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Editorial

Type 2 Diabetes and More Gene Panel: A Predictive Genomics Approach for a Polygenic Disease

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Type 2 diabetes (T2D) is the leading cause of morbidity and mortality worldwide, and its incidence has increased by 50% in the past ten years. T2D consists of a series of impairments such as insulin resistance, insufficient insulin secretion, and dysregulated glucagon secretion; the combination of these factors leads to hyperglycemia. The disease is one of the world's oldest, being described in the historical records of ancient Egypt, Persia and India. T2D is an endemic metabolic syndrome with a higher prevalence in the Eastern Mediterranean Region, South-Eastern Asia, and the Arabian Peninsula. It has been observed that the Persian Gulf states have a higher prevalence than other Middle Eastern countries. This suggests that Arabs are at higher risk of developing T2D than other ethnicities.

Advances in the field of molecular genetics and genomics have boosted our knowledge of the genetic factors involved in this polygenic disease. Predictive genomics combines multiple fields, such as predictive and personalized medicine, genomics, and bioinformatics. It is a new discipline that deals with the imminent phenotypic outcomes of complex human diseases, such as T2D, and its complications. However, phenotypes can be influenced or significantly altered by environmental and nutritional factors, especially if detected or predicted early. Thus, predictive genetic profiling of susceptible individuals can help to reduce or reverse the pattern of diabetes and its complications. Predictive nutrigenomics can also help since it has the potential to modify the inflammatory response, antioxidant ability, antioxidant protection, detoxification ability, and several biological processes involved in T2D development and progress.

Recently, we designed and evaluated the Arab Diabetes Gene-Centric Array (ADGCA) that contains 643,745 SNPs including 50,617 diabetes associated SNPs. This array might serve for screening and predicting the incidence of T2D among susceptible individuals. However, genotyping methods are relatively old-fashioned and have several disadvantages. This was the reason for me to propose the "T2D and more gene panel" that target all exons, intron-exon boundaries, and UTRs of the genes involved in the pathophysiology of T2D, its complications and even the monogenic forms of diabetes.

Gene panels have several advantages that make them a better choice over genotyping arrays or even all exome sequencing. They have a deeper focus on all genes and gene regions associated with a specific disease. They allow a much higher sequencing depth, 2,000 - 10,000x, that enables the identification of novel and rare genetic variants. Also, they allow dealing with different types of samples with varying concentrations of DNA and conditions. They can contain all parts of the genes, both structural and regulatory regions, or selected important regions of the genes of interest. Additionally, gene panel workflows are more straightforward, less time consuming, and can easily be pooled and multiplexed; most importantly, they are reasonably less expensive than other genetic screening methods. Furthermore, in a population with a high T2D prevalence, it is better to design a panel than to perform the very costly whole exome sequencing. My extensive personal investigation of all genes involved in T2D lead me to classify these genes according to their ontology (Figure 1) as follows:

1) Lipid metabolism and lipid binding.
2) Glucose metabolism, transport, and binding.
3) Inflammatory response.
4) Immune response.
5) ATP binding and ion transport.
6) Signal transduction.
7) Angiotensin I converting process.
8) Neurological process.
9) β-cell related effects.
10) Oxidative stress.
11) DNA binding.
12) Protein binding.

13) Hormone-mediated processes.
14) Protein (amino acid) metabolism.
15) Insulin-like growth factor.
16) Transcription regulation process.
17) Insulin transcription, secretion, and binding.
18) General metabolism.
19) Others.

