

Publications de l'U 383 (Inserm) (1999-2005)

2005

ALLARD D., AMSELLEM S., ABIFADEL M., TRILLARD M., DEVILLERS M., LUC G., KREMPF M., REZNIK Y., GIRARDET J.P., FREDENRICH A., JUNIEN C., VARRET M., BOILEAU C., BENLIAN P., RABES J.P.

Novel mutations of the PCSK9 gene cause variable phenotype of autosomal dominant hypercholesterolemia (erratum in : *Hum.Mutat.*, 26(6):592).

Hum. Mutat., 26 (5), 497, 2005

(Services cités : U383)

Autosomal dominant hypercholesterolemia (ADH) is a frequent (1/500) monogenic inherited disorder characterized by isolated elevation of LDL leading to premature cardiovascular disease. ADH is known to result from mutations at two main loci: LDLR (encoding the low density lipoprotein receptor), and APOB (encoding apolipoprotein B100), its natural ligand. We previously demonstrated that ADH is also caused by mutations of the PCSK9 (proprotein convertase subtilisin/kexin type 9) gene that encodes Narc-1 (neural apoptosis-regulated convertase 1). However, the role of this novel disease locus as a cause of hypercholesterolemia remains unclear. In the present study, we analysed the PCSK9 coding region and intronic junctions in 130 adult or pediatric patients with ADH, previously found as being non LDLR/non APOB mutation carriers. Four novel heterozygous missense variations were found: c.654A>T (p.R218S), c.1070G>A (p.R357H), c.1405C>T (p.R469W), and c.1327G>A (p.A443T). All mutations were absent in 340 normolipidemic controls. Except for the A443T, all mutations are nonconservative and modify a highly conserved residue. Segregation with hypercholesterolemia is incomplete in one pedigree. Type and severity of hyperlipidemia and of cardiovascular disease could vary among subjects from the same family. Finally, the proband carrying the R357H mutation exhibited very high plasma cholesterol during pregnancy, whereas the proband carrying the p.R469W mutation exhibited a severe phenotype of hypercholesterolemia in combination with a LDLR mutation resulting from a frameshift at residue F382 (1209delC). These observations suggest that variations in PCSK9 are a rare cause of non LDLR/non APOB ADH (approximately 2.3%) and that additional environmental or genetic factors may contribute to the phenotype caused by PCSK9 missense mutations in humans. (c) 2005 Wiley-Liss, Inc.

BEROUD C., HAMROUN D., COLLOD-BEROUD G., BOILEAU C., SOUSSI T., CLAUSTRES M.

UMD (Universal Mutation Database): 2005 update.

Hum. Mutat., 26 (3), 184-191, 2005

(Services cités : U383)

With the completion of the Human Genome Project, our vision of human genetic diseases has changed. The cloning of new disease-causing genes can now be performed in silico, and thousands of mutations are being identified in diagnostic and research laboratories yearly. Knowledge about these mutations and their association with clinical and biological data is essential for clinicians, geneticists, and researchers. To collect and analyze these data, we developed a generic software called Universal Mutation Databases (UMD) to create locus-specific databases. Here we report the new release (September 2004) of this freely available tool

(www.umd.be), which allows the creation of LSDBs for virtually any gene and includes a large set of new analysis tools. We have implemented new features to integrate noncoding sequences, clinical data, pictures, monoclonal antibodies, and polymorphic markers (SNPs). Today the UMD retains all specifically designed tools to analyze mutations at the molecular level, as well as new sets of routines to search for genotype-phenotype correlations. We also created specific tools for infrequent mutations such as gross deletions and duplications, and deep intronic mutations. A large set of dedicated tools are now available for intronic mutations, including methods to calculate the consensus values (CVs) of potential splice sites and to search for exonic splicing enhancer (ESE) motifs. In addition, we have created specific routines to help researchers design new therapeutic strategies, such as exon skipping, aminoglycoside read-through of stop codons, or monoclonal antibody selection and epitope scanning for gene therapy.

BOILEAU C., JONDEAU G., MIZUGUCHI T., MATSUMOTO N.

Molecular genetics of Marfan syndrome.

Curr. Opin. Cardiol., 20 (3), 194-200, 2005

(Services cités : U383)

PURPOSE OF REVIEW: Marfan syndrome, the founding member of connective tissue disorders, is characterized by involvement of three major systems (skeletal, ocular, and cardiovascular) due to alteration in microfibrils. FBN1 at 15q21.1 was found to cause Marfan syndrome in 1991, and in 2004 TGFBR2 at 3p24.1 was newly identified as the Marfan syndrome type II gene. Several studies implied that fibrillin-1 and transforming growth factor-beta (TGF-beta) signaling are functionally related in extracellular matrix. Identification of TGFBR2 mutations in Marfan syndrome type II provided the direct evidence of the relation in humans. **RECENT FINDINGS:** More than 500 FBN1 mutations have been found in Marfan syndrome, tentative genotype - phenotype correlations have emerged, and mouse models are providing insight into pathogenic mechanisms. TGFBR2 mutations are still limited, however, in 2005 were also reported to cause a new aneurysm syndrome. Functional association between fibrillin-1 and TGF-beta signaling in extracellular matrix has been presented. **SUMMARY:** This review focuses on recent molecular genetics advances in Marfan syndrome and overlapping connective tissue disorders. Mutation spectrum of FBN1 and TGFBR2 in relation to phenotype is presented. Functional relation between fibrillin-1 and TGF-beta signaling is discussed. Future prospects in the study of Marfan syndrome are presented.

FAUSSILLON M., MONNIER L., JUNIEN C., JEANPIERRE C.

Frequent overexpression of cyclin D2/cyclin-dependent kinase 4 in Wilms' tumor.

Cancer Lett., 221 (1), 67-75, 2005

(Services cités : U383)

The expression status of the three cyclin D genes (CCND1, CCND2 and CCND3), the two cyclin D-dependent kinase genes (CDK4 and CDK6) and the p16(INK4a) gene was studied in a series of 47 Wilms' tumors, 16 normal mature kidneys and two fetal kidneys. We showed predominant overexpression of CCND2 and CDK4 compared to CCND1/D3 and CDK6 respectively. We found a specific correlation between relapse and CDK4 overexpression, but not CDK6 overexpression. We did not identify any methylation of the p16(INK4a) promoter. This suggests that dysregulation of CCND2 and CDK4 plays a specific role in WT tumorigenesis.

GALLOU-KABANI C., JUNIEN C.

Nutritional epigenomics of metabolic syndrome: new perspective against the epidemic.

Diabetes, 54 (7), 1899-1906, 2005

(Services cités : U383)

Human epidemiological studies and appropriately designed dietary interventions in animal models have provided considerable evidence to suggest that maternal nutritional imbalance and metabolic disturbances, during critical time windows of development, may have a persistent effect on the health of the offspring and may even be transmitted to the next generation. We now need to explain the mechanisms involved in generating such responses. The idea that epigenetic changes associated with chromatin remodeling and regulation of gene expression underlie the developmental programming of metabolic syndrome is gaining acceptance. Epigenetic alterations have been known to be of importance in cancer for approximately 2 decades. This has made it possible to decipher epigenetic codes and machinery and has led to the development of a new generation of drugs now in clinical trials. Although less conspicuous, epigenetic alterations have also been progressively shown to be relevant to common diseases such as atherosclerosis and type 2 diabetes. Imprinted genes, with their key roles in controlling fetoplacental nutrient supply and demand and their epigenetic lability in response to nutrients, may play an important role in adaptation/evolution. The combination of these various lines of research on epigenetic programming processes has highlighted new possibilities for the prevention and treatment of metabolic syndrome.

JUNIEN C., GALLOU-KABANI C., VIGE A., GROSS M.S.

Nutritional epigenomics: consequences of unbalanced diets on epigenetics processes of programming during lifespan and between generations.

Ann. Endocrinol., 66 (2P3), S19-S28, 2005

(Services cités : U383)

Epigenetic changes associated with DNA methylation and histone modifications leading to chromatin remodeling and regulation of gene expression underlie the developmental programming of obesity, type 2 diabetes, cardiovascular diseases and metabolic syndrome. This review focuses on converging data supporting the hypothesis that, in addition to "thrifty genotype" inheritance, individuals with obesity, type 2 diabetes, and metabolic syndrome (MetS) with an increased risk of cardiovascular diseases have suffered improper "epigenetic programming" during their fetal/postnatal development due to maternal inadequate nutrition and metabolic disturbances and also during their lifetime, that could even be transmitted to the next generation(s). We highlight the susceptibility of epigenetic mechanisms controlling gene expression to environmental influences due to their inherent malleability, emphasizing the participation of transposable elements and the potential role of imprinted genes during critical time windows in epigenetic programming, from the very beginning of development, throughout life. Increasing our understanding on epigenetic patterns significance and their role in development, evolution and adaptation and on small molecules (nutrients, drugs) that reverse epigenetic (in)activation should provide us with the means to "unlock" silenced (enhanced) genes, and to "convert" the obsolete human thrifty genotype into a "squandering" phenotype.

JUNIEN C., GALLOU-KABANI C., VIGE A., GROSS M.S.

Nutritional epigenomics of metabolic syndrome.

M S-Méd. Sci., 21 (Sp.Iss.), 44-52, 2005

(Services cités : U383)

The importance of epigenetic alterations has been acknowledged in cancer for about two decades by an increasing number of molecular oncologists who contributed to deciphering the epigenetic

codes and machinery and opened the road for a new generation of drugs now in clinical trials. However, the relevance of epigenetics to common diseases such as metabolic syndrome and cardiovascular disease was less conspicuous. This review focuses on converging data supporting the hypothesis that, in addition to << thrifty genotype >> inheritance, individuals with metabolic syndrome (MetS) - combining disturbances in glucose and insulin metabolism, excess of predominantly abdominally distributed weight, mild dyslipidemia and hypertension, with the subsequent development of obesity, type 2 diabetes mellitus (T2D) and cardiovascular disease (CVD) have suffered improper << epigenetic programming >> during their fetal/postnatal development due to maternal inadequate nutrition and metabolic disturbances and also during their lifetime. Moreover, as seen for obesity and T2D, MetS tends to appear earlier in childhood, to be more severe from generation to generation and to affect more pregnant women. Thus, in addition to maternal effects, MetS patients may display << transgenerational effects >> via the incomplete erasure of epigenetic marks endured by their parents and grandparents. We highlight the susceptibility of epigenetic mechanisms controlling gene expression to environmental influences due to their inherent malleability, emphasizing the participation of transposable elements and the potential role of imprinted genes during critical time windows in epigenetic programming, from the very beginning of development throughout life. Increasing our understanding on epigenetic patterns significance and small molecules (nutrients, drugs) that reverse epigenetic (in)activation should provide us with the means to << unlock >> silenced (enhanced) genes, and to << convert >> the obsolete human thrifty genotype into a << squandering >> phenotype.

JUNIEN C., GALLOU-KABANI C., VIGE A., GROSS M.S.

Nutritional epigenomics of metabolic syndrome.

M S-Méd. Sci., 21 (4), 396-404, 2005

(Services cités : U383)

The importance of epigenetic alterations has been acknowledged in cancer for about two decades by an increasing number of molecular oncologists who contributed to deciphering the epigenetic codes and machinery and opened the road for a new generation of drugs now in clinical trials. However, the relevance of epigenetics to common diseases such as metabolic syndrome and cardiovascular disease was less conspicuous. This review focuses on converging data supporting the hypothesis that, in addition to << thrifty genotype >> inheritance, individuals with metabolic syndrome (MetS) - combining disturbances in glucose and insulin metabolism, excess of predominantly abdominally distributed weight, mild dyslipidemia and hypertension, with the subsequent development of obesity, type 2 diabetes mellitus (T2D) and cardiovascular disease (CVD) - have suffered improper << epigenetic programming >> during their fetal/postnatal development due to maternal inadequate nutrition and metabolic disturbances and also during their lifetime. Moreover, as seen for obesity and T2D, MetS tends to appear earlier in childhood, to be more severe from generation to generation and to affect more pregnant women. Thus, in addition to maternal effects, MetS patients may display << transgenerational effects >> via the incomplete erasure of epigenetic marks endured by their parents and grandparents. We highlight the susceptibility of epigenetic mechanisms controlling gene expression to environmental influences due to their inherent malleability, emphasizing the participation of transposable elements and the potential role of imprinted genes during critical time windows in epigenetic programming, from the very beginning of development throughout life. Increasing our understanding on epigenetic patterns significance and small molecules (nutrients, drugs) that reverse epigenetic (in)activation should provide us with the means to << unlock >> silenced

(enhanced) genes, and to << convert >> the obsolete human thrifty genotype into a << squandering >> phenotype.

KAPUT J., ORDOVAS J.M., FERGUSON L., VAN OMMEN B., RODRIGUEZ R.L., ALLEN L., AMES B.N., DAWSON K., GERMAN B., KRAUSS R., MALYJ W., ARCHER M.C., BARNES S., BARTHOLOMEW A., BIRK R., VAN BLADEREN P., BRADFORD K.J., BROWN K.H., CAETANO R., CASTLE D., CHADWICK R., CLARKE S., CLEMENT K., COONEY C.A., CORELLA D., MANICA DA CRUZ I.B., DANIEL H., DUSTER T., E EBBESSON S.O., ELLIOTT R., FAIRWEATHER-TAIT S., FELTON J., FENECH M., FINLEY J.W., FOGG-JOHNSON N., GILL-GARRISON R., GIBNEY M.J., GILLIES P.J., GUSTAFSSON J.A.

The case for strategic international alliances to harness nutritional genomics for public and personal healthdagger.

Br. J. Nutr., 94 (5), 623-632, 2005

(Services cités : Biostatistique, U383)

Nutrigenomics is the study of how constituents of the diet interact with genes, and their products, to alter phenotype and, conversely, how genes and their products metabolise these constituents into nutrients, antinutrients, and bioactive compounds. Results from molecular and genetic epidemiological studies indicate that dietary unbalance can alter gene-nutrient interactions in ways that increase the risk of developing chronic disease. The interplay of human genetic variation and environmental factors will make identifying causative genes and nutrients a formidable, but not intractable, challenge. We provide specific recommendations for how to best meet this challenge and discuss the need for new methodologies and the use of comprehensive analyses of nutrient-genotype interactions involving large and diverse populations. The objective of the present paper is to stimulate discourse and collaboration among nutrigenomic researchers and stakeholders, a process that will lead to an increase in global health and wellness by reducing health disparities in developed and developing countries.

2004

ABIFADEL M., JAMBART S., ALLARD D., RABES J.P., VARRET M., DERRE A., CHOUERY E., SALEM N., JUNIEN C., AYDENIAN H., BOILEAU C.

Identification of the first Lebanese mutation in the LPL gene and description of a rapid detection method.

Clin. Genet., 65 (2), 158-161, 2004

(Services cités : U383)

BENJANNET S., RHAINDS D., ESSALMANI R., MAYNE J., WICKHAM L., JIN W., ASSELIN M.C., HAMELIN J., VARRET M., ALLARD D., TRILLARD M., ABIFADEL M., TEBON A., ATTIE A.D., RADER D.J., BOILEAU C., BRISSETTE L., CHRETIEN M., PRAT A., SEIDAH N.G.

NARC-1/PCSK9 and its natural mutants: zymogen cleavage and effects on the low density lipoprotein (LDL) receptor and LDL cholesterol.

