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Short-chain acyl-CoA dehydrogenase (SCAD) deficiency: An examination of the medical and neurodevelopmental characteristics of 14 cases identified through newborn screening or clinical symptoms

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Abstract

The medical and neurodevelopmental characteristics of 14 children with short-chain acyl-CoA dehydrogenase deficiency (SCADD) are described. Eight were detected as neonates by newborn screening. Three children diagnosed on the basis of clinical symptoms had normal newborn screening results while 3 were born in states that did not screen for SCADD. Treatment included frequent feedings and a low fat diet. All children identified by newborn screening demonstrated medical and neuropsychological development within the normative range on follow-up, although one child had a relative weakness in the motor area and another child exhibited mild speech delay. Of the 3 clinically identified children with newborn screening results below the cut-off value, 2 were healthy and performed within the normal range on cognitive and motor tests at follow-up. Four clinically identified children with SCADD experienced persistent symptoms and/or developmental delay. However, in each of these cases, there were supplementary or alternative explanations for medical and neuropsychological deficits. Results indicated no genotype-phenotype correlations. These findings suggest that SCADD might be benign and the clinical symptoms ascribed to SCADD reflective of ascertainment bias or that early identification and treatment prevented complications that may have occurred due to interaction between genetic susceptibility and other genetic factors or environmental stressors.

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Keywords

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Short-chain acyl-CoA dehydrogenase deficiency (ec 1.3.99.2) [1], catalyzes the first step in mitochondrial short-chain fatty acid oxidation. Its deficiency (SCADD; OMIM #201470) is an autosomal recessive condition that was originally described in two neonates who presented with metabolic acidosis and excretion of ethylmalonic acid. One of the babies recovered and demonstrated normal growth and development. The other baby became profoundly ill and died on day five of life [2]. Confusion about the SCADD clinical phenotype has persisted to this day. In addition, the frequency of SCADD is unknown, but results from newborn screening suggest frequencies varying between 1:33,000, using a cut-off for butyrylcarnitine (C4) of 1.9 μmol/L, [3] and 1:340,000 (cut-off not available) [4].

The neonatal features of SCADD reported in clinically ascertained infants have included a broad range of symptoms, such as feeding difficulties [2], hypotonia [5], lethargy [6], hypoglycemia [7, 8, 9, 10], dysmorphic features [7, 9], brain malformations with infantile spasms [11] and death [12]. During later infancy and childhood, reported features have included failure to thrive [5, 13], developmental delay [7, 10, 13], seizures [7, 8, 10, 14, 15], hepatomegaly and jaundice [16], and optic atrophy [17]. The biochemical hallmarks are elevated levels of butyrylcarnitine (C4) as detected by acylcarnitine analysis and urinary excretion of ethylmalonic acid (EMA) [18]. Newborn screening using tandem mass spectrometry (MS/MS) has led to the identification of many newborns with the biochemical phenotype of SCADD and with genotypes affecting SCAD activity. However, in contrast to infants who have come to attention clinically, these infants have been largely asymptomatic in the newborn period [19]. In an unpublished survey by one of the authors (HLL), 16 metabolic centers reported on 44 cases of SCADD identified in newborn screening. Symptoms, including recurrent episodes of transient hypotonia and mild hypoglycemia, were noted in only 5 cases. Follow-up of 12 newborn screened patients ranging from several weeks to 4 years revealed only one child with speech delay, and that child had a strong family history for speech delay [20]. Five other newborn screened cases have been reported, of whom 4 were symptomatic, including low IQ [7], seizures and hypoglycemia [8, 9]. Varying experiences such as these have led to considerable debate on the clinical significance of the disorder [10, 21, 22].

We studied 14 cases of SCADD, diagnosed since the introduction of acylcarnitine analysis by MS/MS into the newborn screening program in Massachusetts in February, 1999. Eight of these cases were detected by newborn screening. Subjects were enrolled 6 or more months after their diagnosis was confirmed and examined prospectively. We are reporting the medical and neurodevelopmental status as well as the biochemical and molecular characteristics in these 14 children.

