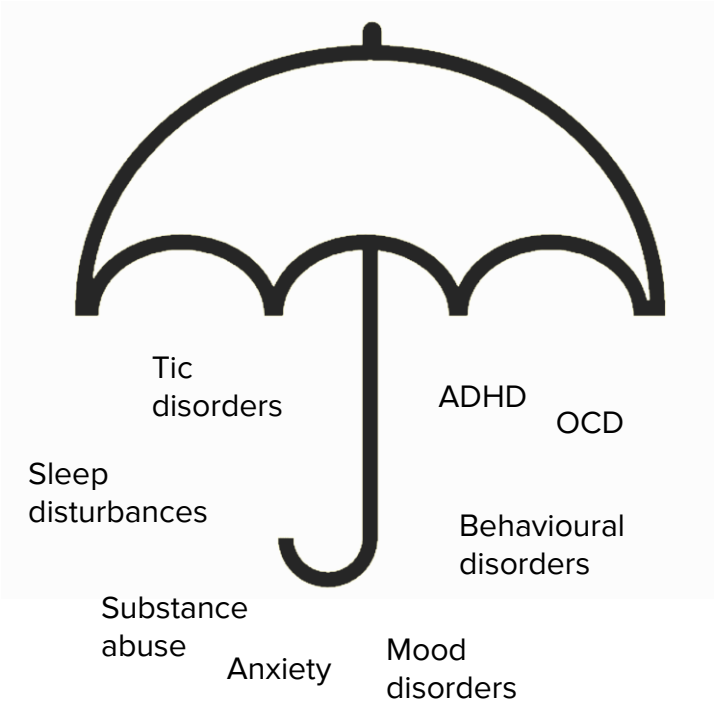
- **47%** of patients with Tourette have a tic family history.

  Robertson, 2015 (n=90)

- Prevalence of OCD in 1st degree relatives: **10-12%.**

  Nestadt *et al.*, 2000 (n=80)

The neurodevelopmental umbrella



Genetic studies have investigated the mode of transmission of both disorders in recent decades.

Tourette syndrome

DSM 5 criteria	A. Presence of two or more motor tics and at least one vocal tic (not necessarily concurrently).
	B. Occurring beginning before 18 years of age.
	C. Lasting more than 1 year.

Epidemiology of Tourette syndrome

- **Prevalence: 0.77%** in children
  1.06% in boys.
- **4 males : 1 female.**
- **Peak: 6 years old.**

Meta analysis, Knight *et al.*, 2012

Obsessive Compulsive Disorder

DSM 5 criteria	A. Presence of obsessions, compulsions, or both.
	B. The obsessions or compulsions are time-consuming (e.g. > 1h/day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
	C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
	D. The disturbance is not better explained by the symptoms of another mental disorder.

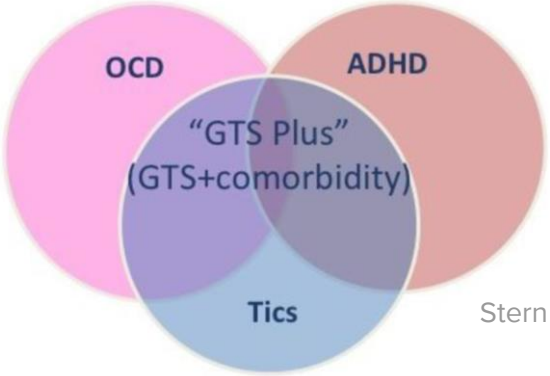
Epidemiology of OCD

- **Lifetime prevalence: 1-3%** Mahjani *et al*, 2021
- **1.6 female : 1 male** in adolescence and adulthood.
- **Peak: 13-18 years and early adulthood.**

Fawcett *et al*, J Clin Psychiatry. 2020

Comorbid OCD and TS

Overlapping neurodevelopmental syndromes



Stern *et al*, 2018

Shared symptomatology and epidemiology:

- Repetitive patterns of behaviours.
- **Tic-related compulsive behaviors:** subtype of tic. — APA, 2013
- **Tic-related OCD:** subtype of OCD. — Brander *et al*, 2019
- **OCD in 50.0% of TS patients**; subclinical OCD in 66.1%. — Hirschtritt *et al*, 2015 (n=1374 TS)
- **Females with TS: more likely to have comorbid OCD** (57.1% vs 47.5%; $p < .01$). — Hirschtritt *et al*, 2015
- Both are associated with anxiety, major depressive disorder, ADHD, ASD.

Heritability of Tourette syndrome and OCD

Genetic risk in Tourette: family and twin studies (1)

Concordance: the rate at which a pair of individuals share a diagnosis.

Population	Results of the studies	Reference
43 twin pairs	**Tourette syndrome** **Monozygotic concordance 53% > dizygotic concordance 8%**	Price *et al.* 1985
	Any tics **Monozygotic concordance 77% > dizygotic concordance 23%**	
86 TS, 338 relatives	Recurrence: 5% (females) and > 10% (males) in 1st-degree relatives.	Pauls *et al.* 1991
Review of family studies	10-100 fold increase in risk for 1st-degree relatives.	O'Rourke *et al.*, 2009

Genetic risk in Tourette: family and twin studies (2)

Heritability: estimate of how well differences in people's genes account for differences in their traits.

Population	Results of the studies	Reference
2658 MZ pairs, 3780 DZ pairs	**Tic disorders: Monozygotic concordance 63%** **> dizygotic concordance 34%**	Polderman *et al.* 2015
Clinical family study, n=4,826 with TS or chronic tic disorders in the Swedish National Patient Register	**Heritability of tic disorders: 77%**	Mataix-Cols *et al.* 2015

And what about OCD?

Family studies

- **Recurrence risk among 1st degree relatives for lifetime OCD**: **6%-55%**

  Bienvenu *et al.*, 2012, do Rosario-Campos *et al,* 2005, Browne *et al.,* 2014

- **Risk is also higher in relatives for OC symptoms and behaviours.**

  do Rosario-Campos *et al,* 2005

Twin studies

- **OCD concordance rate in twins:**
  - **52%** in monozygotic twins
  - **21%** in dizygotic twins

    Monzani *et al.,* 2014 (n=5409 female twins)

- **Similar patterns observed for OC symptoms:**
  - **87%** concordance rate in 15 MZ twin pairs
  - **47%** in 15 DZ twin pairs.

