

COMMENTARY

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# Overview: referrals for genetic evaluation from child psychiatrists

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## Abstract

A growing multitude of known genetic diagnoses can result in presentation to child psychiatry. For numerous reasons, it is important to identify a genetic etiology in child psychiatry patients when it is present. Genetic diagnoses can guide treatment and enable access to specialized clinics and appropriate screening measures. They can also allow for genetic counseling for the patient and family. A better understanding of etiology with a named diagnosis can itself be of great value to many patients and families; prognostic information can be empowering. Since patients with genetic conditions may present to psychiatric care in diverse ways, child psychiatrists must decide who to refer for genetic evaluation. Here we create a table to provide a framework of concerning/notable history and exam features that a practicing child psychiatrist may encounter that should prompt one to consider whether a larger, unifying genetic diagnosis is at hand. We hope this framework will facilitate referral of child psychiatry patients to genetics so that more patients can benefit from an appropriate diagnosis.

**Keywords:** Diagnosis, Genetics, Child psychiatry

## Background

A growing multitude of known genetic diagnoses can result in presentation to child psychiatry. The prevalence of genetic diagnoses among child psychiatry patients is best studied for autism, where 10–20 % of cases have a diagnosable genetic cause [e.g. Fragile X (FXS)] [1–6]. There is little information about the prevalence of genetic conditions in child psychiatry patients more generally. There are a large number of different genetic conditions that may lead to psychiatric presentation in a child. A December 2015 search of the Online Mendelian Inheritance in Man database (OMIM.org<sup>®</sup>), a catalog of genetic conditions, reveals 42 genetic etiologic associations for both psychiatric symptoms and autism. As genetic understanding continues to progress, the overlap with child psychiatry grows and it becomes increasingly important for child psychiatrists to recognize signs of a possible underlying genetic diagnoses [7].

In some instances, a genetic condition may have a typical psychiatric presentation and psychiatric symptoms may appear isolated. In such cases, presentation may be indistinguishable from that of a typical psychiatric patient whose disease is polygenic and multifactorial and genetic diagnosis is more difficult [8]. However, in many cases a genetic etiology may be suggested by features of history or physical exam. If child psychiatrists are aware of red flags signifying possible genetic condition, more patients can be appropriately diagnosed.

This article addresses two questions: Why is it important to diagnose genetic conditions in child psychiatry patients? What should prompt a child psychiatrist to request a genetic consult for a patient?

## Main text

### Benefits of diagnosing genetic conditions

Identifying a genetic etiology in child psychiatry patients has many benefits [9]. Diagnosis of specific genetic conditions can guide treatment and allow access to specialized healthcare. For example, depression may herald Wilson disease, which can be effectively treated with chelators [10]. In metabolic disorders with psychiatric symptoms, a diagnosis can allow for appropriate management

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to avoid metabolic decompensations, which worsen both psychiatric and somatic symptoms [8]. In children with FXS, hyperactivity responds particularly well to methylphenidate. Hyperactivity is more responsive to methylphenidate as part of FXS versus part of autism spectrum disorder or intellectual disability, or possibly even non-specific ADHD [3]. When diagnosed, these patients can be put directly on methylphenidate and avoid many medication trials, which carry associated risks. Furthermore, because psychiatric symptoms may arise years before more specific organic signs, certain treatments may be more effective at the ‘psychiatric stage’ before occurrence of irreversible lesions. This is particularly true for metabolic disorders [11]. Genetic diagnosis also enables access to specialized clinics with greater understanding of and experience with these complex presentations [12]. There are a growing number of condition-specific and neuro-genetic clinics that may be very beneficial to patients. Because wait times to appointments can be challenging, other consultation strategies (e.g. telehealth) may be considered.

Additionally, some genetic conditions are associated with known medical complications and may require routine screening or further medical work-up. For example, a patient presenting with autism spectrum disorder and macrocephaly who is found to have a PTEN mutation can then be enrolled in a cancer screening protocol. Further, diagnosis can allow for appropriate genetic counseling for the patient and family [12, 13].

Finally, a better understanding of etiology with a named diagnosis may itself be of great value to many. Most individuals would rather know they have a serious disease than continue without a diagnosis [14]. Diagnosis allows for improved understanding, educational planning, and social support, and peer networking [15, 16]. Prognostic information can be empowering.

**Indications for genetic consultation**

It is not practical to conduct a genetic workup on all patients, so child psychiatrists must decide whom to

refer for genetic evaluation [1]. Child psychiatrists are in an important position to diagnose genetic conditions, as they often see children for whom a diagnosis has been elusive, who have unusual presentations, or who have been difficult to treat.

