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Medical conditions in autism spectrum disorders

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Abstract Autism spectrum disorder (ASD) is a behaviourally defined syndrome where the etiology and pathophysiology is only partially understood. In a small proportion of children with the condition, a specific medical disorder is identified, but the causal significance in many instances is unclear. Currently, the medical conditions that are best established as probable causes of ASD include Fragile X syndrome, Tuberous Sclerosis and abnormalities of chromosome 15 involving the 15q11-13 region. Various other single gene mutations, genetic syndromes, chromosomal abnormalities and rare de novo copy number variants have been reported as being possibly implicated in etiology, as have several ante and post natal exposures and complications. However, in most instances the evidence base for an association with ASD is very limited and largely derives from case reports or findings from small, highly selected and uncontrolled case series. Not only therefore, is there uncertainty over whether the condition is associated, but the potential basis for the association is very poorly understood. In some cases the medical condition may be a consequence of autism or simply represent an associated feature deriving from an underlying shared etiology. Nevertheless, it is clear that in a growing proportion of individuals potentially causal medical conditions are being identified and clarification of their role in etio-pathogenesis is necessary. Indeed, investigations into the causal mechanisms underlying the association between conditions such as tuberous sclerosis, Fragile X and chromosome 15 abnormalities are beginning to cast light on the molecular and neurobiological pathways involved in the pathophysiology of ASD. It is evident therefore, that much can be learnt from the study of probably causal medical disorders as they represent simpler and more tractable model systems in which to investigate causal mechanisms. Recent advances in genetics, molecular and systems biology and neuroscience now mean that there are unparalleled opportunities to test causal hypotheses and gain fundamental insights into the nature of autism and its development.

Keywords Autism · Genetics · Medical disorders · Epidemiology · Risk pathways

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Introduction

Ever since it was realized that autism was a result of a neurodevelopmental abnormality, there have been an increasing number of reports of various medical conditions in individuals with autism and autistic-like conditions. For the most part the early papers comprised case reports and small case series that described a wide variety of medical conditions including genetic disorders, chromosomal abnormalities and infectious diseases. In addition, various markers of abnormal brain development (e.g. minor and major congenital anomalies) and risk factors for brain damage (e.g. pregnancy and birth complications) were also described. In general the prevalence of these medical conditions in individuals with autism was quite low, so it was often unclear whether they represented a chance co-occurrence or a true association.

Over the last two decades changes and broadening of our diagnostic concepts [1–3] and improvements in the methods of case identification and diagnosis [4, 5] have led to the notion that autism is a prototypical form of 'spectrum disorder'. Autism spectrum disorder (ASD) includes con-

ditions such as Asperger's syndrome, atypical autism and 'other' pervasive developmental disorders (ICD-10). The prevalence of autism spectrum disorder in the UK is now thought to be in the order of 1% [6].

Parallel developments in medical diagnostics have also lead to improvements in the detection and diagnosis of medical conditions, so the prevalence of these conditions in individuals with ASD has also increased. Table 1 summarises the rates of medical conditions reported in a [7–11] number of population based studies of individuals with ASD. It can be anticipated that these prevalence figures will increase further, as the recent technical advances that have been made in the identification of submicroscopic chromosomal abnormalities (copy number variants [12]) are applied more routinely in the investigation of children with autism spectrum disorders. Currently, the evidence indicates that the conditions are more common in individuals with mental retardation / intellectual disabilities and those with atypical autism [13]. The findings raise the possibility of etiological heterogeneity.

