ORIGINAL ARTICLE

Growth impairment in the very preterm and cognitive and motor performance at 7 years

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Background: Infants born of low birth weight often have poor subsequent growth (especially if they were born very preterm), which has been shown to relate to later motor and cognitive development.
Aims: To assess a cohort of preterm infants at the age of 7 years for growth, motor, and cognitive measures, and investigate the effects of growth impairment on school performance.
Methods: A cohort of 280 children born before 32 completed weeks of gestation were tested, together with 210 term controls.
Results: Pretem children were significantly lighter and shorter than term controls and had smaller heads and lower body mass index (BMI). Median centiles for weight, height, head circumference, and BMI were 25, 25, 9, and 50 for boys and 50, 25, 9, and 50 for girls compared with 50, 50, 50, and 75 for controls. They performed significantly less well on all tests with a mean score of 91 (9.2) on the Developmental Test of Visual-Motor Integration, 89 (14.5) on the Wechsler-III IQ test, and 30.7% scoring at or below the 5th centile on the Movement Assessment Battery for Children. In boys, short stature and small heads were the best predictors of poor performance; in girls, a small head alone was a predictor for poor motor and cognitive performance.
Conclusion: Poor postnatal growth in preterm infants, especially of the head, is associated with increased levels of motor and cognitive impairment at 7 years of age. This growth restriction appears to occur largely in the postnatal rather than antenatal period and may be amenable to intervention and subsequent improvement in outcome.

It has been recognised for some time that preterm children of low birth weight grow less well in their early years than full term infants.[1–5] Poor growth, particularly of the head, has been associated with poorer cognitive outcomes at school age in many studies.[1–5] There has, however, been a lack of agreement about whether catch-up growth subsequently reduces these differences. Earlier studies examined infants who were mainly growth restricted but near term, or samples of very preterm infants who had been selected by referral and absence of major neonatal illness. Catch-up growth in these children was almost complete and school performance similar to their peers.[6 7]

When very preterm infants were followed in later years, especially if they had required neonatal intensive care, considerable and lasting deficits in height, weight, head circumference, and cognitive performance were noted.[8] Factors such as respiratory disease,[9] cerebral haemorrhage,[10] and poor nutrition in the neonatal period[11] may have contributed to growth failure in these children. Recent improvements in neonatal care such as antenatal steroids, exogenous surfactants, and improved nutrition have the potential to reduce the degree of growth failure seen in previous years.

This study aimed to examine the relation between growth and development of a geographically selected cohort of very preterm infants born over a two year period within the past decade. These children were born after the widespread introduction of recent improvements in care, and comparisons were made with term children drawn from the same school class.

METHODS

Participants

All infants born before 32 completed weeks in 1991–92 in the eight hospitals within the Liverpool postal districts were ascertained. Those who died before discharge from hospital, or whose mothers were not resident within a Liverpool postal district at the time of birth were excluded.

Initial contact was made with the family doctor via the child's hospital paediatrician to ascertain current health status and school placement. The parents of those children who were alive and attending mainstream schools were then approached to seek consent to take part in the study. The individual children's schools were then contacted to arrange assessment visits, and to request that the class teacher choose the child of same sex and first language in the class whose birthday was closest to that of the index child. The parents of that control child were then approached with information about the study, and consent for their child to participate sought. Most children were tested at their schools, although a few were tested at the Institute of Child Health, Royal Liverpool Children's Hospital, at their parents' request. The study protocol was approved by the local research ethics committee.

Growth measurements

Height, weight, and head circumference (occipitofrontal circumference, OFC) were measured by a single observer (LF-H) using standardised procedures recommended by the Child Growth Foundation UK.[12] A portable Leicester height stick was used to measure the child's height in centimetres (to nearest millimetre). The children were measured in bare feet standing with their back to the height stick, feet together, and heels, buttocks, and shoulder blades touching the vertical measure. Upward pressure was applied to the mastoid processes. Children were measured at the same time of day. Weight was assessed

Abbreviations: BMI, body mass index; DCD, developmental coordination disorder; IQR, interquartile range; Movt-ABC, Movement Assessment Battery for Children; OFC, occipitofrontal circumference; PIQ, performance intelligence quotient; SDS, standard deviation score; TIQ, total intelligence quotient; VIQ, verbal intelligence quotient; VMI, visual-motor integration; WISC, Wechsler Intelligence Scale for Children