Patients with genetic conditions may present to psychiatric care in diverse ways. Table 1 shows genetic conditions that may in rare cases account for typical child psychiatry presentations. Psychiatric symptoms may be apparently isolated, making genetic diagnosis difficult. However, often a careful history and physical provides hints to a genetic diagnosis.

Some unusual psychiatric presentations or behaviors may suggest a particular genetic etiology. Skin picking may occur in Prader-Willi syndrome [25] while severe disruptions of sleep and nail pulling suggest Smith-Magenis syndrome [26]. In many cases, non-psychiatric features of the history or exam will provide clues to genetic etiology.

The purpose of Table 2 is to present a framework of notable history and exam features that should prompt a child psychiatrist to consider whether there is a larger, unifying genetic diagnosis at hand. All of these features are recognized as markers in pediatric genetic practice, however here the goal is to isolate the flags most likely to present in a child psychiatry practice [27]. This table is just a starting point and should not be considered exhaustive.

If one or more of these red flags are present, a child psychiatrist should consider requesting a genetic consultation. Whenever possible, genetic tests should be ordered in conjunction with a genetic team. On a practical level, determining which genetic tests to order can be confusing and outside the usual practice of most child psychiatrists. Even more important, many child psychiatrists are not comfortable explaining the intricacies of genetic testing and lack the infrastructure to deal with ramifications of positive results [28]. Informed consent must include discussion of the risks of genetic testing, which include harms associated with

**Table 1 Genetic syndromes may in rare cases manifest in more general child psychiatry presentations**

Psychiatric presentation	Example of genetic syndrome that may result in this presentation
Anxiety	22q11 deletion [17], Fragile X syndrome [18], Williams syndrome [19]
Acute psychosis	Adrenoleukodystrophy [20], Porphyria [21], Niemann-Pick [21], 22q11 deletion [17]
Conduct disorder/poor judgment/anger	Monoamine oxidase A deficiency [22]
Hyperactivity	Turner syndrome [23], Fragile X syndrome [3]
Depression	Wilson disease [24]

**Table 2 Red flags for a possible genetic diagnosis in child psychiatry patients**

Red flag	Explanation	Examples of genetic conditions that may include specific psychiatric components
<p>Medical history Autism spectrum disorder</p>	<p>Genetic causes can be identified in 10–20 % of autism patients [1–6]</p>	<p>Rett syndrome PTEN mutations Tuberous sclerosis Chromosomal copy number variants</p>
<p>Intellectual disability or global developmental delay</p>	<p>While these findings may be purely developmental, they should be investigated further when the findings seem out of proportion to the level of developmental delay</p>	<p>Rett syndrome fragile X</p>
<p>Psychiatric symptoms worsening with conditions leading to increased protein catabolism, such as fever, surgery, or prolonged fasting</p>	<p>May indicate metabolic dysfunction</p>	<p>Acute intermittent porphyria</p>
<p>Unusually severe presentation or prolonged recovery after minor illness</p>	<p>Cyclic or recurrent vomiting, particularly with protein intake</p>	<p>Organic acidemias Inborn error in pyruvate metabolism</p>
<p>Poor or atypical treatment response to medications or behavioral interventions</p>	<p>May indicate an alternate or additional diagnosis to explain non-standard response/components</p>	<p>Prader-Willi syndrome</p>
<p>Severely disrupted sleep Self-injurious behavior or skin picking</p>	<p>Family history</p>	<p>Smith-Magenis syndrome Lesch-Nyhan syndrome, Prader-Willi syndrome</p>
<p>Significant family history of psychiatric conditions</p>	<p>Though purely psychiatric conditions may also follow a familial pattern, this could indicate an underlying genetic diagnosis</p>	<p>22q11 deletion syndrome</p>
<p>Significant family history of neurologic regression or progressive neurologic disorders</p>	<p>May represent certain autosomal dominant traits for which first symptoms are sometimes psychiatric</p>	<p>Huntington disease Spinocerebellar ataxias</p>
<p>Family history of relatives with intellectual disabilities or many with learning disabilities</p>	<p>Intellectual disability and learning disabilities are part of many genetic syndromes that also have psychiatric features</p>	<p>Fragile X syndrome</p>
<p>Born to a parent with a known cytogenetic abnormality (e.g. balanced translocation) or recurrent pregnancy loss</p>	<p>Translocations may become unbalanced in subsequent generations causing a variety of presentations including psychiatric disease and pregnancy loss</p>	<p>Unbalanced chromosomal complement</p>
<p>Physical exam</p>	<p>May be caused by genetic syndrome</p>	<p>22q11 deletion syndrome Fragile X Submicroscopic chromosomal deletions and duplications Lysosomal storage diseases</p>
<p>Single major or multiple minor and/or major physical anomalies</p>		<p>Branchio-oto-renal syndrome Holt Oram syndrome</p>
<p>Striking inability to learn after many well-controlled trials</p>	<p>May suggest cortical dysfunction</p>	<p>Chromosomal deletions or deletions Fragile X</p>

