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The Human Genome Diversity and the Susceptibility to Autism Spectrum Disorders

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Introduction

The diagnosis of autism is based on impairments in reciprocal social communication and stereotyped behaviors. The term "autism spectrum disorders" (ASD) is used to refer to any patient that meets these diagnostic criteria. But beyond this unifying definition lies an extreme degree of clinical heterogeneity, ranging from profound to moderate impairments. Indeed, autism is not a single entity, but rather a complex phenotype thought to be caused by different types of defects in common pathways, producing similar behavioral phenotypes. The prevalence of ASD overall is about 1/100, but closer to 1/300 for typical autism [1]. ASD are more common in males than females with a 4:1 ratio [2, 3].

The first twin and family studies performed in last quarter of the 20th century conclusively described ASD as the most 'genetic' of neuropsychiatric disorders, with concordance rates of 82-92% in monozygotic (MZ) twins versus 1-10% in dizygotic (DZ) twins; sibling recurrence risk is 6% [2, 3]. However, recent studies have indicated that the concordance for ASD in DZ twins might be higher (>20%) than previously reported [4]. Furthermore the concordance for ASD in MZ could also be lower than originally suggested [5, 6]. All these studies pointed at a larger part of the environment and/or epigenetic factors in the susceptibility to ASD. For example, in a twin study using structured diagnostic assessments (Autism Diagnostic Interview – Revised and Autism Diagnostic Observation Schedule), a large proportion of the variance in liability was explained by shared environmental factors (55%; 95% CI, 9%-81% for autism and 58%; 95% CI, 30%-80% for ASD) in addition to moderate genetic heritability (37%; 95% CI, 8%-84% for autism and 38%; 95% CI, 14%-67% for ASD). However, most likely due to the high genetic and clinical heterogeneity of autism/ASD, the very large confidence interval of the results makes the gene/environment debate still unresolved.

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From a cognitive perspective, 15 to 70% of children diagnosed as suffering from ASD have intellectual disabilities [7], and it is now understood that autism symptoms can be caused either by gene mutations or by chromosomal aberrations. In approximately 10-25% of the affected individuals, autism is 'syndromic', i.e. occurring in a child with a known genetic or environmental toxin disorder, such as fragile X, tuberous sclerosis, neurofibromatosis, valproic syndrome, or autism caused by brain herpes simplex infection [2, 7].

In the last years, various independent studies and large-scale international efforts have identified a growing number of candidate genes for ASD and suggest a set of mechanisms that could underlie the ASD phenotype. In this chapter, I will briefly review the recent advance in understanding the human genome diversity and the genes that increase the risk of ASD. Finally, I will expose recent genetic and functional results supporting that an alteration in synaptic homeostasis could be one of the mechanisms leading to ASD.

The human genome diversity

The human genome project was launched in the mid-1980s and consequently the first genetic and physical maps were presented in the mid-1990s. But it was only in 2001 that both the academic institutions and the private company *Celera Genomics* achieved the first (almost) complete sequence of the human genome [8, 9]. Ten years after, the 19th version of the human genome assembly (hg19) is available with less gaps and errors than the first release. The human genome is made of 3.102 billion base pairs (the so-called ATGC bases) and contains approximately 33000 genes (among them 21000 are coding for proteins). The comparison of the human genomes with those of other species such as (*pan troglodyte* and *mus musculus*) led to the identification of genomic sequences that were highly conserved during evolution. This comparison could provide great helps in identifying gene sequences within the raw sequence (exons and introns) as well as conserved regulatory elements (promoters, enhancers, silencers…). On the other hand, the identification of rapidly evolving regions could point at compelling candidate genes that could have played crucial roles in shaping phenotypic differences between species. More recently, the genome of *Homo neanderthalensis* could also inform us on the recent genomic events that appeared in the homo lineage.

However, both the academic and the *Celera Genomics* sequences were obtained from the collection of the DNA of very few individuals. For the academic sequence the majority of the DNA fragments were obtained from a genomic DNA library (RP-11) originating from one donor after a request for volunteers that was advertised in a local USA newspaper, *The Buffalo News*. For the *Celera Genomics* sequence, DNA from five different individ-

uals was used for sequencing. The lead scientist of Celera Genomics at that time, Craig Venter, later acknowledged (in a public letter to the journal *Science*) that his DNA was one of 21 samples in the pool, five of which were selected for use.

Therefore, if these initial sequences allowed researchers to do genomic comparison between species and to map genes, very little was known on the genetic diversity between humans. Ascertaining this variability was the next step required to better understand the history of human populations and to identify the variations that contribute to the heredity of human physical traits such as height as well as to the genetic risk factors for frequent diseases such as diabetes and cardiovascular disorders. In order to ascertain the human genetic variability, two main international consortia were launched. First, in 2002, the HapMap project had the goal to identify the most frequent variations within human populations (http://hapmap.ncbi.nlm.nih.gov/). In parallel, different groups identified genomic imbalances (loss or gain of genetic materials) within the genome and therefore produced maps of these events (http://projects.tcag.ca/variation/). Then, thanks to the recent improvements in sequencing technology ('next-gen' sequencing platforms) that have sharply reduced the cost of sequencing, the 1000 Genomes Project was launched in 2008 (http://www.1000genomes.org/). The first goal of this project was to sequence the genomes of a large number of people and therefore to provide a comprehensive resource on human genetic variation.