Despite these advances, the aetiological significance of many medical conditions in individuals with ASD remains uncertain. Figure 1 outlines the main reasons why a medical condition may be identified in somebody with an autism spectrum disorder. Clearly, the first task is to determine whether the presence of the medical condition is a coincidental finding, or whether it derives from a true association. The possibility of chance co-occurrence can not be dismissed as a theoretical concern that is unlikely to be relevant. Instead it represents a real possibility for several reasons. Firstly, individuals with an ASD are more systematically and intensely investigated for medical conditions than individuals from the general population. Thus, a condition is more likely to be identified. Moreover, the true prevalence of the medical disorder in the general population is often not well specified, as the rarity of many conditions means that estimation of accurate prevalence figures would require the investigation of extremely large sized populations. The challenge is well illustrated by the difficulty in obtaining accurate estimates of the prevalence of fragile X in the general population [14]. Taken in conjunction with the fact that many studies of medical conditions in ASD are uncontrolled, this is a potentially important limitation. Second, medical conditions in clinical populations will be over represented, because individuals with two or more conditions are more likely to come to medical attention—the so called Berkson bias [15, 16]. As such, studies of clinic series really do require data from comparison clinic populations for the results to be interpretable, unless of course the effect observed were so large that the null hypothesis would be implausible. In most examples this is not the case.

Table 1 Medical conditions in autism spectrum disorder population samples

Study	Rate
Gillberg & Coleman (1996)	25%
Fombonne et al (1997)	10%
Skjeldal et al (1998)	8%
Barton & Volkmar (1998)	9.8%
Lauritsen et al (2002)	11.9%
Kielinen et al (2004)	12.3%
Oliveira et al (2007)	20%
Total	13.9%

The most unbiased test for association is to undertake an epidemiologically designed case control study. In this context it would be best to test a population based sample of individuals with ASD and an appropriately matched control population for the medical condition under investigation. Conversely, it is also valuable to determine the prevalence of autism spectrum disorder in a population derived sample of individuals with the specified medical condition as well as an appropriately selected population based comparison group. These two sources of information can then be used to determine the presence and strength of any association between ASD and the medical condition Clearly however, the rarity of some of the medical conditions that are potentially implicated (sometimes less than 1 in 1000 in the general population and less than 5% in ASD) as well as the relatively low prevalence of autism spectrum disorder in the general population means that very large samples would be required to establish whether a true association exists. In many cases, the costs of such a study would be prohibitive. Accordingly, data from carefully conducted case-control studies of clinic populations may be the only feasible strategy for initially demonstrating association.

In any case, the selection of the control group requires careful consideration. The choice partly depends on the design and aim of the study. Within the context of epidemiological studies, an age and sex matched general population sample would help determine if the two disorders are associated. In studies of a series of clinic cases, a decision has to be taken as to what other clinical population to choose as the comparison group. The choice primarily lies between a series of cases with another neuropsychiatric or neurodevelopmental disorder (e.g. ADHD or mental retardation / intellectual disability) or if the case series comprises a specific medical condition, some other medical disorder (e.g. Down syndrome). The exact choice will depend on the specific question being addressed. It is noteworthy in this regard that some studies have compared the frequency of medical condition in series of cases with autism spectrum disorder to the prevalence in

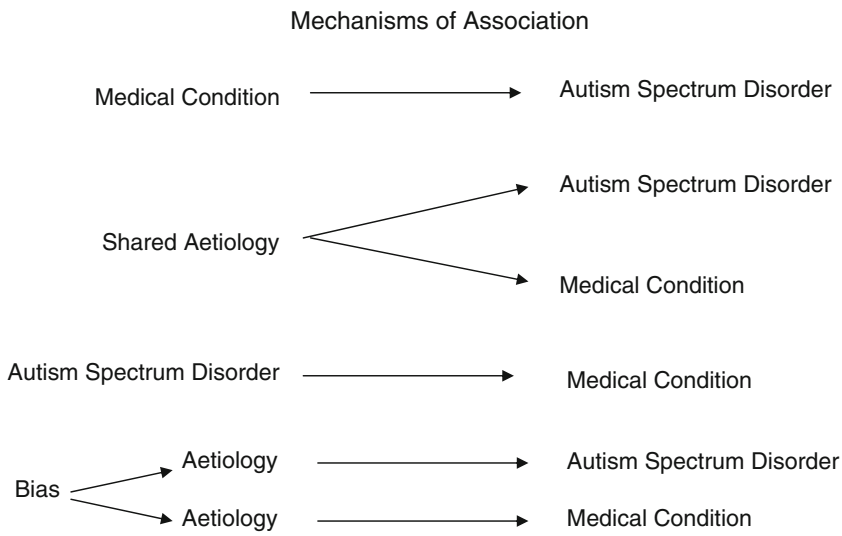

Fig. 1 Mechanisms of association

individuals with non autistic mental retardation / intellectual disability. Sometimes, if no difference in frequency has been observed, it has been concluded that there is no evidence for association between the medical condition and autism spectrum disorder. However, the only formal conclusion from studies of this kind is that the medical condition is not *specifically* associated with ASD, rather than the condition is not associated with ASD.

