

Major difference in aetiology and phenotypic abnormalities between transient and permanent neonatal diabetes

E Marquis, J J Robert, C Bouvattier, C Bellanné-Chantelot, C Junien, C Diatloff-Zito

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Neonatal diabetes (ND) is a rare entity with an estimated incidence of 1/400 000 births in Europe. Hyperglycaemia usually occurs in the first few days of life and patients require insulin treatment. Intrauterine growth retardation, low birth weight, and decreased adipose tissue are frequently associated. ND is permanent in some patients (permanent ND), and in other cases hyperglycaemia is transient (transient ND, OMIM 601410). Type 2 diabetes (T2D) frequently arises in adolescence or adulthood in transient ND patients.¹ Chromosome 6 abnormalities are specifically associated with transient ND,^{2–4} with imprinting effects unmasked by uniparental disomy (UPD) of paternal chromosome 6 and duplications in 6q24.^{3–7} Two imprinted genes expressed from the paternal allele in various tissues, *ZAC/PLAGL1* (zinc finger, apoptosis, cell cycle/pleomorphic adenoma of the salivary gland gene like 1) and *HYMAI* (hydratidiform mole associated and imprinted transcript), lie in the transient ND locus in 6q24.^{7–8}

The genetic causes of permanent ND forms are less known. Homozygous mutation in the glucokinase gene (*GK*)⁹ and in the insulin promoter factor-1 (*IPF1*) gene¹⁰ may lead to permanent ND owing to complete deficiency of the *GK* or *IPF1* gene product. Mutations of the eukaryotic translation initiation factor-2-alpha kinase 3 (*EIF2AK3*) gene were found to segregate with the Wolcott-Rallison syndrome (OMIM 226980), a rare autosomal recessive disorder with early onset permanent diabetes mellitus and multiple epiphyseal dysplasia (spondyloepiphyseal dysplasia).¹¹ Clinical information and a molecular genetic study of 14 patients with transient or permanent ND forms are reported. The phenotypes of ND patients from previous reports together with cases reported here provide an initial outline for further studies and molecular mechanisms.

PATIENTS

Fourteen patients with ND were studied. Their main clinical features are summarised in table 1. The patients were all born at term, mean birth weight was 2288 g (SD 570 g), and nine patients displayed intrauterine growth retardation (>2 SD). Diabetes was diagnosed within the first month of life in 13 of the patients. The proband referred to as O7 is a child from a multiplex family, with permanent diabetes appearing before 6 months of age. Four other members of family O in two generations were affected in a manner suggestive of an autosomal dominant pattern of inheritance. Patients I3 and I4 were brother and sister with permanent ND. All nine patients with transient ND were sporadic cases. All the patients were found to be negative for autoantibodies against islet cells (ICA) or insulin (AIA). Sequences of HLA-DRB1 and DQB1 loci were achieved for all the patients and relatives and alleles classically associated with juvenile diabetes were not found.¹² Ultrasound scans were performed to exclude pancreatic agenesis in permanent ND patients. The patients were all white, except for patient J who originated from Guyana.

METHODS

Molecular genetic studies

Peripheral blood (10–20 ml) was drawn from each participant. Written informed consent was obtained from all the parents. DNA was prepared and microsatellite marker analysis performed as previously described.¹³ Microsatellite markers

Abbreviations: IDDM, insulin dependent diabetes mellitus; ND, neonatal diabetes; MODY, maturity onset diabetes of the young; T1D, type 1 diabetes; T2D, type 2 diabetes; UPD, uniparental disomy

Table 1 Main clinical features of patients with insulin dependent neonatal diabetes (ND)

Clinical features	Patients													
	A	B	C	D	E	F	G	I3	I4	J	K	M*	N	O
Sex	F	F	F	M	F	M	M	F	M	M	M	F	M	M
Birth weight (g)	1670	2190	2800	2600	1750	1960	na	1900	2020	1840	3200	1600	3160	3050
Age at diagnosis	13 d	5 d	2 d	2 d	1 d	na	5 d	1 d	1 d	1 d	26 d	6 d	na	6 mth
Diabetes form	Tr	Tr	Tr	P	Tr	Tr	P	P	P	Tr	Tr	Tr	Tr	P
Insulin†	12 d	5 mth	2.5 mth		4 mth	4.5 mth				3.5 mth	13 mth	5 mth	na	
Family diabetes history	–	–	T1D	T1D	–	–	–	T1D	T1D	–	T1D	–	–	yes‡
Congenital birth anomalies§	–	T2D	T2D	+	–	–	–	–	–	–	T2D	T2D	T2D	–

Tr=transient ND; P=permanent ND; na=not available.

