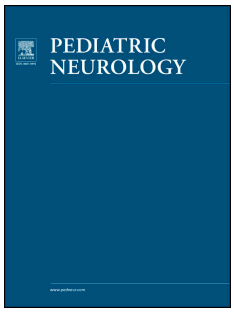

Syndromic autism revisited: review of the literature and lessons learned

Catherine A. Ziats, Wesley G. Patterson, Michael Friez

PII: S0887-8994(20)30211-3

DOI: https://doi.org/10.1016/j.pediatrneurol.2020.06.011

Reference: PNU 9803

To appear in: *Pediatric Neurology*

Received Date: 11 March 2020

Revised Date: 1 May 2020

Accepted Date: 19 June 2020

Please cite this article as: Ziats CA, Patterson WG, Friez M, Syndromic autism revisited: review of the literature and lessons learned, *Pediatric Neurology* (2020), doi: https://doi.org/10.1016/j.pediatrneurol.2020.06.011.

Title: Syndromic autism revisited: review of the literature and lessons learned

Authors: Catherine A. Ziats,[1] Wesley G. Patterson,[1] and Michael Friez[1]

Affiliations:

[1]J.C. Self Research Institute, Greenwood Genetic Center, Greenwood, SC

Corresponding author:
Catherine A. Ziats
106 Gregor Mendel Circle
Greenwood, SC 29646
cziats@ggc.org

Word count: 2506

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, while the advancement in genetic molecular technologies has brought an increased understanding of the pathophysiology of autism, the majority of this success has been in the diagnosis of syndromic disease, while the etiology of nonsyndromic autism remains less understood. In this review, we provide an updated reference of common and rare genetic syndromes with autism as a feature of disease, 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 suggest how study of these disorders can be helpful in understanding disease mechanisms implicated in nonsyndromic autism.

Keywords: autism; ASD; autism spectrum disorders; autistic behaviors

Introduction

Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental disorder characterized clinically by repetitive stereotyped behaviors, restricted interests, and impaired social and communication skills.[1] The first descriptions of autism by Leo Kanner in the 1930's described a primarily behavioral phenotype, without the presence of other neurologic and/or medical comorbidities, and would be described as 'idiopathic' autism today.[2] However, it is now known that the behavioral and neurologic phenotype of autism disorders is wide, and can be a feature of other primary neurologic disorders such as Rett syndrome or Fragile X syndrome, or of other 'syndromic' autism disorders.

The last decade has brought a tremendous increased understanding of autism genetics, with over 1000-gene or gene loci implicated to date, and with current molecular techniques, a genetic diagnosis can now be identified in about 15-30% of cases.[3] However, the greatest progress in autism genetics has been in gene discovery of monogenic disorders, which cause syndromic disease. These disorders typically present with a number of other clinical symptoms in addition to autism, however only account for a minority of all autism cases.[4] Yet, both *in-vivo* and *in-vitro* models have shown that genes and gene loci implicated in both syndromic and idiopathic autism converge on common biological pathways and implicate several key processes as causative of the neurobehavioral phenotype of autism.[5] This is important for a number of reasons but perhaps most importantly because it provides a rationale for studying syndromic autism as a way to better understand mechanisms that may be contributing to neurobehavioral disease in idiopathic autism.

In this manuscript, we provide an updated review of syndromic autism conditions, providing relevant clinical and molecular information on common and rare chromosomal and single gene autism disorders. We highlight several disorders that share molecular mechanisms implicated in idiopathic autism—highlighting how syndromic autism conditions can provide important insights into idiopathic disease. Additionally, we show that disorders with autism as a feature of disease cover a wide range of conditions of varying severity and of diverse molecular underpinnings, suggesting that mechanisms driving the autism phenotype may be broader than traditionally suspected.

