On the Relationship of Diabetes and Sleep Apnea: Evolution and Epigenetics

Nancy Wilson

Follow this and additional works at: https://scholarsarchive.byu.edu/studentpub_uht

Part of the Microbiology Commons, and the Molecular Biology Commons

BYU ScholarsArchive Citation
https://scholarsarchive.byu.edu/studentpub_uht/213

This Honors Thesis is brought to you for free and open access by BYU ScholarsArchive. It has been accepted for inclusion in Undergraduate Honors Theses by an authorized administrator of BYU ScholarsArchive. For more information, please contact ellen_amatangelo@byu.edu.
ON THE RELATIONSHIP OF DIABETES AND SLEEP APNEA: EVOLUTION AND EPGENETICS

by

N. R. C. Wilson

Submitted to Brigham Young University in partial fulfillment of graduation requirements for University Honors

Department of Microbiology and Molecular Biology
Brigham Young University
August 2021

Advisor: Professor Steven Johnson, Ph. D
Faculty Reader: Professor Byron Adams, Ph. D
Honors Coordinator: Professor R. Paul Evans, Ph. D
ABSTRACT

ON THE RELATIONSHIP OF DIABETES AND SLEEP APNEA: EVOLUTION AND EPIGENETICS

Nancy Wilson
Department of Microbiology and Molecular Biology
Bachelor of Science Honors

This thesis gives an overview of the relationship between diabetes, sleep apnea, obesity, and heart disease. It then addresses evidence that the traditional understanding of this relationship is incomplete or misleading. In the process, there is a brief discussion of the evolutionary rationale for the development and retention of sleep apnea in light of blood sugar dysregulation, as an adaptive mechanism in response to environmental stressors, followed by a brief overview of the general concepts of epigenetics. Finally, this paper presents the results of a literature search on the epigenetic marks and changes in gene expression found in sleep apnea and diabetes. (While some of these marks will also correlate with obesity and heart disease, that is beyond the scope of this project.) This thesis concludes with an exploration of alternative explanations for the etiology of these interlinking diseases.
ACKNOWLEDGEMENTS

This thesis has been the result of many years of work by many people. All the authors whose work I’ve drawn on, both scholarly and popular, are the first but hardly the last who deserve recognition. I also appreciate the efforts of professors in all the classes I’ve taken, both in feeding my curiosity and in helping me rein in my explorations to a size that could be (mostly) accomplished in the allotted time. Particularly the professors of my major and minors, Molecular Biology, English Language (also known as English linguistics), and Chemistry: you have shaped my ways of viewing the world, which has inexorably changed who I am. I thank you all for your efforts; any of my remaining errors of science or language are a result of my own intractability, rather than due to a lack of instruction.

Perhaps the most important thing I learned from my editing minor is the value of a good editor - and how much I need one (or many). Kudos are also due to my editing team, that string of intrepid students and freelancers who have helped me standardise spelling, straighten out the bibliography, and otherwise align this document with the practices of readability: Tina Hawley, Beau Hunsaker, Angela Griffin, and Amy Carpenter.

Of the many associations I’ve been granted over the last few years, I would be most remiss not to recognize the tremendous privilege it’s been to work in the lab of Dr. Steven M. Johnson, learning about epigenetics in an atmosphere of good humor and camaraderie. I also owe a debt of gratitude to my other committee members: Dr. Byron Adams, who teaches the principles of evolution at one of the most well-known religious universities in
the world, and who does it with kindness and flair: thank-you. And Dr. R. Paul Evans, for introducing me to the world of molecular biology, and setting me on the path of learning to answer my unending questions on the subject. For every class I’ve had from you, and most especially my first class with you, I thank you. Here I’ll also mention Davis Garner, who took that first molecular biology class from Dr. Evans with me, and who told me about Dr. Johnson’s lab when I mentioned my own interest in epigenetics. It made a difference.

Most of all, I thank my family. My parents, the late Lynn T. Cox, who died while I was working on this. You weren’t killed by the first three rounds of cancer. You weren’t killed by tangling with a semi on I-15. You departed this life holding hands with Mom, after a painful struggle with that last round of cancer. I miss you, Dad. Thanks for showing me how to always get up again. My mother, B. Ann Cox, whose commitment to education mirrors her mother’s, the late Tommy Leota Bascom. Mom, I couldn’t have done this without you. At every stage, you’ve always encouraged my education. And I know you would have been there for my graduation, Grandma Tommy. I hope you see how much I appreciate your example and encouragement. My siblings, Sarah Ann, Karla, Alexis, Day, Benjamin. For late night talks and early morning counsel, and too many favors to ever count.

Our family. The children: Helaman, Eve, and Enoch, Abraham, Shiphrah Quintillia, Elijah, Ruth, and Isaiah. This project would have left our household even more short-staffed if not for your willingness to step in and babysit or help with housework. Your sacrifices are noted. I hope that in some way this makes your futures a little bit better than they would have been otherwise. Finally, my husband, Alma Teao Wilson. You clean,
you edit, you raise our children with me. Words seldom fail me, as you are aware. But I
cannot find a way to write how much you mean to me. In a pale shadow of what I wish to
say, thank you.
TABLE OF CONTENTS

Title page ........................................................................ i
Abstract ........................................................................ iii
Acknowledgements ..... vi
List of figures ................................................................. xi
List of tables ................................................................. xiii
Importance ........................................................................ 1
Purpose ........................................................................ 1
Overview ........................................................................ 2
A well-known solution .............................
A Brief Overview of Epigenetics ..................... 13
Hypothesis. ................................................................. 15
Methods ........................................................................ 15
Results and discussion .............................
Genes Upregulated in both Sleep Apnea and Diabetes ........................................... 15
Genes Downregulated in both Sleep Apnea and Diabetes ........................................... 18
Genes Regulated in Opposition to Each Other in Sleep Apnea and Diabetes ........... 19
Cascades. ................................................................. 24
Conclusions ................................................................. 27
Bibliography ................................................................. 31
Appendix ........................................................................ 52
LIST OF FIGURES

Figure 1 *Neat, plausible, and wrong.* This naive model posits obesity as the lynchpin of lifestyle disease. If obesity is the lynchpin, weight loss is the self-evident treatment and cure. Unfortunately, this model doesn’t fit the data we have.

Figure 2 An indicative model of lifestyle disease. While simplicity is generally preferred, the complexity of this model is outweighed by the fact that it does not contradict the data in hand.
AGT (angiotensin) .......................................................... 15
LEP (leptin) ................................................................. 16
MMP-9 ......................................................................... 17
SIRT1 (Sirutin), a class III HDAC (Histone deacetylase) ........ 18
SOD2 ............................................................... 19
sRAGE(Soluble RAGE) and RAGE(MOK protein kinase). ....... 20
FOXP3(scurfin) ............................................................ 21
miR-26b ................................................................. 22
miR-31 ................................................................. 22
miR-107 ................................................................. 23
miR-155 ................................................................. 23
FOXO4 (Forkhead box 04), IGFBP1(Insulin like growth factor binding protein 1), IGF-1 (Insulin like growth factor 1), and IGF-2 (Insulin like growth factor 2) ........ 24
NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells), TNF-α (Tumor necrosis factor alpha), assorted miRNAs ............................................. 24
miR-29c and the miR-21/Spry1/ERK/MMP-9 signaling pathway ........................................... 26
Importance

Diabetes is the seventh leading cause of death in the United States today,\(^1\) with type II diabetes representing over 90% of all diabetes cases.\(^2\) Of the top ten causes of death in the United States over the last decade, diabetes has been known to exacerbate or trigger all of the others.\(^3\) Between thirty\(^4\) and eighty\(^5\) percent of diabetics (including type I diabetics) also have sleep apnea; sleep apnea has been shown to be independently associated with insulin resistance,\(^6\) with the severity of sleep apnea corresponding with the severity of insulin resistance.\(^7\) Sleep apnea is even associated with gestational diabetes.\(^8\) While both sleep apnea and diabetes are believed to spring from obesity, the two conditions occur together more often than can be explained by obesity alone.\(^9\)

Purpose

The purpose of this paper is to improve our understanding of the relationship between sleep apnea and diabetes. This will be done by exploring the evolutionary background of these diseases and by examining epigenetic marks common to both conditions.\(^10\) This should give a clearer picture of the underlying etiology of these diseases and point to

---

2 Reutrakul and Mokhlesi 2017, 1070-86
3 While this claim may at first appear worthy of skepticism, the careful reader will note that it is, in fact, perfectly accurate.
4 Papanas et al. 2009, 751-56
5 Aronsohn et al. 2010, 507-13
6 While insulin resistance is widely regarded as a major precursor for type II diabetes, type I diabetics can also experience insulin resistance. For purposes of this paper, I will be specific where my sources allow me to, but I may at times use the terms “diabetes,” “type II diabetes,” “metabolic syndrome,” and “insulin resistance” somewhat interchangeably.
7 Ip et al. 2002, 670-76; also Araújo et al. 2015, 1351-57
8 Facco et al. 2014, 559.e1–559.e6
10 Evo-Devo (evolutionary developmental biology) teaches us that evolutionarily successful changes usually target regulatory processes more than underlying DNA sequences. The science of epigenetics is the study of regulatory signaling of the genome. This is why I am looking at epigenetic marks. For an enjoyable, scientifically accurate overview of evo-devo, I recommend A Capella Science’s “Evo-Devo (Despacito Biology Parody)” (2017).
productive future avenues of research in the search for cures to these major health issues.

Overview

What are sleep apnea and diabetes? What causes them, and what are the results of these diseases?

Sleep apnea is a condition in which breathing stops during sleep, either because the brain is not correctly signaling the body to breathe (central sleep apnea, or CSA) or because soft tissues, primarily the tongue, collapse across the airway, obstructing it (obstructive sleep apnea, or OSA). Sleep apnea is associated with inflammation, metabolic syndrome and diabetes mellitus, obesity, heart disease, stroke, and death.

Diabetes, on the other hand, is a condition characterized by hyperglycemia. Type I Diabetes is generally regarded as an autoimmune disorder brought on by the body’s attack on the insulin producing cells of the pancreas. Type II Diabetes is generally regarded as a progressive disease, with metabolic syndrome and insulin resistance giving way to full-blown type II Diabetes, characterized by insufficient insulin production. Diabetes is associated with heart disease, some cancers, stroke, respiratory sensitivity, blurred thinking and dementia, kidney disease, nerve damage, blindness, depression, and death. Together, sleep apnea, diabetes, and cardiovascular disease make up a large proportion of the diseases of modern life.

11 Lochan 2011, 7-14
12 Araújo et al. 2015, 1351-57
13 Dobrota et al. 2021, 76-84
14 Kapur 2010, 1155-67
15 Araújo et al. 2015, 1351-57
16 NHLBI 2010
18 While we do not address causes of autoimmunity here, it should be noted that type I Diabetes, along with allergies, arthritis, and other autoimmune disorders, is increasing alongside more obvious diseases of modern lifestyles, such as type II Diabetes. See National Diabetes statistics report, found at CDC (2020, “National Diabetes Statistics Report”).
Widely held views of these diseases of modern life can be strung into a sort of narrative, which goes something like this:

“Once upon a time, humans had to work very hard all the time and were always a little bit hungry. Fat and sugar were especially difficult to obtain, so humans evolved to be very efficient at using fat and sugar and also to constantly seek them out. Unfortunately, if we ingest very much fat or sugar we become obese. This is because obesity is caused by eating too much and exercising too little. Obesity itself is a disease state with no benefit to the individual. Because of industrialization, fat, sugar, and calories in general are now widely available for the first time in human history. Industrialization also made life easier, so we don’t have to work so hard. The abundance of calories with the lack of physical labor created a mismatch between calories taken in and those expended: this mismatch is the underlying cause of diseases of modern life, especially obesity, diabetes, and heart disease. Sedentary individuals who indulge themselves by eating too many calories are the people who get those diseases. In particular, obesity causes sleep apnea, diabetes, and heart disease.”

For an otherwise well-written article which uses this chain of reasoning as the backdrop for the research, see, for example, Ling and Rönn 2019.

Kapur 2010 is a great example of how this reasoning works: establishing from well-structured studies that sleep apnea is correlated with weight gain, and that increased severity of sleep apnea is correlated with increased weight gain, the author goes on to casually state that the weight gain clearly caused the sleep apnea, though in the same paragraph he states that weight loss does not decrease severity of sleep apnea to the same extent that weight gain increased it. Relevant here is the aphorism, “correlation is not causation.”
and heart disease. To cure those diseases, we would have to change human nature such that people would choose to eat less and exercise more. Those who exert themselves to eat less and exercise more can cure themselves of these diseases, including obesity."

This is a tidy story which carries the appeal of placing responsibility for “lifestyle disease” squarely on the individual experiencing it. It’s also appealing because it suggests that we can avoid said diseases through practice of willpower — by denying ourselves the pleasures of sugar and fat and forcing ourselves to exercise enough. This tale of willpower-derived redemption from the diseases of modern life holds grave significance for many of us. Unfortunately, it also has the possibility of living up to H.L. Mencken’s dictum, “There is always a well-known solution to every human problem—neat, plausible, and wrong.” Let us examine the elements of this story, then, and see how they bear up to scrutiny.