Apart from the sampling issues another methodological consideration concerns the assessment and diagnosis of autism spectrum disorder. In many studies the established semi standardised diagnostic tools currently in use were not available or utilised at the time of the study, so there is some uncertainty about the validity of diagnoses in some cases / case series. Moreover, the limited use of any semi standardised measures means that the details of the patterns of impairments are not well characterised, so the extent and degree of homology in symptoms and signs of ASD remain unknown. The issue is well illustrated in the reports of the behavioural signs and symptoms founds in individuals with fetal alcohol syndrome Fetal alcohol [17–21], where detailed characterisation of the manifestations reveals that there are different features and profiles of deficits associated with the medical condition. Clearly therefore, careful assessment and characterisation is important in order to determine the degree to which there is specificity in symptomatology and signs.

Tables 2, 3, 4 and 5 summarises the evidence base for association between autism spectrum disorder and various medical conditions, according to the type of study design. The list of disorders reported is not exhaustive, but focuses on the conditions where evidence from a combination of sources

Table 2 Medical conditions and autism spectrum disorder

Condition	Pop ASD	Pop Med	Case-control ASD	Case control Med	Case series ASD	Case series Med	Case report
Obstetric complications	**x**	**x**	**x**		**x**		**x**
Congenital Rubella					x	x	
Valproate Embyopathy						x	x
Neonatal Encephalopathy		x				x	x
Congenital anomalies	**x**		**x**		**x**	**x**	**x**
Ear infection	x				x		x
Malaria						x	
Herpes simplex						x	x
Macrocephaly	**x**	**x**	**x**		**x**		**x**
Bowel habit	x				x	x	x
Infantile Epilepsy	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Later onset Epilepsy	**x**				**x**	**x**	**x**
Cerebral Malaria						x	
Thalidomide Embryopathy						x	

Table 3 Genetic syndromes

Condition	Pop ASD	Pop Med	Case-control ASD	Case control Med	Case series ASD	Case series Med	Case report
Tuberous Sclerosis	**x**	**x**	**x**		**x**	**x**	**x**
Fragile X Full	**x**		**x**		**x**	**x**	**x**
Pre	**x**				**x**	**x**	**x**
Rett syndrome					x	x	x
Smith Lemli Opitz						x	x
Phenylketonuria						x	x
Neurofibromatosis 1	x		x		x	x	x
Myotonic Dystrophy							
DMPK						x	x
Sotos syndrome							
(NSD1)						x	x
Timothy syndrome						x	
Cornelia De Lange						x	
Cohen syndrome						x	

suggests a possible link. For recent reviews the reader should refer to Zafeiriou et al. (2007) and Abrahams and Geschwind (2008) [22, 23].

Even so, most findings still primarily stem from case reports or small uncontrolled case series, so a good deal of uncertainty remains as to whether the findings reflect chance co-occurrences. Where the evidence for association is fairly clear, the medical condition has been highlighted in the table in bold. Convincing evidence for an association exists for tuberous sclerosis [8, 24–29] Fragile X [30, 31, abnormalities in the chromosome 15q11-13 region [32–52], macrocephaly [53–57] minor congenital anomalies [58–60] and pre- / per-natal complications [61–74].

Even amongst these examples, the design and methodology of the studies entails one or other weakness so the findings can not be considered indisputably conclusive. In particular, most studies were not specifically set up to test for comorbidity between autism spectrum disorder and the specific medical condition. Rather, the finding comes from a secondary analysis of the data and the methods of assessment and diagnosis of the autism spectrum disorder and / or the medical condition may not have been conducted as rigorously as would be desirable. Nevertheless, in the case of tuberous sclerosis and fragile X syndrome, it is clear that the evidence base is sufficiently strong to indicate that a true association is highly likely: the strength of the association, however, may not have been accurately estimated.

