Ⅲ. 研究成果の刊行に関する一覧表

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書籍

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Flamein F, Riffault L, Muselet-Charlier C, Pernelle J, Feldmann D, Jonald L, Durand-Schneider AM, Coulomb A, Maurice M, Nogee LM, Inagaki N, Amselem S, Dubus JC, Rigourd V, Brémont F, Marguet C, Brouard J, de Blic J, Clement A, Epaud R, Guillot L.	Molecular and cellular characteristics of ABCA3 mutation associated with diffuse parenchymal lung diseases in children.	***Hum. Mol. Genet.***,	in press		2012
Funakoshi S, Fujimoto S, Hamasaki A, Fujiwara H, Fujita Y, Ikeda K, Takahara S, Seino Y, Inagaki N.	Analysis of factors influencing postprandial C peptide levels in Japanese patients with type 2 diabetes: Comparison with C peptide levels after glucagon load.	***J. Diabtes Invest.***	in press		2012

Ikeda K, Fujimoto S, Goto M, Yamada C, Hamasaki A, Shide K, Kawamura T, Inagaki N.	Imapact of endogenous and exogenous insulin on basal energy expenditure in patients with type 2 diabetes under standard treatment.	***Am. J. Clin. Nutr.***	94	1513-1518	2011
Fujimoto H, Toyoda K, Okitsu T, Liu X, Mukai E, Zhuang X-T, Uemoto S, Mochizuki N, Inagaki N.	Three dimensional ex vivo imaging and analysis of intraportal islet transplants.	***Transpl. Int.***	24	839-844	2011
Takeda Y, Amano A, Noma A, Nakamura Y, Fujimoto S, Inagaki N.	Systems analysis of GLP-1 receptor signaling in pancreatic β-cells.	***Am. J. Physiol.-Cell Physiol.***	301	C792-803	2011
Himeno T, Kamiya H, Naruse K, Harada N, Ozaki N, Seino Y, Shibata T, Kondo M, Kato J, Okawa T, Fukami A, Hamada Y, Inagaki N, Seino Y,	Beneficial effects of exendin-4 on experimental polyneuropathy in diabetic mice.	***Diabetes***	60	2397-2406	2011
Cha C-Y, Nakamura Y, Himeno Y, Wang J, Fujimoto S, Inagaki N, Earm YE, Noma A.	Ionic mechanisms and Ca^{2+} dynamics underlying the glucose response of pancreatic β-cells: A simulation study.	***J. Gen. Physiol.***	138	21-37	2011
Nishi Y, Fujimoto S, Sasaki M, Mukai E, Sato H, Sato Y, Tahara Y, Nakamura Y, Inagaki N.	Role of mitochondrial phosphate carrier in metabolism-secretion coupling in rat insulinoma cell line INS-1.	***Biochem. J.***	in press		2011

Yamane S, Hamamoto Y, Harashima S, Harada N, Hamasaki A, Toyoda K, Fujita K, Joo E, Seino Y, Inagaki N.	GLP-1 receptor agonist attenuates endoplasmic reticulum stress-mediated β-cell damage in Akita mice.	*J. Diabetes Invest.*	in press		2011
Harada N, Hamasaki A, Yamane S, Muraoka A, Joo E, Fujita K, Inagaki N.	Plasma gastric inhibitory polypeptide and glucagon-like peptide-1 levels after glucose loading are associated with different factors in Japanese subjects	*J. Diabetes Invest.*	in press		2011
Funakoshi S, Fujimoto S, Hamasaki A, Fujiwara H, Fujita Y, Ikeda K, Takahara S, Nagashima K, Hosokawa M, Seino Y, Inagaki N.	Utility of indices using C peptide levels for indication of insulin therapy to achieve good glycemic control in Japanese patients with type 2 diabetes.	*J. Diabetes Invest.*	in press		2011
Kuwabara A, Nakase H, Tsuji H, Shide K, Chiba T, Inagaki N, Tanaka, K.	Fat restriction is associated with impaired quality of life (QOL) in patients with ulcerative colitis and Crohn's disease. Ulcers.	*Ulcers*	in press		2011
Ogawa E, Hosokawa M, Harada N, Yamane S, Hamasaki A, Toyoda K, Fujimoto S, Fujita Y, Fukuda K, Tsukiyama K, Yamada Y, Seino Y, Inagaki N.	The effect of gastric inhibitory polypeptide on intestinal glucose absorption and intestinal motility in mice.	*Biochem. Biophys. Res. Commun.*	404(1)	115-120	2011

