domain responsible for binding to the APC protein.[7–12] Most frequently affected codons were localised in exon 3 (33, 44, and 45). Therefore, we additionally analysed exon 3 by direct DNA sequencing using the same primers as for SSCP, the Thermosequenase labelled primer cycle sequencing kit (Amersham), and an automated DNA sequencer (LI-COR) without identifying any changes in the nucleotide sequence.

As there were no differences detected in the coding region, β-catenin gene expression in patients' lymphocytes was examined using reverse transcription PCR. PCR amplification of cDNA was performed in two separate PCR reactions using PCR primer pairs 3.1/6.2 and 6.1/13.2, as listed in table 2. This showed that in all persons tested the expected β-catenin transcript was present and of expected size, suggesting that differential splicing did not occur. However, as our experiments regarding β-catenin expression were performed on lymphocytes, differential expression in colonic or other tissues affected in FAP, which were not available for our study, cannot be excluded.

Taken together, using a combination of several techniques for the mutational analysis, in our group of 14 FAP APC negative families, no hereditary alterations were identified in the β-catenin coding sequence or gene expression, suggesting that β-catenin germline mutations do not account for APC negative FAP cases. Even though these results need confirmation in a larger sample of APC negative FAP families, they indicate that β-catenin might play a different role in the pathogenesis of hereditary colon carcinoma compared to sporadic colorectal cancer.

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Simpson-Golabi-Behmel syndrome and attention deficit hyperactivity disorder in two brothers

EDITOR—Simpson-Golabi-Behmel syndrome (SGBS, MIM 312870) is an X linked condition characterised by pre- and postnatal overgrowth, coarse facial appearance, large mouth, predisposition to embryonic neoplasia,[1] and a variety of visceral and skeletal abnormalities. Psychomotor development in the syndrome is extremely variable, ranging from normal intelligence,[2] to moderate impairment, to severe impairment evident from birth.[3 4] We report the cases of two male sibs with normal psychomotor development, diagnosed at 6 and 7 years of age with SGBS, who manifest significant behavioural disturbances consistent with a diagnosis of attention deficit hyperactivity disorder (ADHD). This is the first report of an association between SGBS and a specific behavioural phenotype (ADHD).

Case 1, the older of the two boys, was the first born to non-consanguineous, healthy, white parents. The pregnancy was complicated at 36 weeks by polyhydramnios and pregnancy induced hypertension. An ultrasound performed at this time discovered a left sided diaphragmatic hernia. No other fetal abnormalities were reported. Labour was induced at 39 weeks and the child was delivered by forceps assisted vaginal delivery. Birth weight was 4400 g (well above the 97th centile) and immediate transfer for stabilisation and surgical repair of the diaphragmatic hernia was undertaken. Other birth indices were not recorded. The primary surgical repair was successful but was complicated by a left pneumothorax on day 4 of life. This complication was successfully managed and the subsequent postsurgical course was uneventful. The child was discharged from hospital aged 14 days.

At 5 months bilateral inguinal hernias were noted and surgically repaired. From 6 months onwards the child was noted to be extremely unsettled, seldom sleeping for more than two hours at a time. From 10 months onwards he began to wake screaming several times a night. His behaviour became increasingly unpredictable and aggressive over the next year, with high levels of activity and very poor attention span reported. He was assessed at 3 years 11 months by a mutidisciplinary team consisting of a paediatrician, speech pathologist, clinical psychologist, child psychiatric nurse, and occupational therapist. The McCarthy Scales of Children's Abilities was administered and he performed at a 4 year old level on the verbal (score 46, mean score for age 50, SD 10), perceptual performance (score 50), and quantitative (score 53) scales and at a 3.5 year old level on the memory scale (score 44). The general cognitive index was age appropriate (score 96, mean for age 100, SD 16) and his overall cognitive age was placed at 4 years ± 6 months. He also showed relative strengths in conceptual grouping tests (performed at the 6.5 year old level), counting and sorting (6 year old level), and opposite analogies (5.5 year old level). These data indicated sound verbal concept formation skills, arithmetic ability, and a sound capacity for abstraction. Areas of greatest difficulty were in Verbal Memory tests I and II where he performed at the 3.5 year old level. Short term memory and attention span were noted to be extremely poor in relation to other abilities documented above. On Word Knowledge tests I and II he performed at the 3 year old level and he was noted to dis-