J. Biol. Chem., 279 (47), 48865-48875, 2004

(Services cités : U383)

The discovery of autosomal dominant hypercholesterolemic patients with mutations in the PCSK9 gene, encoding the proprotein convertase NARC-1, resulting in the missense mutations suggested a role in low density lipoprotein (LDL) metabolism. We show that the endoplasmic

reticulum-localized proNARC-1 to NARC-1 zymogen conversion is Ca²⁺-independent and that within the zymogen autocatalytic processing site SSVFAQ [downward arrow]SIP Val at P4 and Pro at P3' are critical. The S127R and D374Y mutations result in approximately 50-60% and > or =98% decrease in zymogen processing, respectively. In contrast, the double [D374Y + N157K], F216L, and R218S natural mutants resulted in normal zymogen processing. The cell surface LDL receptor (LDLR) levels are reduced by 35% in lymphoblasts of S127R patients. The LDLR levels are also reduced in stable HepG2 cells overexpressing NARC-1 or its natural mutant S127R, and this reduction is abrogated in the presence of 5 mM ammonium chloride, suggesting that overexpression of NARC-1 increases the turnover rate of the LDLR. Adenoviral expression of wild type human NARC-1 in mice resulted in a maximal approximately 9-fold increase in circulating LDL cholesterol, while in LDLR^{-/-} mice a delayed approximately 2-fold increase in LDL cholesterol was observed. In conclusion, NARC-1 seems to affect both the level of LDLR and that of circulating apoB-containing lipoproteins in an LDLR-dependent and -independent fashion.

FOURNET J.C., JUNIEN C.

Genetics of congenital hyperinsulinism.

Endocr. Pathol., 15 (3), 233-240, 2004

(Services cités : U383)

Congenital hyperinsulinism (CHI) is a clinically and genetically heterogeneous entity and causes severe hypoglycemia in neonates and infants. The clinical heterogeneity is manifested by severity ranging from extremely severe, life-threatening disease to very mild clinical symptoms, which may even be difficult to identify. Furthermore, clinical responsiveness to medical and surgical management is extremely variable. Recent discoveries have begun to clarify the molecular etiology of this disease in about 50% of cases. Mutations in five different genes have been identified in patients with this clinical syndrome. Most cases are caused by mutations in the genes ABCC8 and KCNJ11 coding for either of the two subunits of the beta-cell KATP channel (SUR1 and Kir6.2). Recessive mutations of the beta-cell K(ATP) channel genes cause diffuse HI, whereas loss of heterozygosity together with inheritance of a paternal mutation causes focal adenomatous HI. In other cases, CHI is caused by mutations in genes coding for the beta-cell enzymes glucokinase (GK), glutamate dehydrogenase (GDH), and SCHAD. However, for as many as 50% of the cases, no genetic etiology has yet been determined. The study of the genetics of this disease has provided important new information regarding beta-cell physiology.

GALLOU C., CHAUVEAU D., RICHARD S., JOLY D., GIRAUD S., OLSCHWANG S., MARTIN N., SAQUET C., CHRETIEN Y., MEJEAN A., CORREAS J.M., BENOIT G., COLOMBEAU P., GRUNFELD J.P., JUNIEN C., BEROUD C.

Genotype-phenotype correlation in von Hippel-Lindau families with renal lesions.

Hum. Mutat., 24 (3), 215-224, 2004

(Services cités : Néphrologie Adulte, Radiologie Adulte, U383)

von Hippel-Lindau (VHL) disease arises from mutations in the VHL gene and predisposes patients to develop a variety of tumors in different organs. In the kidney, single or multiple cysts and renal cell carcinomas (RCC) may occur. Both inter- and intrafamilial heterogeneity in clinical expression are well recognized. To identify VHL-dependent genetic factors, we investigated the renal phenotype in 274 individuals from 126 unrelated VHL families in whom 92 different VHL mutations were characterized. The incidence of renal involvement was increased in families with mutations leading to truncated protein (MLTP) or large rearrangement, as

compared to families with missense changes (81 vs. 63%, respectively; $P=0.03$). In the latter group, we identified two mutation cluster regions (MCRs) associated with a high risk of harboring renal lesions: MCR-1 (codons 74-90) and MCR-2 (codons 130-136). In addition, the incidence of RCC was higher in families with MLTP than in families with missense changes (75 vs. 57%; $P=0.04$). Furthermore, mutations within MCR-1 but not MCR-2 conferred genetic susceptibility to develop RCC. Overall, our data argued for a substantial contribution of the genetic change in the VHL gene to susceptibility to renal phenotype in VHL patients. *Hum Mutat* 24:215-224, 2004. Copyright 2004 Wiley-Liss, Inc.

GALLOU C., CHAUVEAU D., RICHARD S., JOLY D., GIRAUD S., OLSCHWANG S., MARTIN N., SAQUET C., CHRETIEN Y., MEJEAN A., CORREAS J.M., BENOIT G., COLOMBEAU P., GRUNFELD J.P., JUNIEN C., BEROUD C.

Genotype-phenotype correlation in von Hippel-Lindau families with renal lesions.

Hum. Mutat., 24 (5), 435-436, 2004

(Services cités : Néphrologie Adulte, U383, Radiologie Adulte)

The original article to which this Erratum refers was published in *Human Mutation* 24:215-224. In the published version of this article, the key to Figure 2 was omitted. Please find Figure 2 printed here in its entirety.

JUNIEN C., GALLOU C.

Cancer Nutrigenomics.

in: *Nutrigenetics and Nutrigenomics*. (Simopoulos A.P., Ordovas J.M. eds.)

Karger (Basel), 2004, pp.210-269.

(Services cités : U383)

MIZUGUCHI T., COLLOD-BEROUD G., AKIYAMA T., ABIFADEL M., HARADA N., MORISAKI T., ALLARD D., VARRET M., CLAUSTRES M., MORISAKI H., IHARA M., KINOSHITA A., YOSHIURA K., JUNIEN C., KAJII T., JONDEAU G., OHTA T., KISHINO T., FURUKAWA Y., NAKAMURA Y., NIKAWA N., BOILEAU C., MATSUMOTO N.

Heterozygous TGFBR2 mutations in Marfan syndrome.

Nat. Genet., 36 (8), 855-860, 2004

(Services cités : U383)

Marfan syndrome is an extracellular matrix disorder with cardinal manifestations in the eye, skeleton and cardiovascular systems associated with defects in the gene encoding fibrillin (FBN1) at 15q21.1 (ref. 1). A second type of the disorder (Marfan syndrome type 2; OMIM 154705) is associated with a second locus, MFS2, at 3p25-p24.2 in a large French family (family MS1). Identification of a 3p24.1 chromosomal breakpoint disrupting the gene encoding TGF-beta receptor 2 (TGFBR2) in a Japanese individual with Marfan syndrome led us to consider TGFBR2 as the gene underlying association with Marfan syndrome at the MFS2 locus. The mutation 1524G-->A in TGFBR2 (causing the synonymous amino acid substitution Q508Q) resulted in abnormal splicing and segregated with MFS2 in family MS1. We identified three other missense mutations in four unrelated probands, which led to loss of function of TGF-beta signaling activity on extracellular matrix formation. These results show that heterozygous mutations in TGFBR2, a putative tumor-suppressor gene implicated in several malignancies, are also associated with inherited connective-tissue disorders.

OUGUERRAM K., CHETIVEAUX M., ZAIR Y., COSTET P., ABIFADEL M., VARRET M., BOILEAU C., MAGOT T., KREMPF M.

Apolipoprotein B100 Metabolism in Autosomal-Dominant Hypercholesterolemia Related to Mutations in PCSK9.

Arterioscler. Thromb. Vasc. Biol., 24 (8), 1448-1453, 2004

(Services cités : U383)

OBJECTIVE: We have reported further heterogeneity in familial autosomal-dominant hypercholesterolemia (FH) related to mutation in proprotein convertase subtilisin/kexin type 9 (PCSK9) gene previously named neural apoptosis regulated convertase 1 (Narc-1). Our aim was to define the metabolic bases of this new form of hypercholesterolemia. **METHODS AND RESULTS:** In vivo kinetics of apolipoprotein B100-containing lipoproteins using a 14-hour primed constant infusion of [(2)H(3)] leucine was conducted in 2 subjects carrying the mutation S127R in PCSK9, controls subjects, and FH subjects with known mutations on the low-density lipoprotein (LDL) receptor gene (LDL-R). Apo B100 production, catabolism, and transfer rates were estimated from very LDL (VLDL), intermediate-density lipoprotein (IDL), and LDL tracer enrichments by compartmental analysis. PCSK9 mutation dramatically increased the production rate of apolipoprotein B100 (3-fold) compared with controls or LDL-R mutated subjects, related to direct overproduction of VLDL (3-fold), IDL (3-fold), and LDL (5-fold). The 2 subjects also showed a decrease in VLDL and IDL conversion (10% to 30% of the controls). LDL fractional catabolic rate was slightly decreased (by 30%) compared with controls but still higher than LDL-R-mutated subjects. **CONCLUSIONS:** These results showed that the effect of the S127R mutation of PCSK9 on plasma cholesterol homeostasis is mainly related to an overproduction of apolipoprotein B100.

SAVOURET C., JUNIEN C., GOURDON G.

Analysis of CTG repeats using DM1 model mice.

Meth. Mol. Biol., 277 185-197, 2004

(Services cités : U383)

This chapter describes how transgenic mice can be made with human genomic DNA fragments cloned from DM1 patients' DNA and how the CTG repeat instability is assessed over generations and in different tissues. Construction of cosmid libraries is fully reported from the extraction of high-molecular-weight DNA from patients' lymphoid cell lines, to the screening and mapping of the positive clones. After establishment of transgenic lines, we explained the methods used to analyze (a) the CTG repeats that are inherited from the transgenic parents, with regard to age, sex, and parental CTG repeat sizes, and (b) the CTG repeat-length variations that can be observed in somatic tissues and in sperm.

SAVOURET C., GARCIA-CORDIER C., MEGRET J., TE RIELE H., JUNIEN C., GOURDON G.

MSH2-Dependent Germinal CTG Repeat Expansions Are Produced Continuously in Spermatogonia from DM1 Transgenic Mice.

Mol. Cell. Biol., 24 (2), 629-637, 2004

(Services cités : IRNEM, U383)

SENEE V., VATTEM K.M., DELEPINE M., RAINBOW L.A., HATON C., LECOQ A., SHAW N.J., ROBERT J.J., ROOMAN R., DIATLOFF-ZITO C., MICHAUD J.L., BIN-ABBAS B., TAHA D., ZABEL B., FRANCESCHINI P., TOPALOGLU A.K., LATHROP

G.M., BARRETT T.G., NICOLINO M., WEK R.C., JULIER C.

Wolcott-Rallison Syndrome: Clinical, Genetic, and Functional Study of EIF2AK3 Mutations and Suggestion of Genetic Heterogeneity.

Diabetes, 53 (7), 1876-1883, 2004

(Services cités : U383)

Wolcott-Rallison syndrome (WRS) is a rare autosomal-recessive disorder characterized by the association of permanent neonatal or early-infancy insulin-dependent diabetes, multiple epiphyseal dysplasia and growth retardation, and other variable multisystemic clinical manifestations. Based on genetic studies of two inbred families, we previously identified the gene responsible for this disorder as EIF2AK3, the pancreatic eukaryotic initiation factor 2alpha (eIF2alpha) kinase. Here, we have studied 12 families with WRS, totalling 18 cases. With the exception of one case, all patients carried EIF2AK3 mutations resulting in truncated or missense versions of the protein. Exclusion of EIF2AK3 mutations in the one patient case was confirmed by both linkage and sequence data. The activities of missense versions of EIF2AK3 were characterized in vivo and in vitro and found to have a complete lack of activity in four mutant proteins and residual kinase activity in one. Remarkably, the onset of diabetes was relatively late (30 months) in the patient expressing the partially defective EIF2AK3 mutant and in the patient with no EIF2AK3 involvement (18 months) compared with other patients (<6 months). The patient with no EIF2AK3 involvement did not have any of the other variable clinical manifestations associated with WRS, which supports the idea that the genetic heterogeneity between this variant form of WRS and EIF2AK3 WRS correlates with some clinical heterogeneity.

SOULIE C., NICOLE A., DELACOURTE A., CEBALLOS-PICOT I.

Examination of stress-related genes in human temporal versus occipital cortex in the course of neurodegeneration: involvement of 14-3-3 zeta in this dynamic process.

Neurosci. Lett., 365 (1), 1-5, 2004

(Services cités : U383)

The progressive invasion of the brain by neurofibrillary tangles characterized by paired helical filaments (PHF) along a precise network is stereotypical and hierarchical from normal aging to severe Alzheimer's disease. We describe here the differential expression of genes in the temporal area with PHF compared with the occipital area non-affected by PHF in cases with cognitive impairment versus the same cortical regions of control human brains without PHF. A stronger overexpression for 14-3-3 zeta gene is demonstrated in the affected temporal cortex of cases with cognitive impairment than in cases with normal mental status. This data obtained directly from human brains confirmed a 14-3-3 zeta implication in the Alzheimer's neuropathology.

2003

ABIFADEL M., VARRET M., RABES J.P., ALLARD D., OUGUERRAM K., DEVILLERS M., CRUAUD C., BENJANNET S., WICKHAM L., ERLICH D., DERRE A., VILLEGER L., FARNIER M., BEUCLER I., BRUCKERT E., CHAMBAZ J., CHANU B., LECERF J.M., LUC G., MOULIN P., WEISSENBACH J., PRAT A., KREMPF M., JUNIEN C., SEIDAH N.G., BOILEAU C.

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia.

Nat. Genet., 34 (2), 154-156, 2003

(Services cités : U383)

Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary

heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes LDLR (encoding low-density lipoprotein receptor) or APOB (encoding apolipoprotein B). We mapped a third locus associated with ADH, HCHOLA3 at 1p32, and now report two mutations in the gene PCSK9 (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. PCSK9 encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.

BAUDRY D., CABANIS M.O., PATTE C., ZUCKER J.M., PEIN F., FOURNET J.C., SARNACKI S., JUNIEN C., JEANPIERRE C.

Cadherins in Wilms' tumor: E-cadherin expression despite absence of WT1.

Anticancer Res., 23 (1A), 475-478, 2003

(Services cités : U383, Chirurgie Pédiatrique, Anatomo-Pathologie)

Loss of heterozygosity of chromosome 16q occurs in 17-25% of Wilms' tumors. Two cadherin genes mapping to 16q22 were chosen as candidate genes: E-CAD, encoding epithelial cadherin, because it is involved in kidney development and it was recently reported to be a WT1 target; and KSP-CAD because it encodes a kidney-specific cadherin. By RT-PCR analysis in a series of 39 Wilms' tumors, we identified a very low expression of E-CAD and KSP-CAD in 72% and 95% of the tumors, respectively. To ascertain whether down-expression of these genes could be related to WT1 alterations in tumors, we looked for a relationship between WT1 and CAD expression. Our data suggest (i) the existence of alternative mechanisms for regulating E-CAD expression, and (ii) that E-CAD does not belong to the WT1 pathway that is altered in Wilms' tumorigenesis.

COLLOD-BEROUD G., LE BOURDELLES S., ADES L., ALA-KOKKO L., BOOMS P., BOXER M., CHILD A., COMEGLIO P., de PAEPE A., HYLAND J.C., HOLMAN K., KAITILA I., LOEYS B., MATYAS G., NUYTINCK L., PELTONEN L., RANTAMAKI T., ROBINSON P., STEINMANN B., JUNIEN C., BEROUD C., BOILEAU C.

Update of the UMD-FBN1 mutation database and creation of an FBN1 polymorphism database.

Hum. Mutat., 22 (3), 199-208, 2003

(Services cités : U383)

Fibrillin is the major component of extracellular microfibrils. Mutations in the fibrillin gene on chromosome 15 (FBN1) were first described in the heritable connective disorder, Marfan syndrome (MFS). FBN1 has also been shown to harbor mutations related to a spectrum of conditions phenotypically related to MFS, called "type-1 fibrillinopathies." In 1995, in an effort to standardize the information regarding these mutations and to facilitate their mutational analysis and identification of structure/function and phenotype/genotype relationships, we created a human FBN1 mutation database, UMD-FBN1. This database gives access to a software package that provides specific routines and optimized multicriteria research and sorting tools. For each mutation, information is provided at the gene, protein, and clinical levels. This tool is now a worldwide reference and is frequently used by teams working in the field; more than 220,000 interrogations have been made to it since January 1998. The database has recently been modified to follow the guidelines on mutation databases of the HUGO Mutation Database Initiative (MDI) and the Human Genome Variation Society (HGVS), including their approved mutation nomenclature. The current update shows 559 entries, of which 421 are novel. UMD-FBN1 is accessible at www.umd.be/. We have also recently developed a FBN1 polymorphism database in order to facilitate diagnostics.