METHODS

Newborn screened children were detected on the basis of elevated butyrylcarnitine (C4) levels of 1.06 μmol/L or greater by acylcarnitine analysis [3]. The diagnosis was confirmed by the finding of elevated plasma butyrylcarnitine and increased excretion of ethylmalonic acid (EMA) and methylsuccinic acid in urine [23]. Additional confirmatory procedures included fibroblast metabolic probing studies [24] and molecular genetic analysis of the SCAD gene [7]…

The patients were followed in the Metabolic Clinic at Children's Hospital, Boston and included in a study to assess expanded newborn screening [25]. Written informed consent was obtained at the time of enrollment in accordance with human studies approval. The children were evaluated at approximately 6 months after diagnosis (Time 1) and then 1 year later (Time 2).

Medical records were obtained from the metabolic center and primary health care providers as well as from any hospitals/centers where care was provided (e.g., birth hospitals, emergency rooms, laboratories). Infants and children received a medical examination with particular attention to medical complications related to the disorder. The Bayley Scales of Infant Development- 2nd Edition [26] or the Stanford-Binet Intelligence Scale, 4th Edition [27] were used to measure the child's cognitive functioning. The Bayley Mental and Motor Scales were administered through age 3 years, and thereafter, the Stanford-Binet was used. Performance on the Bayley was characterized by the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) (mean = 100; standard deviation = 15). Overall performance on the Stanford Binet was characterized by the Test Composite (mean = 100, standard deviation = 15). The Vineland Adaptive Behavior Scale (VABS) was administered to parents to measure child adaptation in various domains (communication, daily living, social, and motor skills) and to obtain an Adaptive Behavior Composite score (mean = 100, standard deviation = 15) [28].

RESULTS

Medical findings in the newborn screened group (Table 1)—Eight children (7 females, 1 male) were diagnosed with SCADD by newborn screening.

Three of these children experienced prenatal or neonatal complications (cases 1, 4, 6) including one instance each of intrauterine growth retardation (IUGR), pre-term birth and ABO incompatibility. Three children (cases 1, 3, 5) were delivered via cesarean section due to minor fetal distress or breech presentation. There were maternal complications in three cases (cases 1, 3, 4), including one instance each of pre-eclampsia, maternal hypertension and maternal bradycardia.

Children in the newborn screened group were identified shortly after birth and the diagnosis was confirmed between 5 and 27 days, except for one child for whom DNA confirmation was delayed until age 9 months. All children began medical monitoring once they were identified with an abnormal newborn screening result. Three children in the newborn

screened group had no clinical symptoms and three children (cases 1, 4, 7) had mild nonspecific clinical symptoms during the first few days and weeks after birth, including recurrent vomiting, recurrent diarrhea, hypoglycemia (with poor feeding and requiring a glucose drip until age 2 days) and hypotonia. Two additional children (cases 5 and 6) were noted to have jaundice and vomiting. Medical notes indicated that parents of three children were advised to feed the children a low fat diet (30% of calories from fat) and all children were to have frequent feedings and glucose levels monitored, especially during illnesses. None were found to be carnitine deficient and therefore, none were treated with carnitine supplements. Riboflavin supplements were not prescribed. One child had been hospitalized twice (case 8), in accordance with the SCADD emergency protocol (http://www.childrenshospital.org/newenglandconsortium/NBS/SCADD.html; last accessed 5/19/2008), for gastroenteritis and dehydration at eight months and for emesis at 9 months of age.

Medical findings in the clinically identified group (Table 1)—Six children (1 female, 5 males) were diagnosed as a result of laboratory work-up prompted by their clinical presentation. All these children experienced fetal or delivery complications, including two with premature births (cases 12, 14), and one child each with bradycardia (case 10), jaundice (case 11), perinatal asphyxia (case 13) and mild respiratory distress syndrome (case 14). Two children were delivered via cesarean section (cases 9, 14). Of the six mothers, two experienced complications during pregnancy, including pre-eclampsia (case 11) and HELLP Syndrome (hemolysis, elevated liver enzyme levels and low platelet count) (case 12). There were two cases of fertility-assisted pregnancies (cases 9, 14).