Methods

In an effort to identify and better understand the current landscape of autism and autistic-syndromes, we manually searched the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) using 'autism syndrome' as our search term. We identified 294 autism syndromes that met our initial search

criteria with 75 syndromes/genes considered duplicates that were able to be consolidated under another syndrome name (Supplemental Figure 1). After review of primary literature reports another 39 syndromes were removed if they represented single-case reports and/or the association with autism was considered questionable. Reports that noted autistic-features/autistic behaviors without evidence of a formal diagnosis of autism as defined by the *Diagnostic and Statistical Manual of Mental Disorders* criteria were also excluded.[1]

After review and curation 180 autism syndromes were included in the final analysis (Supplemental Tables 1-3). Fifty-nine represented unique autism loci and chromosome duplication/deletion syndromes, 6 represented chromosomal aneuploidy disorders, and 115 were single gene disorders. For each disorder, gene and cytoband/chromosomal location, phenotype, associated neurologic or psychiatric disorder and biological pathway implicated in the pathogenesis were noted. Additionally, for each disorder the percentage of patients thought to have autism was recorded. For some disorders, the actual percentage was not found in the literature and so descriptive terms such as 'rare,' or 'common,' were noted as described in the report. In these cases, rare was interpreted to mean less than 25% of patients, and common as more than 50% of patients, respectively. Below, we review autism syndromes caused by deletions and duplications, chromosomal aneuploidies, and single genes separately, highlighting trends within each group.

Results

Deletion and duplication syndromes with ASD as a feature of disease

Chromosomal microarray and karyotype testing are an essential component of the initial genetic work-up for autism patients, with chromosomal alterations and small copy number variations reported in about 5-10% of autism cases.[3, 6] To date, over 50 deletion/duplication syndromes associated with an autism phenotype have been described. In Table 1, we highlight several syndromes where autism is a common feature of disease, with a more extensive list of syndromes included in Supplemental Table 1. The most commonly reported of the deletion/duplication syndromes is chromosome 15q11q13 duplication syndrome, which has been implicated in up to 0.5% of all autism cases.[7] This duplication syndrome is unique in that it is highly penetrant, with a significantly higher penetrance associated with maternal inheritance specifically.[8] However, the clinical consequence of these cytogenetic anomalies is variable as several of the deletion/duplication syndromes are not fully penetrant and are found in unaffected family members, with chromosome 15q13.3 duplication syndrome one example of this phenomenon (Supplemental Table 1). Moreover, expressivity of a neurobehavioral phenotype is variable

even within families, with symptoms ranging from mild behavioral problems such as attention-deficit/ hyperactivity disorder to autism and/or severe intellectual disability, making interpretation of these molecular findings complicated and genetic counseling difficult.

Interestingly, most of the copy number changes implicated in autism and reviewed here are associated with a neurodevelopmental phenotype in both the deletion and reciprocal duplication syndrome, however how differences in gene dosing affect the phenotype is variable (Supplemental Table 1). Notably co-morbid intellectual disability, reflecting a more severe neurologic phenotype, has been reported in all of the deletion/duplication syndromes reviewed here and an expected consequence of disorders predicted to affect multiple genes. Additionally, the duplication/deletion syndromes reviewed here implicate a broad range of cellular and molecular pathways as contributory, although in many cases the exact mechanism(s) specifically responsible for the neurodevelopmental phenotype of the disorder is unclear. Similar to idiopathic ASD and other neurodevelopmental disorders, mechanisms related to transcriptional regulation and to synaptic transport and formation were most common and implicated in 40 of the 59 deletion/duplication syndromes included in this analysis (Supplemental Table 1).

At chromosomal loci with both a deletion and a duplication phenotype (n=29), the deletion syndrome was more often (n=13) associated with a higher incidence of autism. In contrast, at a smaller number of loci (n=9 of 29 total) the duplication syndrome was associated with an equal or greater prevalence of autism, suggesting that duplication syndromes may be more tolerated and/or require other risk factors for expression of the autism phenotype specifically. Additionally, at several of the loci reviewed (n= 20 of 59), even in the absence of autism, neurodevelopmental or neuropsychiatric symptoms are reported with both duplication and deletion of the region. This supports the notion of a mechanistic link between autism and other neuropsychiatric and neurodevelopmental disorders such as attention-deficit/ hyperactivity disorder and intellectual disability, as other groups have shown in idiopathic autism.[9]

Chromosomal aneuploidies with ASD as a feature of disease

Rarely, autism has been implicated in sex chromosomal aneuploidies, with syndromes with increased X or Y dosage such as XXYY and XYY aneuploidies, having the highest association with autism, described in up to 50% of patients (Supplemental Table 2).[10-12] While 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.[12, 13] Several studies have shown that males with a XYY genotype are more likely to exhibit autism behaviors as compared to males with a XXY genotype, however whether this observation is a consequence of increased expression of Y

chromosome genes specifically or a result of increased chromosomal instability in XYY patients is unclear.[11] Further studies are needed to understand if and how increased dosage of genes on the Y chromosome increases the risk of a neurodevelopmental phenotype.

