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Novel insights into genetics and clinics of the HNF1A-MODY

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MODY (Maturity Onset Diabetes of the Young) is a type of diabetes resulting from a pathogenic effect of gene mutations. Up to date, 13 MODY genes are known. Gene HNF1A is one of the most common causes of MODY diabetes (HNF1A-MODY; MODY3). This gene is polymorphic and more than 1200 pathogenic and non-pathogenic HNF1A variants were described in its UTRs, exons and introns. For HNF1A-MODY, not just gene but also phenotype heterogeneity is typical. Although there are some clinical instructions, HNF1A-MODY patients often do not meet every diagnostic criteria or they are still misdiagnosed as type 1 and type 2 diabetics. There is a constant effort to find suitable biomarkers to help with in distinguishing of MODY3 from Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). DNA sequencing is still necessary for unambiguous confirmation of clinical suspicion of MODY. NGS (Next Generation Sequencing) methods brought discoveries of multiple new gene variants and new instructions for their pathogenicity classification were required. The most actual problem is classification of variants with uncertain significance (VUS) which is a stumbling-block for clinical interpretation. Since MODY is a hereditary disease, DNA analysis of family members is helpful or even crucial. This review is updated summary about HNF1A-MODY genetics, pathophysiology, clinics functional studies and variant classification.

Key words: HNF1α, MODY, diabetes, insulin secretion, clinics

HNF1A-MODY is one of the most common subtypes of the Maturity Onset Diabetes of the Young (MODY) (McDonald and Ellard 2013). MODY was defined as monogenic form of diabetes with an autosomal dominant inheritance that occurs before the age of 25 years due to a defect in the function of B-cells (Fajans et al. 2001). The subtypes of MODY traditionally include mutations of the genes *ABCC8*, *CEL*, *GCK*, *HNF1A*, *HNF1B*, *HNF4A*, *INS*, *KCNJ11*, *NEUROD1*, *PDX1*, *BLK*, *KLF11* and *PAX4* but the last three genes are discussed (Plengvidhya et al. 2007; Borowiec et al. 2009; Fernandez-Zapico et al. 2009; Thanabalasingham and Owen 2011). Genes *APPL1* (MODY14), *PCBD1* and *RFX6* are newly associated with MODY (Schwitzgebel 2014; Simaite et al. 2014; Prudente et al. 2015; Vaxillaire and Froguel 2016; Kherra et al. 2017). Population prevalence of MODY is 50–100 per million (Shields et al. 2010). Population prevalence of HNF1A-MODY ranges from 0,0066% (in Croatia; Pavic et al. 2018) to 3,6% (in UK; Shields and Colclough. 2017). HNF1A-MODY is caused by the mutations in the *HNF1A* gene coding the transcription factor – hepatocyte nuclear factor 1 alpha (HNF1α). HNF1A-MODY is nonketotic diabetes with onset during childhood, adolescence, or early adulthood, progressive character of hyperglycemia with a high risk for chronic microvascular diabetes complications. The clinical management of HNF1A-

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MODY individuals differs from people with the most prevalent diabetes types, Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). Nevertheless, majority of the individuals with HNF1A-MODY remain misclassified as T1D or T2D. In our review, we focus on the genetic background of HNF1A-MODY, DNA analysis of the *HNF1A* mutations, clinical diagnostics and treatment strategies.

Genetic background

***HNF1A* gene.** HNF1A-MODY is caused by mutations in the *HNF1A* gene, which is located on the chromosome 12 (NC_000012.12) in the region 12q24.2. It is oriented on the plus strand (Bach et al. 1990; Szpirer et al. 1994; Scherer et al. 2006). Reference *HNF1A* genome sequence is NG_011731.2. The exact genomic position varies depending on genome assembly version, chr12:121,41,549-121,442,315 (30,767 bp) in GRCh37/hg19 assembly and chr12:120,973,746-121,004,512 (30, 767 bp) in GRCh38/hg38 assembly (O'Leary et al. 2016).

Three *HNF1A* transcriptional isoforms (isoform A, B and C) were described to be generated from the same promoter by alternative splicing and different polyadenylation. The longest isoform is *HNF1A* A (10 exons), shorter is *HNF1A* B (7 exons) and the shortest is *HNF1A* C (6 exons) (Harries et al. 2006; Bellanne-Chantelot et al. 2008). Harries et al. (2006) demonstrated tissue specific expression levels of the *HNF1A* isoforms by real-time PCR. Isoform A was mostly transcribed in the hepatocytes, kidney and

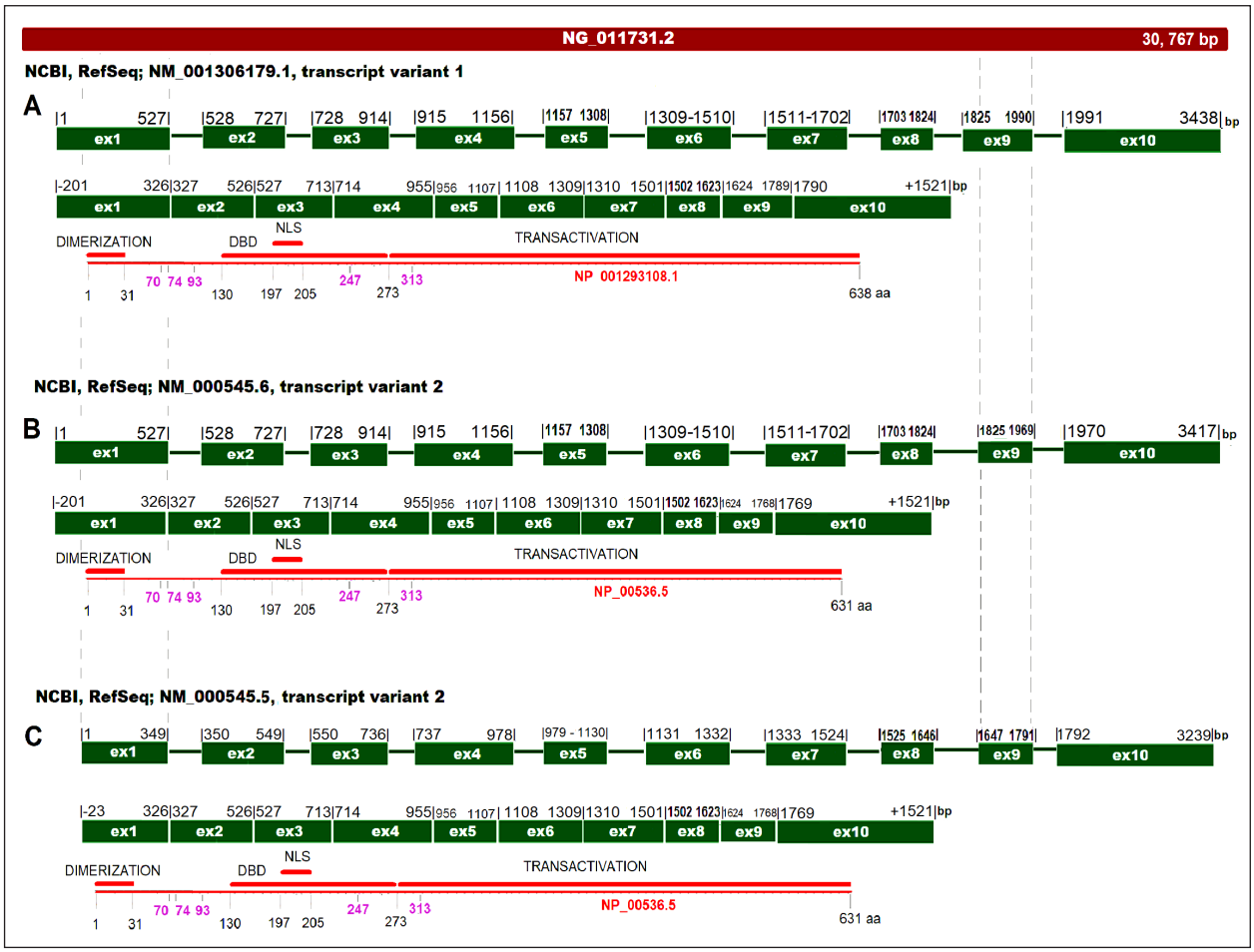

Figure 1. Alignment of *HNF1A* transcripts. NG_011731.2 represents genomic sequence (by NCBI) of the *HNF1A* gene. Green boxes – transcribed exons; green lines – transcribed introns. Spliced transcript is below and numbering corresponds to CDS. Thin red line indicates translated protein. Rough red lines reflect certain HNF1α protein domain presented by NCBI. Amino-acid positions of HNF1α domains are slightly different in the literature (Vaxillaire et al. 1999; Ryffel 2001; Sneha et al. 2017). Purple numbers represent amino acids which are phosphorylated. Dashed line defines that NM_000545.5 (the older version of NM_000545.6) has shorter 5´UTR and NM_001306179.1 has longer 5´ part of exon 9 compared to other *HNF1A* transcripts.