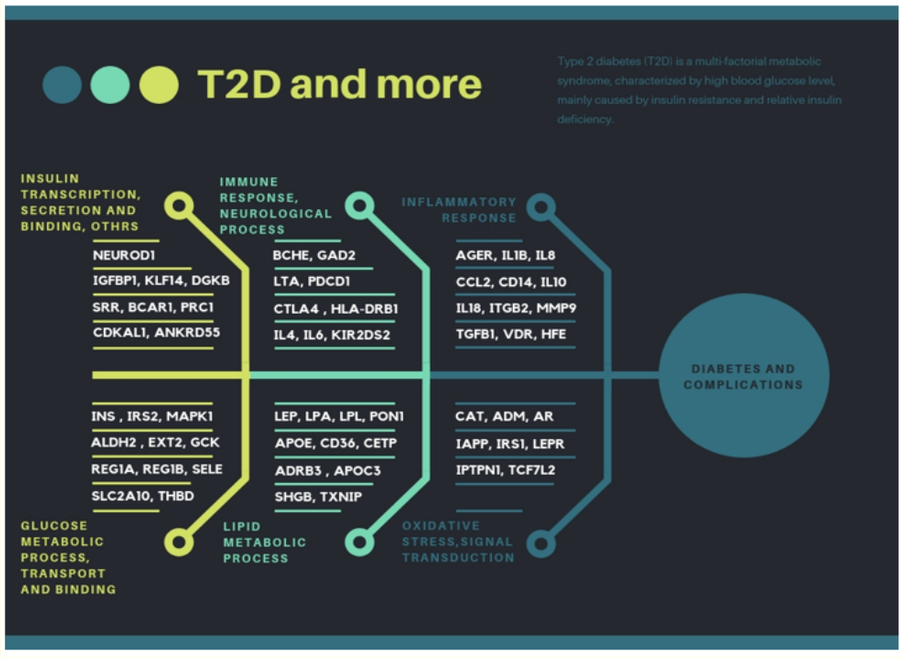

Figure 1: *Fishbone diagram showing some of the genes associated with T2D, classified according to their ontology.*

My suggested panel consists of 148 target genes with 4220 amplicons and target amplification size of 1.1 Mb (Table 1 and Supplementary Table 1). The data show that the target size is relatively high, this can be justified because T2D is a polygenic disease. The suggested gene panel will aid identifying T2D biologically relevant genetic variants, visualizing the impact of identified variants on the disease, and detecting both known and novel gene mutations (SNPs, indels, and CNVs).

Table 1: *Genetic description of "T2D and more" gene panel.*

Name	Chromosome	Number of Amplicons	Overall Coverage	Exon number
PTGS2	chr1	31	1	10
TXNIP	chr1	16	1	8
SELE	chr1	32	1	14
CRP	chr1	10	1	2
IL10	chr1	11	0.857	5
PTPRC	chr1	71	0.968	35
LEPR	chr1	59	0.997	24
MTHFR	chr1	48	0.985	12
PBX1	chr1	37	0.966	10
PROX1	chr1	38	0.952	6
NOTCH2	chr1	84	1	35
CAMTA1	chr1	70	1	26
PDE4B	chr1	40	0.992	20
CXCL12	chr10	29	1	9
TCF7L2	chr10	39	1	20
GAD2	chr10	33	0.997	18

HHEX	chr10	12	0.936	4
ZMIZ1	chr10	63	0.949	25
VPS26A	chr10	22	0.988	9
CDC123	chr10	22	1	13
CAMK1D	chr10	26	0.976	12
NEUROG3	chr10	7	0.987	2
APOC3	chr11	6	1	4
EXT2	chr11	36	0.998	17
INS	chr11	5	0.726	5
IL18	chr11	13	0.842	6
ABCC8	chr11	65	0.961	40
KCNJ11	chr11	16	0.907	3
KCNQ1	chr11	38	0.969	17
ADM	chr11	13	1	4
CAT	chr11	26	1	13
MTNR1B	chr11	11	0.99	2
ARAP1	chr11	65	0.973	36
CYP27B1	chr12	17	0.995	9
ALDH2	chr12	27	1	13
VDR	chr12	35	0.998	12
IAPP	chr12	12	0.984	3
TSPAN8	chr12	13	1	9
LGR5	chr12	37	0.996	18
HMGA2	chr12	25	0.998	6
CCND2	chr12	30	1	5
HIGD1C	chr12	4	1	3
IRS2	chr13	27	0.86	2
SPRY2	chr13	11	1	2
KCTD12	chr13	26	0.998	1
PRC1	chr15	30	0.998	16
AP3S2	chr15	31	0.99	8
ZFAND6	chr15	23	0.903	15
HMG20A	chr15	29	0.998	11
C2CD4A	chr15	14	0.802	2
CCDC33	chr15	42	0.978	24
CETP	chr16	25	0.984	16
FTO	chr16	28	0.996	9
PRKCB	chr16	50	0.958	18
BCAR1	chr16	43	0.985	17
SLC12A3	chr16	55	0.978	28
MIR6863	chr16	2	1	1
ABP	chr17	17	0.966	15
CCL2	chr17	7	1	3
CCL5	chr17	6	0.748	4
ACE	chr17	52	0.991	26
HNF1B	chr17	22	0.996	10
SRR	chr17	19	0.999	8
RAI1	chr17	41	0.905	6

