The ABCC6 transporter: what lessons can be learnt from other ATP-binding cassette transporters?

Olivier M. Vanakker*, Mohammad J. Hosen and Anne De Paepe

Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

Edited by: Theodore Perkins, Ottawa Hospital Research Institute, Canada
Reviewed by: Scott H. Harrison, North Carolina A&T State University, USA
Ayse Meric Ovacik, University at Buffalo, USA
*Correspondence: Olivier M. Vanakker, Center for Medical Genetics, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium e-mail: olivier.vanakker@ugent.be

ABC transporters represent a large family of ATP-driven transmembrane transporters involved in uni- or bidirectional transfer of a large variety of substrates. Divided in seven families, they represent 48 transporter proteins, several of which have been associated with human disease. Among the latter is ABCC6, a unidirectional exporter protein primarily expressed in liver and kidney. ABCC6 deficiency has been shown to cause the ectopic mineralization disorder pseudo-xanthoma elasticum (PXE), characterized by calcification and fragmentation of elastic fibers, resulting in oculocutaneous and cardiovascular symptoms. Unique in the group of connective tissue disorders, the pathophysiological relation between the ABCC6 transporter and ectopic mineralization in PXE remains enigmatic, not in the least because of lack of knowledge of the substrate(s) of ABCC6 and its unusual expression pattern. In this paper, we will summarize relevant knowledge and methods toward understanding the (patho)physiological role of ABCC6 and how its deficiency may be dealt with.

Keywords: pseudo-xanthoma elasticum, ABCC6, ABC transporters, substrate identification, clinical variability, integrated approach, systems biology, modifier genes

In this paper, we will summarize relevant knowledge and methods for analysis on ABC transporters which may be useful for the further study of ABCC6. Pseudo-xanthoma elasticum is an autosomal recessive disorder resulting from aberrant mineralization and fragmentation of elastic fibers in the extracellular matrix of the skin, the eyes and the cardiovascular system. It is characterized by popular skin lesions, a retinopathy prone to hemorrhage due to subretinal neovascularisation, and premature occlusive vessel disease, with considerable inter- and intra-familial variability of severity (Vanakker et al., 2008). Thirteen years after the discovery of the ABCC6 gene (Madon et al., 2000), it has been previously demonstrated that nothing can be learned from previous experiences with functional dissection of ABC transporters. Awareness has risen for the nature of its substrate and hence the physiological function of the transporter. Following unsuccessful comparisons, it is doubtful that the function of other members of the ABC transporter family will imply anything concerning the actual function of ABCC6 (Madon et al., 2000). It has been previously demonstrated in plant ABC transporters that – despite phylegnetic similarities and domain homologies – related ABC transporters can in fact serve diverse physiological functions. In humans, this was endorsed through the comparison of the cystic fibrosis transmembrane conductance regulator (ABCC7 or CFTR, the gene for cystic fibrosis) and P-glycoprotein (ABCB1 or MDR – multidrug resistance protein; Luckie et al., 2003). This however does not imply that nothing can be learned from previous experiences with functional dissection of ABC transporters. Awareness has risen for several of these that the complexity of (patho)physiological mechanisms related to the wild type and mutant transporter is much higher than anticipated. In this respect and based on our current knowledge, ABCC6 will probably not be an exception to the rule. This enlarging complexity began with the changing concept of...
For several ABC transporters either one or a small number of closely related substrates are known. However, there have been reports of other transporters, such as ABCC1, ABCC2 or ABCB1, for which multispecificity for a diverse range of substrates has been shown (Jemnitz et al., 2010; He et al., 2011). The diversity of (patho)physiological observations in PXE – oxidative stress, the PXE serum factor, vitamin K deficiency, the relation with ENPP1, does not make it unthinkable that they result from aberrant transport of more than one substrate, thus influencing more than one physiological process (Le Saux et al., 2006; Pasquali-Ronchetti et al., 2006; Vanakker et al., 2010; Nitschke et al., 2011). For many ABC transporters – including ABCG6 – the specific sequences responsible for substrate recognition have not yet been identified, which may add to the complexity of substrate identification (Glavina et al., 2004). Nevertheless, for some transporters such as ABCC2 and Pgp, binding-site models have been proposed using relatively high accuracy in silico methods. Such models include the presence of one large binding site and multiple smaller ones, primary and secondary binding sites or three distinct sites (Hirono et al., 2005; Borst et al., 2006; Pedersen et al., 2008; Ferreira et al., 2011).