*Patient M developed non-insulin dependent diabetes at 18 years of age with hyperglycaemia controlled by oral sulphonylurea.

†Duration of insulin therapy in transient ND; d=days, mth=months; T1D=type 1 diabetes in the paternal branch for patients D, I3, and I4 and in the maternal grandparents for patients C and K; T2D=type 2 diabetes in the maternal grandparents for the transient ND patients.

‡Case O, is subject O7 of a multiplex family with insulin dependent diabetes appearing before 6 months of age (see pedigree in fig 2[f2]).

§Congenital birth anomalies degree of severity: (–)=absent, (+)=moderate mild, (++)=marked with a combination of more than two organs affected, details in table 2[f2].

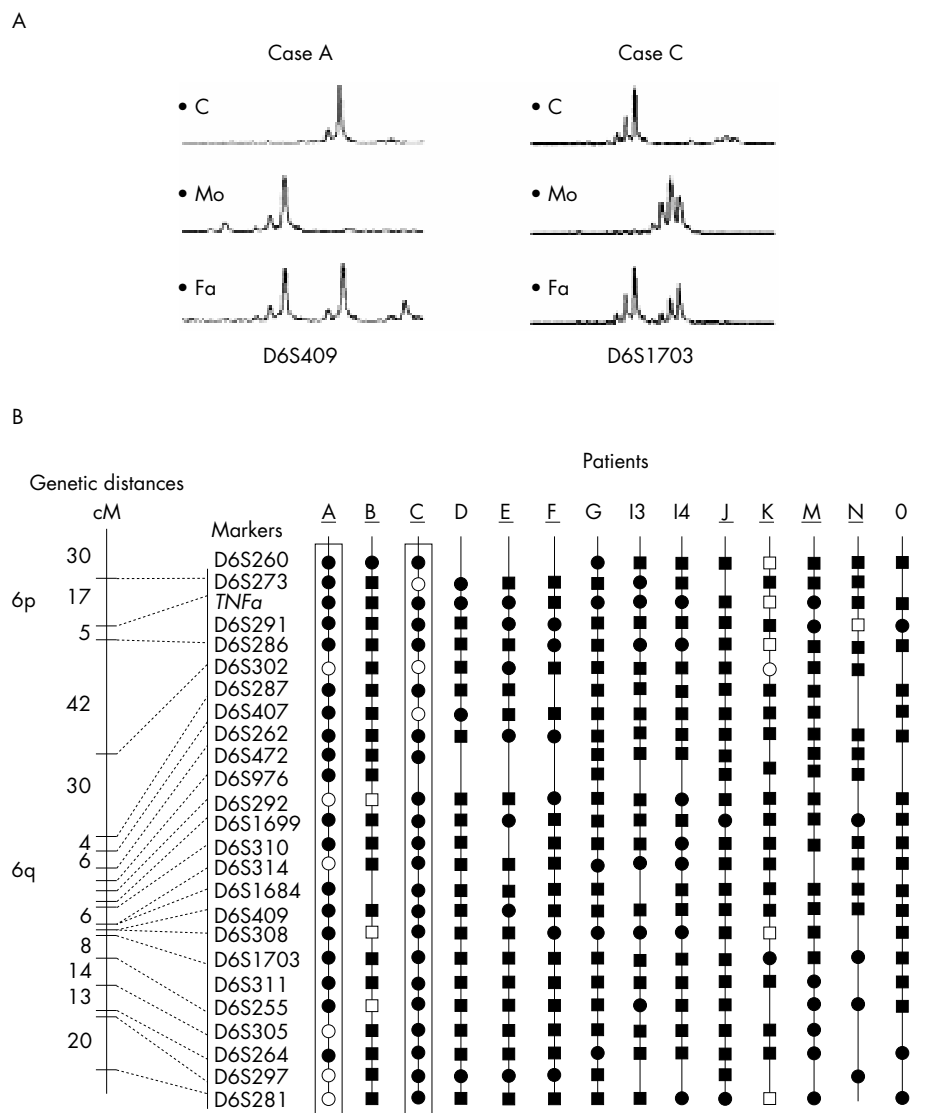


Figure 1 (A) Paternal chromosome 6 isodisomy in two transient ND patients, A and C. Chromosome 6 microsatellite markers D6S409 (case A) and D6S1703 (case C). C=affected child, Mo=mother, Fa=father. The patients have inherited one paternal allele and no allele from the mother. This was observed for all the chromosome 6 markers examined, covering the entire length of the chromosome. (B) Screening for a common region of homozygosity for chromosome 6 microsatellite markers in both transient ND (underlined) and permanent ND patients. The presence of contiguous homozygous markers could be used to identify a disomic region. The genotyping results are shown in terms of allele homozygosity. Black circle=homozygosity, black square=heterozygosity. The marker position in centimorgans (cM) is indicated on the left. Non-informative markers are shown by empty symbols.