Table 1 Perinatal variables for preterm group

Variable examined	n	n (%) affected in n examined
Pregnancy induced hypertension	268	39 (14.6%)
Other maternal illness	267	25 (9.4%)
Preterm rupture of membranes	268	87 (32.5%)
Antepartum haemorrhage	268	49 (18.3%)
Antenatal steroids	268	88 (32.8%)
Fetal distress on CTG	268	62 (23.1%)
Mode of delivery	268	Vertex 115 (42.9%)
		Breech 23 (8.6%)
		Emergency caesarean section 114 (42.5%)
		Elective caesarean section 16 (6%)
Apgar score	262	<5 at 1 min 76 (29%)
	260	<5 at 5 min 11 (4.2%)
Days ventilation	266	126 not ventilated
		Median 5 days (range 1–70)
Days oxygen	265	113 no added oxygen Median 6 days (range 1–150+)
Confirmed sepsis	266	122 (45.9%)
Clinical seizures	266	11 (4.1%)
Persistent arterial duct	266	40 (15%)
Pneumothorax	266	18 (6.8%)
Symptomatic hypoglycaemia	266	35 (13.2%)
Cranial ultrasound scan, right side	266	Grade 0: 229 (86.1%)
		Grade 1: 16 (6%)
		Grade 2: 3 (1.1%)
		Grade 3/4: 2 (0.7%)
Cranial ultrasound scan, left side	266	Grade 0: 234 (88%)
		Grade 1: 15 (5.6%)
		Grade 2: 16 (6%)
		Grade 3: 1 (0.4%)
Cerebral ultrasound scan, parenchymal involvement	266	Persistent ventricular dilatation 15 (5.6%)
		Cystic leucomalacia 3 (1.1%)
Ventriculoperitoneal shunt	260	1 (0.4%)
Retinopathy of prematurity (under 1500 g only screened)	116	Stage 0: 57 (49.1%)
		Stage 1: 31 (26.7%)
		Stage 2: 20 (17.2%)
		Stage 3: 8 (6.9%)

CTG, cardiotocography.

using solar scales provided by the Child Growth Foundation and recorded in kilograms (to nearest 100 grams). They were weighed wearing their school uniforms but without shoes or socks. OFC was measured in centimetres (to the nearest millimetre) using a lasso tape measure. Measurements were taken from midway between the eyebrows and the hair line at

Table 2 Differences between growth variables for preterm subjects and term controls by sex

		n	Mean (SD)	p value
Boys				
Weight (kg)	Subjects	151	23.9 (4.5)	<0.001
	Controls	112	26.2 (3.9)	
Height (cm)	Subjects	151	121.8 (5.5)	<0.001
	Controls	112	124.9 (5.5)	
OFC (cm)	Subjects	151	51.7 (1.9)	<0.001
	Controls	112	52.7 (1.6)	
BMI	Subjects	151	16.0 (2.1)	<0.001
	Controls	112	16.7 (1.8)	
Girls				
Weight (kg)	Subjects	129	24.4 (4.8)	0.003
	Controls	98	26.3 (4.9)	
Height (cm)	Subjects	129	121.5 (6.1)	0.002
	Controls	98	123.9 (4.7)	
OFC (cm)	Subjects	129	51.2 (1.8)	<0.001
	Controls	98	52.4 (1.6)	
BMI	Subjects	129	16.4 (2.1)	0.024
	Controls	98	17.1 (2.3)	

Table 3 Differences in scores for motor and cognitive tests for preterm subjects and term controls (sexes combined)

		n	Mean (SD) or median (IQR)	p value
Movt-ABC	Subjects	280	8.5 (3.1 to 15.4)	<0.001
	Controls	210	3.5 (1.0 to 6.6)	
VMI	Subjects	280	90.5 (9.2)	<0.001
	Controls	210	96.9 (7.8)	
Total IQ	Subjects	268	89.4 (14.2)	<0.001
	Controls	198	100.5 (13.7)	
Performance IQ	Subjects	268	87.8 (15.6)	<0.001
	Controls	198	99.6 (15.8)	
Verbal IQ	Subjects	268	92.9 (13.9)	<0.001
	Controls	198	101.2 (12.7)	

the front of the head and from around the occipital prominence at the back of the head. All measurements were recorded on "4 in 1" growth charts for boys and girls and plotted to obtain age appropriate centiles. Body mass index (BMI) was computed and centiles also derived. Perinatal data for the children born preterm were obtained from hospital records by a clerical research assisstant.