*Once upon a time, humans had to work very hard all the time and were always a little bit hungry.*

There is a great deal of evidence to suggest that our distant ancestors had periods of prosperity, even to the point of allowing obesity. In addition, it has been suggested that the agricultural revolution—in which humans undertook deliberate cultivation of food rather than the nomadic, gatherer-hunter lifestyle they had previously lived—led to various health issues such as anemia and loss of stature. This is hardly the response of people who had previously been underfed. Possibly the strongest evidence that our ancestors were not routinely deprived of calories, though, comes from the field of

---

21 According to the CDC, 1 in 10 Americans adults have diabetes, and 1 in 3 have prediabetes (CDC, n.d. “National Diabetes Statistics Report, 2020”).
22 See, for example, depictions of the “Woman of Willendorf.”
23 See Latham 2013 or Mummert et al. 2011, 284-301.
epigenetics. Many of the studies in this field focus on natural experiments, where humans were starved due to external factors such as war or famine.\textsuperscript{24} Children and grandchildren of those underfed individuals show a strong predisposition toward obesity and heart disease, as well as diabetes and other metabolic problems. We do not yet know how many generations of stable caloric intake are required to reverse these inherited metabolic changes. The fact that the epigenome changed with exposure to starvation conditions tells us that our ancestors had a non-starvation state available.

\textit{Fat and sugar were especially difficult to obtain, so humans evolved to be very efficient at using fat and sugar, and also to constantly seek them out. Unfortunately, if we ingest very much fat or sugar we become obese.}

From 1990s weight-loss guru Susan Powter’s mantra, “Fat makes you fat” to decades of FDA recommendations that Americans limit their refined sugar and fat consumption, we’ve all heard the message that fat and sugar are the biggest culprits in causing obesity and resultant diseases.

Nina Teicholtz addresses this in her groundbreaking book, \textit{The Big Fat Surprise} (2014). She looks at all of the studies on which recommendations of low-fat diets have been made, and she presents the well-researched conclusion: We do not know what we think we know. Fat in our diets has \textit{not} been shown harmful to our health and may well be helpful.\textsuperscript{25} Sugar is obliquely implicated in lifestyle diseases, but the data may not be as clear as we have been led to believe. We don’t know what causes a human to tip over from less than fit into downright unhealthy. Is there a dietary component? Both common

\textsuperscript{24} See, for example, Senaldi and Smith-Raska 2020.
\textsuperscript{25} Reading Teicholtz, one also comes to the realization that some of the first researchers nutritional researchers defined the boundaries of what we study regarding fats and sugars, and those boundaries haven't been changed. We don't know if some animal fats are better or safer than others (like butter vs lard) because the boundary of study was drawn between animal and plant fats (butter and lard vs canola oil and olive oil). The definitional boundaries having been drawn and unchallenged, all we can say for sure is that
sense and research suggest that there is. But particular foods like red meat or fresh
cucumber have neither been exonerated nor incriminated as the source of our troubles.
Even the much-vaunted “Mediterranean diet” of popular fame has never been properly
defined—26—and therefore, it has never been properly studied.

Happily, we do have evidence for a dietary explanation. A Brazilian nutrition
researcher named Monteiro and his team were puzzled at data that showed people in
Brazil were buying less sugar and less oil—but at the same time experiencing more
obesity and more diabetes. Eventually they reached the conclusion that the culprit was
what they have labeled UFPs, or “Ultra Processed Foods.”27 While this classification
has been opposed by some as “nonsensical,” it gained a great deal of traction when a
physicist from the U.S. named Kevin Hall set out to show it was the content, rather than
the processing, that was the problem. After some gold-standard pilot studies, Hall now
suggests avoiding ultra-processed foods.28

Obesity is caused by eating too much and exercising too little.

This assumption is actually based on a truism, namely, if you put more into a
system than goes out, the system must expand. It may expand gradually—as with
obesity—or explode—as with the case of an overfilled water balloon—but expand it
will. The problem with this particular application is that we, do not simply expand or
contract according to how much we are holding. As living, homeostatic systems, we
have numerous mechanisms for maintaining (among other things) our temperature, our
hydration levels, our electrolyte balance—and our weight.

26  Again, see Teicholtz 2014 for a thorough explanation.
27  Monteiro 2009, 729-31. For those who wish a well written summary with commentary, I recommend
    Bee Wilson’s "How Ultra-processed Food Took Over Your Shopping Basket" (2020).
28  For more information about Hall’s work, see Shell (2019: 38-45).
In fact, however large or small we are, our baseline metabolism accounts for the largest proportion of calories we expend, regardless of our physiological overlay.\textsuperscript{29}

Principles of biological homeostasis suggest that a healthy individual will not need to regulate their intake to the exact calorie on a given day—rather, the metabolism changes in mild ways to compensate for the inevitable caloric variability of diet.\textsuperscript{30} In addition, unfortunate natural experiments like the Dutch “hunger winter”\textsuperscript{31} and alternating years of prosperity and famine in record-keeping Scandinavian countries\textsuperscript{32} have given us the data to understand that low-calorie maternal (P0) conditions impel offspring (F1, F2, F3) to greater levels of many undesirable things: obesity, metabolic syndrome\textsuperscript{33}, hypertension, type II diabetes, and other health conditions.\textsuperscript{34} Modern data does not suggest that improving the caloric intake of offspring will reduce obesity in themselves (F1) or their offspring (F2, F3, etc.), either.\textsuperscript{35}

\textbf{Obesity is a disease state with no benefit to the individual.}

As early as 1987, an entire issue of the \textit{Journal of Obesity and Weight Regulation} was devoted to Ernsberger and Haskew’s alternative theories of obesity, namely, that it is not a disease state. They state clearly that obesity might result from a disease state—much as pale skin or heightened stature may indicate disease states, but may also be a desirable

\begin{itemize}
\item \textsuperscript{29} This is why exercise only slims a small part of the population: all of us benefit from exercise, but not all of us are tipped out of our current homeostasis into a more slender form by exertion.
\item \textsuperscript{30} Or, as expressed by St-Pierre and Tremblay (2012, 292-97), “The ability of healthy individuals to maintain body weight in the face of fluctuating energy intake and expenditure is due to an intricate physiological network that acts as the gatekeeper of energy balance. Indeed, under normal physiological conditions, any deviation in energy intake or expenditure is compensated for by physiological and behavioral responses that oppose these changes in order to return to a state of energy balance.”
\item \textsuperscript{31} Roseboom et al. 2001, 93-98.
\item \textsuperscript{32} A good overview can be found in Senaldi and Smith-Raska 2020.
\item \textsuperscript{33} Metabolic syndrome is defined by the World Health Organization as glucose intolerance and insulin resistance, either separately or together, in combination with two or more of the following: hypertension; elevated plasma triglycerides; reduced HDL cholesterol, central obesity, and microalbuminuria.
\item \textsuperscript{34} Painter et al. 2008, 1243-49.
\item \textsuperscript{35} Painter et al. 2008, 1243-49.
\end{itemize}
result of genes, environment, or both. Just as none would suggest that the paleness of anemia should be cured by sending the sufferer to attend a local tanning parlor, Ernsberger and Haskew suggest that we may simply add to the problems of obesity if we try to “cure” it through the panacea of weight loss. Ernsberger and Haskew are not alone in their theories. Indeed, there have been a number of articles published in the last few years bemoaning the “obesity paradox,” as it has been called—namely, that individuals who fall prey to diabetes or a number of other conditions live longer and have fewer complications than those who are slimmer when diagnosed. Additionally, individuals who are “normal weight” have lower death rates than those who are merely 20% under “normal weight;” those who are above the “ideal weight” have lower death rates still.

Evolutionary biology teaches us that conserved traits are generally important—and beneficial—to the group, and by extension, to the individual. The ability to become obese seems to be a conserved trait across species. As such, treating it as a disease state may be misleading and even harmful. One explanation for the apparent paradox of obesity being closely associated with disease states, yet also being associated with better outcomes in those disease states, is that obesity could be protective against the true underlying causes of those health issues. Much as doctors in time past strove to remove blood from the body through leaches and bleeding, the practice of removing adipose tissue through diet and surgery may not be providing the cures we seek.

*Because of industrialization, fat, sugar, and calories in general are now widely available for the first time in human history. Industrialization also made life easier, so we don’t have to work so hard.*

This is, in some ways, a reprise of the idea that humans are getting fatter because

---

36 See, for example, Artham et al. (2008, 24-41) or Bedduh (2004, 229-32).
37 Ernsberger and Haskew 1987
we are failing to properly account for our water-balloon-like nature in a changing environment. But humans aren’t the only animals getting fatter. Such disparate species as wild marmosets and fully supervised lab rats have gotten bigger over the last few decades. This suggests it is neither human character traits nor human diet and lifestyle choices that are causing the changes in human population fatness, but some other factor, be it light pollution or ultra-processed foods (are wild marmosets somehow indulging in leftover Twinkies?) or old-fashioned air pollution or some other, unidentified cause.

The abundance of calories with the lack of physical labor created a mismatch between calories taken in and those expended: this mismatch is the underlying cause of diseases of modern life, especially obesity, diabetes, and heart disease.

Correlation is not causation. While fatness is strongly associated with diseases of modern life, it may be the proverbial “healthy response to an unhealthy situation”—fatness may be protecting us from some of the worst effects of “lifestyle diseases.”

Sedentary individuals who indulge themselves by eating too many calories are the people who get those diseases.

This view is contradicted by the fact that only half of obese people have metabolic syndrome, while fully ten percent of the lean population has metabolic syndrome. It

38 Berreby 2013
39 Here I use the term “fatness” interchangeably with the term, ‘obesity,’ although I prefer the first, as being more precise. As Ernsberger and Haskew (1987) point out, ‘obesity’ is defined by the mathematical derivation of BMI, rather than actual body mass composition, whereas ‘fatness’ refers to the adipose composition of a body. In deference to general convention, however, we have usually used the term ‘obesity,’ here.
40 I do not have space here to explore the possibility of light pollution as a potential source of metabolic disruption but suggest Król and John R Speakman (2007, 271-78) as a starting point. More broadly, on the subject of diurnal regulation, I recommend Till Roenneberg’s excellent book, Internal Time (2012).
41 For a summary of the evidence regarding ultra-processed foods, see Wilson 2020.
42 See McConnell et al. (2016, 1-3) or Ahmed et al. (2018, 336).
43 In “Metabolic Implications of Body Fat Distribution” (1991, 1132-43), Bjorntorp correlates several studies surrounding hormones, fat distribution, and insulin resistance. He declares, “this … suggests that endocrine aberrations may be of more importance than visceral fat accumulation . . . for insulin resistance.”
44 This statistic is reported by Brown (2002, 774-78) from the work done by Mantzoros and Flier (1995, 193-232)
is, of course, important to get this right: If obesity is, after all, the trigger for metabolic syndrome, with its concomitant heart disease and short path to diabetes, it would be logical—perhaps imperative—to target fatness as the first link in the chain for intervention. If it is not, however, the first link in this chain, changing an individual’s body profile (from fatter to slimmer, for example) will at best do nothing to help their long-term health prospects—it may even hurt them by interfering with an important response to an environmental stimulus. Even if weight loss does no harm per se, it may provide a false sense of progress against underlying disease, even while the underlying disease is still at work.

**In particular, obesity causes sleep apnea, diabetes, and heart disease.**

In Mansor et al.’s (2016) research on why the hearts of diabetic patients often fail to repair themselves at the same rate as those of nondiabetic patients, they describe a metabolic shift that takes place when the cells of the heart need repair. Normally, hypoxic events cause a shift in heart-cell metabolism toward a high-glucose energy use. Mansor et al. discovered that this shift mechanism is still fully functional in a diabetic heart cell, but because the underlying diabetes shifts the cellular metabolism to a primarily fatty-acid-based energy use, even a normally functioning hypoxia-induced cascade does not lead to full glucose metabolism or normal cellular repair. Hypoxic events can be caused not only by heart attacks or strokes but also by temporary changes in breathing; if those breathing changes occur during sleep, they are classified as sleep-disordered breathing, or sleep apnea.

The field of linguistics holds other clues to support this possibility. The advent of fricatives in human speech corresponds with a softer diet, around the time of the
first agricultural revolution (Blasi et al. 2019, eaav3218). Blasi et al. point out that softer foods can cause a difference in jaw development, leading to the modern human overbite and allowing fricatives such as “f” and “v” to enter human speech. Soft foods, such as grains (fermented and otherwise) and sweet fruit (more widely available when planted than when stumbled upon), would have been much more available after the first agricultural revolution than before. These soft foods are also much more likely to cause hyperglycemia, the primary diagnostic factor in diabetes.

Richard Wrangham (2017, S303–13) makes a strong case that *Homo habilis*, *Homo erectus*, and *Homo neanderthalensis* all probably cooked some of their food. That corresponds with smaller jaws and teeth in *Homo erectus* than in earlier hominids. So the final transition to having the ability to talk came with the final transition to being dependent on cooking in the most recent hominids: *Homo sapiens*, also known as us.

Davidson et al. (2005) hypothesized that obstructive sleep apnea in humans is a side-effect of our capacity for speech. To evaluate this hypothesis, the authors evaluated men with sleep apnea for severity of sleep apnea and also measured several areas between the face and pharynx/larynx corresponding to the human capacity for speech. They found a strong correlation between some of these measurements (especially cranial base angulation and laryngeal descent) and the severity of the subjects’ sleep apnea; this correlation corroborates the theory that sleep apnea is a result of those same changes that allow speech.

