REVIEW ARTICLE

Transient neonatal diabetes, a disorder of imprinting

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Transient neonatal diabetes (TND) is a rare but distinct type of diabetes. Classically, neonates present with growth retardation and diabetes in the first week of life. Apparent remission occurs by 3 months but there is a tendency for children to develop diabetes in later life. Evidence suggests it is the result of overexpression of an imprinted and paternally expressed gene/s within the TND critical region at 6q24. Two imprinted genes, *ZAC* (zinc finger protein associated with apoptosis and cell cycle arrest) and *HYMAI* (imprinted in hydatidiform mole) have been identified as potential candidates. Three genetic mechanisms have been shown to result in TND, paternal uniparental isodisomy of chromosome 6, paternally inherited duplication of 6q24, and a methylation defect at a CpG island overlapping exon 1 of *ZAC/HYMAI*.

DEFINITION OF TRANSIENT NEONATAL DIABETES

Transient neonatal diabetes is defined as diabetes beginning in the first 6 weeks of life in a term infant with recovery by 18 months of age. A significant proportion of patients go on to develop diabetes in later life and thus the natural history can be split into three phases: phase 1, neonatal diabetes → phase 2, apparent remission → phase 3, relapse of type 2 diabetes.

The incidence in the UK is 1 in 400 000 based on a British Paediatric Association Surveillance Unit (BPASU)) study conducted by Shield *et al*.[1]

HISTORICAL FACTS

Reports of neonatal diabetes date back to Ramsey in 1926,[2] who reported a male infant with a low birth weight at term who was diagnosed with diabetes at 4 weeks of age, required insulin temporarily, and recovered by 10 weeks. The patient was reassessed at 4 years of age and was reported as healthy. However, the early authors did not distinguish between transient and permanent neonatal diabetes in their reports and it was not until the paper of Hutchinson *et al*[3] in 1962 that this was clarified and they called the condition "Congenital temporary diabetes mellitus". It was Lawrence in a letter to the *BMJ*[4] who pointed out that it was neonatal and not congenital diabetes and Cornblath and Schwartz[5] in 1966 who coined the name "transient neonatal diabetes mellitus". In 1986, Briggs *et al*[6] drew attention to a female with TND who developed non-insulin dependent diabetes in later life and Shield and Baum[7] speculated that TDN might be a risk factor for diabetes in later life. In 1995, Muhlendahl and Herkenhoff[8] conducted a long term follow up of published cases and identified 13 infants with TND with later recurrence.

THE SEARCH FOR THE TND GENE

Although there were occasional reports in sibs (Coffey *et al*[9] reported TND in paternal half sibs, and Fergusson *et al*[10] reported diabetes in sibs), as the majority were sporadic a genetic cause was not suspected. The first lead came in 1995 when two children with TND were discovered to have paternal uniparental isodisomy of chromosome 6 (pat UPD(6)).[11] The first case was part of a systematic study to identify the incidence of UPD in carriers of supernumerary marker chromosomes (SMCs).[12] The patient had few developmental or dysmorphic features and was karyotyped because of intrauterine retardation and a large tongue. She developed diabetes within 24 hours of birth but recovered by 4 months and a diagnosis of TND was made clinically. In published reports at that time, two other cases of pat UPD(6) had been identified.[13 14] In both instances the discovery had been made following the development of a rare recessive condition. The first was in a 10 year old child with complete deficiency of complement 4 and no neonatal details were given, and the second developed methyl-malonic acidaemia. However the latter patient, who died at 16 days of age, also had neonatal diabetes. There have now been a further 18 cases reported with paternal UPD(6) and TND[15–23] and it has been found to account for 50% of sporadic cases tested.[20]

In 1996, Temple *et al*[24] discovered that paternal (and not maternal) transmission of a visible duplication of chromosome 6q24 could also lead to TND and this was reproduced in several studies including that of Cave *et al*,[17] who discovered a paternal 6q24 duplication in six of 13 cases with TND. This mechanism accounted for all familial cases. Soon submicroscopic duplications were identified using quantitative PCR.[20 25] Overlapping duplications reduced the TND candidate region to 440 kb.[25] These observations led to the hypothesis that an imprinted region existed on chromosome 6 and that overexpression of an imprinted and paternally expressed gene caused the condition.

