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REVIEW

Advances in Clustering and Classification of Tic Disorders: A Systematic Review

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Purpose: Tic disorders (TD) are common neurodevelopmental disorders characterized by heterogeneous tic symptoms in children, making diagnostic classification difficult. This complexity requires accurate subtyping using data-driven computational methods to identify patterns within clinical data. This systematic review primarily summarizes the current evidence for the classification of TD using a data-driven approach.

Patients and Methods: We conducted a systematic literature search on PubMed and Web of Science up to December 2023 and identified 16 publications analyzing 14 unique samples, totaling approximately 6000 subjects.

Results: Nine studies classified different subtypes of TD based on symptoms and behavior. Seven studies identified novel factor structures based on TD and its complex comorbidity patterns. Seven studies highlighted associations between TD symptom patterns and genetics, reflecting the diversity of underlying genetic mechanisms underlying TD.

Conclusion: This systematic review reveals significant variability in research on the classification of TD, which limits the application of findings for accurate diagnosis and guiding treatment strategies in pediatric psychiatry. Further research incorporating multi-dimensional information (such as genetic, neuroimaging, and environmental and social factors) is essential to improve the understanding of TD subtypes.

Keywords: tic disorders, Tourette syndrome, subtype classification, cluster analysis

Introduction

Tic disorders (TD) are a complex disorder characterized by sudden, rapid, repetitive, and rhythmical movements or vocalizations, typically occurring in childhood. They have a significant impact on the quality of life for patients and their families and contribute to a growing social burden.[1–3] According to the National Survey of Mental Disorders in Children in China, the prevalence of TD is reported to be 2.5%, and the incidence is gradually increasing.[4] TD is a heterogeneous syndrome with multiple symptom patterns, courses, comorbidity and heredity factors that may be caused by different biological imbalances or disturbances.[1,5–8] A comprehensive characterization and identification of clinical subtypes of TD is essential to improve our understanding of patient-specific aetiological mechanisms, leading to the development of biological knowledge and patient-specific diagnosis and treatment.[1,9]

Currently, the most widely accepted classification of TD remains the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which divides TD into three main types based on age and duration of onset: Tourette's syndrome (TS), chronic TD, and transient TD.[10] In light of the current study, some researchers are questioning the validity of existing classification methods. A fundamental problem with the current approach to TD classification is that it relies on heterogeneous clinical descriptions rather than providing a valid diagnosis.[11] Therefore, the development of more homogeneous, evidence-based diagnostic entities is critical.

Data-driven approaches have long been used in psychiatric diagnosis and have gained traction in recent years with the aim of dividing clinical populations into more coherent subgroups.[12,13] This method can identify patterns from initial

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data or observations using computational methods and apply heuristic rules to discover and establish relationships between internal features, thereby revealing various theorems or laws, thus solving the heterogeneity problem of TD.[14] This systematic review includes all published studies based on data-driven analyses of TD subtypes, almost all of them based on classifications based on psychometric characteristics, and we further summaries the associations of these subtypes with genetic factors.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[15]

Eligibility Criteria

Inclusion criteria were as follows: (1) studies that included participants diagnosed with TD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III or later version) or the International Classification of Diseases (ICD-9 or later version) criteria; (2) studies that included children, adolescents, adults, or a combination of these groups; (3) studies that used data-driven methods to identify distinct subtypes; (4) original research articles; and (5) studies published in English with peer-reviewed to maintain the robustness and credibility of our findings. Exclusion criteria were: (1) review articles, conference abstracts, or commentaries; and (2) studies for which the full text was not available.

Search Strategy

A systematic literature search was conducted in PubMed and Web of Science up to December 2023. The search terms included "tic disorder", "subtype", "cluster" and "classification", combined using Boolean operators (AND, OR, NOT). The search strategy also included synonyms and variants of the keywords. See supplementary material for specific search terms (Table S1). The literature screening process consisted of an initial screening based on titles and abstracts, followed by a full-text review of articles that met the inclusion criteria. The final search was conducted on 31 December 2023.

Study Selection

The initial search identified 114 articles. A further 13 articles were identified through analysis of the reference lists of the included studies, and 3 articles were identified through manual searching, giving a total of 130 articles. A total of 11 duplicate records were identified and removed prior to the screening process. Two independent reviewers screened the titles and abstracts of all 130 articles, followed by a full-text review of articles that met the inclusion criteria. Disagreements between the two reviewers were resolved by discussion or, if necessary, by consultation with a third reviewer. After full-text screening, articles were excluded for reasons such as irrelevance to the study population, inappropriate study design, or insufficient methodological detail. A total of 16 articles were considered eligible for inclusion. Reference management and de-duplication was performed using NoteExpress V3.7.0. The study selection process was detailed in a PRISMA flowchart to ensure transparency (Figure 1).

Data Collection

We extracted detailed information for each study, including: authors, publication year, sample details, statistical modelling methods, subtype characteristics, the number of subtypes or factors, and key findings.