Test instruments

Fine and gross motor skills were assessed using age band 2 of the Movement Assessment Battery for Children (Movt-ABC).[13] The test comprises eight items, divided into four subsections: manual dexterity, ball skills, and static and dynamic balance. The scoring system for each item is from 0 to 5, ranging from no impairment to severe impairment. The scores for each item are added and converted to percentiles. A score between the 5th and 15th centile for age is considered "borderline" impairment; at or below the 5th centile is "definitely impaired", and is sometimes used as a diagnostic criterion for developmental coordination disorder (DCD).

Integration of visual and motor abilities was assessed using the Developmental Test of Visual-Motor Integration (VMI).[14] It consists of 27 geometric forms which increase in complexity and are in a developmental sequence. There is a one point scoring system for each shape. Scores are then standardised for age. Standard scores have a mean of 100 and a standard deviation of 15. The Movt-ABC and VMI were measured by two research assistants (an occupational therapist and a graduate psychologist) trained in their use.

General intelligence was measured using the Wechsler Intelligence Scale for Children UK (WISC III UK),[15] by three research assistants with prior experience in its use (two graduate psychologists and a teacher). Total (TIQ), verbal (VIQ), and performance (PIQ) scores were calculated. Research assistants could not practically be blinded to the birth status of the children being examined.

Statistical analysis of data was carried out using SPSS-10, using parametric or non-parametric tests depending on the distribution of the data.

RESULTS

Of a potential cohort of 382 preterm children identified, 33 had moved out of the area or could not be traced, 18 had died,

Table 4 Correlation coefficients (Pearson) between growth variables and outcome variables for subjects and controls by sex

		Movt-ABC	VMI	Total IQ	Performance IQ	Verbal IQ
Boys						
Weight (kg)	Subjects	–0.129	0.064	0.199*	0.163*	0.180*
	Controls	0.052	–0.180	–0.244*	–0.317**	–0.099
Height (cm)	Subjects	–0.246**	0.208*	0.234**	0.161	0.239**
	Controls	–0.056	–0.153	–0.117	–0.211*	0.008
OFC (cm)	Subjects	–0.081	0.118	0.237**	0.171*	0.228**
	Controls	0.009	0.077	0.098	–0.066	0.236*
BMI	Subjects	–0.016	–0.055	0.131	0.127	0.101
	Controls	0.122	–0.132	–0.249*	–0.271**	–0.136
Girls						
Weight (kg)	Subjects	–0.162	0.115	0.055	0.067	0.049
	Controls	–0.247*	–0.009	–0.006	–0.052	0.036
Height (cm)	Subjects	–0.213*	0.068	0.027	0.028	0.021
	Controls	–0.199*	–0.159	0.044	–0.072	0.143
OFC (cm)	Subjects	–0.341**	0.333**	0.313**	0.283**	0.273**
	Controls	–0.154	0.104	–0.107	–0.181	–0.012
BMI	Subjects	–0.098	0.115	0.073	0.095	0.063
	Controls	–0.208*	0.073	–0.038	–0.038	–0.032

*p<0.05; **p<0.01.

Table 5 Correlations of SDS for head circumference at birth (b-OFC-SDS), at time of testing (OFC-SDS), and the difference between these two (d-OFC-SDS) with motor and cognitive outcomes at 7 years in the preterm group

	VMI	Movt-ABC	Verbal IQ	Performance IQ	Total IQ
b-OFC-SDS	0.029	–0.075	0.046	–0.056	0.009
d-OFC-SDS	0.096	–0.020	0.139*	0.190**	0.184**
OFC-SDS	0.232**	–0.218**	0.252**	0.157**	0.236**

*p<0.05; **p<0.01.

