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¹⁴ **ABSTRACT**

Type 2 Diabetes (T2D) is a metabolic disorder caused (Butler, Janson and Bonner-Weir) due to development of insensitivity of insulin (Butler, Janson and Bonner-Weir) and loss of β -cell functioning (Butler, Janson and Bonner-Weir) (Iqra Hameed) (Vito.) (Rorsmam.). ¹¹ Evidence suggests that exposure to bisphenol-A (BPA) may contribute in the development and progression of type 2 diabetes. Thus, this study integrates bioinformatics and machine learning approaches to identify key genes and pathways involved linking BPA with T2DM. Datasets related to T2D were retrieved from GEO, which were then pre-processed, normalized and batch corrected. DEG analysis was then done to identify the up and down regulating genes. Following of which ²⁵ the data was split into training and test set. BPA related genes were then retrieved from database comparative toxicogenomics database, ³ swiss target prediction and STITCH. While, disease related genes were retrieved from GeneCards, MalaCards and OMIM. Results from these were then overlapped to identify hub genes which were assessed using machine learning approaches RF, SVM and LASSO to identify potential candidate biomarkers. Next, ROC curve analysis was done on the genes i.e ABCG1, AMPD2 and HBA2. This integrated approach also did pathway enrichment of the potential diagnostic biomarkers which highlighted pathways related to metabolic regulation, mitochondrial function and inflammatory responses. Lastly, ⁶ molecular docking was used for assessing the binding interaction occurring between BPA and ABCG1, AMPD2 and HBA2 which yielded a binding affinity of -7.4, -8.1 and - 8.1 kcal/mol respectively. Overall this study helped in identifying a potential link between BPA and T2DM and in identifying the potential candidates that may contribute progression of disease.

Keywords: Type 2 Diabetes, Bisphenol-A, DEG, Machine Learning, Molecular Docking.

2 INTRODUCTION

Type 2 Diabetes (T2D) is a metabolic disorder caused (Butler, Janson and Bonner-Weir) due to development of insensitivity of insulin (Unai Galicia-Garcia) (Butler, Janson and Bonner-Weir) and loss of β -cell functioning (Unai Galicia-Garcia) (Butler, Janson and Bonner-Weir) (Iqra Hameed) (Vito.) (Rorsmam.). Hyperglycaemia, dyslipidaemia, low-grade inflammation (Anne M Minihane), and up to some extent gut microbial dysbiosis (Patricia M. Bock) ¹² play a role in development of type 2 diabetes (Vito.). All these factors contribute to the loss of beta cell functionality and ²⁷ development of insulin resistance, the major hallmarks of type 2 diabetes (Vito.). As discussed before, hyperglycaemia induces insensitivity to insulin and β cell dysfunction (Vito.), as they progress further, they fuel hyperglycaemia further ultimately promoting type 2 diabetes, therefore forming a vicious cycle (Cerf.).

²⁰ Bisphenol A (BPA) a prominent EDC is found in various sources like epoxy resins, lining of food cans, recycled paper and coatings of CD and DVD (Rubin.) (La-or Chailurkit). Since it is used in food packaging and in other day to day products, significant amount of human exposure occurs through the oral route (Francesca Farrugia). BPA acts as a xenoestrogen and binds to the extranuclear receptors ER α and Er β (A. B. Paloma Alonso-Magdalena) (Sergi Soriano). The class of xenoestrogens are also known as foreign estrogens (Xiaoqiang Wang) due to the fact that they exhibit estrogen like behaviour and despite being produced exogenously i.e outside the body (Xiaoqiang Wang). By behaviour we mean that xenoestrogen attaches itself to the extranuclear receptors and govern the expression of associated genes (Xiaoqiang Wang). Apart from activating ER α and Er β (Xiaoqiang Wang).. Xenoestrogen can also stimulate the membrane bound ER (GPER/GPR30) (Pelin Yaşar) (Xiaoqiang Wang). Through literature study it was identified that BPA induced stimulation of GPR30 allows for more activation of the ERK signalling pathways (Wolfgang Völkel) (Dong.). BPA has also been found to suppress production and release of adiponectin, which leads to low level of adiponectin in the body (Francesca Farrugia).

Pregnancy is often associated with gestational diabetes as the body fails to produce adequate amounts of insulin to counter shield insulin resistance (E. V. Paloma Alonso-Magdalena) (M. G.-A. Paloma Alonso-Magdalena). Glucose stimulated insulin secretion or GSIS serves a prominent role by keeping a check on glucose levels in the body (Sergi Soriano). By exhibiting estrogen like behaviour, BPA acts on Era (A. B. Paloma Alonso-Magdalena) to altering insulin levels and enhancing GSIS activity (Vito.). Mouse model studies further highlighted that (Vito.) BPA induced altered glycaemic response and hyperinsulinemia state along with increasing levels of circulating insulin, a characteristic trait of insulin resistance (Tetsuya Adachi). This ultimately leads to metabolic complications which ²²also increases the risk of Type 2 diabetes (Vito.). This work focuses on linking BPA exposure to T2D, and in pinpointing the exact elements or factors at play and outline the emerging mechanisms involved (Francesca Farrugia).

LITERATURE REVIEW

Arguably one of the most widely used industrial synthetic chemical compounds in the world, bisphenol A (BPA) present in epoxy resins (Harner.). Such products are applied as packaging material for food, reusable drinking containers, liners of canned foods, medical devices, thermally printed invoices (Maria K. Björnsdotter), and a number of other household items. Because of such extensive applications and constant discharges into the environment, BPA contamination of the human population has been considered inevitable. Scientific interest in possible adverse health consequences of BPA has been increasing steadily during the last decades due to its endocrine disruption capabilities and association with chronic diseases, especially T2DM. It is a disorder with a complex set of characteristics that include insulin resistance, insulin dysfunction, hyperglycemia, inflammation, oxidative stress, and disorders of lipid metabolism (Unai Galicia-Garcia). Yet recently it has become evident that environmental toxins, among which BPA can be singled out as an example of endocrine disrupting compounds (EDCs), can also serve as significant contributors to diabetes development (Sargis.). First scientific reports showed the harmful influence of BPA on hormonal communication, reproduction, and development (Winn.). But later scientists found out that the negative impact of BPA is much wider – it can greatly change metabolic processes, related to glucose homeostasis and insulin activity. That is why BPA was referred to as a “metabolic disruptor.” (Soheila Rahmani)

One of the first significant epidemiological studies on BPA, was carried out research on NHANES data for the US population (Iain A. Lang). The authors proved that high levels of BPA in urine were significantly related to diabetes, heart diseases, and altered hepatic enzymes (Iain A. Lang). Such research drew much scientific interest because it showed ²³the link between BPA exposure and chronic metabolic diseases at the population level (Iain A. Lang). After such study, several other epidemiological works published around the world supported similar results. Song et al., analyzing NHANES data, found a high correlation between increased BPA content in urine and prevalence of type 2 diabetes mellitus among adults. Similar results were obtained from studies conducted in Chinese, Korean, Japanese, and even European populations. Further meta-analyses have corroborated

these observations. In their systematic review and meta-analysis, researchers analysed epidemiological evidence associating exposure to BPA with cardiometabolic diseases (Fanny Rancière). The authors noted a consistent ¹⁷relationship between BPA exposure and a greater likelihood of developing obesity, insulin resistance, and T2DM (Fanny Rancière). Another meta-analysis was done of cross-sectional and prospective studies which revealed a positive correlation between BPA exposure and T2DM development (Semi Hwang). Despite some conflicting reports related to exposure evaluation methodology, population type, study size, and potential confounders, most evidence indicated a strong association between BPA exposure and metabolic problems (Semi Hwang).

Additional support for this relationship's biological plausibility came from research carried on animals. Since exposure to ⁶endocrine-disrupting substances in the environment during pregnancy and children may cause metabolic problems later in life, the significance of this issue has grown. (Jie Wei). In addition, there is evidence that BPA exposure affects the physiology of pancreatic β cells (S. M. Paloma Alonso-Magdalena). Insulin production and secretion from β cells are necessary to maintain glucose balance in the body (S. M. Paloma Alonso-Magdalena). Although acute exposure to BPA stimulates these β cells, prolonged one causes their exhaustion and dysfunction (S. M. Paloma Alonso-Magdalena). Some researchers demonstrated that BPA exposure can affect β cell Ca^{2+} signalling, cause an increase in oxidative stress and lead to apoptosis. It should be noted that ¹⁶ β cell dysfunction is a hallmark feature of type 2 diabetes development (Francesca Farrugia). The second mechanism through which BPA may induce T2DM is insulin resistance (Francesca Farrugia). This refers to the phenomenon where the ability of target tissues like muscle, liver, and fat tissues to respond to insulin becomes compromised (Francesca Farrugia). Obesity is yet another crucial biological connection between exposure to BPA and T2DM. Exposure to BPA is known to cause obesity owing to its function as obesogen, which means its ability to promote adipogenesis and accumulation of lipids (Mónica García García). It has been proved that BPA exposure causes stimulation of preadipocyte differentiation into adipocytes through transcription factors like $\text{PPAR}\gamma$ and $\text{C/EBP}\alpha$ (Jonathan G Boucher). Formation of more adipocytes results in excess fat deposition, leading to obesity that further