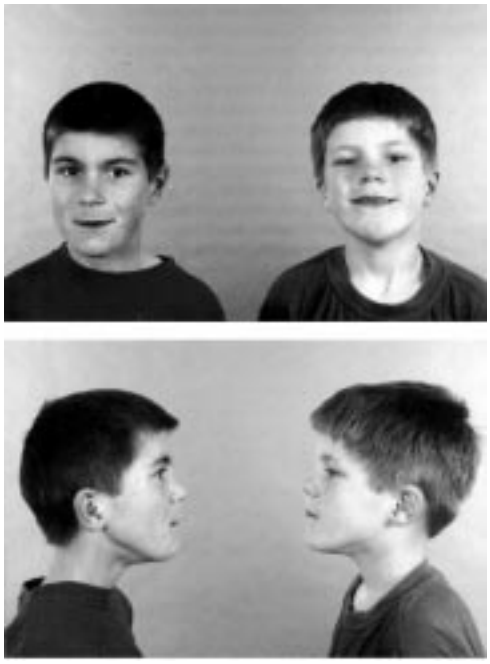

Figure 1 The patients (front and lateral views). Note short noses, macrostomia, and prominent jaws (left case 1, right case 2). (Photographs reproduced with permission.)

play difficulties systematising complex information for purposes of recall owing to attention and concentration deficits. The overall conclusions based on these sets of tests were that performance was at an age appropriate level (or above) on all cognitive tasks. Auditory and verbal memory testing suggested poor short term memory related to marked motor restlessness, short attention span, and concentration. The Vineland Social Maturity Scale was also administered and he scored at the 3 year 9 month level (at a chronological age of 3 years 11 months). Testing was again noted to be compromised by short attention span and "ceaseless" motor activity.

He was noted by all examiners to exhibit poor impulse control and short attention span. Given the results of the above tests and his overall behavioural profile, the diagnosis of ADHD was made according to standard diagnostic criteria.[5] He was started on methylphenidate (5 mg morning and midday) and clonidine (150 μg at night) with minimal improvement in his behaviour.

At 7 years there were continuing concerns about deteriorating behaviour. These included violent temper tantrums, hyperactivity, and reckless behaviour, such as lying prone in the middle of a street and waiting for cars to approach before rolling away. He was referred to a paediatrician at this time, who noted macrosomia and dysmorphic features. Based on these findings a karyotype and urine metabolic profile (including amino acids, organic acids, and mucopolysaccharides) were performed and no abnormalities were detected. He was referred (with his brother) for possible syndrome evaluation. On examination, height was 134 cm (>97th centile), weight 33 kg (>97th centile), and head circumference 55 cm (>98th centile). Dysmorphic features were noted and comprised macrocephaly, coarse facies, hypertelorism, broad nasal bridge with short nose, macrostomia, prominent jaw (fig 1), pectus excavatum chest deformity, one supernumerary, right sided nipple, short fingers with broad thumbs (fig 2), and short, broad toes. Scars indicating the site of previous diaphragmatic and inguinal hernia repairs were present.

The dose of methylphenidate was increased to 10 mg morning and midday shortly after this consultation with

Figure 2 The patients' hands. Note short fingers and short broad thumbs.

marked improvement in overall behaviour and concentration over the next month.

Case 2, the second child of these parents, was born by emergency caesarean section at 39 weeks because of a prolapsed cord after an uneventful pregnancy. Birth weight was 5100 g (well above the 97th centile). Birth length and head circumference were not documented. The baby was noted to have macroglossia on neonatal examination. Karyotype was performed and was normal male. There were no neonatal complications. He had recurrent chest and ear, nose, and throat infections in the first 11 months of life. At 16 months he was referred for genetic opinion and the diagnosis of Beckwith-Wiedemann syndrome (BWS) was proposed and 3 monthly abdominal ultrasound surveillance instituted. At 2 years a tongue reduction was performed. Owing to ongoing recurrent ear infections and night time snoring he was reviewed by an ear, nose, and throat specialist. A submucous cleft palate was discovered and he underwent adenotonsillectomy and insertion of tympanostomy tubes. The submucous cleft was managed conservatively as his speech development was normal. At 5 years, a single renal cyst was found on surveillance ultrasound. His behaviour and sleep patterns (from infancy) were strikingly similar to those described in his brother and a similar developmental assessment documented age appropriate functioning in all areas apart from attention, sequencing tasks, and behaviour. He also fulfilled the criteria for diagnosis of ADHD.[5] He was started on the same medications (and dosage) as his sib with a similarly poor response. He was referred (with his brother) for review aged 6 years. Growth parameters were height 128 cm (>97th centile), head circumference 55 cm (>98th centile), and weight 30 kg (>97th centile). He shared similar dysmorphic features with his brother comprising coarse facial features, hypertelorism, broad nasal bridge, short nose, macrostomia, prominent jaw (fig 1), two right sided supernumerary nipples, a pectus excavatum chest deformity, and short fingers with broad, short thumbs (fig 2). Urine mucopolysaccharide screen was normal. His behaviour and attention span also markedly improved in response to an increased dosage of methlyphenidate (10 mg, twice daily).