Additionally, it is worth noting that while autism has been a well described feature of Down syndrome, the presence of an autism phenotype in patients with Down syndrome is reported in less than 50% of patients.[14, 15] In contrast, patients with isolated deletions or loss of function variants in *DYRK1A*, which is located on chromosome 21 and implicated in the neurodevelopmental phenotype of Down syndrome, commonly have autism (85-90% of patients) as part of their neurodevelopmental phenotype (Supplemental Table 3).[16] Therefore, for this gene specifically, gene dosing seems to heavily influence vulnerability to a neurobehavioral phenotype, and is an important consideration for current gene therapy approaches in Down syndrome aimed at reversing neurodevelopmental phenotypes via down regulation of *DYRK1A*.[17]

Monogenic syndromes with ASD as a feature of disease

Autism is also a feature of many autosomal dominant, autosomal recessive, and X-linked syndromes caused by alterations in single genes.[6] Table 1 highlights several monogenic syndromes with autism reported as a common feature of disease, and a more comprehensive list describing over 100 monogenic syndromes repeatedly associated in autism can be found in Supplementary Table 3. Examining these monogenic autism syndromes as a group provides insight into the complexity of autism biology. Specifically, the number of different pathways involved in monogenic autism syndromes is large and varied. The most common biological pathways were related to transcriptional regulation and synaptic maintenance and implicated in 65 (56%) of monogenic syndromes reviewed here, and these pathways have been repeatedly shown to underlie both the nonsyndromic autism phenotype and several well studied syndromic autism syndromes such as Rett syndrome and Fragile X syndrome. However, we also noted convergence on several other cellular and molecular pathways with a less obvious role in neurodevelopmental circuitry and neurobehavior. For instance, autism was noted as a prominent feature of several metabolic syndromes caused by disrupted amino acid and/or lipid breakdown and recycling (n=11, Supplemental table 3). One example is Smith-Lemli-Opitz syndrome, caused by variants in *DHCR7* involved in cholesterol biosynthesis, and characterized by a characteristic facies, intellectual disability, epilepsy, disordered sleep, short stature, and autism in up to 75% of patients. [18-22]

Additionally, as was the case for deletion/duplication syndromes, review of monogenic autism syndromes highlights the variability in penetrance of the autism phenotype in these conditions. While the

syndromes presented here are associated with a severe neurodevelopmental phenotype that includes intellectual disability and/or epilepsy, our analysis shows autism is rarely a common feature in these disorders despite being frequently reported, with only 17 of 115 (15%) of monogenic syndromes describing presence of autism in more than 75% of patients, and suggests that expression of the autism phenotype in syndromic disease may require the presence or absence of other disease modifiers (Supplemental Table 3).[23, 24]

Discussion and future directions:

Here we provide an updated review of autism syndromes and show that with the rapid advancement of sequencing and microarray technologies our understanding of autism syndromes has greatly expanded, and moreover that from a molecular perspective nonsyndromic and syndromic autism may be more similar than traditionally believed. For instance, in deletion/duplication syndromes associated with a neurobehavioral phenotype, often times the specific phenotype of the copy number change is virtually impossible to predict, even within families. The phenotypes are highly variable, ranging from syndromic disease to idiopathic autism. Additionally, these copy number changes can manifest as other primary neurologic diseases such as attention-deficit/ hyperactivity disorder or epilepsy—and this continuum perhaps provides the best evidence for shared biology among neurobehavioral and neurodevelopmental disorders.[24] Recently, several groups have attempted to apply risk algorithms incorporating factors such as inheritance, size of copy number change, and population data to predict clinical spectrum of disease. While these metrics are not yet validated for clinical use we expect these types of analyses will quickly become an important tool in the counseling and management of patients with congenital neurobehavioral diseases.[25, 26]