Geneticists usually use the term polymorphism when the genetic variation is observed in more than 1% of the population and the term variant when the frequency of this variation is below 1%. The majority of the variations identified in one individual are inherited and shared by other individuals in the population and in his/her family. However, the results of the first phase of the 1000 genomes project indicate that approximately 30 variations (10^{-8}) are present in the genome of one individual and absent in his/her parents [10]. These variant called *de novo* are very few, but they can have dramatic consequences when they affect genes with crucial biological function.

The molecular bases of human genetic diversity can be divided into two major classes. Single Nucleotides Polymorphisms (SNP) are defined as variations of single bases in the genome (see Fig. 1, p. 253). An SNP can be frequently observed in a given population or only present in few individuals (<1%). A very broad estimation of the human genetic diversity has indicated that, in average, one SNP/1200 bp is observed between two humans. This makes an average of 3 million SNP differences between two individuals. To date, the last release of dbSNP (build 132) contains 30.44 million human SNPs (http://www.ncbi.nlm.nih.gov/projects/SNP/). The second class of

variation is called Copy Number Variant (CNV). CNVs are defined as a loss or a gain of genetic material of more than 1000 bp compared with the reference genome. As SNPs, CNVs can be observed in a limited number of individuals or at high frequency (also sometimes called CNP for Copy Number Polymorphism).

These genetic data are very useful, but one of the main challenges for biologists remains to ascertain the consequences of these genetic variations at the phenotypic level. While, it is expected that a large proportion of these variations will be neutral with no functional consequences, some variations can contribute to phenotypic differences between individuals. On average, each person is found to carry approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders [10]. In addition, SNPs can affect the regulation of a gene or a CNV can delete or duplicate one copy of a gene with dramatic consequences at the functional level. One general rule is that variations with high frequency in the population tend to have lower functional effect compared with those rarely observed or that appeared *de novo*. However, there are numerous exceptions and functional studies should be undertaken to address the functional consequence of the variations. To address the role of these variants on gene expression, analyses comparison between SNP and expression data are performed to detect expression quantitative trait loci (eQTL). Finally, the interaction between variations remains largely unknown despite that it might be crucial to understand the genotype-phenotype relationship in complex traits. Indeed, two variations each one with low affect when apart could within the same genome have a dramatic consequence at the phenotypic level (a phenomenon called epistasis).

Genetic variations and the modes of inheritance of ASD

Due to the absence of classical Mendelian inheritance, ASDs were first thought to be a polygenic trait involving many genes, each ones with low effect. Therefore, model free linkage studies, such as affected sib-pair analyses, were performed to identify susceptibility genes. Many genomic regions were detected, but only a restricted number of loci were replicated in independent scans (e.g., chromosome 7q31 and 17q11). To homogenize the genetic and phenotypic data and to gain higher statistical power, collaborative efforts were initiated, such as the autism genome project (AGP), that genotyped 1496 sib-pair families using the Affymetrix 10K single nucleotide polymorphisms (SNP) array [11]. Nevertheless, no genome-wide significant loci could be detected, and the signals on chromosome 7q31 and 17q11 were lost. The absence of relevant targets identified by linkage studies prompted geneticists to

use an alternative method: association studies with dense SNP arrays. In theory, association studies are sensitive to allelic heterogeneity whereas linkage studies are not. Nevertheless, association studies provide major advantages compared with linkage studies. First, studies can include large sample of patients since they are not restricted to multiplex families with two or more affected children. Second, the genomic regions associated with the trait are much narrower than in linkage studies, due to loss of strong linkage disequilibrium between relatively close genomic regions. In addition, SNP arrays can be used to detect structural variants such as CNVs [12].

By using these approaches, several genes were associated with ASD. A list of 190 genes is available at AutDB, a public, curated, web-based, database for autism research (http://www.mindspec.org/autdb.html). However, most of these genes remain only candidates since their association was not always confirmed by replication and/or functional validation. Depending on the impact of the mutation on the risk for ASD (a property call penetrance), two main categories of genes can be made. In the first category, genes or loci appear to have a high penetrance, but are mutated in a limited number of individuals (sometime a single individual). In this category, variations are mostly composed of *de novo* or rare point mutations, CNVs and cytogenetically detected deletions/duplications (Table 1). The second category of genes includes the so-called susceptibility genes to ASD (Table 2). Here, the variations are mostly composed of SNPs or inherited CNVs observed in the general population and associated with low risk for ASD. Especially, in this category of genes, the association with ASD should be taken with great care, since the three largest genome-wide association studies (GWAS) performed on more than 1000 patients in each study could not detect the same genes associated with ASD [13-15]. Nevertheless, if these results seem negative, some relevant results were obtained providing a better understanding on the diverse causes of ASD.