leads to insulin resistance and risk for diabetes. Another study found that BPA increased adipogenesis via transcriptional regulation mechanisms (Jonathan G Boucher). Apart from adipogenesis, BPA exposure has also been shown to lead to changes in lipid metabolism (Jonathan G Boucher). Another paper claimed with their study that low levels of BPA exposure led to the induction of gene expression linked with fat synthesis and triacylglycerol accumulation in liver tissue in mice (Alice Marmugi). BPA-induced oxidative stress was also noted as yet another key factor responsible for metabolic disturbances. Elevated ROS levels affect the normal functioning of proteins, lipids, and nucleic acids, which results in metabolic imbalance (Rosaria Meli). Specifically, pancreatic β -cells appear to be highly susceptible to oxidative stress due to the poor enzymatic antioxidant capacity (Rosaria Meli) (Shehreen Amjad). Disruption of mitochondria function is another important characteristic of BPA-induced metabolic diseases (Y Lin). Mitochondria play an important role in energy metabolism, ATP synthesis, and control of cell's redox status (Y Lin). It was shown that BPA affects the mitochondrial membrane potential, mitochondrial oxidation, and mitochondrial biogenesis. Inflammation is one of the mechanisms thought to mediate BPA-induced T2DM development. It has been found that BPA upregulates inflammatory cascades like ²⁴ **NF- κ B and MAPK pathways** resulting in **induction of inflammation in** adipose tissue, liver, and pancreas (Xu Hong). This chronic inflammation further affects the insulin signalling cascade. There has also been recent interest in the role of epigenetic regulation of BPA-related metabolic disorders (F. J.-B. Paloma Alonso-Magdalena) The dysregulation of miRNAs may have an effect on insulin pathways and β -cell survival, thereby aiding in the development of diabetes (Jin Hee Kim). There is great advancement by high throughput omics in terms of understanding metabolic disorders caused by BPA (Jin Hee Kim). Such pathways include insulin signalling pathways, inflammation pathways, oxidative stress response pathways, lipid metabolism pathways, apoptosis pathways and mitochondrial dysfunction pathways. Recent advancements in bioinformatics and systems biology have led to the identification of biomarkers related to BPA-induced T2DM through various computational approaches. WGCNA facilitates the recognition of interconnected genes and their role in regulatory modules and biological pathways, which help in developing the pathogenesis of a disease. Various genes and their roles in BPA related diabetes have

been recognized using WGCNA. Furthermore, advancements in machine learning have significantly improved biomarker discovery and prediction in the metabolic research related to BPA. These machine learning methods are currently being utilized on large transcriptomic data to find out the hub genes responsible for T2DM development. The combination of WGCNA with machine learning approaches provides more precise identification of biomarkers. Some genes that regulate mitochondrial dysfunction, inflammatory pathway, glucose homeostasis, and lipid metabolism have been proposed as hub genes.

MATERIALS & METHODS

¹ 3.1 Tools Used:

3.1.1 NCBI:

NCBI² s(Conrad L. Schoch) (<https://www.ncbi.nlm.nih.gov/>) houses a series of databases relevant to the field of biotechnology and biomedicine. Major databases include GenBank (Conrad L. Schoch), Gene, Nucleotide, Protein, dbSNP, PubMed etc. All these databases can be accessed through the Entrez search engine.

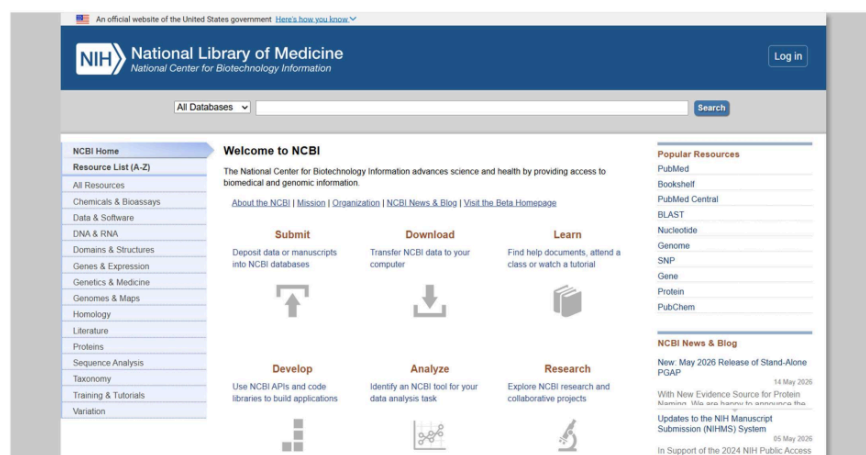


Figure 1: Homepage of NCBI

¹ 3.1.2 GEO:

GEO contains (<https://www.ncbi.nlm.nih.gov/geo/>) various types of high-throughput functional genomics data in its publicly accessible database (Tanya Barrett) (Ron Edgar). GEO was designed with the purpose of providing a strong (Tanya Barrett), extensible database in which high-throughput data can be effectively stored and users may easily query, identify, evaluate, and download studies and gene expression profiles of interest (Tanya Barrett) (Ron Edgar). This database enables accessing raw sequencing data from different experiments around the world, thus enabling using raw data from previous studies in subsequent analyses (Ron Edgar).

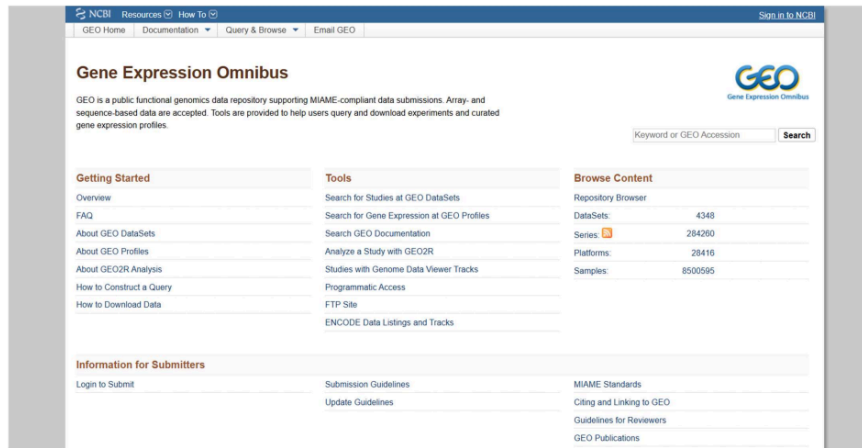


Figure 2: Homepage of GEO

3.1.3 GeneCards:

GeneCards (<https://www.genecards.org/>) currently versioned at 5.26 ³ is a user-friendly database that provides information on all annotated and predicted human genes (N. R.-G. Gil Stelzer). It houses data

on a total of 443,342 genes. The knowledgebase automatically incorporates multi omics level data gene-centric data from myriad number of sources (N. R.-G. Gil Stelzer).

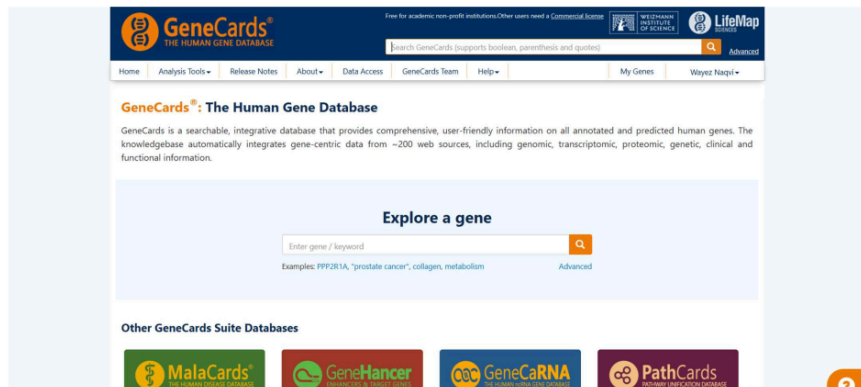


Figure 3: Homepage of GeneCards

3.1.4 MalaCards:

MalaCards (<https://www.malacards.org/>) with current version 5.26; houses information on a total of 22,560 disorders and 15,692 gene-related disorders (Noa Rappaport). It organizes disease-related information into global categories such as cancer, genetic, fetal, infectious, metabolic, and uncommon. It also categorizes disorders based on anatomical categories, such as cardiovascular, endocrine, neurological, and mental problems (Noa Rappaport).

3.1.5 OMIM:

OMIM stands for ¹⁵Online Mendelian Inheritance in Man (<https://www.omim.org/>) was developed for the World Wide Web by NCBI (Ada Hamosh). It is a publicly accessible database housing information human genes and genetic phenotypes (Ada Hamosh). ⁸OMIM focuses on the connection between phenotype and genotype. It is updated daily and has numerous links to other genetics sites (Ada Hamosh). Currently this database contains a total of 28,187 entries which can be accessed via the OMIM statistics which is the summation of genetic and phenotypic description. Additionally, within an OMIM entry are various other resources or subheadings like Clinical Synopsis and Synopsis of the Human Gene Map (Ada Hamosh).