Data-driven subtypes are defined as classifications of individuals identified using statistical clustering techniques, such as latent variable analysis or other clustering algorithms, that reveal underlying heterogeneity in clinical presentation. Psychometric data refer to measures obtained through clinician- or self-reported assessments of symptoms, functioning, or personality traits that provide quantifiable insights into individual experience. Genetic associations describe the statistical relationships between specific genetic variants and the presence of particular phenotypes or disorders, highlighting the hereditary influences on disease risk and manifestation.

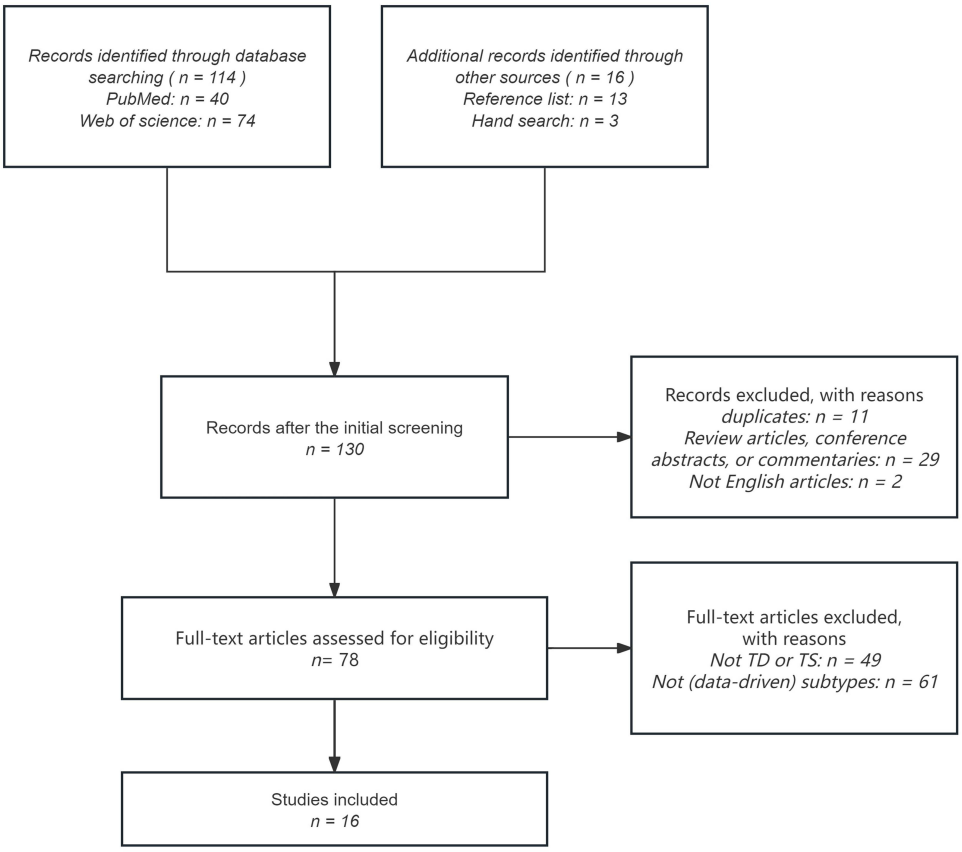

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.[15.]
Abbreviations: TD, Tic disorders; TS, Tourette syndrome.

Evaluation of Study Quality and Risk of Bias

Quality assessment and risk of bias evaluation were carried out independently by two reviewers (K. Yang and T. Y. Lei) using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[16] Discrepancies were resolved by consultation with a third reviewer (Y. H. Cui). The ROBINS-I tool evaluates each study as an attempt to replicate a hypothetical pragmatic randomized trial, focusing on seven domains: bias due to confounding, bias in participant selection, bias in intervention classification, bias due to deviations from the intended interventions, bias due to missing data, bias in outcome measurement, and bias in selective outcome reporting. Assessments in these areas result in an overall risk of bias, which is categorized as "low risk", "moderate risk", "serious risk", "critical risk" or "no information" (Table S2).[16]

Results

We identified 16 studies to identify subtypes of TD, including different analyses across different sample sizes and populations (n ≈ 6000). All studies used data-driven techniques, such as hierarchical cluster analysis (HCA), latent class analysis (LCA), exploratory factor analysis (EFA) and principal component factor analysis (PCFA), to uncover distinct subtypes among individuals with TD. Although numerous factors influence TD, such as psychometric data, environmental and social factors, and neurobiological data (eg, neuroimage), current classification studies predominantly focus on psychometric data. We further categorized the existing studies into two groups: those analyzing features directly related to tics and those incorporating both tic-related features and comorbidity-related features. Finally, we discuss the potential genetic basis associated with these subtypes. Specifically, nine studies focused on tic symptom-based classifications, comparing behavioural and psychometric variables across identified clusters (Table 1). Seven studies also included

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Table 1 Psychometric Subtyping Based on Tic Symptoms and Behavioral Characteristics

