X-linked ichthyosis (steroid sulfatase deficiency) is associated with increased risk of attention deficit hyperactivity disorder, autism and social communication deficits

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ABSTRACT

Background: X-linked ichthyosis (XLI) (steroid sulfatase deficiency) is caused by deletions or point mutations of the steroid sulfatase (*STS*) gene on chromosome Xp22.32. Deletions of this region can be associated with cognitive behavioural difficulties including autism. Animal work suggests the *STS* gene may be involved in attentional processes. We have therefore undertaken a systematic study of autism and attention deficit hyperactivity disorder (ADHD) in boys with XLI.

Methods: Cases of XLI were recruited from families originally ascertained when pregnancies with STS deficiency were identified through a routine maternal screening programme. Boys with XLI were assessed for ADHD and autism using standardised questionnaires and interviews. Deletions of the *STS* gene were identified and characterised by analysis of genomic DNA and/or fluorescent in situ hybridisation.

Results: 25 boys with XLI were assessed for autism and ADHD. 40% fulfilled DSM-IV criteria for a diagnosis of ADHD, 80% of which were inattentive subtype. ADHD diagnoses were present in those with both deletions and presumed point mutations of *STS*. Additionally, five boys, from three unrelated families, fulfilled criteria for an autistic spectrum disorder or related language/communication difficulty, and all had an unusually large deletion of the *STS* gene with loss of the neuroligin 4 (*NLGN4*) gene. None of the boys with the typical deletion or presumed point mutations of *STS* demonstrated autistic difficulties.

Conclusions: STS deficiency may be a risk factor for ADHD with predominantly inattentive symptoms. Boys with XLI and large deletions encompassing *STS* and *NLGN4* are at increased risk of developing autism and related disorders.

X-linked ichthyosis (XLI) is an inherited disorder affecting 1 in 2000 males and characterised by scaly skin on the scalp, trunk and limbs usually from birth. The condition is due to deficiency of the enzyme steroid sulfatase (STS). In obstetric practice this disorder is known as placental sulfatase deficiency and can be associated with longer gestation and complications in labour due to poor cervical dilatation. The majority (approximately 90%) of individuals with XLI have a complete deletion of the *STS* gene at Xp22.32. This deletion is usually the result of aberrant recombination between homologous sequences in the *VCX* (variably charged, X chromosome) genes flanking the *STS* locus.[1] More extensive *STS* deletions give rise to contiguous gene deletion syndromes which can include the genes for short stature (*SHOX*), Kallmann syndrome (*KAL*), X-linked chondrodysplasia punctata (*ARSE*), and X-linked ocular albinism (*OA1*).

Several case reports of patients with Xp deletions and XLI include cognitive behavioural features such as attention deficit hyperactivity disorder (ADHD),[2–4] mental retardation[4–10] and autism.[7 9] The *VCX3A* gene (variably charged, X chromosome, 3A; also known as *VCX-A*) has been proposed to have a role in the occurrence of mental retardation in some XLI individuals.[5 6] The neuroligin 4 (*NLGN4*) gene, which is included in the deleted region in some XLI patients, may have a role in the autism and social communication difficulties since mutations in this gene have been associated with autism.[11 12] Women with Turner syndrome (45XO) who are haploinsufficient for genes that normally escape X-inactivation, including *STS*, demonstrate a number of cognitive deficits including visuospatial, memory, social cognitive and attentional deficits.[13 14]

In this study, we therefore sought to systematically examine the frequency of attention deficit hyperactivity symptoms and disorder (ADHD) and autism in boys with XLI.

