The behavioural phenotype of Angelman syndrome.

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Please use this reference when citing this work:

Horsler, K. and Oliver, C. (2006). The behavioural phenotype of Angelman syndrome. *Journal of Intellectual Disability Research*, **50**, 33-53.

ABSTRACT

Background. The purpose of this review is to examine the notion of a behavioural phenotype for Angelman syndrome and identify methodological and conceptual influences on the accepted presentation.

Method. Studies examining the behavioural characteristics associated with Angelman syndrome are reviewed and methodology is described.

Results. Potential bias in the description of the phenotype emerges with the use of case and cohort studies with the absence of comparison groups. A trend in the literature from a direct gene effect to a socially mediated effect on laughter is evident.

Conclusion. Evidence for a behavioural phenotype of Angelman syndrome has begun to emerge. However, by adopting the concept of a 'behavioural phenotype', attention may become biased towards the underlying biological basis of the syndrome, with developmental and environmental factors being overlooked.

INTRODUCTION

Angelman described three children in 1965 who all presented with intellectual disability and had a short/flat head, a horizontal depression in the occipital region, seizures, jerky movements, a protruding tongue and easily provoked and prolonged paroxysms of laughter (Angelman, 1965). A number of case reports subsequently documented similar clinical presentations (Bower & Jeavons, 1967; Berg & Pukula, 1972; Moore & Jeavons, 1972; Mayo, Nelson & Townsend, 1973; Kibel & Burness, 1973; Elian, 1975; Kuroki, Matsui, Yamamoto & Leshima, 1980; Dooley, Berg, Pakula & MacGregor, 1981; Pashayan, Singer, Bove, Eisenberg & Seto, 1982; Bjerre, Fagher, Ryding, & Rosen, 1984). In 1982, Williams and Frias suggested that the term initially used, "Happy Puppet", was inappropriate as the child's family may feel the term is derisive, and proposed that the name of the disorder should be changed to "Angelman Syndrome".

PREVALENCE AND GENETIC DISORDER

The prevalence estimates for Angelman Syndrome vary widely and range from approximately 1 in 10,000 to 1 in 40,000 live births (Buckley, Dinno & Weber, 1998; Clayton-Smith, 1993). In 1987, Kaplan, Wharton, Elias, Mandell, Donion & Latt, along with others (Magenis, Brown, Lacy, Budden, & LaFrach, 1987) observed a deletion of chromosome 15q11-13 in a child who presented with Angelman syndrome. Previously, deletions on this area of chromosome 15 were associated with Prader-Willi syndrome, characterised by mild intellectual disability, facial characteristics, insatiable appetite, multiple endocrine abnormalities and compulsive like behaviour (Sandanam, Beange, Robson, Woolnough, Buchhozt & Smith, 1997). It was initially proposed that Angelman and Prader-Willi syndromes resulted from deletions of different points along the long arm

of chromosome 15 (Magenis et al., 1987). In 1989, however it was observed that the deletion of 15q11-13, which resulted in Angelman syndrome, was on the chromosome 15 that had been inherited from the mother and in Prader-Willi syndrome the deletion was derived from the father (Knoll, Nicholls, Magenis, Graham, Lalande & Latt, 1989). These two syndromes then provided a human model for genomic imprinting, where genetic information is expressed differently depending on the parent of origin (Clayton-Smith, 1992).

Since the identification of the genetic locus, further genetic classifications of people with Angelman syndrome have been proposed (Smith, Marks, Haan, Dixon & Trent, 1997). In summary, approximately 70% have maternal deletions of chromosome 15q11-13, and between 2% and 5% have a paternal uniparental disomy, where both copies of chromosome 15 have been inherited from the father, leaving them with no maternal copy (Dykens, Hodapp & Finucane, 2000). Between 2% and 4% have an imprinting mutation, resulting in the loss of function of the maternally derived 15q11-13 due to an imprint switch failure (Saitoh, Wada, Kuno, Kim, OtoHashim & NiiKawa, 1999). Until recently, 22%-25% of people with Angelman syndrome showed none of these abnormalities, but in 1997 specific mutations in one of the genes in the Angelman/Prader-Willi critical region UBE3A were identified (Dykens et al., 2000). There are however, 12-15% of people with a clinical diagnosis of Angelman syndrome who have not had a chromosome 15 abnormality identified (Clayton-Smith & Laan, 2003).

CLINICAL CHARACTERISTICS

In 1995, a consensus for diagnostic criteria for Angelman syndrome was developed by the Scientific and Research Advisory Committee of the Angelman Syndrome Foundation (Williams, Angelman, Clayton-Smith, Driscoll, Hendrickson, Knoll, Magenis, Schinzel, Wagstaff, Whidden & Zori, 1995). They solicited input from scientists, predominately geneticists and paediatricians involved in the study of Angelman syndrome to establish consensus about the clinical profile and diagnostic criteria. The criteria identified four clinical characteristics that were 100% consistent in people with Angelman syndrome, these were: developmental delay, speech impairment, movement disorder and "behavioural uniqueness" (any combination of frequent laughter/smiling; apparent happy demeanour; easily excitable personality, hypermotoric behaviour and short attention span). "Frequent" (80%) characteristics comprised of microcephaly, seizures and abnormal EEG and "Associated" (20%-80%) characteristics consisted of flat occiput, occipital groove, protruding tongue, tongue thrusting, feeding problems during infancy, prognathia, wide mouth, widely spaced teeth, frequent drooling, excessive chewing/mouthing behaviours, strabismus, hypopigmented skin, hyperactive lower limb reflexes, uplifted flexed arm position, increased sensitivity to heat, attraction to water and sleep disturbance. However, the criteria did not provide any definitions or descriptions of the behaviours, for example a definition of hypermotoric behaviour, easily excitable personality or hyperactivity.

BEHAVIOURAL PHENOTYPES

Consensus statements that include behaviour alongside physical characteristics raise the issue of behavioural phenotypes and the inevitable interplay between environment and genes. Nyhan first combined behaviours and gene abnormalities into the concept of a

behavioural phenotype in 1972, in his presidential address to the Society for Pediatric Research. He used the term to refer to "the behaviours which are an integral part of certain genetic disorders, and emphasized the role of organic factors in the development of such behaviours" (cited in O'Brien & Yule, 1995, p. 1). However, since this definition, behavioural phenotype research has led to a broader definition being employed, with most etiologically orientated professions adopting Dykens' (1995) conceptualisation of behavioural phenotypes as:

> "the heightened probability or likelihood that people with a given syndrome will exhibit certain behavioural or developmental sequelae relative to those without the syndrome"(Dykens, 1995, p. 523).

Hodapp (1997) described theoretical models underlying the concept of a behavioural phenotype. They consist of the view that: genetic disorders have no specific effects on behaviour (no specificity), each genetic disorder has one or more unique behavioural characteristic (total specificity), and a few genetic disorders lead to a single outcome (partial specificity). He argues that partial specificity is probably the most commonly occurring effect of genetic disorders of intellectual disability as factors such as development, environment and the remainder of the individual's genome all affect behaviour.

The concept of partial specificity is particularly pertinent to Angelman syndrome. In the consensus for Angelman syndrome (Williams et al., 1995), the four clinical characteristics that were 100% consistent (developmental delay, speech impairment, movement disorder

and behavioural uniqueness) are also observed in individuals who do not have Angelman syndrome. Furthermore, in Angelman's (1965) early paper the role of the environment was recognised in his descriptions of three children. He reported that all three children had 'easily *provoked* and prolonged paroxysms of laughter', a characteristic that has continued to be associated with Angelman syndrome.