fetal pancreas and less in adult pancreas and pancreatic islets. *HNF1A* B transcripts were predominant in adult pancreas and islets but less in liver and kidney. *HNF1A* C displayed the lowest expression levels in these tissues and it was measured mostly in adult pancreas and islets than in liver or kidney. They reported that *HNF1A* (A) isoform has 5-fold lower activity than *HNF1A* (B) and *HNF1A* (C). These discoveries supported an idea that mRNA processing resulting in expression of multiple isoforms depends on the tissue and the stage of development. However, based on National Center for Biotechnology Information (NCBI) database, only 2 *HNF1A* transcript variants (1 and 2, both containing 10 exons) are registered with unique index and marked as reference sequences (Figure 1). NM_001306179.1 represents the longer *HNF1A* transcript (3438 bp) with coding sequence (CDS) spanning 202–2118 bp and translated to the longer HNF1α protein labelled as NP_001293108.1 (638 aa). The shorter *HNF1A* isoform 2 is a transcript using an alternate in-frame acceptor splice site of exon 9. The latest version, NM_000545.6, represents processed mRNA sequence (3417 bp) with CDS spanning 202–2097 bp and it is translated to the shorter protein isoform defined as NP_00536.5 (631 aa) (Geer et al. 2009). The Locus Reference Genome (LRG) database that curates stable reference sequences used for reporting of DNA variants with clinical use (Dalgleish et al. 2010), includes the reference sequence for *HNF1A* LRG_522 that is based on the reference sequence NM_00545.5. This is the older version of NM_00545.6 and differs only in the 5′UTR (Figure 1).

HNF1α protein. Hepatocyte nuclear factor 1α (HNF1α or HNF1A) is a tissue specific transcription factor. The protein contains 3 domains (Figure 1). An N-terminal dimerization domain (residues 1–32) forms a four-helix bundle where two α-helices are separated by a turn and that allows the formation of homodimers (Rose et al. 2000b; Narayana et al. 2001).

HNF1α binds to the inverted palindrome 5'-GTTAATNATTAAC-3' as a homodimer via bipartite DNA-binding domain (DBD) which is formed as a helix-turn-helix structure. (Rose et al. 2000a; Chi et al. 2002). The DBD domain includes two POU-sub-domains, POUs (specific domain, amino acids 82–172) and POU_H (homeodomain, amino acids 198–281) (Vaxillaire et al. 1999; Ryffel 2001). Other literature presents slightly different amino acid positions of DBD (82–174 aa for POUs and 197–287 aa for POU_H domain) (Sneha et al. 2017). POUs is an integral part of HNF1α that helps in maintaining the stability of the protein, whereas the POU_H domain acts as a crucial interface initiating the interaction between the protein and DNA (Cleary et al. 1997; Harries et al. 2006).

Nuclear localization signal (NLS) is not exactly specified, but there are three potential regions based on their highly similarity to consensus NLSs. One potential region is within the POUs domain (residues 158–171) and two potential regions are within the POU_H domain (residues 197–205 or 271–282) (Chi et al. 2002; Bjorkhaug et al. 2003).

The transactivation domain is at the C-terminus (residues 282–631) (Baumhueter et al. 1990; Mendel and Crabtree 1991; Chi et al. 2002; Harries et al. 2006). HNF1α physically interacts with histone acetyltransferases (HATs) such as CREB-binding protein (CBP), P300/CBP-associated factor (P/CAF) or steroid receptor coactivator-1 (Src-1) and small GTPase receptor-associated coactivator 3 (RAC3) and they can interact with each other or bind independently to different HNF1α functional domains and synergistically increase HNF1α-mediated transactivation (Soutoglou et al. 2000). However, online protein-protein interaction (PPI) databases present many more HNF1α interaction partners and each differs based on information sources they use. STRING database present 26 HNF1α interaction partners (Figure 2). This database groups known and predicted PPI including direct (physical) and indirect (functional) associations. They stem from computational prediction, from knowledge transfer between organisms, and from interactions aggregated from other (primary) databases (Szklarczyk et al. 2017). GPS-Prot database shows 54 proteins involved in HNF1α transcriptional network (Figure 3, Table 1). GPS-Prot links unique scored human PPI from major curated databases (Biogrid, MINT, IntACT, DIP, HPRD, MIPS) and Curated Human Complexes (Fahey et al. 2011). Since STRING and GPS-Prot are not focused on certain human tissue, IID (Integration Interactions Database) provides tissue-specific PPIs of human. This database shows 56 HNF1α interaction partners in human pancreas (Table 1). IID consist of experimentally detected PPIs (from BioGRID, IntAct, I2D, MINT, InnateDB, DIP, HPRD, BIND and BCI databases), orthologous protein-protein interactions, and high-confidence computationally predicted PPIs from recent studies (Kotlyar et al. 2016).

Pathogenesis

HNF1α physiology. HNF1α plays an important role during embryonic development as it affects intestinal epithelial cell growth and cell lineage differentia-

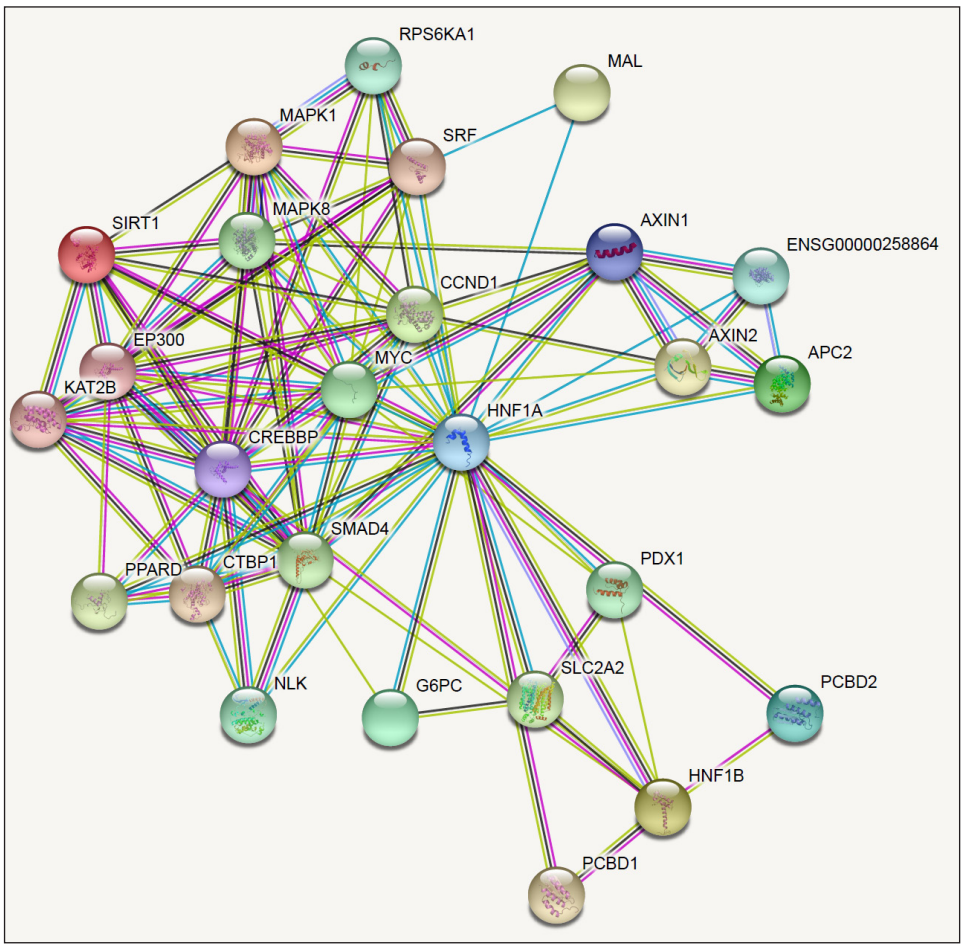

Figure 2. 25 HNF1α protein interaction partners (STRING database). Nodes – each node represents all the splice isoforms produced by a single, protein-coding gene locus. Empty nodes represent proteins of unknown 3D structure and filled nodes represent proteins with known or predicted 3D structure. This interaction network is not focused on any human tissue. Lines – every line color represents different manner of the protein interaction. Light blue – from curated databases. Purple – experimentally determined. Green – predicted interaction based on gene neighborhood. Red – predicted interaction based on gene fusion. Dark blue – predicted interaction based on gene co-occurrence (i.e. phylogenetic distribution of protein orthologs in a human). Yellow – automated text-mining of the scientific literature. Black – co-expression. White – protein homology. Modified by (Szklarczyk et al. 2017).

tion (D'Angelo et al. 2010; Lussier et al. 2010). HNF1α expression was proven also in the adult pancreas, gut, liver and kidney (Harries et al. 2006). Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics revealed various levels of *HNF1A* expression in several human tissues (Figure 4) (Fagerberg et al. 2014). HNF1α binds to at least 222 target genes in the human liver and at least 106 target genes in human pancreatic islets (Odom et al. 2004).