Author (Year)	Number of TD Patients	Statistical Model	Subtyping Based On	Numbers of Subtypes/ Factors	Main Findings
Alsobrook and Pauls (2002)[17]	85	HCA and PCFA	29 tics symptoms (eg, blinking, temper fits, touching of body, picking at things, coprolalia, kicking, self-injury, etc).	4	4 significant factors were identified: 1) aggressive phenomena (eg, kicking, temper fits, argumentativeness), 2) purely motor and phonic tic symptoms, 3) compulsive phenomena (eg, touching of others or objects, repetitive speech, throat clearing), and 4) tapping and absence of grunting.
Storch et al, (2007)[18]	76 (male = 47, mean age = 11.3 ± 2.4 years)	PCFA	Yale Global Tic Severity Scale	3	The 3-factor model of the YGTSS, including motor tics factor, phonic tics factor, and overall impairment factor.
Robertson and Cavanna (2007)[19]	69	HCA and PCFA	37 tics and tic-related symptoms (eg, specific fears/phobias, Counting, evening up, facial grimacing, stuttering, etc).	3	Factor 1 (predominantly 'pure tics'), Factor 2 (predominantly 'ADHD and aggressive behaviours') and Factor 3 (predominantly 'depression–anxiety–obsessional symptoms and self-injurious behaviours'). Only frowning/raising eyebrows and sniffing/smelling loaded significantly on both Factors 1 and 3.
Mathews et al, (2007)[20]	254 (Sample 1: n = 121, male = 98, mean age = 15.7 ± 11.9 years; Sample 2: n = 133, male = 98, mean age = 22.5 ± 15.0 years)	HCA	38 tic and related symptoms (eg, head shaking, throat clearing, shoulder jerking, arm or hand movements, bending or gyrating, etc).	2	Cluster 1: predominantly simple tics, and cluster 2: multiple complex tics. Membership in cluster 2 was correlated with increased tic severity, global impairment, medication treatment, and presence of comorbid obsessive-compulsive symptoms.
Robertson et al, (2008)[21]	410 (male = 311, mean age = 20.4 ± 12.3 years)	HCA and PCFA	32 tic symptoms (eg, touching self, leg and foot movements, grunting, skipping, jumping, forced touching, coughing, etc).	5	5 factors were observed, characterised by: (1) socially inappropriate behaviours and other complex vocal tics; (2) complex motor tics; (3) simple tics; (4) compulsive behaviours; and (5) touching self.
Cavanna et al, (2011)[22]	639 (male = 447, mean age = 26.1 ± 13.2 years)	PCFA	12 tics symptoms (eg, coprolalia, echopraxia, echolalia, palilalia, etc).	3	3 factors models: (1) complex motor tics and echo-paliphenomena; (2) attention deficit and hyperactivity symptoms plus aggressive behaviours; and (3) complex vocal tics and coprophenomena. Obsessive compulsive behaviours loaded significantly on the first two factors.

McGuire et al, (2013)[23]	239 (male = 171, mean age = 21.67 ± 14.10 years)	HCA	Yale Global Tic Severity Scale	4	4 tic clusters model: (1) impulse control and complex phonic tics; (2) complex motor tics; (3) simple head motor/vocal tics; and (4) primarily simple motor tics. Frequencies of tic symptoms showed few differences across youth and adults. Tic clusters had small associations with clinical characteristics and showed no associations to the presence of coexisting psychiatric conditions.
de Haan et al, (2015)[24]	Two cohorts of TS patients from the US (n = 273) and the Netherlands (n = 221), and in 351 Dutch family members	PCFA	Yale Global Tic Severity Scale	3	3 factors model: (1) complex vocal tics and obscene behavior; (2) body tics; (3) head/neck tics. Moderate heritability was found for factor 1 and factor 3.
Hirschtritt et al, (2016)[25]	1191 (male = 944, mean age = 15.3 ± 10.0 years)	EFA and LCA	49 tic symptoms (eg, coprolalia, copropraxia, echolalia, complex words, palilalia, animal noises, syllables, rotating, bending, etc).	6-factor and the 5-class latent class solutions	6-factor model: eye tics, head/facial tics, body tics, socially disinhibited tics, touching tics, and simple vocal tics. 5-class model: unaffected, simple tics, intermediate tics without social disinhibition, intermediate with social disinhibition, and high rates of all tic types. Across models, a phenotype characterized by high rates of social disinhibition emerged. This phenotype was associated with increased odds of comorbid psychiatric disorders, in particular, OCD and ADHD, earlier age at TS onset, and increased tic severity.

Abbreviations: TD, Tic disorders; HCA, hierarchical cluster analysis; PCFA, principal component factor analysis; YGTSS, Yale Global Tic Severity Scale; ADHD, attention deficit hyperactivity disorder; TS, Tourette syndrome; EFA, exploratory factor analysis; LCA, latent class analysis; OCD, obsessive compulsive disorder.

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comorbid psychiatric conditions, such as attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), to refine the classification of TD subtypes, offering a more comprehensive understanding of the heterogeneity of TD (Table 2). Seven studies highlighted associations between TD symptom patterns and genetic factors, reflecting the diversity of genetic mechanisms underlying TD.