Two imprinted genes were identified within the region, *ZAC* (zinc finger protein associated with apoptosis and cell cycle arrest) and *HYMAI* (imprinted in hydatidiform mole),[26] shown in fig 1. The region was also found to contain eight CpG islands (CGIs). One CGI was shown to be differentially methylated in normal subjects such that the paternal CGI was unmethylated and the maternal CGI methylated[25–27] (named TND CGI). The imprinted locus was also identified using

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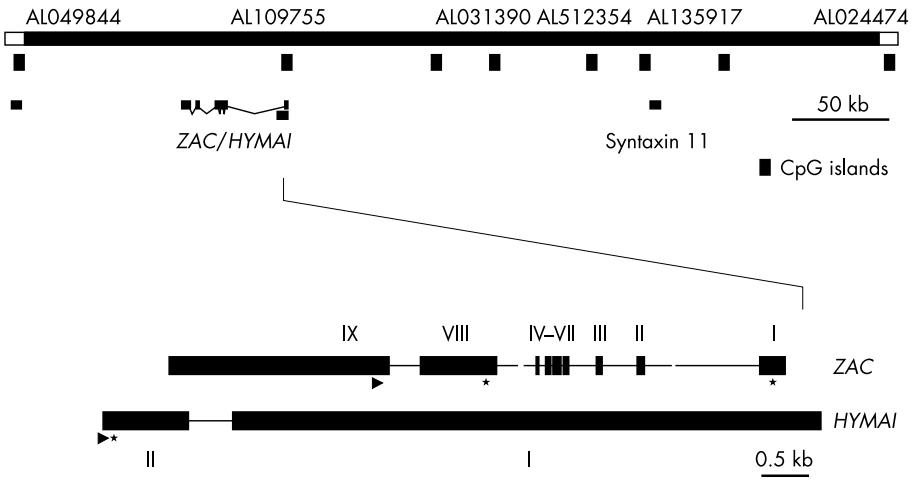

Figure 1 A map to show the minimal TND critical region defined by the smallest region of overlap in duplication cases.[25] The darker hatched CGI overlapping *ZAC* and *HYMAI* is differentially methylated (methylated only on the maternal allele). The other CGIs are unmethylated. The sites of the three genes known within the region are marked. The gene structures of *ZAC* and *HYMAI* are included but are not to scale. Exon numbering of *ZAC* is taken from Varrault *et al*.[28]

restriction landmark genome scanning by Kamiya *et al*.[27] They showed that *ZAC* was an imprinted gene in fetal tissues and hypothesised that this was the candidate gene for TND. Varrault *et al*[28] showed that exon 1 of *ZAC* extended into the imprinted CGI and that unmethylated CG rich sequences within the CGI had promoter activity. This was supported by the work of Arima *et al*[29] who reported that methylation of these sequences silenced promoter activity.

Overexpression of ZAC might cause TNDM through its function as a regulator of cell cycle arrest and apoptosis, altering the absolute number and efficiency of beta islet cells during a critical time of pancreatic development in utero.[30] A reduced absolute number of islets might be sufficient to maintain normoglycaemia during the remission phase of the disease but manifest as diabetes at times of metabolic stress, such as intercurrent illness or adolescence. Alternatively we know that ZAC also regulates the expression of the PACAP (pituitary adenylate cyclase activating polypeptide) receptor 1, PACAP being a very potent insulin secretagogue that acts through the PACAP1 receptor in the pancreas.[31] It is possible that ZAC overexpression alters normal islet cell responsiveness to PACAP in some as yet unknown manner. *HYMAI* sequence overlaps *ZAC* and is also imprinted.[26] However, it has no open reading frame and its function is not clear. It remains, however, a potential candidate for TND as to date no mutations have been reported in either gene. Recently, islet cells from a transgenic mouse overexpressing the TNDM locus have shown an inadequate insulin secretory response to glucose stimulation confirming the importance of the locus to normal pancreatic physiology (G Kelsey, personal communication).