Having established that a true association likely exists, it is necessary to consider the possible basis for the association. The main mechanisms are outlined in Fig. 1. In most instances, the underlying risk mechanisms or pathway have not been fully elucidated, but for the purpose of illustration, some putative pathways can be postulated.

Medical conditions as a consequence of autism spectrum disorder (ASD)

At first sight, it seems quite improbable that autism may be the cause of a medical condition, but Ileal lymphoid hyperplasia serves as a possible example of these mechanisms. Ileal

Table 4 Single gene mutations / rare variants and autism spectrum disorder

Condition	Pop ASD	Pop Med	Case-control ASD	Case control Med	Case series ASD	Case series Med	Case report
Neuroligin 4			x		x		x
Neuroligin 3					x		x
Neurexin 1			X		x		x
CNTNAP2			X		x		x
PTEN					x		x
Reelin			X		x		
Shank3			x		x		x

Table 5 Genomic disorders and autism spectrum disorder

Condition	Pop ASD	Pop Med	Case-control ASD	Case control Med	Case series ASD	Case series Med	Case report
2q37						x	x
7q11.3					x	x	x
15q11-13			**x**	**x**	**x**	**x**	**x**
15q11.2					x		
15q13.3					x		
16p11.2			x		x		x
16p13.1			x		x		x
17p11.2						x	
Trisomy 21					x	x	x
22q11.2					x	x	x
22q13.3					x	x	x
Xp22.3					x	x	
XXY						x	x
XO					x	x	x

lymphoid hyperplasia has been reported in small case series of children with ASD [75]. It is a condition that is also seen in children with constipation [76]. Children with autism sometimes have markedly unusual diets because of extreme food fads. It is therefore quite possible that the abnormal diet deriving from autistic food fads leads to constipation, which in turn leads to Ileal lymphoid hyperplasia. The issue requires investigation.

Medical conditions arising from shared etiology

For some medical conditions, it seems highly likely that their association with ASD reflects the fact that there is some underlying shared risk factor that leads to the medical condition and the ASD. Examples where this mechanism is likely to underlie the association include macrocephaly, minor congenital anomalies and later onset epilepsy.

Macrocephaly

A significant minority of children with ASD develop macrocephaly. [53–57]. In a few individuals with ASD and macrocephaly, mutations in PTEN and NSD1 have been identified [77–82]. These mutations give rise to Cowden and Soto's syndromes respectively and both conditions are associated with macrocephaly. Soto's syndrome has previously been reported in individuals with ASD [83].

The limited available evidence also suggests that the macrocephaly seen in cases of ASD is familial [54], raising the possibility of shared familial liability for macrocephaly and autism spectrum disorder and the broader autism phenotype, but this possibility has not yet systematically examined.

Minor congenital anomalies

Several studies have shown an association between minor congenital anomalies and ASD [58–60]. The current evidence indicates that the presence of minor congenital anomalies indexes a reduced likelihood of familial recurrence of ASD [84]. Recent findings also indicate that *de novo* copy number variants are associated with ASD [85–90]as well as minor congenital anomalies and mental retardation [91, 92]. Taken together, the findings suggest that the presence of minor congenital anomalies may index de novo copy number variants and possibly other non familial risk factors for ASD.

Epilepsy

Epilepsy occurs in around 20–30% of individuals with autism and the age of onset tends to be in late childhood or adolescence [93–97]. The basis for the association is however poorly understood. There is evidence that the familial liabilities to epilepsy and autism spectrum disorder are correlated (at least in the group with onset in later childhood or beyond), indicating shared familial risks. The picture may be different however in the group with early onset epilepsy (see below).

Medical conditions as correlated risk factors

In some instances, the risk pathway may be more complex. For example, there may be a shared aetiology underlying the association, but in addition there may be a path between the medical condition and ASD, modifying or exacerbating the manifestations of the behavioural syn-

drome. Infantile epilepsy constitutes a potential example [28, 98–103]. In these conditions, the etio-pathogenesis of the epilepsy is poorly understood, but markers of the presence of an underlying brain abnormality have been reported to index an increased risk for ASD. This suggests that there may be a shared, poorly specified, underlying cause for ASD and epilepsy. In addition however, there is some evidence to suggest that epilepsy in this early sensitive period of development may also be detrimental to brain development and the instantiation of social cognitive representations, thereby predisposing to a risk for ASD or exacerbating the risk stemming from the underlying brain abnormality [28, 103].

