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REVIEW ARTICLE

Genetics of autism spectrum disorders: a long road to pass

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ABSTRACT

Autism spectrum disorder (ASD) or (OMIM #209850), which is a devastating neurodevelopmental disorder (NDD), is a severe childhood-onset disorder characterized by insufficiencies in social communication, verbal, and nonverbal communication and restricted or repetitive behavior or interests and/or activities. Until recently, the etiology of ASD has remained unclear. Over the last decade, a pivotal role for *de novo* germ line mutations has been established, conclusively. Such mutations have led to the discovery of a lot of ASD risk loci and genes. Autism belongs to a spectrum of disorders that share core symptoms; however, show considerable variation in severity. ASD affects approximately 0.6%–0.7% of children worldwide, inducing a substantial public health burden and a cause of suffering for the affected families. Despite having a very high heritability, ASD has shown remarkable genetic heterogeneity, which has complicated the identification of risk variants and left the etiology mostly unknown. Last, we have observed an extraordinary and unprecedented revolution in the understanding of ASD's biology, genetics, and intervention. However, the increases in ASD incidence highlight the need for persistent efforts to identify novel ASD findings that may help in the development of effective medical interventions for all individuals with ASD. In this paper, we aim to highlight some significant studies of the genetic basis of ASD from genomic architecture, genome-wide, and single-candidate genes. Furthermore, we presented future research directions that might accelerate the pace of scientific discovery and eventually translate into empirically supported interventions for those affected with ASD.

Keywords: Autism spectrum disorder, neuro-genetics, biochemical tests, epidemiology, autistic disorders, diagnosis, review.

Introduction

Autism spectrum disorder (henceforth 'ASD') is a neurodevelopmental disorder (NDD) characterized by persistent deficits in social communication, interaction, and the presence of repetitive behaviors and/or restricted interests (1). It was first reported by Kanner (2), as a developmental disorder in which individual present with intensity affected expressive and receptive language impairments, stereotypical behaviors, and diminished social communicating skills (2). The prevalence of this condition appears 1:100 children, and accurately diagnosed in 1%–2% of the population worldwide (3). However, the prevalence of ASD has been increasing dramatically worldwide in the last three decades due to the improvement of diagnostic criteria and public awareness of the disorder (3). ASD constitute complex genetic disorders, where apparently environmental and genetic factors play important roles. Current genetic advancements in the field of genetic diagnosis have solved some of the complexity of the genetic architecture underlying ASD by identifying several genetic variants that contribute to the ASD etiology (4). However, still, a long road to pass in order to know the causes of autism in many children over the world. Researchers around the globe continue to pursue a better understanding of the symptoms, comorbidities, and the exact underline genetic variability of ASD. In this review, we aim to discuss definition, etiology, contemporary findings on the genetic architecture of ASD, its complicated relationship to phenotype, address the clinical findings, the prospects for genetic studies in ASD, and finally propose new clinical approaches to identify ASD genetic etiology.

Definition of ASD

ASD is included among three out of five pervasive developmental disorders found in the Diagnostic and

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Statistical Manual of Mental Disorders, Fourth Edition and the International Classification of Diseases, Tenth Edition. These include Asperger syndrome, autistic disorder, and pervasive developmental disorder-not otherwise specified (Figure 1). By definition, ASD is characterized by a clinically heterogeneous class of neurodevelopmental disorders and the affected patients have a deficiency in the verbal and nonverbal communicative behaviors used for social interaction, and they are ranging from just poorly verbal and non-verbal communicative behaviors to abnormalities in eye contact and body language (5).

Clinical Phenotype

ASD is usually developed before the age of 3 years or pre-school (6). Repetitive, purposeless behaviors, as well as attention dysfunctions are frequent findings in subjects with ASD (7). Moreover, hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment is also found in the affected individuals. The onset of symptoms ordinarily happens in early childhood; however, it may not become fully manifest until social demands exceed limited capacities (7,8). ASD manifests with broad phenotypic variability and evolves along heterogeneous developmental trajectories (9). The severity of ASD symptoms is variable and inversely correlates with adaptive functioning (8). Language abilities and cognitive function are the two main domains that strongly affect adaptive behavior and predict later outcomes, which also have a broad range in ASD (10). For example, ~30% of individuals with ASD remains minimally verbal throughout life, and ~60% have co-occurring intellectual disability (ID) (11). Other associated phenotypes include attention deficit hyperactivity disorder (ADHD), schizophrenia, neurological disorders (e.g., motor deficits, sleep disturbances, and epilepsy), and other medical conditions (e.g., gastrointestinal problems, congenital anomalies, and allergies) are frequent comorbidities with ASD, although their presence is highly variable (12).

Etiology of ASD

ASD is a complex genetic disorder and up to 40%–50% of variance in ASD liability might be determined by environmental factors although the exact causes are still unknown. Environmental factors have been implicated specifically radiation, mercury, and lead (13). Environmental factors are divided into three major categories, such as prenatal, natal, and postnatal risk factors and each category represents specific period of child development. A collection of these factors might be associated with the pathogenesis of ASD. The involvement of heavy metals in the cause of autism is controversial and need more research (14). Additionally, the perinatal infections with rubella and cytomegalovirus have been suggested as a cause for

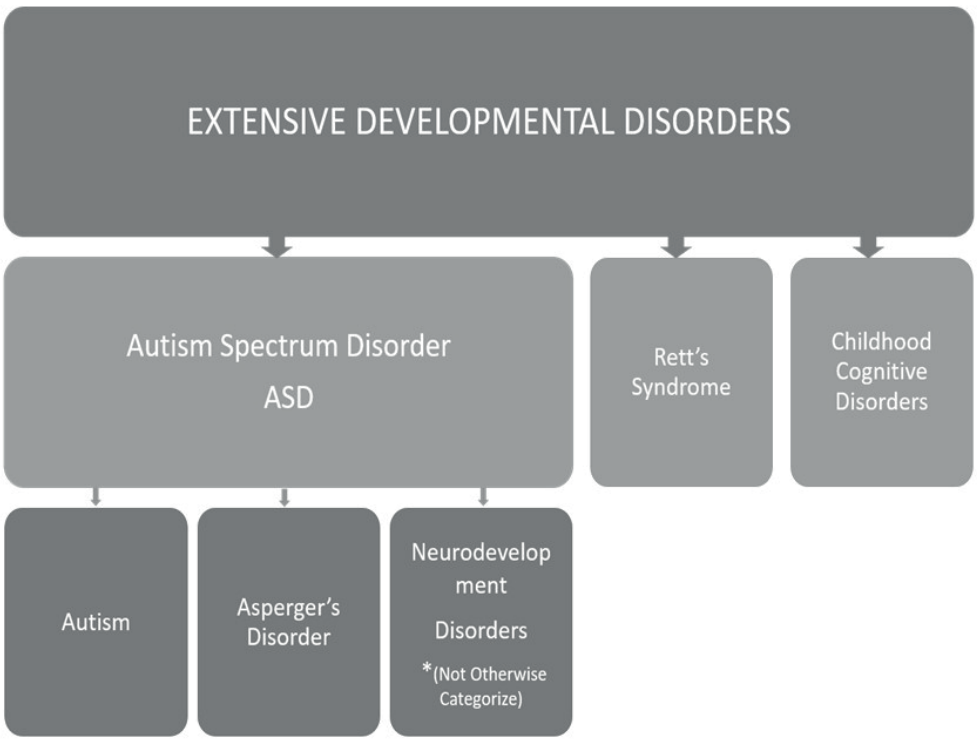

Figure 1. *Schematic diagram explaining the extensive developmental disorders that are a group of disorders, including ASD that comprise three subcategories, which include autism, Asperger's disorders and NDD.*

ASD. On the other hand, single genes disorders have been discovered as the etiology of several children with ASD. The heritability of autism is very high as several studies have shown that ASD aggregates in families (15) and twin studies predict the proportion of the phenotype variation due to genetic factors heritability to about 90%–95% (16). Moreover, molecular genetic studies revealed that the genetic risk for autism is associated with a combination of rare and common genetic variants (15). Since, it is a highly heterogeneous disease, to precisely identify the underlying genetics factors is a very challenging task.