Children in the clinically identified group were diagnosed between 7 and 61 months. The significant clinical problems included, developmental delay, hypotonia, failure to thrive, seizures and feeding problems. Hypoglycemia was reported in medical records in 3 cases (with recorded levels hovering around the control range of < 2.6 mmol/L). Case 9 had blood glucose levels of 3.0 and 3.5 mmol/L within the first two weeks of life when he was feeding poorly, but was not noted to be hypoglycemic since the neonatal period. Case 11 had recurrent glucose levels around 2.2 mmol/L, accompanied by fever. His symptom was lethargy. Case 12, had recurrent hypoglycemia reported when he had a urinary tract infection or was otherwise sick. His symptoms were fatigue and recurrent morning lethargy. His recorded glucose levels were 2.8, 3.0, and 3.3 mmol/L, with “recurrent hypoglycemia” annotated by the physician.

From this group, all had been hospitalized at least once prior to diagnosis (range 1–6 times). In addition to a low fat diet, frequent feedings and glucose monitoring, four of the most seriously delayed children in this group were treated with carnitine supplements, in hopes that the treatment might be therapeutic, despite normal carnitine levels (cases 10, 12, 13, 14). One child (case 13) was also given riboflavin.

Laboratory findings in the newborn screened group (Table 2)

C4 levels measured at newborn screening ranged from 2.0 μmol/L to 5.16 μmol/L. Confirmatory testing revealed that all children in this group had increased levels of urinary

ethylmalonic acid (> 20.2 μg/mg creatinine). Three children (cases 2, 3, 4) identified through newborn screening are homozygous for inactivating mutations in the SCAD gene (ACADS; OMIM 606885); cases 2 and 4 for the 319C>T mutation and case 3 for the 529T>C mutation. Two other cases (cases 1, 5) are doubly heterozygous for these mutations and the 625G>A variant. Other SCAD mutations in this group included 505A>C, 319C>T, 988C>T, 991G>A, and 529T>C.

Laboratory findings in the clinically identified group (Table 2)—Of the six clinically identified children, three were reported to have newborn screening results below cut-off (as noted in the medical records for cases 9, 11, 14) and three were born in states where MS/MS based acylcarnitine analysis was not part of newborn screening at the time of their births. At the time of diagnosis or follow-up, C4 levels ranged from 0.35 μmol/L (within the control range) to 5.11 μmol/L, and all but one child in this group (case 11) had increased levels of urinary ethylmalonic acid (> 20.2 μg/mg creatinine). All clinically identified patients had at least one copy of the 625G>A variation and five of these children were homozygous for this variant. Two children had one copy of the 511C>T variant (cases 11, 12).

Neurodevelopmental findings in the newborn screened group (Table 3)—In the newborn screened group, children were evaluated between the ages of 5 and 29 months. All of the eight children in the newborn screened group obtained scores within the average range on the Vineland Adaptive Behavior Scale (Time 1: mean = 110 ± 13, range 85–119, Time 2: mean = 98 ± 8, range 87–109). At the time of the first evaluation, all but case 1 performed within the average or accelerated range for their age on both indices of the Bayley Scales of Infant Development-2nd Edition. At the time of the second evaluation, all children received scores within the average range. On the cognitive scale, the mean MDI was 108 ± 18 (range 88 – 145) for Time 1 and 105 ± 6 (range 96 – 112) for Time 2. On the performance scale, the mean PDI was 92 ± 21 (range 59 – 117) for Time 1 and 105 ± 14 (range 87 – 121) for Time 2. In the newborn screened group, four children (cases 1, 2, 3, 7) initially received a score on the motor scale of the Bayley (PDI) that was 10-points lower than their score on the mental scale (MDI). Only one child in this group (case 5) had significantly lower motor scores during the second evaluation, although scores were within the average range. Currently, all eight children have normal development; the one possible exception is case 7 who is experiencing language delays. None of the children have had significant medical complications.