These in silico approaches such as molecular docking, though insufficiently reliable to pinpoint with certainty the physiological substrates, may also have the advantage to generate a list of potential substrates in a cost- and time-efficient manner. Subsequently, these predictions need to be validated in vivo. Several approaches can be applied to identify physiologically compounds transported by ABC proteins, such as in vivo hepatobiliary elimination studies in mutant animal models, and using membrane vesicles or functional assays based on mass spectrometry (Ci et al., 2007; Katona et al., 2009; Jennitz et al., 2010). Though routine model organisms are commonly used for such experiments and the Abcc6 knock-out mouse model largely recapitulates the clinical features of PXE, there have been reports emphasizing the differences in the physiological mechanisms between rodents and humans, which may slow down substrate identification (Ivan et al., 2013). This has been the case for the ABCG2 protein, recently discovered to be an urate transporter (Nakayama et al., 2013). It should remind us to be cautious to extrapolate findings (positive or negative) in other species to the human disease. Remembering the adage that humans remain the most optimal model to search for substrate(s), an interesting approach for substrate screening has been reported for ABCG2 (Krumpochova et al., 2012). To determine the extent of its substrate spectrum, a variant on the classic vesicular transport experiments has been applied to extract substrates from body fluids. Classic vesicular transport studies have as a drawback that an upfront hypothesis about the transported compounds is necessary and that only one substrate can be evaluated at a time. Certainly, the necessity of an upfront hypothesis is a major disadvantage with respect to ABCG6. By incubating the vesicles in body fluids (in the case of Abcc2 murine urine) and analyzing the vesicle content by LC/MS, several novel compounds were identified. To apply this technique for ABCG6 would imply the use of human plasma and/or hepatocytes. This transportomics technique has great potential with several advantages including a reduced number of experimental animals and would mean that identification of compounds is not a prerequisite to study their transport in vesicular transport experiments as one can fish for new substrates. Combining transportomics with untargeted metabolomics analysis would further increase the range of potential substrates that can be identified. Disadvantages of the technique include that it is less suitable for identifying hydrophobic substrates. The complex composition of body fluids may require fractionation to limit the effect of regulators of the transporter which could mask transport of some substrates (Krumpochova et al., 2012).

After several years of tranquility, the expression profile of ABCC6 has again been the subject of debate. ABCG6 is predominantly expressed at the basolateral side of liver and kidney cells, though the transporter also has differential expression in the gut and gastro-intestinal tract (Sinko et al., 2003; Much, 2004; Pomozi et al., 2013). Recently, a supposed intracellular location in the mitochondria-associated membrane (MEM) – part of the ER complex – has been described (Martin et al., 2012). Though the shift in the paradigm linking the expression and function of ABCG6 to the hepatic and renal plasma membrane (PM), which is declared in this paper, should be reviewed with skepticism – the amount of evidence locating ABCG6 in the PM is after all overwhelming – the concept of an additional intracellular localization is potentially interesting and may further increase the complexity of the pathophysiological enigma at hand. This issue has been the topic of debate in recent papers by respectively Martin et al. (2012, 2013) and Pomozi et al. (2013). Demonstrating again the PM localization of ABCG6, the latter group could not confirm the MEM localization while the former called on methodological arguments to defend their findings (Martin et al., 2013; Pomozi et al., 2013). Challenging the cellular localization of proteins is not unprecedented in the ABC superfamily. Recently, the position of the ABCB6 transporter, originally thought to function in mitochondrial porphyrin metabolism, was challenged and extensively documented with experimental and literature data (Kiss et al., 2012). Despite the critical review and convincing evidence of the true physiological function of ABCB6, the authors did not completely exclude a contribution of ABCB6 to porphyrin metabolism and appealed for further and thorough study of the true pathophysiological function(s) of this transporter (Kiss et al., 2012). The knowledge on the subcellular localization of a native protein is of critical importance to model and understand the pathophysiology of any disease. Therefore, unity should be achieved regarding the expression and function of any disease. Therefore, unity should be achieved regarding the expression and function of
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ABC protein may have different organ-specific functions (Jemnitz et al., 2010). Where in the liver it functions in biliary transport, in the kidney it is involved in the excretion of small organic anions. A similar tissue-dependent function was shown for ABCA1 and ABCG1 (Tarling et al., 2013). Specifically addressing these extrahepatic ABCC6 proteins is necessary as it is not unconsiderable that for example the mucosal involvement in PXE may depend on or be modulated by the intestinal ABCC6 transporter.