Genetic Causes of ASD

The genetic cause of ASD discovered so far has been summarized (Tables 1–4). Several online available websites, such as OMIM (https://omim.org/), Orphanet (https://www.orpha.net), and DECIPHER (https://decipher.sanger.ac.uk/), were used to summarize the genes and disorders associated with ASD. These can be sub-classified into four different categories: ASD due to chromosomal abnormalities (Table 1), single gene defects and syndromes (Table 2), inborn errors of metabolism (Table 3), and others with unknown gene defect (Table 4). The phenotype of these disorders usually involves multisystem associated disorders. Therefore, autism is a part of other severe syndromic clinical features. It has been estimated that genetic factors might cause 90% of the ASD cases, while the environmental factors constitute not more than 10% (17). Nevertheless, because ASD is a highly heterogeneous disease, it is somewhat critically challenging to describe the genetics underlying this disorder specifically (18). However, using multiple parallel strategies, the several possible loci underlying the etiology of ASD have been identified (19).

Methods Used for Identifying the Underlying Causes of ASD

Various methods can be utilized for identification of the underlying genetic cause associated with ASD. These can be subdivided into three categories: (a) biochemical studies, (b) Cytogenetic studies, and (c) molecular genetic studies.

Cytogenetic methods include chromosomal analysis, such as comparative genomic hybridization (CGH) microarray, copy number variations (CNV), and florescent *in situ* hybridization. The molecular genetic investigations include single gene testing, gene panels, linkage analysis, association studies, whole exome sequencing (WES) and whole genome sequencing (WGS) (20). While the biochemical studies include acylcarnitine profile, plasma aminoacids, biotinidase enzyme level, very long chain fatty acids (VLCFA) profile, urine organic acids, urine for purine and pyrimidines, urine for creatine and guanidinoacetate, urine for oligosaccharides and urine for mucopolysaccharides (Figure 2).

Genotype–Phenotype Associations

ASD is an etiologically and clinically heterogeneous group of disorders, which is typically diagnosed exclusively by the complex association between genotype and phenotype. Because of the high heritability of the disease, ASD has a genetic basis that can be established (21), yet clarifying the genotype of ASD is challenging than anticipated. The scenario of the heterogenous evolving from these few examples shows how the ASD risk loci and genes identified so far rarely map exclusively to ASD alone but also to other related NDD, which raises a question about the mechanisms of action and the sophisticated genotype–phenotype correlations (20). Chromosomal microarray and sequencing studies have found extraordinary genetic overlap between ASD and other NDD and neurological conditions, including ID, epilepsy, and schizophrenia, which indicated that these genetic commonalities might extend beyond NDDs (22). For example, recent discoveries showed shared genes and pathways between ASD and congenital heart disease (CHD) (23).

Using a genotype-first approach, studies reporting the comprehensive clinical characterization of cohorts of patients with a shared etiology have exhibited a high degree of variability in the articulateness of recurrent CNVs and mutations in single genes (24,25). Among the best examples are (22q11.2) and (16p11.2) deletions (24). Both deletions are associated with various neuropsychiatric disorders as well, including ASD, ID, and schizophrenia. The deletions can also be identified in healthy individuals, an observation that is consistent with incomplete penetrance and is valid for most of the genes and loci that have been identified (20,26). One intriguing hypothesis is that common variation may be a factor that determines the expression of specific traits when a highly penetrant mutation occurs (Figure 2), and recent findings in both (22q11.2) and (16p11.2) deletion syndromes provide support for this hypothesis (27).

A study focusing on the variable expressivity of CHD carriers of the (22q11.2) deletion has identified a common CNV that could act as a modifier of the CHD phenotype in individuals with the ASD (28). Furthermore, by examining the quantitative intellectual, social and motor traits that are highly heritable, a recent study of 56 individuals with *de novo* (16p11.2) deletions have shown the significance of family background (which mediated by common genetic variation) to clinical variability. It was observed that the value of using quantitative measures rather than binary measures can better evaluate such familial influence (29). However, the etiological and clinical heterogeneity of ASD is commonly recognized, and when considered as a single entity, ASD does not fit any known inheritance patterns so in clinical practice; heterogeneity should be taken into account.

Among the most studied connections are autistic phenotypes linked to ID. Despite their high concurrence, there is also interdependence between cognitive function

Table 1. *Autism caused by chromosomal abnormalities.*

Disease ID	Disease name	Associated genes
ORPHA:276413	10q22.3q23.3 Microdeletion Syndrome	
ORPHA:238446	15q11q13 Microduplication Syndrome; Angelman syndrome	***UBE3A [OMIM 601623]***
ORPHA:199318	15q13.3 Microdeletion Syndrome	***CHRNA7 [OMIM 118511]***
ORPHA:261190	15q14 Microdeletion Syndrome; Cleft palate, cardiac defects, and mental retardation	***MEIS2 [OMIM 601740]***
ORPHA:261204	16p11.2p12.2 Microduplication Syndrome	
ORPHA:261243	16p13.11 Microduplication Syndrome	
ORPHA:261250	16q24.3 Microdeletion Syndrome; KBG syndrome	***ANKRD11 [OMIM 611192]***
ORPHA:1713	17p11.2 Microduplication Syndrome; Smith-Magenis syndrome	***RAI1 [OMIM 607642]***
ORPHA:261265	17q12 Microdeletion Syndrome; Renal cysts and diabetes syndrome	***HNF1B [OMIM 189907]***
ORPHA:217340	17q21.31 Microduplication Syndrome	
ORPHA:1606	1p36 Deletion Syndrome; Shprintzen-Goldberg syndrome; Left ventricular noncompaction 8; Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart; Epilepsy, idiopathic generalized, 10	***SKI [OMIM 164780]*** ***PRDM16 [OMIM 605557]*** ***RERE [OMIM 605226]*** ***GABRD [OMIM 137163]***
ORPHA:250989	1q21.1 Microdeletion Syndrome	
ORPHA:250994	1q21.1 Microduplication Syndrome	
DECIPHER:67	1q21.1 Recurrent Microduplication (possible Susceptibility Locus For Neurodevelopmental Disorders)	
ORPHA:567 OMIM: 192430	22q11.2 Deletion Syndrome (Velocardiofacial syndrome)	*TBX1 [**OMIM 602054**]* *COMT [**OMIM 116790**]* *GP1BB [**OMIM138720**]*
ORPHA:1727	22q11.2 Microduplication Syndrome ; Tetralogy of Fallot	*TBX1 [**OMIM 602054**]*
DECIPHER:20	22q13 Deletion Syndrome (phelan-mcdermid Syndrome)	
ORPHA:261349	2p15p16.1 Microdeletion Syndrome	
ORPHA:251019	2q32q33 Microdeletion Syndrome; Glass syndrome	*SATB2 [**OMIM 608148**]*
ORPHA:1001	2q37 Microdeletion Syndrome	
ORPHA:65286	3q29 Microdeletion Syndrome	
ORPHA:96263	48,xxxy Syndrome	
ORPHA:10	48,xxyy Syndrome	
ORPHA:96264	49,xxxxy Syndrome	
ORPHA:238750	4q21 Microdeletion Syndrome	
ORPHA:171829	6q16 Microdeletion Syndrome	
ORPHA:96092	8p Inverted Duplication/deletion Syndrome	
OMIM: 612513	Chromosome 2p16.1-p15 deletion syndrome	
OMIM: 600430	Chromosome 2q37 deletion syndrome	
OMIM: 613603	Chromosome 4q32.1-q32.2 triplication syndrome	
OMIM: 615668	Chromosome 5q12 deletion syndrome	
OMIM:612242	Chromosome 10q22.3-q23.2 Deletion Syndrome	
OMIM:616902	Chromosome 11p13 Deletion Syndrome, Distal	
OMIM:613604	Chromosome 16p12.2-p11.2 Deletion Syndrome, 7.1- To 8.7-mb	