Neurodevelopmental findings in the clinically identified group (Table 3)—In this group, the average age at diagnosis was 28 ± 19 months. These children were evaluated the first time at an average age of 43 ± 19 months. The mean Vineland Adaptive Behavior Composite score was 72 ± 25 (range 37– 108) for Time 1 and 66 ± 25 (range 38–105) for Time 2. By the time of the second evaluation, four children (cases 10, 12 13, 14) had scores less than 70 (greater than two standard deviations below the normative mean) on the Vineland, indicative of mental retardation. Two children (cases 9, 11) who had had normal newborn screening results were functioning at age-level in all areas of development at the time of most recent report. One child (case 14) with a normal newborn screening result has

severe motor and speech delays, mental retardation, and Rett syndrome. She is one of a triplet and was born at 31 gestational weeks. The other clinically diagnosed children with mental retardation include one child who experienced perinatal asphyxia (case 13) and a twin born at 36 weeks to a mother who experienced HELLP syndrome during her pregnancy (case 12). Case 10 has severe aphasia, some motor delay and autistic spectrum features.

DISCUSSION

Our series of 14 patients demonstrates the difference between children identified by newborn screening compared to those identified because of clinical symptoms. It provides clinical and biochemical information that should be considered in the continuing debate about SCADD. None of the eight newborn screened children experienced significant health issues beyond the immediate newborn period and none demonstrated developmental delay beyond infancy, except for one child with language delay. However, several of these children experienced transient problems at birth or within the first days of life. In addition, one of these children (case 6) recently experienced an episode of unexplained drooling and loss of expressive language at age 2 years and was hospitalized shortly thereafter with hypoglycemia. Six months later, when she returned to the metabolism clinic for her regularly scheduled appointment, her speech had returned and her developmental score on the Bayley Scales was comparable to her previous scores.

All of the children in the clinically identified group demonstrated serious clinical symptoms which were initially ascribed to SCADD. For each of these children, supplementary or alternative explanations have been entertained. These include prematurity, perinatal asphyxia, and maternal HELLP syndrome. In another child (case 10), clinical symptoms, including hypoglycemia and lactic acidosis, did not appear until age 17 months, after which time aphasia and autistic spectrum features were noted. Still another child (case 14) has been diagnosed with genotypically proven Rett Syndrome. We have also recently evaluated another girl (not included in this study) with biochemical evidence of SCADD and Rett syndrome, although genotype was not available.

The SCAD encoding gene, ACADS, is located in the terminal region of the long arm of chromosome 12. It spans approximately 13kb and consists of 10 exons [29]. Twenty-two different pathogenic mutations have now been associated with SCADD and two variants have been found, 625G>A and 511C>T [30], that are relatively common in the general population, with variation in frequency among different ethnic groups [6,17, 31] . It has been suggested that these polymorphisms, when homozygous or heterozygous with a known pathogenic mutation, increase susceptibility to symptoms in certain environmental situations, such as fever [6, 32] . However, it is still unknown why only certain individuals carrying these variations develop clinically relevant disease. A similar situation appears to emerge with respect to the 319C>T mutation which has been shown to cause complete loss of SCAD activity in vitro [7]. This mutation was identified in seven homozygote (3/7) or compound heterozygote (4/7) cases who presented from birth to six years with significant neuromuscular symptoms [17]. While this mutation was not detected among our clinically identified patients, 2 children detected by newborn screening are homozygotic for 319C>T (cases 2 and 4) and are healthy at ages 4 years and 29 months, respectively. However, one

child (case 6), who is doubly heterozygous for 319C>T and 991G>A experienced a temporary neurological deficit at age 2 years. Given these results, a definitive genotype-phenotype association for the 319C>T mutation in terms of neurological outcome is not possible.