REGULATION OF ABCC6

Distinct pathways are involved in the regulation of ABC transporters, comprising genetic, epigenetic and nuclear-receptor mediated mechanisms, as well as post-transcriptional target repression by microRNAs (miRNAs), which can be triggered by hormones, growth factors and exogenous factors. Several examples exist of ABC transporters, such as Pgp, MRP4, BCRP, whose regulation depends on a combination of mechanisms (Masereeuw and Russel, 2012). Nuclear factor regulation and methylation dependent epigenetic regulation has been described for ABCC6 (Aranyi et al., 2005; de Boussac et al., 2010; Ratajewski et al., 2012). So far, no correlation with the PXE phenotype, its variability or potential therapeutic approaches has been attempted. The influence of epigenetic changes, such as promoter DNA methylation, on disease variability has been shown for ABCA1 and coronary artery disease and various drug transporters such as ABCB1 and MDR1 (Baker et al., 2005; Reed et al., 2008; Guay et al., 2012). Therapeutic consequences may include the use of histone deacetylase inhibitors, as reported for MDR1 (Jiang et al., 2009).

MicroRNA is a family of short non-coding RNAs involved in the negative regulation of gene expression at the posttranscriptional level (He and Hanson, 2004). With a few hundred miRNAs identified, it is estimated that 50% of the protein-coding genes are regulated by them. Among ABC transporters, miRNA dependent regulation has been documented for CFTR, MRP2 and 4, Pgp and BCRP; either directly or indirectly through nuclear factors (Bord et al., 2012; Oglesby et al., 2013). In the CFTR gene, variants have been described that may influence the miRNA target sites in the 3’ UTR (Amato et al., 2013). It has been suggested that certain single nucleotide polymorphisms (SNPs) can influence the affinity for inhibitory miRNAs and may explain the differences in clinical expression between patients with an identical genotype. Mutations in the 3’ UTR have also been described in the ABCC6 gene, so the involvement of miRNAs in PXE pathophysiology may not be purely theoretical. Identification of such miRNAs does not only open the possibility of using modulators, such as chemically engineered oligonucleotides called antagonists, with the goal of influencing mechanisms that underlie disease initiation or progression (Masereeuw and Russel, 2012). Of interest is that miRNAs have been demonstrated useful biomarkers in kidney disease (Amato et al., 2013; De Guire et al., 2013). The development of an accurate biomarker set for PXE, which does not yet exist, will enable clinical studies to determine whether a compound has a clinically significant effect on the PXE phenotype.