BEHAVIOURAL PHENOTYPE OF ANGELMAN SYNDROME

This review aims to examine critically the notion of a behavioural phenotype for Angelman syndrome. Studies that have reported behaviours associated with Angelman syndrome will be reviewed. To demonstrate the need for more 'sophisticated interactive models' of behavioural phenotypes that "enable the bringing together of clinical, genetic and neuropathological studies"(Holland, 1999, p. 244), reports of the laughing and smiling behaviour of people with Angelman syndrome will be examined. This will highlight their initial emphasis on biological factors to the detriment of considering developmental and environmental factors, the implications of which will be discussed.

Whilst evidence for a behavioural phenotype for people with Angelman syndrome has begun to emerge (Summers, Allison, Lynch & Sandler, 1995), there are still very few studies that are methodologically robust and the majority of reports comprise of case studies**.** A search of MEDLINE (1966 to present day) and psycINFO (1887 to present day) was carried out using the keywords 'Angelman syndrome', 'Happy Puppet', '15q11-13' and '15q deletion'. The final sample comprised clinical studies in which: (1) the words 'behaviour', 'clinical', 'phenotype', 'phenotypic' occurred or actual behaviours were reported e.g. hyperactive, paroxysms of laughter either in the title or abstract, (2) a

diagnosis of Angelman syndrome had been given (and was the only diagnosis), (3) the report was in English. Table 1 lists all the studies that were identified from the search and the behaviours that were reported.

++++++++++++ Insert Table 1 here++++++++++++

Within a number of the studies, some reported clinical characteristics such as speech difficulties, ataxic gait and protruding tongue were often placed in different categories. For example ataxic gait has been categorised as a musculoskeletal (Zori, Hendrickson, Woolven, Whidden, Gray & Williams, 1992) or neurological phenomenon (Dorries, Spohr & Kunze, 1988) or behaviour characteristic (Cassidy, Dykens, Williams, 2000). For the purpose of this review, speech difficulties, ataxic gait and protruding tongue will not be categorised as behaviours, consistent with studies by Zori et al., (1992), Clayton-Smith and Laan (2003), and Clayton-Smith (1992).

A total of 64 studies reported on 842 cases of Angelman syndrome**,** with ages ranging from a couple of months to 75 years old. However, several cases may have been reported more than once. 56 studies, (88%) made reference to laughing (uncontrollable, paroxysms of, unfounded, outbursts of, frequent, inappropriate, characteristic, vacant, contingent, attacks of, as a concern), smiling (easily, always, frequent, demeanour, constant) or happy demeanour (disposition, sociable). An additional four studies reported 'behavioural uniqueness' that was described by Williams et al., (1995) to include any combination of frequent laughter/smiling; apparent happy demeanour; easily excitable personality, often with hand flapping movements, hypermotoric behaviour and short attention span.

Therefore, only four studies did not make reference to any laughing, smiling or happy demeanour. Of the 734 cases that reported behaviours for each individual with Angelman syndrome**,** 568 (77%) reported either laughing, smiling or happy demeanour and 46 cases (6%) reported behavioural uniqueness.

The second most commonly reported behaviour was feeding problems (mostly in infancy), sucking/swallowing and eating problems. It was reported in 15 (23%) studies and in 266 (36%) of the total number of cases. Sleep disturbance was reported in 18 studies (26%) and in 213 (29%) of cases. Interestingly, although restlessness/hyperactivity/short attention span was reported in 28 (43%) studies, which is more than for sleeping disturbance, the number of cases was less (184; 25%). Other behaviours reported included excessive chewing/mouthing (14% of studies and 12% of cases), hand flapping (6% of studies, 10% of cases), attraction/love of water (14% of studies, 9% of cases), aggression (15% of studies, 6% of cases), stereotypical behaviour (5% of studies, 3% of cases), self injury/self destruction (3% of studies, 3% of cases), noncompliance/stubbornness (5% of studies, 3% of cases), tantrums (8% of studies, 2% of cases), euphoria (2% of studies, 2% of cases) and anxiety was reported in one study.

Within the studies identified in Table 1 there are few operationally defined behaviours and different terms are used to describe the behaviours. For example: uncontrollable, paroxysms of, unfounded, outbursts of, frequent, inappropriate, characteristic, vacant, contingent, attacks of, as a concern, were all used to describe laughing. Table 1 also illustrates the variability of behaviours across people with Angelman syndrome. There are no behaviours that are reported to occur 100% of the time across all the studies. Therefore,

if incorporating these behaviours into a behavioural phenotype of Angelman syndrome, Dyken's (1995) definition of a behavioural phenotype needs to be adopted as described above.

Of the 64 studies, 58 were case reports. The reliance on such reports to develop a behavioural phenotype is problematic. Summers et al., (1995) suggests that there is a tendency to under-report behaviour problems for three reasons. Firstly, the focus tends to be on diagnostic and medical issues, secondly, there is a lack of objective or standardised criteria for reporting data across studies which may have lead to selectivity, and thirdly, the reliance on retrospective reporting may have increased inaccuracies.

As a genetic basis for Angelman syndrome was not observed until 1987 (Kaplan et al.), and a consensus for a diagnostic criteria was not established until 1995 (Williams et al.), the majority of people in the earlier case reports were diagnosed clinically and may therefore have included children who did not have Angelman syndrome or who had a pronounced behaviour profile. This is supported by Williams, Lossie, and Driscoll (2001) who stated that there is uncertainty about the veracity of the clinical diagnosis. They present a review of several other disorders that appear to mimic Angelman syndrome e.g. Rett syndrome, Cerebral Palsy, Lennox-Gastaut syndrome, Prader-Willi syndrome, childhood autism (during age 2-4 years), and pervasive developmental disorder. Additionally, the case reports in Table 1 do not compare the behaviours found within individuals with Angelman syndrome to other children. If a behavioural phenotype is to be established for Angelman syndrome and the definition provided by Dykens (1995) is adopted (that a particular genetic disorder's behaviour phenotype involves a greater probability or likelihood of

particular behaviours compared to others without the syndrome), comparison groups need to be employed.

Table 1 illustrates that the length of time from the first publication of a case report by Angelman in 1965 up to the present time is 38 years. This has implications for scientists and clinicians when using such case reports to develop a behavioural phenotype. As Finegan (1998) points out, the children in more recent case reports have developed in a completely different environment than the children in case reports 30 years ago. For example, most children with intellectual disabilities today are living at home and may be involved in early intervention programs. When incorporating behaviours reported in case reports, the environment that child has developed in needs to be reported and considered.

Similarly, Table 1 shows that of the individuals reported, the ages range from two months old to 75 years old. A strength of using case reports is that the age of the individual is often reported. The age of the individual is important as some behaviours become more prominent as an individual gets older, others less prominent (Dykens et al., 2000; Clayton-Smith, 2001). Buntinx, Hennekam, Broummer, Stroink, Beuten, Mangelschots and Fryns (1995) suggest that individuals with Angelman syndrome may present with a different clinical picture at different ages, and that clinical diagnosis in children with Angelman syndrome who are less than two years old may be difficult as not all of the diagnostic criteria may be present. Likewise, it is suggested that a clinical diagnosis may also be complicated in older individuals, as they appear to 'calm down' and have less bursts of laughter. Buntinx and colleagues conclude that the clinical picture of Angelman syndrome is most distinct between the ages of 2-16 years old.

To conclude, although case reports are argued to be valuable (Finegan, 1998), they have limited use when establishing behavioural phenotypes and are suggested by Dykens (1995) to be typically based on global impressions with a lack of systematic measurement.

There are four studies that have attempted to systematically measure the behaviours of people with Angelman syndrome, using four different questionnaires (Summers et al., 1995; Summers & Feldman, 1999; Clarke & Marston, 2000; Walz & Benson, 2002). In order to further consider the notion of a behavioural phenotype for Angelman syndrome, these four studies will be briefly described and critically examined.