It seems of interest that all but one of the children identified by newborn screening but none of the clinically identified children is homozygous or doubly heterozygous for SCAD mutations. Conversely, the clinically identified children, with one exception, harbor only SCAD gene variants. The clinically exceptional child is case 13 who carries the 136C>T mutation. This observation is counterintuitive to the usual assumption that a genetic disorder is more likely to produce clinical disease in those with mutations than in those with polymorphisms. Indeed, the prevalence of the 625G>A variants in the general population has led to questioning its relevance for clinical disease [30, 31]. Nevertheless, the number of cases of clinical disease reported in individuals who harbor the 625G>A variants has led to the hypothesis that environmental stress or malfunctioning metabolic systems lead to clinical disease in those who have “susceptibility” gene variants [6, 30, 32] .

A clinically abnormal phenotype in the mouse models for SCADD is equally uncertain. There are two mouse models, one identified by screening mice for organic acidemias [33] and the other produced transgenically [34]. The first, a BALB/cByJ mouse, is asymptomatic except when subjected to an 18-hour fast at which time severe fatty liver and hypoglycemia are observed [33]. The transgenic mouse is continually asymptomatic [34].

Newborn screening failed to identify the 3 clinically identified children. This is consistent with the reports of Nagan et al [31] who found higher concentrations of C4 but below the threshold that would lead to follow-up in newborn screening among those homozygous for the 625G>A variant and van Maldegem et al [30] who found no significant differences in the newborn screening C4 concentration between children in the 625G>A homozygous, heterozygous and non-carrier groups who had mean scores of 0.16, 0.13 and 0.15 μmol/L respectively. Acylcarnitine levels, however, may be sensitive to timing of the sample collection in relation to fasting and may not be consistently elevated, as found in some cases of VLCADD [35].

Increased ethylmalonic aciduria (EMA) is also a common biochemical marker in children diagnosed with SCADD [7, 32]. In our study, all children in the newborn screened group excreted increased EMA, ranging from 41–330 μg/mg creatinine. A study by Corydon et al [32] found that 60% of patients with elevated EMA levels were homozygous for the 625G>A variant and 30% were heterozygous for this genetic variation.

Another potentially significant observation is the possible association between maternal pregnancy complications and an elevated C4 on newborn screening. In this study, four of the eight mothers in the newborn screened group and three of the six mothers in the clinically identified group experienced pregnancy complications including maternal hypertension, pre-eclampsia and mild HELLP syndrome. Thirty-one percent of women in the general population experienced at least 1 obstetric complication or at least 1 pre-existing medical condition [36]. For HELLP syndrome, the rate is 0.17–0.85% in the general population [37].

In another study, a patient with SCADD was born to a mother who had developed acute fatty liver of pregnancy (AFLP) [38]. Others have demonstrated a correlation between maternal HELLP syndrome and children with fatty acid-oxidation defects [16, 39, 40]. They hypothesized that carrying a fetus with a fatty acid oxidation defect imposes an environmental burden that leads to the expression of maternal liver disease in a woman who has a genotypic or other susceptibility, although Holub et al [41] reported no such association.

In summary, this study highlights the unsettling questions regarding the outcomes associated with SCADD. The essentially normal growth and development of the children identified by newborn screening and treated primarily with frequent feedings and early medical intervention during acute illness, in contrast to the severe symptoms in children identified clinically, suggests the possibility that SCADD is usually a benign condition. If so, SCADD would be added to histidinemia [42] and Hartnup disease [43] as other examples of inborn errors believed to be clinically significant before newborn screening but, as a result of follow-up studies in children identified by newborn screening, was found to be usually benign. Individuals with SCADD who develop clinical disease without obvious cause could be an example of interaction between genetic susceptibility and environmental stressors, as has been the explanation in histidinemia and Hartnup disease [44]. At this time, supplementary/alternative diagnoses for clinical symptoms should also be considered when symptomatic patients with a biochemical phenotype of SCADD appear.