METHODS

Sample

Children with X-linked ichthyosis were recruited during 2006 through the East Anglian Medical Genetics Service at Addenbrooke's Hospital, Cambridge, UK. The study was approved by the local research ethics committee and parents gave written informed consent to participate. The families approached had originally been ascertained by the Genetics Service between 1991 and 2001 through the finding of a very low or undetectable concentration of unconjugated oestriol in pregnancy in women undergoing maternal serum screening for Down syndrome. This is a universal finding in male pregnancies affected by placental sulfatase deficiency irrespective of genotype. Twenty-two families were invited to take part in the study, and 16 (73%) agreed to participate. In four of these families there were two affected siblings ascertained through maternal serum screening, and in another five families additional affected boys (four siblings and a maternal cousin

of the index case) were secondarily ascertained through family assessment and recruited to the study. This made a total sample of 25 affected boys. This sample is of particular value because it avoids any ascertainment bias towards cases with cognitive or behavioural difficulties.

Measures

Behavioural assessment of the 25 boys was completed between 2006 and 2007. In the first stage, parents completed well established, validated behavioural screening measures for ADHD and autistic spectrum disorders. Children scoring near cut-offs for possible diagnoses underwent a more thorough assessment procedure employing validated semi-structured diagnostic interviews to determine the presence of ADHD or autism. Two of the families had previously been referred for routine assessment of behavioural difficulties between 2000 and 2005 and these records were reviewed.

The Conners Parent Rating Scale (1998)[15] is a widely used screening questionnaire in both clinical and research settings for ADHD. Each raw score is converted to a T score dependent on the age and sex of the child. Subscale T scores are provided for oppositional, hyperactivity, inattention/cognitive deficits and an overall ADHD Index. Established cut-off points for possible (T>55) and likely (T>65) ADHD caseness were adhered to. Parents of children who had Conners T scores over 55 for hyperactivity, inattention or overall ADHD Index were interviewed. The Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) interview[16] is a well validated diagnostic research instrument widely used in child psychiatry and epidemiology studies. It covers a number of domains of behaviour such as conduct and emotional problems, attention problems, and hyperactivity. The relevant sections for each child were completed to establish possible diagnoses.

Parents also completed the Childhood Asperger Syndrome Test (CAST), a validated screening measure for social communication difficulties,[17] and the Strengths and Difficulties Questionnaire (SDQ).[18] This is a 25 item test with five subscales, one of which assesses prosocial ability. Boys scoring over 15 on the CAST and scoring below 5 on the prosocial subscale of the SDQ questionnaire were further assessed using the Autism Diagnostic Observation Schedule (ADOS)[19] and/or the Autism Diagnostic Interview-Revised (ADI-R).[20] These cut-offs were employed as suggested by published data.[17 18]

Deletion analysis

Fifteen (94%) of the families had been tested by the East Anglian Medical Genetics Service for deletion of the *STS* gene by analysis of genomic DNA from affected males for the presence of sequences at the 5′ and 3′ ends of the *STS* gene and/or by fluorescent in situ hybridisation (FISH) with an *STS* probe (Oncor) in affected males or carrier females. In 10 of the 13 families found to have a deletion, the extent of the deletion had been estimated by analysis of genomic DNA for the markers DXS278, DXF22S1, DXS1139 and DXS996 and/or by FISH using probes for these loci. For this report, FISH was used to determine the deletion size in two additional families, and to confirm the extent of the deletion in nine others. This included three families already shown to have unusually large deletions in whom detailed FISH analysis was carried out in carrier females to localise the breakpoints, using the BAC (bacterial artificial chromosome) probes listed in fig 1 obtained from the BACPAC Resource Centre (Children's Hospital Oakland Research Institute, Oakland, California, USA).

RESULTS

The mean (SD) age of the sample was 10.4 (3.5) years. With one exception, all the children attended mainstream school and did not demonstrate any evidence of mental retardation, although cognitive ability was not formally assessed.