  Carey et Gottesman, 1981

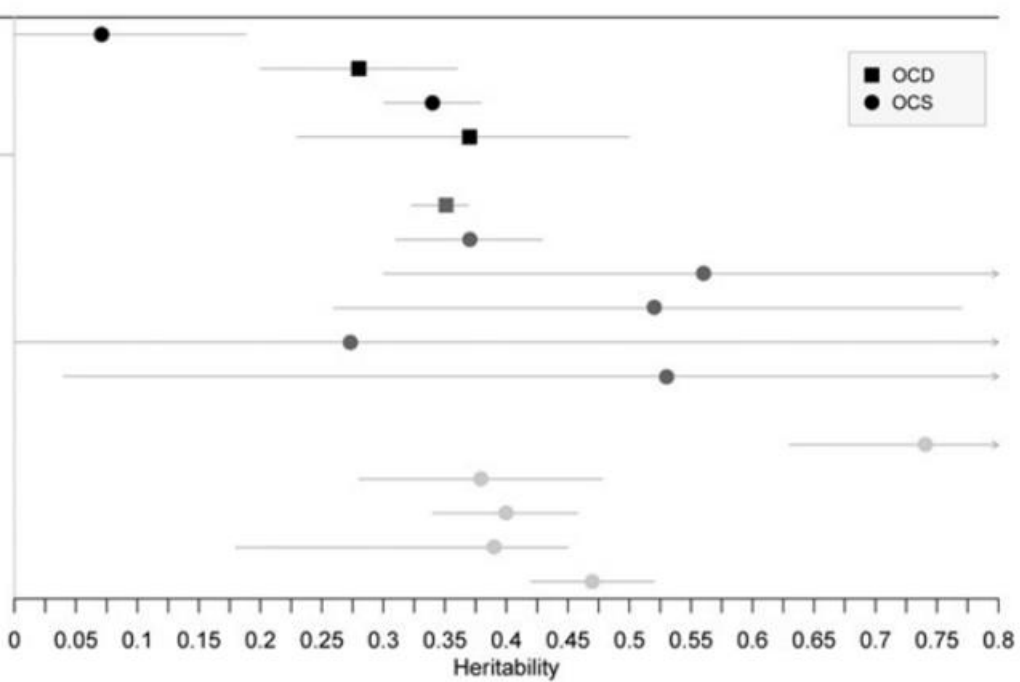
Heritability of OCD and OC symptoms

Heritability of OCD: 42-65%

Pinto *et al,* 2016 (n=21,911 Swedish adult twins)

Mahjani *et al,* 2021

	Authors/Study type	Age at measurment	Measure
GWAS	Burton, 2021	Child and adolescent	TOCS
	IOCDF-GC, 2017	Mixed ages	Dx
	den Braber, 2016	Adults	PI-R-ABBR
	Davis, 2013	Mixed ages	Dx
Pedigree design	**(Family studies)**		
	Mahjani, 2020	Adults	Dx
	Hirschtritt, 2018	Mixed ages	TSAICG Tic and TICS
	Mathews, 2011	Mixed ages	YBOCS
	Katerberg, 2010	Adults	YBOCS-CL
	Mathews, 2007	Child and adolescent	LOI-CV
	Mathews, 2007	Child and adolescent	YBOCS
	(Twin studies)		
	Burton, 2018	Child and adolescent	TOCS
	Zilhão, 2016	Adults	PI-R-ABBR
	Mathews, 2014	Adults	PI-R-ABBR
	López-Solà, 2014	Adults	OCI-R
	Mataix-Cols, 2013	Adults	Validated questionnaires



(using different study types and assessment methods)

TS and OCD: both heritable disorders.

The familial aggregation of Tourette syndrome (77%) is substantially higher than the familial aggregation of OCD (42-65%).

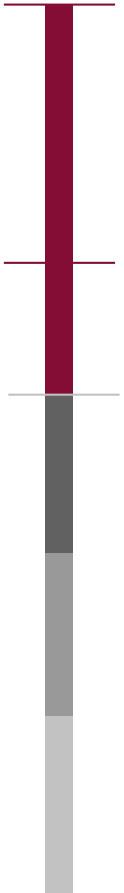
How genes might contribute to TS and OCD?

1. Linkage studies in TS

1990-2000s

Hypothesis: TS and OCD are autosomal dominant diseases.

Genetic linkage analysis



Domènech *et al.*, 2021

Map trait-chromosome region in families.
Several candidates loci.

No gene or causal mutation of major effect has been discovered.

- HDC locus (chr 15) in 9 relatives with TS

  Ercan-Sencicek *et al*, 2010
- Not reproducible in 720 TS cases and recent studies.

Hypotheses:

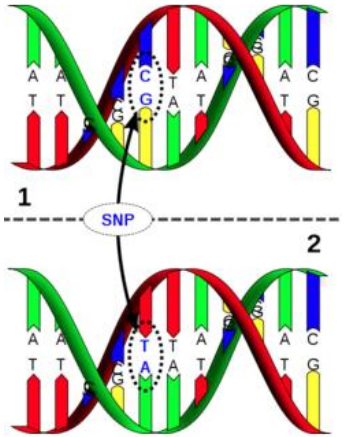
- some families carry a heavy load of common risk variation?
- or high penetrance of rare noncoding risk variants?

2. Candidate gene association studies: TS

1990-2000s

Hypothesis: TS and OCD are autosomal dominant diseases.

Genetic linkage analysis
Candidate gene association studies

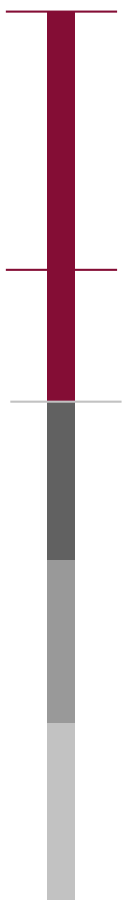


These studies: assess allele frequencies within populations (Single Nucleotide Polymorphism, SNP).

In TS, candidate genes:

- dopamine receptor/transporter genes; (Herzberg *et al.* 2010)
- noradrenergic transcripts; (Chou *et al.*, 2007)
- genes affecting neurotransmission (e.g. MAO-A) (Díaz-Anzaldúa *et al*. 2004)
- genes involved in neurodevelopment, neuroendocrine, metabolic functions. (Bertelsen *et al*. 2016)

No significant reproducible findings have been found.