There are three plausible interpretations of our data: 1) There is clinical heterogeneity in SCADD, 2) newborn screening and prevention of hypoglycemia prevent adverse consequences of this disease, 3) SCADD is benign and the clinical features ascribed to SCADD reflect ascertainment bias. The correct interpretation awaits further evidence. To obtain this evidence it may help if regions where SCADD is included in the newborn screening program compare long-term outcome data to those programs where SCADD was excluded from newborn screening. The following elements should be considered in such a comparison: newborn screening findings, genotype, confirmatory laboratory values, and longitudinal follow-up at least through age 7 or 8 years, the time when most learning disabilities will become apparent and when IQ tends to stabilize [45]. Evaluations should include a medical history, physical examination, and neuropsychological testing with measures of intelligence, attention, executive functioning, motor skills, speech and language, achievement, behavior and emotional well-being. Parents and siblings should be genotyped to detect previously undiagnosed relatives and affected individuals should be thoroughly evaluated. Pregnancy history and co-morbid conditions should be described. Results from comparison groups of clinically identified children and unaffected siblings as well as peers matched for age and gender would bring to light possible neuropsychological or clinical findings associated with SCADD. In conclusion, this study illustrates the critical need for long-term medical and neuropsychological follow-up in newborn screening.

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Table 1

Medical Background

Case	Gender	Age Diagnosed	Clinical Symptoms	Birth/ Pregnancy Complications	# of Hospitalizations	Treatment
Newborn Screened						
Case 1	M	9 days	Hypoglycemia, hypotonia, jaundice	37 weeks C-section IUGR Maternal hypertension	0	Frequent feeding and Glucose monitoring (during illness)
Case 2	F	19 days	None	40 weeks	0	Frequent feeding and Glucose monitoring (during illness)
Case 3	F	10 days	None	41 weeks C-section Maternal Bradycardia, Fetal distress	0	Frequent feeding and Glucose monitoring (during illness)
Case 4	F	10 days	Recurrent diarrhea, vomiting	36 weeks Cerclage procedure Pre-eclampsia	0	Frequent feeding Glucose monitoring (during illness)
Case 5	F	9 months	Recurrent vomiting	40 weeks C-section Breech	0	Low fat diet * Frequent feeding and Glucose monitoring (during illness)
Case 6	F	21 days	Jaundice	39 weeks ABO incompatibility Mother diagnosed with MS	0	Low fat diet Frequent feedings Glucose monitoring
Case 7	F	5 days	Mild jaundice, vomiting	37 weeks	0	Frequent feeding and Glucose monitoring (during illness)
Case 8	F	27 days	None	40 weeks	2	Low fat diet Frequent feeding(during illness) Glucose monitoring
Identified because of Clinical Symptoms						
Case 9	M	7 months	Hypoglycemia, feeding problems, lethargy	40 weeks IUI pregnancy C-section Breech	1	Low fat diet Frequent feedings Glucose monitoring
Case 10	M	17 months	developmental delays, recurrent vomiting, autism spectrum symptoms	40 weeks Fetal bradycardia, Hypotonia, feeding problems,	6	Low fat diet Frequent feeding Glucose monitoring Carnitine
Case 11	M	37 months	Hypoglycemia, lethargy, mild jaundice	40 weeks Pre-eclampsia	2	Low fat diet Frequent feeding Glucose monitoring
Case 12	M	38 months	Hypoglycemia, hypotonia, lethargy, strabismus	36 weeks Maternal toxemia & mild HELLP	3	Low fat diet Frequent feeding

Case	Gender	Age Diagnosed	Clinical Symptoms	Birth/ Pregnancy Complications	# of Hospitalizations	Treatment
				Syndrome Fraternal twin		Glucose monitoring Carnitine
Case 13	M	61 months	Developmental delay, microcephaly, failure to thrive, seizures	40 weeks Shoulder dystocia Perinatal asphyxia	5	Low fat diet Carnitine
Case 14	F	17 months	Hypotonia, developmental delays	31 weeks IVF pregnancy – triplets C-section Significant IUGR Mild respiratory distress syndrome	5	Low fat diet Frequent feeding Carnitine Glucose monitoring