FISH results

Thirteen families (20 boys) out of the 15 tested for a deletion had the *STS* gene deleted. FISH analysis in eight families (11 boys) showed typically sized deletions not extending distal to *VCX3A* or proximal to *VCX2*; a ninth family (two boys) with only marker data available had similar findings to these families with retention of the flanking markers DXS278 proximally and DXS996 distally. Families 1–3 had larger deletions ranging in size from 2.3–4.8 Mb. The results of detailed FISH analysis are shown in fig 1 together with the findings for the usual 1.5 Mb XLI deletion for comparison. In all three families the deletion included the RP11 clones 769N24, 259L9, 366M24, 594H22 and 323P4 that span the *NLGN4* gene. The two families (three boys) who did not have a deletion of the *STS* gene are presumed to have small intragenic mutations, but this was not investigated further.

ADHD assessment results

Table 1 shows the Conners T score means and percentage of boys scoring over cut-offs for possible and likely caseness. The one child requiring special school placement scored in the T>65 range on all Conners subscales. Questionnaire data were not available for one boy.

Of the sample of 25 children, 15 were eligible for further investigation and 13 of these consented to parental interview with the K-SADS. Interviews were conducted by a researcher (JE) blind to the molecular results, and two interviews were tape recorded for the purposes of checking reliability. Of the 13 interviewed, three had no diagnosis of ADHD, and 10 fulfilled Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV)[21] criteria for ADHD, with eight fulfilling criteria for inattentive subtype, and two fulfilling criteria for combined subtype. The two with combined subtype were brothers (cases B and C; see appendix), one of which was the child in special school placement, and these were the only two children who fulfilled criteria for ADHD and who also fulfilled criteria for an autistic spectrum disorder (ASD). Therefore, in our sample of 25 XLI children, eight (32%) had inattentive ADHD, and two (8%) had ASD and combined type ADHD.

The Conners questionnaire results for the two children who were unable to be interviewed demonstrated T scores for inattention, hyperactivity and overall ADHD of 61, 67 and 64 in one child and 49, 70 and 74 in the other child, who also had an ASD.

Autism assessment results

Based on the questionnaire scores, four boys were eligible for further assessment. Their mean (SD) CAST score was 20.8 (2.3) and their mean SDQ prosocial score was 3.0 (1.8). The mean CAST score for the remaining 19 boys was 3.78 (2.1) and their prosocial SDQ score was 8.3 (1.9). The boy for whom questionnaire data were missing was also included for further assessment, as he was known to have social communication difficulties, and his brother with XLI had a diagnosis of an autistic spectrum disorder. All five boys who were eligible for further assessment (families 1–3) had either an autistic spectrum disorder or language/communication difficulties.

BAC probe*	Location (Mb from Xp telomere)	Genes	Typical XLI deletion	Family 1	Family 2	Family 3
RP13–824C8	3.0					
418N20	3.05					
325L9	3.1	CXorf28				
428I5	3.3	MXRA5, novel				
558O12	3.55	PRKX				
631N21	4.04					
465A24	4.1					
1F14	4.3					
315B16	4.4					
707P20	4.6					
413F15	4.7					
585K14	4.95					
615L18	5.25					
323G19	5.6					
I09P4	5.7					
366M24	5.79	NLGN4				
769N24	5.8	NLGN4				
259L9	5.9	NLGN4				
594H22	5.94	NLGN4				
323P4	6.0	NLGN4				
280C22	6.2					
44F2	6.25					
10G18	6.3					
459A10	6.35					
359O20	6.5	VCX3A				
1M18	6.65					
RP13–898E12	6.76					
343N7	6.8					
RP13–926M18	6.9					
483M24	7.0	HDHD1A				
RP13–302M16	7.27	STS				
26709	7.3	STS				
791N19	7.4					
323F16	7.54					
143E20	7.7					
274G7	7.8	VCX				
94C13	7.9	PNPLA4				
692P14	8.0					
527B14	8.1	VCX2				
657D19	8.2					
589J20	8.3					
119H11	8.4	VCX3B				
606J16	8.5	KAL1				