Another example concerns pre and perinatal complications. A number of studies have reported an association between ASD and pre and perinatal complications [61–74]. However, the current evidence suggests that these putative environmental risk factors occurring during pregnancy and birth may in fact represent a form person-environment correlation. That is that the genetic factors associated with ASD lead the individuals to being more likely to experience certain environmental events. This may apply to the association with pre and peri - natal problems [71, 104] Nevertheless, it is possible that these experiences may modify or exacerbate the manifestations of ASD.

Medical conditions as a cause of ASD

In addition to the better known Mendelian genetic conditions (e.g. Smith Lemli Opitz [105–107]; Neurofibromatosis 1 [29, 108–113]; Rett syndrome [114–117], there are a growing number of genomic disorders and single gene mutations / rare variants that are being identified in individuals with ASD. These include mutations in Neuroligin 3+4 / neurexin 1 [32, 118–124]; Shank3 [89, 125, 126]; Contactin associated protein-like 2 [127]; Reelin [128] and PTEN [77, 79]

In addition, ASD has been associated with various microscopic chromosomal abnormalities involving the 15q11-13 region [33–39, 41–47, 49–52, 129–135]; 22q11.2 [136–139] and submicroscopic de novo copy number variants including those that involve [85, 88, 90, 140–144] various regions (see Table 5). Intriguingly, there are a number of reports suggesting that both micodeletions and microduplications may predispose to ASD at some loci, suggesting that the genes involved are dosage sensitive and that both up and down regulation may perturb the pathway underlying the risk for ASD [145–147].

There are very good reasons to think that when a genetic condition is confirmed to be associated with ASD, that the genetic disorder is the cause of the ASD. However, an important caveat needs to be borne in mind. That is that the causal factors leading to ASD may also lead to the genetic condition. Although this is highly unlikely in many cases, the mechanisms could plausibly underlie the reported association between genomic disorders (e.g. copy number variants — CNV's) and ASD. For example, some factor that leads to ASD could also give rise to chromosomal instability and a propensity to develop CNV's. The current data do not suggest that this is likely to be the case, but the issue needs further investigation.

Risk pathways

For conditions that are established as being probably causal, questions arises about the nature of the risk mechanisms underlying the association. Figure 2 illustrates the potential risk pathways in schematic form. With recent developments in network and systems biology, much richer models of causal pathways have been elaborated [148, 149]. Thus, it is now appreciated that the genetic risk factors ($G_{1\text{-}n}$) interact with the entire genome to create a disease genome ($D_{1\text{-}n}$), which also interacts with environmental risk factors ($E_{1\text{-}n}$) to produce intermediate phenotypes ($I_{1\text{-}n}$) and pathophysiological states that finally lead to the emergence of disease phenotypes ($P_{1\text{-}n}$). This model can be applied to complex disorders and with simplification (reductions in n) to simpler single gene