1990-2000s

Hypothesis: TS and OCD are autosomal dominant diseases.

Genetic linkage analysis
Candidate gene association studies

2. Candidate gene association studies: OCD

> 100 candidate gene studies of OCD have been published.

OCD has been associated with polymorphisms in:

- serotonin genes (SLC64A; HTR2A)
- dopamine genes (COMT; MAOA)
- glutamate genes (*SLC1A1*)
- genes involved in immune and white matter pathways.

But mixed results & few replicated findings (small sample sizes, statistical significance based on singles studies).

Pauls *et al.*, 2014

Yanjie Qi *et al.*, 2019;

1990-2000s

Hypothesis: TS and OCD are autosomal dominant diseases.

Genetic linkage analysis
Candidate gene association studies

2010s

Hypothesis: TS and OCD are polygenic diseases.

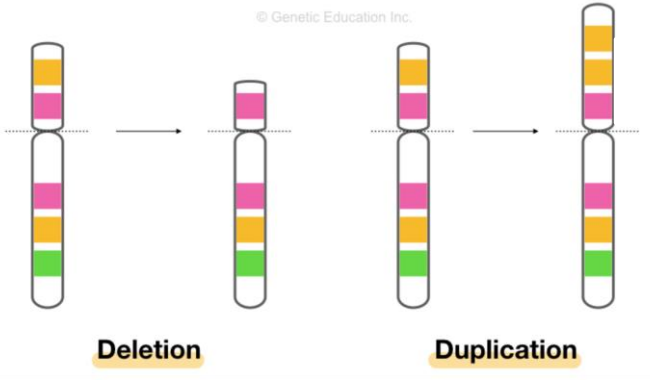
CNVs

3. Copy Number Variants (CNVs)

CNV: structural variation (duplication, deletion, insertion) that affects large segments of DNA. May encompass genes and lead to dosage imbalances. Rare.

Detected by CGH array.

Have shown to be significant risk factors for several neuropsychiatric disorders.



3. Copy Number Variants (CNVs)

Tourette

Significant excess of rare CNVs potentially pathogenic:

- *NRXN1* and *CNTN6* Sundaram *el al.*, 2010
- *NRXN1 del (OR 20.3) and CTNNA3 dup (OR 10.1)* Huang *et al.*, 2017
- rare de novo CNVs in TS in 802 parent-child trios Wang *et al.*, 2018

These CNVs were previously implicated in schizophrenia, autism, and ADHD (overlap).

Domènech *et al.*, 2021

OCD

The overall rate of CNV burden does not differ between OCD patients and controls.

- Potential higher frequency of rare CNVs affecting “brain genes or loci” (e.g. PTPRD, BTBD9, NRXN1, ANKS1B, 16p13.11) previously linked to OCD, TS and neurodevelopmental disorders.

Gazzellone *et al.*, 2016; Grünblatt *et al.*, 2017; McGrath *et al.*, 2014

1990-2000s

Hypothesis: TS and OCD are autosomal dominant diseases.

Genetic linkage analysis
Candidate gene association studies

2010s

Hypothesis: TS and OCD are polygenic diseases.

CNVs

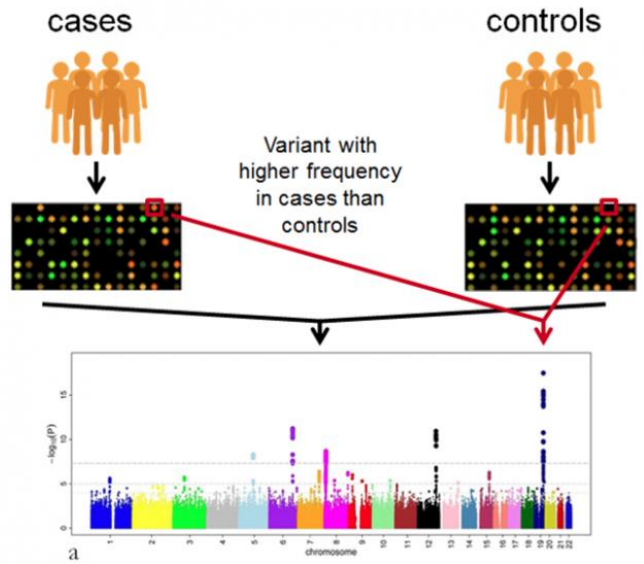
GWAS

4. Genode-Wide Association Study (GWAS)

Correlation between genetic variants (common SNPs-frequency ≥ 5%) with a trait in different individuals.

Case-control study, or family-based.

SNP array



Powerful tool to detect genetic risk factors at the human genome-wide level.

4. Genode-Wide Association Study (GWAS)

Tourette

1st GWAS of common genetic variants: no significant loci was detected. Insufficient sample size.

Scharf *et al.*, 2013 (n=1285 cases/ 4964 controls)

Largest / most recent GWAS: significant locus in FLT3 / failed to replicate in an independent cohort.

Yu *et al.*, 2019 (n=4819 cases/ 9488 controls, combined analysis)

Polygenic risk scores: predictive of TS affected status and tic severity?

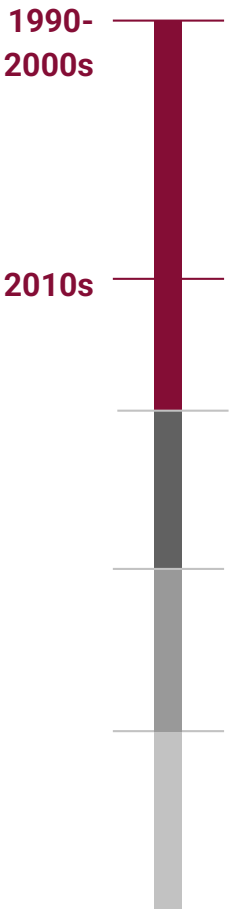
Domènech *et al.*, 2021

OCD

Six GWAS + a meta-analysis.

- Until 2021, no genome-wide significant loci identified.
- 2021: a locus in the gene encoding **PTPRD** protein was associated with OC traits.