Figure 1 Deletion analysis in families 1–3 with large deletions. *All clones are BAC RP11 library clones unless otherwise indicated. Black shading, normal hybridisation; grey shading, reduced hybridisation; unshaded, no hybridisation, region deleted. CXorf28, chromosome X open reading frame 28. HDHD1A, haloacid dehalogenase-like hydrolase domain containing 1A; alias GS1. KAL1, Kallmann syndrome 1. MXRA5, matrix-remodelling associated 5. NLGN4, neuroligin 4. Novel, novel ensembl gene ENSG00000215325. PNPLA4, patatin-like phospholipase domain containing 4; alias GS2. PRKX, protein kinase, X-linked. STS, steroid sulfatase. VCX, variable charge, X linked; alias VCX-B1. VCX2, variable charge, X-linked, 2; alias VCX-B. VCX3A, variable charge, X-linked, 3A; alias VCX-A. VCX3B, variable charge, X-linked, 3B; alias VCX-C. Data for the typical deletion found in X-linked ichthyosis is shown for comparison.

The clinical details of their assessments for autism are given in the appendix.

Genotype phenotype correlation

Of the eight boys with inattentive ADHD subtype, two had a presumed point mutation in the *STS* gene, four had a deletion similar in size to that usually seen in XLI families, one had a large deletion (case A, family 1; see appendix) and one was from a family that had not been genotyped.

All five boys who had either an autistic spectrum disorder or language/communication difficulty came from families 1–3 with large deletions (see appendix and fig 1). None of the boys with the usual sized XLI deletion or with presumed point mutations of *STS* demonstrated any difficulties in these domains and had CAST and SDQ scores well within the normal range. All three large deletions differed from the usual XLI deletion in having loss of the *NLGN4* gene. The deletion in family 2 had the most distal breakpoint with loss of the *PRKX* and *MXRA5* genes as well as a novel ensembl gene (*ENSG00000215325*) and a stretch of open reading frame (*CXorf28*). The deletion in family 3 had the most proximal breakpoint with loss of the *VCX2* gene.

DISCUSSION

This study is the first to address systematically the cognitive behavioural phenotype of boys with X-linked ichthyosis, and

Table 1 Mean Conners T score for 24 boys and number (%) over cut-offs

Measure	Mean score (SD)	n (%) scoring T>55	n (%) scoring T>65
Conners Inattention	57.4 (20.8)	14 (58.3)	6 (25)
Conners Hyperactivity	63.0 (15.2)	16 (66.6)	8 (33.3)
Conners ADHD Index	62.4 (13.7)	14 (58.3)	8 (33.3)
Conners Oppositional	52.7 (15.8)	7 (29)	4 (16.6)

provides evidence for an increased risk of inattentive ADHD subtype diagnosis and autistic spectrum difficulties. Within the general population, rates of ADHD in boys in the UK are reported as 3.6% (1% have the inattentive subtype, 0.28% the hyperactive subtype and 2.34% the combined subtype).[22] In this study, 40% fulfil DSM-IV criteria for ADHD; even after removing the two children with an ASD, a 32% diagnostic rate is still considerably higher than the general population. A major strength of this study was the ascertainment of families through the maternal serum screening programme, in order to avoid bias, suggesting that these results are generalisable to boys with XLI in general.

Intriguingly, of the 32% with an ADHD diagnosis, all of these children fulfilled criteria for inattentive subtype only, and there was no correlation with the underlying molecular pathology of the *STS* gene. Both deletions and presumed point mutations were associated with these symptoms, suggesting that it may be STS deficiency per se that is causing the increased risk of inattentive symptoms in these boys, rather than the presence of a deletion. There are several lines of evidence in the literature to support this hypothesis. Of particular interest is a recent finding from animal studies suggesting that haploinsufficiency of the *STS* gene may account for the attentional deficits seen in 39XO mice.[23] STS converts the sulfated form of dehydroepiandrosterone, known as DHEA-S, to DHEA. Both are neurosteroids with effects on neurophysiological and behavioural processes, including some evidence for an inverse relationship between DHEA blood values and clinical symptomatology in boys with ADHD.[24] Additionally, a 3 month treatment course of methylphenidate, the most common treatment for ADHD, produced significant clinical improvement in boys with ADHD and increases in serum concentrations of DHEAS and DHEA, suggesting that these neurosteroids may play a role in the therapeutic effects of methylphenidate.[25] DHEA administration to patients with schizophrenia, alongside their usual antipsychotic medication, has also been shown to improve visual sustained attention.[26]