Tic Symptoms and Behavioral Characteristics

Numerous studies consistently support the phenotypic heterogeneity of TD, suggesting that tic symptoms are not simple manifestations of a single disorder, but rather involve several distinct dimensions or factors. Three studies have established different factor models based on the Yale Global Tic Severity Scale (YGTSS). Storch (2007) proposed a three-factor structure aligned with Leckman's model,[18,33] including a motor tics factor, a phonic tics factor, and an overall impairment factor. De Haan's study (2015) analyzed lifetime tic symptom data from 494 patients in two cohorts from the US and the Netherlands.[24] Item-level factor analysis identified three factors associated with complex vocal tics, motor tics, and head/neck tics.[24]

McGuire et al (2013) found that tic symptoms clustered into four distinct categories based on the YGTSS: impulse control and complex phonic tics, complex motor tics, simple head motor/voice tics, and primarily simple motor tics.[23] However, their analysis revealed few differences in tic symptom frequencies between adolescents and adults, with tic clusters showing little association with clinical features and no significant associations with comorbid psychiatric conditions. In addition, cluster membership scores did not predict treatment response to the Comprehensive Behavioral Intervention for Tics (CBIT) or reductions in tic severity. These findings suggest that tic symptom profiles respond similarly to CBIT, suggesting consistent treatment outcomes across different tic symptom characteristics.[23] Importantly, this type of study aims to explore treatment differences between different subgroups, making it valuable for personalizing precision medicine. In the future, a wider range of treatment modalities could be used to further investigate these differences.

Five studies used HCA and/or PCFA to explore factors based on characteristics of tic symptoms. The number of characteristics identified varied considerably, ranging from 12 to 49. Cavanna et al (2011) extended Robertson et al's findings by examining 639 TS individuals for 12 tic symptoms and identified three factors: (1) complex motor tics and paliphenomena; (2) attentional, hyperactive, and aggressive behaviors; and (3) complex vocal tics and coprophenomena.[22] The three factors accounted for 48.5% of the variance.[22] Obsessive-compulsive behaviors loaded significantly on the first two factors.[22] In the study by Alsobrook and Pauls (2002),[17] structured interviews were conducted with 85 patients diagnosed with TS to collect data on 29 tic symptoms. Using HCA and PCFA, they identified four key factors: Factor 1 was characterized by behaviors such as coprolalia, aggressive, and self-injurious; Factor 2 included both simple and complex motor tics, as well as simple vocal/phonic tics (eg, noises without actual words); Factor 3 was defined by compulsive-like behaviors, including forced touching, repetitive actions, and echophenomena; and Factor 4 was marked by the absence of grunting tics and the presence of finger and hand tapping, which was distinct from forced touching. Robertson et al (2008) reported clusters of 32 tic and behavioral symptoms,[21] identifying five factors characterized by: (1) socially inappropriate behaviors and complex vocal tics; (2) complex motor tics; (3) simple tics; (4) compulsive behaviors; and (5) self-touching. Individuals with co-occurring ADHD had significantly higher factor scores on factors 1 and 3, whereas individuals with co-occurring OCD had elevated scores on factors 1–4.[21] In 2007, Robertson and Cavanna analyzed 69 members of multigenerational families.[19] They used HCA and PCFA to identify three significant factors of 37 tic and behavioral symptoms: Factor 1 included predominantly "pure tics" (both simple and complex motor and vocal/phonic tics); Factor 2 included symptoms related to ADHD and aggressive behaviors, as well as complex motor and vocal tics, including coprophenomena; and Factor 3 was characterized by symptoms of depression, anxiety, obsessionality, and self-injurious behaviors, explaining 42% of the symptom variance. Mathews (2007) used HCA on 121 Costa Rican and 133 Ashkenazi Jewish TS patients on 38 tic and behavioral symptoms and found significant differences between pure tics (cluster 1) and complex tics (cluster 2).[20] Individuals in cluster 2 were associated with greater tic severity, global impairment, and presence of comorbid obsessive-compulsive symptoms.[20]

Table 2 Psychometric Subtyping Based on Comorbidity Features

Author (Year)	Number of TD Patients	Statistical Model	Subtyping Based On	Numbers of Subtypes/ Factors	Main Findings
Eapen et al, (2004)[26]	91 (male = 58, mean age = 29 ± 12.5 years)	PCFA	11 psychopathology rating scales (eg, Leyton trait, Leyton state, CCEI obsessional score, Beck score, BSI score, etc).	2	A 2 factors model 'obsessionality' and 'anxiety/ depression' with regard to adult psychopathology. High occurrence of anxiety, depression and obsessionality in adult TS subjects.
Grados and Mathews (2008)[27]	952 individuals from 222 GTS families (596 subjects had GTS diagnoses)	LCA	TS, OCD and ADHD	5	3 TS-affected groups: TS + OCS/OCB (class III), TS + OCD (class IV), and TS + OCD + ADHD (class V), in addition to a minimally affected class (I) and a small chronic tic + OCD class (II). Only the TS + OCD + ADHD class was highly heritable
Rodgers et al, (2014)[28]	80	LCA	6 selected indicators included: OCD screening items, an ADHD inattention screening item, an ADHD impulsivity screening item, depression screening items, phobia screening items and a panic attack screening item	4	4 classes models: ADHD + DEP (class 1), DEP (class 2), OCD excluding ADHD multimorbid (class 3) and ANX + DEP (class 4). Four subtypes with relevant sex-related differences in their comorbidity profiles. Two male-related classes, one exhibited both ADHD and depression, the second class comprised males with only depression. Class three was a female-related class depicting obsessive thoughts/compulsive acts, phobias and panic attacks, manifested high psychosocial impairment. Class four had a balanced sex proportion and comorbid symptoms/syndromes such as phobias and panic attacks. The complementary occurrence of comorbid obsessive thoughts/compulsive acts and ADHD impulsivity was remarkable.
Huisman-van Dijk et al, (2016)[29]	225 (male = 144, mean age = 30.15 ± 15.65 years)	PCFA	Tics, OCS, ADHD, autism (ie YGTSS, Y-BOCS, CAARS and AQ)	5	5 factors model: (1) tic, aggression, symmetry, (2) OC symptoms, compulsive tics, numbers and patterns, (3) ADHD symptoms, (4) autism symptoms, (5) hoarding and inattention symptoms.