DIAZ-MEYER N., DAY C.D., KHATOD K., MAHER E.R., COOPER W., REIK W., JUNIEN C., GRAHAM G., ALGAR E., DER KALOUSTIAN V.M., HIGGINS M.J.

Silencing of CDKN1C (p57(KIP2)) is associated with hypomethylation at KvDMR1 in Beckwith-Wiedemann syndrome.

J. Med. Genet., 40 (11), 797-801, 2003

(Services cités : U383)

CONTEXT: Beckwith-Wiedemann syndrome (BWS) arises by several genetic and epigenetic mechanisms affecting the balance of imprinted gene expression in chromosome 11p15.5. The most frequent alteration associated with BWS is the absence of methylation at the maternal allele of KvDMR1, an intronic CpG island within the KCNQ1 gene. Targeted deletion of KvDMR1 suggests that this locus is an imprinting control region (ICR) that regulates multiple genes in 11p15.5. Cell culture based enhancer blocking assays indicate that KvDMR1 may function as a methylation modulated chromatin insulator and/or silencer. OBJECTIVE: To determine the potential consequence of loss of methylation (LOM) at KvDMR1 in the development of BWS. METHODS: The steady state levels of CDKN1C gene expression in fibroblast cells from normal individuals, and from persons with BWS who have LOM at KvDMR1, was determined by both real time quantitative polymerase chain reaction (qPCR) and ribonuclease protection assay (RPA). Methylation of the CDKN1C promoter region was assessed by Southern hybridisation using a methylation sensitive restriction endonuclease. RESULTS: Both qPCR and RPA clearly demonstrated a marked decrease (86-93%) in the expression level of the CDKN1C gene in cells derived from patients with BWS, who had LOM at KvDMR1. Southern analysis indicated that downregulation of CDKN1C in these patients was not associated with hypermethylation at the presumptive CDKN1C promoter. CONCLUSIONS: An epimutation at KvDMR1, the absence of maternal methylation, causes the aberrant silencing of CDKN1C, some 180 kb away on the maternal chromosome. Similar to mutations at this locus, this silencing may give rise to BWS.

EDERY P., CHABRIER S., CEBALLOS-PICOT I., MARIE S., VINCENT M.F., TARDIEU M.

Intrafamilial variability in the phenotypic expression of adenylosuccinate lyase deficiency: a report on three patients.

Amer. J. Med. Genet., 120A (2), 185-190, 2003

(Services cités : U383, Biochimie Médicale)

We report on the striking variable expression of adenylosuccinate lyase (ADSL) deficiency in three patients belonging to a family which originates from Portugal. ADSL deficiency is a rare autosomal recessive disorder of the de novo purine synthesis which results in accumulation of succinylpurines in body fluids. As a result, patients may have variable combinations of psychomotor retardation and/or regression, seizures, autistic features and cerebellar vermis hypoplasia. However, intrafamilial variable expression of the phenotype has not been documented to date in this disease and is not commonly observed in metabolic disorders. Here, while the proband had marked psychomotor regression and progressive cerebellar vermis atrophy, the other two affected patients presented mainly autistic features. Mutation analysis of the ADSL gene revealed the presence of a homozygous R426H mutation in this family. Finally, although ADSL deficiency is a rare disorder, this diagnosis should be considered and assessed using a simple urinary screening method for the presence of succinylpurines in any patient with mental retardation of unexplained origin.

EL MESSAL M., AIT CHIHAB K., CHATER R., VALLVE J.C., BENNIS F., HAFIDI A.,

RIBALTA J., VARRET M., LOUTFI M., RABES J.P., KETTANI A., BOILEAU C., MASANA L., ADLOUNI A.

Familial hypercholesterolemia in Morocco: first report of mutations in the LDL receptor gene. *J. Hum. Genet.*, 48 (4), 199-203, 2003

(Services cités : U383)

Familial hypercholesterolemia (FH) is a genetic disorder mainly caused by defects in the low-density lipoprotein receptor (LDLR) gene, although it can also be due to alterations in the gene encoding apolipoprotein B (familial defective apoB or FDB) or in other unidentified genes. In Morocco, the molecular basis of FH is unknown. To obtain information on this issue, 27 patients with FH from eight unrelated families were analyzed by screening the LDLR (PCR-SSCP and Southern blot) and apoB genes (PCR and restriction enzyme digestion analysis). None of the patients carried either the R3500Q or the R3531C mutation in the apoB gene. By contrast, seven mutations in the LDLR gene were identified, including five missense mutations on exons 4, 6, 8, and 14 (C113R, G266C, A370T, P664L, C690S) and two large deletions (FH Morocco-1 and FH Morocco-2). The two major rearrangements and the missense mutation G266C are novel mutations and could well be causative of FH in the Moroccan population. This study has yielded preliminary information on the mutation spectrum of the LDLR gene among patients with FH in Morocco.

FAIVRE L., GORLIN R.J., WIRTZ M.K., GODFREY M., DAGONEAU N., SAMPLES J.R., LE MERRER M., COLLOD-BEROUD G., BOILEAU C., MUNNICH A., CORMIER-DAIRE V.

In frame fibrillin-1 gene deletion in autosomal dominant Weill-Marchesani syndrome.

J. Med. Genet., 40 (1), 34-36, 2003

(Services cités : U393, U383, Génétique Médicale Pédiatrique)

Weill-Marchesani syndrome (WMS) is a connective tissue disorder characterised by short stature, brachydactyly, joint stiffness, and characteristic eye anomalies including microspherophakia, ectopia of the lenses, severe myopia, and glaucoma. Both autosomal recessive (AR) and autosomal dominant (AD) modes of inheritance have been described and a gene for AR WMS has recently been mapped to chromosome 19p13.3-p13.2. Here, we report on the exclusion of chromosome 19p13.3-p13.2 in a large AD WMS family and show that, despite clinical homogeneity, AD and AR WMS are genetically heterogeneous entities. Because two AD WMS families were consistent with linkage to chromosome 15q21.1, the fibrillin-1 gene was sequenced and a 24 nt in frame deletion within a latent transforming growth factor-beta1 binding protein (LTBP) motif of the fibrillin-1 gene was found in a AD WMS family (exon 41, 5074_5097del). This in frame deletion cosegregated with the disease and was not found in 186 controls. This study strongly suggests that AD WMS and Marfan syndrome are allelic conditions at the fibrillin-1 locus and adds to the remarkable clinical heterogeneity of type I fibrillinopathies.

FOURNET J.C., JUNIEN C.

The genetics of neonatal hyperinsulinism.

Hormone Res., 59 Suppl 1 30-34, 2003

(Services cités : U383)

Congenital hyperinsulinism (CHI) is the most important cause of persistent hypoglycaemia in the neonate and infant. It is a clinically and genetically heterogeneous entity. The clinical heterogeneity is manifested by severity ranging from extremely severe life-threatening disease to very mild clinical symptoms which may even be difficult to identify. Furthermore, clinical

responsiveness to medical and surgical management is extremely variable. Two histopathological forms have been described: a diffuse form of CHI and a focal form of CHI. Recent discoveries have begun to clarify the molecular aetiology of the disease and therefore the mechanisms responsible for its clinical heterogeneity are becoming clearer. Mutations in four different genes have been identified in patients with CHI. Most cases are caused by mutations in genes coding for either of the two subunits of the beta-cell K(ATP) channel (ABCC8 and KCNJ11). In the diffuse form of CHI, the hyperinsulinism is due to a recessive mutation of both alleles of these genes (rare dominant mutations have been described). In the focal form of CHI, two events intervene: first, the inheritance of a paternal ABCC8/KCNJ11 mutation; second, the focal reduction to homozygosity of the mutation during pancreatic development by a localized loss of the maternal 11p15 region. Others cases of CHI are due to rare mutations in the beta-cell enzymes glucokinase (only one family described) and glutamate dehydrogenase in hyperammonaemia-associated hyperinsulinism. However, in as many as 50% of cases, no genetic aetiology has yet been identified.

GALLOU C., MEJEAN A., BOUVIER R., LUCIEN F., PERENNOU M., ZINDY P.J., GRIFONE R., CHRETIEN Y., JUNIEN C., BEROUD C.

Delineation of a 2.8 megabases region harboring a potential tumor suppressor gene involved in renal cell carcinoma, that is commonly deleted from chromosome 14.

Anticancer Res., 23 (6C), 4865-4870, 2003

(Services cités : U383)

MATERIALS AND METHODS: To investigate the genetic alterations that occur during the development of renal cell carcinomas (RCC), we used 20 microsatellite markers to examine 48 renal cell carcinomas for allelic losses of chromosome arm 14q. **RESULTS:** We identified 14q LOH in 31% of cases. Twelve tumors were entirely lacking the 14q arm and three were partially deleted. For the first time on fresh tumors, these findings led to the delineation of a 17.9 Mb region between markers D14S281 and D14S277 that is commonly deleted. Interestingly, this segment overlaps with the previously reported 37.8 Mb commonly deleted region.

CONCLUSION: Taken together these results allowed us to define a new 2.8 Mb segment between markers D14S588 and D14S277 that potentially harbors a tumor suppressor gene involved in the development of RCC which can be reached by positional cloning.

GUBLER M.C., JEANPIERRE C.

WT1-Associated Disorders.

in: *The Kidney. The Kidney From Normal Development to Congenital Disease.* (Vize P.D., Woolf A.S., Bard B.L. eds.)

Academic Press (), 2003, pp.395-409.

(Services cités : U383, U574)

JAUBERT F., VASILIU V., PATEY-MARIAUD de SERRE N., AUBER F., JEANPIERRE C., GUBLER M.C., NIHOUL-FEKETE C., FELLOUS M.

Gonad development in Drash and Frasier syndromes depends on WT1 mutations.

Ark. Patol., 65 (2), 40-44, 2003

(Services cités : Néphrologie Pédiatrique, Chirurgie Pédiatrique, Anatomo-Pathologie, U383)

The study of the gonads of 8 cases of Drash syndrome (6 ambiguous males, 2 females) and of 2 Frasier syndrome shows that WT1 mutations gives a dysgenetic testis which is the cause of the genital ambiguity observed at birth. By contrast the same mutations have no effect on ovary

development giving normal females. However intron mutations in KTS with isoforms imbalance of WT1 proteins cause streak gonads with a female phenotype in XY patients. In consequence WT1 mutations are the cause of a spectrum of male genital malformations associated with glomerulonephritis and tumors. The absence of WT1 protein detection in sertoli cells shown by immunohistochemistry for 3 cases suggests an imprinting effect of the normal WT1 allele promotor rather than a low level of protein production. A caryotype is mandatory for a correct diagnosis.

JUNIEN C.

in: *Nutrigénétique du risque cardiovasculaire ; terrains génétiques et nutrition.* (Junien C. eds.) EMinter ; TEC & Doc (Cachan (F-94)), 2003, pp.1-336.

(Services cités : [U383](#))

La nutriginétique est une discipline nouvelle qui étudie les interactions gènes-environnement dans le cadre de la nutrition. Alors que la médecine prédictive est une réalité pour près d'un millier de maladies monogéniques rares, son application à des affections polyfactorielles comme les affections cardiovasculaires, le diabète de type II ou l'obésité suscite en effet, à tort ou à raison, à la fois des doutes et des certitudes. Le premier chapitre expose les champs d'étude de la nutriginétique et de la nutriginomique. Il présente les stratégies et les méthodes de recherche et d'étude des gènes de susceptibilité ou de vulnérabilité aux nutriments, tout en précisant les limites et les espoirs de ces approches. Le deuxième chapitre décrit pour la première fois les variants (simples polymorphismes ou haplotypes) de près de 300 gènes impliqués dans différentes affections ayant toutes en commun la capacité de conférer un risque d'atteinte cardiovasculaire (dyslipidémies, thrombose, hypertension, croissance endothéliale et adhésion, inflammation, diabète, obésité). Le troisième chapitre détaille près de 200 gènes impliqués dans la variabilité individuelle de la réponse à un nutriment, à un régime ou à un exercice physique. Le quatrième chapitre permet de mieux comprendre les distinctions à établir entre les différents types de tests génétiques, de mieux distinguer les contours des champs d'application possibles, et de mettre en balance la réflexion éthique et les incontestables bénéfices médicaux. Nutriginétique du risque cardiovasculaire est ainsi le premier ouvrage à aborder les principes d'étude et d'analyse des maladies polygéniques appliqués à un domaine aussi vaste que les affections cardiovasculaires, première cause de mortalité dans les pays développés, et à synthétiser les connaissances actuellement disponibles quant à l'implication des différents gènes incriminés. Cet ouvrage s'adresse aux professionnels de santé, enseignants et chercheurs en génétique, cardiologie, nutrition, endocrinologie, biochimie, biologie médicale...

METTEY Y., GOMPEL M., THOMAS V., GARNIER M., LEOST M., CEBALLOS-PICOT I., NOBLE M., ENDICOTT J., VIERFOND J.M., MEIJER L.

Aloisines, a New Family of CDK/GSK-3 Inhibitors. SAR Study, Crystal Structure in Complex with CDK2, Enzyme Selectivity, and Cellular Effects.

J. Medic. Chem., (2), 222-236, 2003

(Services cités : [U383](#))

Cyclin-dependent kinases (CDKs) regulate the cell cycle, apoptosis, neuronal functions, transcription, and exocytosis. The observation of CDK deregulations in various pathological situations suggests that CDK inhibitors may have a therapeutic value. In this article, we report on the identification of 6-phenyl[5H]pyrrolo[2,3-b]pyrazines (alosisines) as a novel potent CDK inhibitory scaffold. A selectivity study performed on 26 kinases shows that alosisine A is highly selective for CDK1/cyclin B, CDK2/cyclin A-E, CDK5/p25, and GSK-3 α /beta; the two latter

enzymes have been implicated in Alzheimer's disease. Kinetic studies, as well as the resolution of a CDK2-aloisine cocrystal structure, demonstrate that aloisines act by competitive inhibition of ATP binding to the catalytic subunit of the kinase. As observed with all inhibitors reported so far, aloisine interacts with the ATP-binding pocket through two hydrogen bonds with backbone nitrogen and oxygen atoms of Leu 83. Aloisine inhibits cell proliferation by arresting cells in both G1 and G2.

SAVOURET C., BRISSON E., ESSERS J., KANAAR R., PASTINK A., TE RIELE H., JUNIEN C., GOURDON G.

CTG repeat instability and size variation timing in DNA repair-deficient mice.

EMBO J., 22 (9), 2264-2273, 2003

(Services cités : U383)

Type 1 myotonic dystrophy is caused by the expansion of an unstable CTG repeat in the DMPK gene. We have investigated the molecular mechanisms underlying the CTG repeat instability by crossing transgenic mice carrying >300 unstable CTG repeats in their human chromatin environment with mice knockout for genes involved in various DNA repair pathways: Msh2 (mismatch repair), Rad52 and Rad54 (homologous recombination) and DNA-PKcs (non-homologous end-joining). Genes of the non-homologous end-joining and homologous recombination pathways did not seem to affect repeat instability. Only lack of Rad52 led to a slight decrease in expansion range. Unexpectedly, the absence of Msh2 did not result in stabilization of the CTG repeats in our model. Instead, it shifted the instability towards contractions rather than expansions, both in tissues and through generations. Furthermore, we carefully analyzed repeat transmissions with different Msh2 genotypes to determine the timing of intergenerational instability. We found that instability over generations depends not only on parental germinal instability, but also on a second event taking place after fertilization.

SEMPOUX C., GUIOT Y., DAHAN K., MOULIN P., STEVENS M., LAMBOT V., LONLAY PD P., FOURNET J.C., JUNIEN C., JAUBERT F., NIHOUL-FEKETE C., SAUDUBRAY J.M., RAHIER J.

The Focal Form of Persistent Hyperinsulinemic Hypoglycemia of Infancy: Morphological and Molecular Studies Show Structural and Functional Differences With Insulinoma.