So we see that paleoarchaeological evidence in conjunction with modern research allows for the coevolution of sleep apnea and hyperglycemia in response to a softer, cooked diet, though of course it cannot prove any such thing. But there are further clues.
Evolutionary theory informs us that co-evolution indicates advantage to the organism—not as individuals but as a species. Did our ancestors from 10,000 years ago get fat in conjunction with snoring? Possibly.\textsuperscript{45}

\textit{To cure those diseases, we would have to change human nature such that people would choose to eat less and exercise more.}

This, of course, is true insofar as the underlying assumptions are true, namely: people get sick because they got fat, and they get fat because of personal choices to eat too much and exercise too little. If, however, the diseases of modern life have a more complex pathogenesis involving interactions between personal choices and a host of environmental factors, it may be possible to stem the tide of lifestyle-based diseases by changing the environment. Importantly, even if only a small part of lifestyle-based diseases were caused by environmental factors, changing those factors could cure that portion of lifestyle-based diseases.

Those who exert themselves to eat less and exercise more can cure themselves of these diseases, including of obesity.

While there is much anecdotal evidence of long-term weight loss accompanied by a return to full health, a preliminary survey of the literature on weight loss and exercise interventions for treatment of diabetes revealed a very low long-term success rate.\textsuperscript{46} While reduced calories and increased exercise appear to help ameliorate the health problems of

\textsuperscript{45} Anecdotal evidence suggests that we are much more likely to snore if sleeping alone or after physically demanding activities. This being the case, it has been postulated that snoring may serve as a last-ditch protection against predators who would risk going up against a sole human but not against a roaring crowd of humans—an impression some snorers do indeed give. This could replace the theory of sleep-apnic snoring coevolving in conjunction with high carbohydrate diets, or it could stand beside it as additional adaptation.

\textsuperscript{46} The most successful studies found reported 5% body weight lost through non-surgical means, maintained for 3 years. Even surgical weight loss provided lowered dependence on (but not independence from) anti-diabetes drugs. See Kheniser, Saxon, and Kashyap (2021, 1854-66). Other studies reported similar numbers over a similar time scale.
modern life, they are not, of themselves, a cure.

**A Brief Overview of Epigenetics**

Epigenetics, sometimes known as non-Mendelian inheritance, refers to the heritable changes in gene expression that occur without alterations to the underlying DNA sequence. Epigenetic mechanisms regulate interactions between the genome and environmental factors such as infection and nutritional changes. The three primary epigenetic mechanisms currently being studied are DNA methylation, histone modifications, and noncoding RNAs.

DNA methylation is a covalent addition of a methyl group to the cytosine residues in CpG (5’-C-phosphate-G-3’) dinucleotides. While hypomethylation of CpG islands is associated with gene activation, DNA methylation of promoter CpG islands is associated with gene repression. In addition to transcriptional regulation, DNA methylation is critical for maintaining genome integrity, most of the genome being highly methylated. DNA methylation is not a stable epigenetic modification. It changes throughout the lifespan of the organism, sometimes very rapidly, and dynamic DNA methylation remodeling occurs during development and cell differentiation. DNA methylation is catalyzed by DNA methyltransferases (DNMTs): DNMT3A and DNMT3B are *de novo* methyltransferases. DNMT1 is involved in the maintenance of DNA methylation after replication. Hydroxymethylation via 10–11 translocase (Tet) is the main mechanism for demethylation.

Histone modifications alter chromatin compaction and the recruitment of transcriptional regulators, modifying gene expression. Histone modification primarily

---

47 An excellent summary of DNA methylation and histone modifications can be found in Fodor, Cozma, and Karnieli (2017, 531-49). Information on miRNAs can be found in Mishra, Zhong, and Kowluru (2014, 7256-65).
refers to the acetylation or methylation of the N-terminal tail of a histone. Histone acetylation on lysine residues leads to increased gene expression. H3K9ac, H3K14ac, and H4K5ac are all marks associated with active transcription. Histone methylation is more stable. Histone methylation can cause activation or repression of genes, depending on the location of histone modification. H3K4me1/2/3 and H3K36me2/3 are transcriptionally active, but H3K9me2/3 and H3K27me3 are repressive marks. There are many families of histone-modifying enzymes, including histone deacetylases (HDACs), acetyltransferases (HATs), methyltransferases (HMTs), and demethylases.

Noncoding RNAs include small noncoding RNAs, also known as miRNAs, which are 21-25 nucleotides in length. The category of noncoding RNAs also includes long noncoding RNAs, or lncRNAs, which are more than 200 nucleotides in length. miRNAs can bind to the 3’ untranslated region of target mRNA transcripts, disrupting translation or leading to degradation. miRNAs provide a rapid but reversible regulation of about 60% of protein-coding genes. lncRNAs can control mRNA degradation and, unlike miRNAs, can impact gene expression by means such as recruiting epigenetic modifier proteins (such as transcription factors).

In addition to all of this, some epigenetic marks trigger other epigenetic marks: histone acetylation, for instance, can trigger a change in the methylation of the associated gene. Any disease that has genetic components that doesn’t manifest until adulthood may be suspected of having an epigenetic component, or trigger. Diabetes, with its multitude of associated genes but unclear lines of inheritance, is a clear suspect for epigenetically triggered disease. Sleep apnea, also common in some ethnic groups but without clear inheritance patterns, may also have a strong epigenetic component.
Hypothesis

This author hypothesizes that sleep apnea and diabetes coevolved, and if this is the case, one would expect to see common epigenetic marks between the two conditions.

Methods

This section undertakes to present a review of extant literature regarding epigenetic marks associated with diabetes and sleep apnea. While many of the marks surveyed are unique to one of these conditions, there are several which appear in both of these conditions which do not appear in healthy controls. After cleaning the data and entering it in a database, sorting was done according to gene, protein/RNA expression, and associated disorder(s).

Results and discussion

The following tables are selected from the dataset to show the overlapping epigenetic marks between diabetes and sleep apnea. For the full dataset and useful extracts, please see the appendices.

*Genes Upregulated in both Sleep Apnea and Diabetes*

AGT (angiotensin)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone/RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>angiotensin</td>
<td>Sleep apnea</td>
<td>Hypomethylated enhancer regions of AGT</td>
<td>Chu et al. (2015)</td>
<td></td>
</tr>
<tr>
<td>angiotensin</td>
<td>Diabetes</td>
<td>Hypomethylation of AGT</td>
<td>Marumo et al. (2015)</td>
<td></td>
</tr>
</tbody>
</table>

The angiotensin promoter is hypomethylated in both sleep apnea and diabetes, leading
to increased expression of the angiotensin protein. Angiotensin is a vasoconstrictor\textsuperscript{48}; therefore, the increased production of angiotensin may be the reason behind the higher blood pressures associated with these two conditions. The question that remains, then, is how sleep apnea and diabetes induce this disruption of normal, homeostatic vasocontrol.

LEP (leptin)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone/ RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>H4K20me increased</td>
<td>diabetes</td>
<td>increased methylation of leptin H4K20</td>
<td>Masuyama and Hiramatsu (2012), Masuyama et al (2015)</td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
<td>diabetes</td>
<td>reduced leptin promoter methylation</td>
<td>Jousse et al (2011)</td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
<td>diabetes</td>
<td>leptin methylation reduced</td>
<td>Khalyfa et al (2013)</td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
<td>sleep apnea</td>
<td>increased leptin expression</td>
<td>Gur et al (2016)</td>
</tr>
</tbody>
</table>

Leptin is a key player in the regulation of energy balance and body weight control. Leptin is normally produced by certain types of adipose tissue and serves as a sort of feedback regulator of fat storage, signaling satiety to the brain and also signaling the body to stop storing fat when there is enough\textsuperscript{49}. The existence of “leptin-resistance,” akin to “insulin-resistance,” has been hypothesized on the basis that humans with high levels of leptin as well as large fat deposits appear to resist the hunger-damping signals of leptin\textsuperscript{50}. Reduced methylation in the leptin promoter (see table 1, above), seen in animal models of diabetes, is consistent with the increased expression of leptin found in sleep apnea. Finally, increased methylation of the

\textsuperscript{48} The Human Protein Atlas, n.d.
\textsuperscript{49} Pan, Guo, and Su- 2014, 157-59
\textsuperscript{50} Król and Speakman 2007, 271-78
histones around the leptin genes would also tend toward increased expression of the
gene product. This is a very consistent picture.

MMP-9

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone/ RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix metallopeptidase 9</td>
<td>miR-21</td>
<td>Sleep apnea</td>
<td>upregulation of miR-21</td>
<td>Zhang et al (2018)</td>
</tr>
<tr>
<td>Matrix metallopeptidase 9</td>
<td>H3K9ac increased</td>
<td>Diabetes</td>
<td>hypomethylation of MMP-9</td>
<td>Kowluru et al (2016)</td>
</tr>
<tr>
<td>Matrix metallopeptidase 9</td>
<td>H3K9me2 decreased</td>
<td>Diabetes</td>
<td>increased H3K9ac on MMP-9</td>
<td>Zhong and Kowluru (2013)</td>
</tr>
<tr>
<td>Matrix metallopeptidase 9</td>
<td>Sleep apnea</td>
<td></td>
<td>increased MMP-9</td>
<td>Volná et al (2011)</td>
</tr>
</tbody>
</table>

MMP-9 is also known (among other things) as matrix metallopeptidase 9\textsuperscript{51}.

MMPs are important in breakdown of the extracellular matrix and are involved in
such diverse processes as wound healing, learning, and memory\textsuperscript{52}. In diabetes we see an increased expression of this protein, as mediated by reduced methylation in
the promoter. We also see increased acetylation of H3K9, which is a transcriptionally
active mark, and decreased H3K9me2. Since H3K9me2 tends to repress transcription,
this reduction is also consistent with increased expression of MMP-9. Consistent with
a common etiology, Volna et al. found increased levels of MMP-9 in sleep apnea. The
over-expression of this protein could be the cause of slow diabetic wound healing and
the brain fog associated with sleep apnea, or the overexpression could be a result of the
body’s efforts to overcome those deficits, much as high insulin is generally a sign of poor
insulin uptake (insulin resistance) rather than a cause of high blood sugars, of itself.

\textsuperscript{51} https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailViej%27w&TermToSearch=4318
\textsuperscript{52} Parks 1998
MMP-9 in humans has three fibronectin type II domains, which are collagen-binding domains, which is especially interesting given that several collagen-binding miRNAs are increased in diabetes⁵³.

**Genes Downregulated in both Sleep Apnea and Diabetes**

SIRT1 (Sirutin), a class III HDAC (Histone deacyetylase)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone/ RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirtuin 1</td>
<td>miR-195</td>
<td>Diabetes</td>
<td>Increased miR-195</td>
<td>Mortuza et al (2016)</td>
</tr>
<tr>
<td>Sirtuin 1</td>
<td>miR-23b-3p</td>
<td>Diabetes</td>
<td>Increased miR-23b-3p</td>
<td>Mortuza et al (2016)</td>
</tr>
<tr>
<td>Sirtuin 1</td>
<td></td>
<td>Diabetes</td>
<td>reduced expression of SIRT1</td>
<td>Chuang et al (2011)</td>
</tr>
</tbody>
</table>

SIRT1 is a histone deacyetylase that has been shown to be down regulated with both sleep apnea and diabetes. Histone acetylation is generally an activating mark; deacyetylation would tend to reduce expression of the relevant gene. A reduction in active deacyetylases would tend toward upregulation of genes.

This is consistent with the findings of this paper, namely that more genes are downregulated in both sleep apnea and diabetes than are upregulated. While possibly an artifact of the limitations posed by the necessarily incomplete state of knowledge, it is, nevertheless, a consistency.

⁵³ See appendix
**Genes Regulated in Opposition to Each Other in Sleep Apnea and Diabetes**

SOD2

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone modification or RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superoxide dismutase 2</td>
<td>H4K20me3 increased</td>
<td>Diabetes</td>
<td>Increased H4K20me3 on Sod 2</td>
<td>Zhong and Kowluru (2011), He et al (2007).</td>
</tr>
<tr>
<td>Superoxide dismutase 2</td>
<td></td>
<td>Sleep apnea</td>
<td>DNA methylation of Sod2 gene incremented 6- and 12-fold</td>
<td>Nanduri et al (2012)</td>
</tr>
<tr>
<td>Superoxide dismutase 2</td>
<td></td>
<td>Sleep apnea</td>
<td>Reduced expression of Sod 2; increased DNA methylation of Sod2</td>
<td>Nanduri et al (2017)</td>
</tr>
</tbody>
</table>

This enzyme is manganese-dependent and binds to the superoxide byproducts of oxidative phosphorylation\(^\text{54}\). This mark is unusual, in that we’ve found contradictory states between sleep apnea and diabetes: the increased methylation found in sleep apnea would tend to reduce transcription, in direct opposition to the H3K9 acetylation found in diabetic retinopathy, as H3K9 tends to promote active transcription. This contradiction should put SOD2 in the crosshairs as a protein of interest in determining what is causing damage and what is promoting repair in both diabetes and sleep apnea. The change in activation status of this protein could signal a tipping point between diabetes and sleep apnea, or the manganese-dependent nature of this protein could indicate that nutrition status plays a role.