* Low fat diet = 30% of calories from fat

IUI = intrauterine insemination

HELLP = Hemolysis, Elevated Liver enzymes, Low Platelet count

IVF = in vitro fertilization

IUGR = Intrauterine Growth Retardation

Table 2

Laboratory Values and Genetic Mutations

Case	Acylcarnitine C4 Labs Normal < 1.06 μmol/L	Ethylmalonic Acid Labs Normal = .5–20.20 μg/mg creatinine	Genotype Allele 1	Genotype Allele 2
Newborn Screened				
Case 1	2.96 NBS 2.51 Repeat	247.00 265.00	505A>C 625G>A	505A>C 625G>A
Case 2	2.0 NBS 1.77 Repeat 2.04 at follow-up	330.93	319C>T	319C>T
Case 3	2.83 NBS 3.14 Repeat	67.84	529T>C	529T>C
Case 4	2.6 NBS 2.33 Repeat	249.17	319C>T	319C>T
Case 5	3.7 NBS 1.04 Repeat	41.25 41.60	625G>A	625G>A
Case 6	2.11 NBS 1.93 Repeat 1.72 at follow-up	Elevated (NA)	319C>T	991G>A
Case 7	5.16 NBS 2.38 Repeat	182.00 372.00	529T>C	988C>T
Case 8	2.86 NBS .96 Repeat	118.00	625G>A	988C>T
Identified because of Clinical Symptoms				
Case 9	Normal NBS .35 at follow-up	33.29	625G>A	625G>A
Case 10	No NBS in state .74 Initial at 17 months .91 at follow-up 1.68 at follow-up	38.98	625G>A	625G>A
Case 11	Normal NBS	Normal	625G>A	511C>T
Case 12	No NBS in state 5.11 at follow-up	30.00	625G>A	511C>T
Case 13	No NBS in state 2.44 at follow-up 1.38 at follow-up	24.28	625G>A 136C>T	625G>A
Case 14	Normal NBS 1.09 at follow-up	21.96 54.42	625G>A	625G>A

*NBS = Newborn Screening

Table 3

Developmental Outcome

Case	Age at Time 1 in months	Vineland Adaptive Behavior Composite	MDI	PDI	Stanford -Binet	Age at Time 2 in months	Vineland Adaptive Behavior Composite	MDI	PDI	Stanford -Binet	Developmental Outcome
Newborn Screened											
Case 1	6	NA	88	73	-	20	87	110	90	-	Normal at 3 years
Case 2	6	112	100	88	-	20	95	102	113	-	Normal at 4 years
Case 3	6	119	145	117	-	NA	-	-	-	-	Normal at 1 year
Case 4	9	110	111	102	-	21	95	112	116	-	Normal at 29 months
Case 5	15	114	113	113	-	29	106	96	87	-	Normal at 29 months
Case 6	5	118	102	94	-	15	109	107	121	-	Normal at 15 months
Case 7	16	85	98	59	-	-	-	-	-	-	Language delay at 26 months
Case 8	NA	-	-	-	-	NA	-	-	-	-	Normal at 20 months
Identified because of Clinical Symptoms											
Case 9	26	91	103	104	-	41	105	-	-	124	Normal at 4 years
Case 10	21	64	49	49	-	32	51	-	-	-	Autism, mental retardation and delays in language and motor skills at 6 years
Case 11	48	108	-	-	95	64	94	-	-	116	Normal at 5 years
Case 12	56	71	-	-	110	67	64	-	-	85	Hypotonia, learning disabilities at 8 yrs
Case 13	70	37	-	-	36	90	38	-	-	51	Mental retardation and delays in language and motor skills at 8 yrs
Case 14	35	45	49	49	-	49	42	49	49	-	Mental retardation (non-verbal, non-ambulatory) at 4 years, Rett Syndrome

Time 1 = age at time of first study assessment ; Time 2 = age at time of second study assessment

MDI = Mental Development Index from the Bayley Scales of Infant Development

PDI = Psychomotor Development Index from the Bayley Scales of Infant Development