Diabetes, 52 (3), 784-794, 2003

(Services cités : U383, Chirurgie Pédiatrique, Anatomo-Pathologie, Métabolisme-Neurologie Génétique Pédiatrique)

Paternal mutation of ATP-sensitive K(+) (K(ATP)) channel genes and loss of heterozygosity (LOH) of the 11p15 region including the maternal alleles of ABCC8, IGF2, and CDKN1C characterize the focal form of persistent hyperinsulinemic hypoglycemia of infancy (FoPHHI). We aimed to understand the actual nature of FoPHHI in comparison with insulinoma. In FoPHHI, the lesion consists in clusters of beta-cells surrounded by non-beta-cells. Compared with adjacent islets, proinsulin mRNA is similar and proinsulin production higher ($P \leq 0.02$), indicating regulation at a translational level, with slightly lower insulin stock and lower ABCC8 peptide labeling ($P < 0.05$). Insulinomas, composed of beta-cell nests or cords, have similar proinsulin mRNA compared with adjacent islets, highly variable proinsulin production, lower insulin stock ($P \leq 0.02$), and higher ABCC8 peptide labeling ($P < 0.05$). Proinsulin mRNA is lower than in FoPHHI ($P < 0.001$). Islets adjacent to FoPHHI appear to be resting, in contrast to those adjacent to insulinomas, evidencing intrapancreatic regulation of islet beta-cell activity. IGF2 peptide is present inside and outside both lesions, but IGF2 mRNA is restricted to the

lesions. The 11p15 LOH and absence of CDKN1C peptide staining are demonstrated in all FoPHHI but also in three of eight insulinomas. Despite some molecular similarities, FoPHHI is thus fundamentally different from insulinoma.

2002

BAUDRY D., FAUSSILLON M., CABANIS M.O., RIGOLET M., ZUCKER J.M., PATTE C., SARNACKI S., BOCCON-GIBOD L., JUNIEN C., JEANPIERRE C.

Changes in WT1 splicing are associated with a specific gene expression profile in Wilms' tumour.

Oncogene, 21 (36), 5566-5573, 2002

(Services cités : Chirurgie Pédiatrique, U383)

Wilms' tumour (WT) or nephroblastoma is the most frequent kidney cancer in children. In a previous study, we reported alterations to WT1 transcription in 90% of WT tested, with decreased exon 5 +/- isoform ratio being the most frequent alteration (56% of WT). We now report an approach based on cDNA profiling of tumour pools to identify genes likely to be dysregulated in association with a decreased WT1 exon 5 +/- ratio. We compared the expression profiles of pools of tumours classified according to whether this isoform imbalance was present (five tumours) or not (four tumours), using Atlas Cancer cDNA expression arrays. Fourteen of 588 genes tested displayed specific up-regulation (CCND2, PCNA, N-MYC, E2F3, TOP2A, PAK1, DCC and PCDH2) or down-regulation (VEGF, IGFBP5, TIMP3, ARHB, C-FOS and CD9) in the pool of tumours with decreased exon 5 +/- ratio. These results were validated by RT-PCR analysis of four genes (CCND2, PCNA, VEGF and IGFBP5). We extended the analysis of VEGF expression to 51 tumours by real-time RT-PCR and ascertained differential expression of this gene associated with WT1 expression pattern. Moreover, our results suggest that the VEGF expression level may be of prognosis relevance for relapsed patients. doi:10.1038/sj.onc.1205752

COLLOD-BEROUD G., BOILEAU C.

Marfan syndrome in the third Millennium.

Eur. J. Hum. Genet., 10 (11), 673-681, 2002

(Services cités : U383)

The Marfan syndrome (MFS) is a prominent member of heritable disorders of connective tissue with manifestations involving primarily the skeletal, ocular and cardiovascular systems but also and less systematically investigated the lung, skin and integument, and dura. Over the last two decades, a considerable amount of clinical, molecular and protein data had accumulated. In combination with the study of natural and transgenic animal models, this new information provides greater insight into the pathogenic mechanisms underlying not only the pleiotropic manifestations of MFS but also the important degree of clinical variability (age of onset and severity) observed between patients. The following aspects will be described in this review: the structure and function of fibrillin-1; the fibrillin proteins; mutations in the FBN1 gene and pathogenic mechanisms; animal models. Finally, the currently available laboratory diagnostic tests and their limits will be discussed. doi:10.1038/sj.ejhg.5200876

DE LONLAY P., CORMIER-DAIRE V., AMIEL J., TOUATI G., GOLDENBERG A., FOURNET J.C., BRUNELLE F., NIHOUL-FEKETE C., RAHIER J., JUNIEN C., ROBERT J.J., SAUDUBRAY J.M.

Facial appearance in persistent hyperinsulinemic hypoglycemia.

Amer. J. Med. Genet., 111 (2), 130-133, 2002

(Services cités : Anatomo-Pathologie, Chirurgie Pédiatrique, Département de Pédiatrie, Métabolisme-Neurologie Génétique Pédiatrique, Radiologie Pédiatrique, U383, U393)

Persistent hyperinsulinism is the most common cause of recurrent hypoglycemia in infancy because of inappropriate oversecretion of insulin by the pancreas. Pancreatic lesions can be either focal or diffuse, and they have distinct molecular bases. We have studied the facial features in 17 unrelated patients presenting with neonatal (n = 8) or infancy-onset (n = 9) hyperinsulinism. Hyperinsulinism was related to focal adenomatous hyperplasia (n = 7), diffuse hyperinsulinism (n = 5), non-operated hyperinsulinism (n = 2), and hyperinsulinism with hyperammonemia (n = 3). SUR1 or Kir6.2 mutations were found in six of seven focal adenomatous hyperplasia and three of five diffuse hyperinsulinism. A loss of the maternal allele from chromosome 11p15 in the lesion was found in all focal adenomatous hyperplasia. GLUD1 mutations were found in all patients with hyperammonemia. Large birth weight (mean > 3,800 g) was consistently observed (11/17) but protruding tongue, exomphalos, or visceromegaly were never noted and Wiedemann-Beckwith syndrome could always be ruled out. All patients presented with high forehead, small nasal tip, and short columella giving the impression that the nose is large and bulbous, smooth philtrum, and thin upper lip. A square appearance to the face was more obvious in younger patients. These specific facial features, observed in patients with hyperinsulinism of various molecular mechanisms, could be the consequence of fetal intoxication by insulin. However, to date, facial anomalies have not been noted in infants of diabetic mothers and inversely, malformations that are commonly reported in infants of diabetic mothers were not present in our hyperinsulinemic patients.

DE LONLAY P., FOURNET J.C., TOUATI G., GROOS M.S., MARTIN D., SEVIN C., DELAGNE W., MAYAUD C., CHIGOT V., SEMPOUX C., MARIE-CLAIRE C.S., LABORDE B.K., BELLANE-CHANTELOT C., VASSAULT A., RAHIER J., JUNIEN C., BRUNELLE F., NIHOUL-FEKETE C., SAUDUBRAY J.M., ROBERT J.J.

Heterogeneity of persistent hyperinsulinaemic hypoglycaemia. a series of 175 cases.

Eur. J. Pediat., 161 (1), 37-48, 2002

(Services cités : Anatomo-Pathologie, Fédération de Pédiatrie, Radiologie Pédiatrique, Chirurgie Pédiatrique, U383, Biochimie Générale, Métabolisme-Neurologie Génétique Pédiatrique)

Hyperinsulinism is a heterogeneous disorder characterised by severe hypoglycaemia due to an inappropriate oversecretion of insulin. In a personal series of 175 patients investigated for hyperinsulinaemic hypoglycaemia over the last 20 years, we review clinical presentations, molecular studies and therapeutic management of hyperinsulinism. There were 98 neonatal-onset patients, including 86 permanent hyperinsulinism and 12 transient forms, 68 with infancy-onset and nine with childhood-onset. Hyperammonaemia was found in 12 out of 69 patients tested, 4 neonates and 8 infants. Neonates were clinically more severely affected than infants. Diagnosis of infancy-onset hyperinsulinism was often delayed because of less profound hypoglycaemia and better tolerance to hypoglycaemia. Neonates required higher rates of iv glucose than infants to maintain normal plasma glucose levels (16 mg/kg per min versus 12 mg/kg per min). Only 16% of neonates were diazoxide-sensitive compared to 66% of the infants. Neonates with hyperammonaemia or transient hyperinsulinism were diazoxide-sensitive. Most neonates were pancreatectomised whereas 65% of the infants were treated medically. Among surgically-treated patients, 47% had a focal adenomatous hyperplasia (31 neonates and 13 infants) and 53% a diffuse form of hyperinsulinism (39 neonates and 11 infants). Diazoxide-responsiveness in the focal and diffuse forms did not differ in both neonates and infants; it depended only upon the age of onset of hypoglycaemia. One or two mutations, SUR1 or KIR6.2, were found in 41 of 73

neonates who were investigated and in 13/38 infants using polymerase chain reaction-single strand conformational polymorphism analysis of both genes. Almost all patients with SUR1 (38/41) or KIR6.2 (5/7) mutations were resistant to diazoxide. Ten patients with hyperinsulinism-hyperammonaemia syndrome had a mutation in the glutamate dehydrogenase gene (three neonates and seven infants) after reverse transcriptase-polymerase chain reaction and sequence analysis of cDNA. No mutation was found by polymerase chain reaction-single strand conformational polymorphism in the glucokinase gene. Eight of nine patients with childhood onset hyperinsulinism were treated surgically and histological examination confirmed an adenoma in each case. Conclusion: the clinical severity of hyperinsulinism varies mainly with age at onset of hypoglycaemia. The heterogeneity of hyperinsulinism has major consequences in terms of therapeutic outcome and genetic counselling. [References: 27]

DIATLOFF-ZITO C., MARQUIS E.

Diabète néonatal et diabète du nourrisson insulino-dépendants : aspects génétiques et physiopathologiques, implications.

Pathol. Biol., 50 (4), 233-242, 2002

(Services cités : U383)

Insulin-dependent neonatal diabetes (ND) mellitus is uncommon with a frequency of 1/500,000 neonates in Europe. ND is characterised by hyperglycaemia, very low or undetectable insulin levels associated with intrauterine growth retardation and malformations. HLA haplotypes of juvenile diabetes or autoimmunity are not present in ND patients. Sporadic and familial forms are observed. ND could be persistent (PND) or transient (TND). Diabetes relapses occur in approximately 40% of TND patients. Hypothesis for ND aetiology such as pancreatic or beta pancreatic islets of Langerhans immaturity or abnormalities of pancreas organogenesis are postulated. Different genetic basis underlie transient or permanent forms though their clinical features do not allow to distinguish them. TND may in about 20-30% of the cases be associated with chromosome 6 paternal uniparental disomy. A candidate locus for an imprinted gene is mapped to 6q24. The permanent forms are less understood. Homozygous mutations of the IPF1/PDX1 (MODY4) and of the Glucokinase (GK, MODY2) genes have been reported. The association of a ND with a macroglossia should be a strong indicator for genetic testing. The genetic findings of a paternal disomy uniparental allows the prediction of a transient rather than a permanent form. Mutation in the Glucokinase gene should be sought in an infant with ND whose first degree relatives have glucose intolerance.

DOLLFUS H., MASSIN P., TAUPIN P., NEMETH C., AMARA S., GIRAUD S., BEROUD C., DUREAU P., GAUDRIC A., LANDAIS P., RICHARD S.

Retinal Hemangioblastoma in von Hippel-Lindau Disease: A Clinical and Molecular Study.

Invest. Ophthalmol. Vis. Sci., 43 (9), 3067-3074, 2002

(Services cités : Biostatistique, CERTO, U383, Néphrologie Adulte, Ophtalmologie)

PURPOSE. To assess the natural history of retinal manifestations in von Hippel-Lindau (VHL) disease and to study the genotype-phenotype correlation. **METHODS.** Data concerning 103 patients with VHL retinal manifestations and 108 patients without VHL retinal manifestations were extracted from the French VHL database. A retrospective study was performed by questionnaire. Patients were classified into three visual morbidity groups. Molecular analysis of the VHL gene was performed in 196 patients. **RESULTS.** The mean age of ocular manifestations detection was 24.8 years. In half of the cases, the ocular manifestations revealed the disease. Half of the cases had bilateral involvement. Visual morbidity was significantly associated with the

retinal hemangioblastoma count but not with other ocular or general characteristics. One third of the patients were classified in the worst visual morbidity group at the end of follow-up. Mutations were detected in 81% of patients with retinal hemangioblastomas and in 71% of patients without retinal involvement. Using a Poisson model and a marginal approach, the number of hemangioblastomas, age-adjusted, was 2.1 times higher in patients who had a substitution than in patients with a truncation (95% CI, 1.05-4.44; $P < 0.05$). CONCLUSIONS. Visual loss remains one of the major complications of VHL disease, confirming the importance of early ophthalmologic screening. Visual morbidity was not related to the type of extraocular manifestation but appeared to be related to the type of germline mutation. However, only further genetic and clinical studies in a larger series of patients will clearly determine the genotype-phenotype relationship.

GALLOU C., BEROUD C., JUNIEN C.

Characterization of molecular events in renal cell carcinoma.

Néphrologie, 23 (2), 97-99, 2002

(Services cités : U383)

Renal cell carcinoma accounts for more than 90% of adult renal cancer. This work concerns sporadic RCC and RCC in the VHL syndrome, which represents the first cause of death in this context. The aims of this work were: 1) characterize mutations in the VHL gene; 2) identify new genes and prognostic factors; 3) estimate the importance of genetic background in the etiology of RCC. We have shown, by the molecular characterization of mutations in the VHL gene of 173 sporadic RCC and 126 VHL french families, that the nature of germline mutations constitute a risk factor to develop RCC for VHL patients. Studies of chromosome 14 on sporadic RCC led us to delimitate a commonly deleted region of 3 megabases and suggested that several 14q tumor suppressor genes are involved in the pathogenesis of RCC. Then, we have shown that the activity of polymorphic human xenobiotic-metabolizing enzymes can modulate the susceptibility to RCC and that transversions in the VHL gene are associated with specific genotypes, our findings suggest that the combination of the genotype with particular toxic constitute a pathway that promotes the formation of transversion in the VHL gene during the nephrocarcinogenesis.

JUNIEN C.

Genes, lipids and cardiovascular diseases: nutrigenomics and nutrigenetics.

Sci. Aliments, 22 (4), 471-487, 2002

(Services cités : U383)

MARQUIS E., ROBERT J.J., BOUVATTIER C., BELLANNE-CHANTELOT C., JUNIEN C., DIATLOFF-ZITO C.

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

J. Med. Genet., 39 (5), 370-374, 2002

(Services cités : U383, Fédération de Pédiatrie)

MATYAS G., de PAEPE A., HALLIDAY D., BOILEAU C., PALS G., STEINMANN B.

Evaluation and application of denaturing HPLC for mutation detection in Marfan syndrome: Identification of 20 novel mutations and two novel polymorphisms in the FBN1 gene.

Hum. Mutat., 19 (4), 443-456, 2002

(Services cités : U383)

Mutations in the human fibrillin 1 gene (FBN1) cause the Marfan syndrome (MFS), an autosomal dominant connective tissue disorder. Knowledge about FBN1 mutations is important for early diagnosis, management, and genetic counseling. However, mutation detection in FBN1 is a challenge because the gene is very large in size (similar to 200 kb) and the similar to 350 mutations detected so far are scattered over 65 exons. Conventional methods for large-scale detection of mutations are expensive, technically demanding, or time consuming. Recently, a high-capacity low-cost mutation detection method was introduced based on denaturing high-performance liquid chromatography (DHPLC). To assess the sensitivity and specificity of this method, we blindly screened 64 DNA samples of known FBN1 genotype exon-by-exon using exon-specific DHPLC conditions. Analysis of 682 PCR amplicons correctly identified 62 out of 64 known sequence variants. In three MFS patients of unknown FBN1 genotype, we detected two mutations and eight polymorphisms. Overall, 20 mutations and two polymorphisms are described here for the first time. Our results demonstrate 1) that DHPLC is a highly sensitive (89-99%, $P = 0.05$) method for FBN1 mutation detection; but 2) that chromatograms with moderate and weak pattern abnormalities also show false positive signals (in all 45-59%, $P = 0.05$); 3) that the difference in the chromatograms of heterozygous and homozygous amplicons is mostly independent of the type of sequence change; and 4) that DHPLC column conditions, additional base changes, and the amounts of injected PCR products influence significantly the shape of chromatograms. A strategy for FBN1 mutation screening is discussed. *Hum Mutat* 19:443-456, 2002. (C) 2002 Wiley-Liss, Inc.