with a heterozygote frequency of about 70% were selected from the Centre d'Etude du Polymorphisme (CEPH-Fondation Jean Dausset, <http://www.ceph.fr/ceph-genethon>). The genetic location and order of the markers were deduced from the integrated map of the Whitehead Institute (<http://www-genome.wi.mit.edu/>) and from the integrated cytogenetic and physical maps of the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/genemap/>). For genotyping, DNA microsatellite markers were amplified by PCR in a GeneAmp 9600 thermocycler (Perkin-Elmer). The PCR products were then analysed with GeneScan and GENOTYPER software (Applied Biosystems-(ABI)-Perkin Elmer, USA) after separation of the alleles by electrophoresis on a 6% denaturing polyacrylamide gel for two and a half hours in a model ABI 377 DNA sequencer (ABI-Perkin-Elmer). The markers for chromosome 6 are listed in fig 1B.

The exons encoding the *GK* gene were screened for mutations in members of family O and in patients B, C, K, M, and N with T2D in relatives by direct sequencing. The insulin promoter

factor-1 (*IPF1*) exons were analysed by direct sequencing of polymerase chain reaction (PCR) products in all the patients.

RESULTS

Molecular studies

We found no mutation in the *GK* or *IPF1* genes in the genomic DNA of the patients examined. The genotypes of the patients and their parents were determined using 24 polymorphic microsatellite markers covering the entire length of chromosome 6. Paternal isodisomy of chromosome 6 was found in two transient ND (22.2%) patients. One paternal allele and the complete absence of a maternal allele were found in cases A and C (fig 1A). All of the chromosome 6 markers were homozygous along the length of chromosome 6 (fig 1B). The other patients with transient or permanent ND displayed normal biparental inheritance of alleles (not shown). Additional markers tested for patients F, G, I3, I4, K, and N with homozygosity for either D6S308 or D6S1703 ruled out the presence of