Tanaka D, Nagashima K, Sasaki M, Yamada C, Funakoshi S, Akitomo K, Takenaka K, Harada K, Koizumi A, M, Inagaki N.	*GCKR* mutations in Japanese families with clustered type 2 diabetes.	***Mol. Genet. Metab.***	102(4)	453-460	2011
Yoshihara E, Fujimoto S, Inagaki N, Ogawa K, Masaki S, Yodoi J, Masutani H.	Disruption of TBP-2 ameliorates insulin sensitivity and secretion without affecting obesity.	***Nature Communications***	1	127	2010
Uonaga T, Toyoda K, Okitsu T, Zhuang X, Yamane S, Uemoto S, Inagaki N.	FGF-21 enhances islet engraftment in mouse syngeneic islet transplantation model.	***Islets***	2(4)	247-251	2010
Mukai E, Fujimoto S, Sato H, Oneyama C, Kominato R, Sato Y, Sasaki M, Nishi Y, Okada M, Inagaki N.	Exendin-4 suppresses Src activation and reactive oxygen species production in diabetic GK rat islets in an Epac-dependent manner.	***Diabetes***	60(1)	218-226	2010

Fujita Y, Hosokawa M, Fujimoto S, Mukai E, Abudukadier A, Obara A, Ogura M, Nakamura Y, Toyoda K, Nagashima K, Seino Y, Inagaki N.	Metformin suppresses hepatic gluconeogenesis and lowers fasting blood glucose levels through reactive nitrogen species in mice.	***Diabetologia***	53(7)	1472-1481	2010
Kawasaki Y, Harashima S, Sasaki M, Mukai E, Nakamura Y, Harada N, Toyoda K, Hamasaki A, Yamane S, Yamada C, Yamada Y, Seino Y, Inagaki N.	Exendin-4 protects pancreatic beta cells from the cytotoxic effect of rapamycin by inhibiting JNK and p38 phosphorylation.	***Horm. Metab. Res.***	42(5)	311-317	2010
Toyama K, Yonezawa A, Tsuda M, Masuda S, Yano I, Terada T, Osawa R, Katsura T, Hosokawa M, Fujimoto S, Inagaki N, Inui K.	Heterozygous variants of multidrug and toxin extrusions (MATE1 and MATE2-K) have little influence on the disposition of metformin in diabetic patients.	***Pharmacogenet. Genomics***	20(2)	135-138	2010
Shimodahira M, Fujimoto S, Mukai E, Nakamura Y, Nishi Y, Sasaki M, Sato Y, Sato H, Hosokawa M, Nagashima K, Seino Y, Inagaki N.	Rapamycin impairs metabolism-secretion coupling in rat pancreatic islets by suppressing carbohydrate metabolism.	***J. Endocrinol.***	204(1)	37-46	2010