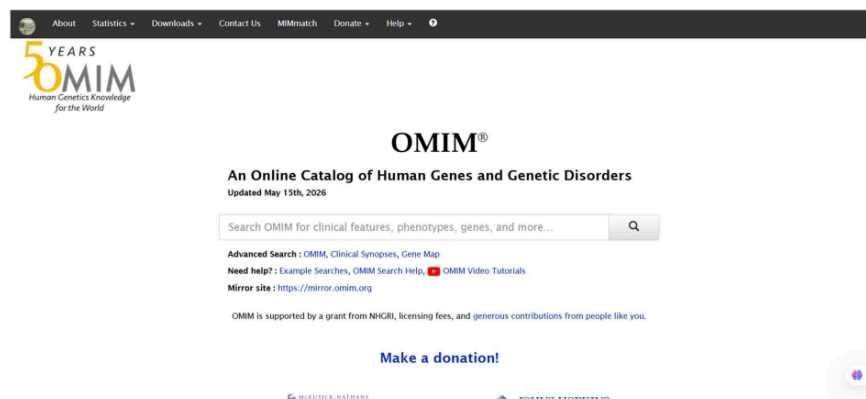


Figure 5: Homepage of OMIM

¹3.1.6 PubChem:

PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) is a freely available chemical database which houses information on a plethora of chemical compounds and how they react with the body (Sunghwan Kim).

This database curate's information related to a chemical from over a 750 data sources (Sunghwan Kim). One may obtain descriptive datasets and millions of complex structures at no cost. PubChem has tiny compounds with less than 1,000 bonds and 100 atoms, as well as several descriptions of substances. There are three dynamic databases within PubChem i.e Compounds, Substance and BioAssay. Substance database is publicly accessible repository which houses information on chemicals deposited by the user having about 293 million entries (Sunghwan Kim). Compound database is a slightly improved version of the Substance database as it contains only the unique, pure and characterized chemical structures extracted from Substance database, it has about 111 million entries (Sunghwan Kim). BioAssay database as the name implies stores information related to biological assays and tests. This database has about 1.25 million entries (Sunghwan Kim). With support for SMILES/SMARTS and InChI, PubChem has its own online molecule editor that lets users search for structures and fragments by importing and exporting files in all popular chemical file formats (Sunghwan Kim).

3.1.7 CTD:

CTD (<https://ctdbase.org/>) is a massive, open-access database dedicated to better understanding how environmental exposures influence human health (C. J. Allan Peter Davis). It provides information on chemical-gene/protein interactions (C. J. Allan Peter Davis), chemical-disease (C. J. Allan Peter Davis), and gene-disease linkages (C. J. Allan Peter Davis), which has been manually curated (C. J. Allan Peter Davis). ⁴ These data are combined with functional and pathway data to help researchers build theories about the mechanisms causing diseases that are influenced by the environment (C. J. Allan Peter Davis).

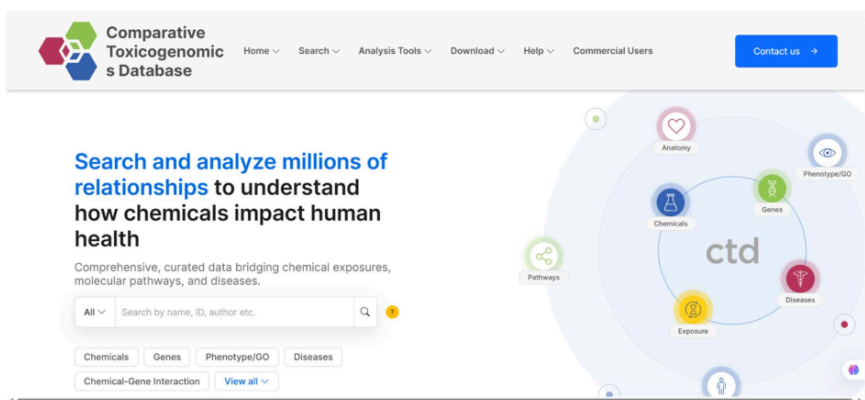


Figure 7: Homepage of Comparative Toxicogenomics Database (CTD)

3.1.8 STP:

STP is the abbreviation for ⁹Swiss Target Prediction (<http://www.swisstargetprediction.ch/>) a web-based tool for predicting ligand-based targets for bioactive small molecules (Antoine Daina).

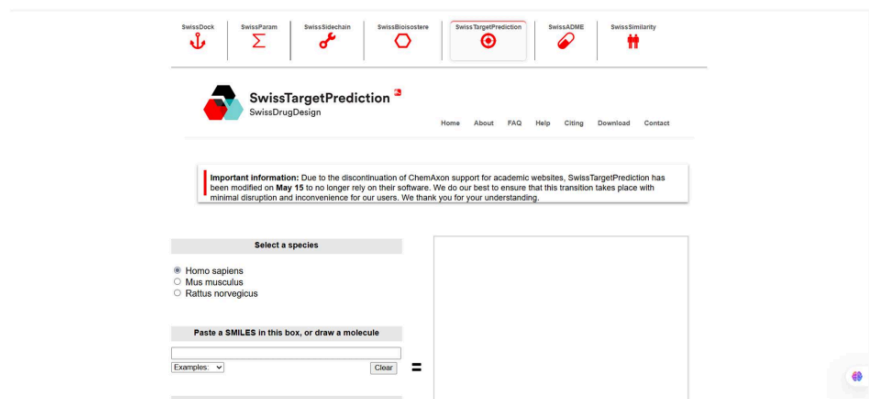


Figure 8: Homepage of Swiss Target Prediction Database

3.1.9 STITCH:

STITCH (<https://stitch-db.org/>) short for ²¹Search Tool for Interacting Chemicals is a database built exclusively for assessing and identifying all the interactions occurring ²⁸between proteins and small molecules. STITCH is the amalgamation of a myriad sources (Vivian Law). STITCH (Damian Szklarczyk).

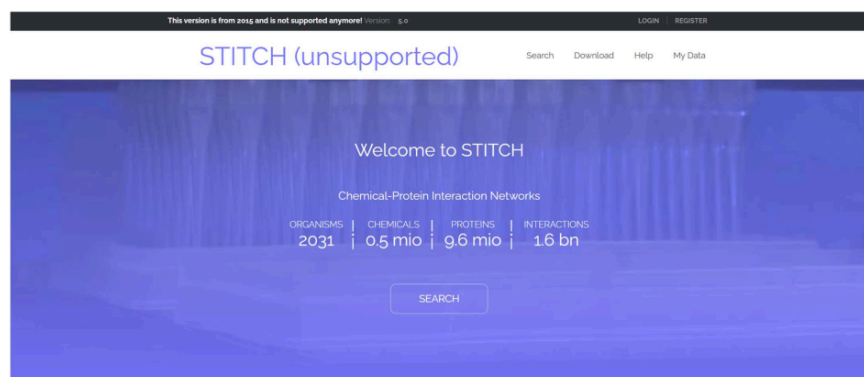


Figure 9: Homepage of *STITCH*

3.1.10 UniProtKB:

UniProt is a database that houses sequences (T. U. Consortium.) and functional information of proteins (F. G. Rasko Leinonen) (Shadab Ahmad) (T. U. Consortium.) (<https://www.uniprot.org/>). Over 100 people are active in various responsibilities at the three institutes, including database curation, software development, and support (Shadab Ahmad). As of now there are a total of 574,627

total entries in Swiss-Prot and a total of 202,556,313 total entries in TrEMBL (T. U. Consortium.) (Shadab Ahmad). The Uniprot database is updated once in every eight weeks (Shadab Ahmad).

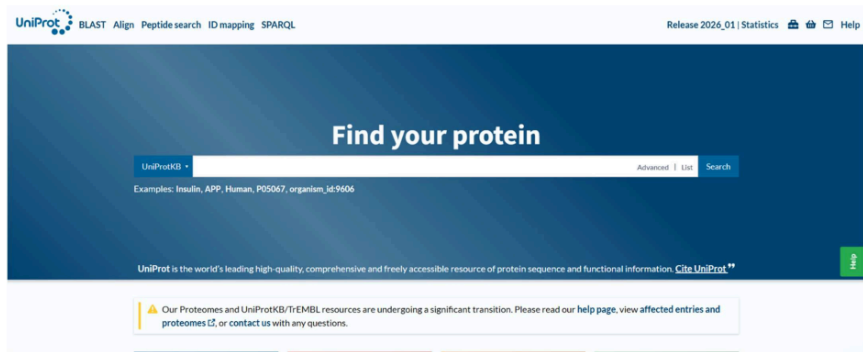


Figure 10: Homepage of UniProt

3.1.11 RCSB PDB:

The Protein Data Bank (PDB) (<https://www.rcsb.org/>) was the first open access repository of digital data in the history of biology and medicine (Helen Berman) (Helen M. Berman). It is now a prominent worldwide source for experimental data essential to advancements in science (Helen M. Berman). A wealth of 3D structure data has been deposited in the PDB, which has helped considerably to increase our understanding of protein architecture (Helen M. Berman). All this has led to recent advances in the prediction of protein structure, greatly accelerated by deep learning and artificial intelligence (Helen M. Berman). The latest version of PDB is currently PDB 3.1 that contains information on 3D structure of 217,157 proteins. And information about 1,068,577 Computed Structure Models (CSM)

(Helen M. Berman). Usually, the data comes from ² X-ray crystallography, NMR spectroscopy and cryo-electron microscopy (Helen M. Berman).