\(^{54}\) National Center for Biotechnology Information 2021, “Gene Search Results.”
sRAGE(Soluble RAGE) and RAGE(MOK protein kinase)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone modification or RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble RAGE (sRAGE)</td>
<td>Sleep apnea</td>
<td>Low levels of sRAGE</td>
<td>Volná et al (2011)</td>
<td></td>
</tr>
<tr>
<td>MOK protein kinase</td>
<td>H3K27me3 decreased</td>
<td>Diabetes</td>
<td>decreased H3K27me3 over RAGE</td>
<td>Reddy et al (2014).</td>
</tr>
<tr>
<td>MOK protein kinase</td>
<td>H3K9/14Ac increased</td>
<td>Diabetes</td>
<td>Increased H3K9/14Ac on RAGE</td>
<td>Reddy et al (2014).</td>
</tr>
<tr>
<td>MOK protein kinase</td>
<td>H3K9me2 decreased</td>
<td>Diabetes</td>
<td>decreased H3K9me2 over RAGE</td>
<td>Reddy et al (2014).</td>
</tr>
<tr>
<td>MOK protein kinase</td>
<td>H3K9me3 decreased</td>
<td>Diabetes</td>
<td>decreased H3K9me3 over RAGE</td>
<td>Reddy et al (2014).</td>
</tr>
</tbody>
</table>

RAGE belongs to the MAP kinase superfamily. In diabetes, we see a reduction in specific epigenetic markers (H3K9me2, H3K9me3, and H3K27me3) which normally repress expression\(^55\). Reduction of those markers would tend toward increased expression of RAGE. In sleep apnea, we see lower levels of sRAGE than would be expected.

From the abstract of Al Rifai et al. (2015): “Advanced glycation end products (AGEs) may cause inflammation by binding to their cellular receptors (RAGE). Soluble RAGE (sRAGE) acts as a decoy receptor for AGEs and may prevent inflammation.” While RAGE and sRAGE are not the same marker, this is an example of the two conditions having biochemical interactions that play off of each other in important ways. Curiously, RAGE is also regulated by CDX2 (Caudal type homeobox 2), which binds preferentially to methylated DNA.\(^56\)

\(^{55}\) Punt, Stranford, Jones, and Owen 2018, 639
\(^{56}\) [https://www.proteinatlas.org/ENSG00000165556-CDX2](https://www.proteinatlas.org/ENSG00000165556-CDX2)
FOXP3(scurfin)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone/RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>scurfin, forkhead box P3</td>
<td>Sleep apnea</td>
<td></td>
<td>Hypermethylated intron1 region (mean of 11 CpG sites)</td>
<td>Kim et al. (2012)</td>
</tr>
<tr>
<td>scurfin, forkhead box P3</td>
<td>Diabetes</td>
<td></td>
<td>FOXP3 mRNA more highly expressed in Diabetic patients without nephropathy than in those with nephropathy or in healthy controls.</td>
<td>Telikani et al. (2019)</td>
</tr>
</tbody>
</table>

Foxp3 is both “necessary and sufficient to induce differentiation to the TREG lineage.” TREGs are understood to reduce autoimmunity, though the mechanism is not well understood. What makes this protein especially interesting is that diabetics with nephropathy express Foxp3 at similar rates to controls. In diabetics without nephropathy, however, Foxp3 is expressed at much higher levels than in controls (diabetics with diagnosed sleep apnea were excluded from this study). In patients with sleep apnea, on the other hand, Foxp3 is hypermethylated, leading to downregulation. This suggests a situation where sleep apnea could be the body’s attempt to counteract the negative effects of metabolic syndrome. The reverse, of course, may also be true.
miRNAs Found to be Associated with Diabetes and Sleep Apnea

miR-26b

<table>
<thead>
<tr>
<th>notes</th>
<th>associated RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-26b</td>
<td>Diabetes</td>
<td>change in miR-26b</td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>Promote cognitive</td>
<td>miR-26b</td>
<td>Sleep apnea</td>
<td>Gao et al (2017)</td>
<td></td>
</tr>
<tr>
<td>dysfunction</td>
<td></td>
<td>upregulation of miR-26b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gao et al. (2017) inform us that miR-26b is believed to be crucial in the process of OSA-induced cognitive dysfunction and that miR-26b is upregulated with intermittent hypoxia in rats (used as a model for sleep apnea in humans). Khurana et al. (2019) inform us that miR-26b expression changes in diabetes as well\(^{57}\). Perhaps this also provides a window to some of the cognitive deficits associated with diabetes.

miR-31

<table>
<thead>
<tr>
<th>Gene or gene target</th>
<th>Protein</th>
<th>notes</th>
<th>RNA</th>
<th>condition</th>
<th>Specific epigenetic mark</th>
<th>original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKCε</td>
<td>Protein kinase C epsilon</td>
<td>Promotes cardiac hypertrophy</td>
<td>miR-31</td>
<td>Sleep apnea</td>
<td>upregulation of miR-31</td>
<td>Ren et al (2018)</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor A</td>
<td></td>
<td>miR-31</td>
<td>Diabetes</td>
<td>Increased miR-31</td>
<td>Kovacs et al (2011)</td>
</tr>
</tbody>
</table>

Low levels of this RNA are associated with gastric cancer invasion and metastasis\(^{58}\). Given that this miRNA is upregulated in both sleep apnea and diabetes, in combination with the nutritional component of diabetes, and the question is raised: What evolutionary advantage is conferred by diabetes? A ubiquitous phenotype must

---

\(^{57}\) The reader doubtless joins the author in preferring to know in what direction this miR expression changes in diabetes. The information that miR-107 changes comes from Khurana et al. (2019); neither source nor methodology were cited, and alas the direction of change remains unknown.

\(^{58}\) National Center for Biotechnology Information 2021, “MIR 31 microRNA 31 [Homo sapiens (human)]”
generally be considered advantageous in some circumstances. What advantage does a diabetes-prone phenotype confer?

miR-107

<table>
<thead>
<tr>
<th>RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-107</td>
<td>Diabetes</td>
<td>change in miR-107</td>
<td>Khurana et al (2019)</td>
</tr>
<tr>
<td>mir-107</td>
<td>Sleep apnea</td>
<td>Downregulation of miR-107</td>
<td>Li et al (2017)</td>
</tr>
</tbody>
</table>

Zhang et al. (2021) found that miR-107 contributes to inflammatory pain, probably by reducing GLT-1 expression. The fact miR-107 is down-regulated in sleep apnea and changes\(^{59}\) in diabetes raises the question: Is miR-107 in any way implicated in diabetic neuropathy? Is a patient with sleep apnea and diabetes more or less likely to experience diabetic neuropathy? These are important questions for further study.

miR-155

<table>
<thead>
<tr>
<th>Gene or gene target</th>
<th>Gene aliases</th>
<th>Protein</th>
<th>notes</th>
<th>RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOXO3a</td>
<td>FOXO3 (AF6q21, FKHRL1, FOXO2, FOXO3A)</td>
<td>Forkhead box O3</td>
<td>Promote kidney injury</td>
<td>miR-155</td>
<td>Sleep apnea</td>
<td>upregulation of miR-155</td>
<td>Wu et al (2018)</td>
</tr>
<tr>
<td>NF-kB</td>
<td>NFKB1 (KBF1, NF-kappaB, NF-kB1, NFkappaB, NFKB-p50, p105, p50)</td>
<td>Nuclear factor kappa B subunit 1</td>
<td>miR-155</td>
<td>Diabetes</td>
<td>Increased miR-155</td>
<td>Kovacs et al (2011)</td>
<td></td>
</tr>
</tbody>
</table>

According to Mahesh and Biswas (2019), highly conserved miRNA 155 is a master regulator of inflammatory diseases, including cancer and lung disease. Furthermore, this miRNA is upregulated in both sleep apnea and diabetes.

\(^{59}\) See the note on miR-26b, above
**Cascades**

FOXO4 (Forkhead box 04), IGFBP1 (Insulin like growth factor binding protein 1), IGF-1 (Insulin like growth factor 1), and IGF-2 (Insulin like growth factor 2)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone/RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forkhead box O4</td>
<td></td>
<td>Diabetes</td>
<td>increased expression of gene</td>
<td>Chuang et al (2011)</td>
</tr>
<tr>
<td>Forkhead box O4</td>
<td>H3K9Ac increased</td>
<td>Sleep apnea</td>
<td>Increased H3K9Ac enrichment over FOXO4</td>
<td>Cortese et al (2017)</td>
</tr>
<tr>
<td>Insulin like growth factor 1</td>
<td>H3K4me reduced</td>
<td>Diabetes</td>
<td>IGF1 H3K4me reduced</td>
<td>Tosh et al (2010)</td>
</tr>
<tr>
<td>Insulin like growth factor 2</td>
<td></td>
<td>Diabetes</td>
<td>reduced methylation of IGF2</td>
<td>Heijmans et al (2008)</td>
</tr>
</tbody>
</table>

FOXO4 is a transcription factor which can activate IGFBP1, a binding factor which prolongs the half-life of IGFs. IGF-1 and IGF-2 are also upregulated in diabetes.

NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells), TNF-α (Tumor necrosis factor alpha), assorted miRNAs

<table>
<thead>
<tr>
<th>Protein</th>
<th>Histone/ RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>Original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear factor kappa B subunit 1</td>
<td>miR-132</td>
<td>Diabetes</td>
<td>Increased miR-132</td>
<td>Kovacs et al (2011)</td>
</tr>
<tr>
<td>Nuclear factor kappa B subunit 1</td>
<td>miR-146</td>
<td>Diabetes</td>
<td>Increased miR-146</td>
<td>Kovacs et al (2011)</td>
</tr>
<tr>
<td>Nuclear factor kappa B subunit 1</td>
<td>miR-155</td>
<td>Diabetes</td>
<td>Increased miR-155</td>
<td>Kovacs et al (2011)</td>
</tr>
</tbody>
</table>

60 https://www.proteinatlas.org/ENSG00000146678-IGFBP1. This author has found no references to epigenetic marks directly regarding IGFBP1.

61 Of some interest here is the fact that not only are Fox03, Fox04, and Foxp3 disregulated in diabetes, but Foxp2 is necessary to human speech. An intriguing avenue for future study. See https://www.proteinatlas.org/ENSG00000128573-FOXP2.
NF-κB is a transcription factor that controls cytokine production and cell survival and shows up in elevated levels in both diabetes and sleep apnea. Kovacs et al. (2011) show that miRNA-146 can act as negative feedback regulator of NF-κB in diabetes and suggest its use as a therapeutic agent against the overexpression of NF-κB. An important direction for future research might be exploring the effects of such therapies not only on diabetes but on sleep apnea.

Ryan et al. (2006) describe TNF-α as NF-κB-dependent and note that it is elevated in sleep apnea. TNF-α is a cytokine used by the immune system and is released by macrophages as part of an inflammatory response to infection. While NF-κB shows up in searches of epigenetic marks in OSA and diabetes, TNF-α shows up only in searches of epigenetic marks related to sleep apnea. Nevertheless, given this context, it seems probable that such epigenetic marks exist, though the relevant research may not yet have been done.

---

62 How the immune system works by Lauren Sompayrac 108-135
miR-29c and the miR-21/Spry1/ERK/MMP-9 signaling pathway

<table>
<thead>
<tr>
<th>Gene or gene target</th>
<th>Gene aliases</th>
<th>Protein</th>
<th>notes</th>
<th>RNA</th>
<th>Associated condition</th>
<th>Specific epigenetic mark</th>
<th>original source paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF-kB (KFB1, NF-kappaB, NF-kB1, NFkappaB, NFKB-p50, p105, p50)</td>
<td>Nuclear factor kappa B subunit 1</td>
<td>Induce atrial remodeling and fibrosis</td>
<td>miR-21</td>
<td>Diabetes</td>
<td>Increased miR-21</td>
<td>Kovacs et al (2011)</td>
<td></td>
</tr>
<tr>
<td>Spry1 (hSPRY1)</td>
<td>SPRY1</td>
<td>Sprouty RTK signaling antagonist 1</td>
<td>Induce atrial remodeling and fibrosis</td>
<td>miR-21</td>
<td>Sleep apnea</td>
<td>upregulation of miR-21</td>
<td>Zhang et al (2018), Wang et al (2018)</td>
</tr>
<tr>
<td>Spry1 (hSPRY1)</td>
<td>SPRY1</td>
<td>protein sprouty homolog 1; Sprouty RTK signaling antagonist 1</td>
<td>Induce atrial remodeling and fibrosis</td>
<td>miR-21</td>
<td>Sleep apnea</td>
<td>upregulation of miR-21</td>
<td>Zhang et al (2018)</td>
</tr>
<tr>
<td>VEGF (VEGF, VEGF-A, VPF)</td>
<td>Vascular endothelial growth factor A</td>
<td></td>
<td>miR-21</td>
<td>Diabetes</td>
<td>Increased miR-21</td>
<td>Kovacs et al (2011)</td>
<td></td>
</tr>
<tr>
<td>Spry1 (hSPRY1)</td>
<td>SPRY1</td>
<td>protein sprouty homolog 1; Sprouty RTK signaling antagonist 1</td>
<td></td>
<td>miR-29c</td>
<td>Diabetes</td>
<td>Increased miR-29c</td>
<td>Long et al (2011)</td>
</tr>
</tbody>
</table>
Long et al (2011) found that miRNA-29c is upregulated in diabetes. They also found that miR-29c is almost perfectly complementary to Spry1 (the gene that produces the Sprouty homolog 1 protein). Furthermore, they established that knockdown of miRNA-29c by an antisense oligonucleotide has great promise in preventing kidney damage in diabetic patients. Zhang et al. (2018) showed the upregulation of MiR-21 with intermittent hypoxia. MiR-21 has been shown to be involved in arrhythmia and myocardial fibrosis; Spry1 is a downstream target of miR-21. The upregulation of miR-21 in sleep apnea, therefore, provides a good window into the etiology of cardiac problems associated with sleep apnea. The fact that both sleep apnea and diabetes induce changes in miRNA profiles associated with the Spry1/ERK/MMP-9 signaling pathway suggests a set of possible therapeutic targets with the potential to address health issues arising from both conditions. Other miRNAs outside of this pathway are also affected by sleep apnea and diabetes\textsuperscript{63}. Certainly VEGF (as it is also associated with miR-21) should be examined as part of this pathway.