Abnormal level of synaptic proteins

Several lines of evidence indicate that mutations in genes regulating various aspects of synaptogenesis and neuronal circuit formation (see Fig. 2, p. 254) are associated with an increased risk for ASD. Among these, several genes seem to regulate the level of proteins at the synapse. Two X-linked genes, *MeCP2* and *FMR1,* are involved in autism 'secondary' to Rett and fragile X syndromes, respectively. *MeCP2* (Fig. 2B, p. 254) is a protein that directly and/or indirectly regulates neurotrophic factors, such as Brain Derived Neurotrophic factor (BDNF), by binding to methylated DNA [16]. Deletions or mutations of *MECP2* are associated with Rett syndrome in females, whereas

Table 1. Genes associated with high risk for ASD

Gene	Chromosome	Function	Evidence	Inheritance	Diagnosis	Reference
FMR1	Xq27	Synaptic translation	Mutations	*de novo* (permutations)	ASD, Fragile X syndrome	71
MECP2	Xq26	Chromatin remodeling	CNV, mutations	*de novo* (rarely inherited)	ASD, Rett syndrome	72
TSC1	9q34.13	mTOR / PI3K pathway	CNV, mutations	*de novo*, inherited	ASD, Tuberous sclerosis	73
TSC2	16p13.3	mTOR / PI3K pathway	CNV, mutations	*de novo*, inherited	ASD, Tuberous sclerosis	73
NF1	17q11.2	mTOR / PI3K pathway	CNV, mutation	*de novo*, inherited	ASD, Neurofibromatosis	74
PTEN	10q23.31	mTOR / PI3K pathway	CNV, mutations	*de novo*, inherited	ASD, Cowden syndrome	75
CACNA1C	12p13.33	Calcium channel	Mutation	*de novo*	ASD, Timothy syndrome	76
DPYD	1p21.3	Pyrimidine base biosynthesis	CNV	*de novo*	ASD	59
RFWD2	1q25.1-q25.2	Ubiquitination	CNV	*de novo*, inherited	ASD	22
NRXN1	2p16.3	Synaptic CAM	CNV, mutations, SNP	*de novo*, inherited	ASD, SCZ	11, 77
CNTN4	3p26.3	Synaptic CAM	CNV	Inherited	ASD, MR	22, 57, 58, 78
MEF2C	5q14.3	Transcription factor	CNV, mutations	*de novo*	MR, Seizures	27
SYNGAP1	6p21.3	Synaptic Ras GAP	CNV	*de novo*	ASD, MR	45
CNTNAP2	7q35-7q36.1	Synaptic CAM	CNV, rare variants ⋆	Inherited	ASD, MR, SCZ, TS,	37, 54-56, 79, 80
DPP6	7q36.2	dipeptidyl-peptidase activity	CNV	*de novo*, inherited	ASD	59
DLGAP2	8p23.3	Synaptic scaffold	CNV	*de novo*	ASD	59
ASTN2	9q33.1	Neuron-Glial Interaction	CNV	Inherited	ASD, SCZ, ADHD	22
SHANK2	11q13	Synaptic scaffold	CNV	*de novo*	ASD	45
NBEA	13q13.2	Synaptic protein	Translocation	*de novo*	ASD	81
UBE3A	15q11-q13	Ubiquitination	CNV	*de novo*, inherited	ASD	22
SHANK3 (del 22q13)	22q13	Synaptic scaffold	CNV, mutations	*de novo*, inherited	ASD, MR, SCZ	43, 44 82
NLGN3	Xq13.1	Synaptic CAM	Mutation	Inherited	ASD	83
IL1RAPL1	Xp21.3-p21.2	Synaptic receptor	CNV, mutations	*de novo*, inherited	ASD, MR	84
NLGN4	Xp22	Synaptic CAM	CNV, mutations	*de novo*, inherited	ASD, MR, TS	83
PTCHD1	Xp22.11	Hedgehog receptor activity	CNV	Inherited	ASD	59
GRIA3	Xp25	Synaptic receptor	CNV	Inherited	ASD	51

ASD Autism Spectrum Disorder; SCZ Schizophrenia; MR Mental Retardation; ADHD Attention-Deficit Hyperactivity Disorder; MDC1D congenital muscular dystrophy; BP Bipolar, TS Tourette syndrome; ⋆ in contrast to mutations, the functional role of the rare variants was not confirmed.