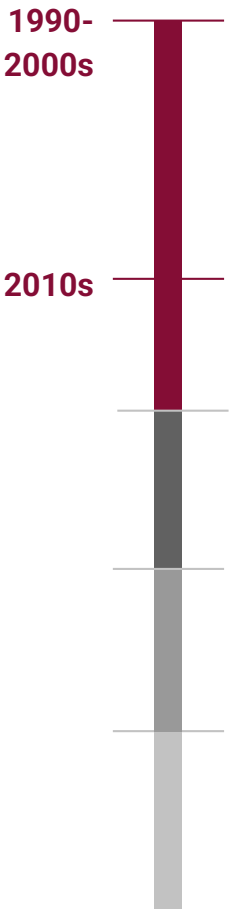
Stewart *et al.* 2013a
Mattheisen *et al.* 2015
IOCDFGC, OCDCGA 2018
Burton *et al.*, 2021



5. Whole-Exome Sequencing (WES)

- Next-generation sequencing (NGS).
- Sequencing all coding regions of the entire human genome.
    - rare variants (frequency ≤ 1%);
    - Indels;
    - single-nucleotide variants (SNV).
- Fast and cost-effective method.

Within psychiatric genetics: used to detect rare coding variants that are near-absent from the general population.



5. Whole-Exome Sequencing (WES) and Tourette syndrome

WES in several TS families cohorts since 2011:

- De novo damaging variants found in 400 genes: contribute to the genetic risk in 12% of cases.

  Willsey *et al.*, 2017

- Identification of likely risk genes for TS (SNV)...

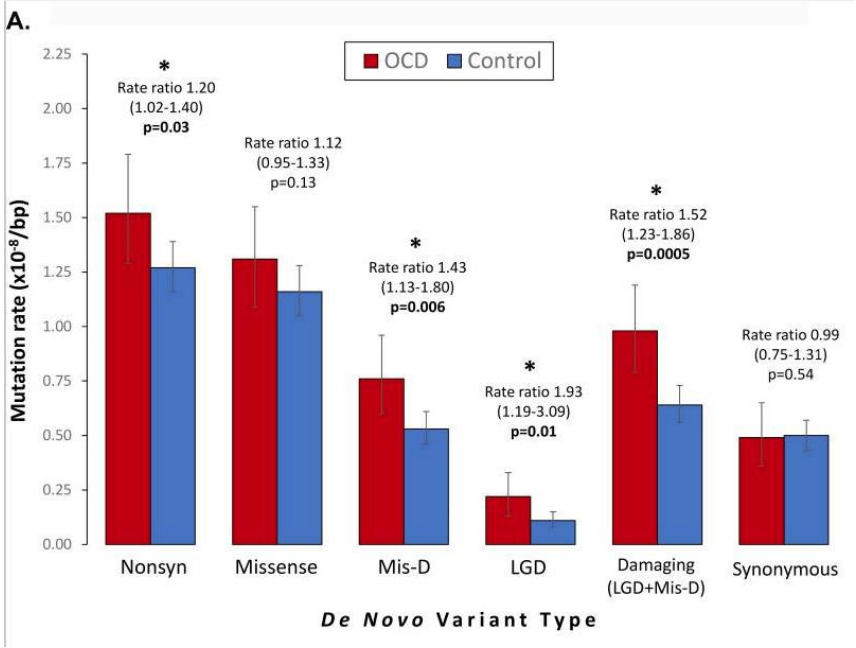
  Sundaram *et al,* 2011
  Sun *et al,* 2018
  Eriguchi *et al.*, 2017

...But none of the results have been confirmed in larger samples or supported by functional studies.

➔ ***not yet classified as TS risk genes.***

5. Whole-Exome Sequencing (WES) and OCD

De novo damaging DNA coding mutations are associated with obsessive-compulsive disorder and overlap with Tourette's disorder and autism



Comparison of the rates of de novo mutation types between **OCD cases** and **controls**.

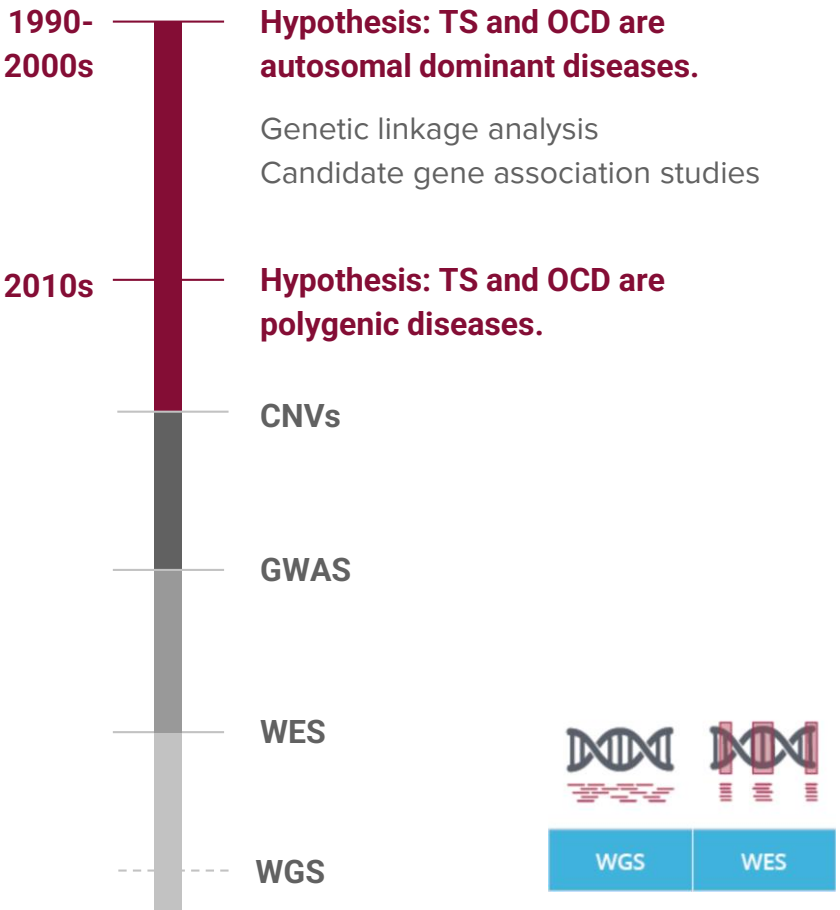
De novo variants in 335 genes contributed to risk of OCD in 22% of cases.