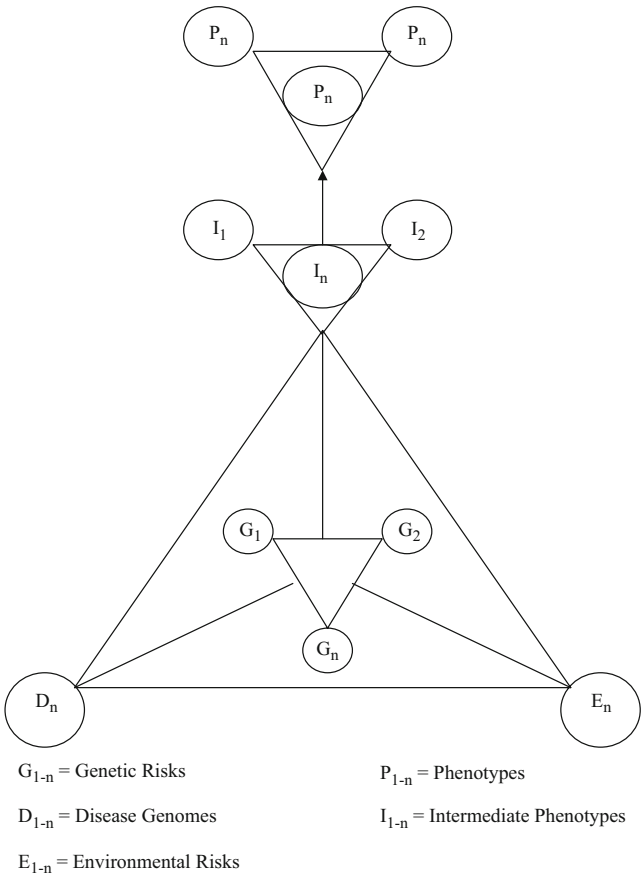

Fig. 2 Interacting pathogenic networks and pathways

disorders etc. According to this model therefore, the association between a medical condition and ASD could derive from shared genetic risk, overlap in the associated disease genome, shared environmental risks, overlapping intermediate phenotypes (i.e. neurobiological and cognitive risks), shared pathophysiological states and similar or partially overlapping phenotypic manifestations. The task therefore is to map the networks of genetic and neurobiological risks leading to ASD in specific medical conditions and determine how this relates to the networks and paths identified in the more complex, 'idiopathic' form of ASD. It should be noted that for almost all the known probably causal medical conditions so far identified, ASD is the outcome in only a subset of cases. For example, about 50% of individuals with tuberous sclerosis do not develop an ASD [28, 40] and similarly around 70–80% of cases of fragile X do not develop an ASD [31]. This means that studies of individuals with specific medical disorders can throw light on the risk pathways leading to ASD. Indeed, mapping the risk mechanisms and paths in simpler and often rather better understood model systems such as tuberous sclerosis and fragile X and developing a full model of the risk and developmental processes involved would be invaluable for the research field.

Mapping perturbations in gene networks and pathways

Some progress has already been made in clarifying the nature of the risk processes involved in some of the medical conditions associated with ASD. For example, it seems that the risk for ASD in tuberous sclerosis is partly dependent on whether the TSC1 or TSC2 gene is mutated [150, 151]. There is also some suggestion that the disease genome expression patterns may be associated with an ASD outcome in tuberous sclerosis. Likewise, the evidence indicates that the risk for ASD in fragile X syndrome is dependent on the presence of the full or pre-mutation [31] and that the risk for ASD deriving from abnormalities of chromosome 15 is dependent on the number and parental origin of the abnormality, with a high risk in individuals with more copies of the abnormality, especially if these are maternally derived [43, 134].

To date the most systematic attempt to map disease gene networks that underlie the risk for ASD has been undertaken by Nishimura and colleague. They studied gene expression profiles in lymphoblastoid cell lines established from individuals with ASD and the fragile X syndrome as well as individuals with ASD and maternally inherited interstitial duplication of 15q11-13. They found not only that there were distinct expression profiles associated with each genetic condition, but also that there were dysregulated expression profiles that were common to both genetic condition and that overlapped with the expression profile seen in cases of idiopathic autism. These investigations have implicated dysregulation of the Janus Kinase and Microtubule interacting protein 1 (JAKMIP1) gene and the G Protein-coupled receptor 155 (GPR155) gene as markers for autism spectrum disorder [152]. Taken together these data indicate that dysregulation of specific genes within networks mark perturbations in the final causal pathway leading to autism spectrum disorder and the broader phenotype of autism. Clearly, there remains much more to be done, but it is evident that the potential exists to use these approaches to map the dysregulated pathways in detail.