Table 2. Proposed susceptibility genes for ASD

Gene	Chromosome	Function	Evidence	Diagnosis	References
ASMT	PAR1	Melatonin pathway	Inherited CNV, SNPs, mutations	ASD	85-87
DISC1/DISC2	1q42.2	Axonal growth	Inherited CNV	ASD, SCZ	88
TSNAX	1q42.2	Cell differentiation	Inherited CNV	ASD, SCZ	88
DPP10	2q14.1	Dipeptidyl-peptidase activity	Inherited CNV	ASD	59
CNTN3	3p12.3	Synaptic CAM	Inherited CNV	ASD	58
FBXO40	3q13.3	Unknown function	Inherited CNV $P = 3.3 \times 10^{-3}$	ASD	22
SLC9A9	3q24	Transporter	Inherited CNV, mutations	ASD, ADHD, MR	58
PCDH10	4q28	Synaptic CAM	Inherited CNV	ASD	58
PARK2	6q26	Ubiquitination	Inherited CNV $P = 3.3 \times 10^{-3}$	ASD, PD	22
IMMP2L	7q31.1	Mitochondrial protease	Inherited CNV	ASD, TS, ADHD	89
PCDH9	13q21	Synaptic CAM	Inherited CNV	ASD	58, 59
MDGA2	14q21.3	GPI anchor protein	Inherited CNV $P = 1.3 \times 10^{-4}$	ASD	90
BZRAP1	17q22	Benzodiazepine receptor binding	Inherited CNV $P = 2.3 \times 10^{-5}$	ASD	90
PLD5	1q43	Phospholipase D	SNP rs2196826 $P = 1.1 \times 10^{-8}$	ASD	15
SLC25A12	2q31.1	Synaptic receptor	SNP rs2056202 $P = 1 \times 10^{-3}$	ASD	91, 92
CDH9/CDH10	5p14.2	Synaptic CAM	SNP rs4307059 $P = 3.4 \times 10^{-8}$	ASD	13
SEMA5A	5p15.2	Axonal guidance	SNP rs10513025 $P = 2 \times 10^{-7}$	ASD	14
TAS2R1	5p15.2	Receptor	SNP rs10513025 $P = 2 \times 10^{-7}$	ASD	14
GRIK2	6q16.3	Synaptic receptor	SNP rs3213607 P = 0.02	ASD, SCZ, OCD, MR	50
POU6F2	7p14.1	Transcription factor	SNP rs10258862 $P = 4.4 \times 10^{-7}$	ASD	15
RELN	7q22.1	Axonal guidance	GGC repeat in the 5' UTR $P < 0.05$	ASD, BP	93
NRCAM	7q31.1	Synaptic receptor	SNP rs2300045 P =0.017	ASD	94
MET	7q31.2	Tyrosine kinase	SNP rs1858830 $P = 2 \times 10^{-3}$	ASD	21
EN2	7q36.3	Transcription factor	SNP rs1861972 $P = 9 \times 10^{-3}$	ASD	95
ST8SIA2	15q26.1	N-glycan processing	SNP rs3784730 $P = 4 \times 10^{-7}$	ASD	15
GRIN2A	16p13.2	Synaptic receptor	SNP rs1014531 $P = 2.9 \times 10^{-7}$	ASD, SCZ	96
ABAT	16p13.2	Enzyme	SNP rs1731017 $P = 1 \times 10^{-3}$	ASD, GABA-AT Deficiency	96
SLC6A4	17q11.2	Serotonin Transporter	Meta analysis $P > 0.05$	ASD, OCD	97
ITGB3	17q21.3	Cell-matrix adhesion	SNP Leu33Pro $P = 8.2 \times 10^{-4}$	ASD	98
TLE2 / TL6	19p13	Wnt receptor signaling pathway	SNP rs4806893 $P = 7.8 \times 10^{-5}$	ASD, FHM2, AHC	99
MACROD2	20p12	Unknown function	SNP rs4141463 $P = 2 \times 10^{-8}$	ASD	15

ASD Autism Spectrum Disorder; SCZ Schizophrenia; PD Parkinson Disease; TS Tourette syndrome; ADHD Attention-Deficit Hyperactivity Disorder; MR Mental Retardation; FHM2 Familial Hemiplegic Migraine 2; AHC Alternating Hemiplegia of Childhood; OCD Obsessive-Compulsive Disorder; BP Bipolar Disorder.

duplications of *MeCP2* are associated with mental retardation and ASD in males and psychiatric symptoms, including generalized anxiety, depression, and compulsions in females [17]. FMRP (Fig. 2A, B, p. 254) is a selective RNA-binding protein that transports mRNA into dendrites and regulates the local translation of some of these mRNAs at synapses in response to activation of metabotropic glutamate receptors (mGluRs). In the absence of FMRP, there is an excess and a dysregulation of mRNA translation leading to altered protein synthesis dependent plasticity [18].