29 were attending special schools, 16 parents refused permission for their children to be tested, and six were not tested as suitable appointments could not be made. In addition to these 280 children, 210 term controls were also recruited. In 70 cases a control was not obtained, or the parents of the selected control would not agree to testing. Time constraints at school meant that a few children did not complete all the tests. The index children comprised 151 (53.9%) males and 129 (46.1%) females. The term controls comprised 112 (53.3%) males and 98 (46.7%) females. There were 215 singleton births, 56 twins, and nine triplets among the preterm group. The mean age at testing was 89.8 (range 82–101) months for the index children and 89.9 (range 72–107) months for the controls.

An idea of the illness severity of the preterm group is given by the frequency of perinatal variables listed in table 1. The mean gestational age for the index group was 29.8 (range 23–32) weeks and the mean birth weight 1467 (range 512–2860) grams. A total of 21.4% were of ⩽28 weeks gestation, and 3.6% ⩽24 weeks; 50.4% were <1500 g birth weight and 14.6% ⩽1000 g. The age specific birth weights followed a normal distribution about the 50th centile; 8.9% preterm infants had a birth weight below the 9th centile for their gestational age.

The preterm index group were significantly lighter, shorter, and had smaller OFC and lower BMI than the term controls (table 2). Median centiles for weight, height, OFC, and BMI for the index children were 25th, 25th, 9th, and 50th for boys, and 50th, 25th, 9th, and 50th for girls, respectively. The median centiles for the term controls of both sexes were 50th, 50th, 50th, and 75th, respectively.

The term control children as a group scored significantly better than the preterm index children on all measures of motor function and intelligence (table 3). Eighty six (30.7%) of the index and 14 (6.7%) of the control group were on or below the 5th centile for the Movt-ABC and could be categorised as having DCD. No significant differences in the frequency of DCD were seen between the sexes in index or control children.

When measures of growth were correlated with test results in the preterm children for Movt-ABC, VMI, and IQ, statistically significant relations were seen (table 4). For boys, height and head circumference were significantly related to Movt-ABC and IQ respectively, while in girls only head circumference was significantly related to all outcomes. In the control children these relations were less evident, with weight and BMI correlating with TIQ and PIQ, and height with PIQ for boys, and height and weight with the Movt-ABC in girls.

OFC data measured within seven days of birth were found in the hospital records for only 219 (78%) of the 280 preterm infants. Mean OFC was 28.7 (2.2) for males and 28.1 (2.4) for females, with a median gestation and sex specific centile of 50 (IQR 25 to 75) and a median gestation and sex specific standard deviation score (birth OFC-SDS) of 0.25 (IQR –0.72 to 1.0). (Standard deviation score = (actual measurement – expected mean for age and sex)/standard deviation around mean.) An SDS was also calculated for OFC at the time of testing standardised for sex and age (OFC-SDS), median –0.58 (IQR –1.51 to 0.19). The difference between individual birth OFC-SDS and OFC-SDS at time of testing was calculated (dOFC-SDS) as an index of postnatal head growth, median –0.67 (IQR –1.80 to 0.25). Significant correlations were seen between OFC-SDS at time of testing and all outcome measures, between dOFC-SDS and measures of IQ, but there was no significant correlation between birth OFC-SDS and any of the outcomes (table 5).

When birth OFC-SDS was plotted against d-OFC-SDS (fig 1), it is clear that it is the infants with normal head circumferences at birth rather than the most growth retarded which grow the poorest between birth and seven years. When birth OFC-SDS is plotted against current OFC-SDS (fig 2), it can be

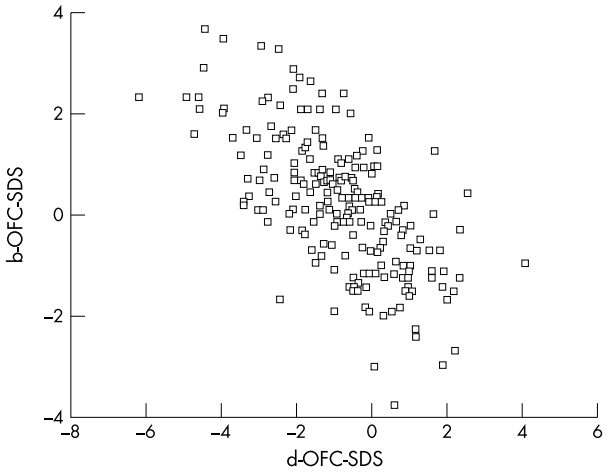

Figure 1 Graph of SDS for head circumference at birth (b-OFC-SDS) against change in SDS between birth and seven years (d-OFC-SDS), showing that those with the greatest loss in relative head circumference were not those most growth restricted at birth.