(*Continued*)

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Table 2 (Continued).

Author (Year)	Number of TD Patients	Statistical Model	Subtyping Based On	Numbers of Subtypes/ Factors	Main Findings
Darrow et al, (2017)[30]	1191 (male = 944, mean age = 15.3 ± 10.0 years)	EFA and LCA	108 tic and OCD items (eg eyeblink, echolalia, knee-bending, illness concern, checks no harm, copropraxia, etc).	4-factor and the 5-class latent class solutions	4-factors model: tics, OCS, disinhibited, symmetry and 5-class model: TS +OCD+ADHD, symmetry symptoms, TS+ADHD, tics only and unaffected classes. Identifying 2 cross-disorder symptom-based phenotypes: symmetry and disinhibition. Heritability estimates for both.
Hirschtritt et al, (2018)[31]	1191 (male = 944, mean age = 15.3 ± 10.0 years)	EFA and LCA	OCD and ADHD symptoms (ie TICS)	3	A 3-class model: few OCD/ADHD symptoms, OCD and ADHD symptoms, symmetry/exactness and hoarding and ADHD symptoms. Symmetry/ exactness and fear-of-harm were associated with TS and OCD, hoarding with ADHD and OCD.
Cravedi et al, (2018)[32]	174 (male = 148, Age at the first evaluation = 11.3 ± 3.3 years)	HAC	TS, ADHD, OCD, ASD, age, sex, abnormalities in psychomotor development and other neurodevelopmental variables.	3	3 clusters models: In cluster 1 many neurodevelopmental comorbidities (including intellectual disabilities, autism spectrum disorder, ADHD, and learning disabilities) and academic impairments. In cluster 2 no other neurodevelopmental comorbidities. In cluster 3 higher intelligence, a high frequency of attentional impairment, school problems related to both ADHD and unspecific attention difficulties, and handwriting problems related to the tics themselves.

Abbreviations: TD, tic disorders; PCFA, principal component factor analysis; CCEI, crown crisp experiential index; BSI, borderline syndrome index; LCA, latent class analysis; OCD, obsessive compulsive disorder; ADHD, attention deficit hyperactivity disorder; TS, Tourette syndrome; DEP, depression; ANX, anxiety; YGTSS, Yale global tic severity scale; Y-BOCS, Yale-Brown obsessive compulsive symptom scale; CAARSD, Connors attention deficit and hyperactivity rating scale; AQ, autism spectrum quotient; EFA, exploratory factor analysis; HAC, hierarchical ascendant clustering.

Based on 49 tic symptoms, Hirschtritt (2016) identified six factors that parallel the somatotopic representation of the basal ganglia: eye tics, head/facial tics, body tics, socially disinhibited tics, touching tics, and simple vocal tics, which further elucidated the characteristics of tics with social disinhibition.[25] In addition, Hirschtritt's five-class LCA model identified categories such as unaffected, simple tics, intermediate tics without social disinhibition, intermediate tics with social disinhibition, and high rates of all tic types. Notably, a phenotype characterized by high rates of social disinhibition emerged, which was associated with increased odds of comorbid psychiatric disorders, particularly OCD and ADHD, earlier age of TS onset, and increased tic severity.

Influence of Comorbidity

Research has consistently shown that TD are not single disorders but have complex comorbidity patterns, often closely associated with symptoms of OCD, ADHD, anxiety, and autism spectrum disorder (ASD).[1,8,34–36] Several studies suggest that these comorbid symptoms play a crucial role in the clinical subtyping of TD and in the understanding of their underlying pathological mechanisms (Table 2).