It is also the transcription regulator of angiotensin-converting enzyme 2 which can be involved in mitochondrial metabolism (Shi et al. 2018). In addition, HNF1α is the transcriptional regulator of bile acid transporters in the intestine and kidneys thus is important in HDL metabolism (Shih et al. 2001a).

HNF1α helps to promote the expression of organic cation transporter 1 (OCT1) in the liver which is responsible for hepatic uptake of small, hydrophilic, positively charged organic molecules (Koepsell et al. 2007). Genetic variations in HNF1α may change OCT1 expression and affect the liver uptake and drug metabolism of OCT1 substrates such as metformin, tropisetron, ondansetron. tramadol and morphine (Shu et al. 2007; Tzvetkov et al. 2011, 2012; O'Brien et al. 2013).

HNF1α directly regulates the expression of low afinity/high capacity glucose cotransporter (SGLT2) which is responsible for renal reabsorbtion of glucose (Pontoglio, 2000). HNF1α regulates also the tran-

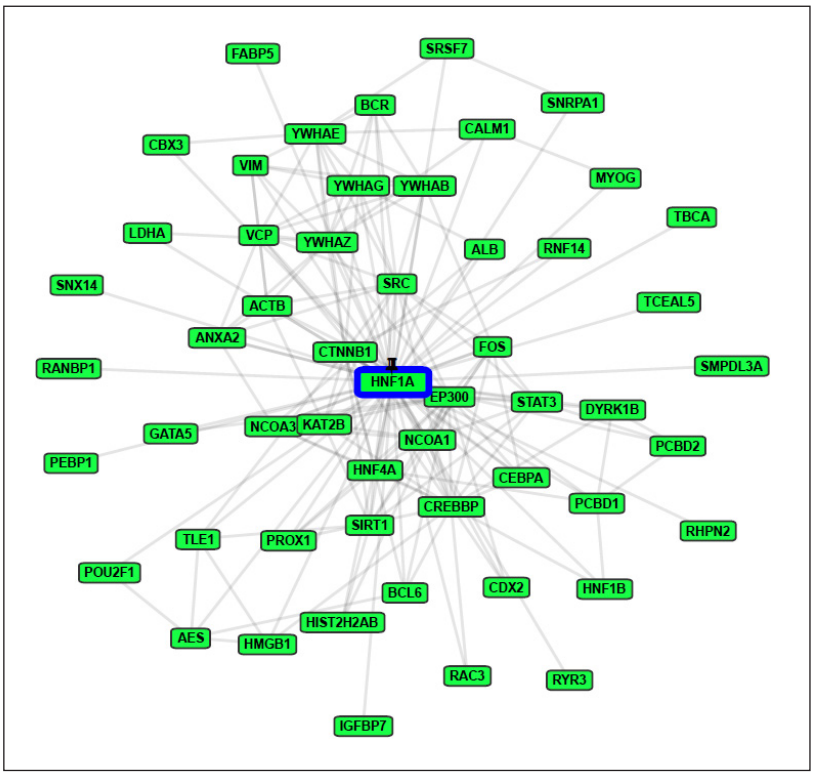

Figure 3. 54 HNF1α protein interaction partners (GPS-Prot database). GPS-Prot links unique scored human protein-protein interactions from major curated databases (Biogrid, MINT, IntACT, DIP, HPRD, MIPS) and Curated Human Complexes. This interaction network appertains to reference HNF1α protein NP_000536.5 (UniProt: P20823). It is not focused on any human tissue. Green boxes represent HNF1α protein interaction partners. Lines represent experimentally based protein-protein interactions (more detailed in Table 1) (Fahey et al. 2011).

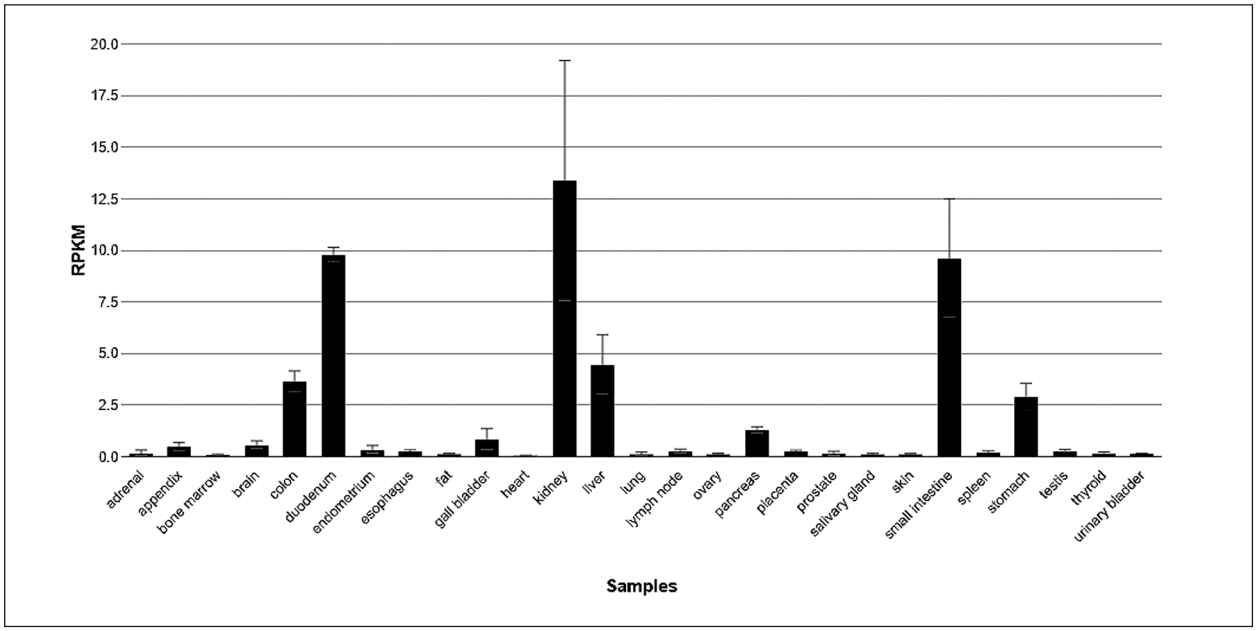

Figure 4. Expression profile of HNF1α in different human tissues. HNF1α tissue-specific expression was researched by quantitative transcriptomics analysis (RNA-Seq) of samples from 27 different tissues from 95 human individuals. This analysis was combined with antibody-based profiling of the same tissues. RPKM (Reads Per Kilobase Million) indicates the transcript abundance (Geer et al. 2009; Fagerberg et al. 2014).

Table 1
Comparison of the lists of HNF1α interaction partners from GSP-Prot and IID database