Over the last few decades, insight into the pathophysiology of idiopathic autism has been aided by studying a number of monogenic syndromes associated with a high penetrance of autism as part of the neurobehavioral phenotype. For instance, models of tuberous sclerosis complex caused by variants in *TSC1* or *TSC2,* and of Rett syndrome caused by variants in *MECP2,* have helped highlight how deficits in synaptogenesis and circuit formation can lead to specific neurobehavioral symptoms.[27, 28] However, our review shows that these highly penetrant autism syndromes do not represent the majority of syndromes associated with an autism phenotype. In contrast, in the majority of autism associated syndromes reviewed here, even though autism is a repeatedly reported feature of disease it is uncommonly observed. One explanation for this observation may be the additional presence or absence of genetic risk factors such as larger size of copy number change and/or environmental factors such as maternal illness.

However additionally, the effect of familial genetic background on the penetrance of neurodevelopmental phenotypes is increasingly being recognized. Moreover, with recent evidence suggesting that familial genetic background can even influence traits such as social responsiveness score and full-scale IQ, it is likely that bi-parental behavioral and cognitive ability scores may start to play a role in the interpretation of scoring systems used to diagnose neurodevelopmental and neurobehavioral disorders in the future.[29]

Finally, it is worth noting that there have been several changes in the way autism is defined and diagnosed over the last 30 years and therefore, we suspect that for many of the autism syndromes reviewed, differing percentages of autism penetrance are at least in part a consequence of these definition changes. Perhaps the biggest definition change occurred in 2013 with the release of the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders.*[1] This new edition broadened the diagnostic criteria by requiring deficits in two core domains instead of three, combining the language and communication domains into one. Additionally, several diagnoses previously included under the umbrella of autism spectrum disorders such as pervasive developmental disorder not otherwise specified and childhood disintegrative disorder were removed due in large part to differences in how these additional diagnoses were made and interpreted.[1]

Our review of syndromic autism shows that with increased availability and advancement of molecular testing techniques, the phenotypic spectrum of autism syndromes has expanded, and with this, what constitutes syndromic versus nonsyndromic autism has become less clear. Moving forward we suspect that this historical terminology will change and give way to a classification that incorporates genetic diagnoses and implicated molecular pathway. Examples of classification schemes incorporating this information have already taken hold in several neurobehavioral disorders, with the SHANKopathies and RASopathies as two examples, and we anticipate several other autism and neurobehavioral syndromes will start to be grouped in similar ways.[30, 31]

Conclusions:

In this report we provide an updated review of syndromic autism genetics, highlighting the molecular and phenotypic heterogeneity of these disorders. Specifically, we review known common and rare deletion and duplication syndromes, chromosomal anomalies, and monogenic disorders with autism as a feature of disease. We show how several syndromes have been helpful in understanding the pathology of idiopathic autism, and additionally highlight other less understood mechanisms of disease repeatedly implicated syndromic disorders that may also have a role in idiopathic autism pathology. Finally, we show that while studying monogenic autism syndromes has greatly enhanced our

understanding of neurodevelopmental pathways, current molecular techniques that have expanded the clinical spectrum of these disorders are causing a reconsideration of what constitutes a syndromic versus nonsyndromic disease. We anticipate that moving forward this terminology will give way to molecular and pathway specific subgrouping of autism disorders.

Acknowledgments: The authors would like to thank the Greenwood Genetic Center Autism Research Project for their continued support.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Web resources:

PubMed database: https://www.ncbi.nlm.nih.gov/pubmed/

References:

1. Association AP. *Diagnostic and Statistical Manual of Mental Disorders*. 5th Edition edn. American Psychiatry Association Arlington, VA, 2013.

2. Kanner L. Autistic disturbances of affective contact. *Acta paedopsychiatrica.* 1968; **35**(4)**:** 100-136.

3. Srivastava S, Love-Nichols JA, Dies KA, Ledbetter DH, Martin CL, Chung WK *et al.* Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. *Genetics in medicine.* 2019; **21**(11)**:** 2413-2421.