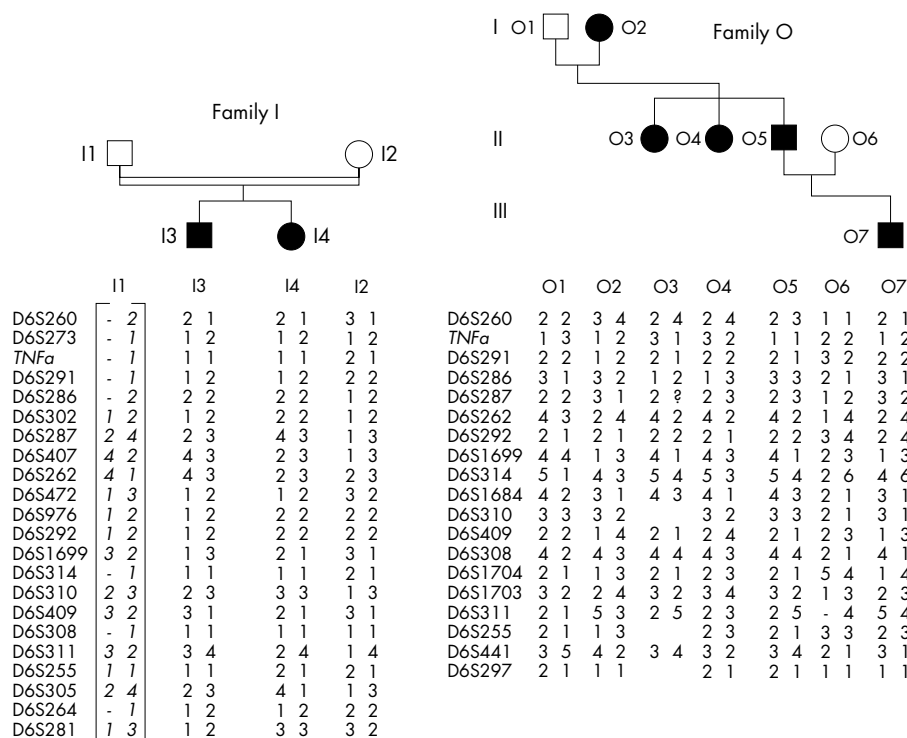


Figure 2 Results of dinucleotide repeat marker analysis for chromosome 6 in two familial permanent ND cases, families I and O. Markers are ordered from pter to qter (top to bottom) and are shown on the left. The haplotypes are shown with one possible phasing. Filled symbols: patients with permanent ND. Deduced haplotypes for subject I1 are shown in brackets.

a partial paternal uniparental disomy in the transient ND candidate region (not shown).

Two familial permanent ND cases were analysed by haplotyping chromosome 6 microsatellite markers. Family I was consanguineous; a meiotic recombination occurred in patients I3 and I4 between D6S255 and D6S305 on the maternal chromosome 6 and between D6S286 and D6S287 on the paternal chromosome 6, respectively (fig 2). The genotypes for family O are shown in fig 2. In each family, the affected patients inherited different haplotypes of the transient ND candidate region. Multipoint linkage analyses were performed using the MLINK component of the LINKAGE package version 5.1¹⁴ and the VITESSE algorithm¹⁵ for pedigrees I and O (not shown). Two point linkage analysis gave a maximum lod score of -4 at $\theta=0$ for marker D6S409, -2.10 at $\theta=0.001$, and ∞ at $\theta=0.0$ for multipoint calculation in pedigree I. In pedigree O, lod scores were -4.70 at $\theta=0.0$ multipoint calculation and -4.70 at $\theta=0.0$ for marker D6S308. All lod scores calculated in the interval were negative (markers used for pedigree O: D6S1699, D6S314, D6S1684, D6S310, D6S409, D6S308, D6S1704, D6S1003, and D6S1703, and for pedigree I: D6S292, D6S1699, D6S314, D6S1684, D6S310, D6S409, D6S308, D6S1003, and D6S311 (data not shown)). Both haplotype reconstruction and negative lod score values suggested that the locus on chromosome 6q24 was not linked to the disease in families I and O.

Developmental abnormalities in ND patients

Table 2 shows the congenital abnormalities present in eight of 14 cases in both transient and permanent ND forms. Three patients had thyroid abnormalities: thyroid agenesis in case I4 and hypothyroidism in cases C and I3. Skeletal abnormalities were also observed: multiple epiphyseal and metaphyseal dysplasia in case E and retardation of skeletal maturation in three patients, E, I4, and J. Congenital heart defects were present in patient C who had valvular mitral insufficiency and patient E who had an incomplete aortic arch interruption. Patient K had right kidney agenesis and brain atrophy.