CLINICAL VARIABILITY

The clinical variability of the PXE phenotype remains a challenge for patients and physicians, making an individualized approach at this moment nearly impossible. Because of the lack of correlations between the patients phenotype and ABCC6 genotype, the possibility of modifier genes has been suggested (Hendig et al., 2005; Zarbock et al., 2010, 2009). The number of potential modifier genes in PXE is currently still limited, which is not totally unexpected; for many ABC transporters the identification of clinical modulators remains challenging. The clinical variability in PXE shows similarities with the variability in cystic fibrosis (CF), the clinical course of which is also difficult to predict using the ABC7 mutations. Consequently, the quest for modifier genes has started and several modifiers of pulmonary outcome in CF have been described (Blaisdell et al., 2004; Boyle, 2007; Weiler and Drumm, 2012; von Kanel et al., 2013). The search for CF modifiers has lead to several recommendations which are equally valid for ABCC6. First, the importance of an in depth, unambiguous and universal definition of the phenotype has been deemed extremely important. Indeed, the description of the clinical features of the PXE phenotype is often inconsistent in different reports, even when tools such as the Phenodex® are available (Pfendner et al., 2007). A more standardized definition of the phenotypic features will allow a more reliable identification and comparison of modifiers. Further, the limitations of association studies where the relationship between phenotype and polymorphisms in candidate modifier genes is examined have become clear, with the possibility of false positive studies or the causal effect of other genes which may travel with the candidate gene(s) (Nadeau, 2001; Accurso and Sontag, 2003). Finally, a study in twins and siblings in CF indicates that functions directly related to CFTR, membrane ion transport and/or intracellular trafficking of mutant protein are subject to modifier effects (Bronveld et al., 2000, 2001). Identification of modifiers for functions directly related to the ABC transporter may also yield further insights in the pathophysiology of PXE and provide novel therapeutic targets. Next generation sequencing (NGS), a revolutionizing sequencing technique enabling parallel sequencing of multiple genes and whole exome sequencing is also an opportunity to identify modifier genes and variants, particularly in rare disorders in which large cohorts are often difficult to gather. By combining analysis of extreme phenotypes with pathway analysis, significant power can still be obtained, as was demonstrated by using NGS in CF (Emond et al., 2012).

Modifier genes may not be the only mechanism involved in the variability of PXE. For several ABC transporters, compensatory mechanisms have been described. These include upregulation of MRP3 expression in Dubin-Johnson syndrome, thus compensating for the impaired ABC2 function (Masereeuw and Russel, 2012). Such compensatory mechanisms have also been suggested for PXE. Gene expression profiling of ABC transporters in dermal...
fibroblasts revealed increased expression of seven genes, including ABCG2 and several members of the A-subfamily (Hendig et al., 2008). The latter was further explored in hepatocytes of a knock-out mouse model where tissue specific upregulation of Abcg4 was demonstrated in the liver (Li and Uitto, 2011). However, no further studies have investigated other potential compensatory mechanisms, though they may be of significant importance in understanding PXE, for aiming a more personalized approach to clinical and functional annotation of mutations in the CFTR gene. Within this project, clinical and molecular data are gathered from CF registries and centers, in a standardized way and under the control of data managers. Further data on functional assessment of mutations was added (Castellani and CFTR2 team, 2013). Though valuable initiatives have been taken to establish mutation database for ABCG6, and linking these molecular data to phenotypical characteristics, no such comprehensive database is currently available. A comprehensive database would improve our ability to identify biomarkers and interpret underlying mechanisms of disease variability in PXE. This database would ideally incorporate information on functional mutation data, potential or established modifier variants, exome sequencing data, serum measurements of patients, fibroblast observations, proteomics, metabolomics and other -omics in clinically well-characterized patients. This is expected to enhance diagnostics, carrier testing and screening, genotype-phenotype correlations, modifier analysis and insights into pathogenesis and therapies. It can be concluded that the other members of the ABC transporter family can provide us with valuable information and useful precedents for further characterizing the ABCG6 transporter. Perhaps the most important lesson to incorporate in current PXE research is the concept that only an integrative approach will finally enable us to elucidate this disease completely. To this purpose, it is therefore imperative that joint initiatives can be outlined to merge and integrate past, present and future research data.

REFERENCES
Accursio, F. J., and Sonntag, M. K. (2005). Seeking modifier genes in cystic fibrosis. Am. J. Resp. Crit. Care Med. 170, 289–290. doi: 10.1164/rccm.200502-009OC
Arányi, T., Ratajewski, M., Bardóczy, A., Amato, F., Seia, M., Giordano, S., et al. (2008). The latter was further explored in hepatocytes of a knock-out mouse model where tissue specific upregulation of Abcg4 was demonstrated in the liver (Li and Uitto, 2011). However, no further studies have investigated other potential compensatory mechanisms, though they may be of significant importance in understanding PXE, for aiming a more personalized approach to follow-up of patients and for the introduction of novel therapeutic approaches.