Mutations of other genes associated with ASD seem to affect the level of synaptic proteins by dysregulating overall cellular translation [18]. Patients with neurofibromatosis, tuberous sclerosis, or Cowden/Lhermitte Duclos syndromes have a higher risk of having ASD than the general population. These disorders are caused by dominant mutations in the tumor suppressor genes *NF1*, *TSC1/TSC2* and *PTEN* (Fig. 2, p. 254). These proteins act in a common pathway as negative effectors of the rapamycin-sensitive *mTOR*-raptor complex, a major regulator of mRNA translation and cellular growth in mitotic cells [18]. The mutations observed in ASD have been predicted to enhance the *mTORC1* complex, which could lead to abnormal synaptic function due to an excess of protein synthesis. Interestingly loss of *Tsc1/Tsc2* or *Pten* in mice results in neuronal hypertrophy [19], and patients presenting mutations in *NF1*, *TSC1/TSC2* and *PTEN* have a higher risk for macrocephaly. Further modulation of the *PTEN* and *mTOR* pathways is exerted by serotonin and the proto-oncogene cMET, two pathways that were also associated with ASD [20, 21].

Consistent with the hypothesis of a relationship between abnormal levels of synaptic proteins in ASD, many studies have reported mutations in genes involved in synaptic protein ubiquitination, including *UBE3A*, *PARK2*, *RFWD2* and *FBXO40* [22] (Fig. 2A, p. 254). Protein degradation through ubiquitination proceeds through the ligation of ubiquitin to the protein to be degraded. This post-translational modification directs the ubiquitinilated proteins to cellular compartments or to degradation into the proteasome. The ligation of ubiquitin is reversible and could be used to regulate specific protein levels at the synapse. In mice, many proteins of the post-synaptic density, including the mouse orthologs of the ASD-associated SHANK proteins, have been demonstrated to be targeted by ubiquitination in an activity-dependent homeostatic manner [23]. Ubiquitination involves activating enzymes (E1), conjugating enzymes (E2) and ligases (E3). Substrate specificity is usually provided by the E3 ligases, which typically have substrate-binding sites. *UBE3A* (also called E6-AP) is an E3 ligase encoded by an imprinted gene (only expressed from the maternal copy) and is responsible

for Angelman syndrome [24]. In ASD, *de novo* maternal duplications of chromosome 15q11-q13 including *Ube3A* have been observed in 1-3% of the patients [24]. It is still not clear whether *Ube3A* alone contributes to the risk of ASD, since other candidate genes are also duplicated on chromosome 15q11-q13; however, its role at the synapse has been recently demonstrated in mice [25, 26]. In cultured hippocampal neurons *Ube3A* is localized at the pre- and post-synaptic compartments, but also at the nucleus. Experience-driven neuronal activity induces *Ube3A* transcription, and *Ube3A* then regulates excitatory synapse development by controlling the degradation of Arc, a synaptic protein that promotes the internalization of the AMPA subtype of glutamate receptors [26]. This might have many consequences for synaptic structure, as suggested by *Ube3A* maternal-deficient mice, which exhibit abnormal dendritic spine development, including spine morphology, number and length [25], and a reduced number of AMPA receptors at excitatory synapses [26].

Finally, the transcription factor *MEF2C* (Fig. 2B, p. 254), involved in the regulation of the number of synapses appears to be a risk factor for intellectual disability [27], and could therefore also be associated with ASD. Taken together, the genetic results obtained in humans and the functional studies mostly obtained in mice suggest that different independent mechanisms could alter the level of synaptic proteins; however, the actual nature of the impaired synaptic function(s), and its association with ASD phenotype remains to be characterized.

Abnormal formation of neuronal circuits in ASD

The main category of genes associated with ASD is related to the development and the function of neuronal circuits [28]. At the synaptic membranes, cell adhesion molecules, such as NLGNs and NRXNs (Fig. 2, p. 254) are major organizers of excitatory glutamatergic and inhibitory GABAergic synapses, and contribute to the activity-dependent formation of neuronal circuits in mice [29]. Mutations identified in patients with ASD were found to alter the ability of NLGNs to trigger synapse formation in cultured neuronal cells [30, 31]. The disorders associated with NLGN-NRXN mutations can greatly vary among individuals, and this appears to be the case even for subjects of the same family, carrying the same mutation Mutations of the X-linked *Nlgn4X* have been associated with mental retardation [32], typical autism [31, 33], Asperger syndrome [34] and more recently with Tourette syndrome [35]. In one case, a *Nlgn4X* deletion was observed in a male with normal intelligence and apparently no autistic features [36]. *Nrxn1*, by contrast, has been implicated in disor-

ders such as schizophrenia and Pitt-Hopkins-like syndrome, but has been also found in asymptomatic carriers [37].

Interestingly, *Nlgn* and *Nrxn* might also play a role in social interaction in other species than humans without affecting overall cognitive functions. Mutant mice carrying a R451C *Nlgn3* mutation displayed an increased number of GABAergic synapses and inhibitory currents [38], normal [39] to reduced social interaction [38] and a reduction of ultrasonic vocalization in pups [39]. The knockout mice for *Nlgn4* displayed reduced social interactions and ultrasonic vocalizations at the adult stage [40]. By contrast, mutant knock-in *Nlgn3* and knock-out *Nlgn4* displayed enhanced to normal learning compared with wild-type mice [38, 40]. Furthermore, in the mouse model for fragile X, an enhanced *Nlgn1* expression improved social behavior, whereas no effect on learning and memory was observed [41]. Finally, in the honeybee, sensory deprived animals had a lower level of *Nlgn1* expression, but a generally increased level of the *Nlgn2-5* and *Nrxn1* expression compared with hive bees [42].