SIMONNET H., ALAZARD N., PFEIFFER K., GALLOU C., BEROUD C., DEMONT J., BOUVIER R., SCHAGGER H., GODINOT C.

Low mitochondrial respiratory chain content correlates with tumor aggressiveness in renal cell carcinoma.

Carcinogenesis, 23 (5), 759-768, 2002

(Services cités : U383)

A mechanism decreasing oxidative metabolism during normal cell division and growth is expected to direct substrates toward biosyntheses rather than toward complete oxidation to CO₂. Hence, any event decreasing oxidative phosphorylations (OXPHOS) could provide a proliferating advantage to a transformed or tumor cell in an oxidative tissue. To test this hypothesis, we studied mitochondrial enzymes, DNA and OXPHOS protein content in three types of renal tumors from 25 patients. Renal cell carcinomas (RCCs) of clear cell type (CCRCCs) originate from the proximal tubule and are most aggressive. Chromophilic RCCs, from similar proximal origin, are less aggressive. The benign renal oncocytomas originate from collecting duct cells. Mitochondrial enzyme and DNA contents in all tumor types or grades differed significantly from normal tissue. Mitochondrial impairment increased from the less aggressive to the most aggressive RCCs, and correlated with a considerably decreased content of OXPHOS complexes (complexes II, III, and IV of the respiratory chain, and ATPase/ATP synthase) rather than to the mitochondrial content (citrate synthase and mitochondrial (mt)DNA). In benign oncocytoma, some mitochondrial parameters (mtDNA, citrate synthase, and complex IV) were increased 4- to 7-fold, and some were slightly increased by a factor of 2 (complex V) or close to normal (complexes II and III). A low content of complex V protein was found in all CCRCC and chromophilic tumors studied. However F(1)-ATPase activity was not consistently decreased and its impairment was associated with increased aggressiveness in CCRCCs. Immunodetection of free F(1)-sector of complex V demonstrated a disturbed assembly/stability of complex V in several CCRCC and chromophilic tumors. All results are in agreement with the

hypothesis that a decreased OXPHOS capacity favors faster growth or increased invasiveness.

SOULIE C., NICOLE A., CHRISTEN Y., CEBALLOS-PICOT I.

The Ginkgo biloba extract EGb 761 increases viability of hnt human neurons in culture and affects the expression of genes implicated in the stress response.

Cell. Mol. Biol., 48 (6), 641-646, 2002

(Services cités : U383)

There are numerous studies describing the neuroprotective effects of Ginkgo biloba extract EGb 761 on patients with disturbances of vigilance, memory and cognitive functions associated with aging and senility. Describing the pattern of gene expression in EGb 761-treated human hNT neurons may elucidate the molecular pathways leading to the neuroprotection. We used cDNA macroarrays including genes implicated in the antioxidant and stress responses to define the transcriptional effects of EGb 761 (250 microg/ml, 24 hr) on human hNT neurons. Seven genes were identified whose expression was strongly modified by the EGb 761 treatment. Three groups are distinguished: genes encoding transcription factors (increase of NF-kappaB p65 subunit and zinc finger protein 91 mRNAs, and decrease of c-myc transcripts), genes involved in antioxidant defenses (increase of the CuZn SOD mRNAs, and decrease of glutathione reductase and glutathione S-transferase pi mRNAs) and genes involved in stress responses (up-regulation of HSP70 transcripts). Consistent with the modulation of mRNAs by EGb 761, the enzymatic activities of glutathione reductase and glutathione S-transferase were decreased. Surprisingly, CuZn SOD activity was decreased despite increased abundance of the mRNAs; furthermore MnSOD activity was unmodified, and thus the effect of EGb 761 was specific to CuZn SOD. These results support the idea that modulation of target genes and transcription factors may be involved in the neuroprotective action of EGb 761.

VILLEGER L., ABIFADEL M., ALLARD D., RABES J.P., THIART R., KOTZE M.J., BEROU D., JUNIEN C., BOILEAU C., VARRET M.

The UMD-LDLR database: additions to the software and 490 new entries to the database.

Hum. Mutat., 20 (2), 81-87, 2002

(Services cités : U383)

Mutations in the LDL receptor gene (LDLR) cause familial hypercholesterolemia (FH), one of the most frequent hereditary dominant disorders. The protein defect was identified in 1973, the gene was localized by in situ hybridization in 1985, and since, a growing number of mutations have been reported. The UMD-LDLR database is customized software that has been developed to list all mutations, and also to provide means to analyze them at the nucleotide and protein levels. The database has been recently modified to fulfill the recommendations of the Nomenclature Working Group for human gene mutations. However, in the current version, both the nomenclature and usual LDLR gene mutation names are reported since the latter are more commonly used. The software has also been modified to accommodate the splicing mutations and alleles that carry two nucleotide variations. The current version of UMD-LDLR contains 840 entries, of which 490 are new entries. Point mutations account for 90% of all mutations in the LDLR gene; the remaining are mostly major rearrangements, due to the presence of Alu sequences. Three new routines have been implemented in the software, thus giving users access to 13 sorting tools. In addition to the database, a Web site containing information about polymorphisms, major rearrangements, and promoter mutations is available. Both are accessible to the scientific community (www.umd.necker.fr) and should help groups working on LDLR to check their mutations and identify new ones, and greatly facilitate the understanding of functional

classes/genotype relationships and of genotype/phenotype correlations.

WAUTOT V., VERCHERAT C., LESPINASSE J., CHAMBE B., LENOIR G.M., ZHANG C.X., PORCHET N., CORDIER M., BEROUD C., CALENDER A.

Germline mutation profile of MEN1 in multiple endocrine neoplasia type 1: search for correlation between phenotype and the functional domains of the MEN1 protein.

Hum. Mutat., 20 (1), 35-47, 2002

(Services cités : [U383](#))

Multiple Endocrine Neoplasia type 1 (MEN1) is an autosomal dominant disease characterized by endocrine tumors of the parathyroids, the pancreatic islets, and the anterior pituitary. The MEN1 gene encodes menin, a nuclear protein interacting with JunD/AP1, Smad3, NFkappaB, and other proteins involved in transcription and cell growth regulation. Here, by exhaustive sequence analysis of 170 probands/families collected through a French clinical network, we identified 165 mutations located in coding parts of the MEN1 gene, which represent 114 distinct MEN1 germline alterations. These mutations have been included in a MEN1-locus specific database available on the world wide web together with approximately 240 germline and somatic MEN1 mutations listed from international published data. Our mutation series included 56 frameshifts, 23 nonsense, 27 missense, and eight deletion or insertion in-frame mutations. Mutations were spread over the entire coding sequence. Taken together, most missense and in-frame MEN1 genomic alterations affect one or all domains of menin interacting with JunD [codons 1-40; 139-242; 323-428], Smad3 [distal to codon 478], and NFkappaB [codons 276-479], three major effectors in transcription and cell growth regulation. No correlation has been observed between genotype and MEN1 phenotype. We suggest that the knowledge of structure and location of a specific mutation has not been useful in clinical practice for the follow-up of affected patients and asymptomatic gene carriers. Our results provide the largest series of MEN1 mutations published to date. They will be a useful tool for further studies focusing on the functional effects of missense mutations and understanding which mechanisms or pathways related to multiple menin interactions might be involved in tumorigenesis of endocrine cells.

2001

BEROUD C.

Molecular diagnostic techniques in oncogenetics.

Ann. Méd. Intern., 152 (5), 326-331, 2001

(Services cités : [U383](#))

BOURC'HIS D., LE BOURHIS D., PATIN D., NIVELEAU A., COMIZZOLI P., RENARD J.P., VIEGAS-PEQUIGNOT E.

Delayed and incomplete reprogramming of chromosome methylation patterns in bovine cloned embryos.

Curr. Biol., 11 (19), 1542-1546, 2001

(Services cités : [U383](#))

Full-term development has now been achieved in several mammalian species by transfer of somatic nuclei into enucleated oocytes [1, 2]. Although a high proportion of such reconstructed embryos can evolve until the blastocyst stage, only a few percent develop into live offspring, which often exhibit developmental abnormalities [3, 4]. Regulatory epigenetic markers such as DNA methylation are imposed on embryonic cells as normal development proceeds, creating differentiated cell states. Cloned embryos require the erasure of their somatic epigenetic markers

so as to regain a totipotent state [5]. Here we report on differences in the dynamics of chromosome methylation between cloned and normal bovine embryos before implantation. We show that cloned embryos fail to reproduce distinguishable parental-chromosome methylation patterns after fusion and maintain their somatic pattern during subsequent stages, mainly by a highly reduced efficiency of the passive demethylation process. Surprisingly, chromosomes appear constantly undermethylated on euchromatin in morulae and blastocysts, while centromeric heterochromatin remains more methylated than that of normal embryos. We propose that the abnormal time-dependent methylation events spanning the preimplantation development of clones may significantly interfere with the epigenetic reprogramming, contributing to the high incidence of physiological anomalies occurring later during pregnancy or after clone birth. [References: 32]

DE ALMEIDA-TOLEDO L.F., FORESTI F., VIEGAS-PEQUIGNOT E., DANIEL-SILVA M.F.

XX:XY sex chromosome system with X heterochromatinization: an early stage of sex chromosome differentiation in the Neotropic electric eel *Eigenmannia virescens*.

Cytogenet. Cell Genet., 95 (1-2), 73-78, 2001

(Services cités : [U383](#))

An early stage of sex chromosome differentiation is reported to occur in the electric eel *Eigenmannia virescens* (Pisces, Sternopygidae) from populations of two tributaries of the Parana river system (Brazil). Cytogenetic studies carried out in the two populations showed that the Mogi-Guacu population is characterized by $2n = 38$ chromosomes and undifferentiated sex chromosomes and the Tiete population presents $2n = 38$ both for males and females and an XX:XY sex chromosome system. The X-chromosome is acrocentric, easily recognized by the presence of a conspicuous heterochromatin block in its distal portion; the Y-chromosome is probably one of the medium sized acrocentrics present in the male karyotype. BrdU induced R-bands of the two populations did not reveal any difference in the euchromatic regions of the chromosomes. AluI and HaeIII restriction enzyme digestion patterns and chromomycin A3 staining of the X-chromosome are presented. The possible role of heterochromatinization in the evolution of sex chromosomes in fish is discussed.

ERBEL R., ALFONSO F., BOILEAU C., DIRSCH O., EBER B., HAVERICH A., RAKOWSKI H., STRUYVEN J., RADEGRAN K., SECHTEM U., TAYLOR J., ZOLLIKOFER C.

Diagnosis and management of aortic dissection - recommendations of the task force on aortic dissection, european society of cardiology.

Eur. Heart J., 22 (18), 1642-1681, 2001

(Services cités : [U383](#))

FOURNET J.C., MAYAUD C., de LONLAY P., GROSS-MORAND M.S., VERKARRE V., CASTANET M., DEVILLERS M., RAHIER J., BRUNELLE F., ROBERT J.J., NIHOUL-FEKETE C., SAUDUBRAY J.M., JUNIEN C.

Unbalanced expression of 11p15 imprinted genes in focal forms of congenital hyperinsulinism - association with a reduction to homozygosity of a mutation in *abcc8* or *kcnj11*.

Amer. J. Pathol., 158 (6), 2177-2184, 2001

(Services cités : [Anatomo-Pathologie, Département de Pédiatrie, U383, Chirurgie Pédiatrique, Radiologie Pédiatrique](#))

Congenital hyperinsulinism (CHI), previously named persistent hyperinsulinemic hypoglycemia of infancy, is characterized by profound hypoglycemia because of excessive insulin secretion. CHI presents as two different morphological forms: a diffuse form with functional abnormality of islets throughout the pancreas and a focal form with focal islet cell adenomatous hyperplasia, which can be cured by partial pancreatectomy. Recently, we have shown that focal adenomatous hyperplasia involves the specific loss of the maternal 11p15 region and a constitutional mutation of a paternally inherited allele of the gene encoding the regulating subunit of the K-ATP(+) channel, the sulfonylurea receptor (ABCC8 or SUR1). In the present study on a large series of 31 patients, describing both morphological features and molecular data, we report that 61% of cases (19 out of 31) carried a paternally inherited mutation not only in the ABCC8 gene as previously described but also in the second gene encoding the K-ATP(+) channel, the inward rectifying potassium channel (KCNJ11 or KIR6.2), in 15 cases and 4 cases, respectively. Moreover our results are consistent with the presence of a duplicated paternal 11p15 allele probably because of mitotic recombination or reduplication of the paternal chromosome after somatic loss of the maternal chromosome. In agreement with the loss of the maternal chromosome, the level of expression of a maternally expressed tumor suppressor gene, H19, was greatly reduced compared to the level of expression of the paternally expressed growth promoter gene, IGF2. The expression of IGF2 was on average only moderately increased. Thus, focal forms of CHI can be considered to be a recessive somatic disease, associating an imbalance in the expression of imprinted genes in the 11p15.5 region to a somatic reduction to homozygosity of an ABCC8- or KCNJ11-recessive mutation. The former is responsible for the abnormal growth rate, as in embryonic tumors, whereas the latter leads to unregulated secretion of insulin. [References: 52]

FURLING D., COIFFIER L., MOULY V., BARBET J.P., ST GUILY J.L., TANEJA K., GOURDON G., JUNIEN C., BUTLER-BROWNE G.S.

Defective satellite cells in congenital myotonic dystrophy.

Hum. Mol. Genet., 10 (19), 2079-2087, 2001

(Services cités : U383)

In this study we have developed an in vitro cell culture system which displays the majority of the defects previously described for congenital myotonic dystrophy (CDM) muscle in vivo. Human satellite cells were isolated from the quadriceps muscles of three CDM fetuses with different clinical severity. By Southern blot analysis all three cultures were found to have approximately 2300 CTG repeats. This CTG expansion was found to progressively increase in size during the proliferative life span, confirming an instability of this triplet in skeletal muscle cells. The CDM myoblasts and myotubes also showed abnormal retention of mutant RNA in nuclear foci, as well as modifications in their myogenic program. The proliferative capacity of the CDM myoblasts was reduced and a delay in fusion, differentiation and maturation was observed in the CDM cultures compared with unaffected myoblast cultures. The clinical severity and delayed maturation observed in the CDM fetuses were closely reflected by the phenotypic modifications observed in vitro. Since the culture conditions were the same, this suggests that the defects we have described are intrinsic to the program expressed by the myoblasts in the absence of any trophic factors. Altogether, our results demonstrate that satellite cells are defective in CDM and are probably implicated in the delay in maturation and muscle atrophy that has been described previously in CDM fetuses. [References: 49]

GALLOU C., LONGUEMAUX S., DELOMENIE C., MEJEAN A., MARTIN N., MARTINET S.P., PALAIS G., BOUVIER R., DROZ D., KRISHNAMOORTHY R.,

JUNIEN C., BEROUD C., DUPRET J.M.

Association of gstm1 non-null and nat1 slow/rapid genotypes with von hippel-lindau tumour suppressor gene transversions in sporadic renal cell carcinoma.