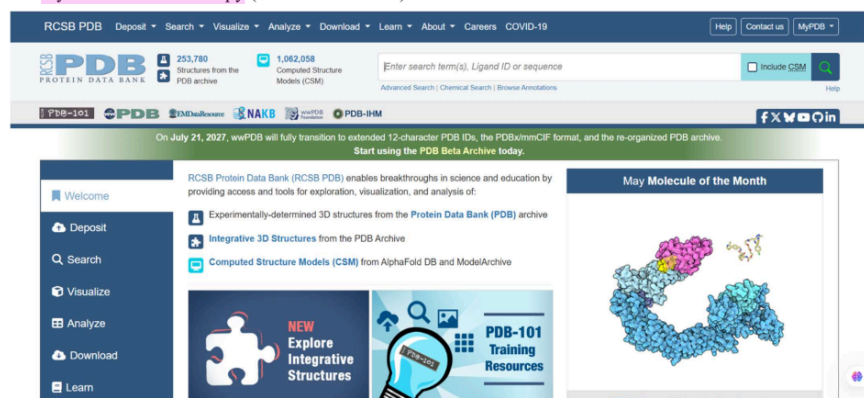


Figure 11: Homepage of RCSB PDB

3.1.12 Discovery Studio Visualizer:

A fully fledged software package, Discovery Studio is tailored to the analysis and modelling of sequences, molecular structures and data of relevance to the life science field (Biovia.). This software provides features such as simple data analysis, data viewing and editing (Biovia.). Data produced by other Discovery data products can be viewed using the free Discovery Studio Visualizer (Biovia.). All other options pale in comparison to tool panels for accessing the tools (Biovia.). Tool panels are used to organize tools into groups for specific tasks. Besides, the tool panels are grouped in large sets, such as receptor-ligand interactions and pharmacophores (Biovia.).

3.1.13 Rstudio:

Rstudio is an Integrated Development Environment (IDE) that is cross-platform and designed to enhance the functionality and usability of the R programming language (Racine.). RStudio offers a unified and easy to use solution, by bringing together key components in a single interface (Racine.). It consists of four large panels: editor for writing scripts, console for running commands,

workspace/history window, and file management, charting, handling packages, and help documentation (Racine.). The design is flexible and can be used in any way to suit individual user habits (Racine.). RStudio is well known for its platform independence, as it supports Windows, macOS and Linux (Racine.). It features a tabbed source editor, syntax highlighting, auto-completion, and even code execution, a searchable command history for easy retrieval and reuse of past code, and built-in code transformation tools (Racine.).

3.1.14 AutoDock Vina:

Molecular docking was underdone using Vina to estimate the binding relationship between the receptor and ligand (O. T. Olson.). Vina predicts the shape of the complex generated and the binding affinity, or in simpler terms, the strength of the interactions that occur between the receptor and the ligand (O. T. Olson.). Used far and wide in drug discovery process (O. T. Olson.). AutoDock Vina is the molecular docking software used which is better than its predecessor i.e AutoDock 4 in terms of prediction speed and accuracy (O. T. Olson.). Vina utilizes a gradient based optimization algorithm to assess the binding conformations accurately. Vina uses a scoring function which evaluates the receptor ligand interaction based upon hydrogen bonding, hydrophobic interactions, steric hindrance and ligand flexibility (O. T. Olson.).

3.1.15 GTEx:

² Genotype-Tissue Expression (GTEx) database (<https://gtexportal.org/home/>) helps in understanding how different gene expression is across males and females established (A. S. Wayez Naqvi) (Moore.).

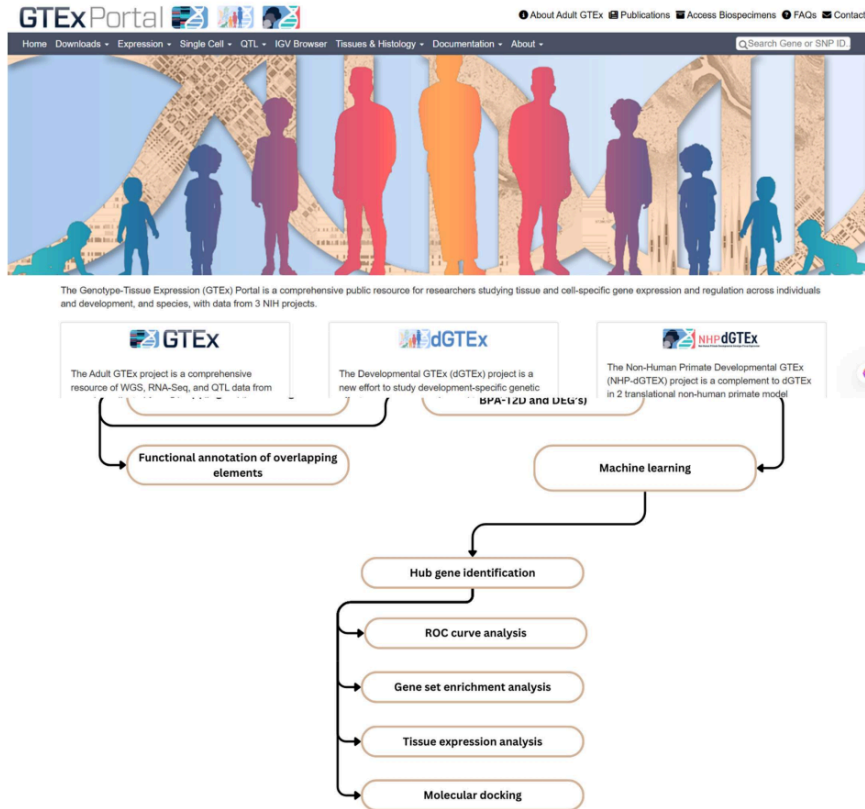


Figure 13: Flowchart depicting the pipeline followed in this study (P. G. Wayez Naqvi)

3.2 Methodology:

3.2.1 Dataset Retrieval

Through GEO (Tanya Barrett) and SRA (Rasko Leinonen) of NCBI (Conrad L Schoch) datasets were retrieve datasets for this study. Selection was based on the criteria that the studies had type 2 diabetes as the disease condition, had blood as the sample source and had transcriptomic data type

3.2.2 Data Preprocessing:

Following dataset retrieval, the raw counts file were imported and mapped against org.Hs.eg.db to convert entrez id to gene symbols. Following of which only the common genes across all datasets were identified and retained in the merged expression matrix. Then the low count genes were removed to reduce background noise. Using DESeq2 package normalization and variance stabilizing transformation was done followed by which using sva package batch correction was done (Yuqing Zhang).

3.2.3: Differential Gene Expression Analysis:

Following preprocessing, normalization and batch correction, differential gene expression analysis was underdone. Log2 fold change shrinkage was done using apeglm's lfcshrink function and genes with null p-values were filtered out.

3.2.4 Retrieval of BPA targets and T2DM genes:

Next, the gene targets associated with BPA were retrieved using Swiss Target Prediction database, Comparative Toxicogenomic Database and STITCH. While using GeneCards, Malacards and OMIM, genes related to Type 2 Diabetes Mellitus were retrieved. The obtained lists were then overlapped to identify the intersecting elements between BPA and T2DM genes.

3.2.5 Functional annotation:

Next, functional enrichment analysis was carried out on the BPA-T2D intersecting genes (Bobak.). GO and KEGG enrichment (Bobak.) was underdone using clusterProfiler package (Bobak.) (Weiqing Yang).

3.2.6 Identification of candidate genes:

The genes obtained from differential gene expression analysis were then overlapped with intersecting elements of BPA and T2D. The interacting entries were then retained and utilized for further analysis.

3.2.7 Training and Validation Set Construction:

Following DEG analysis, samples were distributed into training and test set (Weiqing Yang) through random stratified sampling (Weiqing Yang) at a ratio of 7:3 (Weiqing Yang).

3.2.8 Machine learning analysis:

RF (Breiman.), SVM-RFE (Mei-Ling Huang) and LASSO (Monica M. Vasquez) were used employed for identifying candidates genes. (Weiqing Yang).

3.2.9 Diagnostic validation using ROC curve:

Using pROC package (Linlin Song), the hub genes obtained after machine learning approaches (P. G. Wayez Naqvi) evaluated on the test set to assess the diagnostic performance (Linlin Song).

3.2.10 Pathway Analysis:

Using the clusterProfiler package, GSEA was underdone (Weiqing Yang) to map out the associated pathways (Weiqing Yang). Genes were ranked using Wald statistic first and then pathways were evaluated using adjusted p-value and normalized enrichment scores. (Weiqing Yang)

3.2.11 Tissue expression analysis:

Using GTEx database, expression of the potential diagnostic biomarkers across different human tissues was assessed.

3.2.12 Molecular Interaction Analysis:

Molecular docking was performed to assess the binding interaction occurring between bisphenol A and potential diagnostic biomarkers using AutoDock Vina.

RESULT & DISCUSSION

4.1 Dataset Retrieval:

Through GEO and SRA of NCBI datasets were retrieved for this study. Table 1 shows the summary of the four datasets utilized in this research. Selection was based on the criteria that the studies had type 2 diabetes as the disease condition, had blood as the sample source, and had transcriptomic data type. Three out of four datasets were manually filtered to remove samples associated with some other disease condition apart from Type 2 diabetes.

Table 1: Summary of the selected datasets available on GEO with their respective Bioproject and SRA accession ID's, and sample sizes.