GSP-Prot			IID	
UniProt	**Symbol**	**References**	**UniProt**	**Symbol**
P60709	ACTB	Yu et al. (2008)	P60709	ACTB
P20823	AES	Brantjes et al. (2001)	Q08117	AES
P02768	ALB	Courtois et al. (1988)	P01019	AGT
P07355	ANXA2	Yu et al. (2008)	P02768	ALB
P20823	BCL6	Miles et al. (2005)	P07355	ANXA2
P11274	BCR	Ress and Moelling (2006)	P41182	BCL6
P62158	CALM1	Ewing et al. (2007)	P11274	BCR
Q13185	CBX3	Yu et al. (2008)	Q13185	CBX3
P20823	CDX2	Mitchelmore et al. (2000)	P49715	CEBPA
P49715	CEBPA	Wu et al. (1994)	Q92793	CREBBP
P20823	CREBBP	Soutoglou et al. (2000); Dohda et al. (2004)	P35222	CTNNB1
P35222	CTNNB1	Ishigaki et al. (2002); Brantjes et al. (2001); Ress and Moelling (2006)	Q5SW24	DACT2
Q9Y463	DYRK1B	Lim et al. (2002); Zou et al. (2003)	Q09472	EP300
P20823	EP300	Ban et al. (2002); Dohda et al. (2004)	Q01469	FABP5
P20823	FABP5	Ewing et al. (2007)	P01100	FOS
P20823	FOS	Leu et al. (2001)	P52655	GTF2A1
P20823	GATA5	van Wering et al. (2002); Divine et al. (2004)	P17096	HMGA1
Q8IUE6	HIST2H2AB	Yu et al. (2008)	P09429	HMGB1
P09429	HMGB1	Yu et al. (2008)	P20823	HNF1A
P20823	HNF1A	Chi et al. (2002); Mendel et al. (1991); Yu et al. (2008)	P35680	HNF1B
P20823	HNF1B	Mendel et al. (1991)	Q16270	IGFBP7
P20823	HNF4A	Magee et al. (1998)	Q92831	KAT2B
Q16270	IGFBP7	Yu et al. (2008)	P00338	LDHA
P20823	KAT2B	Soutoglou et al. (2000)	Q9UJU2	LEF1
P00338	LDHA	Yu et al. (2008)	P15173	MYOG
P20823	MYOG	Funk and Wright (1992)	Q15788	NCOA1
P20823	NCOA1	Soutoglou et al. (2000)	Q9Y6Q9	NCOA3
P20823	NCOA3	Soutoglou et al. (2000)	P08651	NFIC
P61457	PCBD1	Sourdive et al. (1997); Ewing et al. (2007); Wang et al. (2011); Rho et al. (2010)	Q9C056	NKX6-2
Q9H0N5	PCBD2	Ewing et al. (2007); Lim et al. (2002)	O75469	NR1I2
P30086	PEBP1	Yu et al. (2008)	P04150	NR3C1
P20823	POU2F1	Ishii et al. (2000)	P61457	PCBD1
P20823	PROX1	Qin et al. (2009)	Q9H0N5	PCBD2
P20823	RAC3	Soutoglou et al. (2000)	P30086	PEBP1
P43487	RANBP1	Yu et al. (2008)	Q14859	POU1F1
Q8IUC4	RHPN2	Ewing et al. (2007)	Q01851	POU4F1
Q9UBS8	RNF14	Wu et al. (2013)	Q92786	PROX1
Q15413	RYR3	Miyamoto-Sato et al. (2010)	P43487	RANBP1
P20823	SIRT1	Grimm et al. (2011)	Q8IUC4	RHPN2
Q92484	SMPDL3A	Miyamoto-Sato et al. (2010)	Q9UBS8	RNF14

Table 1
Continued ...

GSP-Prot			II D	
UniProt	**Symbol**	**References**	**UniProt**	**Symbol**
P09661	SNRPA1	Ewing et al. (2007)	Q15413	RYR3
Q9Y5W7	SNX14	Yu et al. (2008)	Q96EB6	SIRT1
P20823	SRC	Soutoglou et al. (2000)	Q92484	SMPDL3A
P16629	SRSF7	Yu et al. (2008)	P09661	SNRPA1
P40763	STAT3	Leu et al. (2001)	Q9Y5W7	SNX14
Q75347	TBCA	Ewing et al. (2007)	P12931	SRC
Q5H9L2	TCEAL5	Miyamoto-Sato et al. (2010)	Q16629	SRSF7
P20823	TLE1	Eastman et al. (1999)	P40763	STAT3
P55072	VCP	Yu et al. (2008)	O75347	TBCA
P08670	VIM	Yu et al. (2008)	Q04724	TLE1
P31946	YWHAB	Yu et al. (2008)	P55072	VCP
P62258	YWHAE	Yu et al. (2008)	P08670	VIM
P61981	YWHAG	Yu et al. (2008)	P31946	YWHAB
P63104	YWHAZ	Yu et al. (2008)	P62258	YWHAE
			P61981	YWHAG
			P63104	YWHAZ

GPS-Prot links unique scored human protein-protein interactions from major curated databases (Biogrid, MINT, IntACT, DIP, HPRD, MIPS) and Curated Human Complexes. This interaction network appertains to reference HNF1α protein NP_000536.5 (UniProt: P20823). It is not focused for any human tissue. IID (Integration Interactions Database) is database providing tissue-specific protein–protein interactions of human. This protein selection is focused on human pancreas. HNF1α protein partners occurred in both databases are black colored and red colored are proteins occurring in only one of the databases (Fahey et al. 2011; Kotlyar et al. 2016).

scription of acute phase proteins involved in inflammation, such as fibrinogen, C-reactive protein (CRP), and interleukin 1 receptor (Armendariz and Krauss 2009). Significantly lower levels of HNF1α protein were observed in pancreatic tumors and hepatocellular adenomas than in normal adjacent tissues (Bluteau et al. 2002; Luo et al. 2015), so HNF-1α might be a tumor suppressor protein, too.

More detailed information about HNF1α function in different tissues is summarized in Table 2. In addition, Gene Ontology (GO) Consortium provide experimentally-supported GO annotations accompanied with web access and analytical tools that use the GO knowledgebase (Carbon et al. 2009; Kohler et al. 2017). GO database shows 29 different ontologies determining the biological processes related to HNF1α protein (Table 3).

Transcriptional network. The development and function of adult liver, pancreatic islets or kidney is not regulated by HNF1α alone (Figure 5, Table 4). HNF1α is co-expressed with other transcription factors, e.g. HNF1β, HNF4α and HNF6 (Stoffers et al. 1997; Edlund 1998; Shih and Stoffel 2001; Nammo et al. 2008; De Vas et al. 2015). Together with HNF3 (hepatocyte nuclear factor 3), they constitute a functional network regulating the expression of different tissue genes that contain promoter or enhancer DNA sites for these HNFs (Shih et al. 2001b; Costa et al. 2003; Jacquemin et al. 2003; Lau et al. 2018). Interconnection of HNF transcription factors was experimentally supported by *HNF1A*-null mice which pancreas displays decreased expression of *HNF4A*, *HNF4G (HNF4γ)* and *HNF3* genes (Boj et al. 2001; Shih et al. 2001b). In the pancreas and liver, HNF1α and HNF4α make transcriptional loop (Figure 5C) (Kuo et al. 1992; Kritis et al. 1993; Bulla and Fournier 1994; Gragnoli et al. 1997; Godart et al. 2000; Li et al. 2000; Wang et al. 2000; Eeckhoute et al. 2004). Haploinsufficiency of either HNF1α or HNF4α alters bistable transcriptional cascade (Ferrer 2002). Transcription hierarchy in B-cells has unique properties since *HNF1A* mutations can cause B-cell dysfunction while the other tissues expressing *HNF1A* are not damaged (Byrne et al. 1996; Froguel and Velho 1999).

HNF1α pathophysiology. Mutated HNF1α may alter the gene expression cascade which may alter the

Table 2
List of biological processes of HNF1α in certain human tissue

Tissue	Effect	References
Pancreas	Glucose metabolism	Luni et al. (2012)
	Diabetes	
	Glucose transporters GLUT1 and GLUT2 synthesis	
	L-protein kinase synthesis	Vesterhus (2008)
	Insulin synthesis	
	Insulin promoter activity	
	B-cell glucose and leucin sensing	
	Postprandial production of ATPs	
	Transfer of calcium ions	
Gut and intestine	Development and growth of intestinal cells	D`Angelo et al. (2010); Lussier et al. (2010);
	Bile acid transporters synthesis	Shih et al. (2001a)
Liver	Gluconeogenesis	Odom et al. (2004)
	Carbohydrate synthesis and storage	
	Cholesterol synthesis	
	Apolipoprotein synthesis	
	CYP450 monooxygenases synthesis	
	Serum protein synthesis	
	Promotion of hepatic organic cation transporters	O`Brien et al. (2013)
Kidney	Re-uptake of glucose from glomerulate filtrate	Pontoglio et al. (2000)

Table 3
Details about biological processes linked to HNF1α from different human databases

GeneOnthology (GO) – biological process			
GO ID	**Qualified GO term**	**Evidence**	**PubMed ID**
GO:0001824	Blastocyst development	IEA	
GO:0001889	Liver development	IEA	
GO:0001890	Placenta development	IEA	
GO:0048608	Reproductive structure development	IEA	
GO:0031018	Endocrine pancreas development	IEA	
GO:0030326	Embryonic limb morphogenesis	IEA	
GO:0048341	Paraxial mesoderm formation	IEA	
GO:0006338	Chromatin remodeling and histone acetylation	IEA	
GO:0045893	Positive regulation of transcription, DNA-templated	IDA, IEA	1989880
GO:0006357	Regulation of transcription by RNA poly II	IDA, IEA	10330009
GO:0060261	Positive regulation of transcription initiation From RNA poly II promoter	IGI	15355349
GO:0006633	Fatty acid biosynthetic process	IEA	
GO:0006699	Bile acid biosynthetic process	IEA	
GO:0015721	Bile acid and bile salt transport	IEA	
GO:0006783	Heme biosynthetic process	IEA	
GO:0008203	Cholesterol metabolic process	IEA	
GO:0015908	Fatty acid transport	IEA	

Table 3
Continued ...