In 2000, Gardner *et al*[25] showed that in a number of TND cases the TND CGI was completely unmethylated on both alleles in the absence of uniparental disomy. They termed this a "methylation defect". Mackay *et al*[31] later showed aberrant expression of both *ZAC* and *HYMAI* in a TND patient with a methylation defect. They showed a relaxation of the normal monoallelic expression of both genes in skin fibroblasts of the patient and this provides strong support that the presence of two unmethylated alleles at this locus is associated with inappropriate gene expression.

Therefore, three interrelated genetic mechanisms have now been described in TND: paternal UPD(6), paternal duplication of 6q24, and a methylation defect within the TND CGI. All can be predicted to result in overexpression of a paternally expressed gene with provisional evidence that this is the case for both *ZAC* and *HYMAI*.

In a cohort of 30 patients with TND reported by Temple *et al*[20] in 2000, 23 were sporadic cases and seven were familial from two families. One of the three mechanisms was identified as the cause of TND in 24/30 cases studied (80%). Of the sporadic cases 11/23 (≈50%) had pat UPD(6), 4/23 (≈20%) had a paternal duplication of 6q24, and 2/24 had a methylation defect (8%).

CLINICAL FINDINGS: THE 6q24 PHENOTYPE

The genetic classification of TND cases has allowed the 6q24 phenotype to be differentiated from other causes of neonatal diabetes.

Phase 1: neonatal diabetes

The main findings in the neonatal period are growth retardation at term, an onset of diabetes within the first week of life, and recovery within three months. Based on the study of Temple *et al*[20] in 2000, the average birth weight was 1930 g at 39 weeks' gestation. The median age at presentation was 3 days and the average age at presentation was 7 days. The median length of time on insulin was 12 weeks (average 111 days). Glycosuria is often discovered incidentally during investigation for dehydration and weight loss and some of the differences in age of presentation in published reports are likely to be because of delay in diagnosis.

Another feature noted in the neonatal period by many authors is macroglossia. This was found in 1/3 of cases in the series of Temple *et al*[20] and was not related to any specific genetic mechanism. An umbilical hernia is also occasionally described.[20] These findings remain unexplained although it is of interest that the tongue and umbilicus are also abnormal in Beckwith-Wiedemann syndrome, which is another condition resulting from aberrant imprinting mechanisms.

The systematic investigation of neonatal diabetes in patients with TND is difficult, as the condition is so rare. However, in those where further studies have been performed, insulin levels were low or undetectable at presentation but ketonuria was usually absent.[1 8 17 20] There was no association with HLA antigens common in type 1 diabetes[1] and there was no evidence that TND was the result of autoimmunity. Islet cell antibodies were negative.[20]

Phase 2: apparent remission

This phase is associated with normal growth and development in the majority.[20] There is evidence that patients may develop hyperglycaemia during periods of intermittent illness (personal observation). Few studies have been performed on

patients during this remission phase and none has yielded consistent results. Seven patients were studied with a standard intravenous glucose tolerance test (IVGTT) by Shield *et al* (personal communication) during apparent remission. Four cases had low insulin secretion but in three it was normal.