AN INTEGRATIVE APPROACH FOR PXE RESEARCH
Pseudoxanthoma elasticum is one of the diseases where, through the dedicated work of a relatively small group of researchers, a large number of data and observations are gathered. To take on the challenges that we are facing in the field of PXE, integration of all these data and findings may ultimately be the most difficult though imperative step to move forward efficiently. One interesting initiative in this respect is the Clinical and Functional Translation of CFTR (CFTR2) project, which presents a novel approach to clinical and functional annotation of mutations in the CFTR gene. Within this project, clinical and molecular data are gathered from CF registries and centers, in a standardized way and under the control of data managers. Further data on functional assessment of mutations was added (Castellani and CFTR2 team, 2013). Though valuable initiatives have been taken to establish mutation database for ABCG6, and linking these molecular data to phenotypical characteristics, no such comprehensive database is currently available. A comprehensive database would improve our ability to identify biomarkers and interpret underlying mechanisms of disease variability in PXE. This database would ideally incorporate information on functional mutation data, potential or established modifier variants, exome sequencing data, serum measurements of patients, fibroblast observations, proteomics, metabolomics and other -omics in clinically well-characterized patients. This is expected to enhance diagnostics, carrier testing and screening, genotype-phenotype correlations, modifier analysis and insights into pathogenesis and therapies. It can be concluded that the other members of the ABC transporter family can provide us with valuable information and useful precedents for further characterizing the ABCG6 transporter. Perhaps the most important lesson to incorporate in current PXE research is the concept that only an integrative approach will finally enable us to elucidate this disease completely. To this purpose, it is therefore imperative that joint initiatives can be outlined to merge and integrate past, present and future research data.

REFERENCES
Accursio, F. J., and Sonntag, M. K. (2005). Seeking modifier genes in cystic fibrosis. Am. J. Resp. Crit. Care Med. 170, 289–290. doi: 10.1164/rccm.200502-009OC
Arányi, T., Ratajewski, M., Bardóczy, A., Amato, F., Seia, M., Giordano, S., et al. (2008). The latter was further explored in hepatocytes of a knock-out mouse model where tissue specific upregulation of Abcg4 was demonstrated in the liver (Li and Uitto, 2011). However, no further studies have investigated other potential compensatory mechanisms, though they may be of significant importance in understanding PXE, for aiming a more personalized approach to follow-up of patients and for the introduction of novel therapeutic approaches.