The boys had a sister, aged 4 years, who had no medical or behavioural problems nor any abnormalities on examination. The boys' mother was also normal on physical examination and the family history was unremarkable.

Simpson-Golabi-Behmel syndrome is an X linked overgrowth syndrome first reported by Simpson *et al*[2] in two male cousins from an Ashkenazi Jewish kindred. Both of these males had normal developmental milestones and normal intelligence. Nine years later, Golabi and Rosen[4] reported four males with a "new X-linked mental retardation-overgrowth syndrome". The proband in this kindred had "moderate" mental retardation at 8 years and another male was developmentally delayed at 4 months of age. The other two males died in the newborn period and

no comment was made on their development. Opitz[6] coined the term "Golabi-Rosen" syndrome and added the reports of a further three males with similar features, but no prominent overgrowth. Shortly after this, Behmel *et al*[7] reported a five generation family with 13 affected males with features of X linked overgrowth and pointed out the similarities between these cases and the patients described initially by Simpson *et al.*[2] Neri *et al*[8] highlighted the similarities between the above authors' reports and proposed the designation "Simpson-Golabi-Behmel" syndrome to encompass this clinical entity. To date, at least 40 patients have been reported with the syndrome[1 3 9–12] and mutations in GPC3, a glypican gene, have recently been found to cause the condition. GPC3 is an extracellular proteoglycan and is inferred to play a major role in growth control of mesodermal tissues, possibly by modulating the actions of insulin-like growth factor 2.[13]

The two patients reported here both displayed marked neonatal macrosomia and the typical facial features of SGBS. The additional clinical findings of short, broad hands, pectus excavatum chest deformities, and supernumerary nipples, present in both boys, adds further credibility to the diagnosis. The congenital diaphragmatic hernia, reported in case 1, has been previously described in association with SGBS[11] and the inguinal hernias (case 1) are a well established feature of the condition.[9] Similarly, the macroglossia, submucous cleft palate, and single renal cyst, reported in case 2, are all features consistent with the diagnosis of SGBS.[9] The main differential diagnostic consideration in these children was Beckwith-Wiedemann syndrome, given the prenatal macrosomia and macrostomia seen in both boys and macroglossia, seen in case 2. This boy was initially considered to have BWS and the clinical overlap between SGBS and BWS is highlighted by similar examples of diagnostic confusion in published reports.[9] The particular constellation of clinical features in these two male sibs in addition to the presence of supernumerary nipples (a feature not reported in patients with BWS) clearly differentiate them as having SGBS. Another diagnostic possibility, given the coarse facies and behavioural problems present in these cases, was a mucopolysaccharide storage disorder. This diagnosis was excluded in both boys by appropriate urine testing.

Our two cases are distinct from all previously reported cases with SGBS because of their striking behavioural disturbances, not present in their unaffected 4 year old sister. There is relatively little mention of the behavioural phenotype in the published cases of SGBS. In the initial report by Simpson *et al*,[2] one of their cases (case 1, DG) was evaluated psychologically at 30 months of age and reported to have an "attention span of short duration". In the report of Behmel *et al*,[14] passing comment is made of the "severe emotional and behavioural troubles during adolescence" in one of their patients (II.3 in family 2) and "behavioural difficulties during school attendance" (that necessitated psychological treatment) in his nephew. These comments are not further elaborated and comprise the few references to behavioural phenotype in SGBS.

This is the first report of a specific behavioural pattern (ADHD) in patients with SGBS. It raises the question of whether other patients with SGBS are at risk of developing this (or other) neurobehavioural problems. The well recognised neurobehavioural patterns seen in patients with Prader-Willi[15] and velocardiofacial syndromes[16] serve as examples of other multisystemic disorders with clinically significant associated behavioural profiles. If SGBS is associated with a predisposition to specific behavioural disturbances, as indicated by the two cases reported here, it is important that the parents and clinicians who care for these children are aware of this. This knowledge will then allow the opportunity for anticipatory guidance to be provided for these families and for intervention and treatment strategies to be put in place.

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Presence of a deletion in the 5' upstream region of the GALT gene in Duarte (D2) alleles

EDITOR—Galactosaemia is an autosomal recessively inherited metabolic disorder caused by a defect in the galactose-1-phosphate uridyltransferase (GALT) enzyme. Absence or severe reduction of GALT activity results in classical galactosaemia (G/G) while an approximately half reduction of enzyme activity leads to the Duarte variant of galactosaemia (D/D). Mutation Q188R was found to be the most common molecular defect among classical galactosaemia patients,[1] whereas N314D was predominantly detected in Duarte galactosaemia patients.[2] In recent studies, the Duarte (D2) allele with 50% of normal GALT activity and the Los Angeles (D1) allele with 110-130% of normal GALT activity were characterised as having