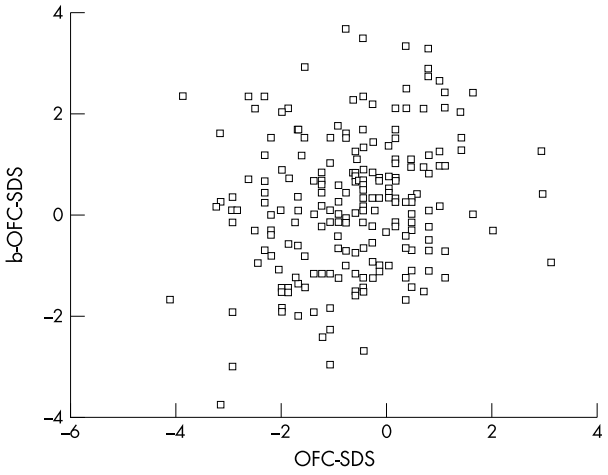

Figure 2 Graph of SDS for head circumference at birth (b-OFC-SDS) against SDS for head circumference at seven years (OFC-SDS), showing that most of the preterm infants now growth restricted were not so at birth.

Table 6 Multiple regression analysis with head circumference at 7 years as independent variable

Model	B	Std error	*t*	p value
(Constant)	47.04	1.701	27.63	0.000
Height (cm)	5.29 E-03	0.012	0.44	0.660
Weight (kg)	3.45 E-02	0.016	2.17	0.031
Sex	6.06 E-02	0.097	0.63	0.533
Birth weight (g)	–8.02 E-02	0.000	–0.41	0.685
Gestation (weeks)	–0.987	0.045	–21.0	0.000
d-OFC-SDS	1.35	0.044	31.02	0.000
Age at testing (months)	3.15 E-03	0.009	0.34	0.729
Birth OFC (cm)	1.18	0.049	24.13	0.000

seen that almost all infants who now have an OFC more than 2 SD below the mean did not have this at birth.

As OFC was the current growth variable most clearly related to outcomes, predictors of OFC at age of testing were sought using multiple regression analysis with OFC as the dependent variable (table 6). Although OFC at age of testing was independently predicted by present weight, height, and OFC at birth, it was most obviously associated with change in OFC since birth.

DISCUSSION

It is clear from the results of this study that very preterm children at school age continue to show significant deficits in weight, height, and particularly OFC when compared to term controls, and that these deficits correlate significantly with motor and cognitive performance. In utero growth restriction has been recognised for a long time as a cause of later reduced growth and cognitive performance, but only if later catch-up growth does not occur. The preterm subjects of this study had a normal birth weight distribution and normal distribution of OFC (where available) and so intrauterine growth retardation is unlikely to explain the present findings. On the other hand, changes in the relative size of OFC indicating postnatal growth failure were associated with poorer outcomes.

The human brain growth velocity is at its peak at term.[16] These infants were born 8–16 weeks preterm, at a time when many are experiencing a variety of adverse influences on growth. Many insults at this time could potentially reduce brain growth at a critical period, leading to a permanent reduction in final brain size, proportionately greater than that to weight or height. Direct cerebral insults such as haemorrhage or periventricular leucomalacia may lead to reduction in both white and grey matter growth, and subsequent brain volume as shown on magnetic resonance imaging scans.[17] Drugs such as steroids given for chronic lung disease have also been shown to contribute to poor subsequent growth.[18] Nevertheless, the majority of infants in this study did not have major perinatal disease. Poor nutrition may also result from present day feeding practices and schedules.[19] An average loss of more than 1 SD in weight over five weeks in otherwise well preterm infants was recently shown to be substantially caused by a cumulative calorie/protein deficiency at this time.[20]

This study has its limitations. Although attempts were made to obtain as complete as possible a geographically determined cohort of preterm infants for testing, adverse press reports concerning the local children's hospital reduced cooperation by parents and teachers during the later part of the study period. Fewer than one control per index case was obtained. The tests used however were well standardised on normal populations, and the control children served largely to confirm the accuracy of the examiners' technique and to control for social and teaching effects on outcomes. Blinding of the observers to the birth status of the children was practically impossible. Many of the preterm children looked smaller and facially different to the controls, and the research assistants performing the tests also made the arrangements for the teachers to select the controls. The preterm children did not have any correction made to their ages for prematurity, which averaged 10 weeks. Such corrections are controversial, especially at 7 years of age. The differences seen between the preterm and term children were far larger than could have been achieved in 10 weeks. The perinatal data were collected retrospectively by a single researcher, but from clinical records of varying quality from eight different centres within the region. Inevitably they are incomplete, and have been recorded by very many different people. The information they contain probably makes their inclusion worthwhile.