Pharmacogenetics, 11 (6), 521-535, 2001

(Services cités : Anatomo-Pathologie, U383, Urologie)

The von Hippel-Lindau (VHL) tumour suppressor gene is commonly mutated in renal cell carcinoma of clear cell type (CCRCC). We investigated the possible relationship between VHL mutations in sporadic CCRCC and polymorphism of genes encoding enzymes involved in carcinogen metabolism: two cytochrome P450 monooxygenases (CYP1A1 and CYP2D6), one NAD[P]H:quinone oxidoreductase (NQO1), three glutathione S-transferases (GSTM1, GSTT1 and GSTP1) and two arylamine N-acetyltransferases (NAT1 and NAT2). We analysed DNA from tumour and nontumoural kidney tissue from 195 CCRCC patients. Single VHL mutations were identified in 88 patients and double mutations were present in two patients. Nine of 18 transversions were GC to TA, four were AT to TA, four were GC to CG and one was AT to CG. Ten of 19 transitions were GC to AT and nine were AT to GC. We also identified 53 frameshifts and two GC to AT at CpG. An excess of transversions was observed in a subset of patients with active GSTT1 [GSTT1 (+) genotype] and probably defective NAT1 (NAT1 S/R variant genotype). All 18 transversions were in GSTT1 (+) patients, whereas only 76% of transitions (P=0.05) and 81%, of the other mutations (P=0.06) occurred in this genotype. We found that 28% of the transversions were in the NAT1 S/R genotype versus 12% of the transitions (P=0.40) and 4% of the other mutations (P=0.01). This suggests that pharmacogenetic polymorphisms may be associated with the type of acquired VHL mutation, which may modulate CCRCC development. *Pharmacogenetics* 11:521-535. (C) 2001 Lippincott Williams & Wilkins. [References: 39]

GEROMEL V., KADHOM N., CEBALLOS-PICOT I., OUARI O., POLIDORI A., MUNNICH A., ROTIG A., RUSTIN P.

Superoxide-induced massive apoptosis in cultured skin fibroblasts harboring the neurogenic ataxia retinitis pigmentosa (narp) mutation in the atpase-6 gene of the mitochondrial DNA.

Hum. Mol. Genet., 10 (11), 1221-1228, 2001

(Services cités : U383, U393)

The oxidative stress resulting from the neurogenic ataxia retinitis pigmentosa (NARP) mutation in the mitochondrial ATPase 6 gene was investigated in cultured skin fibroblasts from two patients presenting an isolated complex V deficiency. Taken as an index for superoxide overproduction, a huge induction of the superoxide dismutase (SOD) activity was observed in these fibroblasts harboring > 90% of mutant mitochondrial DNA. The oxidative stress denoted by the high SOD activity was associated with increased cell death. In glucose-rich medium, apoptosis appeared as the main cell death process associated with complex V deficiency. Complex V-deficient fibroblasts, which showed a high SOD induction and stained positive for all studied apoptosis markers, were successfully rescued by perfluoro-tris-phenyl nitrene, an antioxidant spin-trap molecule. This established that the superoxide production associated with the ATPase deficiency triggered by the NARP mutation could be sufficient to override cell antioxidant defenses and to result in cell commitment to die. The potential participation of superoxides and/or their derivatives in the pathogenic mechanism of specific respiratory chain disorders makes them a promising target for therapy. [References: 59]

JUNIEN C.

Colon cancer and nutrigenetics: modifier genes.

Ann. Méd. Intern., 152 (5), 337-351, 2001

(Services cités : U383)

About 5% of colon cancer cases correspond to classic hereditary monogenic mendelian transmission involving at least 8 major genes of predisposition to this tumor. Genes with more moderate effects, in association with other genes can contribute to the occurrence of sporadic polygenic forms. These genes confer susceptibility to environmental factors and can play the role of aggravating or protective modifier genes in the different hereditary forms. Foods can interact with these genes and modulate their expression. Moreover sequence variations (polymorphisms) in these genes may also be responsible for slower or more rapid metabolism of nutrients leading to toxic or carcinogenic compounds. If some foods, or "pharmafoods" can have beneficial effects in some individuals with a particular subtype of the disease, others can be inefficient or even detrimental in patients with the same disease but with a different genetic origin or if the genetic background is different. Moreover tumorigenic processes are diverse. Tumor progression depends on genetic and environmental factors different from tumor initiation and on the site of the tumor along the colon tract. Interactions with the gut flora, the lymphoid system and specific features of growth of the colon mucosa are also important parameters. Today with a formidable genetic knowledge arising from the genome project, new epidemiological data integrating the genetic data for multiple markers and a better knowledge of the tumorigenic processes involved, a new discipline is emerging. "Nutrigenetics" which is the study of hereditary basis of individual variations in response to foods opens for the oncoming decade the era of a personalised predictive medicine based on a nutrition adapted to the genetic make up of each of us.

[References: 69]

MILLECAMPS S., NICOLLE D., CEBALLOS-PICOT I., MALLET J., BARKATS M.

Synaptic sprouting increases the uptake capacities of motoneurons in amyotrophic lateral sclerosis mice.

Proc. Nat. Acad. Sci. USA, 98 (13), 7582-7587, 2001

(Services cités : U383)

Using adenoviruses encoding reporter genes as retrograde tracers, we assessed the capacity of motoneurons to take up and retrogradely transport adenoviral particles injected into the muscles of transgenic mice expressing the G93A human superoxide dismutase mutation, a model of amyotrophic lateral sclerosis. Surprisingly, transgene expression in the motoneurons was significantly higher in symptomatic mice than in control or presymptomatic mice. Using botulinum toxin to induce nerve sprouting at neuromuscular junctions, we showed that the unexpectedly high level of motoneurons retrograde transduction results, at least in part, from newly acquired uptake properties of the sprouts. These findings demonstrate the remarkable uptake properties of amyotrophic lateral sclerosis motoneurons in response to denervation and the rationale of using intramuscular injections of adenoviruses to overexpress therapeutic proteins in motor neuron diseases. [References: 46]

RIGOLET M., FAUSSILLON M., BAUDRY D., JUNIEN C., JEANPIERRE C.

Profiling of differential gene expression in wilms tumor by cDNA expression array.

Pediat. Nephrol., 16 (12), 1113-1121, 2001

(Services cités : U383)

In order to identify genes or pathways involved in Wilms tumor etiology, we used the Atlas Cancer cDNA expression array to compare the gene expression profiles of five tumors, one Wilms tumor cell line (SK-NEP1), and normal mature and fetal kidneys. Of 588 genes tested,

153 had a different expression pattern in tumors compared with mature kidney. Ninety-six genes were differentially expressed in tumors compared with both normal mature and fetal kidney, and 57 genes had expression profiles similar to that of fetal kidney, which may reflect the developmental stage of the tumor cells. Comparison of the expression patterns of tumors shows that only 13% of the differentially expressed genes are constantly up- or downregulated in the five tumors tested, and this provides molecular evidence of tumor heterogeneity. We then confirmed the differential expression by an independent method, using quantitative reverse transcriptase polymerase chain reaction for two of the differentially expressed genes, MMP-14 and cyclin D2. Analysis of expression levels in a panel of 40 tumors showed that 30% overexpressed MMP-14 and 80% overexpressed cyclin D2. Profiling of gene expression using cDNA arrays in a large tumor panel will ultimately lead to the molecular classification of tumors, the identification of prognosis markers, and the design of targeted therapy. [References: 50]

SANTIARD-BARON D., LACOSTE A., ELLOUK-ACHARD S., SOULIE C., NICOLE A., SARASIN A., CEBALLOS-PICOT I.

The amyloid peptide induces early genotoxic damage in human preneuron nt2.

Mutat. Res.-Fundam. Mol. Mech. Mut., 479 (1-2 Special Issue SI), 113-120, 2001

(Services cités : U383, UMR 8602)

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the extracellular deposition of amyloid beta-peptide (Abeta) in the brain. Abeta is involved in the pathogenesis of AD but the molecular mechanisms of its neurotoxicity are unknown. Here, we report that Abeta exposure on human preneuronal NT2 cells provoked a strong and early up-regulation of growth arrest and DNA damage inducible gene (Gadd45 mRNA), an indicator of DNA damage and DNA excision-repair processes, strongly suggesting that Abeta causes an early DNA strand breakage leading to a cellular DNA repair response. Comet assay clearly demonstrated that both full-length Abeta (1-42), and its minimal cytotoxic fragment Abeta (25-35), caused DNA breakage as early as 3h after the start of Abeta exposure. This extensive DNA damage provoked by Abeta constitutes an early event in the pathogenic cascade leading to neuronal death which could contribute to the neuropathogenesis of AD.

SEZNEC H., AGBULUT O., SERGEANT N., SAVOURET C., GHESTEM A., TABTI N., WILLER J.C., OURTH L., DUROS C., BRISSON E., FOUQUET C., BUTLER-BROWNE G., DELACOURTE A., JUNIEN C., GOURDON G.

Mice transgenic for the human myotonic dystrophy region with expanded ctg repeats display muscular and brain abnormalities.

Hum. Mol. Genet., 10 (23), 2717-2726, 2001

(Services cités : U383)

The autosomal dominant mutation causing myotonic dystrophy (DM1) is a CTG repeat expansion in the 3'-UTR of the DM protein kinase (DMPK) gene. This multisystemic disorder includes myotonia, progressive weakness and wasting of skeletal muscle and extramuscular symptoms such as cataracts, testicular atrophy, endocrine and cognitive dysfunction. The mechanisms underlying its pathogenesis are complex. Recent reports have revealed that DMPK gene haploinsufficiency may account for cardiac conduction defects whereas cataracts may be due to haploinsufficiency of the neighboring gene, the DM-associated homeobox protein (DMAHP or SIX5) gene. Furthermore, mice expressing the CUG expansion in an unrelated mRNA develop myotonia and myopathy, consistent with an RNA gain of function. We demonstrated that transgenic mice carrying the CTG expansion in its human DM1 context (> 45

kb) and producing abnormal DMPK mRNA with at least 300 CUG repeats, displayed clinical, histological, molecular and electrophysiological abnormalities in skeletal muscle consistent with those observed in DM1 patients. Like DM1 patients, these transgenic mice show abnormal tau expression in the brain. These results provide further evidence for the RNA trans-dominant effect of the CUG expansion, not only in muscle, but also in brain. [References: 49]

2000

BAUDRY D., HAMELIN M., CABANIS M.O., FOURNET J.C., TOURNADE M.F., SARNACKI S., JUNIEN C., JEANPIERRE C.

Wt1 splicing alterations in wilms' tumors.

Clin. Cancer Res., **6** (10), 3957-3965, 2000

(Services cités : U383, Chirurgie Pédiatrique, Anatomo-Pathologie)

Hereditary and sporadic forms of tumors are generally related to germ-line and somatic mutations of the same tumor suppressor gene. Unexpectedly, in Wilms' tumor, somatic mutations of the WT1 gene were found only occasionally in sporadic cases, although constitutional mutations of this gene are clearly associated with predisposition. It has been suggested that abnormal splicing may be another mode of somatic WT1 alteration. However, this idea was based on the analysis of a small series of tumors, precluding accurate evaluation of the frequency of such changes. To investigate WT1 changes at the somatic level in more detail, we analyzed the levels of the four isoform transcripts produced by alternative splicing events in a large series of 50 tumors, normal mature kidneys, and fetal kidneys. We characterized splicing alterations in 63% of sporadic Wilms' tumors. Moreover, taking into account the decreased and increased overall levels of WT1 mRNA, the percentage of sporadic tumors with changes in WT1 expression reached 90%. Whether and how these alterations of expression play a role in the tumorigenic process remain to be evaluated. [References: 52]

BAUDRY D., JEANPIERRE C.

Assignment of e-cadherin (cdh1) and ksp-cadherin (cdh16) to chromosome 16q22.1 by radiation hybrid mapping.

Cytogenet. Cell Genet., **88** (3-4), 253-254, 2000

(Services cités : U383)

BEROUD C., COLLODBEROUD G., BOILEAU C., SOUSSI T., JUNIEN C.

UMD (Universal Mutation Database): A Generic software to build and analyze locus-specific databases.

Hum. Mutat., **15** (1), 86-94, 2000

(Services cités : U383)

The human genome is thought to contain about 80,000 genes and presently only 3,000 are known to be implicated in genetic diseases. In the near future, the entire sequence of the human genome will be available and the development of new methods for point mutation detection will lead to a huge increase in the identification of genes and their mutations associated with genetic diseases as well as cancers, which is growing in frequency in industrial states. The collection of these mutations will be critical for researchers and clinicians to establish genotype/phenotype correlations. Other fields such as molecular epidemiology will also be developed using these new data. Consequently, the future lies not in simple repositories of locus-specific mutations but in dynamic databases linked to various computerized tools for their analysis and that can be directly queried on-line. To meet this goal, we devised a generic software called UMD (Universal

Mutation Database). It was developed as a generic software to create locus-specific databases (LSDBs) with the 4(th) Dimension(R) package from ACI. This software includes an optimized structure to assist and secure data entry and to allow the input of various clinical data. Thanks to the flexible structure of the UMD software, it has been successfully adapted to nine genes either involved in cancer (APC, P53, RB1, MEN1, SUR1, VHL, and WT1) or in genetic diseases (FBN1 and LDLR). Four new LSDBs are under construction (VLCAD, MCAD, KIR6, and COL4A5). Finally, the data can be transferred to core databases. Copyright 2000 Wiley-Liss, Inc.

BOURC'HIS D., JEANPIERRE M., VIEGAS PEQUIGNOT E.

Dha methylation and icf syndrome.

M S-Méd. Sci., 16 (1), 105-107, 2000

(Services cités : U383)

CASTELNAU P., LE MERRER M., DIATLOFF ZITO C., MARQUIS E., TETE M.J., ROBERT J.J.

Wolcott-rallison syndrome: a case with endocrine and exocrine pancreatic deficiency and pancreatic hypotrophy.

Eur. J. Pediat., 159 (8), 631-633, 2000

(Services cités : U393, U383, Fédération de Pédiatrie)

Clinical analysis and genetic investigations of new Eases of Wolcott-Rallison syndrome are needed to evaluate the role of the gene(s) directly or indirectly implicated in pancreas development and in the aetiology of the syndrome. [References: 8]

DEREURE O., SAVOY D., DOZ F., JUNIEN C., GUILHOU J.J.

Multiple acral fibromas in a patient with familial retinoblastoma: a cutaneous marker of tumour-suppressor gene germline mutation ?

Br. J. Dermatol., 143 (4), 856-859, 2000

(Services cités : U383)

We report a 40-year-old patient with familial retinoblastoma also affecting his elder son, who developed multiple fibromas on the periungual or subungual areas of all the fingers. Molecular analysis disclosed a loss of heterozygosity for the RB1 gene in the larger tumour, with disappearance of the normal allele and persistence of the mutated allele only. The similarity of this observation with distal fibrous tumours encountered in other diseases with germline mutations of tumour-suppressor genes such as neurofibromatosis type 1, tuberous sclerosis and multiple endocrine neoplasia type 1 led to the hypothesis that multiple acral benign tumours with a fibrous component might be a cutaneous marker of tumour suppressor gene germline mutation with low sensitivity but high specificity. [References: 20]

FOURNET J.C., MAYAUD C., de LONLAYA P., VERKARRE V., RAHIER J., BRUNELLE F., ROBERT J.J., NIHOUL FEKETE C., SAUDUBRAY J.M., JUNIEN C.

Loss of imprinted genes and paternal sur1 mutations lead to focal form of congenital hyperinsulinism.

Hormone Res., 53 (Suppl 1), 2-6, 2000

(Services cités : U383, Radiologie Pédiatrique, Département de Pédiatrie, Anatomopathologie)

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is a heterogeneous disorder characterized by profound hypoglycaemia due to inappropriate hypersecretion of insulin. An important diagnostic goal is to distinguish patients with a focal hyperplasia of islet cells of the

pancreas (FoPHHI) from those with a diffuse abnormality of islets (DiPHHI), because the management differs significantly. The intriguing similarity between islet cell hyperplasia and tumourigenesis prompted us to investigate whether the imprinted genes in the 11p15 region are involved. Results showed that diffuse forms are caused by constitutional homozygous or compound heterozygous mutations of the SUR1 gene. In contrast, focal forms are caused by loss of the maternally inherited 11p15 region, resulting in both loss of the maternally expressed tumour suppressor genes accounting for hyperplasia and somatic reduction to hemizyosity or homozygosity of the paternally inherited SUR1, limited to the lesion. Thus, this somatic disorder, which leads both to P-cell proliferation and to hyperinsulinism, can be considered the somatic equivalent, restricted to a microscopic focal lesion, of constitutional uniparental disomy associated with unmasking of a heterozygous parental mutation. Copyright (C) 2000 S. Karger AG, Basel. [References: 33]

GLASER B., THORNTON P., OTONKOSKI T., JUNIEN C.