Three studies combined TD with symptoms of the two most common comorbidities, OCD and ADHD, to explore new subtypes or factor models of TD. The study by Grados and Mathews (2008) used LCA to identify TS subphenotypes in a large sample of 952 individuals from 222 TS families.[27] A five-class solution was found to be the best model to fit the data, with the following classes: 1) simple tics; 2) chronic tics + OCD; 3) TS + OC behavior; 4) TS + OCD; and 5) TS + OCD + ADHD combined. In 2017, Darrow et al used EFA and LCA to subtype participants.[30] The analysis revealed a four-factor model including tics, obsessive-compulsive symptoms (OCS), disinhibition, and symmetry. In addition, a five-class model was identified, including classes for TS + OCD + ADHD, symmetry symptoms, TS + ADHD, tics only, and unaffected individuals. The study also identified two phenotypes based on cross-disorder symptoms: symmetry and disinhibition. In 2018, Hirschtritt et al used EFA and LCA to subtype participants.[31] The analysis identified a three-class model: one with few OCD/ADHD symptoms, another with both OCD and ADHD symptoms, and a third characterized by symmetry/exactness and hoarding alongside ADHD symptoms. In particular, symmetry/exactness and fear of harm were found to be associated with TS and OCD, whereas hoarding symptoms were associated with ADHD and OCD.

In addition to OCD and ADHD, two studies also included comorbidities such as depression and ASD to explore new subtypes or factor models of TD. Eapen et al (2004) used 11 psychopathology rating scales, including the CCEI obsessional score, the Beck score, and the BSI score, to perform a PCFA.[26] The analysis revealed two factors: obsessionality and anxiety/depression, which together accounted for 72% of the variance. The results of the study support the high prevalence of anxiety, depression, and OCD in adult participants with TS. Huisman conducted a study (2016) in which tic, OC, ADHD, and autism symptoms were measured using various symptom scales, including the YGTSS, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Conners Adult ADHD Rating Scales (CAARS) and the Autism Quotient (AQ).[29] The EFA identified a five-factor model: (1) tics, aggression, and symmetry; (2) OC symptoms, compulsive tics, and patterns involving numbers; (3) ADHD symptoms; (4) autism symptoms; and (5) hoarding and inattention symptoms.

In 2014, Rodgers et al conducted a community-based study using LCA to investigate sex-related and non-sex-related subtypes of TD and their common comorbidities, and this is the only study on the analysis of TD subtypes related to sex.[28] The study utilized data from the PsyCoLaus study, focusing on 80 individuals with motor/vocal tics in children and adolescents. Major comorbidities assessed included ADHD, OCD, depressive symptoms, phobias, and panic symptoms/syndromes. The LCA revealed four latent classes: Class 1 included males with both ADHD and depression; Class 2 consisted of males with depression only; Class 3 was a female -dominated class characterized by obsessive thoughts/compulsive acts, phobias, and panic attacks, with high psychosocial impairment; and Class 4 had a balanced sex distribution with comorbid symptoms such as phobias and panic attacks. Notably, there was a complementary occurrence of obsessive thoughts/compulsive acts and ADHD impulsivity within these classes.

In 2018, Cravedi et al used HCA to subtype participants based on a number of factors, including TS, ADHD, OCD, ASD, age, sex, psychomotor developmental abnormalities, and other neurodevelopmental variables.[32] Three cluster models emerged from the analysis: Cluster 1 was characterized by multiple neurodevelopmental comorbidities, including

intellectual disability, ASD, ADHD, and learning disability, as well as academic impairment. Cluster 2 had no additional neurodevelopmental comorbidities. In contrast, cluster 3 had higher intelligence, a significant frequency of attentional impairments, school-related problems related to both ADHD and unspecified attention difficulties, and handwriting problems related to the tics themselves.

Gene Association

Accumulating studies have shown that TD has a strong genetic basis.[8,37,38] Researchers have used family history data, large pedigrees, and segregation analyses of clinically confirmed probands to suggest that the single major locus hypothesis cannot effectively explain the observed inheritance patterns within families of TD individuals, revealing that TD likely follows a more complex inheritance model.[19] Over the past decade, whole-genome and exome sequencing have identified several novel gene mutations in patients with TS.[5,39] Comparison of the genetic characteristics between the more homogeneous TD subtypes has provided new opportunities for further understanding of the genetic mechanism of TD.

The study by Alsobrook and Pauls (2002) identified four factors in TS probands with 29 tic symptoms that accounted for 61% of the phenotypic variance, suggesting a possible genetic component.[17] High scores on the compulsive factor (Factor 3) were significantly associated with both ADHD and OCD in relatives. The association between high scores on the aggressive factor (Factor 1) and recurrent ADHD in relatives was not statistically significant ($p < 0.10$, Fisher's exact test), but indicated a trend. Eapen's study (2004), using 11 psychopathological rating scales in 91 adults with TS, found two factors: obsessionality and anxiety/depression, and further supports a genetic basis, finding that 57.1% of participants had a family history of tics, 29.7% had a family history of TS, and 52.7% reported a family history of obsessive-compulsive behaviors (OCB), while 49.5% had a family history of psychiatric disorders.[26]