Significant overlap between genes with de novo variants in OCD - genes reported in TS and autism.

Cappi *et al.*, 2020 (WES of 184 trios with an affected OCD proband and 777 trios with unaffected probands)

6. Whole genome sequencing (WGS)

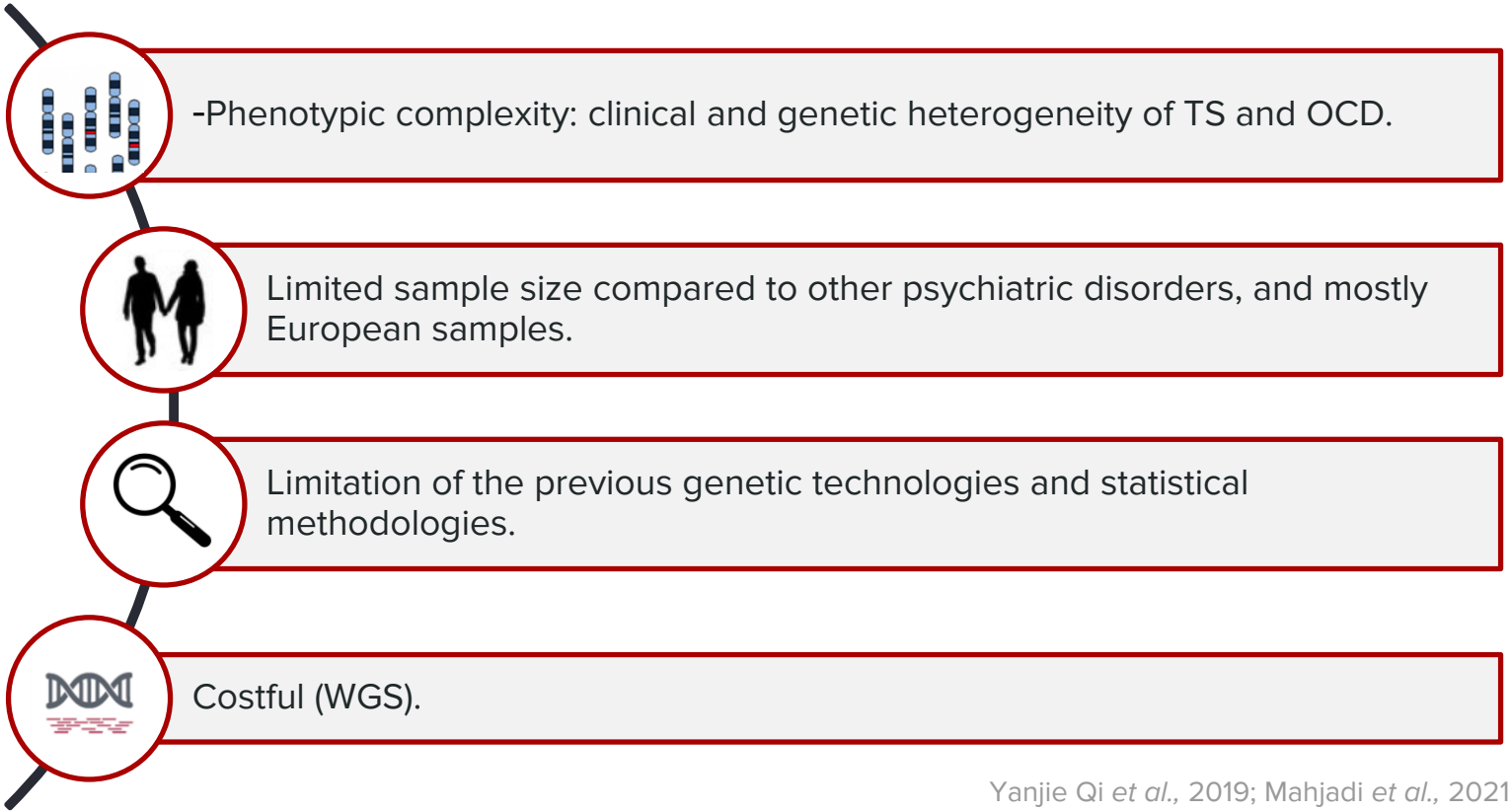
- **Complete characterization of common and rare variation:**
  - all variants detectable in array and WES data;
  - rare noncoding SNVs and “indels”.
- CNV **that are too small to be reliably detected in array data.**
- **But:**
  - Difficult analyses;
  - Costful method.



Domènech *et al*, 2021

TS and OCD are complex, highly heritable and polygenic disorders.

Why can’t we find a responsible gene?



Yanjie Qi *et al.*, 2019; Mahjadi *et al.*, 2021

Genetic risk in comorbid TS and OCD

Co-occurrence tics & OCD

Family studies

Significant genetic correlations:

- TS and OCD **(92%)** / OCD and ADHD (63%)

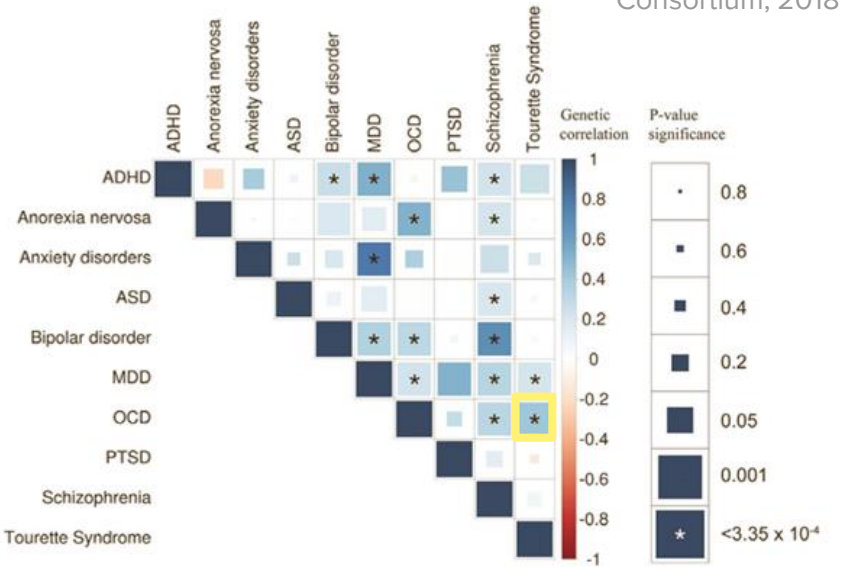
Mathews *et al*, 2011
(n=952 from 222 TS-affected pair families)

- Tics + OCD in twins: **MZ 0.18 > DZ 0.07**

Pinto *et al*, 2016 (n=21911, Sweden)

Genetic correlations across psychiatric phenotypes (GWAS meta-analysis)

The Brainstorm Consortium, 2018



- **Same underlying genetic factors?**
- **OCD: an alternative phenotypic expression of TS-susceptibility genes? Or more severe expression?** (greater genetic loading?)