4. Sztainberg Y, Zoghbi HY. Lessons learned from studying syndromic autism spectrum disorders. *Nature neuroscience.* 2016; **19**(11)**:** 1408-1417.

5. Baudouin SJ, Gaudias J, Gerharz S, Hatstatt L, Zhou K, Punnakkal P *et al.* Shared synaptic pathophysiology in syndromic and nonsyndromic rodent models of autism. *Science.* 2012; **338**(6103)**:** 128-132.

6. Betancur C. Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting. *Brain research.* 2011; **1380:** 42-77.

7. Depienne C, Moreno-De-Luca D, Heron D, Bouteiller D, Gennetier A, Delorme R *et al.* Screening for genomic rearrangements and methylation abnormalities of the 15q11-q13 region in autism spectrum disorders. *Biological psychiatry.* 2009; **66**(4)**:** 349-359.

8. Schroer RJ, Phelan MC, Michaelis RC, Crawford EC, Skinner SA, Cuccaro M *et al.* Autism and maternally derived aberrations of chromosome 15q. *American journal of medical genetics.* 1998; **76**(4)**:** 327-336.

9. Yan Z, Kim E, Datta D, Lewis DA, Soderling SH. Synaptic Actin Dysregulation, a Convergent Mechanism of Mental Disorders? *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2016; **36**(45)**:** 11411-11417.

10. Donnelly SL, Wolpert CM, Menold MM, Bass MP, Gilbert JR, Cuccaro ML *et al.* Female with autistic disorder and monosomy X (Turner syndrome): parent-of-origin effect of the X chromosome. *American journal of medical genetics.* 2000; **96**(3)**:** 312-316.

11. Ross JL, Tartaglia N, Merry DE, Dalva M, Zinn AR. Behavioral phenotypes in males with XYY and possible role of increased NLGN4Y expression in autism features. *Genes, brain, and behavior.* 2015; **14**(2)**:** 137-144.

12. Tartaglia NR, Wilson R, Miller JS, Rafalko J, Cordeiro L, Davis S *et al.* Autism Spectrum Disorder in Males with Sex Chromosome Aneuploidy: XXY/Klinefelter Syndrome, XYY, and XXYY. *Journal of developmental and behavioral pediatrics.* 2017; **38**(3)**:** 197-207.

13. van Rijn S. A review of neurocognitive functioning and risk for psychopathology in sex chromosome trisomy (47,XXY, 47,XXX, 47, XYY). *Current opinion in psychiatry.* 2019; **32**(2)**:** 79-84.

14. Oxelgren UW, Myrelid A, Anneren G, Ekstam B, Goransson C, Holmbom A *et al.* Prevalence of autism and attention-deficit-hyperactivity disorder in Down syndrome: a population-based study. *Developmental medicine and child neurology.* 2017; **59**(3)**:** 276-283.

15. Richards C, Powis L, Moss J, Stinton C, Nelson L, Oliver C. Prospective study of autism phenomenology and the behavioural phenotype of Phelan-McDermid syndrome: comparison to fragile X syndrome, Down syndrome and idiopathic autism spectrum disorder. *Journal of neurodevelopmental disorders.* 2017; **9**(1)**:** 37.

16. van Bon BW, Hoischen A, Hehir-Kwa J, de Brouwer AP, Ruivenkamp C, Gijsbers AC *et al.* Intragenic deletion in DYRK1A leads to mental retardation and primary microcephaly. *Clinical genetics.* 2011; **79**(3)**:** 296-299.

17. Feki A, Hibaoui Y. DYRK1A Protein, A Promising Therapeutic Target to Improve Cognitive Deficits in Down Syndrome. *Brain sciences.* 2018; **8**(10).

18. Bianconi SE, Cross JL, Wassif CA, Porter FD. Pathogenesis, Epidemiology, Diagnosis and Clinical Aspects of Smith-Lemli-Opitz Syndrome. *Expert opinion on orphan drugs.* 2015; **3**(3)**:** 267-280.

19. Paila YD, Murty MR, Vairamani M, Chattopadhyay A. Signaling by the human serotonin(1A) receptor is impaired in cellular model of Smith-Lemli-Opitz Syndrome. *Biochimica et biophysica acta.* 2008; **1778**(6)**:** 1508-1516.

