50TH Anniversary Greenwood Genetic Center
Leading the Way Since 1974

What PAs Should Know About the Genetics of Autism

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Disclosures

I have performed consulting work for Sanofi, AmGen, and Illumina

- Founding Member and Treasurer of the Society of PAs in Genetics and Genomics (SPAGG)
- Founding Member and Planning Committee Member of the Clinical Genetics Advanced Practice Provider (CGAPP) Conference
- Serve on the Workforce Development and Optimization Committee and Membership Committee for the American College of Medical Genetics and Genomics (ACMG)

2

Greenwood Genetic Center

Mission

- Established in 1974, the Greenwood Genetic Center (GGC) is a nonprofit institute, organized to provide **clinical genetic services** and laboratory testing, to develop educational programs and materials, and to conduct research in the field of medical genetics.

3

PAs at the GGC


Laura


Wesley

4

Educational Objectives

At the conclusion of this session, the participants should be able to:

- Discuss the history, definition, diagnosis, epidemiology, and etiology of autism spectrum disorder
- Recognize patients with autism spectrum disorder who may benefit from a genetics evaluation
- Examine the genetic etiology of selected genetic disorders associated with autism spectrum disorder

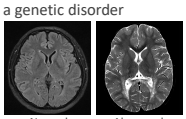
5

Who Gets Referred to Genetics

Individuals with a(n):

- Concern for a genetic disorder
- Family history of a genetic disorder
- Known genetic disorder
- Abnormal blood work or imaging suggestive of a genetic disorder


Normal Abnormal


Normal Abnormal

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Potential Referrals

- Abnormal/asymmetric growth patterns
- Abnormal newborn screen
- **Autism spectrum disorder**
- Developmental delay
- Dermatological findings
- Distinctive features
- Hereditary cancer
- Multiple congenital anomalies
- Other/Unexplained issues

(Saul & Moeschler 2013; https://medlineplus.gov/genetics/)

7

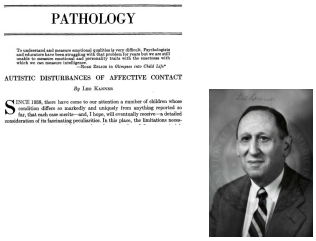
Outline

- History
- Definition
- Diagnosis
- Epidemiology
- Etiology
- Treatment

8

History

- Derived from the Greek word "auto," meaning 'self'
- First proposed by Swiss psychiatrist Eugen Bleuler in 1911
- Used by Leo Kanner in 1938 to describe 11 patients



PATHOLOGY

AUTISTIC DISTURBANCES OF AFFECTIVE CONTACT

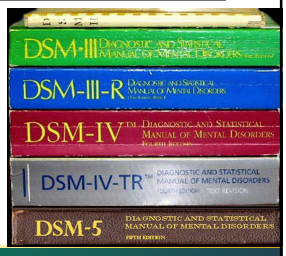
By Leo Kanner

SINCE 1908, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits—and, I hope, will eventually receive—a detailed consideration of its fascinating peculiarities. To this phase, the limitations neces-

9

Definition Changes

- 1975
  - Autism added to ICD-9 diagnoses
- 1980
  - DSM-III -> infantile autism as part of Pervasive Developmental Disorders
- 1987
  - DSM-III-R -> "childhood autism" was replaced by "autistic disorder"



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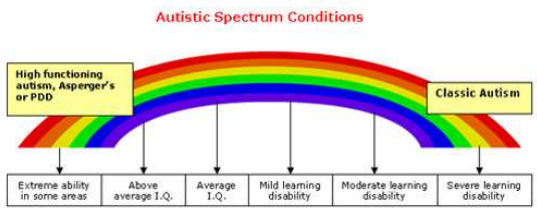
Definition Changes – 1994-2013



11

Definition Changes in 2013

DSM-IV-TR

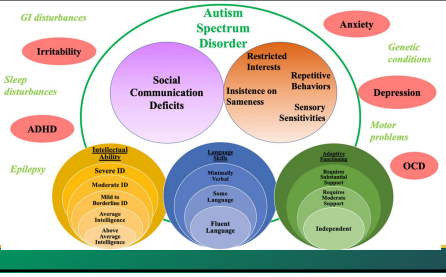
- Autistic Disorder
- Asperger Syndrome
- Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS)
- Rett Syndrome
- Childhood Disintegrative Disorder (CDD)