Genetics of neonatal hyperinsulinism.

Arch. Dis. Child., 82 (2 Special Issue SI), F79-F86, 2000

(Services cités : U383)

Congenital hyperinsulinism (HI) is a clinically and genetically heterogeneous entity. The clinical heterogeneity is manifested by severity ranging from extremely severe, Life threatening disease to very mild clinical symptoms, which may even be difficult to identify. Furthermore, clinical responsiveness to medical and surgical management is extremely variable. Recent discoveries have begun to clarify the molecular aetiology of this disease and thus the mechanisms responsible for this clinical heterogeneity are becoming more clear. Mutations in 4 different genes have been identified in patients with this clinical syndrome. Most cases are caused by mutations in either of the 2 subunits of the beta cell ATP sensitive K⁺ channel (K-ATP), whereas others are caused by mutations in the beta cell enzymes glucokinase and glutamate dehydrogenase. However, for as many as 50% of the cases, no genetic aetiology has yet been determined. The study of the genetics of this disease has provided important new information about beta cell physiology. Although the clinical ramifications of these findings are still limited, in some situations genetic studies might greatly aid in patient management. [References: 51]

**GONZALEZ I., OHSAWA N., SINGER R.H., DEVILLERS M., ASHIZAWA T.,
BALASUBRAMANYAM A., COOPER T.A., KHAJAVI M., LIA BALDINI A.S., MILLER
G., PHILIPS A.V., TIMCHENKO L.T., WARING J., YAMAGATA H., BARBET J.P.,
KLESERT T.R., TAPSCOTT S.J., ROSES A.D., WAGNER M., BAIGET M.,
MARTORELL L., BROWNE G.B., EYMARD B., GOURDON G., JUNIEN C., ET A.L.**

New nomenclature and dna testing guidelines for myotonic dystrophy type 1(dm1).

Neurology, 54 (6), 1218-1221, 2000

(Services cités : U383)

**JUNIEN C., DUPRET J.M., GALLOU C., LONGUEMAUX S., RICHARD S., SAQUET
C., KRISHNAMOORTY R., DELOMENIE C., DROZ D., BOUVIER R., CHAUVEAU D.,
JOLY D., GRUNFELD J.P., CHRETIEN Y., MEJEAN A., BEROUD C.**

Prevention of renal carcinoma: the nutri-genetic approach.

J. Soc. Biol., 194 (1), 29-38, 2000

(Services cités : U383, Néphrologie Adulte, Urologie, Anatomo-Pathologie)

The development of renal cell carcinoma (RCC) has been associated with both genetic and

environmental factors, with somatic and germline mutations in the von Hippel-Lindau (VHL) tumor suppressor gene and with tobacco smoking, obesity, long term exposure to some nutrients, pollutants, and industrial solvents such as trichloroethylene. Intra and interfamilial variability of expression of germline mutations in the VHL gene and variable susceptibility to carcinogens in the sporadic forms strongly suggest the involvement of conditional modifier genes. In order to identify sub groups of individuals at increased risk because of susceptibility genotypes, we have collected a series of 460 patients who developed an RCC and 79 families with the von Hippel Lindau disease. To collect clinical and mutational data for correlation analysis we have developed a unique tool the Universal Mutation Database. Comparison of the spectrum of germline and somatic mutations in the VHL gene showed that: 1) in sporadic RCC mutations lead more often to truncated proteins (83%), while the remaining mutations (17%), include 3/4 of transversions and 1/4 of transitions. This high proportion of transversions supports the involvement of carcinogens the impact of which is conditioned by the genetic variability of xenobiotic metabolizing enzymes; 2) whereas in familial cases missense mutations are more common; this difference allowed us to define a prognostic factor for the occurrence of RCC in a VHL context. In order to look for genotypes conferring a higher risk we genotyped the RCC patients for 8 different genes (50 genotypes). A significant relationship was observed for several combinations of alleles including CYP1A1 ("variant"), NAT2 and NAT1 (slow) and GSTM1 (null allele). Associations between specific mutational profiles and at risk genotypes at different tumoral stages should allow us to: 1) define more precisely the nature of specific patterns of mutations in relation with the deficiency or overexpression of such or such enzymes in presence of particular carcinogens; 2) demonstrate that certain combinations of genotypes confer a particular risk to develop a specific type of tumor in VHL patients. Thus tracking of potentially carcinogenic substances, through their footprints and through identification of conditionally detrimental genotypes of genes participating in their detoxification should permit a better prevention through an appropriate nutrition adapted to each individual.

JUNIEN C.

Parental imprinting: from tug of war to solidarity between the generations.

M/S - Méd. Sci., 16 (3), 336-344, 2000

(Services cités : U383)

While equally to the corresponding gene product, genes that undergo genomic imprinting are monoallelically expressed, either from the paternal allele or from the maternal allele. Until recently, the studies of the effects of departure from this monoallelic expression have been restricted to the impact of this imbalance on fetal growth and development supporting the theory of the parental much less than tug of war much greater than. Now several reports, either in man or in mice, on new genes expressed also in adult brain shed a new light on the possible roles of genomic imprinting in adult social and cognitive behavior with unexpected marked differences between males and females. Moreover, epigenetic alterations such as those responsible for genomic imprinting could represent a buffering system capable to endorse adaption to environmental factors by silencing or enhancing expression of monoallelically expressed genes. Failure to erase these epimutations in the germline would lead to stable transgenerational effects. This may revive the long debate on the inheritance of acquired characters as a tool for adaption/evolution proposed almost a century ago by J.B. Lamarck. It is therefore probably time to think more about the advantages that genomic imprinting could confer to the survival of a species through solidarity between the generations. [References: 49]

JUNIEN C.

Du néolithique au XXI^e siècle, la génomique prépare-t-elle l'avenir alimentaire de l'homme ?
NAFAS Prat., 45-49, 2000
(Services cités : [U383](#))

KAPLAN J.C., JUNIEN C.

Genomics and medicine: an anticipation. from boolean mendelian genetics to multifactorial molecular medicine.

C. R. Acad. Sci. Sér.III Sci. Vie, 323 (12), 1167-1174, 2000

(Services cités : [U383](#))

The major impact of the completion of the human genome sequence will be the understanding of diseases, with deduced therapy. In the field of genetic disorders, we will complete the catalogue of monogenic diseases, also called Mendelian diseases because they obey the Boolean logic of Mendel's laws. The major challenge now is to decipher the polygenic and multifactorial etiology of common diseases, such as cancer, cardio-vascular, nutritional, allergic, auto-immune and degenerative diseases. In fact every gene, when mutated, is a potential disease gene, and we end up with the new concept of 'reverse medicine'; i.e., deriving new diseases or pathogenic pathways from the knowledge of the structure and function of every gene. By going from sequence to function (functional genomics and proteomics) we will gain insight into basic mechanisms of major functions such as cell proliferation, differentiation and development, which are perturbed in many pathological processes. By learning the meaning of some non-coding and of regulatory sequences our understanding will gain in complexity generating a molecular and supramolecular integrated physiology, helping to build a molecular patho-physiology of the different syndromes. Besides those cognitive advances, there are also other issues at stake, such as: progress in diagnostic and prediction (predictive medicine); progress in therapy (pharmacogenomics and gene-based therapy); ethical issues; impact on business. (C) 2000 Academie des sciences/Editions scientifiques et medicales Elsevier SAS. [References: 18]

KONDO T., BOBEK M.P., KUICK R., LAMB B., ZHU X.X., NARAYAN A., BOURC'HIS D., VIEGAS PEQUIGNOT E., EHRLICH M., HANASH S.M.

Whole-genome methylation scan in icf syndrome: hypomethylation of non-satellite dna repeats d4z4 and nbl2.

Hum. Mol. Genet., 9 (4), 597-604, 2000

(Services cités : [U383](#))

The ICF (immunodeficiency, centromeric instability and facial abnormalities) syndrome is a rare recessive disease characterized by immunodeficiency, extraordinary instability of certain heterochromatin regions and mutations in the gene encoding DNA methyltransferase 3B. In this syndrome, chromosomes 1 and 16 are demethylated in their centromere-adjacent (juxtacentromeric) heterochromatin, the same regions that are highly unstable in mitogen-treated ICF lymphocytes and B cell lines. We investigated the methylation abnormalities in CpG islands of B cell lines from four ICF patients and their unaffected parents. Genomic DNA digested with a CpG methylation-sensitive restriction enzyme was subjected to two-dimensional gel electrophoresis. Most of the restriction fragments were identical in the digests from the patients and controls, indicating that the methylation abnormality in ICF is restricted to a small portion of the genome. However, ICF DNA digests prominently displayed multicopy fragments absent in controls. We cloned and sequenced several of the affected DNA fragments and found that the non-satellite repeats D4Z4 and NBL2 were strongly hypomethylated in all four patients, as

compared with their unaffected parents. The high degree of methylation of D4Z4 that we observed in normal cells may be related to the postulated role of this DNA repeat in position effect variegation in facioscapulohumeral muscular dystrophy and might also pertain to abnormal gene expression in ICF. In addition, our finding of consistent hypomethylation and overexpression of NBL2 repeats in ICF samples suggests derangement of methylation-regulated expression of this sequence in the ICF syndrome. [References: 46]

MANOUVRIER HANU S., BESSON R., COUSIN L., JEANPIERRE C., KACET N., CARTIGNY M., DEVISME L., STORME L., de MARTINVILLE B., LEQUIEN P.

Sex reversal and diaphragmatic hernia in phenotypically female sibs with normal xy chromosomes.

J. Med. Genet., 37 (4), 315-318, 2000

(Services cités : U383)

MARQUIS E., ROBERT J.J., BENEZECH C., JUNIEN C., DIATLOFF-ZITO C.

Variable features of transient neonatal diabetes mellitus with paternal isodisomy of chromosome 6.

Eur. J. Human Genet., 8 (2), 137-140, 2000

(Services cités : U383)

We describe two patients who suffered transient neonatal diabetes mellitus (TNDM), due to paternal isodisomy of chromosome 6. One patient, now 5 years old, had severe intra-uterine growth retardation, but recovered normal growth parameters. The other patient, currently 12 years old, had a normal birth weight but showed impaired post-natal growth; in addition to TNDM the patient presented with cardiac and thyroid abnormalities. These cases may suggest that the clinical phenotype of TNDM is more variable than previously believed. The contribution of genetic and epigenetic factors needs to be determined to elucidate the phenotype-genotype relationships of this disease.

MARQUIS E., de GOUVILLE I.L., BOUVATTIER C., ROBERT J.J., JUNIEN C., CHARRON D., HORS J., DIATLOFF-ZITO C.

Hla-drb1 and dqbl genotypes in patients with insulin-dependent neonatal diabetes mellitus. a study of 13 cases.

Tissue Antigen., 56 (3), 217-222, 2000

(Services cités : U383, Métabolisme-Neurologie Génétique Pédiatrique)

Insulin-dependent neonatal diabetes mellitus (NDM) is a rare form of diabetes with a heterogeneous genetic background. The HLA-DRB1 and DQB1 genotypes were determined for 13 patients with NDM, from 9 unrelated families. Four patients had permanent NDM (PNDM) and 9 patients had transient NDM (TNDM). No excess of HLA susceptibility markers for type 1 diabetes (IDDM) was observed in this series of patients, whatever the forms of diabetes PNDM or TNDM. Paternal isodisomy of chromosome 6 was observed in two TNDM cases. These observations are consistent with the current hypothesis that there is a recessive susceptibility gene, at least in the transient form of the disease, unlinked to the MHC locus on chromosome 6. Although established in a short series, our results do not support an additive role of IDDM1 in the progression of the disease. [References: 28]

RABES J.P., VARRET M., DEVILLERS M., AEGERTER P., VILLEGIER L., KREMPF M., JUNIEN C., BOILEAU C.

R3531c mutation in the apolipoprotein b gene is not sufficient to cause hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol.*, 20 (10), E76-E82, 2000

(Services cités : U383)

Familial hypercholesterolemia and familial ligand-defective apolipoprotein B-100 (FDB) are dominantly inherited disorders leading to impaired low-density lipoprotein receptor (LDLR) and apolipoprotein B-100 (APOB) interaction, plasma LDL elevation, and hypercholesterolemia. We previously identified the first French FDB-R3531C proband, a woman with very high total cholesterol, in a group of type IIa hypercholesterolemic families. We report here the investigation of her family at large that revealed the total absence of cosegregation with hypercholesterolemia. Six of the 10 subjects heterozygous for the R3531C mutation had plasma cholesterol lower than the 97.5th percentile for their age and gender, and mean cholesterol levels were not significantly different between affected and unaffected persons. Furthermore, 2 family members with similar high LDL-cholesterol levels were not carriers of the R3531C substitution, suggesting the implication of another mutation. Segregation analysis of the LDLR gene revealed statistically significant genetic linkage with hypercholesterolemia, and analysis of the proband LDLR gene led to the identification of the 664 proline to leucine defective mutation and its detection in all 6 hypercholesterolemic-related members of this family. Therefore, our results show that the family presents with familial hypercholesterolemia and give evidence that the R3531C substitution in the APOB gene is not an allelic variant leading to FDB. Furthermore, thorough analysis of our data suggests that the APOB-R3531C mutation enhances the hypercholesterolemic effect of the LDLR-P664L defect, suggesting that it is a susceptibility mutation. [References: 33]

RICHARD S., DAVID P., MARSOT DUPUCH K., GIRAUD S., BEROUD C., RESCHE F. Central nervous system hemangioblastomas, endolymphatic sac tumors, and von hippel-lindau disease.

Neurosurg. Rev., 23 (1), 1-22, 2000

(Services cités : U383)

Von Hippel-Lindau disease (VHL) is a hereditary cancer syndrome caused by germline mutations of the VHL tumor suppressor gene. Major progress has been made in the last decade in both clinical and fundamental aspects of VHL. The VHL gene product, pVHL, has major and multiple functions: pVHL regulates not only first angiogenesis but also extracellular matrix formation and the cell cycle. A molecular diagnosis of VHL is now available, leading to a transformation in clinical management of patients and their families. Diagnosis of VHL has to be suspected in patients with a VHL-related tumor without familial history and especially in case of hemangioblastoma or endolymphatic sac tumors. Such patients should be systematically investigated for clinical and molecular evidence of VHL disease. Treatment of symptomatic hemangioblastomas remains mainly neurosurgical, often in emergency, but stereotactic radiosurgery is emerging as an alternative therapeutic procedure. In the future, antiangiogenic drugs could represent a potential medical treatment of CNS hemangioblastomas in view of their highly vascular structure. Lastly, visceral manifestations of VHL disease are also of critical importance and require early detection for effective treatment. [References: 220]

SAINT JORE B., VARRET M., DACHET C., RABES J.P., DEVILLERS M., ERLICH D., BLANCHARD P., KREMPF M., MATHE D., CHANU B., JACOTOT B., FARNIER M., BONAITI PELLIE C., JUNIEN C., BOILEAU C.

Autosomal dominant type iia hypercholesterolemia: evaluation of the respective contributions of ldlr and apob gene defects as well as a third major group of defects.