Yabe D, Kuroe A, Lee S, Watanabe K, Hyo T, Hishizawa M, Kurose T, Deacon CF, Holst JJ, Hirano T, Inagaki N, Seino Y.	Little enhancement of meal-induced GLP-1 secretion in Japanese: comparison of type 2 diabetes and healthy controls.	***J. Diabetes Invest.***	1(1-2)	56-59	2010
Sato S, Ishida-Nakajima W, Ishida A, Kawamura M, Miura S, Ono K, Inagaki N, Takada G, Takahashi T.	Assessment of a new piezoelectric transducer sensor for noninvasive cardiorespiratory monitoring of newborn infants in the NICU.	***Neonatology***	98(2)	179-190	2010
Yoneda K, Demitsu T, Manabe M, Igarashi J, Kosaka H, Inagaki N, Takahashi H, Kon A, Kakurai M, Kubota Y.	Expression of wild-type, but not mutant, loricrin causes programmed cell death in HaCaT keratinocytes.	***J. Dermatol.***	37(11)	956-964	2010
Yorifuji T, Fujimaru R, Hosokawa Y, Tamagawa N, Shiozaki M, Aizu K, Jinno K, Maruo Y, Nagasaka H, Tajima T, Kobayashi K, Urakami T.	Comprehensive molecular analysis of Japanese patients with pediatric-onset MODY-type diabetes mellitus.	***Pediatr Diabetes.***	13	26-32	2012

Masue M, Nishibori H, Fukuyama S, Yoshizawa A, Okamoto S, Doi R, Uemoto S, Tokumi T, Kasai T, Yorifuji T.	Diagnostic accuracy of [18F]fluoro-L-DOPA PET scan for persistent congenital hyperinsulinism in Japan: The first study on Asians.	***Clin Endocrinol***	75	342-346	2011
Yorifuji T, Hosokawa Y, Fujimaru R, Kawakita R, Doi H, Matsumoto T, Nishibori H, Masue M.	Lasting 18F-DOPA PET uptake after clinical remission of the focal form of congenital hyperinsulinism.	***Horm Res Pediatr.***	76	286-290	2011
Nagasaka H, Yorifuji T, Takatani T, Okano Y, Tsukahara H, Yanai H, Hirano KI, Hui SP, Hirayama S, Ito T, Chiba H, Miida T.	CD36 deficiency predisposing young children to fasting hypoglycemia.	***Metabolism.***	60	881-887	2011
Nagasaka H, Tsukahara H, Takatani T, Sanayama Y, Takayanagi M, Ohura T, Sakamoto O, Ito T, Wada M, Yoshino M, Ohtake A, Yorifuji T, Hirayama S, Miida T, Fujimoto H, Mochizuki H, Hattori T, Okano Y.	Cross-sectional study of bone metabolism with nutrition in adult classical phenylketonuric patients diagnosed by neonatal screening.	***J Bone Miner Metab.***,	29	737-743	2011

Sanayama Y, Nagasaka H, Takayanagi M, Ohura T, Sakamoto O, Ito T, Ishige-Wada M, Usui H, Yoshino M, Ohtake A, Yorifuji T, Tsukahara H, Hirayama S, Miida T, Fukui M, Okano Y.	Experimental evidence that phenylalanine is strongly associated to oxidative stress in adolescents and adults with phenylketonuria.	***Mol Genet Metab.***,	103	220-225	2011
Hori T, Egawa H, Takada Y, Ueda M, Oike F, Ogura Y, Sakamoto S, Kasahara M, Ogawa K, Miyagawa-Hayashino A, Yonekawa Y, Yorifuji T, Watanabe KI, Doi H, Nguyen JH, Chen F, Baine AM, Gardner LB, Uemoto S.	Progressive familial intrahepatic cholestasis: a single-center experience of living-donor liver transplantation during two decades in Japan.	***Clin Transplant.***	25	776-785	2011
Sasaki K, Okamoto N, Kosaki K, Yorifuji T, Shimokawa O, Mishima H, Yoshiura KI, Harada N.	Maternal uniparental isodisomy and heterodisomy on chromosome 6 encompassing a CUL7 gene mutation causing 3M syndrome.	***Clin Genet.***	80	478-483	2011