Several studies have further estimated heritability using the Sequential Oligogenic Linkage Analysis Routine (SOLAR). Grados and Mathews (2008) reported heritability estimates of 0.49, 0.18, and 0.65 for Classes 2, 4, and 5, respectively, suggesting that classes with more complex behaviors are heritable, whereas those with primarily tics are not.[27] De Haan's study (2015) assessed the heritability in 494 patients and found moderate heritabilities for Factor 1 - complex vocal tics and obscene behaviour ($h^2 = 0.21$) and Factor 3 - head/neck tics ($h^2 = 0.25$), while overall tic severity had a lower heritability estimate ($h^2 = 0.19$).[24] However, bi-variate analyses revealed no genetic associations between tic factors.[24] Hirschtritt's study (2016) provided a heritability estimate of 0.53 (SE = 0.08, $p < 0.001$) for a specific phenotype characterized by high rates of social disinhibition emerged, which was associated with increased odds of comorbid psychiatric disorders, particularly OCD and ADHD, earlier age of TS onset, and increased tic severity.[25] Darrow and Hirschtritt's study (2017) confirmed the existence of two internal phenotypes derived from cross-disorder symptoms: the symmetrical phenotype and the disinhibited phenotype, with high heritability estimates of 0.39 and 0.35, respectively.[30] Notably, a significant association was found between the symmetrical phenotype and TS polygenic risk scores, suggesting that this phenotype may capture additional genetic predispositions not identified by traditional diagnostic criteria.

Hirschtritt et al (2018) argued that the distinct phenotypic and genetic characteristics of OCD and ADHD in patients with TS have not been well characterized. Their study explored the symptom patterns and heritability of OCD and ADHD within families with TS, detailing the heritability of individual OCD and ADHD factors. The heritability estimates for OCD ranged from 0.19 to 0.37, with symmetry/exactness showing the highest heritability ($h^2 = 0.37$) and need for sameness showing the lowest ($h^2 = 0.20$).[31] The ADHD factors showed heritabilities of 0.41 for inattentiveness and 0.38 for hyperactivity/impulsivity. The analysis suggests that there are genetic relationships between ADHD factors and TS, OCD, and ADHD. In particular, certain OCD factors - such as symmetry/exactness, aggressive urges, and fear of harm - show more significant genetic relationships with TS. In addition, only the aggressive urges and hoarding factors had a significant effect on the heritability estimates for ADHD.

Discussion

This systematic review identified 16 publications that published data-driven results for TD subtypes. Through in-depth analysis of tic symptoms, behavioral studies and gene association studies, several subtypes and behavioral patterns of TD

have been identified. Our analysis of various factor models and clustering methods confirms that tic symptoms extend beyond motor and vocal tics. They encompass dimensions like impulse control, complex behaviors, and social disinhibition, revealing diverse symptom clusters and factor structures. These studies highlighted the complex relationship between comorbidities, behavioral characteristics, and symptom presentation. The present study shows the differences in genetic characteristics and pathophysiological mechanisms of different symptom clusters in TD. These findings contribute to a better understanding of the heterogeneity of TD and provide a reference for personalized treatment.

We found that all studies consistently support the phenotypic heterogeneity of TD, suggesting that tics are not a simple manifestation of a single condition, but rather involve multiple dimensions and factors. However, there are considerable differences in the results of heterogeneity classification. First, different studies included different groups of subjects of different ages; some studies focused exclusively on children or adolescents, while others included adults or mixed-age populations. The study by McGuire et al (2013) included 239 adolescents and adults, while the study by Storch et al (2007) included only 76 children and adolescents, and Eapen et al (2004) focused on 91 adult TS patients.[18,23,26] Second, sample sizes varied widely, ranging from small cohorts (eg, Alsobrook & Pauls, 2002, with 85 participants) to larger populations (eg, Hirschtritt et al, 2016, with 1191 probands and 2303 family members), potentially influencing statistical power and the reliability of the subtypes identified.[17,25]

Third, researchers have employed various assessment tools to measure psychometric features of TS and its comorbidities. For instance, when assessing TS severity, de Haan et al (2015) used the YGTSS, whereas Storch et al (2007) utilized a combination of the YGTSS and the Tourette's Disorder Scale–Parent Rated.[18,24] Even with the same measurement tools, differences exist in the methods used, for example, most studies have relied on psychometric tools such as the Yale Global Tic Severity Scale (YGTSS) to quantify tic severity, but differences in data aggregation methods (ie item-level vs total score analyses) have led to varying factor models, such as the three-factor structure proposed by Storch et al (2007) and the six-factor model identified by Hirschtritt et al (2016).[18,25]

Fourth, the choice of clustering/subtyping method influenced the number and type of subtypes or factors identified. Robertson et al (2008) used PCFA and identified five factors characterized by tic symptoms and behavioral patterns.[21] Hirschtritt et al (2016) used LCA to identify five tic subtypes, including a novel phenotype characterized by high social disinhibition.[25] The lack of methodological standardization across studies makes direct comparisons and synthesis of findings difficult. In addition, most of the classification methods currently used are limited to unsupervised learning including exploratory factor analysis (EFA), principal component factor analysis (PCFA), hierarchical cluster analysis (HCA) and latent class analysis (LCA). Further studies should use advanced techniques such as deep learning algorithms.[12,40,41]

Finally, the studies considered different dimensions of features, such as whether the researchers included comorbidities like OCD and ADHD, or whether the classification involving comorbidities accounted for different types of comorbidities. Grados and Mathews (2008) incorporated comorbidities to identify five latent classes, it suggested that TS classes may represent distinct entities, with both shared and unique etiologies.[27] Huisman et al (2016) explored cross-disorder symptoms, including autism spectrum disorder (ASD), revealing a five-factor model that extended beyond tics.[29] Studies consistently show that TD is closely associated with comorbid conditions such as OCD, ADHD, anxiety, and ASD, highlighting the crucial role of comorbid symptoms in the clinical classification of TD and the understanding of its underlying pathological mechanisms.[42,43] Due to the reasons mentioned above, it is challenging to compare the results across studies. However, we conducted a preliminary quality assessment of all 16 articles using the ROBINS-I scale (Table S2) to provide a reference for future research on tic classification.