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and coronary artery disease in familial hypercholesterolemia. Epigenetics 7, 406–427. doi: 10.4161/epi.7.4.16933
He, L. and Hannan, G. J. (2004). MicroRNA-122: small RNA with a big role in gene regulation. Nat. Rev. Genet. 5, 322–331. doi: 10.1038/nrg1379
He, S.-M., Li, R., Kanwar, J. R., Jemnitz, K. K., Heredi-Szabo, K. K., Ivan, S., Breljak, D., Marija, L., and Li, Q., and Uitto, J. (2011). Expression of the three-dimensional pharmacophore of ligands for rat multidrug-resistance transporter 2 using ligand-based drug design techniques. Pharm Res 22, 180–189. doi: 10.1007/s11095-009-9840-9
Hile, M., Kremen, C., Libertchek, E. H., Hörmeier, D., and Hörwege, B. (2015). Are mice, rats, and rabbits good models for physiologi- cal and functional properties of the ABCB6 biliary excretory transporter: a large international case series study in humans? Front. Physiol. 6, 1–26. doi: 10.3389/fphys.2015.00019
Katona, M., Kiss, K., Angyal, V., Nitschke, Y., Baujat, G., Botschen, U., Wittkampf, T., Moulin, du, M., Stella, J., et al. (2011). Generalized arterial calcification of infancy and pseudoxanthoma elasticum: molecular etiology and genotype-phenotype analysis in a large international case series affected by pseudoxanthoma elasticum. J. Med. Genet. 48, 625–636. doi: 10.1136/jmg.2007.051094
Kusuhara, H., Maeda, K., Kanekyo, Y., cachar, S., and Parissenti, A. M. (2008). Hypomethylation of the ABCB1 downstream gene promoter accompa- nies ABCB1 gene amplification and increased expression in docetaxel-resistant MCF-7 breast tumor cells. Epigenetics 3, 270–280. doi: 10.4161/epi.3.3.5808
Lim, E. A., Kim, S., Eom, J., Kim, E., Ki, B., et al. (2009). P-glycoprotein-deficient mice have altered biliary formation in rats. J. Invest. Dermatol. 129, 1497–1505. doi: 10.1038/jid.2009.201
Marnig, A. K., and Meier, S. F. (2009). Malignant tumors with a High-capacity urate trans- porter activity. J. Chromatogr. B 877, 1443–1452. doi: 10.1016/j.jchromb.2009.07.036
Mavragas, M. I., Boraldi, F., Fernandez, M. I., Bercovitch, L. G., Uitto, J., Landmesser, U., et al. (2013). Response to Ponsot et al’s research commentary. Circ. Res. 112, 1922–1925. doi: 10.1161/ CIRCRESAHA.113.306166
Menozzi, B., and Russell, F. G. M. (2012). Regulatory pathways for ATP-binding cassette transport proteins in kidney proximal tubules. J. Am. Physiol. 314, 865–894. doi: 10.1152/japph.00334-2012
Molony, L., Babigian, P., De Ake, G., Bruttini, M., Pratigiani, E., Casano, R., et al. (2013). Pseudoxanthoma elasticum: point mutations in the ABCC6 gene and a large deletion including also ABC1 and MTH1. Hum. Mutat. 18, 85–91. doi: 10.1002/humu.1747
Münch, D. M. (2004). Regional variations in ABC transporter expression along the mouse intesti- nal tract. Physiol. Genomics 17, 11–20. doi: 10.1152/physiogenom.00153.2003
Nakamura, A., Matsuo, H., Takada, T., Ishido, K., Nakamura, T., Irie, S., et al. (2011). ABCG2 is a High-capacity urate trans- porter and its genetic impairment increases serum uric acid levels in humans. Nucleosides Nucleotides Nucleic Acids 30, 1091–1097. doi: 10.1080/15257770.2011.539933
Namba, K. H. (2001). Modifier genes in mice and humans. Nat. Rev. Genet. 2, 165–174. doi: 10.1038/35006505
Nakayama, A., Maruts, H., Takada, T., Ishido, K., Nakamura, T., Irie, S., et al. (2011). Modifier genes in mice and humans. Nat. Rev. Genet. 2, 165–174. doi: 10.1038/nent.2011.1020
Ogledby, I. K., Costello, S. M., McEl- vaney, P. G., and Greene, C. M. (2013). Regulation of cystic fibrosis transmembrane conductance regu- lator by microRNA-145, -223, and -494 is altered in A549 cystic fibro- sis airway epithelial. J. Am. Soc. Nephrol. 190, 3354–3362. doi: 10.1097/ jasn.0b013e318236e5b9
Panagaki-Brenner, I., García- Fernández, M. I., Borelli, F., Quagliaro, D., Gualani, D., De Vincentiis Paulinelli, C., et al. (2006). Osmotically driven fibroblasts in patients with pseudoxanthoma elasticum: possible role in the pathogenesis of clinical manifesta- tions. J. Hypertens. 24, 54–61. doi: 10.1093/ jhype/24.1.54