Matthew *et al*, 2011

OCD and TS: further studies

Higher burden of CNVs in TS and OCD:

McGrath *et al.*, 2014 (1086 TS, 1613 OCD, and 1789 control samples

- 3.3-fold increased burden of large deletions (p=0.09).
- 50% of deletions: in a single locus, 16p13.11 (ID/developmental delay, seizures, and, less strongly, ASD).

Tic-related OCD: higher heritability?

Brander *et al,* 2019, Swedish cohort, n=1257 with tic-related OCD / n=20,975 with non-tic-related OCD

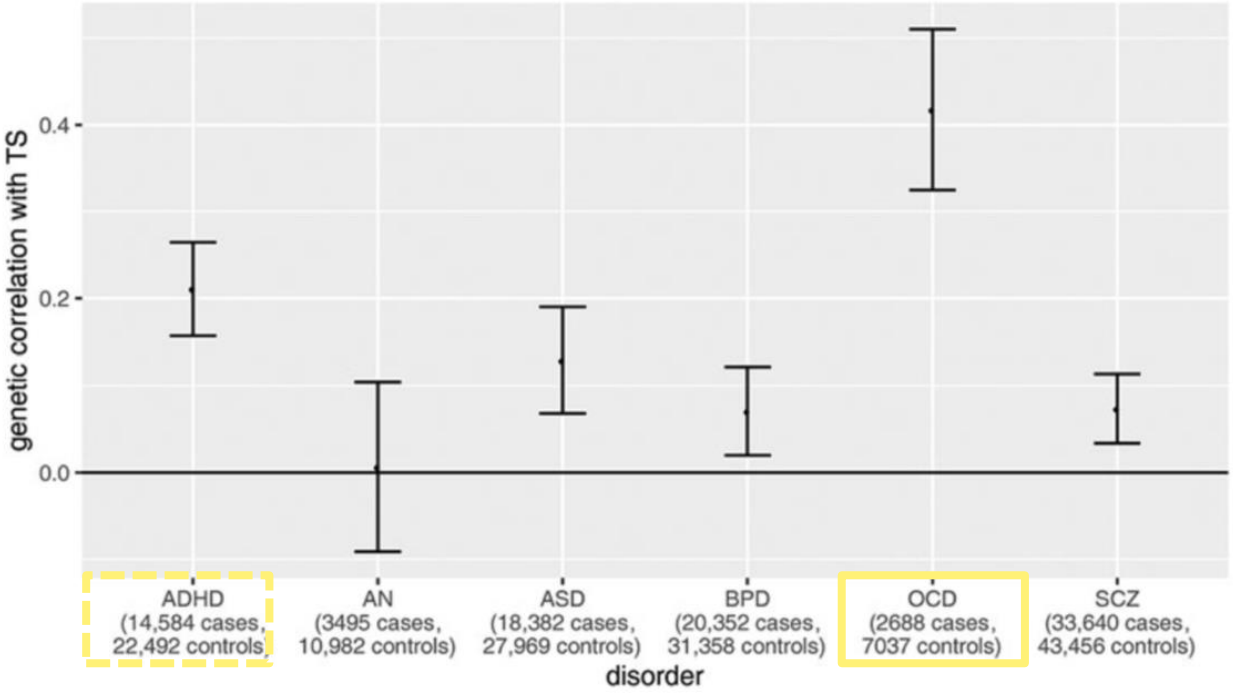
- Earlier age of OCD onset, greater proportion of males, higher rates of symmetry and sexual/ aggressive obsessions.
- Risk of OCD in relatives of individuals with tic-related OCD >>> risk of OCD in relatives of other OCD patients (HR 10.6 versus 4.5).

Genetic correlations between TS and other neuro-psychiatric disorders from GWAS summary statistics

High genetic correlation:

- **TS - OCD: 0.42** (S.E. = 0.09)
- **TS - ADHD: 0.21** (S.E. = 0.05)

Although anorexia nervosa and OCD are highly comorbid, the genetic correlation between TS and anorexia was very low.



TS (4819 cases, 9488 controls).

Domènech *et al,* 2021

Sexual dimorphism in genetic risk?

Sex differences in TS

Male predominance in Tourette (4:1).

Heritability by sex:

39% in boys vs 26% in girls

Twin study, Sweden, Anckarsäter *et al*, 2011
(n=17,220 twins)

Later reports:

Tic heritability levels in males and females are similar.

Qi *et al,* 2017 (review)

Sex differences in OCD

Sex differences in age of onset and clinical presentation.

Discordant results from twin studies:

- Heritability estimate in males (53%) > in females (41%) (n=751)
  - **MZ male correlation 0.56 > 0.24 in DZ**
  - **MZ female correlation 0.39 = 0.36 in DZ** Hur *et al*, 2008
- No genetic sex differences in a Dutch twin study.

Van Grootheest *et al.,* 2008

Analysis of the sex-specific genetic architecture of OCD:

- **No significant sex-specific SNP.**
- 2 genes associated with OCD in females (GRID2, GRP135) and not in males.

Khramtsova *et al.,* 2019.