**Conclusions**

There are clearly a number of epigenetic marks common to sleep apnea and diabetes which are not common to healthy controls. We’ve focused here on DNA methylation, miRNAs, and histone modifications, but it’s interesting to note that histone positioning and other epigenetic factors could also play a role in the pathogenesis of these conditions. Whether the two conditions arise from a common root cause, or whether they are two faces of the same condition, the possibility of coevolution has not been ruled out and remains an intriguing idea for further investigation.

\textsuperscript{63} see appendix
It is perhaps helpful to speculate, here.

One possible route to diabetes might go like this: Light pollution disrupts the sleep cycle, throwing the immune system into difficulty. The chaotic immune system is unable to repair the microbiome, which is also under multiple assault from UPFs, lacking nutrients to properly build the body, and taking on preservatives which continue to do their job, even inside the body, namely: killing bacteria. As this multi-front assault proceeds, the body begins to pack on fat deposits, developing both leptin and insulin resistance in the process. This is a protective mechanism, protecting other body systems from metabolic assault. The poor nutrition from UPFs makes it harder for the body to produce insulin receptors and other needed proteins, hastening progression into full-blown metabolic syndrome. To offset some of the problems of metabolic syndrome, sleep apnea begins to manifest. Eventually, the protective mechanisms of obesity and sleep

---

**Figure 2** An indicative model of lifestyle disease. While simplicity is generally preferred, the complexity of this model is outweighed by the fact that it does not contradict the data in hand.
apnea fail, and blood teeter out of homeostatic equilibrium. Continued air pollution tips the scale into a spiral, landing in full-blown diabetes.

Another possibility: Metabolic syndrome is triggered by some combination of overwork and undernutrition\textsuperscript{64}; sleep apnea itself causes homeostatic glucose control to break, and the cascade begins. Again, obesity is part of this cascade, but (again) as a protective measure. In this scenario, obesity is still a measure of poor health – but curing obesity will no more cure the underlying health problems than removing blood from the skin will cure a gut wound.

Another possible route: Social stressors cause a constant assault of cortisol on body tissues, particularly heart tissue. The body triggers sleep apnea to repair it. The sleep apnea disturbs the immune system and thus the microbiome; the body, in an attempt to regulate and repair all this damage, starts storing up adipose tissue. In this scenario, UPFs then provide the perfect storm of poor fuel under external stressors to throw blood sugar regulation out the metaphorical window.

One last possibility: Chemical exposure (possibly through air pollution) causes the body to pack on fat deposits, as a way to safely store those chemicals away from (literal) circulation. Those fat deposits might trigger leptin resistance, then insulin resistance, and so forth. Note that this is very similar to a conventional view of obesity and diabetes, outlined at the beginning of this paper, with the exception that it recognizes that not all causes of obesity are based on individual choices.

Other possible routes to metabolic syndrome can be envisioned, using the data available to us. Clearly, further rigorous research is needed. Whatever the case, solving this question—using real data rather than imagined scenarios—can change people’s lives.

\textsuperscript{64} While undernutrition often refers to a lack of calories, here it is used to indicate a lack of any essential nutrient, including fiber, minerals, and any other nutrient or vitamin necessary for healthy functioning.
Bibliography


Sanchez-de-la-Torre, M, A Khalyfa, A Sanchez-de-la-Torre, M Martinez-Alonso, MA Martinez-Garcia, A Barcelo, P Lloberes et al. 2015. “Precision Medicine in Patients with Resistant Hypertension and Obstructive Sleep Apnea: Blood Pressure Response to Continuous Positive Airway Pressure Treatment.” *Journal of the American College of Cardiology* 66 (9): 1023–32. doi: 10.1016/j.jacc.2015.06.1315.


Yu, HL, S Dong, LF Gao, L Li, YD Xi, WW Ma, LH Yuan, and R Xiao. 2015. “Global DNA Methylation was Changed by a Maternal High-lipid, High-energy Diet During Gestation and Lactation in Male Adult Mice Liver.” *The British Journal of Nutrition* 113 (7): 1032–1039. doi:10.1017/S0007114515000252.


Zhao S, T Li, J Li, Q Lu, C Han, N Wang, Q Qui et al. 2016. “miR-23b-3p Induces the Cellular Metabolic Memory of High Glucose in Diabetic Retinopathy through a SIRT1-dependent Signalling Pathway.” Diabetologia 59 (3): 644–54. doi:10.1007/s00125-015-3832-0.


<table>
<thead>
<tr>
<th>Gene</th>
<th>Description, Alias(es)</th>
<th>Protein</th>
<th>notes</th>
<th>RNA or Histone</th>
<th>Gen. tested</th>
<th>Associated condition</th>
<th>Associated condition described in paper as</th>
<th>Specific epigenetic mark</th>
<th>original paper</th>
<th>review paper reference</th>
<th>review paper reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abca1</td>
<td>ABCA1 (ABC1, HDLDT1, TGD)</td>
<td>ATP binding cassette subfamily A member 1</td>
<td>Activating histone mark; this protein catalyzes the translocation of specific phospholipids using ATP</td>
<td>H3K9Ac increased</td>
<td>Sleep apnea</td>
<td>CIH</td>
<td>Increased H3K9Ac enrichment over ABca1</td>
<td></td>
<td>Cortese et al (2017)</td>
<td>58</td>
<td>Chen et al (2019)</td>
</tr>
<tr>
<td>ACE1</td>
<td>Angiotensin I converting enzyme</td>
<td>Angiotensin I converting enzyme</td>
<td>Increased Ace gene expression; diminished vasodilatory responses, increased ROS content</td>
<td></td>
<td>Sleep apnea</td>
<td>OSA/IHR</td>
<td>Hypomethylated promoter region of Ace1 in mesenteric endothelial cells</td>
<td></td>
<td>Chu et al (2015)</td>
<td>83</td>
<td>Chen et al (2019)</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>ADIPOQ (ACDC, ACRP30, adiponectin, AdipoQ, apM1, GBP28)</td>
<td>Adiponectin, C1Q and collagen domain containing</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>H3K9me increased</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Increased methylation of H3K9 on ADIPOQ</td>
<td>Masuyama and Hiramatsu (2012); Masuyama et al (2015)</td>
<td>(Masuyama and Hiramatsu, 2012; Masuyama et al., 2015)</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>Adiponectin, C1Q and collagen domain containing</td>
<td>adiponectin</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>F1 diabetes</td>
<td>F1 diabetes</td>
<td>Insulin resistance/metabolic syndrome</td>
<td>hypermethylation of adiponectin promoter</td>
<td>Khalyfa et al (2013)</td>
<td>(Khalyfa et al., 2013)</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper reference</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Avy</td>
<td>Agouti Viable Yellow</td>
<td>Avy</td>
<td>Methyl-rich diet; mark found in adult offspring</td>
<td>F1</td>
<td>Diabetes, Metabolic syndrome</td>
<td>Increased methylation of Avy</td>
<td>Cooney et al (2002)</td>
<td>Avy</td>
<td></td>
<td>Cooney et al., 2002</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>---------------</td>
<td>-------------</td>
</tr>
<tr>
<td>BMAL1</td>
<td>aka ARNTL</td>
<td>Aryl hydrocarbon receptor nuclear translocator like or Brain and Muscle ARNTL-Like 1</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td></td>
<td>Diabtes</td>
<td>Metabolic syndrome</td>
<td>increased BMAL1 methylation in white blood cells</td>
<td></td>
<td>Milagro et al (2012)</td>
<td></td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>Cat</td>
<td>catalase</td>
<td></td>
<td>&quot;-- AOE genes were analyzed (Sod1, Sod2, Cat, Txnr2, Txnr4, Gpx2)</td>
<td></td>
<td>PO</td>
<td>IH</td>
<td>* reduced expression of Sod1, Sod2, Txnr2, and Prdx4 vs. controls</td>
<td>increased DNA methylation of Sod1, Sod2, Txnr2, Prdx4 after 30 days of recovery*</td>
<td>Nanduri et al (2017)</td>
<td>Nanduri et al. (19)</td>
<td>Periklous et al (2018)</td>
</tr>
<tr>
<td>CCL2</td>
<td>Acts as a ligand for C-C chemokine receptor CCR2</td>
<td>C-C motif chemokine ligand 2</td>
<td>Increased expression</td>
<td></td>
<td>Sleep apnea</td>
<td>Sleep apnea (CIH in animals)</td>
<td>CCL2 (MCP-1/3E) increased</td>
<td></td>
<td>Lee et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>CDH23</td>
<td>CDHR23, DFNB12, USH1D</td>
<td>Cadherin related 23</td>
<td>Undernutrition of pregnant subject; mark found in adult offspring</td>
<td>F1</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Increased methylation of CDH23 promoter</td>
<td>Tobi et al (2014)</td>
<td>(Tobi et al., 2014)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOCK</td>
<td>bHLHe8, KAT13D, KIAA0334</td>
<td>Clock circadian regulator</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>F1</td>
<td>Diabetes</td>
<td>metabolic syndrome</td>
<td>increased CLOCK me in white blood cells</td>
<td>Milagro et al (2012)</td>
<td>(Milagro et al., 2012)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>May participate in RNA metabolism in the myelinating cell</td>
<td>2',3'-cyclic nucleotide 3' phosphodiesterase</td>
<td>Increased NPR2 and CNP protein expressions; negatively correlated with Epworth Sleepiness Scale</td>
<td>Sleep apnea</td>
<td>OSA/IHR</td>
<td>Hypomethylated promoter region of CNP (-608/-618 CpG sites)</td>
<td>Chen et al (2016)</td>
<td>81</td>
<td>Chen et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------</td>
<td>--------------------------------</td>
<td>-----------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>collagen-α1</td>
<td>collagen</td>
<td>mRNA associated w. genes significantly increased</td>
<td>H3K9me decreased</td>
<td>Diabetes</td>
<td>Decreased H3K9me across collagen-α1</td>
<td>Sun et al (2010)</td>
<td>58</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX2</td>
<td>CO2, COX2, MTCO2</td>
<td>Cytochrome c oxidase II</td>
<td>increased H3K9ac on COX2</td>
<td>Diabetes</td>
<td>increased H3K9ac on COX2</td>
<td>Perrone et al (2009)</td>
<td>83</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT1a</td>
<td>CPT1A(CPT1, CPT1-L, L-CPT1)</td>
<td>Carnitine palmitoyltransferase 1A</td>
<td>Undernutrition of pregnant subject; mark found in adult offspring</td>
<td>Diabetes</td>
<td>Increased methylation of CPT1a</td>
<td>Tobi et al (2014) (Tobi et al., 2014)</td>
<td>83</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>CRP (PTX1)</td>
<td>C-reactive protein</td>
<td>&quot;CRP levels decreased significantly after bariatric surgery (BS)&quot;</td>
<td>Sleep apnea</td>
<td>Increased level of CRP</td>
<td>&quot;Arismendi et al (2014)&quot;</td>
<td>&quot;Arismendi et al. (2014)&quot;</td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>CRP (PTX1)</td>
<td>C-reactive protein</td>
<td>&quot;CRP increased distinctly with increased BMI and Obesity&quot;</td>
<td>Sleep apnea</td>
<td>Increased level of CRP</td>
<td>&quot;Arnardottir et al (2012)&quot;</td>
<td>&quot;Arnardottir et al. (2012)&quot;</td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper reference</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td>C-reactive protein</td>
<td>&quot;Hs-CRP levels were higher in obese patients with OSA compared with Obese controls and lean controls&quot;</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>Increased level of CRP</td>
<td>&quot;Bhushan et al (2009)&quot;</td>
<td>&quot;Bhushan et al. (2009)&quot;</td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td>C-reactive protein</td>
<td>&quot;CRP levels were higher in OSAHS-ED patients than control!&quot;</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>Increased level of CRP</td>
<td>&quot;Bouloukaki et al (2014)&quot;</td>
<td>&quot;Bouloukaki et al (2014)&quot;</td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper reference</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>CRP</td>
<td>CRP (PTX1)</td>
<td>C-reactive protein</td>
<td>&quot;CRP and nocturnal blood pressure levels were higher in patients with hypertension than the control group.&quot;</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>Increased level of CRP</td>
<td>Li et al. (2016)</td>
<td>Li et al. (2016)</td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>CRP (PTX1)</td>
<td>C-reactive protein</td>
<td>&quot;CRP was the highest in OSA patients with hypertension than control group.&quot;</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>Increased level of CRP</td>
<td>Qian et al (2012)</td>
<td>Qian et al. (2012)</td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper reference</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>CRP</td>
<td>CRP (PTX1)</td>
<td>C-reactive protein</td>
<td><em><strong>Non-obese patients with OSA had significantly higher levels of CRP as compared to those without OSA.</strong></em></td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>Increased level of CRP</td>
<td></td>
<td></td>
<td>&quot;Thunstrom et al (2015)&quot;</td>
<td>&quot;Thunstrom et al (2015)&quot;</td>
<td>Khurana et al (2019)</td>
</tr>
<tr>
<td>CRP</td>
<td>CRP (PTX1)</td>
<td>C-reactive protein</td>
<td>increased in men</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>increased hsCRP, IL-6, insulin resistance, and leptin</td>
<td></td>
<td></td>
<td>Gur et al (2016)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>CRP (PTX1)</td>
<td>C-reactive protein</td>
<td>Increased in women</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>increased hsCRP</td>
<td></td>
<td></td>
<td>Gur et al (2016)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>CRP (PTX1)</td>
<td>C-reactive protein</td>
<td>High levels</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>Increased hsCRP</td>
<td></td>
<td></td>
<td>Volná et al (2011)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTGF</td>
<td>CTGF (CCN2, IGFBP8)</td>
<td>Connective tissue growth factor mRNA associated w. genes significantly increased</td>
<td>H3K9me decreased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>Decreased H3K9me on CTGF</td>
<td></td>
<td></td>
<td>Sun et al (2010)</td>
<td>58</td>
<td>Fodor et al (2017)</td>
</tr>
</tbody>
</table>