GEO Accession ID	Bioproject Accession ID	SRA Accession ID	Sample Size	Sample Size (after filtering)	Total Patient Samples	Total Control Samples	Reference
GSE154881	PRJNA647610	SRP273003	15	10	5	5	(Aleksandr A Tkachenko)
GSE153315	PRJNA642130	SRP268985	30	30	20	10	(Aleksandr A Tkachenko)
GSE184050	PRJNA650123	SRP275718	116	116	50	66	(Hung-Hsin Chen)

GSE114192	PRJNA470512	SRP144997	249	88	52	36	(Clare Eckold)
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4.2 Data Preprocessing:

Following dataset retrieval, the raw counts file imported and mapped against org.Hs.eg.db to convert entrez id to gene symbols. Following of which common genes across all datasets were identified and retained in the merged expression matrix. Then the low count genes were removed to reduce background noise. Using the DESeq2 package, normalization and variance stabilizing transformation

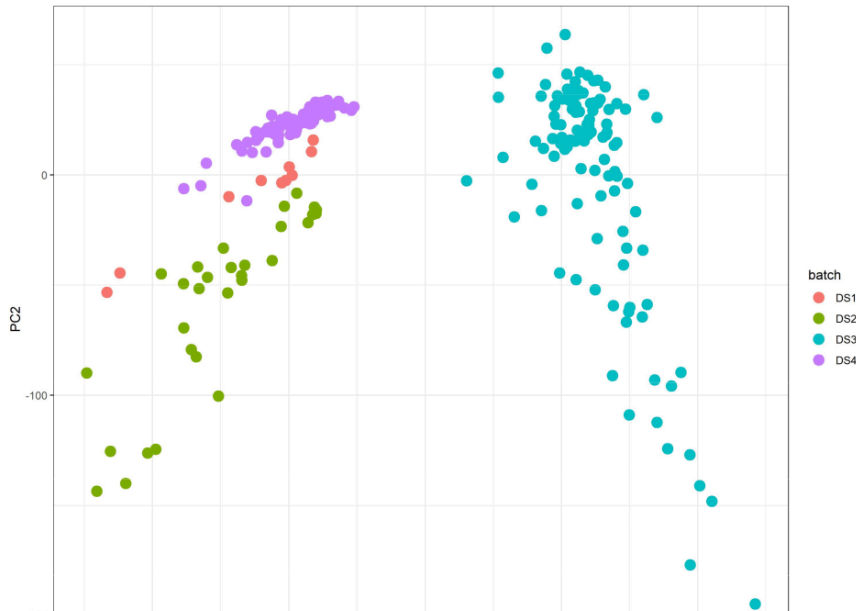


Figure 14: Initial PCA plot of the T2D datasets. Here DS-1 represents samples of GSE154881, DS-2 represents samples of GSE153315, DS-3 represents samples of GSE184050, and DS-4 represents samples of GSE114192

was done and using sva package batch correction was done (Yuqing Zhang). Figures 14 and 15 depict the PCA's before and after batch correction respectively.

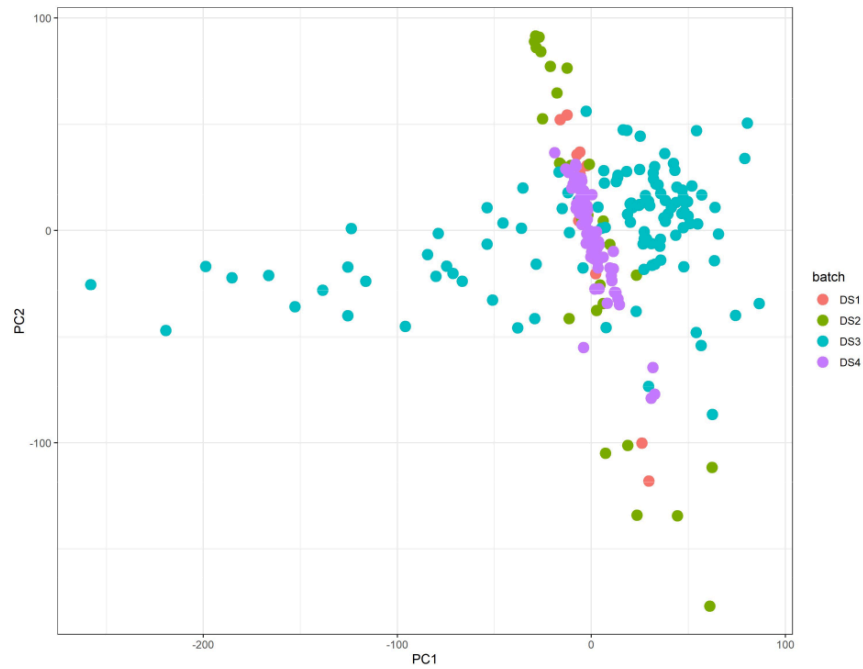


Figure 15: PCA plot after batch correction. Here DS-1 represents samples of GSE154881, DS-2 represents samples of GSE153315, DS-3 represents samples of GSE184050, and DS-4 represents samples of GSE114192

4.3 DEG Analysis:

Following data processing, DEG analysis was done. The `apeglm`'s `lfcshrink` function was used to do log₂-fold change shrinking. By setting the p-value < 0.05 (P. G. Wayez Naqvi) and log 2-fold change

value > 0.25 (P. G. Wayez Naqvi) 355 DEG's were identified (Wayez Naqvi) (figure 16 show the results visualized in a volcano plot) (P. G. Wayez Naqvi).

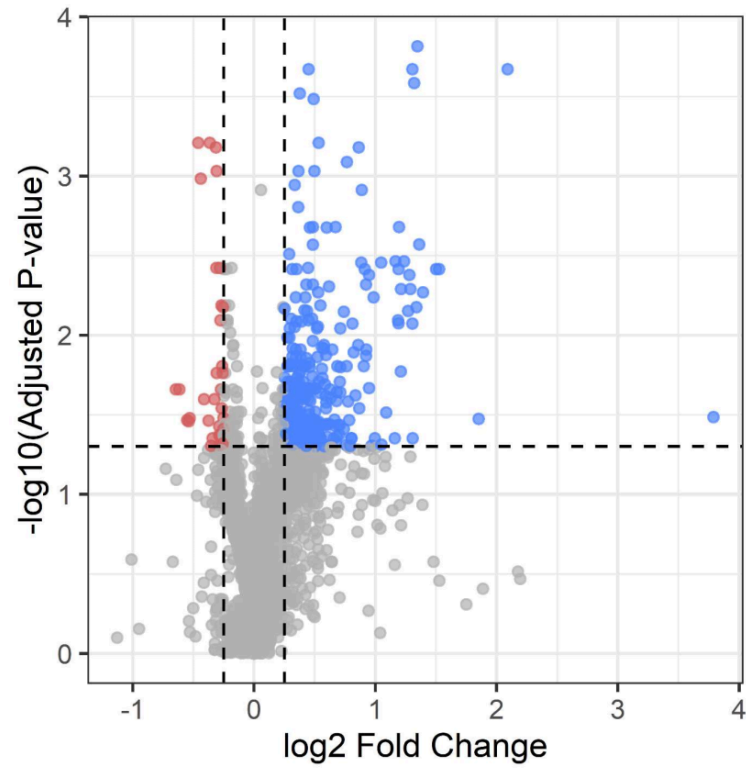


Figure 16: The volcano graphic depicts the differentially expressed genes retrieved from DESeq2 (Wayez Naqvi)

4.4 Retrieval of BPA targets and T2DM genes:

For retrieving the gene targets associated with BPA, three databases were utilized i.e Swiss Target Prediction (STP), Comparative Toxicogenomic Database (CTD) and STITCH (Weiqing Yang). The obtained lists from were then merged and de-duplicated to create a non-redundant list (Chenglin Wang). Similarly, using GeneCards, Malacards and OMIM, Type 2 Diabetes genes were retrieved, out of which only the protein coding genes were taken into consideration (Chenglin Wang). The obtained list was then filtered as well to create a non-redundant list (Bo Wu). Finally, the 19063 BPA genes and 4148 T2D genes were compared against each other with the intersection yielding 3885 genes (as shown in figure 17) These shared genes were then utilized for further research.

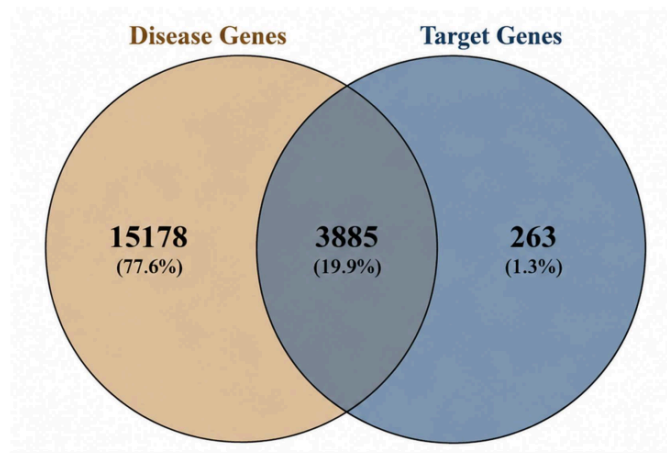


Figure 17: Venn diagram showing the overlapping genes between BPA target genes and T2DM disease genes

4.5 Functional annotation of overlapping elements:

Next, the overlapping elements of BPA-T2D functionally annotated using the clusterProfiler package (Linlin Song) [using gene ontology and KEGG terms] (figures 18 and 19 depict the bar plots for GO and KEGG enrichment analysis). Biological processes like metabolic regulation, hormone

responsiveness, oxidative stress, inflammation, and xenobiotic response were significantly enriched. KEGG pathway analysis revealed pathways like ¹⁸PI3K-Akt signaling, MAPK signaling, AGE-RAGE signaling, cAMP signaling, and apoptosis to be significantly associated. Membrane-associated structures and vesicle-mediated transport processes were the cellular components associated with BPA-T2D intersecting genes while the molecular functions cytokine signaling, growth factor interactions, and transcriptional regulation were significantly enriched.