GeneOnthology (GO) – biological process			
GO ID	**Qualified GO term**	**Evidence**	**PubMed ID**
GO:0043691	Reverse cholesterol transport	IEA	
GO:0046883	Regulation of hormone secretion	IEA	
GO:0050796	Regulation of insulin secretion	IEA	
GO:0009749	Response to glucose	IEA	
GO:0046323	Glucose import	IEA, IMP	11269503
GO:0042593	Glucose homeostasis	IEA, IMP	11269503
GO:0035623	Renal glucose absorption	IMP, IEA	11269503
GO:0045453	Bone resorption	IEA	
GO:0006979	Response to oxidative stress	IEA	
GO:0060395	SMAD protein signal transduction	IEA	
GO:0030111	Regulation of Wnt signaling pathway	IEA	
GO:0008104	Protein localization	IEA	

This list of biological processes is not tissue specified. Gene ontology database is combination of automatically assigned electronic annotations: IEA (Inferred from Electronic annotation) and curator-assigned annotations: IDA (Inferred from direct assay), IGI (Inferred from Genetic Interactions) and IMP (Inferred from Mutant Phenotype) (Carbon et al. 2009).

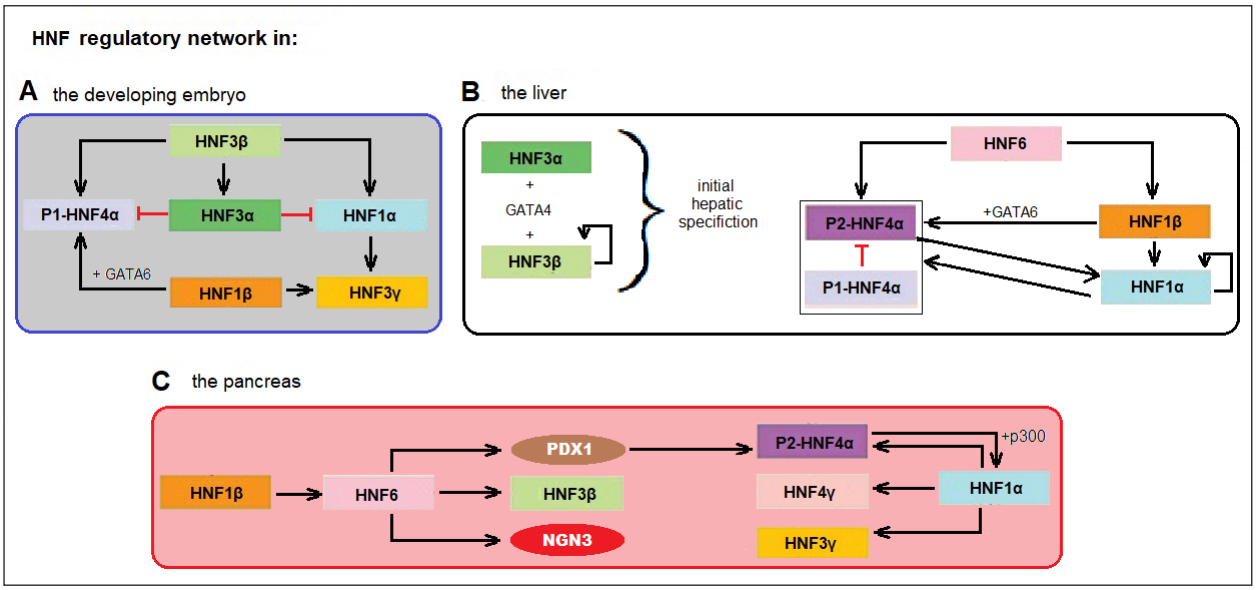

Figure 5. Transcriptional hierarchy of transcription factors in human embryo, liver and pancreas. **(A)** HNF regulatory network in the developing embryo. HNF3β regulates the expression of HNF3α, P1-HNF4α and HNF1α upstream. HNF3α negatively regulates the expression of HNF4α from P1 promoter and HNF1α by competing for DNA binding with HNF3β. HNF1β and GATA6 synergistically enhance the expression of P1-HNF4α in visceral endoderm. HNF1α and HNF1β positively regulate HNF3γ expression. **(B)** HNF regulatory network in liver. HNF3α, HNF3β and GATA4 regulate initial hepatic specification. HNF3β self-regulate its own expression. In adult liver, HNF6 positively regulates expression of HNF1β and HNF4α from the both promoters, P1 and P2. HNF1β regulates the expression of HNF1α and P1-HNF4α and P2-HNF4α. HNF1α regulates expression of P1-HNF4α and P2-HNF4α but only HNF4α expressed from P2 regulates HNF1α. HNF4α expressed P1 promoter inhibits expression of HNF4α from P2 promoter. **(C)** HNF regulatory network in the pancreas. In developing pancreas, HNF1β positively regulates the expression of HNF6 in pancreatic precursor cells. HNF6 activates the onset expression of PDX1 involved in pancreatic specification as well as expression of NGN3 involved in pancreatic endocrine differentiation. In adult pancreatic B-cells, PDX1 is activator of P2-HNF4α expression (Shih and Stoffel 2001). HNF6 regulates also expression of HNF3β. HNF1α regulates transcription of P2-driven HNF4α whereas HNF4α AF-2 and DBD domains regulate HNF1α expression. Cofactor p300 enhances expression of HNF1α. HNF1α regulates also the expression of HNF4γ and HNF3γ. In the other literature, HNF3α can be named as FOXA1, HNF3β as FOXA2, HNF3γ as FOXA3, HNF6 as OC1, PDX1 as IPF1 and NGN3 as Neurogenin 3. Modified from Lau et al. (2018).

Table 4
Detailed characterization of the role of transcription factors during pancreatic development

Protein	Cell type	Effect	Reference
HNF1α	Pancreatic epithelial cells	Maintenance of the (differentiated) islets function in the later phase of development	Shih and Stoffel (2001)
HNF1β	Pre-pancreatic foregut endoderm	Morphogenesis of pancreas	De Vas et al. (2015)
	Multipotent pancreatic progenitor cells		
HNF1α	Bud epithelial cells	Pancreatic development	Nammo et al. (2008)*
HNF1β	Pancreatic cells		
HNF4α	Endocrine precursors		
PDX1	Exocrine pancreatic precursors	Pancreas development	Edlund (1998)
	Endocrine pancreatic precursors	B-cell differentiation	Stoffers et al. (1997)

*Studies on mice.

pancreatic development (Naqvi et al. 2018). Secretion of insulin, secretory response to nutrients, decreased proliferation of B-cells, and abnormal structure of Langerhans islets occur when production of HNF1α protein is insufficient. Impaired B-cell glucose sensing is probably the result of reduced aerobic glycolysis and mitochondrial metabolism (Byrne et al. 1996; Dukes et al. 1998; Pontoglio et al. 1998). Low ATP concentration in B-cells disturbs insulin secretion and leads to HNF1A-MODY diabetes (Vesterhus et al. 2008; Sur and Taipale 2016). In kidneys, HNF1α is involved in the reuptake of glucose from the glomerular filtrate (Pontoglio et al. 2000). In the case of *HNF1A* mutation, uptake is less effective and glucose remains at higher concentrations in urine despite normal glycaemia (i.e. it causes reduced kidney threshold for glucose). Glycosuria usually precedes the B-cell insulin secretion defect for several years (Ellard and Colclough 2006).

There is an evident relationship between certain *HNF1A* variants and T2D risk. This relation can vary among populations. An association of the rare HNF1α variant E508K with T2D was demonstrated in Mexican population (Estrada et al. 2014). In Canadian Oji-Cre population, G319S is connected with an early-onset T2D (Hegele et al. 1999). Although HNF1α polymorphisms I27L and A98V do not influence the function of pancreatic B-cells, they may be associated with insulin resistance and HDL cholesterol levels (Chiu et al. 2000; Holmkvist et al. 2006; Gaulton et al. 2015). In fact, these MODY3 benign variants have mild impact to HNF1α function but their combination can significantly impair HNF1α transactivation activity (Holmkvist et al. 2006; Najmi et al. 2017).

Impaired HNF1α function is, besides the diabetes mellitus, involved in a variety of another health complications. Furthermore, an intergenic variant rs2650000, near the gene *HNF1A*, may influence the levels of LDL-cholesterol and C-reactive protein (Kathiresan et al. 2009; Sabatti et al. 2009). Gene promoter of the protein C acts as a binding site for HNF1α and disruption of this promoter leads to hereditary thrombophilia, a predisposition of an inappropriate clots forming (Berg et al. 1994).