Phase 3: relapse of diabetes

Relapse has been reported in approximately 50-60%[20] of TND cases although no long term follow up of cases diagnosed at birth has yet been reported so this figure is likely to be an over-ascertainment. Of 15 relapsed cases studied in the UK, the earliest age of relapse was 4 years and the average age was 14 years (personal observation). Treatment in this group varied between diet alone (4/15), oral hypoglycaemic agents (2/15), and insulin (9/15). The variability of treatment modalities has been suggested to imply that this condition is more akin to type 2 diabetes.[1] It should be noted that often the exogenous insulin requirement is lower than that usually seen in type 1 diabetes, may be intermittent, and there is some evidence to support insulin resistance in two cases studied by Shield *et al*.[32]

BROADENING THE PHENOTYPE

In 2000, Temple *et al*[20] reported two cases that suggested that the 6q24 phenotype might be broader than that described above. Two relatives with identical paternal 6q24 duplications to the probands were identified who presented first in adulthood with type 2 diabetes and no early history. One was the paternal aunt of the sibs first reported by Fergusson and Milner,[10] who developed gestational diabetes and was treated by diet alone, and the other was a male sib in an unrelated family who developed type 2 diabetes in his teens. This observation led to studies to discover the incidence of chromosome 6 anomalies (as seen in TND) in cohorts of patients with other types of diabetes. These have all been negative and included the only published study by Shield *et al*,[33] who looked at a cohort of MODY cases where known MODY gene mutations had been previously excluded. A cohort of 65 type 2 diabetics has also been studied but with similar negative results (D J G Mackay, personal communication).

It must be concluded therefore that the clinical presentation of an imprinted 6q24 anomaly may not invariably include a neonatal presentation, but that this is not a frequent cause of commoner types of adult diabetes. However, in 2001, Lindsay *et al*[34] showed weak linkage of diabetes in Pima Indians to paternally derived alleles at 6q24 (lodAF=0.9) and this locus may yet be shown to play a role in more common types of diabetes perhaps through common polymorphic variants.

GENETIC COUNSELLING

No phenotypic differences have been found between patients with UPD(6), duplication of 6q, and a methylation defect. The classical natural history of the condition can therefore be used for counselling purposes for all groups of patients with the added proviso that occasionally a child identified, perhaps in utero, may not necessarily develop diabetes in the neonatal period but is at risk of developing it in the long term.

Cases with UPD(6) are predicted to be sporadic with a low recurrence risk to both sibs and offspring. A duplication of 6q24 has been found in all familial cases to date. If the duplication is passed on by a female the offspring risk of developing TND is low but TND may occur in subsequent generations. Males with a duplication will have a 50% risk of passing it on and having an affected child; however, as discussed above it is not inevitable that the child will present in the neonatal period. The sib and offspring risk for the methylation cases are not known. Of seven cases with a methylation defect all have been sporadic (personal observation). However, it is possible that a maternal mutation/deletion (not identified by the technique used to show the abnormal methylation pattern) may be present and could theoretically result in recurrence risks for sibs and offspring as high as 50%, but this is speculative at present.

DIFFERENTIAL DIAGNOSIS

When a patient presents with diabetes in the neonatal period, there are a number of other conditions that must be considered. Cave *et al*[17] estimated that TND accounted for only 50-60% of cases of diabetes presenting in the neonatal period. In the absence of a demonstrable chromosome 6 abnormality it is not possible to differentiate TND from permanent neonatal diabetes mellitus (PNDM) in the neonatal period. PNDM is usually diagnosed by the natural history and is defined as diabetes developing in the neonatal period that never goes into remission. There are likely to be many causes. Stoffers *et al*[35] described the first case to have a specific gene mutation in 1997, when they identified a child with pancreatic agenesis homozygous for a single nucleotide deletion in the *IPF-1* gene encoding the homeodomain protein IPF-1. This protein is a critical regulator of insulin gene function in the islet cell. Imaging of the pancreas may help to differentiate such cases.

Wolcott-Rallison syndrome[36] is an autosomal recessive disorder characterised by infancy onset (often within the neonatal period) diabetes and spondyloepiphyseal dysplasia. The skeletal findings may develop later, however, and this condition is the result of mutations in *EIF2AK3* at 2p12.[37] This gene is highly expressed in islet cells acting as a regulator of protein synthesis.