CRP (C-reactive protein), CTGF (Connective tissue growth factor)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Description, Alias(es)</th>
<th>Protein</th>
<th>notes</th>
<th>RNA or Histone</th>
<th>Gen. tested</th>
<th>Associated condition</th>
<th>described in paper as</th>
<th>Specific epigenetic mark</th>
<th>original paper</th>
<th>review paper reference</th>
<th>review paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyp7a1</td>
<td>CYP7A1 (CYP7)</td>
<td>low protein</td>
<td>F1</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>increased H3K9 methylation across Cyp7a1</td>
<td>Sohie et al (2011)</td>
<td>(Sohie et al., 2011)</td>
<td>Park et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eNOS</td>
<td>Nitric oxide synthase 3, NOS3 (ECNOS, eNOS)</td>
<td>Blood genomic DNA analyzed for epigenetic changes in the core promoter region of eNOS gene</td>
<td>Sleep apnea</td>
<td>Pediatric OSA with high CRP</td>
<td>Hypermethylated CpG in core promoter region of eNOS gene in OSAab group; eNOS mRNA levels significantly decreased in OSAab group vs. OSAan group</td>
<td>Kheirandish-Gozal et al (2013)</td>
<td>Kheirandish-Gozal et al. (17)</td>
<td>Perikleous et al (2018)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alien(s)</td>
<td>Protein</td>
<td>RNA or Histone notes</td>
<td>Associated condition described in paper as</td>
<td>Specific epigenetic mark</td>
<td>Review paper reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>---------------------</td>
<td>---------</td>
<td>----------------------</td>
<td>------------------------------------------</td>
<td>-------------------------</td>
<td>------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET-1</td>
<td>EDN1 (ET1)</td>
<td>Endothelin 1</td>
<td>Histone acetylation at promoter</td>
<td>Diabetes</td>
<td>Increased methylation of ET-1</td>
<td>Chen et al (2010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FADS2</td>
<td>FADS2 (D6D, DES6, FADSD6, LLCDL2, SLL0262, TU13)</td>
<td>Fatty acid desaturase 2</td>
<td>Ununsaturated fatty acid</td>
<td>Diabetes</td>
<td>Increased methylation of FADS2</td>
<td>Fodor et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FG</td>
<td>fibrinogen</td>
<td></td>
<td>High levels</td>
<td>Sleep</td>
<td>mRNA-146a expression</td>
<td>Wu et al (2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN</td>
<td>fibronectin</td>
<td></td>
<td></td>
<td></td>
<td>mRNA-155 expression</td>
<td>Wu et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOXO3a</td>
<td>FOXO3 (AF6q21, FKHRL1, FOXO2, FOXO3A)</td>
<td>Forkhead box O3</td>
<td>Promoting kidney injury</td>
<td>Diabetes</td>
<td>Increased expression of gene</td>
<td>Chen et al (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOXO4</td>
<td>FOXO4 (AFX1, MLLT7)</td>
<td>Forkhead box O4</td>
<td>Activating histone mark</td>
<td>Sleep</td>
<td>High fibrinogen expression</td>
<td>Cortese et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gene tested: Diabetes, metformin, T2D, hyperglycemia, lipopolysaccharide, endotoxin, FADS2 knockout mice.

Notes: Increased methylation; decreased methylation; decreased histone acetylation; increased histone acetylation; increased mRNA expression; decreased mRNA expression; increased miRNA expression; decreased miRNA expression; increased H3K4me3 enrichment over FOXO4.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description, Alias(es)</th>
<th>Protein</th>
<th>notes</th>
<th>RNA or Histone</th>
<th>Gen. tested</th>
<th>Associated condition</th>
<th>described in paper as</th>
<th>Specific epigenetic mark</th>
<th>original paper</th>
<th>review paper reference</th>
<th>review paper reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOXP3</td>
<td>FOXP3 (AIID, DIETER, IPEX, JM2, PIDX, SCURFIN, XPID)</td>
<td>scurfm, forkehead box P3</td>
<td>decreased</td>
<td></td>
<td>Diabetes</td>
<td>T2DM</td>
<td>FOXP3 mRNA more highly expressed in Diabetic patients without nephropathy than in those with nephropathy or in healthy controls.</td>
<td>Telikani et al (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOXP3</td>
<td>FOXP3 (AIID, DIETER, IPEX, JM2, PIDX, SCURFIN, XPID)</td>
<td>scurfm, forkehead box P3</td>
<td>FOXP3 DNA methylation levels were closely correlated with CRP levels</td>
<td>PO</td>
<td>Sleep apnea</td>
<td>Pediatric OSA with high CRP</td>
<td>increased methylation of FOXP3</td>
<td>Kim et al (2012)</td>
<td>Kim et al. (16)</td>
<td>Perikleous et al (2018)</td>
<td></td>
</tr>
<tr>
<td>G6PC</td>
<td>G6PC (G6PT, GSD1a)</td>
<td>Glucose-6-phosphatase catalytic subunit</td>
<td>low protein maternal diet</td>
<td>H3Ac across the promoter increased</td>
<td>F1</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Increased acetylation of H3 on G6PC</td>
<td>Jia et al. (2012)</td>
<td>(Jia et al., 2012)</td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>G6PC</td>
<td>G6PC (G6PT, GSD1a)</td>
<td>Glucose-6-phosphatase catalytic subunit</td>
<td>low protein maternal diet</td>
<td>H3K4me increased</td>
<td>F1</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Increased methylation of H3K4 on G6PC</td>
<td>Jia et al. (2012)</td>
<td>(Jia et al., 2012)</td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>G6PC</td>
<td>G6PC (G6PT, GSD1a)</td>
<td>Glucose-6-phosphatase catalytic subunit</td>
<td>low protein maternal diet</td>
<td>H3K9me decreased</td>
<td>F1</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Decreased methylation of H3K9 on G6PC</td>
<td>Jia et al. (2012)</td>
<td>(Jia et al., 2012)</td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>GABPA</td>
<td>NRF2 aka GABPA (E4TF1-60, E4TF1A, NFT2, NRF2, NRF2A)</td>
<td>GA binding protein transcription factor alpha subunit</td>
<td>Attenuate endothelial dysfunction; a transcription factor which contributes to anti-inflammatory processes</td>
<td>miR-630</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>downregulation of miR-630</td>
<td>Khalyfa et al (2016)</td>
<td>27</td>
<td>Chen et al (2019)</td>
<td></td>
</tr>
<tr>
<td>GAX</td>
<td>Growth arrest-specific homeobox</td>
<td>growth arrest-specific homeobox</td>
<td>miR-130a targets GAX, which potentiates pulmonary hypertension</td>
<td>miR-130a</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>Up regulation of miR-130a</td>
<td>An et al (2017)</td>
<td>62</td>
<td>Chen et al (2019)</td>
<td></td>
</tr>
<tr>
<td>GCLC</td>
<td>GCLC (GCS, GLCL, GLCLC)</td>
<td>Glutamate-cysteine ligase catalytic subunit</td>
<td>review article has typo, listing protein as Gulch, but original article lists as GCLC</td>
<td>H3K4me decreased</td>
<td>Diabetes</td>
<td>diabetic retinopathy</td>
<td>Decreased H3K4me1 on GCLC</td>
<td>Mishra et al (2014)</td>
<td>84</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>GCLC</td>
<td>GCLC (GCS, GLCL, GLCLC)</td>
<td>Glutamate-cysteine ligase catalytic subunit</td>
<td>review article has typo, listing protein as Gulch, but original article lists as GCLC</td>
<td>H3K4me2 increased</td>
<td>Diabetes</td>
<td>diabetic retinopathy</td>
<td>increased H3K4me2</td>
<td>Mishra et al (2014)</td>
<td>84</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>GCLC</td>
<td>GCLC (GCS, GLCL, GLCLC)</td>
<td>Glutamate-cysteine ligase catalytic subunit</td>
<td>review article has typo, listing protein as Gulch, but original article lists as GCLC</td>
<td>H3K4me3 decreased</td>
<td>Diabetes</td>
<td>diabetic retinopathy</td>
<td>Decreased H3K4me3 on GCLC</td>
<td>Mishra et al (2014)</td>
<td>84</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>----------------</td>
<td>-------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>GPX2</td>
<td>GPX2 (GSHPX-G1)</td>
<td>Glutathione peroxidase 2</td>
<td>– AOE genes were analyzed (Sod1, Sod2, Cat, TxnrD2, TxnrD4, Gpx2)</td>
<td>PO</td>
<td>Sleep apnea</td>
<td>IH</td>
<td>&quot;reduced expression of Sod1, Sod2, TxnrD2, and Prdx4 vs. controls increased DNA methylation of Sod1, Sod2, TxnrD2, Prdx4 after 30 days of recovery&quot;</td>
<td>Nanduri et al (2017)</td>
<td>Nanduri et al. (19)</td>
<td>Perikleous et al (2018)</td>
<td></td>
</tr>
<tr>
<td>GR</td>
<td>Glucocorticoid receptor</td>
<td>Undernutrition in test subject; mark found in adult offspring</td>
<td>H3K9Ac increased</td>
<td>F1</td>
<td>diabetes</td>
<td>metabolic syndrome</td>
<td>Increased acetylation of H3K9 on GR</td>
<td>Begum et al (2013)</td>
<td>(Begum et al., 2013)</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>GR</td>
<td>Glucocorticoid receptor</td>
<td>Undernutrition in test subject; mark found in adult offspring</td>
<td>H3K27me decreased</td>
<td>F1</td>
<td>diabetes</td>
<td>metabolic syndrome</td>
<td>Reduced methylation of H3K27 on GR</td>
<td>Begum et al (2013)</td>
<td>(Begum et al., 2013)</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>GR</td>
<td>Glucocorticoid receptor</td>
<td>Undernutrition in test subject; mark found in adult offspring</td>
<td>increased expression</td>
<td>F1</td>
<td>diabetes</td>
<td>metabolic syndrome</td>
<td>DNA methylation of GR reduced</td>
<td>Begum et al (2013)</td>
<td>(Begum et al., 2013)</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>Associated condition described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper reference</td>
<td>review paper reference</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>---------------------------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>HSP60</td>
<td>HSPD1 (GroEL, HSP60, SPG13)</td>
<td>Heat shock protein family D (Hsp60) member 1</td>
<td>Heat shock protein family D (Hsp60) member 1</td>
<td>miR-1</td>
<td>Diabetes</td>
<td>macrovascular complications of diabetes</td>
<td>Increased miR-1 and miR-206</td>
<td>miR-1</td>
<td>Shan et al (2010)</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Protein Name</td>
<td>Description, Alias(es)</td>
<td>RNA or histone modification</td>
<td>Gen. tested</td>
<td>Associated condition described in paper as</td>
<td>Specific epigenetic mark</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>-----------------------------</td>
<td>-------------</td>
<td>-------------------------------------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSP60</td>
<td>HSPD1 (GroEL, HSP60, SPG13)</td>
<td>Heat shock protein family D (Hsp60) member 1</td>
<td>HSP60 is a chaperonin implicated in mitochondrial protein import and macromolecular assembly</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>miR-206</td>
<td>Increased miR-1 and miR-206</td>
<td>Shan et al (2010)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSP60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP3γ</td>
<td>IP3γ</td>
<td>Interferon gamma</td>
<td>IFN-gamma was increased</td>
<td>F1</td>
<td>Diabetes</td>
<td>IFNγ</td>
<td>Metabolic syndrome</td>
<td>Telikani et al (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1</td>
<td>IGF1 (IGF-1, IGF1, IGF1A, IGF1B)</td>
<td>Insulin like growth factor 1</td>
<td>Insulin like growth factor 1</td>
<td>F1</td>
<td>Diabetes</td>
<td>IGF-1</td>
<td>Metabolic syndrome</td>
<td>Park et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF1</td>
<td>IGF1 (IGF-1, IGF1, IGF1A, IGF1B)</td>
<td>Insulin like growth factor 1</td>
<td>Insulin like growth factor 1</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>IGF1</td>
<td>Metabolic syndrome</td>
<td>Park et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF2</td>
<td>IGF2 (C11orf43, FLJ44734, IGF-II)</td>
<td>Insulin like growth factor 2</td>
<td>Insulin like growth factor 2</td>
<td>F1</td>
<td>Diabetes</td>
<td>IGF2</td>
<td>Metabolic syndrome</td>
<td>Park et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-13</td>
<td>IL13/ALPH</td>
<td>Interleukin 13</td>
<td>Interleukin 13</td>
<td>H3K4me reduced</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
<td>Lee et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-17</td>
<td>IL17A (C11orf17, IL-17A / IL-17)</td>
<td>Interleukin 17A</td>
<td>Interleukin 17A</td>
<td>IL-17 increased</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
<td>Lee et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1α</td>
<td>IL1A (IL-1A, IL1-ALPHA, IL1F2)</td>
<td>Interleukin 1 alpha</td>
<td>Interleukin 1 alpha</td>
<td>IL-1α increased</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
<td>Lee et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>IL1B (IL-1B, IL1-BETA, IL1F2)</td>
<td>Interleukin 1 beta</td>
<td>Interleukin 1 beta</td>
<td>IL-1β increased</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
<td>Lee et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>Notes</td>
<td>RNA or histone</td>
<td>Gen. tested</td>
<td>Associated condition described in paper as</td>
<td>Specific epigenetic mark</td>
<td>Specific modification in original paper</td>
<td>Gen. tested</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
<td>-------------------------</td>
<td>--------------------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>IL-4</td>
<td>IL12R-CG1-L, IL-4, IL-4-MGC7946</td>
<td>Interleukin 4</td>
<td>Increased expression</td>
<td>Increased H3K9Ac</td>
<td>Sleep apnea (CHI in animals)</td>
<td>Sleep apnea (CHI in animals)</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>Lee et al (2017)</td>
<td>Chen et al (2019)</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>IL4 (BCGF-1, BSE1, IL-6-1, IL6-2, IL6-3, MGC7914)</td>
<td>Interleukin 6</td>
<td>Activating histone mark</td>
<td>Increased H3K9Ac</td>
<td>Sleep apnea (CHI in animals)</td>
<td>Sleep apnea (CHI in animals)</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>Cortese et al (2017)</td>
<td>Lee et al (2017)</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>IL6 (BSF2, HGF, IGF, IFNB2, IL-6)</td>
<td>Interleukin 6</td>
<td>Increased in men</td>
<td>Increased H3K9Ac</td>
<td>OSA</td>
<td>Sleep apnea (CHI in animals)</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>Gur et al (2016)</td>
<td>Chen et al (2016)</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>IL6 (BSF2, HGF, IGF, IFNB2, IL-6)</td>
<td>Interleukin 6</td>
<td>Increased expression</td>
<td>Increased H3K9Ac</td>
<td>OSA</td>
<td>Sleep apnea (CHI in animals)</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>Gur et al (2016)</td>
<td>Chen et al (2016)</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>CXCL8-13-10C, chemokine ligand 8</td>
<td>IL-8</td>
<td>Increased expression</td>
<td>Increased H3K4Ac</td>
<td>Sleep apnea (CHI in animals)</td>
<td>Sleep apnea (CHI in animals)</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>Gur et al (2016)</td>
<td>Chen et al (2016)</td>
<td></td>
</tr>
<tr>
<td>IL1R2</td>
<td>IL1R2 (CD121b, IL1R3, IL1R4)</td>
<td>Interleukin 1 receptor type 2</td>
<td>Increased IL1R2 protein expression; negatively correlated with oxygen desaturation index*</td>
<td>Increased H200</td>
<td>F2</td>
<td>Diabetes</td>
<td>Metabolism syndrome</td>
<td>increased H200 methylation on insulin gene</td>
<td>Hardikar et al., (2015)</td>
<td>F2</td>
<td></td>
</tr>
<tr>
<td>INS</td>
<td>INS (IDDM1, IDDM2, IDDM3, IDDM4)</td>
<td>insulin</td>
<td>protein expression; load in test subject, increased H3K4Ac methylation on insulin gene</td>
<td>Increased H3K4Ac</td>
<td>F2</td>
<td>Diabetes</td>
<td>Metabolism syndrome</td>
<td>increased H200 methylation on insulin gene</td>
<td>Hardikar et al., (2015)</td>
<td>F2</td>
<td></td>
</tr>
</tbody>
</table>