(Continued)

Table 1. *(Continued)*

Disease ID	Disease name	Associated genes
OMIM: 615656	Chromosome 15q11.2 deletion syndrome	
OMIM: 616898	Chromosome 15q14 deletion syndrome	
OMIM: 614294	Chromosome 15q25 deletion syndrome	
OMIM: 616863	Chromosome 16p13.2 deletion syndrome	
OMIM:614527	Chromosome 17q12 Deletion Syndrome	
OMIM: 617219	Chromosome 19q13.11 deletion syndrome, proximal	
OMIM:612474	Chromosome 1q21.1 Deletion Syndrome, 1.35-mb; Cataract 1, multiple types; Atrial fibrillation, familial, 11	*GJA8 [**OMIM** 600897]* *GJA5 [**OMIM** 121013]*
OMIM:612475	Chromosome 1q21.1 Duplication Syndrome	
OMIM:615433	Chromosome 3q13.31 Deletion Syndrome	
OMIM:609425	Chromosome 3q29 Deletion Syndrome	
OMIM: 300801	Chromosome Xp11.23-p11.22 duplication syndrome	
OMIM:123450	Cri-du-chat Syndrome	
OMIM: 609757	Chromosome 7q11.23 duplication syndrome	
OMIM: 613458	Chromosome 16p13.3 duplication syndrome	
ORPHA:254351	Distal 7q11.23 Microdeletion Syndrome	
ORPHA:96147	Kleefstra Syndrome Due To 9q34 Microdeletion; Kleefstra syndrome 1	*EHMT1 [**OMIM** 607001]*
ORPHA:251009	Maternal Uniparental Disomy Of Chromosome 1	
ORPHA:217377	Microduplication Xp11.22p11.23 SyndromeI; Mental retardation, X-linked 1/78	*IQSEC2 [**OMIM** 300522]*
DECIPHER:19	Potocki-lupski Syndrome (17p11.2 Duplication Syndrome)	
ORPHA:261197	Proximal 16p11.2 Microdeletion Syndrome	
ORPHA:96176	Ring Chromosome 13 Syndrome	
OMIM: 300979	Xq25 duplication syndrome	
DECIPHER:45	Xq28 (*MECP2*) Duplication	

Table 2. *Autism because of single gene defect.*

Disease ID	Disease Name	Associated Genes
OMIM: 616067	46XY sex reversal 9	*ZFPM2[**OMIM 603693**]*
OMIM:614613	Acrodysostosis 2 With Or Without Hormone Resistance	*PDE4D [**OMIM** 600129]*
ORPHA:280651	Acrodysostosis With Multiple Hormone Resistance	*PDE4D [**OMIM** 600129]* *PRKAR1A [**OMIM** 188830]*
ORPHA:324422	Alg13-cdg	*ALG13 [**OMIM** 300776]*
ORPHA:847	Alpha-thalassemia-x-linked Intellectual Disability Syndrome	*ATRX [**OMIM** 300032]*
ORPHA:64	Alström Syndrome	*ALMS1 [**OMIM** 606844]*
OMIM: 615553	Arthrogryposis, mental retardation, and seizures	*SLC35A3 [**OMIM 605632]***
OMIM:608638	Asperger Syndrome, Susceptibility To, 1	
OMIM:608631	Asperger Syndrome, Susceptibility To, 2	
OMIM:300494	Asperger Syndrome, X-linked, Susceptibility To, 1	*NLGN3 [**OMIM** 300336]*
OMIM:300497	Asperger Syndrome, X-linked, Susceptibility To, 2	*NLGN4X [**OMIM** 300427]*
OMIM:209850	Autism	*SNRPN [**OMIM** 182279]*
OMIM:615032	Autism, Susceptibility To, 18	*CHD8 [**OMIM** 610528]*
OMIM:608049	Autism, Susceptibility To, 3	
OMIM:607373	Autism, Susceptibility To, 8	
OMIM:300425	Autism, Susceptibility To, X-linked 1	*NLGN3 [**OMIM** 300336]*

(Continued)

Table 2. *(Continued)*

Disease ID	Disease Name	Associated Genes
OMIM:300495	Autism, Susceptibility To, X-linked 2	*NLGN4X [**OMIM** 300427]*
OMIM:300496	Autism, Susceptibility To, X-linked 3	*MECP2 [**OMIM** 300005]*
OMIM:300830	Autism, Susceptibility To, X-linked 4	*PTCHD1 [**OMIM** 300828]*
OMIM:300872	Autism, Susceptibility To, X-linked 6	*TMLHE [**OMIM** 300777]*
OMIM: 615485	Bainbridge-Ropers syndrome	*ASXL3[**OMIM 615115**]*
OMIM: 615722	Bosch-Boonstra-Schaaf optic atrophy syndrome	*NR2F1[**OMIM 132890**]*
OMIM: 617412	Brachycephaly, trichomegaly, and developmental delay	*RPS23[**OMIM 603683**]*
OMIM:300615	Brunner Syndrome	*MAOA [**OMIM** 309850]*
OMIM: 618479	Cerebellar, ocular, craniofacial, and genital syndrome	*MAB21L1[**OMIM 601280**]*
ORPHA:138 OMIM: 214800	CHARGE Syndrome	*CHD7 [**OMIM** 608892]* *SEMA3E [**OMIM** 608166]*
OMIM: 601338	CAPOS syndrome	*ATP1A3[**OMIM** 182350]*
ORPHA:3474	Chime Syndrome	
OMIM: 600987	Cleft palate, cardiac defects, and mental retardation	*MEIS2[**OMIM 601740**]*
ORPHA:199	Cornelia De Lange Syndrome	*SMC1A [**OMIM 300040**]* *SETD5 [**OMIM 615743**]* *HDAC8 [**OMIM 300269**]* *NIPBL [**OMIM 608667**]* *SMC3 [**OMIM 606062**]* *RAD21 [**OMIM 606462**]* *KMT2A [**OMIM 159555**]*
ORPHA:201	Cowden Syndrome	*KLLN [**OMIM 612105**]* *SDHC [**OMIM 602413**]* *SDHD [**OMIM 602690**]* *AKT1 [**OMIM 164730**]* *PTEN [**OMIM 158350**]* *SDHB [**OMIM 185470**]* *SEC23B [**OMIM 610512**]* *PIK3CA [**OMIM 171834**]*
OMIM:615314	Craniosynostosis 3	*TCF12 [**OMIM 600480**]*
OMIM: 616602	Craniosynostosis 6	*ZIC1[**OMIM 600470**]*
OMIM: 616603	Cutis laxa, autosomal dominant 3	*ALDH18A1[**OMIM 138250**]*
OMIM: 616708	Desanto-Shinawi syndrome	*WAC[**OMIM 615049**]*
OMIM: 617991	Developmental delay, intellectual disability, obesity, and dysmorphism	*PHIP[**OMIM 612870**]*
OMIM: 618454	Developmental delay with or without dysmorphic facies and autism	*TRRAP[**OMIM 603015**]*
OMIM: 618430	Developmental delay with variable intellectual impairment and behavioral abnormalities	*TCF20[**OMIM 603107**]*
ORPHA:239	Dyggve-melchior-clausen Disease	*DYM [**OMIM 607461**]*
OMIM: 617171	Dyskinesia, seizures, and intellectual developmental disorder	*DEAF1[**OMIM 602635**]*
OMIM: 604364	Epilepsy, familial focal, with variable foci 1	*DEPDC5[**OMIM 614191**]*
OMIM:245570	Epilepsy, focal, with speech disorder and with or without mental retardation	*GRIN2A[**OMIM 138253**]*
OMIM: 618357	Epilepsy, idiopathic generalized, susceptibility to, 15	*RORB[**OMIM 601972**]*
OMIM: 300491	Epilepsy, X-linked, with variable learning disabilities and behavior disorders	*SYN1[**OMIM 313440**]*
OMIM: 615369	Epileptic encephalopathy, childhood-onset	*CHD2[**OMIM 602119**]*
OMIM: 300672	Epileptic encephalopathy, early infantile, 2	*CDKL5[**OMIM 300203**]*