The motor, visuoperceptual, and cognitive tests applied all rely on intact cortical development. The poorer performances by the preterm children may reflect their postnatally restricted cerebral, mainly cortical growth.

Recent improvements in perinatal care have resulted in reductions in major neurodevelopmental disabilities such as cerebral palsy,[21] but the rates of minor impairments seen at school age in this cohort appear very similar to studies of similar children born a decade or two earlier. If postnatal growth failure is related to nutritional factors, it and associated poor developmental performance may be open to improvement by dietary means. A prospective study of factors associated with early postnatal brain growth in this population is indicated, followed by experimental studies of early nutritional management.

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ARCHIVIST

Hallervorden-Spatz syndrome*, *PANK2*, and the tiger's eyes

Hallervorden and Spatz reported a rapidly progressive neurodegenerative disease of early onset in a German journal of neurology and psychiatry in 1922. The main clinical features are dystonia, dysarthria and rigidity, rapid progression, and early death. Until recently the diagnosis depended on clinical features and CT or MRI abnormalities in the globus pallidus. Pathologically, there is iron accumulation in the basal ganglia with destruction of the pallidum and substantia nigra. The classic disease is of early onset (infancy or early childhood) and rapidly progressive. Atypical forms present later and progress more slowly.

In 2001 researchers in California and Oregon linked Hallervorden-Spatz syndrome with a defect in the gene (*PANK2*) on the short arm of chromosome 20 (20p13) encoding the enzyme pantothenate kinase 2 which is important in coenzyme A synthesis. They have now delineated the clinical, genetic, and MRI features (Susan J Hayflick and colleagues. *New England Journal of Medicine* 2003;**348**:33–40). By advertising internationally they were able to obtain information about 186 patients from 145 families (123 patients from 98 families had enough clinical information for inclusion in the analysis). Sixty-six patients had classic disease and 57 had atypical forms.

They found that the classic disease was invariably associated with a *PANK2* mutation whereas only 35% of families with atypical disease had such mutations. The gene defect was a null mutation (resulting in premature protein termination) in 36 of 92 alleles associated with the classic disease but in only 2 of 31 alleles in patients with atypical disease. Two null mutations invariably meant classic disease. (The other (non-null) mutations were missence mutations causing amino acid substitutions). Two mutations, both missense, (G411R and T418M) accounted for one third of the faulty genes. Although both classic and atypical diseases were generally autosomal recessive the G411R mutation appeared to be dominant in a few patients. Speech problems early in the course of the disease, psychiatric symptoms, and dementia were features particularly of patients with atypical disease and no *PANK2* mutation and were rare in the classic disease. MRI scans from 69 patients with *PANK2* mutations (65 with classic disease) all showed bilateral hypointensity in the medial globus pallidus on T_2-weighted images with an area of hyperintensity at the anterior margins of the hypointensity—an appearance which has been given the name "eye of the tiger" pattern. The scans of 16 mutation-negative patients showed only the hypointensity without the eye of the tiger pattern.

All cases of classic Hallervorden-Spatz disease have a *PANK2* mutation. One third of atypical cases have such a mutation. The eye of the tiger pattern on MRI signifies a *PANK2* mutation.

*In an annotation (Michael Shevell. Ibid: 3–4) a call is made for the name Hallervorden-Spatz syndrome to be dropped. Julius Hallervorden was implicated in a programme of mass murder of disabled people in Nazi Germany and knowingly used the brains of victims as a basis for his reports; his name should not be perpetuated by the use of the eponym. The conditions should be called pantothenate kinase-associated degeneration or neurodegeneration with brain iron accumulation according to whether or not a *PANK2* mutation is present.