Yorifuji T, Kawakita R, Nagai S, Sugimine A, Doi H, Nomura A, Masue M, Nishibori H, Yoshizawa A, Okamoto S, Doi R, Uemoto S, Nagasaka H.	Molecular and Clinical Analysis of Japanese Patients with Persistent Congenital Hyperinsulinism: Predominance of Paternally Inherited Monoallelic Mutations in the K_{ATP} Channel Genes.	***J. Clin. Endocrinol. Metab.***	in press		2011
Hori T, Egawa H, Miyagawa-Hayashino A, Yorifuji T, Yonekawa Y, Nguyen JH, Uemoto S.	Living-donor Liver Transplantation for Progressive Familial Intrahepatic Cholestasis.	***World J. Surg.***	in press		2011
Kita F, Shibata Y, Yorifuji T, Nakahata T, Kawakami J, Kawakami K.	Prescription trends for treatment of paediatric gastroenteritis at a Japanese hospital between 1997 and 2007.	***J. Clin. Pharm. Ther.***	35(1)	87-92	2010
Ueda M, Kanematsu A, Nishiyama H, Yoshimura K, Watanabe K, Yorifuji T, Mikami Y, Kamoto T, Ogawa O	Testicular thecoma in an 11-year-old boy with nevoid basal-cell carcinoma syndrome (Gorlin syndrome).	***J. Pediatr. Surg.***	45(3)	E1-3	2010

Goto H, Kanematsu A, Yoshimura K, Miyazaki Y, Koyama T, Yorifuji T, Nishiyama H, Ogawa O.	Preoperative diagnosis of congenital segmental giant megaureter presenting as a fetal abdominal mass.	***J. Pediatr. Surg.***	45(1)	269-271	2010
Abe K, Ikeda Y, Kurata T, Ohta Y, Manabe Y, Okamoto M, Takamatsu K, Ohta T, Takao Y, Shiro Y, Shoji M, Kamiya T, Kobayashi H, Koizumi A.	Cognitive and affective impairments of a novel SCA/MND crossroad mutation Asidan.	***Eur J Neurol***	in press		2012
Liu W. Hitomi T, Kobayashi H, Harada K, Koizumi A.	Distribution of Moyamoya Disease Susceptibility Polymorphism p.R4810K in RNF213 in East and Southeast Asian Populations.	***Neurologia medico-chirurugica***	35	1-4	2012
Liu W, Morito D, Takashima S, Mineharu Y, Kobayashi H, Hitomi T, Hashikata H, Matsuura N, Yamazaki S, Toyoda A, Kikuta K, Takagi Y, Harada KH, Fujiyama A, Herzig R, Krischek B, Zou L, Kim JE, Kitakaze M, Miyamoto S, Nagata K, Hashimoto N, Koizumi A.	Identification of RNF213 as a susceptibility gene for moyamoya disease and its possible role in vascular development.	***PLoS One***	6	e22542	2011

Kobayashi H, Abe K, Matsuura T, Ikeda Y, Hitomi T, Akechi Y, Habu T, Liu W, Okuda H, Koizumi A.	Expansion of intronic GGCCTG hexanucleotide repeat in NOP56 causes SCA36, a type of spinocerebellar ataxia accompanied by motor neuron involvement.	***Am J Hum Genet.***	89	121-130	2011
Takahashi I, Yamada Y, Kadowaki H, Horikoshi M, Kadowaki T, Narita T, Tsuchida S, Noguchi A, Koizumi A, Takahashi T.	Phenotypical variety of insulin resistance in a family with a novel mutation of the insulin receptor gene.	***Endocr. J.***	57(6)	509-516	2010
Suzuki S, Koga M, Amamiya S, Nakao A, Wada K, Okuhara K, Hanano S, Sarhat AR, Takahashi H, Matsuo K, Tanahashi Y and Fujieda K	Glycated albumin in patients with neonatal diabetes mellitus is apparently low in relation to glycemia compared with that in patients with type 1 diabetes mellitus.	***Horm Res Paediatr***	in press		2012
Suzuki S, Koga M, Amamiya S, Nakao A, Wada K, Okuhara K, Hanano S, Sarhat AR, Takahashi H, Matsuo K, Tanahashi Y and Fujieda K	Glycated albumin but not HbA1c reflects glycaemic control in patients with neonatal diabetes mellitus.	***Diabetologia***	54	2247-2253	2011
Suzuki S, Fujisawa D, Hashimoto K, Asano T, Maimaiti M, Matsuo K, Tanahashi Y, Mukai T, Fujieda K.	Partial paternal uniparental disomy of chromosome 6 in monozygotic twins with transient neonatal diabetes mellitus and macroglossia,	***Clin. Genet.***	78(6)	580-584	2010