X linked immunodysregulation, polyendocrinopathy, and enteropathy (IPEX)[38] is a disorder of autoimmunity that occurs in males presenting with neonatal diabetes, immune dysregulation, intractable diarrhoea, eczematous or psoriataform skin rash, and very raised levels of IgE. It is usually lethal in the first months or years of life from overwhelming sepsis.

X linked phosphoribosyl-ATP pyrophosphatase hyperactivity[39] causes diabetes early in life and glucose intolerance may persist throughout life. However, it is associated with major problems including mental retardation, ataxia, and a progressive axonal neuropathy.

Glucokinase deficiency (*MODY2*) is caused by mutations in the glucokinase gene[40] and usually leads to mild hyperglycaemia in affected subjects. However, within two families (one Norwegian, one Italian) two infants presented with classical PNDM who were homozygous for missense mutations within the glucokinase gene rendering them completely deficient in glycolytic activity.[41] A further syndrome is an autosomal recessive condition of neonatal diabetes and cerebella hypoplasia.[42] The infants all died within a few months of birth and the genetic basis is unknown.

CONCLUSION

TND is a rare but distinct cause of neonatal diabetes with a good prognosis compared to many other causes of childhood diabetes. It is the result of an imprinted gene(s) at 6q24 and the genetic cause can be identified in 80% of cases.[20] This locus may play a role in other more common types of diabetes.