Postsynaptic density plays a major role in the organization and plasticity of the synapse, and mutations affecting scaffolding proteins, such as *SHANK2*, *SHANK3* and DLGAP2, are recurrently found in ASD [43-45]. Deletions at 22q13 and mutations of *SHANK3* could be present in more than 1-2% of ASD patients (Box 1) [43, 44, 46]. Shank proteins are a family of three members, which are crucial components of the postsynaptic density. Together with their binding partners, they have been shown, *in vitro*, to regulate the size and shape of dendritic spines [47]. They also link glutamate receptors to the cytoskeleton and variations in genes regulating cytoskeletal dynamics were associated with mental retardation and ASD [45, 48].

The role of neurotransmitter transporters and receptors in the susceptibility to ASD is still unclear. Because of the abnormally high levels of serotonin in ASD patients [20], the serotonin transporter *SLC6A4* was extensively analyzed, and the results pointed toward dimensional rather than categorical roles for *SLC6A4* in stereotypic behaviors [49]. For glutamate, only weak associations for *GRIK2* were detected [50], and a duplication of the X-linked *GRIA3* receptor gene was observed in a patient presenting typical autism [51]. Concerning GABA, the most robust findings concern the duplication of the GABA receptor subunit gene-cluster on chromosome 15q11-13 and the observation of maternal over-transmission of a rare variant of the GABA(A) receptor beta3 subunit gene (GABRB3) [52].

Finally, proteins, related to axonal growth and synaptic identity, are now also suspected to play a role in ASD. Semaphorins are membrane or secreted proteins (Fig. 2, p. 254) that influence axon outgrowth and pruning, synap-

togenesis and the density and maturation of dendritic spines. SNPs located close to the semaphorin *SEMA5A* were associated with ASD in a large cohort [14]. Independently, the level of *SEMA5A* mRNA was found to be lower in brain-tissue and B-lymphoblastoid cell lines from patients with ASD compared with controls [53]. The contactin family of proteins is involved in axonal guidance as well as in the connection between axons and glial cells, and ASD patients have been found to have deletions of the contactin genes *CNTN3* and *CNTN4* and the contactin associated protein *CNTNAP2* [54-58]. In addition, inherited CNVs or SNPs have been found in other cell-adhesion proteins – cadherins (*CDH9, CDH10, CDH18*) and protocadherins *PCDH9 and PCDH10* [13, 58, 59] – which might contribute to the susceptibility to ASD by altering neuronal identity.

Abnormal synaptic homeostasis in ASD

Different homeostatic mechanisms allow neuronal cells to maintain an optimal level of neuronal activity despite global changes in the overall activity of the network [60-62]. Recent evidence suggests that homeostasis plays a role in the adaptation of synaptic plasticity by changing levels of activity [23, 60], and might be also associated with the downscaling of synaptic weights during sleep [61]. During development and the first years of life, activity plays an important role in the refinement of brain connections, and many results suggest that these processes are under homeostatic control at the synapse [63]. The genes and the mechanisms that we have surveyed in this chapter might disrupt synaptic homeostasis at various levels [64]. The synthesis and degradation of different postsynaptic density proteins has been shown to vary as a function of activity [23]. Mutations in ubiquitin-dependent degradation could directly interfere with this process, as would also be the case if mutations are present in scaffolding genes such as the Shank family. Synaptic homeostasis has been shown to depend on local protein synthesis, on Ca^{2+} concentration and on a tight regulation between the pre- and the post synaptic sides of the synaptic contact mediated by cell adhesion molecules such as Nlgn and Nrxn [65]. Finally, synaptic homeostasis is not independent from cellular homeostasis and therefore should be affected by mutations altering gene expression level as well as neuronal numbers and shape such as mutations related to the mTOR pathway.

If synaptic homeostasis is altered in ASD, environmental factors that influence this regulatory process could also modulate its severity. As reviewed elsewhere [20, 66], abnormal serotonin and/or melatonin levels and altered sleep or circadian rhythms might constitute risk factors for ASD [67]. Sleep has been proposed as an important mechanism to regulate synaptic home-

ostasis. During wakefulness there appears to be a global increase in the strength of excitatory synapses, scaled down during sleep to a baseline level [61, 68], a mechanism that can play an important role in learning and memory [69]. In addition to mutations of genes directly involved in synaptic processes, we have recently proposed that, in some cases, ASD could result from the interplay between abnormalities in synaptic and clock genes, and that restoring circadian rhythms might therefore be beneficial for the patients and their families [66].