20. Kovarova M, Wassif CA, Odom S, Liao K, Porter FD, Rivera J. Cholesterol deficiency in a mouse model of Smith-Lemli-Opitz syndrome reveals increased mast cell responsiveness. *The Journal of experimental medicine.* 2006; **203**(5)**:** 1161-1171.

21. Garbarino VR, Gilman TL, Daws LC, Gould GG. Extreme enhancement or depletion of serotonin transporter function and serotonin availability in autism spectrum disorder. *Pharmacological research.* 2019; **140:** 85-99.

22. Matta SM, Hill-Yardin EL, Crack PJ. The influence of neuroinflammation in Autism Spectrum Disorder. *Brain, behavior, and immunity.* 2019; **79:** 75-90.

23. Turner TN, Coe BP, Dickel DE, Hoekzema K, Nelson BJ, Zody MC *et al.* Genomic Patterns of De Novo Mutation in Simplex Autism. *Cell.* 2017; **171**(3)**:** 710-722.e712.

24. Du Y, Li Z, Liu Z, Zhang N, Wang R, Li F *et al.* Nonrandom occurrence of multiple de novo coding variants in a proband indicates the existence of an oligogenic model in autism. *Genetics in medicine.* 2020; **22**(1)**:** 170-180.

25. Cogill S, Wang L. Support vector machine model of developmental brain gene expression data for prioritization of Autism risk gene candidates. *Bioinformatics.* 2016; **32**(23)**:** 3611-3618.

26. Duda M, Haber N, Daniels J, Wall DP. Crowdsourced validation of a machine-learning classification system for autism and ADHD. *Translational psychiatry* 2017; **7**(5)**:** e1133.

27. Santini E, Klann E. Reciprocal signaling between translational control pathways and synaptic proteins in autism spectrum disorders. *Science signaling.* 2014; **7**(349)**:** re10.

28. Zoghbi HY, Bear MF. Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities. *Cold Spring Harbor perspectives in biology.* 2012; **4**(3).

29. Moreno-De-Luca A, Evans DW, Boomer KB, *et al.* The Role of Parental Cognitive, Behavioral, and Motor Profiles in Clinical Variability in Individuals With Chromosome 16p11.2Deletions. *JAMAPsychiatry.* 2015;72(2):119–126.

30. Introduction: Shankopathies and related autism spectrum disorders. *Developmental neurobiology.* 2014; **74**(2)**:** 83-84.

31. Rauen KA. The RASopathies. *Annual review of genomics and human genetics.* 2013; **14:** 355-369.

32. Jaillard S, Dubourg C, Gerard-Blanluet M, Delahaye A, Pasquier L, Dupont C *et al.* 2q23.1 microdeletion identified by array comparative genomic hybridisation: an emerging phenotype with Angelman-like features? *Journal of medical genetics.* 2009; **46**(12)**:** 847-855.

33. Mullegama SV, Alaimo JT, Chen L, Elsea SH. Phenotypic and molecular convergence of 2q23.1 deletion syndrome with other neurodevelopmental syndromes associated with autism spectrum disorder. *International journal of molecular sciences.* 2015; **16**(4)**:** 7627-7643.

34. Nag HE, Bergsaker DK, Hunn BS, Schmidt S, Hoxmark LB. A structured assessment of motor function, behavior, and communication in patients with Wolf-Hirschhorn syndrome. *European journal of medical genetics.* 2017; **60**(11)**:** 610-617.

35. Kerzendorfer C, Hannes F, Colnaghi R, Abramowicz I, Carpenter G, Vermeesch JR *et al.* Characterizing the functional consequences of haploinsufficiency of NELF-A (WHSC2) and

SLBP identifies novel cellular phenotypes in Wolf-Hirschhorn syndrome. *Human molecular genetics.* 2012; **21**(10)**:** 2181-2193.

36. Fisch GS, Battaglia A, Parrini B, Youngblom J, Simensen R. Cognitive-behavioral features of children with Wolf-Hirschhorn syndrome: preliminary report of 12 cases. *American journal of medical genetics Part C, Seminars in medical genetics.* 2008; **148c**(4)**:** 252-256.