Penaud, J. M., Matsson, P., Bergstén, C. A. S., Norinder, U., Hoppig, T., and Arnesson, P. (2008). Prediction and identification of drug interactions with the human ATP-binding cassette transporter multidrug-resistance associated pro- tein 2 (MRP2; ABCC2). J. Med. Chem. 51, 3275–3287. doi: 10.1021/ jm101054g
Petrushka, E. G., Vanakker, O. M., Terry, S. E., Vaziri, S., McDonald, P. E., McLennan, M. B., et al. (2007). Mutation detection in the ABCC6 gene and genotype-phenotype analy- sis in a large international case series affected by pseudoxanthoma elasticum. J. Med. Genet. 44, 623–628. doi: 10.1136/jmg.2007.051094
Poncet, V., Le Saux, O., Branchet, C., Apana, A., Biau, A., Streti, F., et al. (2013). ABCG2 is a biliary plasma membrane protein. Circ. Res. 112, e48–e51. doi: 10.1161/CIRCRESAHA.112.309744
Ratajewski, M., de Boussac, H., Schar- jada, I., Vàráki, A., and Atzeczy, T. (2012). ABCG2 expression is regu- lated by CCAAT/enhancer bind- ing protein promoting a primat- specific sequence located in the first intron of the gene. J. Biol. Chem. 287, 1906–1907. doi: 10.1074/jbc.M111.302141
Rudel, K., Hembrell, S. L., Labarge, M. L., Villeneuve, D. J., Gitti, G. R., and Parissenti, A. M. (2008). Hypomethylation of the ABCB1 downstream gene promoter accompa- nies ABCB1 gene amplification and increased expression in docetaxel-resistant MCF-7 breast tumor cells. Epigenetics 3, 270–280. doi: 10.4161/epi.3.3.5808
Sinki, E., Biau, A., Uddhöl, O., Homolya, L., Schoffer, G. I., Bengø, A. A. B., et al. (2003). Functional and structural properties of the ABCG2 protein in AML cell lines. J. Biochem. Biomol. Res. Commun. 308, 265–269. doi: 10.1016/j.jbrc.2004.08.098
Tang, C. C., Lu, Y., Kessler, P. S. P., Vaughan, A. M. A., and Orton, J. F. J. (2008). The macrophage cholesterol exporter ABCA1 functions as an inflammatory receptor. J. Biol. Chem. 284, 3236–3243. doi: 10.1074/jbc.M701568200
Tu, L., Vidal, T. Q., de A., and Edsborgh, P. A. (2013). Role of ABC transporters in lipid transport and human disease. Trends Endocrinol. Metab. 24, 342–350. doi: 10.1016/j.tem.2013.01.006
Vanakker, O. M., Loo, R. P., Cracke, B., Remontv, E. G., Uitto, J., Viljov, D., et al. (2008). Norel—heparin-molecular insights in pseudoxan- thoma elasticum provide an efficient molecular screening tool for gene-04-00203" — 2013/10/15 — 17:14 — page 5 — #5
method and a comprehensive diagnostic flowchart. Hum. Mutat. 29, 205. doi: 10.1002/humu.9514
Vanakker, O. M., Martin, L., Schurgers, L. J., Quaglino, D., Gottrup, L., Vermeer, C., et al. (2010). Low serum
vitamin K in PXE results in defective carboxylation of mineralization inhibitors similar to the GGCX
mutations in the PXE-like syndrome. Lab. Invest. 90, 895–905. doi: 10.1038/labinvest.2010.66
von Kanel, T., Stanke, F., Weber, M., Schaller, A., Racine, J., Kremer, R., et al. (2013). Clinical and molecular
characterization of the potential CF disease modifier syntaxin 1A. Zent. J. Hum. Genet. doi: 10.1007/s13032-013-0057
[Wulf et al. (2010)]
Wulf, C. A., and Drumm, M. L. (2012). Genetic influences on cystic fibrosis lung disease severity. Front.
Pharmacol. 3:40–48. doi: 10.3389/fphar.2012.00040
Zarbock, R., Hendig, D., Szliska, C., Kleesiek, K., and Götting, C. (2009). Vascular endothelial growth
factor gene polymorphisms as prognostic markers for vascular manifestations in pseudoxanthoma
elasticum. Hum. Mol. Genet. 18, 3344–3351. doi: 10.1093/hmg/ddp259
Zarbock, R., Hendig, D., Szliska, C., Kleesiek, K., and Götting, C. (2010). Analysis of MMP2 promoter
polymorphisms in patients with pseudoxanthoma elasticum. Clin. Chim. Acta 411, 1487–1490. doi: 10.1016/j.cca.2010.06.008
Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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Received: 12 July 2013; accepted: 23 September 2013; published online: 16 October 2013.
Gisbert Vanakker OM, Hosen MJ and De Paepe A (2013) The ABCC6 transporter: what lessons can be learnt from other ATP-binding cassette transporters? Front. Genet. 4:203. doi: 10.3389/fgene.2013.00203
This article was submitted to Systems Biology, a section of the journal Frontiers in Genetics.
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