Most of the genes considered in this review are thought to be expressed throughout the brain; however, neuroimaging studies seem to converge into a stereotypical network of brain regions where differences between ASD and control populations can be detected. These two results would not need to be in contradiction, if different brain networks were differently resilient to variations in synaptic homeostasis (see Fig. 3, p. 255). From an evolutionary standpoint, brain networks involved in more recently acquired cognitive skills, such as language or complex social behavior, might have less compensatory mechanisms compared with more ancient biological functions that have been shaped by a much stronger selective pressure.

Concluding remarks and perspectives

It is a matter of time for geneticists to be able to obtain whole genome sequences of ASD patients. Exploring epigenetic alterations should be also more feasible in the near future, thanks to the availability of brain tissue samples and stem cells from patients. Animal models based on genetic results are now under scrutiny in many laboratories and the consequence of the mutations and their reversibility is analyzed from cell to behavior. However, more than ever we need to recognize the inherent heterogeneity of the genetic correlates of ASD. A true understanding of the relationship between genetic mutations and ASD phenotype will not be possible if we persist in considering autism as a binary value in our analyses. Advancement in the research on ASD requires the expertise from different fields, but only clinicians and psychiatrists will be able to determine what we are actually looking at (i.e. the autism phenotype or, rather, the different autism phenotypes). Future studies should tell if increasing sample size or meta-analyses, phenotypic stratification, pathway analyses and SNP x SNP interactions can identify common variants associated with sub groups of patients with ASD. Indeed, to date, it is not clear how many loci can regulate synaptic homeostasis and how these variants interact with each other to modulate the risk for ASD [70]. A better knowledge of these genetic interactions will be necessary to understand the complex inheritance pattern of ASD.

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Databases used in this review

DECIPHER v4.3
https://decipher.sanger.ac.uk/application/
Autism Genetic Database (AGD)
http://wren.bcf.ku.edu/
Autism CNV Database
http://projects.tcag.ca/autism_500k/
AutDB
www.mindspec.org/autdb.html
BioGPS
http://biogps.gnf.org/#goto=welcome
UCSC Genome browser
http://genome.ucsc.edu

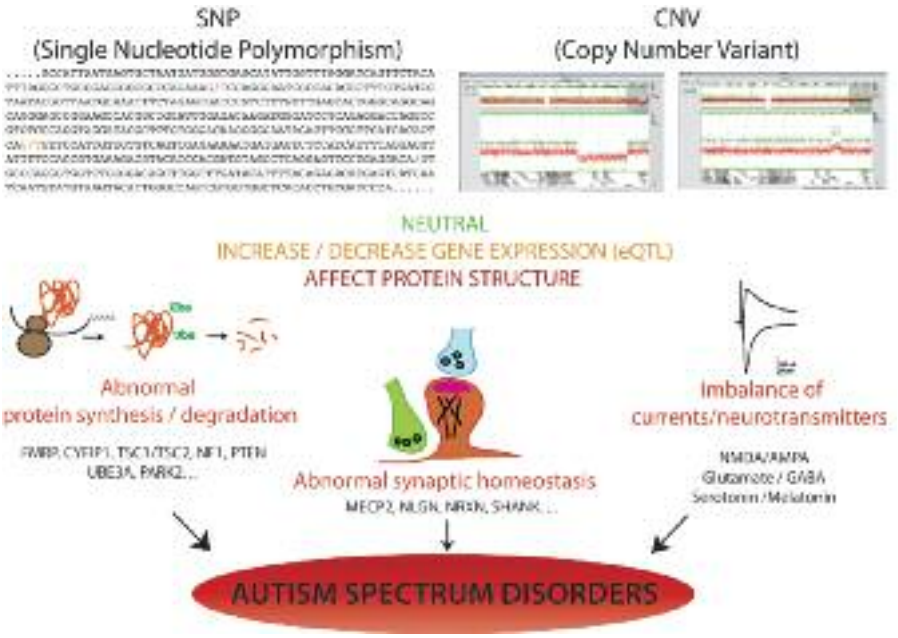

Figure 1. The human genome diversity and the biological processes associated with autism spectrum disorders. Genome diversity is made of single nucleotide polymorphisms (SNP) and of copy number variants (CNV). On the top left, SNPs are indicated by the possibility of two different nucleotides in the human genome sequence. On the top right, CNVs are loss or gain of genomic segment of >1000 kb. They can be detected *via* SNP arrays and visualized by the SnipPeep software. SNPs and CNVs can be neutral or modifying gene expression or protein structure. A subset of these variations can influence protein translation/degradation, synaptic homeostasis and the balance between synaptic currents. All these features are known to increase risk of having autism spectrum disorders.

