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Exploration of gene variations in the transcytosis system as a policy proposal for the personalized therapy in type 2 diabetes mellitus

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Abstract

The gene system of transcytosis, integrated by LRP2, AMN, CUBN, ARH, AMN and CUBN, might be important for the treatment and monitoring of chronic complications of diabetics, as well as for drug interactions, since they mediate the reuptake of vitamins such as B complex, folic acid and lipoproteins, which are closely related to the progression of diabetes. That is why polymorphisms in those genes could be targets of personalized medicine, to improve the quality of health care.

It is important for both the clinical researcher and physician to explore new personalized treatment options for better care of the diabetic patient. The search for genetic or genomic markers in order to predict complications of disease, progression as well as to evaluate the therapeutic response to drugs and the presentation of adverse effects is an area to be explored, considering the high costs that represent the attention of diabetics to hospitals from the public sector. Other reasons are that type 2 diabetes mellitus (T2D) patients develop complications related with the progression of the disease, as well as, adverse and side effects resulting from drug interactions [1,2].

T2D commonly presents deficiency of vitamin B complex, associated with the long-term consumption of metformin. The consequences of this deficiency are increased cardiovascular risk, renal damage and higher risk of peripheral neuropathy and senile dementia [1,2]. Additionally, the chronic consumption of statins for the control of hypercholesterolemia and cardiovascular risk results in secondary dyslipidemia myocytes inflammation [1,2].

The common element that might explain the previously described complications and side effects in T2D diabetic patients is an axis of genes that encode for the system of transcytosis in the cellular membranes from small intestine, kidney, liver, striated muscle, and other tissues. The components of this transcytosis system are LRP2, AMN, CUBN, ARH, Dab2, GIPC, NHE3, ClC5, FcRn and NaPi-IIa, which mediate the reuptake of B complex vitamins, including folic acid among other molecules [3-10].

The clinical effect of these genes might be seen in the development of different diseases or clinical conditions (Table 1). Mutations in LRP2 have been associated with diabetes, aminoglucosides response, Donnai-Barrow syndrome (DBS), Facio-oculo-acoustic-renal syndrome (FOAR) and Alzheimer's disease. While mutations in *AMN* and *CUB* occur with megaloblastic anemia plus albuminuria. *CUB*allelic variants are related to the progression of renal damage and *ARH* variations are associated with hypercholesterolemia [3-10]. *NHE3* mutations show association with congenital sodium diarrhea, whereas ClC5 gene is related to renal failure or Dent disease. *ClC5, FcRn, NaPi-IIa* gene are related with metabolic renal disease. *DAB2, GIPC* has an uncertain meaning in human pathology, but their pathogenic effect must be explored [11-25].

Considering the interaction between these genes, it would be very useful to analyze the relationship between polymorphisms of single base changes (SNP) of these genes, or the blocks of haplotypes and haplogroups that can be constructed with sets of SNP in T2D patients. Specially, the relationship of such variants with the development of peripheral neuropathy and the appropriate metformin doses. Another field of research is to explore the relationship between the response to statin therapy and the development of myocyte inflammation. The results of this genetic exploration might be translated into predictive markers to prevent complications associated with the commonly used drugs in T2D, allowing a better attention to the patient. These and other personalized medicine protocols should be included by many governments, since they would improve the costs of health care, especially since these genes are directly responsible for renal, neurological and vascular damage, as has been demonstrated in genetic diseases, animal and experimental models.

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Gene	Protein	SNP or pathogenicmutation	Reference
LRP2	Megalin	rs133980 (associated with hypertension), rs2544390 (associated with gout and alcohol drinking) rs1050700 (associated with glomerular filtration rate) rs3755166, rs2075252, rs4668123 (associated with central adiposity), rs2075252 and haplotype GA of rs4667591/ rs2075252 (associated with bone mineral density), rs3755166 (associated with Alzheimer's disease p.H498Q (associated with type 2 diabetes mellitus) c.+193826T/C (associated with hypercholesterolemia)	[3-4]
CUB	Cubilin	rs1801239/p.I2984V(associated with diabetic nephropathy and albuminuria) rs1801240/ p.G3002E (associated with diabetic nephropathy and albuminuria) p.L2153F (associated with albuminuria) p.I2984V (associated with diabetic nephropathy) p.Q3002G (associated with diabetic nephropathy) rs7918972 (associated with proteinuria)	[5,8]
AMN	Amnionless	c.35delA, p.Gln12Arg*fs**5 (associated Imerslund-Gräsbeck Syndrome) c.206 T>A, p.Met69Lys 5 (associated Imerslund-Gräsbeck Syndrome) p.Val2865Met 5 (associated Imerslund-Gräsbeck Syndrome) c.363G>A , exon 5 (associated Imerslund-Gräsbeck Syndrome) c.829A>G (T276A), c.1339_1344dup GCCGGG, c.-87C>G ,c.-87C>G , c.-27T>C, c.-23G>C, c.296-75_-66dup GCGTGGCGTG, c.843+11C>T, c.1169+42C>G, c.1170-6C>T, c.1362+38G>C, c.1362+518C>T, c.1362+523G>A (associated with recurrent spontaneous abortions). 14delG, 122C>T (recessive megaloblastic anemia)	[7,12,13]
ARHor LDLRAP1	Low density lipoprotein receptor adaptor protein 1	p.T56M, del 1.6kb exon 4 (recessive hypercholesterolemia). p.P202S, p.P202H, p.R238Trp (determinants of plasma cholesterol levels)	[14-16]
DAB2	Clathrinadaptorprotein	rs148700350, rs200879578 , rs200879578, rs200754366	Gene Bank, Not yet studied, Uncertain significance
GIPC	PDZ domain containing family member 1	rs770458112, rs764183065, rs369693566, rs373945556, rs775587781, rs770090326, rs752071186	Gene Bank, Not yet studied, Uncertain significance
SLC9A3 or NHE3	Solute carrier family 9 member A3	c.1145G>A,c.932C>T , c.[379G>A; 963_964delGT] , c.[379G>A; 963_964delGT] , c.805G>A , c.1446+1G>A , c.782dupG , c.1153G>A c.1145G>A, (congenital sodium diarrhea). p.R474Q, p.V567M, p.R799C (decrease NHE3 transporter activity). G1131A and C1197T (sudden infant death syndrome and sudden infant death syndrome)	[17-19]
CLCN5 o CLC5	Chloridevoltage-gatedchannel 5	p.T657S, p.R345W and p.Q629X, insertion in codon 650 Alu(Dent disease)	[20-21]
FCGRTorFcRn	Fc fragment of IgG receptor and transporter	VNTR of promoter region (Response to **cetuximab)**	[22]
SLC34A1 or NaPi-IIa	Solute carrier family 34 member 1	c.1484G>A, p.R95H (hypophosphatemia and nephrocalcinosis). 91del7, p.A133V and p.H568Y (calcium nephrolithiasis with renal phosphate leak). p.R215W, p.C336G, p.V498E, p.W488R, IVS6(+1)G>A, IVS9(+3_6)del, IVS12(+1)G>A (associated with Idiopathic Infantile Hypercalcemia)	[23-25]

Table 1. Genotype of the of the endocytosis system

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