Eur. J. Human Genet., 8 (8), 621-630, 2000

(Services cités : U383)

Autosomal dominant type I hypercholesterolaemia (ADH) is characterised by an elevation of total plasma cholesterol associated with increased LDL particles. Numerous different molecular defects have been identified in the LDL receptor (LDLR) and few specific mutations in the apolipoprotein B (APOB) gene resulting in familial hypercholesterolaemia and familial defective apoB-100 respectively. To estimate the respective contribution of LDLR, APOB and other gene defects in this disease, we studied 33 well characterised French families diagnosed over at least three generations with ADH through the candidate gene approach. An estimation of the proportions performed with the HOMOG3R program showed that an LDLR gene defect was involved in approximately 50% of the families ($P = 0.001$). On the other hand, the estimated contribution of an APOB gene defect was only 15%. This low estimation of ADH due to an APOB gene defect is further strengthened by the existence of only two probands carrying the APOB (R3500Q) mutation in the sample. More importantly and surprisingly, 35% of the families in the sample were estimated to be linked to neither LDLR nor APOB genes. These data were confirmed by the exclusion of both genes through direct haplotyping in three families. Our results demonstrate that the relative contributions of LDLR and APOB gene defects to the disease are very different. Furthermore, our results also show that genetic heterogeneity is, generally, underestimated in ADH, and that at least three major groups of defects are involved. At this point, the contribution of the recently mapped FH3 gene to ADH cannot be assessed nor its importance in the group of 'non LDLR / non APOB' families. [References: 44]

SEZNEC H., LIA BALDINI A.S., DUROS C., FOUQUET C., LACROIX C., HOFMANN RADVANYI H., JUNIEN C., GOURDON G.

Transgenic mice carrying large human genomic sequences with expanded ctg repeat mimic closely the dm ctg repeat intergenerational and somatic instability.

Hum. Mol. Genet., 9 (8), 1185-1194, 2000

(Services cités : U383)

Myotonic dystrophy (DM) is caused by a CTG repeat expansion in the 3'UTR of the DM protein kinase (DMPK) gene. A very high level of instability is observed through successive generations and the size of the repeat is generally correlated with the severity of the disease and with age at onset. Furthermore, tissues from DM patients exhibit somatic mosaicism that increases with age. We generated transgenic mice carrying large human genomic sequences with 20, 55 or >300 CTG, cloned from patients from the same affected DM family. Using large human flanking sequences and a large amplification, we demonstrate that the intergenerational CTG repeat instability is reproduced in mice, with a strong bias towards expansions and with the same sex- and size-dependent characteristics as in humans. Moreover, a high level of instability, increasing with age, can be observed in tissues and in sperm. Although we did not observe dramatic expansions (or 'big jumps' over several hundred CTG repeats) as in congenital forms of DM, our model carrying >300 CTG is the first to show instability so close to the human DM situation. Our three models carrying different sizes of CTG repeat provide insight on the different factors modulating the CTG repeat instability. [References: 60]

THIART R., VARRET M., LINTOTT C.J., SCOTT R.S., LOUBSER O., DU PLESSIS L., de VILLIERS J.N.P., BOILEAU C., KOTZE M.J.

Mutation analysis in a small cohort of new zealand patients originating from the united kingdom demonstrates genetic heterogeneity in familial hypercholesterolemia.

Mol. Cell. Probe, 14 (5), 299-304, 2000

(Services cités : U383)

Familial hypercholesterolemia (FH) and familial defective apolipoprotein B-100 (FDB) are relatively common lipid disorders caused by mutations in the low-density lipoprotein receptor (LDLR) and apolipoprotein B (apo B) genes, respectively. Molecular analysis at these loci was performed in eight New Zealand subjects with clinical features of heterozygous FH. Utilization of an in vitro lymphocyte receptor assay demonstrated normal receptor function in four patients, three of whom screened positive for the founder-type apo B mutation, R3500Q, causing FDB. Four patients with reduced LDLR function, consistent with heterozygous FH, revealed three previously documented mutations in exons 3 (W66X), 6 (C292Y) and 7 (C322S) of the LDLR gene and, a novel 2-bp deletion (TC or CT) after nucleotide 1204 (or 1205) in exon 9. The remaining patient was found to be FH/FDB negative after extensive mutation screening using both denaturing gradient gel electrophoresis and heteroduplex-single strand conformation polymorphism analysis. Haplotype analysis at the LDLR and apo B loci finally excluded the likelihood that mutations in these two genes underlie the FH phenotype in the molecularly uncharacterized New Zealand family originating from the United Kingdom. This family represents a valuable source of material for future genetic dissection of autosomal dominant hypercholesterolemia (ADH), shown to be a heterogeneous disease through molecular analysis. (C) 2000 Academic Press. [References: 30]

1999

BOURC'HIS D., MINIQU P., JEANPIERRE M., MOLINA GOMES D., DUPONT J., de SAINT-BASILE G., MARASCHIO P., TIEPOLO L., VIEGAS-PEQUIGNOT E.

Abnormal methylation does not prevent X inactivation in ICF patients.

Cytogenet. Cell Genet., 84 (3-4), 245-252, 1999

(Services cités : U383)

DNA undermethylation is a characteristic feature of ICF syndrome and has been implicated in the formation of the juxtacentromeric chromosomal abnormalities of this rare syndrome. We have previously shown that in female ICF patients the inactive X chromosome (Xi) is also undermethylated. This result was unexpected since female ICF patients are not more severely affected than male patients. Here we show that CpG island methylation is abnormal in some ICF patients but in other ICF patients, the difference in methylation pattern between Xi and Xa (active X) is maintained. The consequences of Xi undermethylation on gene expression were investigated by enzyme assays. They showed that significant gene expression did not correlate with CpG island methylation status. The widespread Xi undermethylation does not affect overall Xi replication timing and does not prevent Barr body formation suggesting that a normal methylation pattern is not required for normal chromatin organization of Xi. Molecular investigation of some X-chromosome intron regions showed that the methylation changes in ICF female patients extend to non CpG islands sequences. Our results suggest that the genetic alteration of DNA methylation in ICF syndrome has little consequence on X chromosome gene expression and chromatin organization. [References: 55]

COLLOD-BEROUD G., LACKMY-PORT-LYS M., JONDEAU G., MATHIEU M., MAINGOURD Y., COULON M., GUILLOT M., JUNIEN C., BOILEAU C.

Demonstration of the recurrence of Marfan-like skeletal and cardiovascular manifestations due to germline mosaicism for an FBN1 mutation.

Amer. J. Hum. Genet., 65 (3), 917-921, 1999

(Services cités : [U383](#))

GALLOU C., JOLY D., MEJEAN A., STAROZ F., MARTIN N., TARLET G., ORFANELLI M.T., BOUVIER R., DROZ D., CHRETIEN Y., MARECHAL J.M., RICHARD S., JUNIEN C., BEROUD C.

Mutations of the VHL gene in sporadic renal cell carcinoma: definition of a risk factor for VHL patients to develop an RCC.

Hum. Mutat., **13** (6), 464-475, 1999

(Services cités : [U383](#))

To investigate the nature of somatic von Hippel-Lindau (VHL) mutations, we analyzed 173 primary sporadic human renal cell carcinomas for mutations of the VHL tumor suppressor gene, using polymerase chain reaction (PCR) and single-strand conformational polymorphism analysis (SSCP) of DNA. We detected abnormal SSCP pattern in 73 samples. After sequencing, we identified microdeletions in 58% of cases, microinsertions in 17%, nonsense mutations in 8%, and missense mutations in 17%. Among these mutations, 50% correspond to new mutations. VHL mutations were found only in the nonpapillary renal cell carcinoma (RCC) subtype, as previously reported. To compare somatic and germline mutations, we used the VHL database, which includes 507 mutations. The study of mutational events revealed a significant difference between somatic and germline mutations with mutations leading to truncated proteins observed in 78% of somatic mutations vs only 37% in germline mutations ($P < 0.001$). We postulated that a specific pattern of VHL mutations is associated with sporadic RCC. This pattern corresponds to mutations leading mainly to truncated proteins with few specific missense mutations. We then analyzed the occurrence of RCC in VHL families, based on the nature of mutations. We observed RCC in at least one member of the VHL families in 77% of cases with mutations leading to truncated proteins versus 55% in cases with missense mutations ($P < 0.05$). Thus, mutations resulting in truncated proteins may lead to a higher risk of RCC in VHL patients.

LESCOP S., LELLOUCH-TUBIANA A., VASSAL G., BESNARD-GUERIN C.

Molecular genetic studies of chromosome 11 and chromosome 22q DNA sequences in pediatric medulloblastomas.

J. Neuro-Oncol., **44** (2), 119-127, 1999

(Services cités : [U383](#))

Medulloblastomas are primitive neuroectodermal tumors (PNETs) of the cerebellum with poorly understood pathogenesis. Previous molecular studies suggested a role for loci on chromosome 11 in the development of medulloblastomas-PNETs. In order to identify the frequency of loss and eventually the extent of allelic loss on chromosome 11, we have examined 23 pediatric medulloblastomas for loss of heterozygosity (LOH) with 16 polymorphic microsatellites. Our data reveal that LOH on 11p or 11q occurs rarely (13%) suggesting the unlikely involvement of chromosome 11 in most cases of medulloblastomas. The same frequency of LOH in medulloblastomas was detected using 8 microsatellites on 22q. Alterations of microsatellite length were found in only 4/594 PCR analyses using 28 markers located on chromosomes 2, 9, 11, 18, and 22, demonstrating that genomic instability is uncommon in medulloblastomas.

[References: 45]

SEVENET N., LELLOUCH-TUBIANA A., SCHOFIELD D., KHE H.X., GESSLER M., BIRNBAUM D., JEANPIERRE C., JOUVET A., DELATTRE O.

Spectrum of hSNF5/INI1 somatic mutations in human cancer and genotype-phenotype

correlations.

Hum. Mol. Genet., 8 (13), 2359-2368, 1999

(Services cités : U383)

The hSNF5/INI1 gene which encodes a member of the SWI/SNF chromatin ATP-dependent remodeling complex, is a new tumor suppressor gene localized on chromosome 22q11.2 and recently shown to be mutated in malignant rhabdoid tumors, We have searched for hSNF5/INI1 mutations in 229 tumors of various origins using a screening method based on denaturing high-performance liquid chromatography, A total of 31 homozygous deletions and 36 point alterations were identified, Point mutations were scattered along the coding sequence and included 15 nonsense, 15 frameshift, three splice site, two missense and one editing mutations. Mutations were retrieved in most rhabdoid tumors, whatever their sites of occurrence, indicating the common pathogenetic origin of these tumors. Recurrent hSNF5/INI1 alterations were also observed in choroid plexus carcinomas and in a subset of central primitive neuroectodermal tumors (cPNETs) and medulloblastomas, In contrast, hSNF5/INI1 point mutations were not detected in breast cancers, Wilms' tumors, gliomas, ependymomas, sarcomas and other tumor types, even though most analyzed cases harbored loss of heterozygosity at 22q11.2 loci. These results suggest that rhabdoid tumors, choroid plexus carcinomas and a subset of medulloblastomas and cPNETs share common pathways of oncogenesis related to hSNF5/INI1 alteration and that hSNF5/INI1 mutations define a genetically homogeneous family of highly aggressive cancers mainly occurring in young children and frequently, but not always, exhibiting a rhabdoid phenotype. [References: 38]

VARRET M., RABES J.P., SAINT-JORE B., CENARRO A., MARINONI J.C., CIVEIRA F., DEVILLERS M., KREMPF M., COULON M., THIART R., KOTZE M.J., SCHMIDT H., BUZZI J.C., KOSTNER G.M., BERTOLINI S., POCOVI M., ROSA A., FARNIER M., MARTINEZ M., JUNIEN C., BOILEAU C.

A third major locus for autosomal dominant hypercholesterolemia maps to 1p34.1-p32.

Amer. J. Hum. Genet., 64 (5), 1378-1387, 1999

(Services cités : U383)

Autosomal dominant hypercholesterolemia (ADH), one of the most frequent hereditary disorders, is characterized by an isolated elevation of LDL particles that leads to premature mortality from cardiovascular complications. It is generally assumed that mutations in the LDLR and APOB genes account for ADH. We identified one large French pedigree (HC2) and 12 additional white families with ADH in which we excluded linkage to the LDLR and APOB, implicating a new locus we named "FH3." A LOD score of 3.13 at a recombination fraction of 0 was obtained at markers D1S2892 and D1S2722. We localized the FH3 locus to a 9-cM interval at 1p34.1-p32. We tested four regional markers in another set of 12 ADH families. Positive LOD scores were obtained in three pedigrees, whereas linkage was excluded in the others. Heterogeneity tests indicated linkage to FH3 in similar to 27% of these non-LDLR/non-APOB ADH families and implied a fourth locus. Radiation hybrid mapping located four candidate genes at 1p34.1-p32, outside the critical region, showing no identity with FH3. Our results show that ADH is genetically more heterogeneous than conventionally accepted. [References: 36]

XU G.L., BESTOR T.H., BOURC'HIS D., HSIEH C.L., TOMMERUP N., BUGGE M., HULTEN M., QU X.Y., RUSSO J.J., VIEGAS-PEQUIGNOT E.

Chromosome instability and immunodeficiency syndrome caused by mutations in a DNA methyltransferase gene.

Nature, 402 (6758), 187-191, 1999

(Services cités : [U383](#))

The recessive autosomal disorder known as ICF syndrome(1-3) (for immunodeficiency, centromere instability and facial anomalies; Mendelian Inheritance in Man number 242860) is characterized by variable reductions in serum immunoglobulin levels which cause most ICF patients to succumb to infectious diseases before adulthood. Mild facial anomalies include hypertelorism, low-set ears, epicanthal folds and macroglossia. The cytogenetic abnormalities in lymphocytes are exuberant: juxtacentromeric heterochromatin is greatly elongated and thread-like in metaphase chromosomes, which is associated with the formation of complex multiradiate chromosomes. The same juxtacentromeric regions are subject to persistent interphase self-associations and are extruded into nuclear blebs or micronuclei. Abnormalities are largely confined to tracts of classical satellites 2 and 3 at juxtacentromeric regions of chromosomes 1, 9 and 16. Classical satellite DNA is normally heavily methylated at cytosine residues, but in ICF syndrome it is almost completely unmethylated in all tissues(4) ICF syndrome is the only genetic disorder known to involve constitutive abnormalities of genomic methylation patterns. Here we show that five unrelated ICF patients have mutations in both alleles of the gene that encodes DNA methyltransferase 3B (refs 5, 6). Cytosine methylation is essential for the organization and stabilization of a specific type of heterochromatin, and this methylation appears to be carried out by an enzyme specialized for the purpose. [References: 29]

YANG Y.X., JEANPIERRE C., DRESSLER G.R., LACOSTE M., NIAUDET P., GUBLER M.C.

WT1 and PAX-2 podocyte expression in Denys-Drash syndrome and isolated diffuse mesangial sclerosis.

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Denys-Drash syndrome is a rare disorder of urogenital development characterized by the association of early onset glomerulopathy caused by diffuse mesangial sclerosis, gonadal dysgenesis leading to pseudohermaphroditism in males, and a high risk of developing Wilms' tumor. The syndrome is caused by dominant negative point mutations in the WT1 gene that encodes a tumor suppressor transcription factor normally expressed in podocytes. Mutations usually affect the zinc fingers of the WT1 protein. The basic defect is unknown in most cases of isolated diffuse mesangial sclerosis, a disease characterized by the same glomerular changes as in Denys-Drash syndrome but possibly transmitted as an autosomal recessive trait. Here we show that the distribution of WT1 is abnormal in most patients with Denys-Drash syndrome : WT1 nuclear staining of podocytes is decreased or absent. This finding is consistent with the decreased DNA binding capacity of the mutated protein. One target gene of WT1 is PAX2, the expression of which is down-regulated in podocytes during early stages of nephrogenesis. We demonstrate that WT1 mislocalization is associated with abnormal podocyte expression of PAX2 protein and RNA. We suggest that persistent expression of PAX2 is likely to result from the loss of WT1 dependent transcriptional repression and may participate in the pathological mechanisms leading to glomerular dysfunction. Abnormal distribution of WT1 and PAX2 was also observed in isolated diffuse mesangial sclerosis suggesting that a defect in WT1 could also be operative in isolated diffuse mesangial sclerosis. Primary involvement of PAX2 is an alternative hypothesis because persistent expression of PAX2 in transgenic mice is associated with the occurrence of early and severe glomerulopathy. [References: 57]