We have identified three unrelated families with boys with XLI and large deletions associated in all cases with either autism or language/communication problems. It is possible that in all three families deletion of the *NLGN4* gene accounts for the autistic difficulties, as several cases of autistic spectrum disorders associated with mutations within this gene have been previously reported.[11 12] One of the boys originally described by Jamain *et al*,[11] in addition to a diagnosis of Asperger's syndrome, also had communication difficulties described as "dysarthria", which may be relevant to one of the boys described here with severe verbal dyspraxia.

Previous literature has associated *VCX3A (VCXA)* with mental retardation[5] and suggested that this gene is necessary to maintain normal intellectual development.[6] Other reports have demonstrated a highly variable phenotype associated with *VCX3A* deletions including normal intellectual development.[2 3 8 10 27] A recent study of 80 XLI cases with normal IQ identified 62 with the common deletion and detailed breakpoint analysis showed they all had loss of *VCX3A*.[28] This provides strong evidence against this gene having an important role in mental retardation. Based on these data it is likely that the boys in our study with the common XLI deletion have *VCX3A* deleted, but we have not carried out the detailed molecular genetic analysis necessary to confirm this. FISH analysis shows that families 1–3 all have loss of *VCX3A* but only family 2 shows clear evidence of mental retardation. The lack of formal cognitive testing of this sample is a limitation of the study.

Previous literature has associated *STS* deletions, particularly large deletions, with *learning difficulties* (that is, reading and spelling problems) and *learning disabilities* (the term used for low IQ/mental retardation in the UK), but differing and interchangeable use of this terminology and distinguishing low IQ particularly from poor concentration and attention abilities has confused reporting of genotype–phenotype correlations. Reports of "learning disability or difficulty", which might be interpreted as mental retardation in the absence of formal IQ testing, may in fact be ADHD or even autistic spectrum.

The only other known gene deleted in all of these five boys is haloacid dehalogenase-like hydrolase domain containing 1A (*HDHD1A*; alternative designation *GS1*), which is located about 100 kb telomeric to *STS* and of unknown function. However, this gene is also deleted in the boys with typical XLI deletions, so is unlikely to be contributing to the psychopathology. Family 2 has the most severe phenotype in terms of both autistic symptoms and intellectual development, and differs from families 1 and 3 in having loss of the *MXRA5* and *PRKX* genes as well as a novel ensembl gene (*ENSG00000215325*) and a stretch of open reading frame (*CXorf28*). It is possible that loss of these genes may be contributing to the more severe phenotype but it is clear from the literature that there is no simple genotype–phenotype correlation. Some published cases with deletion of this region have been severely impaired[9 29] while others have been more mildly affected and in some cases had normal intellectual development.[2–4]

Although there are limitations to this study, specifically the modest sample size and the lack of a control group, our findings provide preliminary evidence for a role for STS deficiency in attentional symptoms and this merits further investigation in a larger sample with an appropriate control group. Cognitive testing of attentional abilities would also be advantageous in another sample, as this study describes the *behavioural* diagnosis of ADHD, which does not necessarily reflect underlying *cognitive* deficits. The results of this study may have implications for the search for susceptibility genes for ADHD in general, with the *STS* gene being a novel candidate for further investigation in genetic association studies. We have demonstrated that boys with larger deletions encompassing *NLGN4* had difficulties on the autistic spectrum or related language/communication problems and that none of the boys with the typical deletion or presumed point mutation of *STS* had these difficulties.