Table 2 Phenotypes and developmental abnormalities of patients with neonatal diabetes (ND)

Patients	Phenotypes
Transient ND	
C	Mitral valve insufficiency, thyroid insufficiency, β thalassaemia
E*	Aortic arch defect, multiple epiphyseal dysplasia, high blood pressure
J	Multiple epiphyseal dysplasia
K	Left kidney agenesis, brain atrophy
Permanent ND	
D	Lung dysplasia, high blood pressure
G	Hypogonadism
I3*	Thyroid agenesis, pancreas dysplasia, hepatic failure, kidney failure, high blood pressure
I4*	Thyroid hypoplasia, pancreas dysplasia, multiple epiphyseal dysplasia, hepatic failure, kidney failure

*Case report in Zeller *et al.*²⁹

DISCUSSION

Transmission of the chromosome 6 microsatellite marker was studied for the 14 ND patients. A chromosome 6 paternal isodisomy was identified in 2/9 patients with transient ND, an abnormality which accounts for 20 to 30% of transient ND cases.¹⁶ Biparental transmission of the chromosome 6 alleles was found in seven out of nine patients with transient ND. In some of these patients, the disease is expected to result from an altered epigenotype. Methylation defects at the unique differentially methylated CpG island have been found in 47% of the patients examined: (2/8),⁷ (9/20),⁶ (5/6).¹⁷ However, no mutation at the *ZAC1/PLAGL1* gene locus could be identified in the transient ND patients examined.⁷

Haplotype analysis in two familial permanent ND cases showed the lack of a common haplotype in affected subjects and a negative lod score excluded the involvement of the loci predisposing to T1D on chromosome 6: IDDM15 (6q21),

Table 3 Review of published reports of congenital abnormalities in patients with neonatal diabetes (ND)

ND form/phenotypes	Genetic defect	References
Transient		
Macroglossia*	nd	Dacou Voutekakis <i>et al</i> ¹⁸ Temple <i>et al</i> ¹⁶
Macroglossia, umbilical hernia*	Paternal UPD(6)	Hermann <i>et al</i> ²² Temple <i>et al</i> ¹⁶
Macroglossia, coarse facial features	Paternal inv dup (6)(q22q23)	Arthur <i>et al</i> ³
Pancreatic β cell agenesis, methylmalonic acidaemia	Paternal UPD(6)	Abramovicz <i>et al</i> ⁵
Microcephaly	nd	Shield <i>et al</i> ¹
Macroglossia, anaemia, umbilical hernia	Paternal dup(6)	Temple <i>et al</i> ⁴
Macroglossia, hypertelorism, club foot	Paternal UPD(6)	Christian <i>et al</i> ²¹
Macroglossia, umbilical hernia, bilateral inguinal hernia, asymmetrical growth retardation, large fontanelles, hypospadias	nd	Battin <i>et al</i> ¹⁹
Umbilical hernia, delayed development, minor facial anomalies including "carp mouth", cardiomegaly	Dup(6)(q21q23)	Zneimer <i>et al</i> ²⁰
Permanent		
Pancreatic hypoplasia, congenital heart defect (transposition of the great vessels, ventricular septal defect, pulmonary stenosis, atrial septal defect), necrotic brain mass	nd	Yorifuji <i>et al</i> ²⁸
Dorsal pancreas agenesis, interventricular septal defect	nd	Gurson <i>et al</i> ²⁶
Type 1 diabetes, pancreas hypoplasia	nd	Carroll <i>et al</i> ²⁷
Microcephaly	nd	Reus <i>et al</i> ²⁴
Pancreatic exocrine insufficiency, congenital pancreatic agenesis	nd	Wright <i>et al</i> ²⁴
Primary congenital hypothyroidism	nd	Al Jurayyan <i>et al</i> ²⁰
Hypothyroidism, bilateral neurosensory deafness, myopia, dysmorphic features, congenital stridor, growth retardation	Mitochondrial diabetes eliminated	Muina <i>et al</i> ³¹
Pancreatic agenesis	<i>IPF1</i>	Stoffers <i>et al</i> ¹⁰
Renal hepatic pancreatic dysplasia	nd	Attia <i>et al</i> ²²
Cerebellar agenesis/hypoplasia	nd	Hoveyda <i>et al</i> ²³

nd=not determined.