The latest study revealed that MODY3 and T2D are risk factors for pancreatic cancer (Naqvi et al. 2018). Mutations in the *HNF1A* gene are connected not just with pancreatic but also with hepatal tumors and renal tumors (Bluteau et al. 2002; Rebouissou et al. 2005; Jeannot et al. 2010; Pierce and Ahsan 2011). In addition, *HNF1A* antisense RNA 1 (HNF1A-AS1) is transcribed in the opposite transcription direction from *HNF1A* gene as 2.455 bp long non-coding RNA (lncRNA) (Chambers et al. 2011). Deregulation of HNF1A-AS1 participates in esophageal adenocarcinoma (Yang et al. 2014) and lung adenocarcinoma (Wu et al. 2015). This is a strong evidence that HNF1α has a tumor suppressor function (Hoskins et al. 2014). Genome Wide Association Studies (GWAS) from 2017 have linked *HNF1A* gene with 19 different human diseases or biochemical traits (Table 5) (MacArthur et al. 2017).

Genetics of HNF1A-MODY

Variants in *HNF1A* gene. MODY3 is a monogenic disease with autosomal dominant inheritance due to HNF1α haploinsufficiency. *HNF1A* is a polymorphous gene without specified mutation hot-spot. Up to date (November 2018), 380 *HNF1A* unique DNA variants were recorded in Leiden Open-source Variation Database (LOVD) (Fokkema et al. 2011). Anyway, the most extensive publication summarizing *HNF1A*

Table 5
Disease phenotypes linked to HNF1A gene in Genome-Wide Association Studies (GWAS)

GWAS – phenotypes
C-reactive protein measurements
Total cholesterol measurements
Low density lipoprotein cholesterol measurement
Acute insulin response measurement
Peak insulin response measurement
Type II diabetes mellitus
Pancreatic carcinoma
Urate measurement
Serum gamma-glutamyl transferase measurement
N-glycan measurement
Serum alpha-1-antitrypsin measurement
Homocysteine measurement
Coronary artery disease
Plateletcrit
Percutaneous transluminal coronary angioplasty
Coronary artery bypass
Ischemic cardiomyopathy
Myocardial infarction
Angina pectoris

GWAS are hypothesis free methods to identify associations between genetic regions (loci) and traits (including diseases). Study information are manually extracted from the literature and entered into the GWAS Catalogue (MacArthur et al. 2017).

variants (Colclough et al. 2013) states more than 400 different variants, ExAC database presents 894 variants and GnomAD 1231 variants spanning from the *HNF1A* promoter to 3′UTR region, including missense, frame shift, nonsense, splicing mutations, in-frame amino acid deletions, insertions, duplications or partial and whole-gene deletions (Lek et al. 2016).

The higher number of mutations were observed in *HNF1A* exon 2 and exon 4 and the least in exon 5 and exon 10. Mutations in the *HNF1A* promoter can alter or disrupt the binding site for other transcription factors in the liver and pancreas (Lau et al. 2018). These serious consequences may be the reason of the lowest mutation rate (the number of known variants per one nucleotide of a certain domain) at the promoter part of the gene (Colclough et al. 2013). The site of promoter mutation influences its activity with different force. For comparison, c.-283A>C weakens the promoter activity to 30% of the wild type but c.-218T>C mutation decreases the activity only to 70% of the wild type (Godart et al. 2000; Lausen et al. 2000). HNF1α dimerization domain has the highest mutation rate (0.31 per nt) (Colclough et al. 2013).

Pathogenic mutations in dimerization domain have various impacts to protein function. The potential altered dimerization can result from impaired formation of the complex with crucial dimerization cofactor of hepatocyte nuclear factor 1 (DCoH). DCoH is known also as pterin-4α-carbinolamine dehydratase (PCBD1). Destabilization of this bundle or recessive mutations in *PCBD1* gene lead to antibody-negative monogenic diabetes with normal pancreatic morphology and puberty onset (Mendel et al. 1991; Hua et al. 2000; Simaite et al. 2014). Improper forming of the dimer complex causes impaired binding of HNF1α to its DNA targets and decrease the protein transactivation activity.

Mutations in the DNA-binding homeodomain of the protein attract much attention, as they are related to various human diseases (Chi 2005). High rates of mutations causing MODY3 were observed at the POU_S and POU_H regions of HNF1α DBD domain (Chi et al. 2002; Harries et al. 2006; Bellanne-Chantelot et al. 2008; Colclough et al. 2013). However, reduced DNA-binding does not necessary mean reduced transactivation activity, e.g. missense G191D mutation within HNF1α DNA-binding domain decrease DNA-binding activity to 46% of the wild type but transactivation activity remains 88% or even 100% of the wild type (Yang et al. 1999). On the other hand, V133M mutation causes relatively small decrease of DNA-binding (to 84% of the wild type) but HNF1α transcription activity is only 50% of the wild type (Galan et al. 2011).

HNF1α transactivation domain shows low mutation rate (Colclough et al. 2013). It is important to note, that results of measurements of transactivation activity can be influenced by the cell lines which were used in the experiment.

Since HNF1α is a transcription factor, its localization to nucleus is crucial. Otherwise, HNF1α cannot reach its gene targets. Despite three HNF1α protein regions 158–171 aa, 197–205 aa, and 271–282 aa are considered to be the nuclear localization regions (Chi et al. 2002; Bjorkhaug et al. 2003), several mutations in DBD (R263C) and transactivation domain (P379fs, Q446*, S587fs) are responsible for incorrect or abnormal subcellular localization (Yang et al. 1999; Bjorkhaug et al. 2003).

Identification and classification of *HNF1A* variants. New mutations in *HNF1A* gene are still being

identified. Today, next-generation sequencing (NGS) offers the opportunity of DNA analysis of the great number of patients in one reaction. Based on our experiences, WGS (Whole Genome Sequencing) and WES (Whole Exome Sequencing) did not bring us many new gene discovering as in other diagnoses. Thus, the most frequent methods are Sanger and target panel NGS sequencing of all 13 known MODY genes. These are the most frequent methods by which new MODY mutations are revealed. Multiplex ligation-dependent probe amplification (MLPA) assay is used for detection of long InDels or duplications.

Identification of the gene mutations is the first step. The next one is the **classification of the variants**. The terms mutation and polymorphism may be misleading. To a large extent, "mutation" was considered as a genetic change with prevalence less than 1% in population and/or a genetic change responsible for a certain disease. "Polymorphism" was considered as a genetic change occurring commonly in population and not causing a disease. However, it was shown that some "mutations" have higher prevalence than expected and, vice versa, a rare genetic change can be still just a "polymorphism" (Pearson et al. 2003). Therefore, based on the instructions of American College of Medical Genetics and Genomics (ACMG), the more appropriate term is "variant" and it can be classified as pathogenic (class 5), likely pathogenic (class 4), variant with uncertain significance (class 3), likely benign (class 2) and benign (class 1) (Richards et al. 2015). ACGM classification criteria include information from population databases (e.g. Exome Aggregation Consortium, Exome Variant Server, 1000 Genomes, dbSNP, dbVar), disease databases (e.g. ClinVar, OMIM, Human Gene Mutation Database, Human Genome Variation Society, DECIPHER), sequence databases (e.g. NCBI, RefSeqGene, Locus Reference Genomic, MitoMap), tools for *in silico* analyses (e.g. SIFT, MutationTaster, PolyPhen-2, PROVEAN, CADD, GeneSplicer, Human Splicing Finder, GERP, PhastCons, PhyloP), functional studies, segregation/*de novo* data and allelic data. Information from these databases and tools are sometimes not sufficient or not available and there are many variants classified as VUS (variant with uncertain significance). In this case, confirmation of a VUS variant in more families and/or more functional studies should be useful for resolving such classification uncertainty. Although Human Gene Mutation Database (HGMD) is considered to be central unified repository of mutations associated with human inherited diseases (Stenson et al. 2014) it should be used with caution. Functional studies of some *HNF1A* mutations revealed that they have very small impact on HNF1α protein function despite they were described by HGMD as MODY3 pathogenic variants. Even classification of variants to 5 classes is sometimes insufficient, e.g. the HNF1α E508K variant is considered as benign in relation to MODY3 but is linked with significantly fivefold increased risk of T2D (Najmi et al. 2017). In addition, Najmi et al. (2017) noticed that only 5 of 11 *HNF1A* variants impairing protein function were scored as damaging by *in silico* prediction tools.