Summers et al. (1995) presented empirical data derived from parent ratings on a modified version of the Child Behavior Checklist (Achenbach & Edelbrock, 1983). The study presented the ratings of individual items that corresponded to many of the behavioural characteristics associated with Angelman syndrome that were reported in the literature. Inappropriate laughter, speech delays, hyperactivity, short attention span, mouthing items and sleep problems were among the most prominent features of the syndrome, followed by eating difficulties, tantrums and non compliance. The authors concluded that there was substantial agreement between the constellation of behavioural features that accompany the syndrome, and that differences only arose regarding the frequency of the participants' behavioural problems.

Although this study was the first to systematically measure the behaviours of people with Angelman syndrome, there are methodological limitations. The study only presented the

behaviours that had been previously reported in the Angelman syndrome literature. Additional behaviours that had not been previously reported in cases of Angelman syndrome were not presented, which may have lead to a bias in only confirming established findings. Additionally, as a comparison group was not used, it cannot be established whether the behaviours reported are more likely to be found within children with Angelman syndrome compared to other groups of children with intellectual disabilities. If a behavioural phenotype is to be established for Angelman syndrome and the definition provided by Dykens (1995) is adopted, that a particular genetic disorder's behaviour phenotype involves a greater probability or likelihood of particular behaviours compared to others without the syndrome, comparison groups need to be employed.

However, in 1999, Summers and Feldman conducted a study comparing scores on the Aberrant Behavior Checklist (Aman & Singh, 1986) of 27 individuals with Angelman syndrome, 24 individuals from an outpatient behaviour management service for children and young adults with developmental disabilities (clinical group), and 23 individuals who were participants in a previous survey of the prevalence of behaviour problems amongst people with developmental disabilities in an Ontario wide survey (community group). They found that the participants with Angelman syndrome scored significantly lower than both comparison groups on the irritability and lethargy scales. On the hyperactivity, stereotypy and inappropriate speech scales, both the Angelman syndrome and community comparison group scored lower than the clinic group.

Interestingly, the above study did not appear to investigate adaptive or pro-social behaviours. Walz and Benson (2002) argue that this is particularly important for

individuals with Angelman syndrome, as "happy demeanor and frequent laughter" are included in the diagnostic criteria (Williams et al., 1995). The concept of a behavioural phenotype was investigated by Walz & Benson by comparing behaviour ratings of 211 children with Down syndrome, Prader-Willi syndrome, Angelman syndrome and non specific intellectual disability, matched on age (5-19 years). They used the Nisonger Child Behavior Rating Form (Aman, Tasse, Rojahn & Hammer, 1996), a standardised rating scale validated and designed to assess behavioural and emotional characteristics of children and adolescents who have intellectual disabilities. Importantly, adaptive or prosocial behaviours were also investigated. The results showed that the children with Angelman syndrome were rated as more likely to exhibit cheerful or happy behaviour and engage in repetitive hand flapping. These children were described as frequently eating inedible things or putting things into their mouth. The results also confirmed that children with Angelman syndrome were at significant risk for attention problems and hyperactivity.

In both Summers and Feldman's (1999) and Walz and Benson's (2002) studies, it was not explored whether different phenotypic differences occurred across genetic sub types. Smith, Wiles, Haan, McGill, Wallace, Dixon, Selby, Golley, Marks, and Trent (1996) suggested that there is a distinct phenotype associated with a deletional Angelman syndrome consisting of: intellectual disability, ataxia, lack of speech, happy disposition and epilepsy. In contrast, Bottani, Robinson, DeLozier, Blanchet, Engel, Morris, Schnitt, Thunffonenstein and Schinzel (1994), and Smith and colleagues (1997) found that people with paternal UPD had a milder phenotypic picture. Both of these studies however did not empirically investigate behaviours, illustrating the need for studies to assess behaviour across the different subtypes. Within other genetic syndromes, phenotypic differences have

been identified relating to genotypes. For example, in Prader-Willi syndrome, individuals with a deletion reportedly injure significantly more body sites than individuals with uniparental disomy (Symons, Butler, Sanders, Feurer & Thompson, 1999).

In contrast to the studies above, Clarke and Marston (2000) conducted a study of problem behaviours associated with Angelman syndrome and limited the results to those who had a documented deletion. The Aberrant Behavior Checklist and the Reiss Screen for Maladaptive Behavior (Reiss, 1988) were sent to all the caregivers of people with Angelman syndrome through two support organisations in the UK. They used several comparison groups and compared the mean Aberrant Behavior Checklist subscale scores of their sample of individuals with Angelman syndrome with the results from other studies. The first comparison group consisted of individuals with severe or profound intellectual disabilities aged five to 51 years old who resided in institutions. The second comparison group consisted of 539 individuals with intellectual disabilities aged between six and 21 years of age who resided in community settings. They also made comparisons with 15q- Prader-Willi syndrome, 17p- Smith-Magenis syndrome and 5p-Cri-du-Chat syndrome. They used the Reiss Screen for Maladaptive Behavior to identity sleep problems and symptoms suggestive of psychosis, which are not included in the Aberrant Behavior Checklist.

They reported that on the Aberrant Behavior Checklist's five factors, irritability/agitation, lethargy/withdrawal, stereotypic behaviour, hyperactivity/noncompliance and inappropriate speech, their sample of individuals with Angelman syndrome scored much lower than individuals with Smith-Magenis syndrome and Prader-Willi syndrome. They reported that

the results lend further support that Angelman syndrome is associated with a pattern of behaviours characterised by overactivity, restlessness, eating and sleep problems, and a fascination with water, in addition to the lack of speech development previously reported.

Importantly, this study and Walz and Benson's (2002) study also investigated the influence of developmental stage on behaviour. As discussed previously it has been suggested that individuals with Angelman syndrome may present with a different clinical picture at different ages and that the clinical picture of Angelman syndrome is most distinct between the ages of 2-16 years old (Buntinx et al., 1995). Clarke and Marston (2000) correlated age with behaviour and found that the scores on the Aberrant Behavior Checklist Factor IV, Hyperactivity and Noncompliance, were negatively correlated with age but not with any other factor. Walz and Benson conducted a within-group analysis and did not find that age or gender were significantly correlated with any of the behaviour variables. Although Summers and Feldman (1999) did report the age ranges of the individuals (2-26 years) and the three comparison groups were matched on age, by collapsing the age groups, cohort effects may be operating that may mask important findings. This point is also highlighted in Summers et al.'s (1995) study. Although the ages of the children were reported, there were no analyses regarding age and behaviour. Four of the parents did not report problems with excessive laughter, but by observing the data provided, it was identified that of these four children, one child was the oldest (12.10 years) and the other three were all below four years of age (1.11, 2, and 3.4 years).

Although the above studies have begun to lend support for a behavioural phenotype of Angelman syndrome, they all share methodological limitations. The Child Behavior

Checklist used by Summers and colleagues (1995) has not been normed on individuals with intellectual disabilities, therefore the sensitivity of the measures in identifying characteristics specific to individuals with intellectual disabilities is unknown (Dykens, 1995). The Aberrant Behavior Checklist used in both Summers and Feldman's (1999) study and Clark and Marston's study (2000), and the Reiss Screen for Maladaptive Behavior used in Clark and Marston's study both share several limitations. Although they have been normed on individuals with intellectual disabilities, the construct validity of the measures have been criticised for being vague, heterogeneous and difficult to interpret (Russell, 2000). The authors however do discuss these issues, they concluded that although such measures may identify differences in occurrence of particular behaviours, the topography of the behaviour may vary, for example, aggression in individuals with Angelman syndrome may take the form of grabs or rough hugs but may look different in another diagnostic group (Summers & Feldman, 1999).

