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INTRODUCTION: Recently, interest in "neonatal" diabetes has increased because patients could stop taking insulin and improve glycemic control and associated neurologic features.
OBJECTIVE: Our objective was to determine the anticipated increase in prevalence and incidence of permanent neonatal diabetes in children, adolescents, and adults and investigate the impact of the new definition.
METHODS: We studied 293 (53% male) referrals to the Exeter Laboratory (Devon, United Kingdom) as part of the largest international series to date. The referred patients were diagnosed with diabetes below 6 months of age irrespective of current age, and their conditions had not remitted at the time of study. Data on 27 countries were collected, and age of diagnosis, date of birth, and gender were obtained from standardized forms. All referred patients were tested for *KCNJ11* mutations.
RESULTS: The minimum observed prevalence of the 5 most representative countries was 1.17 (1.01–1.31) per million population, with the estimated true prevalence twice as high. Prevalence was higher for the pediatric versus adult age range (odds ratio: 0.78 [95% confidence interval: 0.54–1.31] vs 0.42 [95% confidence interval: 0–0.50], respectively; $P = .009$). Seventy-five percent of the patients were below 16 years of age with a median (interquartile range) of 5.7 (2.4–10.2) years, which implies underdiagnosis beyond 5 years of age. Age of diagnosis was skewed to a median (interquartile range) of 6 (1–13) weeks, with 62% in the first 8 weeks. During 2000–2004, the minimum observed incidence was 2.95 (0–49.1) per million live births.
CONCLUSIONS: This is the first report to show 2 to 25 times higher prevalence than previous reports from 10 years ago. "Neonatal" should be changed to "diagnosed at <6 months of age irrespective of current age," and awareness should be increased, especially for those who are older than 5 years and present with treatment implications.

Genetics

IDENTIFICATION OF 7 NOVEL TRANSFORMING GROWTH FACTOR β RECEPTOR 2 MUTATIONS IN CHINESE PATIENTS WITH MARFAN SYNDROME

Submitted by Hon Yin Brian Chung

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INTRODUCTION: Marfan syndrome (MFS) (Online Mendelian Inheritance in Man [OMIM] No. 154700) is an autosomal-dominant connective tissue disorder that affects multiple systems including the cardiovascular, ocular, and musculoskeletal systems. Fibrillin 1 (FBN1) (OMIM No. 134797) mutations are causative in >90% of the cases, and recent studies have shown that transforming growth factor β receptor 2 (*TGFBR2*) (OMIM No. 190182) mutations could be identified in ~10% of non-*FBN1* probands (Mátyás G, Arnold E, Carrel T, et al. *Hum Mutat*. 2006;27:760–769).
OBJECTIVE: Our objective was to examine the mutation spectrum of *TGFBR2* in non-*FBN1* Chinese patients with MFS and related phenotypes.
METHODS: All Chinese probands who were referred for evaluation of MFS and tested negative for *FBN1* mutations were included. Mutational screening was performed by denaturing high-pressure liquid chromatography (Kosaki K, Udaka T, Okuyama T. *Mol Genet Metab*. 2005;86:117–123). Amplicons with an abnormal elution pattern were selected for direct sequencing.
RESULTS: Seven novel mutations were identified in 7 of 41 probands. All of them had prominent cardioskeletal phenotypes without ocular or dural involvement, which confirmed previous findings (Disabella E, Grasso M, Marziliano N, et al: *Eur J Hum Genet*. 2006;14;34–38). Six mutations were missense (R190H, D247V, T325P, G357R, I510N, and T530I), and 1 was frameshift (P501fsX17). Except for R190H, all were found in the functionally important kinase domain. Bioinformatic analyses showed that (1) all mutations occurred in conserved positions by cross-species comparison between 6 orthologs, and (2) R190H, T325P, T530I, and G357R were also found in conserved positions among 3 paralogs (*TGFBR1* and activin receptors AVR2A and AVR2B) in the TGFBR superfamily. None of the 7 were found in 50 unaffected individuals (100 normal alleles). With the *TGFBR2* mutations, 4 additional probands would fulfill the diagnostic criteria of MFS.
CONCLUSIONS: *TGFBR2* mutation was identified in 17% of our non-*FBN1* probands. It should be considered in the evaluation for MFS after *FBN1* screening, especially if there are compatible clinical features.