Studies of the genetic basis of TD and its associated behaviors and comorbidities suggest that the heterogeneity of TD is also reflected in its underlying genetic mechanisms. Different tic subtypes may be associated with specific genetic traits, emphasizing genetics' role in symptom expression and comorbidity. These subtypes may exhibit variations in genetic predisposition and clinical features, providing researchers with new perspectives for understanding the complexity of TD.[27,44,45] The presence of comorbid conditions may further influence these genetic traits; such comorbid symptoms not only complicate diagnosis but may also suggest common genetic factors. Although whole genome/exome sequencing has identified new genetic mutations, the exact pathogenic mechanisms are not yet fully understood, and there is also a lack of studies analyzing TD genotype differences using genome-wide association studies (GWAS)

and gene expression profile data, and correlating specific gene variants with clinical TD phenotypes.[45–49] Overall, genetic research on TD is revealing its phenotypic heterogeneity and emphasizing the importance of considering genetic factors and comorbid conditions when analyzing TD subtypes. Such an integrated perspective will provide a richer theoretical basis for future research and clinical interventions.

The current study focuses primarily on the classification of TD based on psychometric data. It does not include other critical dimensions that may influence the clinical manifestations of TD, such as environmental factors, family dynamics, social support systems and neurobiological data. Environmental influences, such as prenatal and perinatal complications (eg, maternal smoking, prenatal stress, low birth weight), are associated with altered neurodevelopment and increased risk of TS and its comorbidities, including ADHD and OCD.[50] These factors can significantly impact the severity and progression of tic symptoms.[50,51] The family environment also plays a crucial role in shaping the progression of TS symptoms. Supportive and stable family dynamics are associated with milder symptoms and better psychosocial adjustment, whereas negative parental reactions or high levels of family stress, such as maternal anxiety or depression, can exacerbate symptom severity.[51,52] Social support, especially for school-aged children, is critical in managing TS. Chronic stressors such as bullying, peer rejection, and academic pressure have been shown to worsen tic severity and increase emotional distress. Acute stressors, such as public speaking, can also trigger an immediate worsening of symptoms.[53] Future research should investigate how environmental and psychosocial factors contribute to TD heterogeneity, aiming to inform targeted interventions and enhance patient outcomes.[50–53]

To date, there remains a notable gap in research on data-driven classification of TD using neurobiological data, such as neuroimaging techniques.[54] While neuroimaging has been widely used in other neuropsychiatric conditions,[9,55,56] its use in tic disorders, especially in combination with machine learning techniques, is still in its infancy.[57,58] Identifying and defining the different phenotypes within the "tic disorder spectrum" has significant clinical relevance for early intervention and prevention efforts.[59] By comprehensively examining diverse clinical features, we can gain deeper insights into the underlying causes of TD and highlight the need for a better understanding of the heterogeneity within these disorders.[1,6,7,29,32] Our team has contributed to this emerging field by developing a study protocol, outlining the potential of using functional magnetic resonance imaging (fMRI) data to identify biologically distinct subtypes of TD.[60] However, this work has not yet progressed to full-scale research. Advancing this area would provide valuable insights into the neural correlates of TD, allowing more precise subtype identification and facilitating the development of targeted treatment approaches.[61,62] Future studies could explore the integration of neurobiological data, such as neuroimaging, neurophysiological, genetic and clinical profiles, to develop comprehensive classification models.[9,63] The integration of personalized medicine and multidisciplinary approaches will advance the accurate subtyping of TD. In particular, the application of new technologies, such as artificial intelligence and big data, can manage and analyze large amounts of complex data and help identify valid clinical subtypes.[64]

This systematic review has several limitations. The first is the limitation to English language peer-reviewed publications. Although this approach was chosen to ensure the inclusion of rigorously peer-reviewed studies with higher methodological quality, it may have introduced a selection bias by excluding relevant studies published in other languages and grey literature (eg, conference abstracts and dissertations). On the other hand, we did not perform a meta-analysis due to the considerable methodological heterogeneity of the selected articles. Future research could benefit from a possible standardization of methodologies, which would allow more rigorous meta-analyses to be conducted and provide stronger evidence for the conclusions drawn.

Conclusion

This review summarizes the clustering and classification of TD using a data-driven approach. They all support the phenotypic heterogeneity of TD. Standardization of analytical approaches and ensuring representative samples could improve the reliability and applicability of future research. Incorporating multidimensional data, such as neurobiological data, information on environmental or psychosocial factors, may also help to understand the inherent heterogeneity of TD and refine classification systems.

Data Sharing Statement

Data for this study came from the open-source literature review websites PubMed and Web of Science.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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