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REFERENCES

1 **Shield JPH**, Gardner RJ, Wadsworth EJK, Whiteford ML, James RS, Robinson DO, Baum JD, Temple IK. Aetiopathology and genetic basis of neonatal diabetes. *Arch Dis Child* 1997;**76**:F39-42.
2 **Ramsey WR**. Glycosuria of the newborn treated with insulin. *Trans Am Pediatr Soc* 1926;**38**:100-1.
3 **Hutchinson JH**, Keay AJ, Kerr MM. Congenital temporary diabetes mellitus. *BMJ* 1962;**2**:436-40.
4 **Lawrence RD**. Congenital diabetes mellitus. *BMJ* 1962;**2**:671-2.
5 **Cornblath M**, Schwartz R. *Disorders of carbohydrate metabolism: major problems in clinical paediatrics*. Philadelphia: Saunders, 1966;**3**:105-12.
6 **Briggs JR**. Permanent non-insulin dependent diabetes mellitus after congenital transient neonatal diabetes. *Scott Med J* 1986;**31**:41-2.
7 **Shield JPH**, Baum JD. Is transient neonatal diabetes a risk factor for diabetes in later life? *Lancet* 1993;**341**:693.
8 **Von Mühlendahl KE**, Herkenhoff H. Long-term course of neonatal diabetes. *N Engl J Med* 1995;**333**:704-8.
9 **Coffey JD**, Womach NC, Natchez M. Transient neonatal diabetes mellitus in half sisters. *Am J Dis Child* 1967;**113**:480-2.
10 **Fergusson AW**, Milner RDG. Transient neonatal diabetes mellitus in sibs. *Arch Dis Child* 1970;**45**:80-3.
11 **Temple IK**, James RS, Crolla JA, Sitch FL, Jacobs P. An imprinted gene(s) for diabetes? *Nat Genet* 1995;**9**:110-12.
12 **James RS**, Temple IK, Dennis NR, Crolla JA. A search for uniparental disomy in carriers of supernumerary markers chromosomes. *Eur J Hum Genet* 1995;**3**:21-6.
13 **Welch TR**, Beischel LS, Choi E, Balakrishnan K, Bishof NA. Uniparental isodisomy 6 associated with deficiency of the fourth component of complement. *J Clin Invest* 1990;**86**:675-8.
14 **Abramowicz MJ**, Andrien M, Dupont E, Dorchy H, Parma J, Duprez L, Ledley FD, Courtens W, Vamos E. Isodisomy of chromosome 6 in a newborn with methyl-malonic acidaemia and agenesis of pancreatic beta cells causing diabetes mellitus. *J Clin Invest* 1994;**94**:418-21.
15 **Hermann R**, Soltesz G. Paternal uniparental disomy of chromosome 6 in transient neonatal diabetes mellitus. *Eur J Ped* 1997;**156**:740.
16 **Whiteford ML**, Narendra A, White MP, Cooke A, Wilkinson AG, Robertson KJ, Tolmie JL. Paternal uniparental disomy of chromosome 6 causes transient neonatal diabetes. *J Med Genet* 1997;**34**:167-8.
17 **Cave H**, Polak M, Drunat S, Denamur E, Czernichow P. Refinement of the 6q chromosomal region implicated in transient neonatal diabetes. *Diabetes* 2000;**49**:108-13.
18 **Hermann R**, Laine AP, Johansson C, Niederland T, Tokarska L, Dziatowiak H, Ilonen J, Soltesz G. Transient but not permanent neonatal diabetes mellitus is associated with paternal uniparental disomy of chromosome 6. *Pediatrics* 2000;**105**:49-52.
19 **Marquis E**, Robert JJ, Benezech C, Junien C, Diatloff-Zito C. Variable features of transient neonatal diabetes mellitus with paternal isodisomy of chromosome 6. *Eur J Hum Genet* 2000;**8**:137-40.
20 **Temple IK**, Gardner RJ, MacKay DJG, Barber JCK, Robinson DO, Shield JPH. Transient neonatal diabetes mellitus: widening our understanding of the aetiopathogenesis of diabetes. *Diabetes* 2000;**49**:1359-66.
21 **Das S**, Lese CM, Song M, Jensen JL, Wells LA, Barboski BL, Roseberry JA, Camacho JM, Ledbetter DH, Schur RE. Partial paternal uniparental disomy of chromosome 6 in an infant with neonatal diabetes, macroglossia and craniofacial abnormalities. *Am J Hum Genet* 2000;**67**:1586-91.
22 **Eggermann T**, Marg W, Mergenthaler S, Eggermann K, Schemmel V, Stoffers U, Zerres K, Spranger S. Origin of uniparental disomy 6: presentation of a new case and review on the literature. *Ann Genet* 2001;**44**:41-5.
23 **Milenkovic T**, Zdravkovic D, Garner RJ, Ignjatovic M, Jankovic B. Transient neonatal diabetes mellitus in a child with paternal uniparental disomy of chromosome 6. *J Pediatr Endocrinol Metab* 2001;**14**:893-5.
24 **Temple IK**, Gardner RJ, Robinson DO, Kibirige MS, Ferguson AW, Baum JD, Barber JCK, James RS, Shield JPH. Further evidence for an imprinted gene for neonatal diabetes localized to chromosome 6q22-23. *Hum Mol Genet* 1996;**5**:1117-21.