Functional studies

***In vitro* studies.** Several functional *in vitro* studies are used for researching whether certain *HNF1A* gene mutation has a pathogenic effect to the protein function. Since HNF1α is a transcription factor, these methods include in particular assays analyzing protein nuclear localization, dimerization, DNA-binding, and transactivation activity. To study the subcellular localization, an immunofluorescence assay with a wild type and a mutated protein can be performed (Bjorkhaug et al. 2003). Altered protein dimerization due to weak HNF1α-cofactor bond can be studied by labelling of DCoH and protein purifying as well as crystallography shows if the HNF1α forms real dimer or just a monomer structure (Rose et al. 2000a). To determine the effect of a mutation to HNF1α DNA-binding ability, Electrophoretic Mobility Shift Assay (EMSA) can be beneficial. This method can outline also whether the protein binds to DNA as monomer or dimer. *HNF1A* promoter and transactivation activity is studied mostly by the luciferase assay. The expression levels of *HNF1A* in different type of tissues can be measured by isolation of mRNA from the target tissue and subsequently reverse transcription (RT) and quantitative (q) PCR as was done by Harries et al. (2006). With the same method may be confirmed molecular mechanism of pathologic effect of splicing, nonsense and frameshift mutations. With an example of a frameshift mutation c.872dupC, qPCR shown the degradation of such mRNAs with premature STOP codons by nonsense-mediated decay.

***In vivo* studies.** All causal genes responsible for monogenic diabetes phenotypes are expressed in the B-cells (Fajans et al. 2001; Shih and Stoffel 2001; Taneera et al. 2014). *In vivo* functional studies with human B-cells are limited. Diabetic and non-diabetic mice are widely used as models for functional studies since their genetic variability is the same as in the human populations (Wang et al. 2000). Neverthe-

less, there are differences between mouse and human phenotypes in the presence of the same genotype. *HNF1A* (+/–) mouse mutant reveals the same phenotype as the wild type (Lee et al. 1998; Boj et al. 2010). *HNF1A*–/– mutations are probably incompatible with human life since no homozygous *HNF1A* mutation has been reported yet. On the contrary, several studies with *HNF1A*–/– knockout mice were done. Lee et al. (1998) is one of the first study where non-insulin-dependent diabetes mellitus (NIDDM), Laron dwarfism, impaired liver development and dysfunctional reproductive system developed in *HNF1A* (–/–) mice within the time range of two weeks after birth (Lee et al. 1998). Hiraiwa et al. (2001) prepared *HNF1A*–/– mice deletant of exon 1 by *Cre-loxP* system. They discovered by Northern Blot analysis that the total number of glucose-6-phosphatase (G6Pase) mRNA in hepatocytes is higher in *HNF1A*–/– mice than in *HNF1A*+/– or *HNF1A*+/+ mice. This supports their hypothesis that high *G6Pase* expression leading to hepatic glucose overproduction can cause the hyperglycemia (Hiraiwa et al. 2001). Other studies discovered, that inactivation of mouse *HNF1A* gene by homologous recombination results in hepatic dysfunction, phenylketonuria and Fanconi syndrome (Pontoglio et al. 1996) as well as decreased expression of the genes encoding glucose transporter 2 (*Glut2)* and L-pyruvate kinase (*pklr*) (Parrizas et al. 2001). Phenotypic differences between human and mice with the same genotype may be explained by the higher expression of the *HNF1A* gene in rodents than in humans (Harries et al. 2009). This might result to higher tolerance of mice to *HNF1A* damaging and heterozygous mutations (Colclough et al. 2013).

Clinics of HNF1A-MODY

General, pathogenic *HNF1A* mutations are causing the clinical picture of early-onset diabetes and in several individuals diabetes manifests after phase of neonatal transient hyperinsulinemia hypoglycemia. Hyperinsulinemia can be caused by deregulation of the insulin secretion but is less frequent compared to *HNF4A* mutations (Dusatkova et al. 2011; Stanescu et al. 2012). During the childhood *HNF1A* mutation carriers are normoglycemic. However, they could have presence of glucose in the urine (glycosuria) despite normoglycemia (Skupien et al. 2008; Colclough et al. 2013). Diabetes mellitus manifests usually at the age of 6–25 years with mild osmotic symptoms (polyuria, polydipsia) or as asymptomatic postprandial hyperglycemia without ketosis or ketoacidosis. C-peptide values are lower than in healthy individuals, but higher than for T1D. Fasting glucose is normal at the onset of disease, but there is a marked increase in the oral glucose tolerance test (oGTT) of 2-h glucose versus baseline (>5 mmol/l). Insulin deficiency is progressive, and blood glucose increases gradually with age (0.06 mmol/l/year), with some patients experiencing a higher insulin secretion failure (a decrease in C-peptide concentrations at the limit of measurability) (Stride et al. 2002). In individuals with an inappropriate treatment and poor collaboration, ketoacidosis could develop over the time (Nyunt et al. 2009; Pruhova et al. 2013). Chronic microvascular complications are common in individuals with poor diabetes control. The incidence of the chronic microvascular complications is only slightly lower than in T1D and T2D – retinopathy has 47% of patients, 19% nephropathy and 4% neuropathy. Hypertension and ischemic heart disease are at the level of T1D, much rarer than in T2D, but more often than in healthy controls (Steele et al. 2010).

Clinical criteria of the HNF1A-MODY. Clinical suspicion on HNF1A-MODY is based on the clinical course of the disease. However, clinical features of HNF1A-MODY are variable not just from one family to another but also within the family (Bellanne-Chantelot et al. 2008; Corrales et al. 2010; Colclough et al. 2013) and that complicates the diagnostic process. To simplify the assessment of patients' clinical features, several approaches could be used. The first of them are the clinical diagnostic criteria (Ellard et al. 2008) which help diabetologists to discriminate patients with HNF1A-MODY from other forms of diabetes:

- Onset of diabetes usually before 25 years (at least one family member).
- Non-insulin-dependent outside the honeymoon phase. The honeymoon period was defined as a period with insulin requirements of less than 0.5 U/kg/day and hemoglobin A1c (HbA1c) level of less or equal to 6% (Abdul-Rasoul et al. 2006).
- Family history of diabetes in at least two generations and at least two family members diagnosed in their 20s or 30s, the grandparents often diagnosed after their 45s. They could be diagnosed as T1D or T2D mellitus.
- The absence of pancreatic islet antibodies.
- Glycosuria at blood glucose levels <10 mmol/l.
- Sensitivity to sulfonylureas (Pearson et al. 2000).
- Several features discriminating HNF1A-MODY from young-onset T2D like no evidence of obesity, insulin resistance or *acanthosis nigricans* skin disease in family members and other.

Disease onset. While MODY penetration of patients up to 25 years is approximately 63%, it is increased to 93.6% in patients up to 50 years and 98.7% among patients up to 75 years (Pearson et al. 2003). It was observed, that mutations in different *HNF1A* gene isoforms may influence the age of disease onset. Patients with *HNF1A* mutations in exons 8–10 (affecting only isoform A) have later onset MODY3 phenotype than patients with the mutations in exons 1–6 (affecting isoforms A, B and C). Patients carrying missense mutations affecting the transactivation domain have later onset as those with truncating mutations or with missense mutations in the dimerization/DBD domain. On the other hand, when comparing missense and truncating mutations within dimerization/DBD domain, there is no influence of onset (Vaxillaire et al. 1999; Harries et al. 2006; Bellanne-Chantelot et al. 2008; Awa et al. 2011; Colclough et al. 2013). In the study of 362 MODY family members, the correlation between the MODY3 onset of child and its exposure to maternal MODY3 diabetes *in utero* was significant. In case that maternal HNF1A-MODY was diagnosed before the pregnancy, HNF1A-MODY onset of a child was at younger age (Stride et al. 2002). Family predisposition to obesity or patients´ physical activity may have an additional effect on insulin sensitivity, secretion or demand. Furthermore, MODY3 patients who inherited *HNF1A* mutation from mother and were exposed to diabetes in utero have earlier disease onset than those who were not. In agreement with this, approximately 50% carriers of *HNF1A* mutation from father have MODY3 onset after age of 25 years (Klupa et al. 2002). *HNF1A de novo* mutations are less frequent (approximately 7% of all HNF1A-MODY patients) (Stanik et al. 2014).