When compared to the Aberrant Behavior Checklist and the Reiss Screen for Maladaptive Behavior, the Nisonger Child Behavior Rating Form used in Walz and Benson's (2002) study does incorporate pro-social and adaptive behaviour. Unfortunately, similarly to the Aberrant Behavior Checklist, the subscales incorporate more than one construct, for example: self-isolated/ritualistic, self-injury/stereotypic, insecure/anxious, obsessive/compulsive and compliant/calm, which may threaten construct validity.

There may have been a sample bias in all of the above studies. All of the samples were contacted either through a support group or a conference about Angelman syndrome, their representativeness is therefore unknown. Walz and Benson (2002) point out certain types

of families might self-select and Finegan, (1998) argues that the parents who are likely to be members of support groups may have children with less impairments. Clarke and Marston (2000) acknowledge this point and suggest also that parents may report behaviours that are believed to be associated with a genetic disorder rather than the behaviours they have observed, although they did not report any evidence supporting this. Similarly, Summers and Feldman (1999) recruited participants through a newsletter provided by support group. As the newsletter stated that the study was of the nature and prevalence of behaviour problems among children with Angelman syndrome, this may have led to a priming effect. However, the authors acknowledge this and suggest that further research should be replicated with randomly selected participants.

Although the studies by Summers and Feldman (1999), Clarke and Marston (2000) and Walz and Benson (2002) all adopted a comparison group, the issue of who constitutes the group is not straightforward. Hodapp and Dykens (2001) suggest that a comparison group matched on age, gender, intellectual disability, consisting of individuals with mixed or heterogeneous intellectual disabilities, including individuals with identified causes for their intellectual disability is preferable. A group of individuals who have non-specific intellectual disabilities includes all individuals who have no known cause for their intellectual disability. They state that this group is similar to the familial or cultural-familial group described by Zigler (1967). Consequently, this group may be of lower socio-economic status and more likely to be of minority status than the individuals they are being compared to. As Walz and Benson employed individuals who had a non-specific intellectual disability, the above points need to be considered when interpreting results. The control group in Summers and Feldman's study, as recommended by Hodapp and Dykens

(2001), consisted of individuals with heterogeneous cause of intellectual disability, but matches for age, gender and level of intellectual disability could not be identified for every person with Angelman syndrome. Therefore their findings that participants with Angelman syndrome scored significantly lower than both comparison groups on irritability and lethargy scales needs to be interpreted with caution.

To conclude, the above studies have begun to lend support for a behavioural phenotype of Angelman syndrome. However, due to the methodological limitations discussed above, further studies are required that: aim to randomly select participants, operationally define behaviours, adopt a control group of children matched on age, gender, intellectual disability with mixed or heterogeneous intellectual disabilities; and control for developmental stage and genetic sub group. It is only when such studies have been conducted that it can be established whether the reported behaviours associated with Angelman syndrome fulfil Dykens' (1995) conceptualisation of a behavioural phenotype.

However, whilst working towards a behavioural phenotype of Angelman syndrome, the risks of utilising such a concept need to be acknowledged. A review of the literature surrounding the laughing and smiling behaviour of individuals with Angelman syndrome will be conducted, as this behaviour is argued to be so characteristic of Angelman syndrome that it is sufficient for the diagnosis (Summers et al., 1995). This will illustrate the initial emphasis on biological factors, to the detriment of considering environmental and developmental factors that can further the understanding of behaviours.

LAUGHING AND SMILING BEHAVIOUR IN ANGELMAN SYNDROME

The laughing behaviour of individuals with Angelman syndrome was proposed by Summers and colleagues (1995) to be pathognomionic, in that it was a sign or symptom that was so characteristic of a disease that it was sufficient for the diagnosis. Although the laughing and smiling behaviour is reported to be one of the most salient features of Angelman syndrome, there appears to be a disagreement as to whether it is influenced by the environment (Angelman, 1965; Kibel & Burness, 1973; Kuroki et al., 1980; Bjerre et al., 1984; Willems, Dijkstra, Brouwer & Smit, 1987; Yamada & Volpe, 1990; Clayton-Smith, 1992, 1993; Buntinx et al., 1995; Oliver, Demetriades & Hall, 2002), is spontaneous (Berg & Pakula, 1972; Dooley & Pakula, 1981; Elian, 1975; Fryburg, Breg & Lindgren, 1991; Mayo et al., 1973; Pashayan et al., 1982; Williams & Frias, 1982; Bjerre et al., 1984; Summers et al., 1995; Magenis, 1987; Dykens et al., 2000; Cassidy et al., 2000) and/or is inappropriate to the context or environment (Berg & Pukula, 1972; Mayo et al., 1973; Dooley & Pakula, 1981; Bjerre et al., 1984; Magenis et al., 1987; Pashayan et al., 1982; Van Lierde, Atza, Giardino & Vianni, 1990; Fryburg et al., 1991; Zori et al., 1992; Clayton-Smith, 1992, 1993; Summers et al., 1995; Fung, Cheong, Smith & Trent, 1998; Clarke & Marston, 2000; Fridman et al., 2000a). This disagreement is illustrated in Table 2, which shows the descriptions that have been used to describe this behaviour since the original paper by Angelman in 1965.

These descriptions appear to reflect disagreement as to the underlying causes of the behaviour. Earlier reports predominantly saw the cause of the behaviour stemming from a neurological impairment. However, although the original paper by Angelman in 1965

suggested that this behaviour was "often in an almost convulsive state" (p. 685) that laughter often proceeded and/or followed the child's seizures, but also stated that it was easily provoked. Williams and Frias (1982) suggested that the spontaneous laughing behaviour was a result of a neurological deficit. Dooley et al., (1981) proposed that these children were not "happy in the traditional sense"(p. 623), and Williams and Frias (1982) suggested that the laughter seemed to be a global expressive outlet independent of happy or sad environments, and that this absence of any emotional association with the laughter suggested that there was an abnormality at the brain stem level. The laughter would be considered a 'forced' laughter that is a randomly generated motor phenomenon.

In 1984 however, Bjerre et al., (1984) reported two children who had *easily provoked* laughing behaviour, suggesting that the environment may play a role, which is contrary to the majority of the earlier reports. The descriptions in the case reports published after 1984 described the behaviour as inappropriate, provoked, unprovoked and spontaneous (Baraister, Patton, Lam, Brett & Wilson, 1987; Willems et al., 1987; Fryburg et al., 1991; Magenis, Toth-Fejel, Allen, Black, Brown, Budden, Cohen, Friedman, Kalousek, Zonana, Lacy, LaFranchi, Lahr, MacFarlane & Williams, 1990), illustrating the continued disparity in descriptions used.

More recent studies have reported that the laughing and smiling behaviour was provoked (Clayton-Smith, 1992; 1993; Kuroki et al., 1980; Willems, 1987; Williams & Frias, 1982). However, to date very few have provided further explanations as to the nature of the provocation. In 1990, Yamada and Volp described an 11-month-old infant with a happy disposition and smiling and laughing on face-to-face contact. Kibel and Burness (1973)

stated that the paroxysms of laughter occurred on any social contact, pleasant or unpleasant and Oliver et al., (2002) reported that smiling and laughing was influenced by social and environmental concomitants. Other studies reported that the behaviour occurred when the child was brought into a new situation (Buntinx et al., 1995) or that it followed vomiting (Magenis et al., 1987). Additionally, Elian (1975) explored the idea that the laughing could have been a mode of communication replacing speech but concluded that as the onset of the behaviour was at five months this argued against such a hypothesis.

Very few studies have reported the onset of smiling or laughing in children with Angelman syndrome and to date there are no studies that have incorporated the developmental literature to further understanding. This is unfortunate as the importance of incorporating a developmental approach to behaviour is highlighted by Dykens (1995) who states that by adopting a developmental approach among persons with different etiologies a better understanding of unique characteristics can be accomplished.