**Table 2 continued**

Red flag	Explanation	Examples of genetic conditions that may include specific psychiatric components
Hepatosplenomegaly	These findings would not be explained by a psychiatric diagnosis alone. In conjunction with psychiatric symptoms, these findings may suggest a unifying genetic diagnosis.	Gaucher disease Niemann-Pick disease Mucopolysaccharidoses
Unusual body odor		Glutaric aciduria type II Phenylketonuria Isovaleric acidemia Maple syrup urine disease
Unusual dermatologic findings: multiple types of lesions, six or more café au lait macules > 1.5 cm in diameter, multiple lipomas, albinism		Neurofibromatosis type I Cowden syndrome Hermansky-Pudlak syndrome
Unexplained neurologic findings		Gaucher disease
Intractable seizures		Neuronal ceroid lipofuscinosis
Hypertonia or hypotonia		Mitochondrial disorders
Peripheral neuropathy		Inborn errors of metabolism including leukodystrophies
Myopathy		Prader-Willi syndrome
Progressive ataxia		Angelman syndrome Charcot-Marie-Tooth disease Spinocerebellar ataxias
Evidence of a connective tissue disorder		Homocystinuria
Joint laxity		Ehlers Danlos syndrome
Poor wound healing		
Marfanoid habitus		
Unexplained lab anomalies		Organic acidemias
Acidosis		Beckwith-Wiedemann syndrome
Persistent hypoglycemia		Adrenoleukodystrophy
Adrenal insufficiency		
Abnormal brain MRI findings		Tuberous sclerosis Leukodystrophies
Microcephaly		Spinocerebellar ataxias, Alexander disease
Failure to thrive or short stature	While psychiatric illness may lead to growth abnormalities, these abnormalities should be evaluated further when they cannot be fully explained by psychiatric disease	Fetal alcohol syndrome, Williams syndrome Various chromosomal conditions

resultant treatments and incidental findings that can be life changing or psychologically disruptive [29]. There may be particular cases in which a child psychiatrist has experience with or training relevant to a certain genetic test and feels comfortable ordering this test, so this remains an individual call. However, in most cases it is best to involve a genetic team and employ their associated infrastructure. It is our hope that this table will help child psychiatrists communicate with genetic teams by allowing them to pinpoint the red flags that led them to consider a genetic etiology.

### Conclusions

It is important to identify a genetic etiology in child psychiatry patients when it is present, as it has implications for treatment and counseling. Patients with genetic conditions may have unusual psychiatric symptoms or other abnormal history and physical findings. Here we present a table of red flags that a practicing child psychiatrist may identify, which could indicate an underlying genetic diagnosis. We hope this table will inspire child psychiatrists to think about genetic possibilities in their patient populations and make referrals for genetic evaluation when appropriate. Future work will be needed to validate this table in practice. However, being aware of these the flags has immediate utility in the clinical practice of child psychiatrists. To highlight how simple practice changes may have a big impact for diagnosing conditions, we provide a short list of tips and resources for making a genetic diagnosis in child psychiatry (Table 3). We hope that this commentary will encourage child psychiatrists to think about their growing overlap with the field of genetics. Recognition of the importance of genetic diagnoses in child psychiatry patients may stimulate more research into the prevalence of genetic disease, effective methods of screening and diagnosis, and strategies for treatment and management for these patients.

**Table 3 Short list of tips and resources for making genetic diagnoses in child psychiatry**

1. Take a family history
2. Measure and plot head circumference percentiles
3. Inspect the skin
4. Take note of dysmorphic features
5. Know your genetics referral colleagues
6. Short list of genetic resources  
GeneReviews®: <http://www.genereviews.org/>  
Online Mendelian Inheritance in Man (OMIM)®: <http://www.omim.org/>  
Genetics Home Reference: <http://ghr.nlm.nih.gov/>

### Authors' contributions

All authors have substantially contributed to the manuscript. All authors read and approved the final manuscript.

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### Competing interests

The authors declare that they have no competing interests.

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