Sugihara S, Ogata T, Kawamura T, Urakami T, Takemoto K, Kikuchi N, Takubo N, Tsubouchi K, Horikawa R, Kobayashi K, Kasahara Y, Kikuchi T, Koike A, Mochizuki T, Minamitani K, Takaya R, Mochizuki H, Nishii A, Yokota I, Kizaki Z, Mori T, Shimura N, Mukai T, Matsuura N, Fujisawa T, Ihara K, Kosaka K, Kizu R, Takahashi T, Matsuo S, Hanaki K, Igarashi Y, Sasaki G, Soneda S, Teno S, Kanzaki S, Saji H, Tokunaga K, Amemiya S; Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes (JSGIT)	HLA-class II and class I genotypes among Japanese children with Type 1A diabetes and their families.	***Pediatr Diabetes***	13	33-44	2012

Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet1 C, Marcovecchio ML, Chiarelli F, on behalf of ESPE-LWPES -ISPAD-APPE S-APEG-SLE P-JSPE and the Insulin Resistance in Children Consensus Conference Group (Amemiya S as a delegate of JSPE).	Insulin Resistance in Children: Consensus, Perspective and Future Directions.	***J. Clin. Endocrinol. Metab.***	95(12)	5189-5198	2010
Nakamura N, Sasaki N, Kida K, Matsuura N, the Study Group of Health Science Research (Amemiya S as a co-author).	Health-related and diabetes-related quality oflife in Japanese children and adolescents with type 1 and type2 diabetes.	***Pediatr. Int.***	52(2)	224-229	2010
Yagasaki H, Kobayashi K, Saitou T, Nagamine K, Mitsui Y, Mochizuki M, Kobayashi K, Cho H, Ohyama K, Amemiya S, Nakazawa S.	Nocturnal blood glucose and IGFBP-1 changes in type 1 diabetes: Differences in the dawn phenomenon between insulin regimens.	***Exp. Clin. Endocrinol. Diabetes***	118(3)	195-199	2010

Matsuno S, Sasaki H, Yamazaki H, Yamaoka H, Ogawa K,,Nakatani M, Hamanishi T, Doi A, Nakano Y, Wakasaki H, Furuta H, Nishi M, Akamizu T, Nanjo K	Pro 198 Leu missense polymorphism of the glutathione peroxidase 1 gene might be a common genetic predisposition of distal symmetric polyneuropathy and macrovascular disease in Japanese type 2 diabetic patient.	***J Diabetes Invest.***	in press		2012
Komori T, Doi A, Furuta H, Wakao H, Nakao N, Nakazato M, Nanjo K, Senba E, Morikawa Y.	Regulation of ghrelin signaling by a leptin-induced gene, negative regulatory element-binding protein, in the hypothalamic neurons.	***J. Biol. Chem.***	285 (48)	37884-37894	2010
Wang Y, Nishi M, Doi A, Shono T, Furukawa Y, Shimada T, Furuta H, Sasaki H, Nanjo K.	Ghrelin inhibits insulin secretion through the AMPK-UCP2 pathway in beta cells.	***FEBS Lett.***	584(8)	1503-1508	2010
Shibasaki S, Imagawa A, Hanafusa T.	Fulminant Type 1 Diabetes Mellitus –a new class of type 1 diabetes. In Diabetes	***An Old Disease, a New Insight***	in press		2012