37. Al Ageeli E, Drunat S, Delanoe C, Perrin L, Baumann C, Capri Y *et al.* Duplication of the 15q11-q13 region: clinical and genetic study of 30 new cases. *European journal of medical genetics.* 2014; **57**(1)**:** 5-14.

38. Nakai N, Nagano M, Saitow F, Watanabe Y, Kawamura Y, Kawamoto A *et al.* Serotonin rebalances cortical tuning and behavior linked to autism symptoms in 15q11-13 CNV mice. *Science advances.* 2017; **3**(6)**:** e1603001.

39. Neira-Fresneda J, Potocki L. Neurodevelopmental Disorders Associated with Abnormal Gene Dosage: Smith-Magenis and Potocki-Lupski Syndromes. *Journal of pediatric genetics.* 2015; **4**(3)**:** 159-167.

40. Laje G, Morse R, Richter W, Ball J, Pao M, Smith AC. Autism spectrum features in Smith-Magenis syndrome. *American journal of medical genetics Part C, Seminars in medical genetics.* 2010; **154c**(4)**:** 456-462.

41. Soorya L, Kolevzon A, Zweifach J, Lim T, Dobry Y, Schwartz L *et al.* Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency. *Molecular autism.* 2013; **4**(1)**:** 18.

42. Chen CH, Chen HI, Liao HM, Chen YJ, Fang JS, Lee KF *et al.* Clinical and molecular characterization of three genomic rearrangements at chromosome 22q13.3 associated with autism spectrum disorder. *Psychiatric genetics.* 2017; **27**(1)**:** 23-33.

43. Shang L, Henderson LB, Cho MT, Petrey DS, Fong CT, Haude KM *et al.* De novo missense variants in PPP2R5D are associated with intellectual disability, macrocephaly, hypotonia, and autism. *Neurogenetics.* 2016; **17**(1)**:** 43-49.

44. Stessman HA, Xiong B, Coe BP, Wang T, Hoekzema K, Fenckova M *et al.* Targeted sequencing identifies 91 neurodevelopmental-disorder risk genes with autism and developmental-disability biases. *Nature genetics.* 2017; **49**(4)**:** 515-526.

45. Helsmoortel C, Vulto-van Silfhout AT, Coe BP, Vandeweyer G, Rooms L, van den Ende J *et al.* A SWI/SNF-related autism syndrome caused by de novo mutations in ADNP. *Nature genetics.* 2014; **46**(4)**:** 380-384.

46. Muthusamy B, Nguyen TT, Bandari AK, Basheer S, Selvan LDN, Chandel D *et al.* Exome sequencing reveals a novel splice site variant in HUWE1 gene in patients with suspected Say-Meyer syndrome. *European journal of medical genetics.* 2019**:** 103635.

47. O'Rawe JA, Wu Y, Dorfel MJ, Rope AF, Au PY, Parboosingh JS *et al.* TAF1 Variants Are Associated with Dysmorphic Features, Intellectual Disability, and Neurological Manifestations. *American journal of human genetics.* 2015; **97**(6)**:** 922-932.

48. Pescosolido MF, Stein DM, Schmidt M, El Achkar CM, Sabbagh M, Rogg JM *et al.* Genetic and phenotypic diversity of NHE6 mutations in Christianson syndrome. *Annals of neurology.* 2014; **76**(4)**:** 581-593.

49. Garbern JY, Neumann M, Trojanowski JQ, Lee VM, Feldman G, Norris JW *et al.* A mutation affecting the sodium/proton exchanger, SLC9A6, causes mental retardation with tau deposition. *Brain : a journal of neurology.* 2010; **133**(Pt 5)**:** 1391-1402.

50. Wu Y, Arai AC, Rumbaugh G, Srivastava AK, Turner G, Hayashi T *et al.* Mutations in ionotropic AMPA receptor 3 alter channel properties and are associated with moderate cognitive impairment in humans. *Proceedings of the National Academy of Sciences of the United States of America* 2007; **104**(46)**:** 18163-18168.