When reviewing the developmental literature it is reported that the emergence of the social smile in infants without intellectual disabilities during the second month is the most endearing and intriguing milestone of human development (Farris, 2000). The development of smiling in infants with intellectual disabilities has predominately investigated infants with Down syndrome. The research tradition of studying Down syndrome is illustrated by Hodapp (1996, cited in Dykens et al., 2000) who stated that there are almost as many empirical articles published about Down syndrome as there have been for all of the other 750 genetic etiologies of intellectual disabilities. Although studies investigating the laughing and smiling behaviours of children with Down syndrome are important to further

our understanding of these behaviours in Angelman syndrome, it needs to be considered how well they represent children with different aetiologies of intellectual disabilities. For example, Burack, Hodapp and Zigler (1998) summarise the literature and state that children with Down syndrome may seem more connected and sociable than children with other forms of intellectual disability as they often smile whilst looking at faces rather than at objects.

However, studies that have investigated the smiling behaviour of children with Down syndrome have found that they follow the same developmental pattern as in typically developing infants, but that there is a delayed emergence of smiling and a shorter duration of smiling during face to face interactions with their mothers than infants who did not have intellectual disabilities (Carvajal & Iglesias, 1997; Berger and Cunningham, 1986). Gallagher, Jens and O'Donnell also found delays in the onset of expressions in a group of infants with intellectual disabilities and physical impairments (1983, cited in Burack et al., 1998). In general, it is reported that high-risk infants show later emergence and less smiling than typical infants (Schmitt & Erickson, 1973; Field, 1983; Rothbart & Hanson, 1983, cited in Farris, 2000). This literature would suggest that given the level of intellectual disability, infants with Angelman syndrome would also show a delayed emergence of smiling. According to Clayton-Smith and Laan (1993), smiling in children with Angelman syndrome usually commenced at 4-6 weeks, which would seem concurrent with the development of smiling in children without intellectual disabilities, although further observational studies are required to confirm this finding.

Elian's early study (1975) was the first to identify the onset of laughing in children with Angelman syndrome at five months. More recently Clayton-Smith (2003) reported the onset within the first few weeks of life. When searching the developmental literature of laughing, there appears to be a lack of studies that have explored both the everyday occurrence of laughing in early development and even less in the development of children with intellectual disabilities (Reddy, Williams & Vaughan, 2002). Sroufe and Wunsch, (1972, cited in Reddy et al., 2002) suggest that in the middle of the first year infants laugh mostly following physical or intense sensory contact. Near the end of the first year it is suggested that infants begin to laugh at funny faces and sounds.

The majority of the sparse literature surrounding the early development of laughing in infants with intellectual disabilities has been investigated with infants who have Down syndrome. Once again how far these behaviours are representative of infants with different etiologies of intellectual disabilities is questioned. This is supported by Norris (1971, cited in Reddy et al., 2002) who reported that the frequency of laughter is greater in infants with Down syndrome than in 'other' infants with intellectual disabilities. Cicchetti and Sroufe, (1976, cited in Reddy et al.,) suggest that infants with Down syndrome may reportedly follow the same pattern as in typically developing infants, with physically intrusive events eliciting laughter earlier than distal events. In children with autism, humorous interactions are suggested by St James and Tager-Flusberg to potentially be unaffected with the more cognitively more complex forms of humour being affected (1994, cited in Reddy et al., 2002). Further studies are required to establish the onset and topography of laughing in infants with Angelman syndrome, to establish if these children laugh more or less

frequently, or laugh in different situations to other children with intellectual disabilities, which appears to be the case with children with Down syndrome.

The study by Oliver and colleagues (2002) was suggested by the authors to be the first experimental demonstration that the laughing and smiling behaviour is dependent on contextual cues. They investigated the occurrence of laughing and smiling with individuals with Angelman syndrome using observational methods. They examined environmental influences on smiling and laughing behaviour in individuals with Angelman syndrome by exposing individuals to several conditions, in which social variables were manipulated. The results showed that this behaviour did appear to be influenced by social and environment concomitants. They found that laughing and smiling was minimal in the absence of social interaction but heightened during the social interaction condition. The rational for this study was that no studies had attempted to further specify or systematically examine the smiling and laughing behaviours in Angelman syndrome and that the qualitative descriptions of the inappropriate laughter varied greatly. This study has been replicated and refined by Horsler and Oliver (In press) who reported higher levels of laughing and smiling in eleven children with Angelman syndrome when levels of social contact were systematically manipulated.

The finding that laughing and smiling was heightened during social interaction is consistent with early psychological theories that suggest that laughing in particular is a relational and social phenomenon (Reddy et al., 2002). This idea is supported by a study carried out by Bainum, Loundsbury and Pollio (1984), who found that that in nursery school children aged 3 to 5 years, laughter co-occurred more frequently than smiling with intentional

produced, silliness/clowning event. Smiling was responsive to a wider variety of events, suggesting it to be a more general-purpose behaviour. Interestingly, Clayton-Smith (2003) reports that children with Angelman syndrome laugh particularly in response to slapstick humour. The most conclusive result from Bainum and colleagues' study was the finding that the vast majority of events accompanying both smiling and laughing occurred in the presence of other people, both children and adults which is consistent with Oliver et al.'s (2002) observations of children with Angelman syndrome.

The laughing and smiling behaviour of students with moderate and severe intellectual disabilities was observed by Berry, Parsons, Hyde and Hilsdon (1981). They found that intellectual ability as measured by the Peabody Picture Vocabulary Test correlated with the amount of time spent laughing and smiling. The majority of laughing and smiling behaviour was clearly contingent upon specific occurrences in a Walt Disney cartoon. They concluded that the study of smiling and laughing in children with intellectual disabilities is under-researched and Kasari and Bauminger (cited in Burack et al., 1998) suggest that more research is needed that considers the effects of etiology and changes in development. This is especially pertinent for individuals with Angelman syndrome as laughing and smiling is reported to be one of the most salient features, but appears to be least understood.

To summarise, although the above reports appear to reflect disagreement as to the underlying causes of the laughing and smiling behaviour, more recent studies have begun to acknowledge the role of environmental and developmental factors. However, to date there are only two experimental studies that have investigated the influence of the

environment on laughing and smiling (Oliver et al., 2002; Horsler and Oliver, In press). Additionally, there is a lack of studies that have incorporated a developmental approach to laughing and smiling in people with Angelman syndrome. Further investigations of this behaviour may enable us to understand other skills that are delayed e.g. expressive speech (Dykens et al., 2000). The study of non-verbal communication skills (including social interaction, requesting and joint attention skills) has attracted recent attention because theory suggests "non verbal communication skills provide a foundation for subsequent language development" (Mundy & Sheinkopt, 1998, cited in Burack et al., 1998, p. 192).

This review has examined critically the notion of a behavioural phenotype for Angelman syndrome. The laughing and smiling behaviour has also been examined illustrating that by using the concept 'behavioural phenotype' attention may become biased towards the underlying biological basis of the disorder, with a host of other influential factors, such as psychological and social influences that also operate to create the observed outcome (O'Brien & Yule, 1995) being overlooked.