Yamaoka M, Kitamura T, Moriyama H, Shima Y, Haseda F, Okita K, Sakaguchi Y, Iwahashi H, Hanafusa T, Funahashi T, Nagata M, Otsuki M, Imagawa A, Shimomura I.	A case of long-standing autoimmune type 1 diabetes with common variable immunodeficiency.	***Diabetol Int***	3	50-53	2012
Tsutsumi C, Imagawa A, Ikegami H, Makino H, Kobayashi T, Hanafusa T.	Class II HLA genotype in fulminant type 1 diabetes –a nationwide survey with reference to GAD antibodies.	***J Diabetes Invest.***	3	62-69	2011
Haseda F, Imagawa A, Murase-Mishiba Y, Sano H, Hirano-Kuwata S, Ueda H, Terasaki J, Hanafusa T.	Low CTLA-4 expression in CD4(+) helper T-cells in patients with fulminant type 1 diabetes.	***Immunol Lett.***	139	80-86	2011

Hotta K, Kitamoto T, Kitamoto A, Mizusawa S, Matsuo T, Nakata Y, Hyogo H, Ochi H, Kamohara S, Miyatake N, Kotani K, Komatsu R, Itoh N, Mineo I, Wada J, Yoneda M, Nakajima A, Funahashi T, Miyazaki S, Tokunaga K, Masuzaki H, Ueno T, Chayama K, Hamaguchi K, Yamada K, Hanafusa T, Oikawa S, Yoshimatsu H, Sakata T, Tanaka K, Matsuzawa Y, Nakao K, Sekine A.	Computed tomography analysis of the association between the SH2B1 rs 7498665 single-nucleotide polymorphism and visceral fat area.	***J Human Genet***	53	716-719	2011
Tanimoto K, Onda S, Sawaki H, Hiraiwa T, Sano H, Ohnishi M, Terasaki J, Hanafusa T.	Hypopituitarism in a patient with transsphenoidal cephalocele: longitudinal changes in endocrinological abnormalities.	***Endocrine J.***	53	193-198	2011
Nagai K, Takeuchi T, Kotani T, Hata K, Yoshida S, Isoda K, Fujiki Y, Shiba H, Makino S, Hanafusa T.	Therapeutic drug monitoring of cyclosporine microemulsion in interstitial pneumonia with dermatomyositis.	***Mod. Rheumatol.***	21(1)	32-36	2011

Okabe T, Hoshiga M, Negoro N, Nakakoji T, Arishiro K, Ishihara T, Ueno H, Hanafusa T.	Rabbit plaque models closely resembling lesions in human coronary artery disease.	***Int. J. Cardiol.***	147(2)	271-277	2011
Nakajima H, Hosokawa T, Sugino M, Kimura F, Sugasawa J, Hanafusa T, Takahashi T.	Visual field defects of optic neuritis in neuromyelitis optica compared with multiple sclerosis.	***BMC Neurol.***	10	45	2010
Shibasaki S, Imagawa A, Terasaki J, Hanafusa T.	Endogenous insulin secretion even at a very low level contributes to the stability of blood glucose control in fulminant type 1 diabetes	***J. Diabetes Invest.***	1(6)	283-285	2010
Hoshiga M, Arishiro K, Nakakoji T, Miyazaki N, Negoro N, Okabe T, Kohbayashi E, Ishihara T, Hanafusa T.	Switching to aggressive statin improves vascular endothelial function in patients with stable coronary artery disease.	***J. Atheroscler Thromb.***	17(7)	705-711	2010

Shibasaki S, Imagawa A, Tauriainen S, Iino M, Oikarinen M, Abiru H, Tamaki K, Seino H, Nishi K, Takase I, Okada Y, Uno S, Murase-Mishiba Y, Terasaki J, Makino H, Shimomura I, Hyöty H, Hanafusa T.	Expression of toll-like receptors in the pancreas of recent-onset fulminant type 1 diabetes.	***Endocr. J.***	57(3)	211-219	2010
Arishiro K, Hoshiga M, Ishihara T, Kondo K, Hanafusa T.	Connexin 43 expression is associated with vascular activation in human radial artery.	***Int. J. Cardiol.***	145(2)	270-272	2011