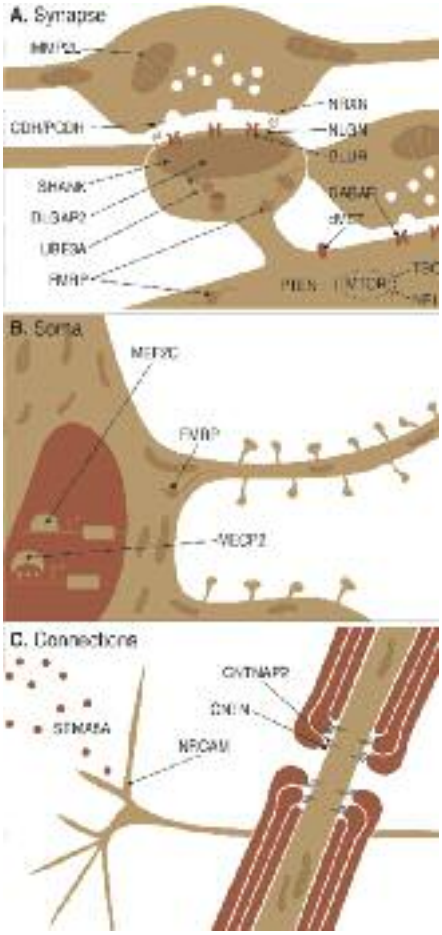

Figure 2 Cellular distribution of the proteins associated with ASD. The proteins associated with ASD appear to participate into three main biological processes. First (panel A), at the synapse cell adhesion proteins such as cadherins (CDH), protocadherins (PCDH), neuroligins (NLGN) and neurexins (NRXN) are involved in synaptic recognition and assembly. Within the postsynaptic density, scaffold proteins such as SHANK3 and DLGAP2 assemble the synaptic components and provide a link between membrane proteins and the actin skeleton. FMRP transports mRNA at the dendrites and regulates local translation of synaptic proteins. In the cytoplasm, the mTOR pathway regulates translation and is influenced by proteins such as PTEN, NF1, TSC1/TS2 and c-MET. The E3 ligase UBE3A is involved in the targeting of synaptic proteins to the proteasome. Receptors for glutamate (GLUR) and GABA (GABAR) are playing a central role in producing excitatory and inhibitory currents, respectively. IMPP2L is a peptidase within the inner membrane of the mitochondria. Second (panel B), in the nucleus the methyl binding protein MECP2 and transcription factors such as MEF2C regulate the expression of neuronal genes involved in the formation of neuronal circuits and synaptic functions. The FMRP protein transports and regulates the translation of mRNA at the synapse. Finally (panel C), at the nodes of Ranvier proteins such as CNTN and CNTNAP2 organize the tight junctions between the axon and the myelinating glia. At the membrane or in the intercellular space, cell adhesion molecules and secreted proteins such as NRCAM or SEMA5A act as guidance cues for axonal outgrowth.

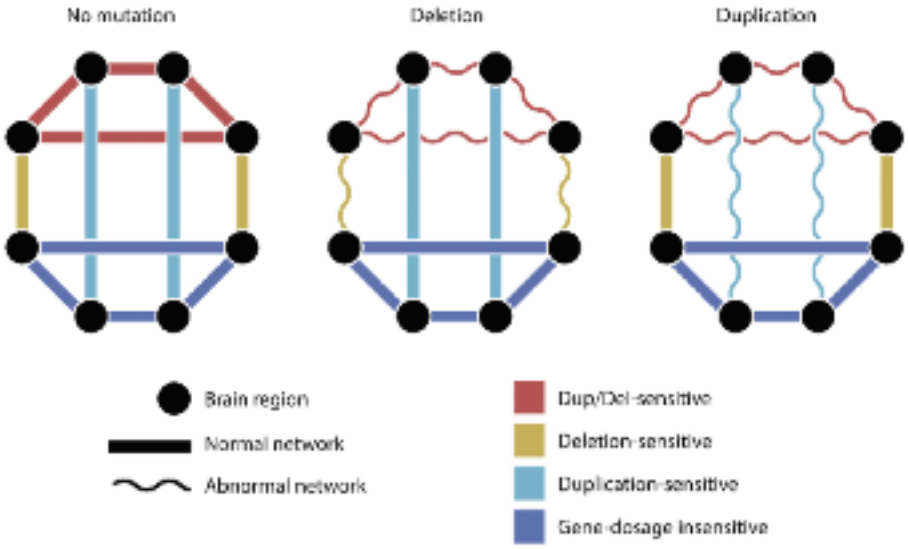

Figure 3. Different resilience of brain networks to gene dosage. Depending on their different resilience, the functional effects of abnormal gene-dosage could seem localized, even if the genetic abnormalities are widespread. Brain networks involved in evolutionary older biological processes might have developed more compensatory mechanisms than those supporting more recent cognitive functions. In the illustration we distinguish four possibilities, networks insensitive to gene-dosage (dark blue), networks only sensitive to duplications (light blue) or deletions (orange), and finally, those unable to compensate for gene-dosage abnormalities (red). Nodes represent brain regions, and edges between nodes represent their functional link. Wavy edges represent sub-optimal functional links.