The concept that a biologically determined behaviour can be affected by environmental situations is not innovative. Gilbert et al. (1979) cited in his thesis when researching Cornelia de Lange that behaviour with "an originally organic cause" can be maintained through a learning process. Skuse (2000) suggests that even if combinations of genes do contribute strongly to the development of behaviour, the interaction of the environment constantly feeds back to the organism, which in turn alters the expression of the genes and the function of the nerve cells (Quartz & Sejnowski, 1997, cited in Skuse 2000). The concept that the brain has a capacity to learn and actively structure its own circuits while

engaged in processing different types of environment input is also endorsed by Karmiloff-Smith (2001). She warns of adopting a 'Nativist' or 'Evolutionary' view of brain development, that view many aspects of human behaviour as genetically determined and that the human brain is innately pre-specified for low-level perceptual processes and higher-level cognitive functions. These views lead to the dynamics of brain development and the interaction between different parts of the brain through development, being ignored (Karmiloff-Smith, 2001). However, whilst environment and/or social factors that operate to create the observed behaviour are considered, both Gilbert (1979) and Rutter (2002) caution that such factors on behaviour cannot be assumed to be equal for all individuals.

Recently, research has begun to explore the indirect effects of how an individual with a genetic disorder may engender different reactions from the people in their surrounding environment (Hodapp, 1997). Indirect effects have been conceptualised by Scarr (1993) who described three types of environments; passive, active and evocative. Dykens and Hodapp, (cited in Bouras, 1999) refer in particular to the evocative genotype-phenotype interactions, which suggests that a person's genotype evokes particular environments and may also seek environments that reinforce their genotype. Dykens et al. (1995) applies this concept to children with Williams syndrome, who may show prominent smiles and well developed social and verbal skills. These skills are likely to elicit engaging and positive reactions from others, which then in turn serve to reinforce their sociability.

These issues have yet to be fully explored in Angelman syndrome as the earlier descriptions of the laughing and smiling behaviour were biased towards a neurological

deficit, with more recent reports acknowledging the environmental influence on the behaviour.

CONCLUSIONS

The aim of this review was to examine critically the notion of a behavioural phenotype for Angelman syndrome. It has been argued that whilst evidence for a behaviour phenotype has begun to emerge (Summers et al., 1995), it has mainly been based on case reports, with very few systematic measures. The methodological limitations of these studies have been examined, illustrating the need for further studies to incorporate more in-depth and qualitative aspects of behaviour alongside psychometric measures (Dykens, 1995).

Whilst working towards a behavioural phenotype of Angelman syndrome, it has been argued that there is a danger of attributing observed behaviours to internal or biological factors to the detriment of considering other influential environmental factors. Reported descriptions of the laughing and smiling behaviour in case reports of individuals with Angelman syndrome, illustrate the bias towards biological understandings of behaviour, although more recently environmental factors have begun to be considered. More studies are required to fully explore the role of the environment in the laughing and smiling behaviour of individuals with Angelman syndrome, particularly the indirect effects as this may have implications for skills teaching or managing more difficult behaviour.

The implications of such a bias is that it may lead to the behaviour being viewed inevitable and therefore reducing the therapeutic endeavour, anticipating and potentially contributing to its occurrence, and possibly of individuals becoming more stigmatised (O'Brien & Yule,

1995). Dykens et al. (2000) however, argue that behavioural phenotype research can lead to more fine grained, carefully targeted and effective interventions that can be applied to a wide range of settings. Importantly, it is also argued that if some behaviours are viewed as genetically determined, to some extent parent's guilt will be reduced (O'Brien & Yule, 1995; Hodapp, 1997).

To conclude, the concept of a behavioural phenotype has been criticised for its overemphasis on biological factors. However, Holland (1999) proposes that if more sophisticated models are adopted the strength of a behavioural phenotype approach is that it provides the foundation for exploring other influences in individuals who have a specific genotype. This move away from the simple nature/nurture dichotomy towards more sophisticated models may lead to further advances in understanding the characteristics associated with genetic disorders, and provide more sophisticated interventions.

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Authors (Year)	*Diagnosis*	*No of cases & age in years*	*Methodology*	*Behaviours*	
Angelman (1965)	Clinical	3 Age 5,6 & 9	Case Reports	Uncontrollable laughter Restless activity	3/3 1/3
Baraitser et al. (1987)	Clinical	7 Age 2-13	Case Reports	Feeding problems Hyperactivity Uncontrollable/spontaneous laughter	1/7 2/7 7/7
Baumer et al. (1999)	Clinical, [4]UBE3A	74	Case Reports	Characteristic laughter	62/74
Berg & Pakula (1972)	Clinical	1 Age 6	Case Report	Paroxysms of laughter Hyperactive	1/1 1/1
Bjerre et al. (1984)	Clinical	2 Age 11 & 75	Case Reports	Unfounded laughter Happy demeanour	***2/2*** 1/2
Botanni et al. (1994)	[2]UPD	2 Age 5 &10	Case Reports	Sleep disturbance Outburst of laughter Hyperactivity Love of water, mirrors Excessive appetite	1/2 2/2 2/2 1/2 1/2
Bower & Jeavons (1967)	Clinical	2 Age 7	Case Reports	Frequent laughter/smiling	2/2
Boyd et al. (1988)	Clinical	19 Age 1-13	Case Reports	Inappropriate laughter	19/19
Brockmann et al. (2002)	[3]IM	1 Age 3	Case Report	Happy demeanour	1/1
Buckley et al. (1998)	Clinical	11 Age 31-64	Case Reports	Excessive chewing & mouthing Attraction to water [b]Behavioural uniqueness Feeding problems (infancy) Sleep disturbance	9/11 2/11 11/11 4/11 4/11
Buntinx et al. (1995)	Clinical	47 Age 1-47	Case Reports	Bursts of laughter Happy disposition Hyperactivity/restlessness Feeding problems	31/47 44/47 46/47 38/47
Burke et al. (1996)	[1]D	1 Age 10	Case Report	Inappropriate happy affect Frequent laughter	1/1 1/1

Table 1. Reported behaviours in studies of Angelman syndrome

Casara et al. (1995)	Clinical	7 Age 2-10	Case Reports	Paroxysms of laughter	1/1
Clark & Marston (2000)	[1]D	73 Age 5-33	Questionnaire	Inappropriate laughter Sleep problems Fascination with water Fascination with plastics/rubber Eating problems Mouthing items Europhoria Self-injury	41/73 30/72 49/72 16/72 46/72 35/72 10 11
Clayton-Smith (1993)	Clinical	82 Age 1-26	Case Reports	Feeding problems (infancy) Frequent smiling Hand Flapping Sleep disorder	59/82 79/82 67/82 74/82
Clayton-Smith (2001)	[2]UPD, [3]IM, [4]Ube3a, [1]D	13 Age 16-40	[e]Case Reports	Happy sociable Anxiety Aggression Love of water	
Dooley et al. (1981)	Clinical	5 Age 7-17	Case Reports	Inappropriate laughter	5/5
Dorries et al. (1988)	Clinical	7 Age 4-9	Case Reports	Paroxysms of laughter Severe Restlessness	7/7 4/7
Elian (1975)	Clinical	2 Age 5 & 11	Case Reports	Paroxysmal/untriggered laughter	2/2
Fisher et al. (1987)	Clinical	5 Age 2-11	Case Reports	Prolonged outbursts of laughter Easily excited Hyperactive Disruptive behaviour	4/5 1/5 1/5 1/5
Fridman et al. (2000a)	[2]UPD	1	Case Report	Frequent laughter Fascination with water Happy disposition	1/1 1/1 1/1
Fridman et al. (2000b)	[2]UPD	2 Age 3-7	Case Report	Happy disposition Hyperactivity Outbursts of laughter Easily excitable personality Constant smile Sleep disturbance Love of water Love of mirror reflection	2/2 1/2 2/2 2/2 2/2 2/2 2/2 2/2
Fridman et al. (2003)	[1]D	1 Age 7	Case Report	Happy disposition Outbursts of laughter Hyperactivity	
Fryburg et al. (1991)	[1]D	4 Age 0.5-2	Case Reports	Inappropriate laughter Feeding difficulties (infancy)	4/4 4/4