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Molecular and cellular characteristics of *ABCA3* mutations associated with diffuse parenchymal lung diseases in children

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ABCA3 (ATP-binding cassette subfamily A, member 3) is expressed in the lamellar bodies of alveolar type II cells and is crucial to pulmonary surfactant storage and homeostasis. *ABCA3* gene mutations have been associated with neonatal respiratory distress (NRD) and pediatric interstitial lung disease (ILD). The objective of this study was to look for *ABCA3* gene mutations in patients with severe NRD and/or ILD. The 30 *ABCA3* coding exons were screened in 47 patients with severe NRD and/or ILD. *ABCA3* mutations were identified in 10 out of 47 patients, including 2 homozygous, 5 compound heterozygous and 3 heterozygous patients. SP-B and SP-C expression patterns varied across patients. Among patients with *ABCA3* mutations, five died shortly after birth and five developed ILD (including one without NRD). Functional studies of p.D253H and p.T1173R mutations revealed that p.D253H and p.T1173R induced abnormal lamellar bodies. Additionally, p.T1173R increased IL-8 secretion *in vitro*. In conclusion, we identified new *ABCA3* mutations in patients with life-threatening NRD and/or ILD. Two mutations associated with ILD acted via different pathophysiological mechanisms despite similar clinical phenotypes.

INTRODUCTION

Pulmonary surfactant, a complex mixture of lipids and specific proteins located at the air–liquid interface, lowers alveolar surface tension, thereby preventing alveolar collapse at the end of expiration. It is synthesized by alveolar type-II cells, stored in lamellar bodies and secreted by exocytosis. Phospholipids make up ~90% of pulmonary surfactant.

Recent studies indicate a role for several genes in diffuse lung diseases (1–3). Genes implicated to date include the

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Table 1. Genetic analysis results in the 10 children harboring homozygous and compound heterozygous (shaded) or heterozygous *ABCA3* mutations

Patient	NRD	Clinical outcome	*ABCA3* mutation cDNA level	Protein level	*ABCA3* SNPs dbSNPs rs# cluster id	*ABCA3* variants Missense variants in conserved amino acid
1	Yes	ILD	c.[3518C>G] + [3518C>G]	p.[T1173R] + [T1173R]	rs149532, rs13332514	
2	Yes	ILD	c.[757G>C] + [757G>C]	p.[D253H] + [D253H]		
3	Yes	Death	c.[1385T>G] + [2890G>A]	p.[L462R] + [G964S]	rs149532	
4	Yes	Death	c.[4747C>T] + c.[384delC]	p.[R1583W] + p.[S128Rfs]	rs149532	c.[450G>A] (het)
5	No	Death	c.[629G>T] + [3079G>C]	p.[G210V] + [A1027P]	rs149532	
6	Yes	ILD	c.[622C>T] + [4561C>T]	p.[R208W] + [R1521W]	rs149532, rs323043	
7	Yes	Death	c.[604G>C] + [907C>G]	p.[G202R] + [L303V]	rs149532, rs323043 (het), rs13332514	
8	Yes	Death	c.[2888A>G] + [?]	p.[Y963C] + [?]	rs149532 (het), rs323043 (het)	
9	Yes	ILD	c.[2125C>T] + [?]	p.[R709W] + [?]	rs149532	
10	Yes	ILD	c.[2614A>G] + [?]	p.[S872G] + [?]	rs149532 (het), rs323043, rs13332514 (het)	

het, heterozygous; NRD, neonatal respiratory distress; ILD, interstitial lung disease.

surfactant protein (SP)-B and SP-C genes (*SFTPB*, MIM 178640; and *SFTPC*, MIM 178620) and the ATP-binding cassette subfamily A member 3 gene (*ABCA3*, MIM 601615). SP-B deficiency has long been known to cause lethal neonatal respiratory distress (NRD) (4). More recently, *SFTPC* mutations were reported in newborns and infants with severe alveolar-interstitial syndrome (3,5). ABCA3 is a 1704-amino acid protein expressed selectively—but not specifically—in the lung, where it is found in the limiting membrane of lamellar bodies (1,6,7). ABCA3 is encoded by an 80 kb gene mapped to 16p13.3 in humans and is thought to regulate lipid transport and organization during lamellar body formation (8,9).