DSM-5

- Autism Spectrum Disorder
  - 3 social/emotional reciprocity and communication deficits
  - 2/4 restricted and repetitive behaviors, interests, or activities
  - Not better explained by intellectual disability or global developmental delay
- Social Communication Disorder

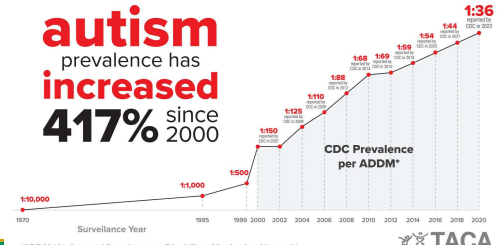
12

Autism Spectrum Disorder (ASD) & Comorbidities



Rosen et al. 2021

Epidemiology

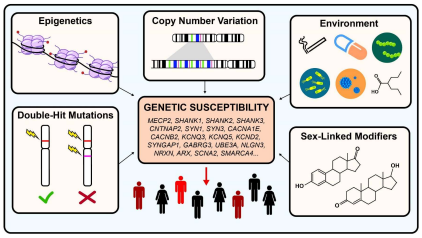


Epidemiology

- 1 in 36 children have autism
- About 4 in 100 boys and 1 in 100 girls have autism
- Boys are nearly 4 times more likely to be diagnosed with autism than girls
- Autism prevalence is lower among white children than other racial and ethnic groups:
  - White – 2.4%
  - Black – 2.9%
  - Hispanic – 3.2%
  - Asian or Pacific Islander – 3.3%

Maenner et al. 2023

Etiology



Etiology

- Traditionally, autism is divided into syndromic and nonsyndromic by clinical distinction
  - Syndromic
    - In conjunction with additional phenotypes and/or distinctive features
    - Different clinical entities with different developmental trajectories
  - Nonsyndromic
    - I.e. classic autism, idiopathic autism
    - Most cases etiology unknown
- Propose: overlapping genes and pathways

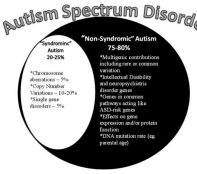


Figure 2. Causes of 'syndromic' and 'non-syndromic' autism.

Ivanov et al. 2015

Literature Review

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Syndromic Autism Revisited: Review of the Literature and Lessons Learned

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Genetic etiologies

ABSTRACT

Autism spectrum disorder is a neurodevelopmental disorder characterized by deficits in communication, stereotyped behaviors, restricted interests, and impaired social skills. The severity of the neurobehavioral phenotype is variable and historically has been distinguished based on the presence or absence of additional symptoms, termed syndromic and nonsyndromic or idiopathic autism, respectively. However, although the advancement in genetic molecular technologies has brought an increased understanding of the pathophysiology of autism, most of this success has been in the diagnosis of syndromic disease, whereas the etiology of nonsyndromic autism remains less understood. Here we review the common and rare genetic syndromes that feature autism, specifically highlighting deletion and duplication syndromes, chromosomal anomalies, and monogenic disorders. We show that the study of syndromic autism provides insight into the phenotypic and molecular heterogeneity of neurodevelopmental disease and suggests how study of these disorders can be helpful in understanding disease mechanisms implicated in nonsyndromic autism.

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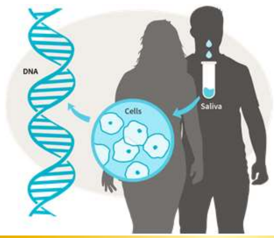
Genetic Testing and Etiologies

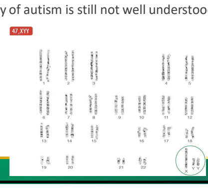


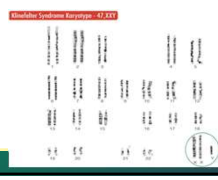
Etiology – Chromosomes

High-resolution chromosome analysis
- Previously, the gold standard
- Resolution >5 Mb
- Identify ~5% autism cases; higher if distinctive (dysmorphic) or have intellectual disability

Chromosomal Aneuploidies

- Syndromes with increased X or Y dosage have the highest association with autism, described in up to 50% of patients
- Although similar observations have long been noted and contribute to the evidence implicating the X chromosome in neurobehavioral phenotypes, the role of the Y chromosome in the etiology of autism is still not well understood





Supplemental Table 2. Chromosomal aneuploidies with autism as a feature of disease