Fung et al. (1998)	[4]UBE3A	2 Age 3 & 5	Case Reports	Characteristic laughter Flapping hands Happy disposition Disrupted sleep	1/2 2/2 2/2 2/2
Gyftodimou et al (1999)	[2]UPD	1 Age 6	Case Report	Frequent provoked laughter	1/1
Hersh et al. (1981)	Clinical	9 Age 1-7	Case Reports	Paroxysmal laughter Unfocussed behaviour Short attention span Aggressiveness	8/9 7/9 7/9 4/9
Hou et al. (1997)	[1]D & clinical	22 Age 0-15	Case Reports	[b]Behaviour uniqueness Sucking/swallowing disorders Fascination with water Hyperactivity Self destruction Sleep disorder	20/22 13/22 12/22 12/22 8/22 8/22
[a]Imaizumi et al. (1990)		2	Case Report	Paroxysms of laughter	2/2
Ishmael et al. (2002)	[1]D	1 Age 9	Case Report	Fascination with water Sleep disturbances	1/1 1/1
Kibel & Burness (1973)	Clinical	1 Age 6	Case Report	Paroxysms of laughter	1/1
Kuroki et al. (1980)	Clinical	2 Age 7 & 8	Case Reports	Paroxysms of laughter Restless	2/2 1/2
Laan et al. (1998)	Clinical, [1]D	40 Age 11-50	Case Reports	Paroxysms of laughter	36/40
Magenis et al. (1987)	Clinical	2 Age 5 & 10	Case Reports	Inappropriate laughing Inability to sit still Constantly smiling	2/2 2/2 2/2
Magenis et al. (1990)	[1]D	8 Age 0.4 – 33	Case Reports	Feeding problems Inappropriate laughter Sleep difficulties Tantrums Distractible behaviour Hyperactive behaviour	7/8 7/8 8/8 1/8 1/8 6/8
Mastroyianni & Kontopoulos (2002)	[1]D	1 Age 2	Case Report	Happy facial expression	1/1
Mayo et al. (1973)	Clinical	3 Age 2-5	Case Reports	Frequent laughter Smiling continuously Chewing objects	2/3 2/3 2

Moore & Jeavons (1972)	Clinical	2 Age 4 & 9	Case Reports	Vacant Laughter Restlessness Short attention span Chewing objects Feeding difficulties	1/2 1/2 1/2 1/2 1/2
Nicholls et al. (1992)	[2]UPD	1 Age 2	Case Report	Happy disposition	1/1
Oliver et al. (2002)	[1]D	3 Age 7-17	Observations	Contingent Laughing and smiling	3/3
Poyatos et al. (2002)	[2]UPD	2 Age 3 & 9	Case Reports	Hyperactivity Easily excitable personality Happy disposition Hand Flapping Disrupted sleep Fascination with water Smiling demeanour Laughter attacks Masticating movements	2/2 1/2 2/2 1/2 1/2 1/2 1/2 1/2 1/2
Prasad & Wagstaff (1997)	[2]UPD	1 Age 10	Case Report	Short attention span	1/1
Reish & King (1995)	[1]D	1 Age 40	Case Report	Frequent bursts of laughter	
Rubin et al. (1997)	[1]D	3 Age 1 - 3	Case Reports	Happy appearing child	3/3
Saitoh et al. (1999)	[3]IM, [4]Ube3a, clinical	14	Case Reports	[b]Behaviour uniqueness Feeding problem	14/14 2/14
Sandanam et al. (1997)	[1]D	11 Age 24-36	Case Reports	Happy demeanour Frequent outbursts of laughter Aggressive episodes Sleep problems	11/11 3/11 3/11 6/11
Smith et al. (1996)	[1]D	27 Age 3-34	Case Reports	Paroxysmal laughter Happy disposition Sleeping problems Feeding problems	21/23 21/22 18/21 20/26
Smith et al. (1997)	[2]UPD	4 Age 7-11	Case Reports	Happy disposition Hyperactive behaviour Inappropriate laughter Drooling and mouthing	4/4 4/4 4/4 4/4
Smith et al. (1998)	[2]UPD	2 Age 4 & 30	Case Reports	Frequent laughter Happy disposition	2/2 2/2

Steffenburg et al. (1996)	Clinical & [1]D	4 Age 10 - 16	Case Reports	Feeding difficulties (infancy) Hyperactive Destructive Aggressive Excessive mouthing/chewing Sleep difficulties Inappropriate laughter Always smiling Stereotypical behaviour Throws tantrums Sleep difficulties Attraction to water	3/4 2/4 1/4 2/4 4/4 1/4 3/4 1/4 2/4 1/4 4/4 1/4
Summers et al. (1995)	[5]G & clinical	108 Age 1-33	Case Reports	Laughter Hyperactivity/restlessness Feeding problems (infants) Attention deficits Aggression Repetitive/stereotyped beh Chewing/mouthing objects Sleep problems Tantrums Non-compliance	90/108 27/108 25/108 13/108 11/108 10/108 10/108 7/108 3/108 2/108
		11 Age 1 - 12	Questionnaire	laughter as a concern Hyperactivity Short attention span Aggression Over/under eating Mouthing items Sleep problems Tantrums Non compliance Repetitive/stereotyped beh	11/11 11/11 11/11 11/11 5/11 11/11 10/11 5/11 9/11 8/11
Summers & Felman (1999)	[5]G & clinical	27 Age 2-25	[c]Questionnaire	Irritability Lethargy Stereotypy Hyperactivity Temper tantrums	
Tekin et al. (2000)	[1]D	1 Age 2	Case Report	Apparent happy demeanour Frequent laughter/smiling Sleep disturbance	1/1 1/1 1/1
Thompson & Bolton (2003)	[2]UPD	1 Age 15	Case Report	Severe agitation/aggression Overeating Short attention span Physically active Happy demeanour Frequent laughter	1/1 1/1 1/1 1/1 1/1 1/1
Tonk et al. (1996)	[2]UPD	1 Age 2	Case Report	Hand flapping Hyperactivity	1/1 1/1

Trent et al. (1997)	[4]Ube3a	1 Age 5	Case Report	Behaviour uniqueness Attraction to water Sleep disturbance	1/1 1/1 1/1
Van Lierde et al (1990)	[1]D	1 Age 2	Case Report	Feeding problems Smiled easily	1/1 1/1
Walz & Benson (2000)	Unknown	68 Mean age 10	[d]Questionnaire	Cheerful/happy behaviour Eating inedible items Attention problems Hyperactivity	
Willems et al. (1987)	Clinical	2 Age 3 & 9	Case Reports	Happy disposition Paroxysms of laughter Short attention span	2/2 1/2 1/2
Williams et al. (1989a)	[1]D	6 Age 3-31	Case Reports	Frequent laughter/smiling Hyperactive Chewing hands	4/6 1/6 1/6
Williams et al. (1989b)	[1]D	1 Age 4	Case Report	Frequent laughter/smiling	1/1
Williams & Frias (1982)	[1]D & Clinical	6 Age 23-39	Case Reports	Paroxysms of laughter Temper tantrums Hyperactive Chewing objects Aggressive behaviour	3/6 1/6 2/6 1/6 2/6
Yamada & Volp (1990)	[1]D	1	Case Report	Paroxysmal laughter	1/1
Zori et al. (1992)	[1]D & Clinical	66	Questionnaire & Lit review	Inappropriate laughter Sleeping difficulties Eating problems Overeating Hyperactivity Stubbornness Aggressive behaviour	46/66 38/66 42/66 2/66 42/66 11/66 7/66

[a]Clinical findings, cytogenic and molecular Reports reported by Laan et al. (1998)
[b]Behavioural uniqueness includes: frequent bursts of laughter/smiling, easily excitable personality, often hand flapping
[c]Behaviours rated significantly lower than groups of participants with developmental disabilities of mixed etiology
[d]Behaviours rated higher than groups of participants with Down syndrome, Prader-Willi syndrome and non-specific intellectual disability
[e]Behaviours reported, but figures for each participant not available