51. Philips AK, Siren A, Avela K, Somer M, Peippo M, Ahvenainen M *et al.* X-exome sequencing in Finnish families with intellectual disability--four novel mutations and two novel syndromic phenotypes. *Orphanet journal of rare diseases.* 2014; **9:** 49.

Table 1. Selected syndromes with autism as a common feature of disease. Note that this table is not a comprehensive list of syndromes with a high rate of autism, and a more comprehensive review of autism syndromes can be found in Supplemental Tables 1-3.

Syndrome	**OMIM number**	**Percentage of patients with autism**	**Associated neurologic or psychiatric disease**	**Other features of disease**	**Gene(s) implicated**	**Pathway(s) implicated**	**References**
2q23.1 microdeletion and microduplication syndromes	156200	reported in over 90% of patients with either the duplication or the deletion	ID, epilepsy	microcephaly, distinctive facies, speech delay, ataxia, short stature, mild skeletal anomalies, eye abnormalities	*MBD5*	unknown	[32, 33]
4p16.3 deletion (including Wolf-Hirschhorn) syndromes	194190	up to 80%	ID, epilepsy (duplication associated with ADHD and ID)	growth retardation, distinctive facies, cardiac septal defects, coloboma, orofacial clefts	*SLBP*, *NELFA*, *LETM1*	cell cycle, DNA replication, mitochondria	[34-36]
15q11-q13 duplication syndrome	608636	50-90%	ID, epilepsy, anxiety, depression, ADHD	ataxia, hypotonia, speech delay, motor delay, behavioral problems, distinctive facies	*UBE3A*, *MKRN3*, *MAGEL2*	transcription, ribosome, protein recycling	[37, 38]
17p11.2 microdeletion (including Smith Magenis) syndrome	182290	up to 90%	ID, anxiety, ADHD, epilepsy	obesity, behavioral problems, skeletal anomalies, hearing loss, distinctive facies, cardiac defects	*RAI1*	transcription	[39, 40]
22q13 deletion (including Phelan-McDermid) syndrome	606232	75-85%	ID, epilepsy, psychosis/ catatonia	skeletal anomalies, hypotonia, motor and speech delay, distinctive facies, behavioral problems	*SHANK3*	synapse	[41, 42]
Autosomal dominant intellectual disability 35	616355	80-85%	ID, epilepsy	macrocephaly, obesity, overgrowth, behavioral problems, speech delay, cardiac and skeletal anomalies, visual acuity issues, hypotonia	*PPP2R5D*	phosphatase active in mitotic cells	[43]

Autosomal dominant intellectual disability 51	617788	80-85%	ID, epilepsy, ADHD	behavioral problems, speech delay, distinctive facies, skeletal anomalies, cryptorchidism	*KMT5B*	transcriptional regulation	[44]
Helsmoortel-van der AA syndrome	615873	over 90%	ID, ADHD, anxiety, obsessive compulsive disorder, epilepsy	hypotonia, distinctive facies, congenital heart defect, short stature, joint laxity, recurrent infections, speech delay, behavioral problems	*ADNP*	transcription	[45]
Autosomal dominant intellectual disability 7	614104	85-90%	ID, ADHD, anxiety, epilepsy	speech delay, microcephaly, short stature, gait problems, hypertonia, skeletal anomalies	*DYRK1A*	cell signaling	[16]
Turner type X-linked intellectual disability	300697	65-90%	ID, epilepsy, ADHD	behavior problems, skeletal and genitourinary anomalies, distinctive facies, short stature	*HUWE1*	synapse	[46]
X-linked intellectual disability 33	300966	80-85%	ID, epilepsy	distinctive facies skeletal anomalies, growth retardation, hearing loss	*TAF1*	transcriptional regulation	[47]
Christianson type X-linked intellectual disability	300243	over 90%	ID, epilepsy	microcephaly, dystonia, skeletal anomalies, eye abnormalities, speech delay, behavioral problems, ataxia, motor delay	*SLC9A6*	ion transport	[48, 49]
X-linked intellectual disability 94	300699	80%	ID, epilepsy	distinctive facies, behavioral problems, macrocephaly, short stature	*GRIA3*	synapse	[50, 51]

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

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

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

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