Disorder	% with autism as a feature	Other associated neurologic or psychiatric disorder	Phenotype	Gene(s) implicated in ASD	Pathway(s) implicated	References
Down syndrome (Trisomy 21)	20-40%	ID, ADHD	distinctive facies, speech delay, hypotonia, hypothyroidism, recurrent infections, cardiac defects, leukemia, myeloproliferative disorders	*DYRK1A*	neurogenesis	149-151
Turner syndrome (monosomy X)	rare	ID, ADHD	distinctive facies, skeletal anomalies, congenital heart defects, ovarian dysgenesis, short stature	unknown	unknown	152-154
Klinefelter syndrome (XXY)	10-50%	ID, ADHD, schizophrenia	infertility, speech delay, learning problems	unknown	unknown	155,156
XYY	20-50%	ID, ADHD	macrocephaly, tall stature, speech delay	*NLGN4Y*	synapse	157-160
XXYY	25-50%	ID, ADHD, tics, epilepsy	distinctive facies, skeletal anomalies, congenital heart defects, tremor, diabetes, tall stature, cryptorchidism	*NLGN4Y*	synapse	161,162
45, X/ 46, XY mosaicism	7% in one study	ID	range of phenotypes including infertility, short stature, skeletal anomalies	unknown	unknown	163

Abbreviations: intellectual disability (ID); attention-deficit/ hyperactivity disorder (ADHD)

Deletion/Duplication Syndromes

Chromosomal Microarray
- Significant increase in diagnostic yield; detects ~10-20% of ASD
- >50 deletion/duplication syndromes associated with ASD and counting; assigning risk difficult
- Increased variants of uncertain significance

2010:

Review > Am J Hum Genet. 2010 May 14;86(5):749-64. doi: 10.1016/j.ajhg.2010.04.006.

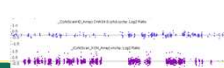
Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies

David T Miller[1], Margaret P Adam, Swaroop Aradhya, Leslie G Biesecker, Arthur R Brothman, Nigel P Carter, Deanna M Church, John A Crolla, Evan E Eichler, Charles J Epstein, W Andrew Faucett, Lars Feuk, Jan M Friedman, Ada Hamosh, Laird Jackson, Erin B Kaminsky, Klaas Kok, Ian D Krantz, Robert M Kuhn, Charles Lee, James M Ostell, Carla Rosenberg, Stephen W Scherer, Nancy B Spinner, Dimitri J Stavropoulos, James H Tepperberg, Erik C Thorland, Joris R Vermeesch, Darrel J Waggoner, Michael S Watson, Christa Lese Martin, David H Ledbetter

Affiliations + expand

PMID: 20466091 PMCID: PMC2869000 DOI: 10.1016/j.ajhg.2010.04.006

Free PMC article



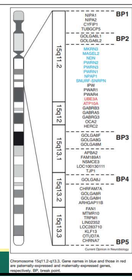
Supplemental Table 1. Deletion and duplication syndromes with autism as a feature of disease

Disorder	Percentage (%) with autism as a feature	Other associated neurologic or psychiatric disorder	Phenotype	Gene(s) implicated in ASD	Pathway(s) implicated	References
1p36 microdeletion syndrome *	rare; duplication associated with ID, microcephaly	ID, epilepsy	growth delay, hypotonia, hearing loss, orofacial clefting, cardiomyopathy, renal anomalies, distinctive facies, microcephaly	*PRKCZ, RERE*	cell signaling and transport	1-3
1q21.1 microdeletion/ duplication syndromes	10% with deletion, 40% with duplication	ADHD, bipolar, anxiety, depression, ID, schizophrenia	short stature, cataracts, macrocephaly (duplication), microcephaly (deletion), scoliosis, gastric ulcers, hypotonia	unknown	unknown	4-6
1q31 duplication syndrome	rare; deletion associated with hyperparathyroidism - jaw syndrome	ID	absent speech, distinctive facies	unknown	unknown	2
2p16.3 deletion syndrome *	40-45%; duplication associated with schizophrenia	ID, schizophrenia, epilepsy	distinctive facies, speech delay, behavior problems, skeletal issues, heart and eye abnormalities	*NRXN1*	synapse	7,8
2p15-p16.1 microdeletion syndrome *	up to 60%; duplication associated with ID, ADHD, OCD, atypical physical features	ID, epilepsy	microcephaly, distinctive facies, renal and eye anomalies	*BCL11A, REL, USP34, XP01*	transcription, cell growth, cell signaling	9-11
2q13 deletion/ duplication syndromes	30-35% deletion; 15-20% duplication	ID, ADHD	congenital heart disease, behavioral problems, liver disease	*MALL, NPHP1, RGPD6, BUB1*	signaling, inflammation, cell cycle	12-14
2q23.1 deletion/ duplication syndromes	up to 98% in both deletion and duplication	ID, epilepsy	microcephaly, distinctive facies, speech delay, ataxia, short stature, mild skeletal anomalies, eye anomalies	*MBD5*	unknown	15,16
2q33.1 deletion/ duplication (including 2q32-q33) syndromes	rare in deletion;15% in duplication	ID, epilepsy	atypical physical features, dental and palatal anomalies, behavioral problems, speech delay, hypotonia, skeletal anomalies	*SATB2*	transcription	17,18