(Continued)

Table 2. *(Continued)*

Disease ID	Disease Name	Associated Genes
OMIM: 300088	Epileptic encephalopathy, early infantile, 9	*PCDH19[**OMIM 300460**]*
OMIM:614558	Epileptic Encephalopathy, Early Infantile, 13	*SCN8A [**OMIM 602780**]*
OMIM: 615871	Epileptic encephalopathy, early infantile, 24	*HCN1[**OMIM 602780**]*
OMIM: 616341	Epileptic encephalopathy, early infantile, 30	*SIK1[**OMIM 605705**]*
OMIM: 616409	Epileptic encephalopathy, early infantile, 33	*EEF1A2[**OMIM 602959**]*
OMIM: 617391	Epileptic encephalopathy, early infantile, 54	*HNRNPU[**OMIM 602869**]*
OMIM: 617665	Epileptic encephalopathy, early infantile, 56	*YWHAG[**OMIM 605356**]*
OMIM: 617830	Epileptic encephalopathy, early infantile, 58	*NTRK2[**OMIM 600456**]*
OMIM: 618067	Epileptic encephalopathy, early infantile, 66	*PACS2[**OMIM 610423**]*
OMIM: 618141	Epileptic encephalopathy, early infantile, 67	*CUX2[**OMIM 610648**]*
OMIM: 618298	Epileptic encephalopathy, early infantile, 70	*PHACTR1[**OMIM 608723**]*
OMIM: 617711	Epileptic encephalopathy, infantile or early childhood, 1	*PPP3CA[**OMIM 114105**]*
OMIM:300624	Fragile X Mental Retardation Syndrome	*FMR1 [**OMIM 309550**]*
ORPHA:908	Fragile X Syndrome	*FMR1 [**OMIM 309550**]*
OMIM: 617557	Gabriele-de Vries syndrome	*YY1[**OMIM 600013**]*
OMIM: 618482	Generalized epilepsy with febrile seizures plus, type 10	*HCN1[**OMIM 602780**]*
OMIM: 618010	Glycosylphosphatidylinositol biosynthesis defect 17	*PIGH[**OMIM 600154**]*
OMIM: 615873	Helsmoortel-van der Aa syndrome	*ADNP[**OMIM 611386**]*
OMIM: 618314	Hypomagnesemia, seizures, and mental retardation 2	*ATP1A1[**OMIM 182310**]*
OMIM: 618402	Intellectual developmental disorder, autosomal recessive 70	*RSRC1[**OMIM 613352**]*
OMIM: 618089	Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities	*FBXO11[**OMIM 607871**]*
OMIM: 617452	Intellectual developmental disorder with dysmorphic facies, seizures, and distal limb anomalies	*OTUD6B[**OMIM 612021**]*
OMIM: 618092	Intellectual developmental disorder with dysmorphic facies, speech delay, and T-cell abnormalities	*BCL11B[**OMIM 606558**]*
OMIM: 618060	Intellectual developmental disorder with or without epilepsy or cerebellar ataxia	*RORA[**OMIM 600825**]*
OMIM: 617101	Intellectual Developmental Disorder With Persistence Of Fetal Hemoglobin (Dias-Logan syndrome)	*BCL11A[**OMIM 606557**]*
OMIM: 618470	Intellectual developmental disorder with severe speech and ambulation defects	*ACTL6B[**OMIM 612458**]*
OMIM:617450	Jansen de Vries syndrome (Intellectual Developmental Disorder With Gastrointestinal Difficulties And High Pain Threshold)	*PPM1D[**OMIM 605100**]*
OMIM: 301026	Keipert syndrome	*GPC4[**OMIM 300168**]*
OMIM:610253	Kleefstra Syndrome	*EHMT1 [**OMIM 607001**]*
OMIM: 617768	Kleefstra syndrome 2	*KMT2C[**OMIM 606833**]*
OMIM: 610443	Koolen-De Vries syndrome	*KANSL1[**OMIM 612452**]*
OMIM: 607432	Lissencephaly 1	*PAFAH1B1[**OMIM 601545**]*
OMIM: 617255	Lissencephaly 8	*TMTC3[**OMIM 617218**]*
OMIM:309520	Lujan-fryns Syndrome	*MED12 [**OMIM 300188**]*
OMIM: 616831	Luscan-Lumish syndrome	*SETD2 [**OMIM 612778**]*
OMIM:618286	Macrocephaly, Acquired, With Impaired Intellectual Development	*NFIB[**OMIM 600728**]*
OMIM:605309	Macrocephaly/autism Syndrome	*PTEN [**OMIM 601728**]*

(Continued)