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Ethics approval: The study was approved by the local research ethics committee.

Patient consent: Parental/guardian consent obtained.

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APPENDIX

Family 1

Case A is a 5-year-old boy who was diagnosed prenatally with STS deficiency following the finding of very low unconjugated oestriol at routine maternal serum screening for Down syndrome. At 12 months of age he showed obvious delay in motor skills and had only just started to crawl. He was walking by 2 years but at 5 years he continues to be clumsy and has significant fine motor difficulties. He requires adult supervision with self help skills and is not yet toilet trained. He had two febrile convulsions at the age of 2 years, but no seizures since.

By 2 years, he had no words that he used regularly and would demonstrate his needs by pointing or crying. By 5 years, his understanding of spoken language is at the three word level and he now uses two to three word phrases to communicate. He is literal in his understanding. Although he has some developmental delay, he is managing in a mainstream school with additional teacher support. He plays alongside his peers, not with them, and has difficulties with turn taking and sharing. He demonstrates little pretend play and tends to be repetitive in his play activities but can be moved on to other play without distress. An ADOS assessment (module 2 for phrase speech) was completed at 5 years of age. Although he fulfilled criteria for an autism spectrum diagnosis on the Communication subscale, his score on the Social interaction subscale was within normal limits and therefore he did not meet overall criteria for an autistic spectrum disorder. He did fulfil criteria for an ADHD inattentive subtype diagnosis.

Family 2

Case B is a 10-year-old boy who was diagnosed prenatally with STS deficiency when maternal serum screening showed very low unconjugated oestriol. He was born at full term by emergency caesarean section for fetal distress following a 40 h trial of labour but was well neonatally. His motor milestones were delayed and he did not walk unsupported until 22 months. He began to use single words at 13 months but stopped doing so at around 15 months.

At age 10 years he uses a few single words, sometimes babbles and sometimes echoes words that are said to him. He demonstrates his needs by screaming or leading carers to what he wants. He does not point things out and uses few gestures to communicate. He is very sensitive to noises such as washing machine noise or children crying. He probably understands some dozens of words. He shows a limited range of facial expressions when encouraged and makes little eye contact. He smiles in greeting and is very (sometimes overwhelmingly) physically affectionate but does not show or share toys or activities unless he needs help.

He shows a number of repetitive behaviours, such as spinning things, turning the hands round on a toy clock, or spinning round himself. He also flicks and twiddles items, flaps his hands, opens and shuts doors, and enjoys flickering light patterns. He shows other sensory interests such as feeling silk, hair and leather. He does not tolerate even small changes in his routine or environment, such as the television being moved or his mother getting new glasses. He has negative reactions to some stimuli such as washing or hair brushing and shows a number of motor stereotypies including complex behaviours like flapping while jumping on the spot, and some toe-walking. When distressed he sometimes bites himself. Motor coordination continues to be impaired, he is not yet toilet trained, and has difficulty eating solids. He has never had clear epileptic seizures but ''absence'' episodes have been noted on a number of occasions.

During the structured play assessment at the age of four-and-a-half (ADOS-G, module 1 for children with no or minimal language) he was not spontaneously interested in toys but did some basic play when encouraged directly. He showed eye contact and vocalisation only when requesting an action to be repeated, used adults' hands as tools to perform tasks, did not demonstrate social interaction or pretend play, and showed some hand flapping and twirling behaviours. During informal observation he walked around the room staring at lights and making repetitive vocalisations of single syllables. Employing the ADI standardised assessment, he fulfilled all the diagnostic criteria for autism, with: delayed language development; clear impairment in social communication and reciprocal social interaction; repetitive and stereotyped behaviour and sensory abnormalities. He also has significant global developmental delay, sleep difficulties, some aggressive behaviour and self-harm when upset, and although he fulfilled criteria for combined type ADHD in this study, this diagnosis has not been formally made given his other difficulties.