Mapping perturbations in neurobiological networks

Of course, there is a parallel need to map the nature of the perturbations in the development of neurobiological systems that underlie the risk for ASD in individuals with associated medical disorders. Here again, some, albeit limited, progress has been made in identifying neuroanatomical and neurophysiological correlates of outcome. For example, in tuberous sclerosis there is some evidence to suggest that the number and location of cortical tubers may index the risk for ASD [28]. Similarly, there are indications that the extent and location of brain changes in individuals with fragile X syndrome are associated with the fragile x mental retardation protein levels and the degree of cognitive impairment and autistic behaviour. The research in this area is in its infancy, but there is clearly much more that can potentially be learnt. Similar considerations apply to the mapping of putative intermediate cognitive phenotypes, where some work has also started to help determine which cognitive processes are key in the pathway to the behavioural syndrome, but as yet the map is just beginning to be outlined.

The selection of disorders and focus of investigation

It is evident that different disorders provide different windows onto the potential risk mechanisms that give rise to autism spectrum disorder. For example, the study of genetic conditions that result from mutations in genes coding for transcription factors (e.g. fragile X) or complex genomic disorders provide special insights into the nature of the disease genome associated with ASD. However, because these conditions are likely to give rise to widespread effects on the gene networks and because the genetic effects are also likely to be pleitropic, the extent to which these conditions can be used to map the neurobiological systems that underlie ASD is likely to be limited. Other medical condition may be more informative about the neurobiological basis of the disorder, so for example investigation of individuals with neurexin 1, neuroligin 3+4 and Shank 3 mutations would

help map the effects of disruptions to synaptic development and function. Similarly, the stochastic nature of the second hit events that give rise to the brain abnormalities seen in tuberous sclerosis mean that this model has special potential in mapping which brain systems are involved in creating a risk for ASD and testing theories about whether single or multiple primary hits in social brain or mirror neuron networks underlie the risk for ASD. The single deficit hypothesis postulates that some single underlying neurobiological abnormality may give rise to autism by setting in motion a cascade of developmental events that ultimately leads to autism spectrum disorder. The multiple primary deficit model postulates that ASD is the result of several separate neurobiological abnormalities (perhaps arising from the pleitropic effects of genes) each giving rise to specific components of the cognitive / behavioural phenotype.

Cross disorder comparisons

Further insights may be gained from comparing cases with different medical conditions according to whether they have ASD. Comparisons of this kind would help determine which conditions are necessary and sufficient for the emergence of ASD. As yet almost no work of this kind has been undertaken, but opportunity clearly exists and holds considerable promise.

High risk designs and developmental processes

Medical conditions that are identified and diagnosed early in infancy can also provides an opportunity to study the developmental pathways leading to ASD and the sequence of events that unfold as the developmental cascade progresses [28, 103, 153]. Insights into these processes may help identify targets for early therapeutic intervention, both in individuals with medical conditions that carry a high risk for ASD as well as in cases at risk for idiopathic ASD.

Testing phenotypic models

Another potential value of investigating individuals with medical disorders that carry a risk for ASD is to test models of the architecture of the phenotype and determine the extent to which the phenotype can be dimensionalized and/or fractionated. The notion that ASD is not a cohesive, unitary phenotype has been raised by recent twin study findings that propose that the phenotype comprises several dimensions (social, communication, repetitive behaviours) each with their own genetic underpinnings, as well as shared genetic risks [154, 155]. The findings from investigations of individuals with Fragile X syndrome [156–160], lend support to the notion that the phenotype can be dimensionalized and that ASD may be at the extreme end of a quasi normally distributed set of traits, but the extent to which this also applies to the phenotypic manifestations seen in other disorder (e.g. tuberous sclerosis) is unclear. Similarly, it is not know whether the phenotype fractionates in these conditions and if so what risk factors underlie each component of the compound phenotype.

Conclusions

An increasing number of medical conditions are being identified in individuals with ASD and studies are starting to identify the conditions that probably play a causal role in etio-pathogenesis. Moreover, it is now appreciated that rather just representing rare phenomena that should be excluded from studies of ASD, that research aimed at understanding why these conditions carry a risk for ASD can cast light on the key risk processes that lead to ASD. The investigation of these simpler and potentially more tractable model systems is in its infancy but it is evident that it is a fertile area of investigation that can provide important insights on developmental mechanisms and risk processes. In addition, the study of these conditions can help answer current questions about the architecture of the phenotype.

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