Table 2. *(Continued)*

Disease ID	Disease Name	Associated Genes
OMIM: 618273	Mega-corpus-callosum syndrome with cerebellar hypoplasia and cortical malformations	*MAST1[**OMIM 612256**]*
OMIM: 300148	MEHMO syndrome	*EIF2S3[**OMIM 300161**]*
OMIM:616789	Mental Retardation And Distinctive Facial Features With Or Without Cardiac Defects	*MED13L [**OMIM 608771**]*
OMIM: 156200	Mental retardation, autosomal dominant 1	*MBD5[**OMIM 608771**]*
OMIM: 612621	Mental retardation, autosomal dominant 5	*SYNGAP1[**OMIM 603384**]*
OMIM:614104	Mental Retardation, Autosomal Dominant 7	*DYRK1A [**OMIM 600855**]*
OMIM: 614563	Mental retardation, autosomal dominant 13	*DYNC1H1[**OMIM 600112**]*
OMIM: 613443	Mental retardation, Autosomal Dominant 20	*MEF2C[**OMIM 600662**]*
OMIM: 615502	Mental retardation, autosomal dominant 21	*CTCF[**OMIM 604167**]*
OMIM: 615761	Mental retardation, autosomal dominant 23	*SETD5[**OMIM 615743**]*
OMIM: 615828	Mental retardation, autosomal dominant 24	*DEAF1[**OMIM 602635**]*
OMIM:615834	Mental Retardation, Autosomal Dominant 26	*AUTS2 [**OMIM 607270**]*
OMIM: 616393	Mental retardation, autosomal dominant 38	*EEF1A2[**OMIM 602959**]*
OMIM: 616521	Mental retardation, autosomal dominant 39	*MYT1L[**OMIM 613084**]*
OMIM: 616579	Mental retardation, autosomal dominant 40	*CHAMP1[**OMIM 616327**]*
OMIM: 616944	Mental retardation, autosomal dominant 41	*TBL1XR1[**OMIM 608628**]*
OMIM: 616977	Mental retardation, autosomal dominant 43	*HIVEP2[**OMIM 143054**]*
OMIM: 617061	Mental retardation, autosomal dominant 44	*TRIO[**OMIM 601893**]*
OMIM: 617600	Mental retardation, autosomal dominant 45	*CIC[**OMIM 612082**]*
OMIM: 617635	Mental retardation, autosomal dominant 47	*STAG1[**OMIM 604358**]*
OMIM: 617752	Mental retardation, autosomal dominant 49	*TRIP12[**OMIM 604506**]*
OMIM: 617787	Mental retardation, autosomal dominant 50	*NAA15[**OMIM 608000**]*
OMIM: 617788	Mental retardation, autosomal dominant 51	*KMT5B[**OMIM 610881**]*
OMIM: 617796	Mental retardation, autosomal dominant 52	*ASH1L[**OMIM 607999**]*
OMIM: 617799	Mental retardation, autosomal dominant 54	*CAMK2B[**OMIM 607707**]*
OMIM: 617831	Mental retardation, autosomal dominant 55, with seizures	*NUS1[**OMIM 610463**]*
OMIM: 618050	Mental retardation, autosomal dominant 57	*TLK2[**OMIM 608439**]*
OMIM: 618522	Mental retardation, autosomal dominant 59	*CAMK2G[**OMIM 602123**]*
OMIM: 607417	Mental retardation, autosomal recessive 2	*CRBN[**OMIM 609262**]*
OMIM: 611091	Mental retardation, autosomal recessive 5	*NSUN2[**OMIM 610916**]*
OMIM: 615516	Mental retardation, autosomal recessive 38	*HERC2[**OMIM 605837**]*
OMIM: 617188	Mental retardation, autosomal recessive 57	*MBOAT7[**OMIM 606048**]*
OMIM: 617773	Mental retardation, autosomal recessive 61	*RUSC2[**OMIM 611053**]*
OMIM: 618221	Mental retardation, autosomal recessive 66	*C12orf4[**OMIM 616082**]*
OMIM: 309530	Mental retardation, X-linked 1/78	*IQSEC2[**OMIM 300522**]*
OMIM:300143	Mental Retardation, X-linked 21	*IL1RAPL1 [**OMIM 300206**]*
OMIM:309549	Mental Retardation, X-linked 9	*FTSJ1 [**OMIM 300499**]*
OMIM: 300912	Mental retardation, X-linked 98	*NEXMIF[**OMIM 300524**]*
OMIM: 300958	Mental retardation, X-linked 102	*DDX3X[**OMIM 300160**]*
OMIM: 300676	Mental retardation, X-linked, syndromic 14	*UPF3B[**OMIM 300298**]*
OMIM:300143	Mental retardation, X-linked 21/34	*IL1RAPL1[**OMIM 300206**]*
OMIM: 300966	Mental retardation, X-linked, syndromic 33	*TAF1[**OMIM 313650**]*

(Continued)

Table 2. *(Continued)*

Disease ID	Disease Name	Associated Genes
OMIM: 300387	Mental retardation, X-linked 63	*ACSL4[**OMIM 300157**]*
OMIM: 300271	Mental retardation, X-linked 72	*RAB39B[**OMIM 300774**]*
OMIM: 300803	Mental retardation, X-linked 97	*ZNF711[**OMIM 314990**]*
OMIM: 300983	Mental retardation, X-linked 104	*FRMPD4[**OMIM 300838**]*
OMIM: 300986	Mental retardation, X-linked, syndromic, Bain type	*HNRNPH2[**OMIM**]*
OMIM: 300243	Mental retardation, X-linked syndromic, Christianson type	*SLC9A6[**OMIM 300231**]*
OMIM: 300534	Mental retardation, X-linked, syndromic, Claes-Jensen type	*KDM5C[**OMIM 314690**]*
OMIM: 309548	Mental retardation, X-linked, FRAXE type	*AFF2[**OMIM 300806**]*
OMIM: 300260	Mental retardation, X-linked syndromic, Lubs type	*MECP2[**OMIM 300005**]*
OMIM: 309590	Mental retardation, X-linked syndromic, Turner type	*HUWE1[**OMIM 300697**]*
OMIM:300699	Mental Retardation, X-linked, Syndromic, Wu Type	*GRIA3 [**OMIM 305915**]*
OMIM: 613670	Mental retardation with language impairment and with or without autistic features	*FOXP1[**OMIM 605515**]*
OMIM: 300486	Mental retardation, X-linked, with cerebellar hypoplasia and distinctive facial appearance	*OPHN1[**OMIM 300127**]*
OMIM: 616486	Microcephaly 15, primary, autosomal recessive	*MFSD2A[**OMIM 614397**]*
OMIM: 617914	Microcephaly 20, primary, autosomal recessive	*KIF14[**OMIM 611279**]*
OMIM: 617983	Microcephaly 21, primary, autosomal recessive	*NCAPD2[**OMIM 615638**]*
OMIM: 615877	Microphthalmia/coloboma and skeletal dysplasia syndrome	*MAB21L2[**OMIM 604357**]*
OMIM: 309800	Microphthalmia, syndromic 1	*NAA10[**OMIM 300013**]*
OMIM: 139210	Myhre syndrome	*SMAD4[**OMIM 600993**]*
OMIM: 616421	Myoclonic-atonic epilepsy	*SLC6A1[**OMIM 137165**]*
OMIM:302350	Nance-horan Syndrome	*NHS [**OMIM 300457**]*
OMIM: 618170	Neurodegeneration, childhood-onset, stress-induced, with variable ataxia and seizures	*ADPRHL2[**OMIM 610624**]*
OMIM:610217	Neurodegeneration with brain iron accumulation 2B	*PLA2G6[**OMIM 603604**]*
OMIM: 618354	Neurodevelopmental disorder and language delay with or without structural brain abnormalities	*PPP2CA[**OMIM 176915**]*
OMIM: 616975	Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart	*RERE[**OMIM 605226**]*
OMIM: 614254	Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal dominant	*GRIN1[**OMIM 138249**]*
OMIM: 617820	Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal recessive	*GRIN1[**OMIM 138249**]*
OMIM:618443	Neurodevelopmental disorder with or without variable brain abnormalities	*MAPK8IP3[**OMIM 605431**]*
OMIM: 618505	Neurodevelopmental disorder with coarse facies and mild distal skeletal abnormalities	*KDM6B[**OMIM 611577**]*
OMIM: 617393	Neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination	*NACC1[**OMIM 610672**]*
OMIM: 617268	Neurodevelopmental disorder with hypotonia, seizures, and absent language	*HECW2[**OMIM 617245**]*
OMIM: 617865	Neurodevelopmental disorder with movement abnormalities, abnormal gait, and autistic features	*ZSWIM6[**OMIM 615951**]*
OMIM: 617903	Neurodevelopmental disorder with poor language and loss of hand skills	*GABBR2[**OMIM 607340**]*
OMIM: 617804	Neurodevelopmental disorder with severe motor impairment and absent language	*DHX30[**OMIM 616423**]*

(Continued)