[1]D = Deletion of chromosome 15q11-13
[2]UPD = Uniparental disomy for chromosome 15
[3]IM = Imprinting defect
[4]UBE3A = Mutations within gene encoding ubiquitin protein ligase UBE3A
[5]G = Genetic analysis performed but unable to determine specific test or classification

Authors (Year)	No of cases & age in years	Methodology	Descriptions of Laughing and Smiling
Angelman (1965)	3 Age 5,6 & 9	Case Reports	Uncontrollable, easily provoked and prolonged paroxysms of laughter. Was often in an almost convulsive state of laughter. Laughter often preceded and followed the fit and spike and wave forms were present during the period of laughter.
Baraitser et al. (1987)	6 Age 3-10	Case Reports	Bursts of uncontrollable, inappropriate and spontaneous laughter during voluntary actions. Happy and laughing inappropriately when not disturbed.
Berg & Pakula (1972)	1 Age 6	Case Report	Paroxysms of Laughter, outbursts of spontaneous laughter, for no apparent reason. Prone to paroxysms of apparently causeless laughter.
Bjerre et al. (1984)	2 Age 11 & 75	Case Reports	He is characteristically docile and of happy demeanour, singing most of the time. Easily provoked often spontaneous paroxysmal laughter, causeless laughter. Unfounded, periods of laughter were not connected with periods of epileptogenic activity.
Bower & Jeavons (1967)	2 Age 7	Case Reports	She laughed for no reason and periods of causeless laughter have been a prominent feature. Could not talk but laughed and chuckled to an unusual degree. Appears happy because of continuous smile and frequent laughing and giggling.
Brockmann et al (2002)	1 Age 3	Case Report	Exceptionally happy demeanour and frequent laughter.
Buckley et al (1998)	11 Age 31-64	Case Reports	Happy disposition with occasional bursts of laughter. Two of the eleven had been diagnosed with bipolar disorder because their happy disposition and bursts of laughter were seen as manic behaviour.
Buntinx et al. (1995)	47 Age 1-47	Case Reports	Burst of laughter were noted at an early age. In some of them this only occurred in certain situations: after convulsions, during the days of menstruation or if they were brought to a new situation.

Table 2. Descriptions of laughing and smiling in reported cases of Angelman syndrome

Clayton-Smith (1992)	-	Annotation	These children have a happy, sociable affect and laugh frequently, and sometimes inappropriately, for example on venepuncture. The laughter is not uncontrollable, however, and is always provoked, even though the stimulus may be minimal. It is not related to electrical activity within the brain as in gelastic epilepsy.
Clayton-Smith (1993)	82 Age 1-26	Case Reports	Almost all patients were happy, with frequent smiling. Their laughter, although never unprovoked, was caused by minimal stimuli and was occasionally inappropriate. The children find "slap-stick" humour particularly funny but do not, on the whole, enjoy cartoons. Smiling commenced at 4-6 weeks and usually very frequent, often not in response to social overtones.
Clayton-Smith (2003)	-	Review	Paroxysms of easily provoked laughter begin within the first few weeks of life and almost all patients are happy and smile frequently. Laughter is usually provoked, but the stimulus is often minimal and the laughter can be inappropriate.
Dooley et al. (1981)	5 Age 7-17	Case Reports	Bouts of inappropriate laughter to the immediate circumstances were often dramatic, they occurred spontaneously and sometimes even in uncomfortable circumstances like venipuncture. Such episodes are presumably the basis of the use of the term 'happy' in 'happy puppet' syndrome, though whether these children are happy in the traditional sense of the word is questionable.
Elian (1975)	2 Age 5 & 11	Case Reports	Developmentally inappropriate laughter, fails to have clear environmental antecedents. They would suddenly burst into loud laughter for several minutes without apparent reason. "It is a nice, natural health laughter, resembling the laughter of a more mature child. But I am afraid that this laughter makes me uneasy". The laughter though paroxysmal, could by no means be classified as an ictal sign in any of the children. Although one could speculate that it might be a mode of communication replacing speech, the onset of the paroxysmal in the first case at the age of five months would argue against this hypothesis.
Fisher et al. (1987)	5 Age 2-11	Case Reports	Prolonged outburst of laughter.
Fridman et al. (2003)	1 Age 7	Case Report	Happy disposition and constant smile or outburst of laughter that sometimes looked inappropriate.

Fryburg et al. (1991)	4 Age 0 & 2	Case Reports	Smiling was described as unprovoked, inappropriate and prolonged.
Fung et al. (1998)	2 Age 3 –5	Case Reports	Inappropriate laughing.
Hersh et al. (1981)	9 Age 1-7	Case Reports	Seizure discharge did not correlate with episodic laughter. Although we cannot rule out the possibility that the children's laughter originates from pathological substrates.
Kibel & Burness (1973)	1 Age 6	Case Report	Paroxysms of laughter on any social contact, pleasant or unpleasant. Even the taking of blood would induce gales of giggles.
Kuroki et al. (1980)	2 Age 7 & 8	Case Reports	Easily provoked and prolonged paroxysms of laughter.
Magenis et al. (1987)	2 Age 5 & 10	Case Reports	Laughed inappropriately when not disturbed. Parents were concerned about behaviour episodes during which there was prolonged laughter up to half an hour in duration followed by vomiting. Constant smiling expression.
Mayo et al. (1973)	2 Age 2-5	Case Reports	Frequent outbursts of giggling and laughing, without provocation.
Moore & Jeavons (1972)	2 Age 4& 9	Case Reports	Vacant laughter.
Oliver et al. (2002)	3 Age 7-17	Observations	Laughing and smiling increased during social situations and occurred at low levels during non-social situation. The behaviours did not occur totally inappropriately as has been suggested.
Smith et al. (1997)	4 Age 7-11	Case Reports	Outburst of inappropriate laughter.

Summers et al. (1995)	108 Age 1-33	Questionnaire	Laughter may be considered a pathognomonic (a sign or symptom that is so characteristic of a disease that it makes the diagnosis) sign because of its low threshold for occurrence, the relative frequency of outburst or episodes and their apparent dissociation from contextual events.
Tekin et al. (2000)	1 Age 2	Case Report	Notes to be always in a happy mood with frequent smiling.
Van Lierde et al. (1990)	1 Age 2	Case Report	Smiled easily, but did not smile in response to social overtures. Did not yet have outburst of unprovoked laughter typical of the syndrome.
Willems et al. (1987)	2 Age 3-9	Case Reports	Easily provoked or unprovoked paroxysms of laughter and frequent smiling. Nearly always smiling.
Williams et al. (1995)	-	Diagnostic criteria	Behaviour uniqueness, any combination of frequent laughter and smiling, apparent happy demeanour.
Williams & Frias (1982)	6 Age 23-39	Case Reports	Grinned inappropriately. The paroxysms of laughter have not been consistently associated with electroencephalyographic evidence of seizure activity. Consequently they do not fit the common description of gelastic epilepsy. Laughter in these patients seems to be a global expressive outlet independent of happy or sad environments. This absence of any emotional association with the laughter suggests an abnormality at the brain stem level. As such, this laughter might be considered a 'forced' laughter that is primarily a motor phenomenon. Clinicians caring for patients with this condition should be aware that these laughing individuals may not necessarily by happy.
Yamada & Volp (1990)	1	Case Report	Smiling and laughing on face to face contact.
Zori et al.	66	Questionnaire Literature review	By their first birthday, most infants were notable for their cheeriness and frequent and persistent (1992) outbursts of laughter (generally inappropriate for the situation).