Beyond the clinical criteria. A big clinical variability of monogenic diabetes considerably complicates the selection of patients for genetic testing. MODY is primarily nonketotic and non-autoimmunity form of diabetes (Fajans et al. 2001), however, in some individuals with HNF1A-MODY positive B-cell autoantibodies and diabetes ketoacidosis were described (Pruhova et al. 2013; Lebenthal et al. 2018). The absence of GAD-65 and IA-2 autoantibodies has been proposed as a discriminator between MODY and T1D as the presence of one antibody was established with the 99% sensitivity and 82% specificity for T1D (McDonald et al. 2011a). Positive pancreatic autoantibodies have been found in several MODY cohorts: 1% of MODY individual tested positive for autoantibodies in British cohort (McDonald et al. 2011a), 17% in German/Austrian cohort (Schober et al. 2009) and 28%, in Czech cohort (Urbanova et al. 2014). Moreover, in two studies, different levels of islet cell autoantibodies were observed in HNF1A-MODY patients (Urbanova et al. 2014; Lebenthal et al. 2018).

MODY calculator was developed to estimate the likelihood of monogenic diabetes for individuals with onset of diabetes before 35 years (Shields et al. 2012). Although calculator does not distinct between the different forms of monogenic diabetes, this method is very useful for the selection of diabetes patients for genetic testing (Kherra et al. 2017).

Role of the biomarkers in the diagnostic process. Several biomarkers for HNF1A-MODY have been considered to support the selection of patients for the genetic testing. Most of the biomarkers are disease specific, i.e. could discriminate HNF1A-MODY from only one other type of diabetes. For example, apolipoprotein M has been suggested as a discriminator between HNF1A-MODY and T1D, but not T2D (Mughal et al. 2013).

Next, significantly higher ghrelin concentration was measured in HNF1A-MODY and GCK-MODY patients compared to diabetics with T1D or T2D. Ghrelin is a peptide hormone which regulates appetite control and it is encoded by the *GHRL* gene. HNF1α interacts with the *GHRL* promoter and suppresses its expression. Despite that it was confirmed also by an animal studies, ghrelin is not sufficient discriminator of diabetes subtypes (Nakazato et al. 2001; Lussier et al. 2010; Brial et al. 2013; Nowak et al. 2015).

HDL-cholesterol could discriminate between HNF1A-MODY and T2D since HNF1A-MODY patients have higher levels of HDL. Despite of that, HNF1A-MODY patients have similar lipid constituents of HDL and plasma-lipid profiles as people without diabetes (McDonald et al. 2012). It was observed that also colonic microbiome composition differs among patients with HNF1A-MODY, T2D, and the control group (Mrozinska et al. 2016).

Cystain C was also studied as a biomarker for HNF1A-MODY but it was shown that this is not a good candidate (Nowak et al. 2013).

One discriminator between MODY and T1D is measurable C-peptide level in MODY patients. However, C-peptide may be detectable in early T1D, and even in 8% of patients with long-duration T1D what makes the separation of MODY from T1D more difficult. (Oram et al. 2014).

Human acute phase C-reactive protein (CRP) seems to be the best biomarker for HNF1A-MODY so far. Expression of CRP is regulated in the liver by the HNF1α transcription factor. This attribute of CRP is commonly used for detection of infection and

inflammation since its expression rises during that time (Pepys and Hirschfield 2003; Armendariz and Krauss 2009). High-sensitivity CRP (hs-CRP) is an assay for detection of small variations in low CRP levels (Soeki and Sata 2016). Several studies have confirmed that hs-CRP levels were significantly lower in patients with HNF1A-MODY than in patients with HNF4A-MODY, GCK-MODY, T2D and T1D or without diabetes (Bacon et al. 2013; Owen et al. 2010; McDonald et al. 2011b; Thanabalasingham et al. 2011; Shah et al. 2014).

Some researchers claim that hs-CRP is not useful for distinguishing HNF1A-MODY from (familial) young-onset T2D (Ley et al. 2010; Bellanne-Chantelot et al. 2016; Majidi et al. 2018). Another limitation of hs-CRP are high CRP levels during the infection (Owen et al. 2014). On the other hand, statin therapy, which is widely used for decreasing the level of total or LDL-cholesterol in T2D, decreases also the CRP levels (Albert et al. 2001). In addition, data from independent studies, Pharmacogenomics and Risk of Cardiovascular Disease (PARC) and Cardiovascular Health Study (CHS), pointed out to correlation of plasma CRP concentration and *HNF1A* common gene variants. SNPs rs1169288 (I27L), rs1169286 (c.326+2159T>C), rs2464196 (S486N), rs1169303 (c.1502-695A>C) and rs1169310 (c.*438G>A) were significantly associated with lower plasma CRP levels (Reiner et al. 2008). hs-CRP has a big potential to be a cost-effective and helpful biomarker for selecting of HNF1A-MODY patients (Szopa et al. 2019).

Another biomarker considered for HNF1A-MODY is miRNA-244 – biomarker for B-cell demise (Bacon et al. 2015). It was found, that miRNA-103 is consistently deregulated in pancreatic and adipose tissue and in serum of patients with T2D (Zhu and Leung 2015). In the study Bonner et al. (2013), miRNA-103 and miRNA-244 serum levels were measured in patients with HNF1A-MODY and their MODY-negative family members as well as T2D patients. They have detected higher levels of miRNA-103 and miRNA-244 in serum of HNF1A-MODY patients compared with their MODY-negative family members. Increased levels of serum miRNA-103 may distinguish HNF1A-MODY carriers from T2D patients selected by their HbA1c-levels. miRNA array showed overexpression of miRNA-103, miRNA-244 and miRNA-292-3p also in rat INS-1 cells carrying Pro291fsinsC HNF1A mutation (Bonner et al. 2013). However, all of the biomarkers need to be verified in large studies and need to be combined with clinical diagnostic features to make the diagnostic process of HNF1A-MODY more effective.

Epidemiology. HNF1A-MODY is the most common disease in the group of MODY-type diabetes, and is the most common type of the monogenic diabetes in several countries. The certain proportion of HNF1A-MODY among all MODY patients depends on the country. In the Scandinavian countries and Great Britain, HNF1A-MODY is the most common type of monogenic diabetes, while in the Southern Europe, less than 15% of MODY patients have HNF1A-MODY (Eide et al. 2008; Borowiec et al. 2012). These proportion variations may be related to geographical location but also to patient search system. HNF1A-MODY is less common among children as the hyperglycemia usually manifests after 10th year of life. In Poland, where a system for identification of children with monogenic diabetes was developed, HNF1A-MODY accounts for less than 15% of all MODY patients (Borowiec et al. 2012). A similar situation is in Slovakia and the Czech Republic (Pruhova et al. 2010). In contrast, in the Scandinavian countries and Great Britain, the DNA analysis for MODY is performed particularly in adults or children treated with low insulin doses.

Therapeutic consequences of the genetically confirmed HNF1A-MODY. Treatment of the HNF1A-MODY depends on the age and HbA1c levels. In case of HbA1c below 6.5% (DCCT), diet without saccharides excess may be temporarily successful. Since the rise of HbA1c, sulfonylurea derivatives may be the useful treatment (Shepherd et al. 2009). Patients with HNF1A-MODY are sensitive to sulfonylureas because of its reduced hepatic degradation (Pearson et al. 2000). This results in higher sulfonylurea plasma levels and longer plasma persistence; thus, low doses of short-acting sulfonylureas are sufficient (Pearson et al. 2000). Several patients were successfully switched from insulin therapy to sulfonylureas (Shepherd et al. 2003, 2009). Compared to insulin treatment, sulfonylurea derivatives increase endogenous insulin secretion, which allows the body to respond spontaneously to glycemic changes (Shepherd et al. 2009). Glycemia is so more stable and diabetes compensation is also improved (Pearson et al. 2000). In sulfonylurea treatment, low doses should be initiated for the possible occurrence of post-initiation hypoglycemia. Even in patients initially treated with insulin, treatment may be successfully changed to sulfonylureas getting better diabetes control (Bazalova et al. 2010). However, confirmation of the HNF1A-MODY by DNA analysis prior the therapy change is required. This treatment is usually effective for several decades, but in a case of severe decrease in B-cell insulin production,

it may be necessary to switch back to insulin treatment in some patients.

Conclusions

Pathogenic mutations located within *HNF1A* gene are one of the most common causes of monogenic diabetes. Improper classification of HNF1A-MODY patients as T1D or T2D diabetics based on their clinical manifestation can leads to improper treatment. Bad compensation of HNF1A-MODY may cause microvascular complications. DNA analysis still remains the only way how to definitely confirm the suspicion of HNF1A-MODY. Decision whether the variant is pathogenic or benign is the latest challenge of clinical scientists and doctors. Identification of *HNF1A* pathogenic variants is highly important not only in terms of a treatment but particularly for determination of genetic risk for descendants of HNF1A-MODY patients.

In Slovakia, the DNA diagnostics of *HNF1A* gene is available in the DIABGENE Laboratory (diabgene@savba.sk; www.diabgene.sk).

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