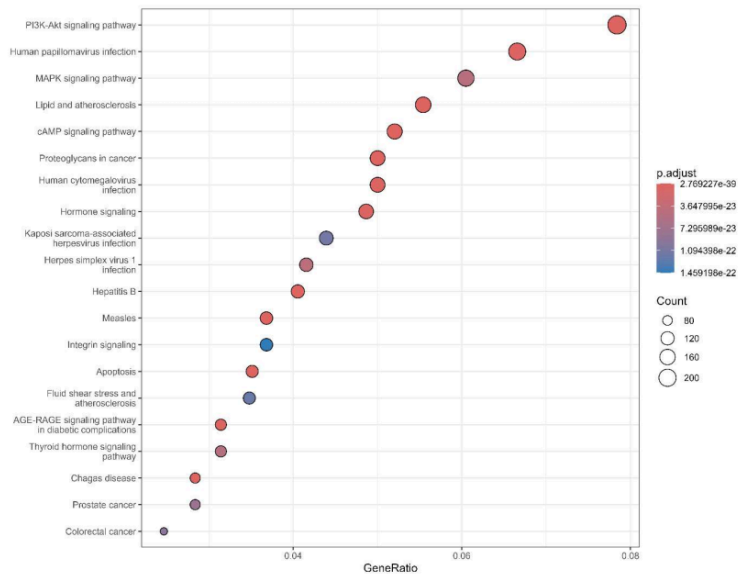


Figure 18: Functional profiling of the intersecting BPA T2D genes using KEGG terms

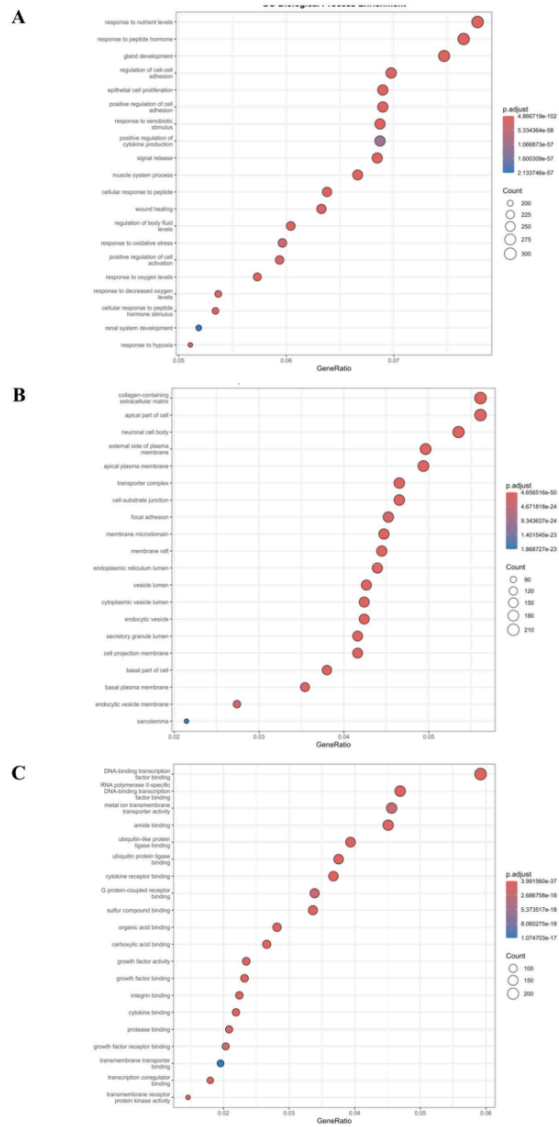


Figure 19: Functional profiling of the intersecting BPA T2D genes using Gene ontology terms

4.6 Identification of candidate genes:

The genes obtained from DEG's were then compared BPA-T2D intersecting genes which resulted in the identification of 52 overlapping genes (shown in table 2) which were then utilized for further analysis.

Table 2: Table showing the 52 genes obtained after the overlap of DEG, BPA and T2D genes.

Gene Symbols			
HNFI1A	PAPSS2	OTOF	DRD4
RETN	IGF2R	NEK8	CCDC40
PRKAR1A	AMPD2	NDUFS8	GP1BB
ATP7A	LTA	MMP8	RAPGEF2
CXCL8	FXD2	LDB3	CERS2
CDKL5	SOCS1	ABCG1	MORC3
COL9A2	MAPK10	S1PR2	GP9
CPT1A	CCL3	LIF	SIRT4
ATP8B1	CRB2	FOXH1	INHBA
LCN2	BAD	ARMC5	RDH5
JAK1	RRAD	EDARADD	H2AC20
HBA2	ANGPTL4	LAMP1	IFI27
FOXC1	CLU	GLUL	PXDNL

4.7 Training and Validation Set Construction:

Following preprocessing and batch correction, samples were distributed into training and test set (Weiqing Yang) through random stratified sampling (Weiqing Yang) at a ratio of 7:3 (Weiqing Yang).

4.8 Machine learning based hub gene identification:

RF (Breiman.), SVM-RFE (Mei-Ling Huang) and LASSO (Monica M. Vasquez) were employed for identifying candidates genes. (Weiqing Yang), feature selection and model building. In RF, the randomForest package was used with 1000 trees to rank genes depending on the mean decrease scores (figure 20 shows the feature importance curve with top 10 genes). A total of 20 genes were obtained through this. Next, the out of bag error estimation was done (shown in figure 21) which yielded a value of 30.59% (Weiqing Yang).

Next, SVM-RFE was used to determine the number of genes or features retained during recursive feature selection and the least informative genes were removed. As shown in figure 22, an accuracy of 69.9% was obtained when 9 genes were taken into consideration (Weiqing Yang).

Lastly, LASSO regression model was built with a 10-fold cross validation using glmnet package of R. Lambda.min was used for assessing the penalty strength, out of the 52 candidate genes 18 were retained as they retained non-zero coefficients while the remaining genes shrunk towards zero coefficients (shown in figure 23 and 24). Outcomes of these three approaches (shown in table 3) were then overlapped using a venn diagram (shown in figure 25) to identify the genes uniformly distributed which were identified to be ABCG1, AMPD2 and HBA2 (Weiqing Yang).

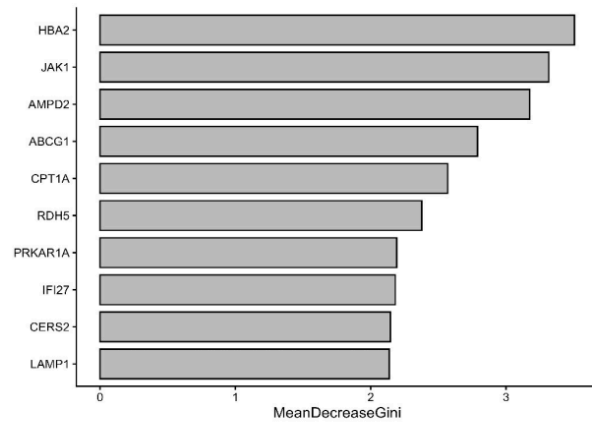


Figure 20: Feature importance curve of the top 10 Random forest genes

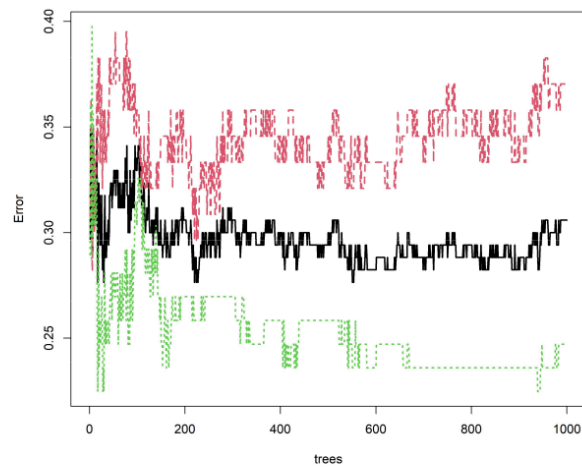


Figure 21: Out of bag error estimation of the Random Forest model

Table 3: Table showing the set genes obtained through the use of machine learning approaches.