*Macroglossia in 5/30 transient ND, association of macroglossia and umbilical hernia in 2/30 transient ND.¹⁶

IDDM5 (6q25), and IDDM8 (6q27) as well as the candidate locus for the transient ND form at 6q24. None of the five patients with permanent ND had abnormal chromosome 6 marker inheritance. The data support the concept of a different aetiology for transient and permanent ND forms.

Associations of developmental abnormalities that have not been previously highlighted occurred in eight of the 14 (57%) ND patients, affecting 4/9 transient ND and 4/5 permanent ND. As the mothers of the patients were not exposed to drugs or chemicals and were not overtly diabetic during pregnancy, the condition is probably not coincidental and is more likely to be the result of innate errors of development, probably of genetic origin. The classical features of transient ND include macroglossia^{16,18} and umbilical hernia^{3,4,16,19-22} (table 3). Other defects arising in the patients in this report show a larger than expected number of congenital abnormalities in transient ND¹³ that may be related to the nature of the genetic and epigenetic alterations involved.^{4,6,7} Congenital malformations in patients with permanent ND are different from those of transient ND with combinations including organs derived from branching to the main visceral tube²³ (table 3). The nature of the associated birth defects in ND patients suggests that the events responsible occurred during the early stages of embryogenesis.²³⁻³⁵ Three patients, cases E, J, and I4, had birth defect associations overlapping those of some patients with the Wolcott-Rallison syndrome (OMIM 226980).^{36,37} Although the *EIF2AK3* gene was not mutated in these three patients (not shown), this raises the possibility of functional pathway interactions. It is therefore important to assess critically currently held concepts of pathological development within carefully defined ND patient subgroups.

Low birth weight is a classical feature of ND patients. This condition is known to be associated with a later risk of dyslipidaemia, hypertension, cardiovascular disease,³⁸ and T2D.³⁹

Variants of ND responsible genes and epigenetic determinants involved in transient ND may be key contributors to suboptimal pancreatic development which later predisposes the child to long term abnormalities in insulin production, obesity, and metabolic disturbances or common complex diseases arising with age, such as T2D. The elucidation of genetic and molecular mechanisms in rare neonatal diabetes may provide evidence for new pathways connecting development and glucose metabolism with further insight into consequences in later life.

- Fourteen patients with transient or permanent ND were analysed at the molecular level and their main clinical features were recorded and integrated into a data collection of previously published case reports.
- Two of nine infants with transient ND displayed paternal chromosome 6 isodisomy. Haplotype analysis in two familial permanent ND cases were consistent with the non-involvement of the 6q24 candidate transient ND locus.
- Birth defects were observed in eight of 14 (57%) ND patients with different associations. Macroglossia and umbilical hernia were exclusively associated with the transient ND form. In permanent ND, associations of thyroid, pancreas, liver, heart, kidney, and skeletal abnormalities were found.
- Alterations in genes essential for glucose metabolism may lead to early onset insulin dependent diabetes mellitus with non-random patterns of early embryonic developmental abnormalities. Assigning patients to subgroups for further genetic analysis may help to unravel genetic and molecular mechanisms leading to these phenotypes.

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Authors' affiliations

E Marquis, C Junien, C Diatloff-Zito, Inserm-U383, Hôpital Necker-Enfants Malades, 149-161 rue de Sèvres, 75743 Paris Cedex 15, France

J J Robert, Fédération de Pédiatrie, Hôpital Necker-Enfants Malades, Université de Paris V, 149-161 rue de Sèvres, 75743 Paris Cedex 15, France

C Bouvattier, Hôpital Saint Vincent de Paul, Paris, France

C Bellanné-Chantelot, Laboratoire de Génétique Médicale, Fondation Jean Dausset CEPH, Paris, France

Correspondence to: Dr C Diatloff-Zito, Inserm U383, Hôpital Necker-Enfants Malades, 149-161 rue de Sèvres, 75743 Paris Cedex 15, France; diatloff@necker.fr

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