MUTATIONAL ANALYSIS OF *PTPN11* AND *KRAS* GENES IN TAIWANESE CHILDREN WITH NOONAN SYNDROME

Submitted by Fu-Sung Lo

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INTRODUCTION: Noonan syndrome (NS) is an autosomal-dominant disorder that presents with a characteristic face, short stature, skeletal anomalies, and congenital heart defects. Protein-tyrosine phosphatase nonreceptor-type 11 (*PTPN11*), encoding SHP-2, mutation was the first reported gene involved and accounted for 31% to 60% of cases of NS. The *KRAS* gene was the second reported gene and was recently identified in a small number of patients with NS.
OBJECTIVE: Our goal was to perform mutational analysis of *PTPN11* and *KRAS* genes in children with NS.
METHODS: In this study we screened for mutation of the *PTPN11* and *KRAS* genes in 73 Taiwanese patients with NS. The mutation analysis of the 15 coding exons and exon/intron boundaries was performed by polymerase chain reaction and direct sequencing of the *PTPN11* gene. The mutation analysis of 5 coding exons and exon/intron boundaries was performed by polymerase chain reaction and direct sequencing of the *KRAS* gene. We identified 12 different missense *PTPN11* mutations in 15 (21%) patients with NS and 2 different missense *KRAS* (V14I and I36M) mutations in 2 (3%) patients with NS. These *PTPN11* gene mutations were clustered in exon 3 ($n = 6$) encoding the N-SH2 domain and 13 ($n = 5$) encoding the PTP domain.
CONCLUSIONS: This study provides support that *PTPN11* and *KRAS* mutations are responsible for NS in Taiwanese patients.

SCREENING OF MUTATIONS IN THE *NPHS2* GENE IN GREEK PATIENTS WITH AUTOSOMAL-RECESSIVE STEROID-RESISTANT NEPHROTIC SYNDROME

Submitted by Spyridon Megremis

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INTRODUCTION: Mutations in the *NPHS2* gene, encoding podocin, are a major cause of autosomal-recessive steroid-resistant nephrotic syndrome (SRNS) in childhood and have been observed in 6.4% to 30% of sporadic and 20% to 40% of familial cases.
OBJECTIVE: We investigated mutations in the coding region of the *NPHS2* gene in Greek patients with SRNS and identified a novel A295T mutation.
METHODS: The study included 16 child patients with SRNS (14 families); 11 cases were sporadic, and 5 (from 3 families) were familial. All 8 exons of *NPHS2*, including intron boundaries, were screened for sequence variations by using denaturing gradient gel electrophoresis followed by specific characterization using direct DNA sequencing.
RESULTS: The results revealed 2 pathogenic genotypes in 2 patients with sporadic SRNS (R138Q/R138Q and R229Q/A295T). In addition, 3 previously described *NPHS2* intronic polymorphisms (IVS3–46C→T, IVS3–21C→T, and IVS7+7A→G), 1 thus-far-unreported intronic variant (IVS3–17C→T), and 4 known silent mutations (G34G, S96S, A318A, and L346L) were detected in sporadic and familial cases as well as in healthy controls.
CONCLUSIONS: These findings indicate that *NPHS2* mutations are not a frequent cause of familial SRNS in Greek patients. Among patients with sporadic SRNS, the genotypes R138Q/R138Q and R229Q/A295T account for an allelic frequency of 18.2%. The R138Q mutation is well characterized. The novel mutation, A295T (883G→A), is predicted in silico to cause a structural alteration in the cytoplasmic domain of podocin (see the PolyPhen database at http://genetics.bwh.harvard.edu/pph). This is the first report of *NPHS2* mutations in the Greek population and the first description of the A295T amino acid substitution.

CLINICAL STUDIES AND ANALYSIS OF THE RETT SYNDROME GENE (*MECP2*) IN CHILDREN WITH MENTAL RETARDATION IN THE GREEK POPULATION

Submitted by Stavroula Psoni

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INTRODUCTION: Mutations in the methyl CpG-binding protein 2 (*MECP2*) gene are responsible for 70% to 95% of cases of Rett syndrome (RS), an X-linked dominant neurodevelopmental disorder that mostly affects girls. Classical RS is characterized by normal early development followed by psychomotor regression and gradual onset of microcephaly, although variable atypical forms have also been observed. *MECP2* has also been implicated in a variety of other mental retardation (MR) phenotypes, including X-linked MR, fragile X syndrome–like and Angelman syndrome (AS)–like phenotypes.
OBJECTIVE: Our goals were to evaluate the incidence and spectrum of *MECP2* mutations in children with RS

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Pediatrics 2008;121;S116
DOI: 10.1542/peds.2007-2022MMM

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