Deletion/Duplication Syndromes

Dup15q11-13
- ~0.5% of all ASD risk
- ~69% with ASD
  - Higher with maternal inheritance
  - Comorbid with ID, ADHD, epilepsy

Del15q11.2
- Angelman syndrome
- Prader-Willi syndrome

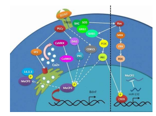


Takumi & Tamada 2018

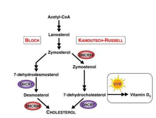
Monogenic Syndromes

>100 monogenic (single-gene) syndromes repeatedly associated in ASD

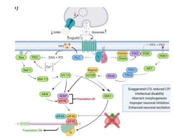
>900 genes associated with ASD



Díaz de León-Guerrero et al. 2011



Prabhu et al. 2016



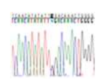
Romagnoli and Marino 2021

Supplemental Table 3. Monogenic syndromes with autism as a feature of disease

Disorder	Gene	Cytoband	Pathway(s) implicated	% with autism as a feature	Other associated neurologic or psychiatric disorder	Phenotype	References
Cerebellar ataxia, non-progressive with intellectual disability syndrome	*CAMTA1*	1p36.31-p36.23	transcriptional regulation	rare	ID, epilepsy	ataxia, hypotonia, distinctive facies, speech delay, behavioral problems	164
Xia-Gibbs syndrome	*AHDC1*	1p36.1-p35.3	transcription regulation	25-30%	ID, epilepsy	speech delay, distinctive facies, behavioral and sleep problems, hypotonia	165
Neurodevelopmental disorder with or without anomalies of the brain, eye or heart syndrome	*RERE*	1p36	nuclear receptor	30%	ID, epilepsy, ADHD	genitourinary and eye anomalies, congenital heart defect, hypotonia, behavioral problems	166
Muscle-eye-brain disease	*POMGNT1*	1p34.1	post-translational modification	20-25%	ID	congenital muscular dystrophy, structural eye anomalies, cobblestone lissencephaly, hypotonia	167
Arthrogryposis, intellectual disability and seizures syndrome	*SLC35A3*	1p21.2	post-translational modification	1 family (8 affected)	ID, epilepsy	congenital contractures, musculoskeletal anomalies, hypotonia	168
White-Sutton syndrome	*POGZ*	1q21.3	transcriptional regulation	50%	ID, seizures	distinctive facies, hearing impairment, gastrointestinal symptoms, joint laxity, visual defects, hypotonia	169
Autosomal dominant intellectual disability 52	*ASH1L*	1q22	transcriptional regulation	65-70%	ID, seizure, ADHD, anxiety	distinctive facies, speech delay, skeletal anomalies, hypotonia, cryptorchidism	169,170
Early infantile epileptic encephalopathy 54	*HNRNPU*	1q44	RNA regulation	rare	ID, epilepsy	microcephaly, hypotonia, joint laxity, speech delay	171,172
Autosomal dominant intellectual disability 39	*MYT1L*	2p25.3	transcriptional regulation	45%	ID, epilepsy, ADHD	hyperphagia and obesity, speech delay, hypotonia, distinctive facies, motor delay, behavioral problems	173
Tatton-Brown-Rahman syndrome	*DNMT3A*	2p23.3	transcription	35%	ID, epilepsy, anxiety, psychosis, bipolar	postnatal overgrowth, distinctive facies, cardiac defect, skeletal anomalies	161

Testing – Single Gene or Panel

Sanger sequencing
- Gold standard
- Rarely used today

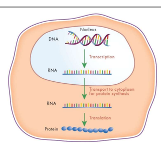


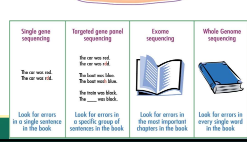
Next-generation sequencing
- Single gene versus panel

Examples:
- *PTEN* Hamartoma Tumor Syndrome
  - Significant macrocephaly
  - ~4.7% of macrocephalic autism cases
- Rett syndrome
  - *MECP2*
  - Consider overlapping phenotype:
    - CDKL5, FOXG1, MEF2C, SLC9A6, TCF4, UBE3A, etc.