SREBF1	chr17	42	0.979	20
MC4R	chr18	6	1	1
APOE	chr19	11	0.997	4
TGFB1	chr19	18	0.898	7
CD158B2	chr19	16	1	8
AKT2	chr19	42	0.972	15
GIPR	chr19	24	0.986	14
IL1RN	chr2	17	1	8
REG1A	chr2	11	1	6
REG1B	chr2	10	1	6
IL1B	chr2	14	1	7
CTLA4	chr2	11	1	4
PDCD1	chr2	17	0.99	5
IRS1	chr2	36	0.984	2
CAPN10	chr2	28	0.943	12
NEUROD1	chr2	14	1	2
GRB14	chr2	23	0.889	14
RBMS1	chr2	32	1	15
BCL11A	chr2	35	1	7
THADA	chr2	75	0.99	42
GCKR	chr2	27	0.99	19
CXCR4	chr2	10	1	3
HNF4A	chr20	37	0.998	15
SLC2A10	chr20	23	0.977	5
THBD	chr20	17	1	1
MMP9	chr20	22	0.968	13
PTPN1	chr20	26	1	10
TRIB3	chr20	15	0.953	4
ITGB2	chr21	35	0.993	17
MAPK1	chr22	33	0.996	10
SREBF2	chr22	49	0.987	22
PPARG	chr3	20	0.975	10
BCHE	chr3	14	1	4
GHRL	chr3	12	1	11
IGF2BP2	chr3	36	0.972	16
ADCY5	chr3	56	0.995	22
ADAMTS9	chr3	73	0.993	40
UBE2E2	chr3	15	1	6
IL8	chr4	13	1	4
WFS1	chr4	27	0.971	9
MAEA	chr4	23	1	9
CD14	chr5	11	0.987	6
IL13	chr5	10	1	4
IL4	chr5	7	1	4
AHH	chr5	37	0.989	12
ANKRD55	chr5	23	0.999	12
LPA	chr6	56	0.672	40
TNF	chr6	12	1	4

AGER	chr6	14	0.993	18
HFE	chr6	14	0.955	8
HLA-DRB1	chr6	13	0.895	8
LTA	chr6	10	0.918	5
KCNK16	chr6	14	1	8
ZFAND3	chr6	18	0.884	6
CDKAL1	chr6	34	0.932	16
ENPP1	chr6	59	0.996	25
SUMO4	chr6	5	1	1
CD36	chr7	43	0.993	22
LEP	chr7	18	0.995	3
PON1	chr7	18	0.994	9
GCK	chr7	29	0.965	12
IL6	chr7	10	0.969	5
NOS3	chr7	52	0.991	31
NPY	chr7	8	1	4
CDK5	chr7	15	1	13
IGFBP1	chr7	12	0.971	4
SERPINE1	chr7	26	1	9
JAZF1	chr7	16	0.893	5
KLF14	chr7	6	0.749	1
DGKB	chr7	64	0.992	26
ELMO1	chr7	57	1	26
ADRB3	chr8	14	0.993	2
LPL	chr8	29	1	10
SLC30A8	chr8	38	0.976	16
TP53INP1	chr8	26	0.971	5
ANK1	chr8	91	0.976	48
TLE1	chr9	39	1	20
TLE4	chr9	52	0.997	24
CDKN2A	chr9	15	0.981	6
CDKN2B	chr9	18	1	3
PTPRD	chr9	97	0.987	50
GLIS3	chr9	45	0.996	12
AR	chrX	51	1	9
ACE2	chrX	39	1	19

There is no doubt that T2D is an important and costly disease in all aspects, both altruistic and materialistic. Globally, countries spend 825 billion of dollars per year in diabetes, with the most significant contributors being China ($170 billion), the USA ($105 billion), and India ($73 billion). Additionally, if existing trends remain, over 700 million adults worldwide will be affected by diabetes in 2025. Every scientist, expert, and physician no matter their locations should put as more effort as they can in combating this disease. Here, I present a proposal for a gene panel that can be used for predicting and screening T2D and its complications by interested parties worldwide. And even though I cannot implement it myself because of funding and logistic reasons, I am willing to help any interested party providing all the technical details they might need to implement it and help alleviate this hideous illness and its complications.

Supplementary Table

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