Case C is the younger brother of case B, and STS deficiency was confirmed prenatally with very low maternal serum unconjugated oestriol. He underwent developmental assessments at the age of 2 years and 2 years 10 months using Griffiths Mental Development Scales. He was found to be performing at a developmental level

equivalent to half his chronological age on locomotor, personal, hearing, language, and eye and hand coordination skills, suggesting moderate learning disability.
At about the age of 3, he was assessed for a possible autistic spectrum disorder as he was exhibiting some behaviours similar to his brother described above, such as walking on tiptoes and some hand flapping. He had intense interests—for example, a particular video which he watched repetitively. He was noted to be fixated on cars and trains, which he lined up and gazed at sideways. He showed some pretend play but it was basic and repetitive and he played very much to his own agenda. He also liked repetitively pressing light switches and buttons on and off. He showed limited use of gestures and pointing, limited eye contact and facial expression. His speech was mainly in single words and he was echoing the language of others. He often whined and cried, unable to communicate what he wanted. He did not enjoy being cuddled. He was aware of other children but tended to be aggressive if they came too close and did not like sharing toys. He had a few friends but did not acknowledge them if seen out of context. Following an ADOS-G module 1 and ADI-R assessment, he was given a diagnosis of atypical autism. An IQ assessment demonstrated an overall full scale IQ of 95 but his cognitive profile was uneven with strengths in geometric design and picture completion and weaknesses in comprehension and similarities. He fulfilled criteria for combined type ADHD.

Family 3

Case D is a 10-year-old boy who was diagnosed prenatally with STS deficiency when maternal serum screening showed very low unconjugated oestriol. He was delivered by emergency caesarean section following a failed induction of labour. His early motor skills were delayed; he sat at 11 months and walked unaided around 2 years. His speech and language development were slightly delayed on formal testing, and he was slow to develop imaginative play. He was assessed on several occasions and his general developmental skills, apart from motor skills, were reported to be at the lower end of the normal range. He has significant difficulty with peer interactions and the use of appropriate social skills. Currently, he uses a lot of repetitive phrases, with a loud voice and unusual intonation. He struggles with reciprocity and often loses his listener because of his fixation on his particular preoccupations and interests. He shows little interest in the lives or emotions of other people. He has a large vocabulary, his reading is advanced for his age and he has a preference for factual material such as books on dinosaurs.
He has little awareness of social boundaries and has few friends. Any social interactions that he does engage in, he expects to control the agenda. He makes variable eye contact, and demonstrates few gestures or facial expressions and poor joint attention. His play is repetitive and unimaginative. He does not accept others' suggestions for play unless they agree with his own and does not like changes to his routine or environment. He suffers from anxiety and has had several episodes of obsessional compulsive symptoms, including fear of germs with excessive hand washing. He has had a number of assessments, including an ADOS and structured interview from several specialists, and has a diagnosis of high functioning autism.
Case E is a 7-year-old boy, the younger brother of case D, who was born by elective caesarean section at 38 weeks and was known to have STS deficiency from the results of maternal serum screening. At 10 months old he was described as socially aware and interactive, able to sit unsupported and crawling actively. He developed his first word by 18 months. By 2 years of age, he was clearly delayed in his speech with single words appearing at two-and-three-quarters and two word joining around 3 years. His expressive language was delayed although appropriate, but only really intelligible within the family. His comprehension was normal. He was diagnosed with severe verbal dyspraxia and attended a speech and language unit before moving to a mainstream school. He also has motor dyspraxia and particularly problems with fine motor skills. He had a number of behavioural problems and was described as extremely active, with very short attention span and not requiring much sleep. Although he liked to control his environment and did not respond to adult direction, he was not considered to be autistic.

X-linked ichthyosis (steroid sulfatase deficiency) is associated with increased risk of attention deficit hyperactivity disorder, autism and social communication deficits

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