Table 2. *(Continued)*

Disease ID	Disease Name	Associated Genes
OMIM: 615075	Neurodevelopmental disorder with spastic diplegia and visual defects	*CTNNB1[**OMIM 116806**]*
ORPHA:649	Norrie Disease	*NDP [**OMIM 300658**]*
OMIM: 613886	Obesity, hyperphagia, and developmental delay	*NTRK2[**OMIM 600456**]*
OMIM: 618512	O'Donnell-Luria-Rodan syndrome	*KMT2E[**OMIM 608444**]*
OMIM: 300855	Ogden syndrome	*NAA10[**OMIM 300013**]*
OMIM:606232	Phelan-mcdermid Syndrome	*SHANK3 [**OMIM 606230**]*
OMIM: 617682	Pilarowski-Bjornsson syndrome	*CHD1[**OMIM 602118**]*
OMIM: 610042	Pitt-Hopkins like syndrome 1 (Cortical dysplasia-focal epilepsy syndrome)	*CNTNAP2[**OMIM 604569**]*
OMIM: 614325	Pitt-Hopkins-like syndrome 2	*NRXN1[**OMIM 600565**]*
OMIM: 617695	Pontocerebellar hypoplasia, type 11	*TBC1D23[**OMIM 617687**]*
OMIM: 618428	Popov-Chang syndrome	*YWHAZ[**OMIM 601288**]*
OMIM: 615960	Poretti-Boltshauser syndrome	*LAMA1[OMIM 150320]*
OMIM:610883	Potocki-lupski Syndrome	*FLCN [**OMIM 607273**]*
OMIM:176270	Prader-willi Syndrome	*HERC2 [**OMIM 605837**]* *SNRPN [**OMIM 182279**]* *SNORD115-1 [**OMIM 609837**]* *PWRN1 [**OMIM 611215**]* *IPW [**OMIM 601491**]* *MKRN3-AS1 [**OMIM 603857**]* *NPAP1 [**OMIM 610922**]* *MKRN3 [**OMIM 603856**]* *SNORD116-1 [**OMIM 605436**]* *PWAR1 [**OMIM 600161**]* *MAGEL2 [**OMIM605283**]* *NDN [**OMIM 602117**]*
OMIM:259050	Primrose Syndrome	*ZBTB20 [**OMIM 606025**]*
OMIM: 300114	Raynaud-Claes syndrome	*CLCN4[**OMIM 302910**]*
ORPHA:461	Recessive X-linked Ichthyosis	*STS [**OMIM 300747**]*
OMIM: 309500	Renpenning syndrome	*PQBP1[**OMIM 300463**]*
ORPHA:778 OMIM: 312750	Rett Syndrome	*MECP2 [**OMIM 300005**]*
OMIM:180849	Rubinstein-taybi Syndrome 1	*CREBBP [**OMIM 600140**]*
OMIM: 613684	Rubinstein-Taybi syndrome 2	*EP300[**OMIM 602700**]*
OMIM: 615547	Schaaf-Yang syndrome	*MAGEL2[**OMIM 605283**]*
OMIM: 615009	Schuurs-Hoeijmakers syndrome	*PACS1[**OMIM 607492**]*
OMIM: 616682	Seizures, scoliosis, and macrocephaly syndrome	*EXT2[**OMIM 608210**]*
ORPHA:3157	Septo-optic Dysplasia Spectrum	*PROKR2 [**OMIM 607123**]* *OTX2 [**OMIM 600037**]* *HESX1 [**OMIM 601802**]* *SOX3 [**OMIM 313430**]* *SOX2 [**OMIM 184429**]* *ARNT2 [**OMIM 606036**]* *FGFR1 [**OMIM 136350**]*
OMIM: 617190	Shashi-Pena syndrome	*ASXL2[**OMIM 612991**]*
OMIM: 617164	Short stature, rhizomelic, with microcephaly, micrognathia, and developmental delay	*ARCN1[**OMIM 600820**]*
OMIM: 301029	Shukla-Vernon syndrome	*BCORL1[**OMIM 300688**]*
OMIM: 617616	Skraban-Deardorff syndrome	*WDR26[**OMIM 617424**]*

(Continued)

Table 2. *(Continued)*

Disease ID	Disease Name	Associated Genes
OMIM: 616638	Smith-Kingsmore syndrome	*MTOR[**OMIM 601231**]*
OMIM: 618205	Snijders Blok-Campeau syndrome	*CHD3[**OMIM 602120**]*
OMIM: 614753	Sotos syndrome 2	*NFIX[**OMIM 164005**]*
OMIM: 615432	Specific language impairment 5	*TM4SF20[**OMIM 615404**]*
OMIM: 616354	Spinocerebellar ataxia, autosomal recessive 20	*SNX14[**OMIM 616105**]*
OMIM: 616723	Spondyloepimetaphyseal dysplasia, Faden-Alkuraya type	*RSPRY1[**OMIM 616585**]*
OMIM: 617516	Stankiewicz-Isidor syndrome	*PSMD12[**OMIM 604450**]*
OMIM: 300434	Stocco dos Santos X-linked mental retardation syndrome	*SHROOM4[**OMIM 300579**]*
ORPHA:281090	Syndromic Recessive X-linked Ichthyosis	*STS [**OMIM 300747**]*
ORPHA:85279	Syndromic X-linked Intellectual Disability Due To Jarid1c Mutation	*KDM5C [**OMIM 314690**]*
OMIM: 218340	Temtamy syndrome	*C12orf57[**OMIM 615140**]*
OMIM:601005	Timothy Syndrome	*CACNA1C[**OMIM 114205**]*
OMIM: 300978	Tonne-Kalscheuer syndrome	*RLIM[**OMIM 300379**]*
OMIM:191100	Tuberous Sclerosis	*TSC1 [**OMIM 605284**]*
OMIM:613254	Tuberous Sclerosis 2	*IFNG [**OMIM** 147570]* *TSC2 [**OMIM 191092**]*
OMIM: 618371	Turnpenny-Fry syndrome	*PCGF2 [**OMIM600346**]*
ORPHA:442835	Undetermined Early-onset Epileptic Encephalopathy	*NTRK2 [**OMIM 600456**]* *SCN8A [**OMIM 600702**]* *KCNB1 [**OMIM 600397**]* *SYNGAP1 [**OMIM 603384**]* *AARS [**OMIM 601065**]* *TRAK1 [**OMIM 608112**]* *DHDDS [**OMIM 608172**]* *NECAP1 [**OMIM 611623**]* *HCN1 [**OMIM 602780**]* *EEF1A2 [**OMIM 602959**]* *ARV1 [**OMIM 611647**]* *GRIN2D [**OMIM 602717**]* *PPP3CA [**OMIM 114105**]* *NUS1 [**OMIM 610463**]* *CLTC [**OMIM 118955**]* *YWHAG [**OMIM 605356**]* *SLC1A2 [**OMIM 600300**]* *DNM1 [**OMIM 602377**]* *AP3B2 [**OMIM 602166**]* *CYFIP2 [**OMIM 606323**]* *SLC13A5 [**OMIM 608305**]* *CNKSR2 [**OMIM 300724**]* *UBA5 [**OMIM 610552**]* *SYNJ1 [**OMIM 604297**]* *FGF12 [**OMIM 601513**]* *WWOX [**OMIM 605131**]* *STXBP1 [**OMIM 602926**]* *ATP6V1A [**OMIM 607027**]* *SCN3A [**OMIM 182391**]* *SZT2 [**OMIM 615463**]* *GABRB2 [**OMIM 600232**]* *CACNA1A [**OMIM 601011**]* *KCNA2 [**OMIM 176262**]*
OMIM: 301030	Van Esch-O'Driscoll syndrome	*POLA1[**OMIM 312040**]*
OMIM: 618223	Vertebral anomalies and variable endocrine and T-cell dysfunction	*TBX2[**OMIM 600747**]*

(Continued)