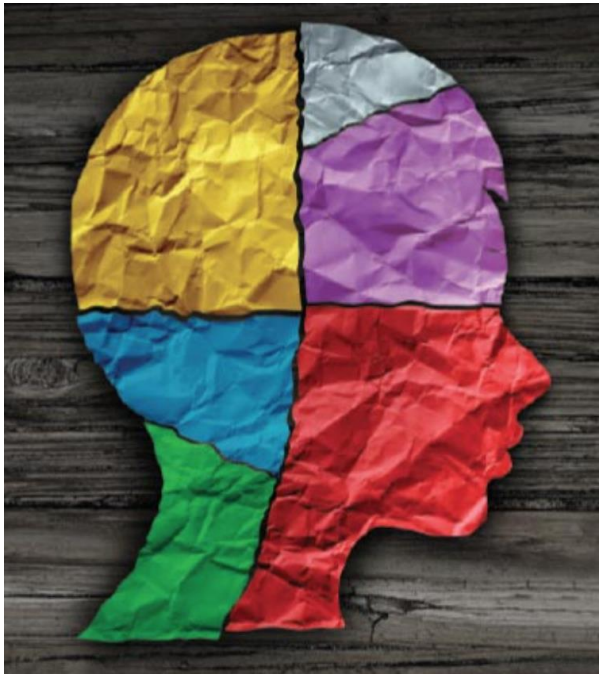
Clinical and therapeutic implications

Informing the patients and the families

Giving reliable information & fight against preconceived ideas:

- OCD and Tourette are complex disorders with polygenic risk. This is not “the fault” of one parent.
- OCD is not secondary to trauma, but is influenced by life experiences like many other disorders.
- Remind that TS and OCD are very common disorders.

Informing that the understanding of the genetics of TS and OCD remains incomplete.



Advantages of knowing about the familial risk

1. Providing a mechanism for the comorbidities

- Common genetic risk?

2. Early diagnosis of OCD/TS & comorbidities in the patient and siblings

- Knowing the familial risk: knowing what to look for.
- Improving the quality of life++.

Pringsheim *et al.*, 2019

- Early diagnosis and treatment of OCD: important for a positive outcome.

Eisen *et al.*, 2021

  - OCD: long duration of untreated illness (≃ 7 years).
  - Late interventions and poor therapy response.

Dell'Osso *et al.*, 2010, 2019; Albert *et al.*, 2019

An example of novel therapeutic targets

Hyperactivity of cortico-striato-thalamo-cortical circuitry in OCD. Glutamate involved in this pathway.

➔ **Glutamate-modulating drugs: potential treatment options for OCD?** Pauls *et al.*, 2014

- **Memantine:** positive effects in OCD. Meta-analysis, Modarresi *et al.*, 2019
- **Lamotrigine, topiramate, riluzole ?** Marinova *et al.*, 2017
- **Ketamine?** Rodriguez et al., 2011, 2013, 2016

Further randomized placebo-controlled trials in larger study populations are necessary.

Genomics and therapeutics in OCD

Pharmacogenetics define genetic variants that influence drug metabolism, delivery, affinity to receptors or transporters
which may contribute to the prediction of drug efficacy or toxicity.

Hess *et al*, 2015

1/4 of OCD patients do not respond to treatment with either SSRIs or/and CBT.

Hirschtritt *et al*., 2017

One locus in DISP1 **associated with treatment response to SRIs.**

GWAS, Qin *et al*, 2015

Greater knowledge about the specific genetic risks for OCD and Tourette will:

- help understand of the underlying biological mechanisms .
- provide opportunities to develop new animal and cellular models;
- help identify new biomarqueurs:
  - for diagnosis
  - for prognosis
- and allow testing new therapy avenues.

Are there nongenetic risk factors?

Environment: pre and perinatal birth risk factors

Brander *et al*, 2016	Tourette syndrome	OCD
Impaired fetal growth	⩽ 2500g: **HR 1.26** (95% CI: 1.06–1.51) 2501–3500g: **HR 1.12** (95% CI: 1.06–1.19)	1501-2500g: **HR 1.30** (95% CI, 1.05-1.62) 2501 -3500g: **HR 1.08** (95% CI, 1.01-1.16)
Preterm birth	**HR 1.35** (1.21-1.51)	**HR 1.24** (1.07-1.43)
Breech presentation	**HR 1.20** (1.02-1.41)	**HR 1.35** (1.06-1.71)
Cesarean section	**HR 1.48** (1.37-1.59)	**HR 1.17** (1.01-1.34)
Maternal smoking	**HR 1.44** (1.31–1.57) Dose response manner; No longer significant when familial factors were controlled for or after excluding ADHD.	**HR 1.27** (1.02-1.58) Smoking 10 or more cigarettes per day during pregnancy
Apgar score at 5 min	**Not significant**	**HR 1.50** (1.07-2.0)

Environmental risk factors in OCD

Stressful life events (childhood trauma, amount of life events)?

Brander, Pérez, Mataix-Cols, 2016

- **25%-64%** reported stressful life events before the onset of OCD.

Cross-sectionnal studies: Lensi *et al*., 1996; Rasmussen *et al.,* 1986; Real *et al.,* 2011; Rosso *et al.,* 2012

- Stressful life events in the past 12 months: **21%** increased likelihood of OCD.

Valleni-Basile *et al*., 1996, Cromer *et al.*, 2007; Real *et al.*, 2011; Rosso *et al.*, 2012

- **Especially in women** (incidence of 56.0% vs 44.0% in men, $p < 0.001$).

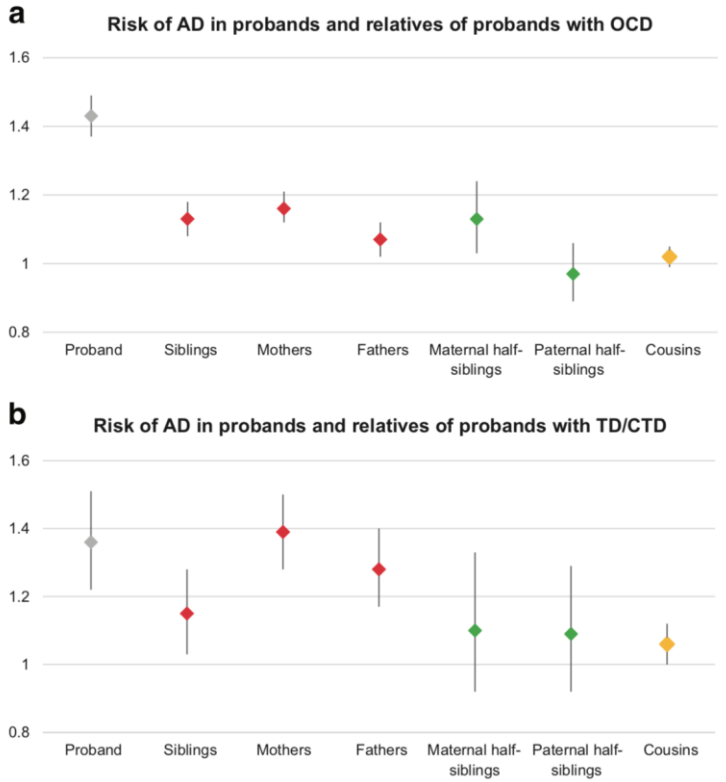
Rosso *et al.*, 2012

Autoimmunity, Tourette syndrome and OCD

- **Individuals with OCD: 43% increased risk** of any autoimmune disease

- **Individuals with TS/CTD: 36% increased risk** of any autoimmune disease.