* indicates increased methylation in the insulin gene

** indicates increased expression in the insulin gene
<table>
<thead>
<tr>
<th>Gene</th>
<th>Description, Alias(es)</th>
<th>Protein</th>
<th>notes</th>
<th>RNA or Histone</th>
<th>Gen. tested</th>
<th>Associated condition</th>
<th>described in paper as</th>
<th>Specific epigenetic mark</th>
<th>original paper</th>
<th>review paper reference</th>
<th>review paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS</td>
<td>INS (IDDM1, IDDM2)</td>
<td>insulin</td>
<td></td>
<td>H3K9me increased</td>
<td>F2 Diabetes</td>
<td>Metabolic syndrome</td>
<td>increased H3K9 methylation on insulin gene</td>
<td>Hardikar et al. (2015)</td>
<td>(Hardikar et al., 2015)</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>INSR</td>
<td>INSR (CD20)</td>
<td>Insulin receptor</td>
<td>Undernutrition of pregnant subject; mark found in adult offspring</td>
<td>Diabetes Metabolic syndrome</td>
<td>Increased methylation of INSR</td>
<td>Tobi et al (2014)</td>
<td>(Tobi et al., 2014)</td>
<td>Park et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRF1</td>
<td>Keap1 (INrf2, KIAA0132, KHL19, MGC10050, MGC1114, MGC20887, MGC4407, MGC9454b)</td>
<td>Kelch like ECH associated protein 1</td>
<td>Kelch like ECH associated protein 1</td>
<td>H3K4me increased</td>
<td>Diabetes diabetic retinopathy</td>
<td>Increased H3K4 methylation over Keap1</td>
<td>Mishra et al (2014)</td>
<td>85</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keap1</td>
<td>Keap1 (INrf2, KIAA0132, KHL19, MGC10050, MGC1114, MGC20887, MGC4407, MGC9454b)</td>
<td>Kelch like ECH associated protein 1</td>
<td>Kelch like ECH associated protein 1</td>
<td>H3K4me increased</td>
<td>Diabetes diabetic retinopathy</td>
<td>Increased H3K4 methylation over Keap1</td>
<td>Mishra et al (2014)</td>
<td>85</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>Protein</td>
<td>notes</td>
<td>Associated condition described in paper as specific epigenetic mark</td>
<td>Cite</td>
<td>Park et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------------------------------------------------------------</td>
<td>------</td>
<td>------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEP</td>
<td>Key player in the regulation of energy balance and body weight control. LEP (OB, OBS)</td>
<td>Leptin</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>H4K20me increased</td>
<td>Diabetes metabolic syndrome</td>
<td>increased methylation of leptin H4K20</td>
<td>Masuyama and Hiramatsu (2012); Masuyama et al. (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leptin</td>
<td>Low protein diet (P0)</td>
<td>F1</td>
<td>Diabetes Metabolic syndrome</td>
<td>reduced leptin promoter methylation</td>
<td>Jousse et al (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leptin</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>F1</td>
<td>Diabetes</td>
<td>Insulin resistance/metabolic syndrome</td>
<td>leptin me reduced</td>
<td>Khalyfa et al (2013)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leptin</td>
<td>increased in men</td>
<td></td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>increased hsCRP, IL-6, insulin resistance, and leptin</td>
<td>Gur et al (2016)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRTM2</td>
<td>Leucine rich repeats and transmembrane domains 2</td>
<td>Repressive histone mark</td>
<td>H3K27me3 increased</td>
<td>Sleep apnea</td>
<td>CIH</td>
<td>increased H3K27 tri-methylation over LRTM2</td>
<td>Cortese et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LXRα</td>
<td>NR1H5 (LXR-a, RLD-1)</td>
<td>Nuclear receptor subfamily 1 group H member 3</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>Diabetes Metabolic syndrome</td>
<td>increased methylation of LXRα</td>
<td></td>
<td>Yu et al (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCL2 (GDCF-2, HC11, MCAF, MCP-1, MCP1, MGC9434, SCYA2, SMC-CF)</td>
<td>(monocyte chemoattractant protein-1) or C-C motif chemokine ligand 2</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>increased H3K4 methylation over MCP-1</td>
<td>Chen et al (2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MEG3</td>
<td>Maternally expressed gene 3 (MEG3) is a long non-coding RNA (lncRNA) located on chromosome 14q22.3.</td>
<td>vitamin B-6</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>increased methylation of MEG3</td>
<td>McCullough et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: LEP: Leptin; LRTM2: Leucine rich repeats and transmembrane domains 2; LXRα: Nuclear receptor subfamily 1 group H member 3; MCP-1: CCL2 (GDCF-2, HC11, MCAF, MCP-1, MCP1, MGC9434, SCYA2, SMC-CF); MEG3: Maternally expressed gene 3 (MEG3) is a long non-coding RNA (lncRNA) located on chromosome 14q22.3.*