Table 2. *(Continued)*

Disease ID	Disease Name	Associated Genes
OMIM: 617982	Ververi-Brady syndrome	*QRICH1 [**OMIM617387**]*
OMIM: 615663	Warburg micro syndrome 4	*TBC1D20[**OMIM 611663**]*
OMIM: 616364	White-Sutton syndrome	*POGZ[**OMIM 614787**]*
OMIM: 605130	Wiedemann-Steiner syndrome	*KMT2A[**OMIM 159555**]*
ORPHA:904	Williams Syndrome	*ELN [**OMIM 130160**]*
OMIM:613406	Witteveen-kolk Syndrome	*SIN3A [**OMIM 607776**]*
OMIM:614296	Wolfram-like Syndrome, Autosomal Dominant	*WFS1 [**OMIM 606201**]*
ORPHA:137831	X-linked Intellectual Disability-cerebellar Hypoplasia Syndrome	*OPHN1 [**OMIM 300127**]*

Table 3. *Autism as a result of inborn error of metabolism.*

Disease ID	Disease Name	Associated Genes
OMIM:102700	Adenosine deaminase deficiency	*ADA[**OMIM** 608958]*
OMIM:103050	Adenylosuccinase Deficiency	*ADSL [**OMIM** 608222]*
OMIM: 300100	Adrenoleukodystrophy	*ABCD1[**OMIM 300371**]*
ORPHA:3137	Alpha-n-acetylgalactosaminidase Deficiency	*NAGA [**OMIM 104170**]*
ORPHA:79279	Alpha-n-acetylgalactosaminidase Deficiency Type 1	*NAGA [**OMIM 104170**]*
ORPHA:79281	Alpha-n-acetylgalactosaminidase Deficiency Type 3	*NAGA [**OMIM 104170**]*
OMIM: 253260	Biotinidase deficiency	*BTD[**OMIM 609019**]*
OMIM:614923	Branched-chain Ketoacid Dehydrogenase Kinase Deficiency	*BCKDK [**OMIM 614901**]*
OMIM: 300352	Cerebral creatine deficiency syndrome 1	*SLC6A8[**OMIM 300036**]*
OMIM: 612736	Cerebral creatine deficiency syndrome 2	*GAMT[**OMIM 300127**]*
OMIM:612718	Cerebral Creatine Deficiency Syndrome 3	*GAMT[**OMIM 300127**]*
ORPHA:79254	Classic PKU	*PAH [**OMIM 612349**]*
OMIM: 603585	Congenital disorder of glycosylation, type IIf	*SLC35A1[**OMIM 605634**]*
OMIM: 220120	D-glyceric aciduria	*GLYCTK[**OMIM 610516**]*
OMIM:274270	Dihydropyrimidine Dehydrogenase Deficiency	*DPYD [**OMIM 612779**]*
OMIM: 266100	Epilepsy, pyridoxine-dependent	*ALDH7A1[**OMIM 107323**]*
OMIM: 232200	glucose-6-phosphatase deficiency	*G6PC[**OMIM 613742**]*
OMIM: 617384	Hyperphenylalaninemia, mild, non-BH4-deficient	*DNAJC12[**OMIM 606060**]*
OMIM: 239500	Hyperprolinemia, type I	*PRODH[**OMIM 606810**]*
OMIM: 615824	Mitochondrial complex III deficiency, nuclear type 7	*UQCC2[**OMIM 614461**]*
OMIM: 613068	Neurodegeneration due to cerebral folate transport deficiency	*FOLR1[**OMIM 136430**]*
OMIM: 606054	propionic acidemia	*PCCA[**OMIM 232000**]* *PCCB[**OMIM 232050**]*
OMIM: 252920	Sanfilippo syndrome	*NAGLU[**OMIM 609701**]*
ORPHA:818	Smith-lemli-opitz Syndrome	*DHCR7 [**OMIM 602858**]*
OMIM:270400	Smith-lemli-opitz Syndrome	*DHCR7 [**OMIM 602858**]*
OMIM:271980	Succinic Semialdehyde Dehydrogenase Deficiency	*ALDH5A1 [**OMIM 610045**]*

and response to social cues associated with individuals having ASD (30). For instance, recent observations in the Simons Simplex Collection (SSC) suggest that ASD risk architecture might differ between individuals with lower and higher IQ (31). In the SSC study, individuals with ASD and IQ < 100 have an excess of *de novo* loss-of-function mutations compared with their higher IQ counterparts (32). Although individuals with ASD but not ID have a higher rate of family history of psychiatric disease and thus, a greater familial burden (33). The stratification of patients by IQ score, as well as other clinical variables, has been proposed as an

Table 4. *Autism as a result of other syndromic disorders.*

Disease ID	Disease Name
OMIM:500007	Cyclic Vomiting Syndrome
ORPHA:374	Goldenhar Syndrome
OMIM:238350	Hyperlexia
OMIM:240000	Hyperuricemia, Infantile, With Abnormal Behavior And Normal Hypoxanthineguanine Phosphoribosyltransferase
OMIM:606053	Intellectual Developmental Disorder With Autism And Speech Delay
ORPHA:550	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS)
OMIM: 614346	Mental retardation, autosomal recessive 25
OMIM:614333	Mental Retardation, Autosomal Recessive 29
OMIM: 300355	Mental retardation, X-linked 73
OMIM: 300518	Mental retardation, X-linked 82
OMIM:300852	Mental Retardation, X-linked 88
OMIM: 614407	Microcephaly, Cerebellar Hypoplasia, And Cardiac Conduction Defect Syndrome
ORPHA:570	Moebius Syndrome
ORPHA:2563	Momo Syndrome
ORPHA:439167	Placental Insufficiency
OMIM:268850	Richieri-costa/guion-almeida Syndrome

approach to reduce phenotypic variability and enhance genetic discoveries (34). However, in one recent study, grouping by ASD diagnostic category, IQ, ASD severity, persistence on uniformity and symptom profiles did not significantly increase genetic homogeneity, at least as determined by single nucleotide polymorphisms, nor did it yield more findings of common variation (32).

All of these observations may complicate the validity of ASD as a specific construct and support the possibility of a shared risk among various NDDs. To capture this complexity, Ledbetter and colleagues have proposed the term "developmental brain dysfunction" to harmonize and merge classically defined categorical diagnoses, including minimal brain disorders, such as learning disabilities, language disorders, developmental coordination disorder and ADHD, NDDs, ID, ASD, cerebral palsy, and some neuropsychiatric disorders (schizophrenia and major affective disorders, to a certain extent) (29), while in another study performed by Gillberg (35) has proposed something different to describe the children and their parents presenting at a clinic with impairing child symptoms before age 3–5 years in association with general cognitive development, such as communication ability, social skills, motor coordination, attention, activity, behavior, mood, and sleep (35). Gillberg (35) proposed the acronym ESSENCE is referred to Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (35). These perspectives, cognitive, motor, neurodevelopmental, and traits would be as a matter of choice articulated as quantitative measures that account the importance of familial background and penetrance for any specific traits (35). Accordingly, ASD represents a significant health and economic burdens in most populations around the world as it is one of the common reasons for referral to genetics and developmental pediatrics clinics for a diagnostic workup and long-term follow up (36).

Clinical Approach

Detailed history, three-generation family history, developmental history and detailed clinical examination looking for other system involvement should be documented. Hearing test and ophthalmological examination should be performed. Radiological investigations like Magnetic Resonance Imaging of the brain, echocardiogram, and renal ultrasound should be pursued. Additionally, detailed psychological evaluation and psychometric assessment, such as intelligence quotient (IQ), should be done. Several studies suggest that WES and CGH microarray should be the first tier test in investigating patients with an unclear phenotype of ASD (37–39). WGS offers a 7%–10% higher detection rate compared to WES and CGH microarray (40), however, its cost currently triple the cost of WES. Therefore, until the cost of WGS reduced, it cannot be considered as first tier test (Figure 2).