RF Genes	SVM Genes	LASSO Genes
HBA2	AMPD2	ABCG1
JAK1	JAK1	AMPD2
AMPD2	HBA2	CCDC40
ABCG1	ABCG1	CDKL5
CPT1A	PRKAR1A	CPT1A
RDH5	LAMP1	DRD4
PRKAR1A	IGF2R	FXVD2
IFI27	CERS2	GLUL
CERS2	CRB2	GP1BB
LAMP1		H2AC20
RAPGEF2		HBA2
CRB2		IFI27
LCN2		MMP8
SOCS1		PXDNL
CCDC40		RDH5
LIF		RETN
GP1BB		RRAD
DRD4		SOCS1
IGF2R		
S1PR2		

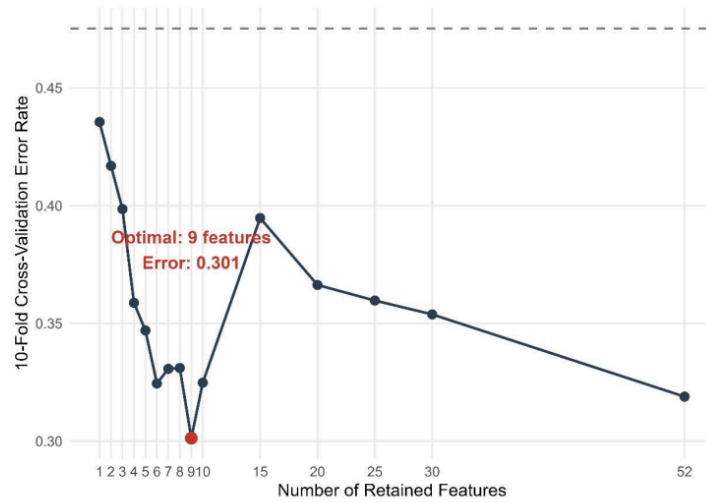


Figure 22: Feature selection performance of the SVM-RFE using 5-fold cross-validation

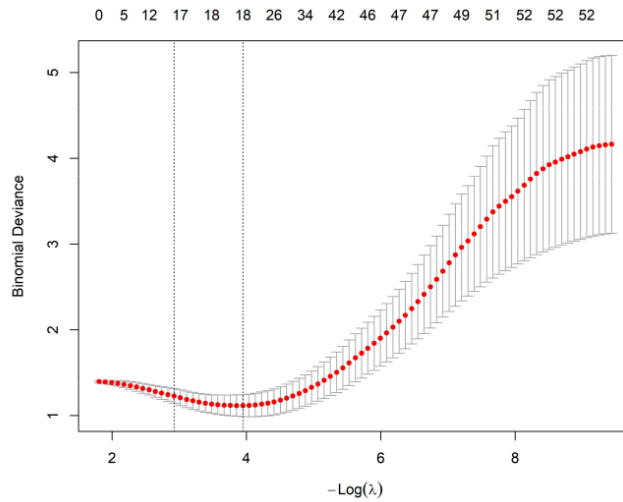


Figure 23: 10-fold cross-validation error curve of LASSO regression analysis

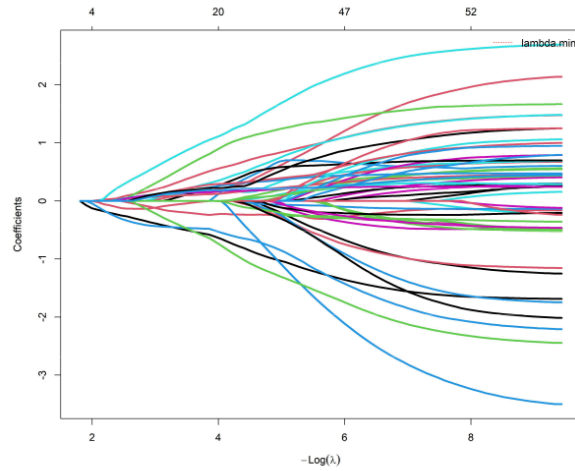


Figure 24: Coefficient trajectory plot of LASSO model, where each coloured lines represents the coefficient of each candidate genes taken in consideration

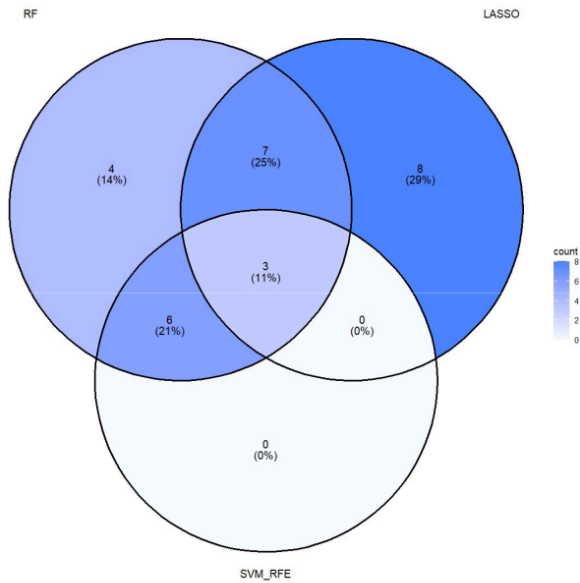


Figure 25: Venn diagram showing overlapping genes obtained from the three machine learning approaches

4.9 ROC curve analysis and diagnostic validation:

Through the use the pROC package, ROC curves for the candidate hub genes were generated using the test set. Wilcoxon rank-sum test was also done (Shaoheng Liang) to rectify the gene expression differences between control and disease groups (Shaoheng Liang). The genes yielded the p-values 5.12×10^{-7} (APMD2), 2.69×10^{-8} (ABCG1) and 2.98×10^{-7} (HBA2) respectively (shown in figure 27)(Yuqin Tang). The genes ABCG1, AMPD2 and HBA2 yielded the following AUC values on the test set respectively: 0.737 (ABCG1), 0.634 (AMPD2) and 0.677 (HBA2) (shown in figure 27). Furthermore, a combined logistic model with all the three hub genes yielded an AUC value of .0745 (shown in figure 26). These findings indicate that AMPD2, ABCG1, and HBA2 possess potential diagnostic value and may contribute to of BPA-associated T2DM.

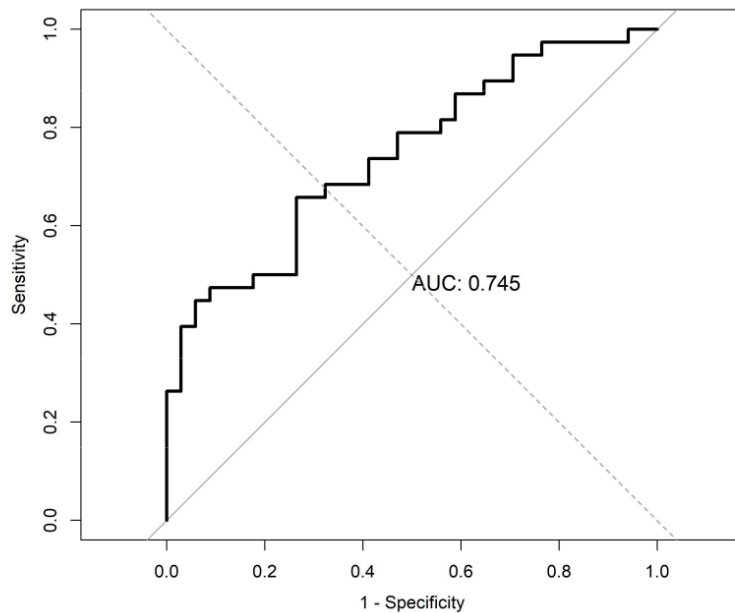


Figure 26: Figure showing the 3 gene ROC curve

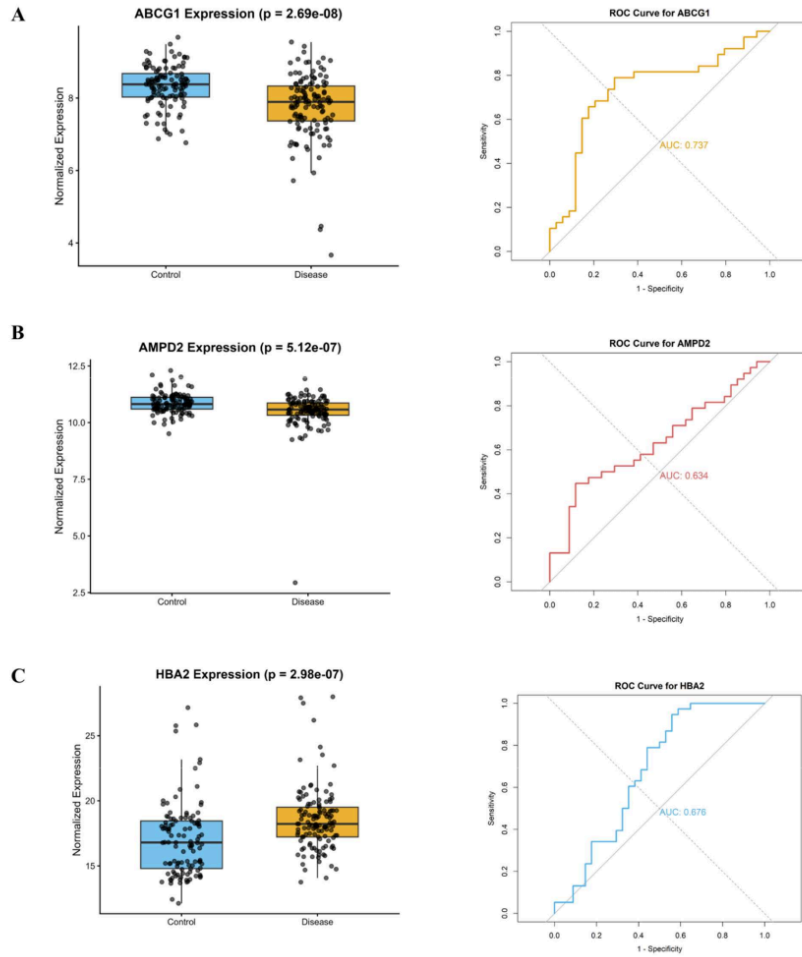


Figure 27: Figure showing the jittered boxplot and single gene ROC curve of (A) *ABCG1*; (B) *AMPD2*; and (C) *HBA2*

4.10 Gene set enrichment analysis:

Gene set enrichment analysis was carried out to identify the significantly enriched pathways associated with the potential candidate biomarkers (Weiqing Yang). The genes were first ranked on the basis of

DESeq2 wald statistics, p adjusted value and normalized enrichment scores. KEGG and Gene ontology terms were used for mapping out the GSEA pathways. Gene ontology significantly enriched pathways all had negative enrichment scores meaning that the pathways were all associated with downregulating genes. The most notable ones were vesicle cargo loading, regulation of autophagosome assembly, regulation of vacuole organization and post-Golgi vesicle-mediated transport. Some pathways also had positive enrichment scores like spinal cord patterning, oxygen transport and mucosal immune response. KEGG based GSEA highlighted pathways like autophagy, endocytosis, natural killer cell-mediated cytotoxicity (Alex M Abel), B-cell receptor signalling pathway (Dimitar G Efremov) and maturity onset diabetes of the young (as shown in figure 28).