Testing – All Genes

- Whole exome sequencing
  - Analyzes the coding regions (1-2% of the genome) of the ~20,000 genes, simultaneously
  - Increased variants of uncertain significance
  - Incidental findings
- Whole genome sequencing
  - Same, except analyzes whole genome (coding and non-coding)
  - Some platforms include mitochondrial and trinucleotide repeats





New Testing Approach

Meta-Analysis > Genet Med. 2019 Nov;21(11):2413-2421. doi: 10.1038/s41436-019-0554-6. Epub 2019 Jun 11.

Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders

Siddharth Srivastava [#, 1], Jamie A Love-Nichols [#, 1], Kira A Dies [1], David H Ledbetter [2], Christa L Martin [2], Wendy K Chung [3, 4], Helen V Firth [5, 6], Thomas Frazier [7], Robin L Hansen [8], Lisa Prock [1, 9], Han Brunner [10, 11, 12], Ny Hoang [13, 14, 15], Stephen W Scherer [14, 15, 16, 17], Mustafa Sahin [18], David T Miller [19]; NDD Exome Scoping Review Work Group

Affiliations + expand

PMID: 31182824 PMCID: PMC6831729 DOI: 10.1038/s41436-019-0554-6

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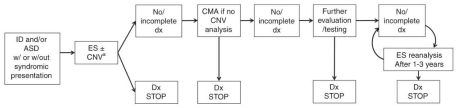
New Testing Approach



Diagnostic algorithm incorporating exome sequencing (ES) in the clinical evaluation of individuals with unexplained neurodevelopmental disorders (NDDs) (global developmental delay/intellectual disability [GDD/ID] and/or autism spectrum disorder [ASD]). An incomplete diagnosis represents a diagnosis that explains only part of an individual's phenotype. Factors such as the turnaround time of test, availability of tests, and availability of genetic counseling may be considerations in application of this algorithm in clinical use. [a]Or technology that supersedes ES such as genome sequencing. *CMA* chromosomal microarray, *CNV* copy-number variant.

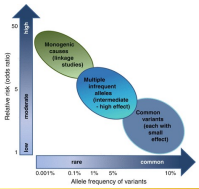
Diagnostic yield of ES = 36%

Srivasrava et al. 2019

31

Importance of Genetic Testing

- Autism spectrum disorder is highly prevalent in some genetic conditions:
  - Fragile X syndrome
  - Tuberous sclerosis complex
  - Rett syndrome



32

Importance of Genetic Testing

- Fragile X syndrome
  - Most common inherited cause of intellectual disability in males
  - Autosomal dominant
  - Affects 1:4,000 males; 1:8,000 females
  - 1-2% of all ASD? (depends on source)
  - ASD is present in ~15-70% (controversial)
  - Physical/dysmorphology exam: long and narrow face, prominent forehead, large ears, prominent jaw

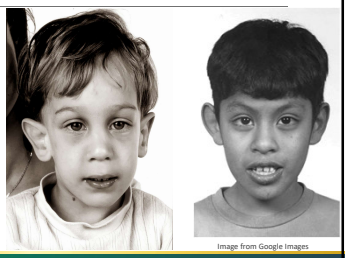
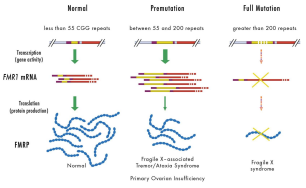