ABCA3 gene mutations are transmitted by autosomal recessive inheritance. As with SP-B deficiency, ABCA3 deficiency should be suspected in full-term infants with severe NRD refractory to maximal conventional treatment (10,11). In addition, *ABCA3* gene mutations have been found in children and young adults with interstitial lung disease (ILD) (1,3,12). For instance, the heterozygous c.875A>T (p.Glu292Val, p.E292V) *ABCA3* mutation was identified in several older children and young adults with desquamative interstitial pneumonitis (1). The large size and marked allelic heterogeneity of the *ABCA3* gene create challenges in mutation identification.

The objectives of this study were to identify and characterize *ABCA3* variations in a large population of pediatric patients with NRD and/or ILD. We identified new *ABCA3* gene mutations and found that these mutations were not associated with a specific expression profile of SP-B and SP-C in bronchoalveolar lavage fluid (BALF). Functional analysis of two mutations associated with ILD showed different pathophysiological mechanisms, despite the similar clinical phenotype.

RESULTS

Study patients

Of the 47 children enrolled in the study (Supplementary Material, Supporting Information 1), 23 (49%) were male and 24 (51%) female. The patients were from Europe ($n = 27$), North Africa ($n = 12$), Reunion Island ($n = 6$), West Africa ($n = 1$) and Haiti ($n = 1$). Among them, 6 (13%) were born prematurely (<36 weeks) and 31 (66%) had NRD. ILD developed in 31 (66%) patients, and 21 (36%) patients had both NRD and ILD. Nine (19%) patients died of respiratory failure.

Genetic analysis

Of the 47 patients, 10 had *ABCA3* mutations. We identified 15 mutations, including 13 that had not been described previously. The two mutations p.G210V and p.R208W have been already identified (13,14). There were 14 missense mutations and 1 heterozygous nonsense mutation (p.Ser128ArgfsX23, designated hereafter as p.S128Rfs) (Table 1).

Analysis of genomic DNA from the parents and kindred showed that the compound heterozygous p.R1583W/p.S128Rfs (Fig. 1A) and p.R208W/p.R1521W (Fig. 1B) mutations were inherited, as well as the homozygous mutations p.T1173R (Fig. 1C) and p.D253H (Fig. 1D). For the other mutations, genomic DNA samples from family members were not available.

None of these newly identified *ABCA3* mutations has been previously described as polymorphisms (http://ncbi.nih.gov/SNP). In addition, none of the new variants was detected in the 46 alleles from our 23 controls. Alignment of the human and other mammalian amino acid sequences (by Multiple Sequence Comparison using Log-Expectation, MUSCLE analysis) indicated that almost all the *ABCA3* mutations occurred in highly conserved residues (not illustrated). They were located across the protein in the extracellular domains (ECD1 and ECD2), as well as in internal domains (NBD1 and NBD2) (Fig. 2). Finally, complete *ABCA3* sequencing disclosed previously described single-nucleotide polymorphisms (SNPs) (Table 1), as well as a missense variant affecting a conserved amino acid in the patient harboring the c.[4747C>T]+[384delC] mutation.

In the 37 patients without *ABCA3* mutations, four SNPs were identified in the coding region of *ABCA3*. These SNPs were in exons 7, 9, 14 and 26, respectively, and did not induce amino acid variations. A missense variant in the conserved amino acid c.1059C>T was identified in nine children. We found these variants neither in the public polymorphism database nor in our controls.