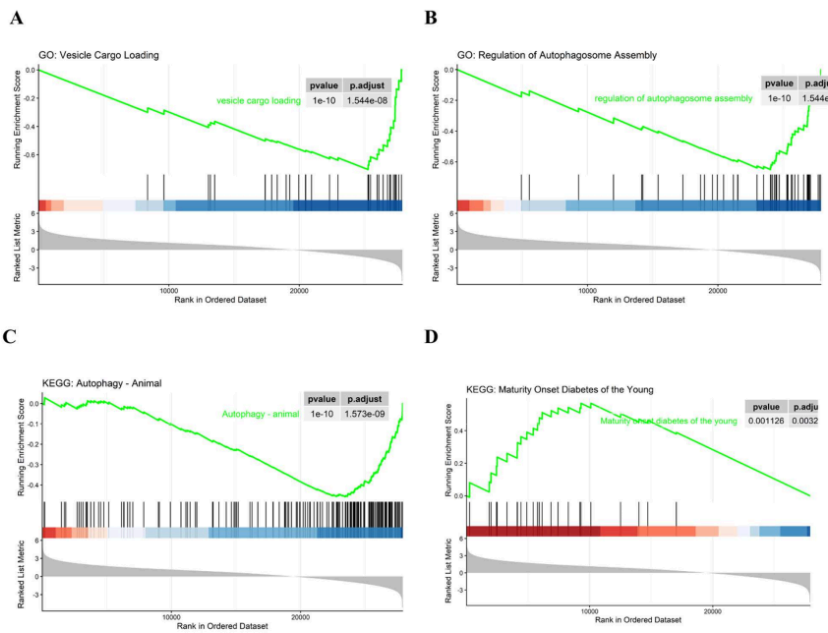


Figure 28: Panelled image depicting the top significantly enriched GO-GSEA pathways (A&B); and top significantly enriched KEGG GSEA pathways (C&D)

A

log₂(TPM+1)

Control

Control + 100 ng/ml

Control + 100 ng/ml + 100 ng/ml

B

log₂(TPM+1)

Control

Control + 100 ng/ml

Control + 100 ng/ml + 100 ng/ml

C

log₂(TPM+1)

Control

Control + 100 ng/ml

Control + 100 ng/ml + 100 ng/ml

Figure 29: Figure depicting gene expression analysis of (A) *ABCG1*; (B) *AMPD2*; and (C) *HBA2* across all the tissues

4.12 Molecular Interaction Analysis:

Using AutoDock Vina, interaction occurring between bisphenol A and the candidate biomarkers was done. 3-dimensional structures for ABCG1, AMPD2 and HBA2 were retrieved from PDB (with PDB ID's 7R8D, 4NO3 and 1A01 respectively). Canonical SMILE structure of bisphenol A was retrieved from PubChem. The complex of AMPD2 and BPA yielded a binding affinity of -7.4 kcal/mol (shown in figures 30 and 31). While the complex of BPA and ABCG1 and HBA2 yielded a binding affinity of -8.1 respectively.

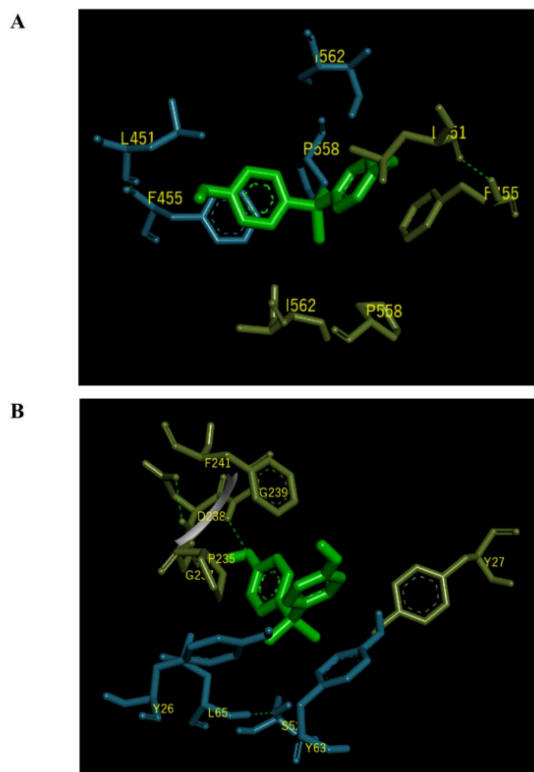


Figure 30: Complex formed between Bisphenol A and (A) Adenosine monophosphate deaminase 2; (B) ATP Binding Cassette sub family G member 1

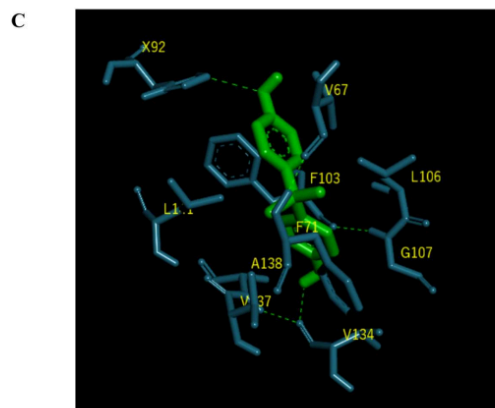


Figure 31: Complex formed between Bisphenol A and (C) Haemoglobin Subunit Alpha 2

CONCLUSION

This study used transcriptomic and machine learning methodologies to evaluate the connection between bisphenol-A and type 2 diabetes (Yan Zhang). Differential expression analysis helped in identifying 355 dysregulated genes which were compared against intersection of BPA-T2D genes to find 52 overlapping elements. Followed by which machine learning based hub gene identification was done using SVM, RF and LASSO; followed by ROC curve analysis which lead to the identification of potential candidate biomarkers ABCG1, AMPD2 and HBA2. Lastly docking studies and functional enrichment was done to identify the role of these candidate genes in individuals suffering from type 2 diabetes. Adenosine Monophosphate Deaminase 2 (AMPD2) is an enzyme involved in energy and glucose metabolism (Athanasius Wrin Hudoyo). Mouse model studies have identified that done on mice with and without AMPD2 highlighted that AMPD2 can effectively regulate gluconeogenesis through the action of specific enzymes and absence of AMPD2 leads to low amounts of glucose being produced (Athanasius Wrin Hudoyo). This study took another parameter in consideration as the mice were given high fructose diet which showed that downregulation of AMPD2 protects against the glucose metabolism due to consumption of high levels of fructose (Athanasius Wrin Hudoyo). AMPD2 is involved in AMPK activity, gluconeogenesis, glucose tolerance, and hepatic lipid metabolism through literature study (Athanasius Wrin Hudoyo). Functional enrichment analysis of AMPD2 also related to pathways like insulin signaling, mTOR signaling, autophagy, sphingolipid signaling, and lipid metabolism which are closely associated with glucose homeostasis and metabolic regulation; factors involved in pathogenesis of T2D (Scherthaner.). HBA2 gene is involved in oxygen transport and erythrocyte function, under the state of hyperglycaemia alterations in the levels of haemoglobin are observed (Joseph Malaba). A scientific study done with case and control samples highlighted that individuals with diabetes had a somewhat different blood composition (Joseph Malaba). This can be used for monitoring or assessing diabetes as under hyperglycaemia this altered composition is observed (Joseph Malaba). Another study highlighted the role of ABCG1 in diabetes (Yinxia Su), it showed that methylation of this gene increased susceptibility of diabetes in individuals (Yinxia Su). It also showed

comorbidity with conditions like obesity, dyslipidaemia and hypertension (Yinxia Su). The gene ABCG1 is involved in cholesterol efflux, lipid homeostasis and insulin secretion (Yinxia Su). This helps us in stating that exposure to BPA can induce or drive epigenetic modification which further promote disease progression (Yinxia Su). All these findings sound promising and form a relation between BPA and Type 2 diabetes, supported with the docking studies which yielded binding interactions of -7.4 and - 8.1 kcal/mol respectively. However, the exact mechanism still remains elusive. And the findings of this study need robust wet lab validation in order to concretely claim that the identified hub genes can act as diagnostic biomarkers and what exact role do they play in BPA induced metabolic disease progression.

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