Neurometabolic Disorders and ASD

The role or association of neurometabolic disorders with an autism phenotype is not clear. Although most of the ASD are not associated with neurometabolic disorders; however, there are many neurometabolic disorders with an autistic phenotype, such as phenylketonuria (PKU),

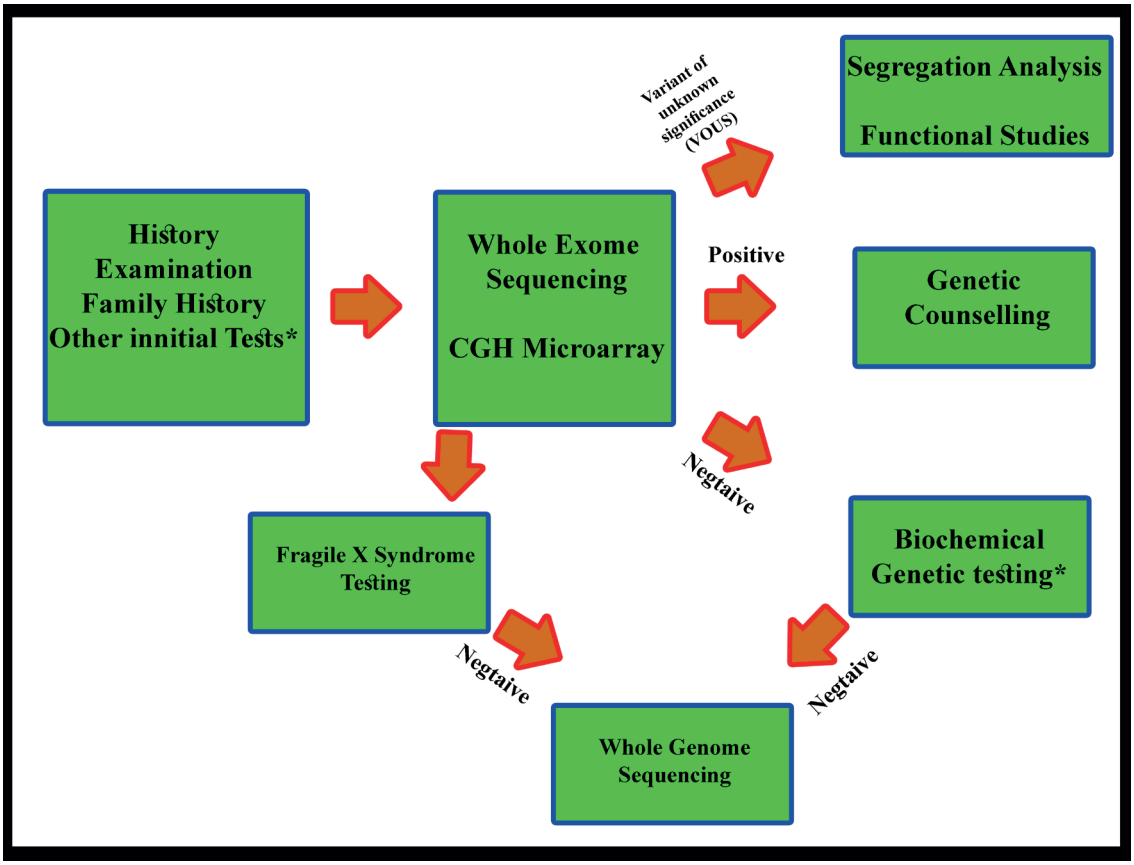

Figure 2. *Schematic representation of various methods utilized for identification of ASD. Other initial tests include *(Chromosomal analysis, acylcarnitine profile, plasma amino acids, urine organic acids CK level, total homocysteine, ammonia and lactic acids, liver enzymes, electrolytes, liver function tests and renal function test. Biochemical genetic testing includes biotinidase enzyme level, VLCFA profile, urine organic acids, urine for purine and pyrimidines, urine for creatine and guanidinoacetate, urine for oligosaccharides and urine for mucopolysaccharides).*

biotinidase deficiency, disorders of purine metabolism, and cerebrospinal fluid neurotransmitters associated disorders, such as folic acid deficiencies, and Smith–Lemli–Opitz syndrome etc. The tests usually used to diagnose the common neurometabolic disorders include plasma amino acids, plasma ammonia, urine organic acids, acylcarnitine profile, and lactate/pyruvate. Clearly, a better understanding of possible metabolic abnormalities in autism is needed. Further research could help to elucidate the important biologic defects, which might lead to development of specific future interventions future (41).

ASD and Saudi Arabia

Unsurprising given the highly inbred nature of the Saudi population in which common ancestry is suspected even in apparently non-consanguineous unions as parents are often unaware of consanguinity in previous generations. In the Kingdom of Saudi Arabia, there is no data about the number of cases of ASD, although it is estimated to be over 167,000 in a population of over 28 million people (42).

Although there has been many reports regarding identification of mutations causing ASD in Saudi populations, still the genetic characteristics of ASD in Arab populations remain largely unexplored (43–45).

Future Directions

A wide range of genomic variations are involved in ASD with gene-gene and gene-environment interactions. Both genotypic and phenotypic heterogeneity contributes to the difficulty in the investigation and validation of ASD pathogeneses. However, recent technological developments, including NGS, along with the accumulation of clinical informatics, will hopefully bridge the gap in the application of availability of genetic information towards clinical practice. Even though there is a strong concordance between remarked structural alterations in autistic patients and the underlying genetic predisposition loci identified so far, however, this is not the only mechanism involved in ASD predisposition. The findings from several WGS projects will afford wealthy data of genetic variants in individuals with ASD. Besides, there will be a necessity to determine which variants are

likely associated with the disease phenotype and must be examined through functional experiments.

Additionally, to better understand the genotype, it is necessary to understand the underlying linking pathways. These essential tasks should be taken into account, if we aim to translate current genetic and biological ASD knowledge into a clinical diagnostic setting. Moreover, a better understanding of new ASD mechanisms will be critical for advancing the early detection of ASD, since earlier intervention is associated with better clinical outcomes (46).

Conclusion

Collectively, research studies have enlightened our understanding of the genetic architecture of ASD and will have immense potentials to indicate to the biology underlying autistic behavior. Besides, it would help in the development of therapeutic approaches by selecting a common molecular or biomarkers. A precise picture of genomic architecture could lead to the stratification of epidemiologic studies and clinical trials. There remains a tremendous unmet demand for interventions that assuredly and robustly address the core symptoms of autistic patients, and translational work linking more basic research findings with clinical practice, which remains somewhat limited. Even though there has been remarkable progress in the ASD associated etiology that has improved our understanding of ASD biology, genetics, early detection, and early intervention. However, recent increases in ASD prevalence suggest an urgent need to translate these gains into access to more efficient interventions for individuals with ASD. The number of genes associated with ASD is increasing, but few studies have been performed on epidemiological cohorts and in isolated populations. Therefore, research in this area is needed.

Understanding this noncoding sequence could provide novel insights into ASD pathogenicity. Little is known about the role of mutations in noncoding regions, including whether they contribute to childhood developmental disorders or which noncoding regions are most vulnerable to disruption in ASD patients. ASD is a sizeable public health and economic burden and may continue until remarkable findings, treatments, or cures are identified. This is a complex disorder with multiple environmental and genetic risk factors, and novel research developments will result in a substantial discovery in the prevention and treatment of individuals with ASD. This is a time of exceptional opportunity in autism research. Armed with broad knowledge about how various types of genetic variants cause autism to arise and with robust new research tools, the autism research community, is poised to reduce the burden of this disease around the world at an accelerated pace.

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