- **Risk of any autoimmune disease: consistently higher among 1st-degree relatives** than among 2nd- and 3rd-degree relatives of probands with OCD and TS/CTD



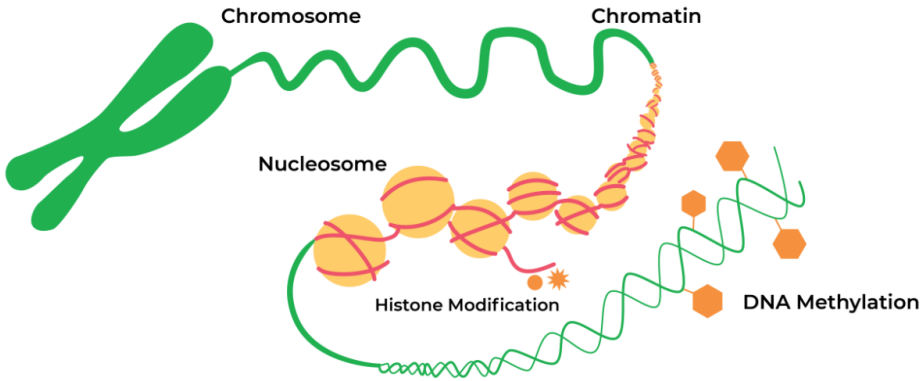
Large-scale population study from the Swedish birth cohort Mataix-Cols *et al*, 2017

Epigenetic risk factors

Epigenetics: ongoing regulation of gene expression.

Reprogram the genome in response to environmental inputs.

Valuable hypothesis for neurodevelopmental behavioral problems.



Arif *et al.*, 2018

Epigenetic risk factors: contributors to the molecular etiology? Novel disease biomarkers?

Tourette syndrome

The 1st Epigenome-Wide Association Study (EWAS) of tic disorders: DNA methylation

Zilhao *et al*, 2015 (n=188 cases/ 1490 controls), the Netherlands Twin Register

- No methylation sites reached genome-wide significance.
- Several of the top ranking probes: in or nearby genes previously associated with neurological disorders.

OCD

EWAS comparing OCD & controls: variable results.

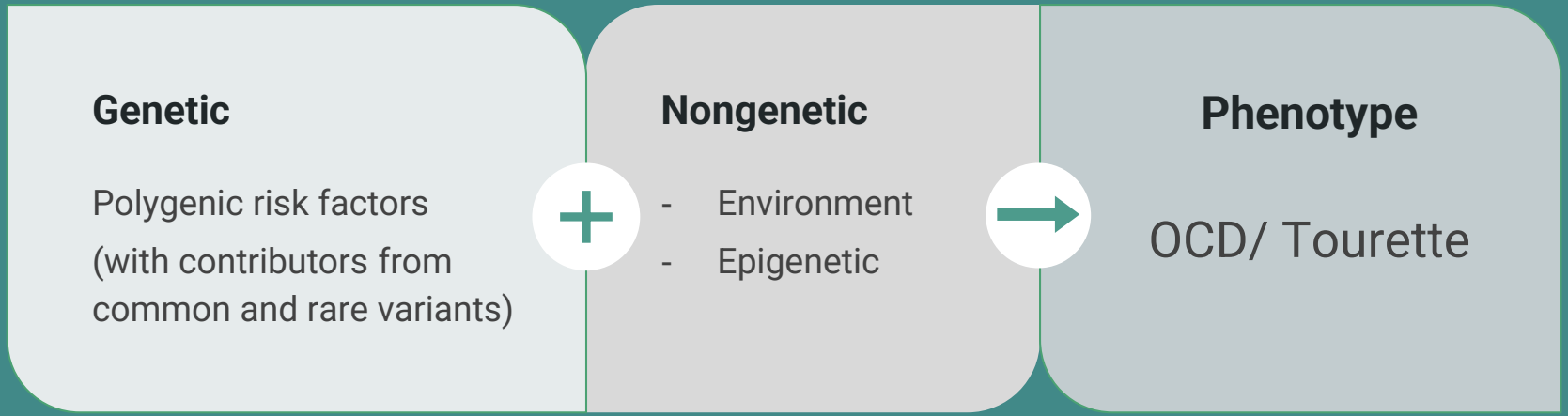
- No significant differential methylation.

Nissen *et al.*, 2016

- Association between DNA methylation (GABBRI1 and MOG) and baseline OCD severity, treatment effect and responder status.

Goodman *et al.*, 2020, Song *et al*, 2018

→ **Need for further investigation.**


Genetic
Polygenic risk factors
(with contributors from common and rare variants)
Nongenetic
- Environment
- Epigenetic
Phenotype
OCD/ Tourette

Perspectives

- Studies with **larger sample sizes.**
- **Four large collaborative groups** are jointing effort and resources for TS genetic research (more variants?).
- **Epigenetic research** (link genomic variations - environmental exposures & diseases outcomes)
- Understanding the mechanism behind some clinical features (e.g. **sex differences).**

On the beach
by Benjamin Edwards (age 11)

Tourette and OCD genetic risk: takeaways

- **Tourette syndrome and OCD are both complex, heritable, heterogeneous disorders:**
  - Higher heritability of TS (0.77) than OCD (0.42-0.65).
  - Correlation between TS and OCD: same underlying genetic factors?

- **Useful to communicate it to the families as clinicians and to understand it better as researchers** (treatment).

- **Other risk factors:**
  - **Environment** (pre and perinatal risk factors);
  - **Epigenetic** (research++).

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