25 **Gardner RJ**, Mackay DJG, Mungall AJ, Polychronakos C, Siebert R, Shield JPH, Temple IK, Robinson DO. An imprinted locus associated with transient neonatal diabetes mellitus. *Hum Mol Genet* 2000;**9**:589-96.
26 **Arima T**, Drewell RA, Oshimura M, Wake N, Surani MA. A novel imprinted gene, HYMAI, is located within an imprinted domain on human chromosome 6 containing ZAC. *Genomics* 2000;**67**:248-55.
27 **Kamiya M**, Judson H, Okazaki Y, Kusakabe M, Muramatsu M, Takada S, Takagi N, Arima T, Wake N, Kamimura K, Satomura K, Hermann R, Bonthron DT, Hayashizaki Y. The cell cycle control gene ZAC/PLAGL1 is imprinted - a strong candidate gene for transient neonatal diabetes. *Hum Mol Genet* 2000;**9**:453-60.
28 **Varrault A**, Bilanges B, Mackay DJG, Basyuk E, Ahr B, Fernadez C, Robinson DO, Bockaert J, Journot L. Characterization of the methylation-sensitive promoter of the imprinted ZAC gene supports its role in transient neonatal diabetes mellitus. *J Biol Chem* 2001;**276**:18653-6.
29 **Arima T**, Drewell RA, Arney KL, Inoue J, Makita Y, Hata A, Oshimura M, Wake N, Surani MA. A conserved imprinting control region at the HYMA1/ZAC domain is implicated in transient neonatal diabetes. *Hum Mol Genet* 2001;**10**:1475-83.
30 **Varrault A**, Ciani E, Apiou F, Bilanges B, Hoffmann A, Pantaloni C, Bockaert J, Spengler D, Journot L. hZAC encodes a zinc finger protein with antiproliferative properties and maps to a chromosomal region frequently lost in cancer. *Proc Natl Acad Sci USA* 1998;**95**:8835-40.
31 **Ciani E**, Hoffmann A, Schmidt P, Journot L, Spengler D. Induction of the PAC1-R (PACAP-type I receptor) gene by p53 and Zac. *Mol Brain Res* 1999;**69**:290-4.
32 **Mackay DJG**, Coupe AM, Shield JPH, Storr JNP, Temple IK, Robinson DO. Relaxation of imprinted expression of ZAC and HYMAI in a patient with transient neonatal diabetes mellitus. *Hum Genet* 2002;**110**:139-44.
33 **Shield JPH**, Baum JD. Transient neonatal diabetes and later onset diabetes - a case of inherited insulin-resistance. *Arch Dis Child* 1995;**72**:56-7.
34 **Shield J**, Owen K, Robinson DO, Mackay D, Ellard S, Hattersley A, Temple IK. Maturity onset diabetes of the young (MODY) and early onset type II diabetes are not caused by loss of imprinting at the transient neonatal diabetes (TNDM) locus. *Diabetologia* 2001;**44**:924.
35 **Lindsay RS**, Kobes S, Knowler WC, Bennett PH, Hanson RL. Genome-wide linkage analysis assessing parent-of-origin effects in the inheritance of type 2 diabetes and BMI in Pima Indians. *Diabetes* 2001;**50**:2850-7.
36 **Stoffers DA**, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in human IPF-1 coding region. *Nat Genet* 1997;**15**:106-10.
37 **Wolcott CD**, Rallison ML. Infancy-onset diabetes mellitus and multiple epiphyseal dysplasia. *J Pediatr* 1972;**80**:292-336
38 **Delepine M**, Nicolino M, Barrett T, Golamaully M, Lathrop GM, Julier C. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nat Genet* 2000;**25**:406-9.
39 **Brunkow ME**, Jeffery EW, Hjerrild KA, Paeper B, Clark LB, Yasayko SA, Wilkinson JE, Galas D, Ziegler SF, Ramsdell F. Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. *Nat Genet* 2001;**27**:68-73.
40 **Christen HJ**, Hanefield F, Duley JA, Simmonds HA. Distinct neurological syndrome in two brothers with hyperuricaemia. *Lancet* 1992;**340**:1167-8.
41 **Ellard S**. Hepatocyte nuclear factor 1 alpha (HNF-1alpha) mutations in maturity-onset diabetes of the young. *Hum Mutat* 2000;**16**:377-85.
42 **Njolstad PR**, Oddmund S, Cuesta-Munoz A, Bjorkhaug L, Massa O, Barbetti F, Permanent neonatal diabetes mellitus due to glucokinase deficiency: an inborn error of the glucose/insulin signaling pathway. *N Engl J Med* 2001;**344**:1588-92.
43 **Hoveyda N**, Shield JPH, Garrett C, Chong WK, Beardsall K, Bentsi-Enchill E, Mallya H, Thompson MH. Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: report of an association in three members of a consanguineous family. *J Med Genet* 1999;**36**:700-4.