Image from Google Images

33

Importance of Genetic Testing

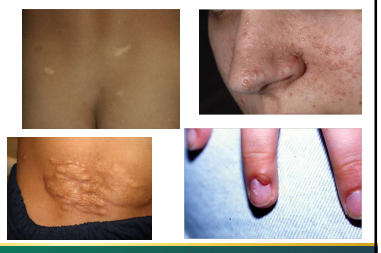
- Fragile X syndrome
  - Due to a trinucleotide repeat expansion (CGG) in the *FMR1* gene
    - *FMR1* gene codes for FMRP, a protein that helps regulate multiple proteins and plays a role in the development of synapses
    - >200 repeats leads to methylation and silencing of gene expression
  - Family Implications (premutations):
    - Fragile X-associated tremor/ataxia syndrome (FXTAS)
    - Fragile X-associated primary ovarian insufficiency (FXPOI)



34

Importance of Genetic Testing

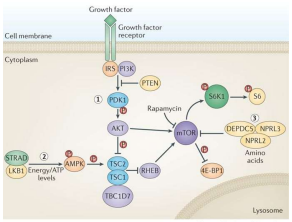
- Tuberous sclerosis complex
  - Affects 1:5,800 births
  - Autosomal dominant
  - *De novo* in 2/3
  - ASD is present in ~16-61%
  - Physical/dysmorphology exam (skin): hypomelanotic macules, confetti skin lesions, facial angiofibromas, shagreen patches, ungual fibromas



35

Importance of Genetic Testing

- Tuberous sclerosis complex
  - Caused by pathogenic variants in the *TSC1* and *TSC2* genes
  - *TSC1* gene encodes hamartin, a protein that interacts with tuberin (*TSC2*) to form a protein complex that inhibits signal transduction to the downstream effectors of the mammalian target of rapamycin
  - Treatment: mTOR inhibitors (rapamycin) for facial angiofibromas (topical), symptomatic cardiac rhabdomyomas, and lymphangioleiomyomatosis



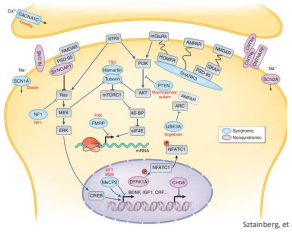
36

Importance of Genetic Testing

- Rett syndrome
  - Autosomal dominant
  - Affects 1:10,000 live births
  - De novo in 99%
  - ASD is present in ~60%
  - Marked by regression; acquired microcephaly
  - Physical/dysmorphology exam (movements): repetitive, stereotypic hand movements replace purposeful hand use; fits of screaming and inconsolable crying; bruxism; gait ataxia; tremors

Importance of Genetic Testing

- Rett syndrome
  - Caused by pathogenic variants in the *MECP2* gene
  - *MECP2*, which binds methylated CpGs, is a chromatin-associated protein that can both activate and repress transcription
  - Treatment: trofinetide – improves neuronal and synaptic functioning and morphology



Sztainberg, et al. 2016

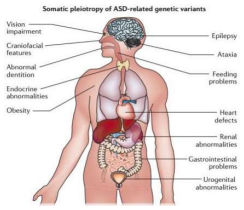
Importance of Genetic Testing

Identification of treatable somatic comorbidities
- *CHD8* and GI problems

Additional phenotypes
- *PTEN* and tumor screening
- *ADNP* and heart defects

Informed choice of pharmacotherapy
- Side effect profile
- 17q12 del and nephrotoxicity

Focusing on the right behavioral interventions
- *SHANK3*: receptive > expressive language ability



Vorstman et al. 2017

Conclusion

Prevalence of autism spectrum disorder is increasing
- Heightened awareness
- Changing definition; broadened diagnostic criteria
- Possible environmental influences

Autism is a multifactorial disorder with many interacting genetic factors
- No single genetic etiology accounts for more than 1-2% of autism
- Common variants may modify autism-related phenotypes
- Consider genome-first approach

Studying autism-associated syndromes may reveal common molecular features leading to the identification of shared pathway(s) which could guide the development of specific treatments and better screening methods for autism

Take Home Points

- Autism spectrum disorder is becoming more prevalent
- *All* individuals with unexplained autism spectrum disorder should undergo a genetics evaluation
- Early diagnosis is key as more interventions and potential treatments are becoming available in the era of precision medicine

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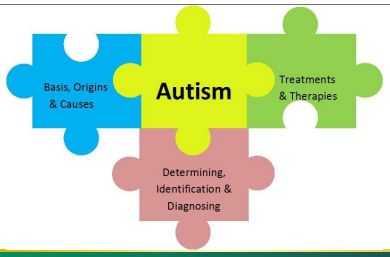
- Greenwood Genetic Center

GGC Family

43

Questions?



44

Questions?

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https://spagg.wildapricot.org/

45