*Reference Cites:*
- Masuyama and Hiramatsu (2012); Masuyama et al. (2015)
- Jousse et al (2011)
- Khalyfa et al (2013)
- Gur et al (2016)
- Cortese et al (2017)
- Chen et al (2012)
- McCullough et al (2016)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Description, Alias(es)</th>
<th>Protein</th>
<th>notes</th>
<th>RNA or Histone</th>
<th>Gen. tested</th>
<th>Associated condition</th>
<th>described in paper as</th>
<th>Specific epigenetic mark</th>
<th>original paper</th>
<th>review paper reference</th>
<th>review paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-9</td>
<td>MMP9 (CLG4B)</td>
<td>Matrix metallopeptidase 9</td>
<td>High levels</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>increased MMP-9</td>
<td>Volná et al (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>NF-kB</td>
<td>NFKB1 (KBF1, NF-kappaB, NF-kB1, NFkappaB, NFKB-p50, p105, p50)</td>
<td>Nuclear factor kappa B subunit 1</td>
<td>Review article has typo, listing this as NFκ β, but the original article lists it as NFκB.</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>increased nuclear factorkB</td>
<td>Ryan et al (2006)</td>
<td>10</td>
<td>Gur et al (2016)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nos2</td>
<td>NOS2 (HEP-NOS, iNOS, NOS, NOS2A)</td>
<td>Nitric oxide synthase 2</td>
<td>Repressive histone mark</td>
<td>H3K27me3 increased</td>
<td>Sleep apnea</td>
<td>CIH</td>
<td>increased H3K27 tri-methylation over Nos2</td>
<td>Cortese et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nos2</td>
<td>NOS2 (HEP-NOS, iNOS, NOS, NOS2A)</td>
<td>Nitric oxide synthase 2</td>
<td>Activating histone mark</td>
<td>H3K9Ac increased</td>
<td>Sleep apnea</td>
<td>CIH</td>
<td>Increased H3K9Ac enrichment over Nos2</td>
<td>Cortese et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTK2</td>
<td>NTRK2 (TRKB)</td>
<td>Neurotrophic receptor tyrosine kinase 2</td>
<td>Increased expression</td>
<td>Diabetes</td>
<td>Diabetes (animal)</td>
<td>increased expression of NRTK2</td>
<td>Thomas et al (2013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------------</td>
<td>--------------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Opn</td>
<td>SPP1 (BNSP, BSPI, ETA-1, OPN)</td>
<td>Secreted phosphoprotein 1</td>
<td>deactivating histone marks increased in promoter</td>
<td>H3K27me3 decreased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>decreased H3K27me3 across OPN</td>
<td></td>
<td>Cai et al (2016)</td>
<td>61</td>
<td>Fodor et al (2017)</td>
</tr>
<tr>
<td>Opn</td>
<td>SPP1 (BNSP, BSPI, ETA-1, OPN)</td>
<td>Secreted phosphoprotein 1</td>
<td>activating histone marks increased in promoter</td>
<td>H3K4me increased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>Increased H3K4me1 across OPN</td>
<td></td>
<td>Cai et al (2016)</td>
<td>61</td>
<td>Fodor et al (2017)</td>
</tr>
<tr>
<td>Opn</td>
<td>SPP1 (BNSP, BSPI, ETA-1, OPN)</td>
<td>Secreted phosphoprotein 1</td>
<td>activating histone marks increased in promoter</td>
<td>H3K4me3 increased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>Increased H3K4me3 across OPN</td>
<td></td>
<td>Cai et al (2016)</td>
<td>61</td>
<td>Fodor et al (2017)</td>
</tr>
<tr>
<td>p300</td>
<td>EP300 (KAT3B, p300)</td>
<td>E1A binding protein p300</td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>macrovascular complications of diabetes</td>
<td>p300 expression increases with glucose; p300 siRNA prevented basal (except for VEGF) and glucose-induced overexpression of all vasoactive factors and ECM proteins.</td>
<td></td>
<td>Chen et al (2010)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper reference</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>-------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>PACT/RAX</td>
<td>Pact is a protein kinase, interferon-inducible double stranded RNA dependent activator;</td>
<td>PACT is human, RAX is the murine ortholog; paper records this as PACT/RAX</td>
<td></td>
<td>Diabetes</td>
<td>diabetic retinopathy</td>
<td>Increased miR-29b</td>
<td></td>
<td>Silva et al (2011)</td>
<td>90</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>PAI-1</td>
<td>SERPINE1 (PAI, PAI1, PLANH1)</td>
<td>Serpin family E member 1; as PLAT inhibitor, it is required for fibrinolysis down-regulation</td>
<td>H3K27me3 decreased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>decreased H3K27me3 over PAI-1</td>
<td></td>
<td>Reddy et al (2014)</td>
<td>63</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>PAI-1</td>
<td>SERPINE1 (PAI, PAI1, PLANH1)</td>
<td>Serpin family E member 1; as PLAT inhibitor, it is required for fibrinolysis down-regulation</td>
<td>mRNA associated w. genes significantly increased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>increased H3K4me over PAI-1</td>
<td></td>
<td>Sun et al (2010)</td>
<td>58</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>PAI-1</td>
<td>SERPINE1 (PAI, PAI1, PLANH1)</td>
<td>Serpin family E member 1; as PLAT inhibitor, it is required for fibrinolysis down-regulation</td>
<td>H3K9/14Ac increased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>Increased H3K9/14Ac on PAI-1</td>
<td></td>
<td>Reddy et al (2014)</td>
<td>63</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>PAI-1</td>
<td>SERPINE1 (PAI, PAI1, PLANH1)</td>
<td>Serpin family E member 1; as PLAT inhibitor, it is required for fibrinolysis down-regulation</td>
<td>H3K9me2 decreased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>decreased H3K9me2 over PAI-1</td>
<td></td>
<td>Reddy et al (2014)</td>
<td>63</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>PAI-1</td>
<td>SERPINE1 (PAI, PAI1, PLANH1)</td>
<td>Serpin family E member 1; as PLAT inhibitor, it is required for fibrinolysis down-regulation</td>
<td>H3K9me3 decreased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>decreased H3K9me3 over PAI-1</td>
<td></td>
<td>Reddy et al (2014)</td>
<td>63</td>
<td>Fodor et al (2017)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Aliases</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>--------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>----------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>PGC1-α</td>
<td>PPARGC1A (POC-1alpha, PGC1, PGC1A, PPARGC1)</td>
<td>PPARG coactivator 1 alpha</td>
<td>Methyl donor-deficiency</td>
<td></td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>decreased methylation of (d21) PGC1-α</td>
<td>Pooya et al (2012)</td>
<td></td>
<td>(Pooya et al., 2012)</td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>PKCε</td>
<td>PRKCE</td>
<td>Protein kinase C epsilon</td>
<td>Promote cardiac hypertrophy</td>
<td>miR-31</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>upregulation of miR-31</td>
<td>Ren et al (2018)</td>
<td>71</td>
<td>Chen et al (2019)</td>
<td></td>
</tr>
<tr>
<td>Polg1</td>
<td>&quot;</td>
<td>POLG(POLG1, POLGA)*</td>
<td>DNA polymerase gamma, catalytic subunit</td>
<td></td>
<td>Diabetes</td>
<td>diabetic retinopathy</td>
<td>Hypermethylation of POLG1</td>
<td>Tewari et al (2012)</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POSTN</td>
<td>POSTN (OSF-2, periostin, PN)</td>
<td>Periostin</td>
<td>Increased expression</td>
<td></td>
<td>Sleep apnea</td>
<td>Sleep apnea (CIH in animals)</td>
<td>increased periostin</td>
<td>Lee et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPARγ</td>
<td>PPARG (NR1C3, PPARG1, PPARG2, PPARGamma)</td>
<td>Peroxisome proliferator activated receptor gamma</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>F1</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>increased methylation of PPARγ</td>
<td>Fujiki et al (2009)</td>
<td></td>
<td>Fujiki et al., 2009</td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>PPARγ</td>
<td>PPARG (NR1C3, PPARG1, PPARG2, PPARGamma)</td>
<td>Peroxisome proliferator activated receptor gamma</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td></td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>increased methylation of PPARγ</td>
<td>Yu et al (2015)</td>
<td></td>
<td>(Yu et al., 2015)</td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>Associated condition described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper reference</td>
<td>review paper reference</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>---------------------------------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Prdx4</td>
<td>PRDX4 (AOE37-2)</td>
<td>Peroxiredoxin 4</td>
<td>-- AOE genes were analyzed (Sod1, Sod2, Cat, Txnrd2, Prdx4, Gpx2) [typo in review article read trdx4, amended from original article]</td>
<td>PO Sleep apnea</td>
<td>IH</td>
<td></td>
<td>&quot;reduced expression of Prdx4 vs. controls increased DNA methylation of Prdx4&quot;</td>
<td>Nanduri et al (2017)</td>
<td>Nanduri et al. (19)</td>
<td>Perikleous et al (2018)</td>
<td></td>
</tr>
<tr>
<td>PRKAA1</td>
<td>Protein kinase AMP-activated catalytic subunit alpha 1</td>
<td>AMP kinase</td>
<td>Attenuate endothelial dysfunction</td>
<td>miR-630</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>downregulation of miR-630</td>
<td>Khalyfa et al (2016)</td>
<td>27</td>
<td>Chen et al (2019)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>----------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PTEN/PI3K/AKT</td>
<td>an important pathway regulating the signaling of multiple biological processes such as apoptosis, metabolism, cell proliferation and cell growth. May induce atrial remodeling and fibrosis.</td>
<td>miR21</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>up-regulated mir21 which targets this pathway</td>
<td>Zhang et al (2018), Wang et al (2018)</td>
<td>69,70</td>
<td>Chen et al (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAGE</td>
<td>MOK (RAGE, RAGE1, STK30)</td>
<td>MOK protein kinase</td>
<td>H3K27me3 decreased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>decreased H3K27me3 over RAGE</td>
<td>Reddy et al (2014)</td>
<td>63</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAGE</td>
<td>MOK (RAGE, RAGE1, STK30)</td>
<td>MOK protein kinase</td>
<td>H3K9me3 decreased</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>decreased H3K9me3 over RAGE</td>
<td>Reddy et al (2014)</td>
<td>63</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper reference</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>RFTN1</td>
<td>RFTN1 (FLJ23866, KIAA0084, MIG2, Raftlin)</td>
<td>Raftlin, lipid raft linker 1</td>
<td>Undernutrition of pregnant subject; mark found in adult offspring</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Decreased methylation of RFTN1</td>
<td>Tobi et al (2014)</td>
<td>(Tobi et al., 2014)</td>
<td>Park et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUNX3</td>
<td>RUNX3 (AML2, CBFA3, PEBP2A3)</td>
<td>Run related transcription factor 3</td>
<td>Diabetes</td>
<td>miR-218</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRT1</td>
<td>SIRT1 A Class III HDAC (SIR2L1)</td>
<td>Sirtuin 1</td>
<td>miR-195</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>Increased miR-23b-3p and miR-195</td>
<td>Mortuza et al (2016)</td>
<td>87,92</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRT1</td>
<td>SIRT1 A Class III HDAC (SIR2L1)</td>
<td>Sirtuin 1</td>
<td>miR-23b-3p</td>
<td>Diabetes</td>
<td>Diabetic nephropathy</td>
<td>Increased miR-23b-3p and miR-195</td>
<td>Mortuza et al (2016)</td>
<td>87,92</td>
<td>Fodor et al (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRT1</td>
<td>SIRT1 A Class III HDAC (SIR2L1)</td>
<td>Sirtuin 1</td>
<td>Sirt1 targets Foxo4 for deacetylation</td>
<td>Diabetes</td>
<td>Diabetic</td>
<td>reduced expression of SIRT1</td>
<td>Chuang et al (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slc2a4</td>
<td>SLC2A4 (GLUT4)</td>
<td>Solute carrier family 2 member 4</td>
<td>H3K9me3 increased</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>increased trimethylation of H3K9 on Slc2a4</td>
<td>Yonamine et al (2019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slc3a2</td>
<td>SLC3A2 (4F2, 4F2HC, 4T2HC, CD98, CD98HC, MDU1, NACAE)</td>
<td>Solute carrier family 3 member 2</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>F1</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Increased methylation of Slc3a2</td>
<td>de Castro Barbosa et al (2016)</td>
<td>(de Castro Barbosa et al., 2016)</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>Slc1a1</td>
<td>solute carrier organic anion transporter family, member 1a1</td>
<td>Mus musculus (house mouse) gene</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Smad3</td>
<td>SMAD3 (HsT17436, JV15-2, MADH3)</td>
<td>SMAD family member 3</td>
<td>Attenuate aortic remodeling and sympathetic nerve sprouting</td>
<td>miR-145</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>downregulation of miR-145</td>
<td></td>
<td>Yu et al (2017)</td>
<td>76</td>
<td>Chen et al (2019)</td>
</tr>
<tr>
<td>SMAD7</td>
<td>SMAD7 (MADH7, MADH8)</td>
<td>SMAD family member 7</td>
<td>Undernutrition of pregnant subject; mark found in adult offspring</td>
<td></td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Increased methylation of SMAD7</td>
<td>Tobi et al (2014)</td>
<td>(Tobi et al., 2014)</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>Sod1</td>
<td>SOD1 (ALS, ALS1, IPOA)</td>
<td>Superoxide dismutase 1</td>
<td>AOE genes were analyzed (Sod1, Sod2, Cat, Txnrd2, Txnrd4, Gpx2)</td>
<td></td>
<td>Sleep apnea</td>
<td>IH</td>
<td>&quot;AM displayed reduced expression of Sod1 increased DNA methylation of Sod1&quot;</td>
<td>Nanduri et al (2017)</td>
<td>Nanduri et al. (19)</td>
<td>Perikleous et al (2018)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------</td>
<td>---------</td>
<td>-------</td>
<td>-------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Sod2</td>
<td>SOD2</td>
<td>Superoxide dismutase 2</td>
<td>^- DNMT mRNA levels in AM and CB and corresponding proteins were analyzed – Analysis of DNA methylation status of CpG islands in rat Sod2 and Duox2 genes ^</td>
<td>F1</td>
<td>Sleep apnea</td>
<td>IH</td>
<td>DNA methylation of Sod2 gene incremented 6- and 12-fold in CB and AM, respectively, in rats exposed to IH ^</td>
<td>Nanduri et al (2012)</td>
<td>Nanduri et al. (18)</td>
<td>Perikleous et al (2018)</td>
<td></td>
</tr>
<tr>
<td>Sod2</td>
<td>SOD2</td>
<td>Superoxide dismutase 2</td>
<td>^- AOE genes were analyzed (Sod1, Sod2, Cat, Txmd2, Txmd4, Gpx2)</td>
<td>PO</td>
<td>Sleep apnea</td>
<td>IH</td>
<td>DNA methylation of Sod2 gene incremented 6- and 12-fold in CB and AM, respectively, in rats exposed to IH ^</td>
<td>Nanduri et al (2017)</td>
<td>Nanduri et al. (19)</td>
<td>Perikleous et al (2018)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>SP140</td>
<td>SP140 (LYSP100-A, LYSP100-B)</td>
<td>SP140 nuclear body protein</td>
<td>Decreased SP140 protein expression; positively correlated with Epworth Sleepiness Scale</td>
<td></td>
<td>Sleep apnea</td>
<td>OSA/HHR</td>
<td>Hypermethylated promoter region (-194 CpG site) of SP140</td>
<td></td>
<td>Chen et al (2016)</td>
<td>81</td>
<td>Chen et al (2019)</td>
</tr>
<tr>
<td>Spry0</td>
<td>SPRY1 (hSPRY1)</td>
<td>Sprouty RTK signaling antagonist 0</td>
<td></td>
<td>miR 29c</td>
<td>Diabetes</td>
<td>diabetic nephropathy</td>
<td>Increased miR-29c</td>
<td></td>
<td>Long et al (2011)</td>
<td>73</td>
<td>Fodor et al (2017)</td>
</tr>
<tr>
<td>Spry1</td>
<td>SPRY1 (hSPRY1)</td>
<td>protein sprouty homolog 1; Sprouty RTK signaling antagonist 1</td>
<td></td>
<td>miR 29c</td>
<td>Diabetes</td>
<td>diabetic nephropathy</td>
<td>Increased miR-29c</td>
<td></td>
<td>Long et al (2011)</td>
<td>73</td>
<td>Fodor et al (2017)</td>
</tr>
<tr>
<td>Spry1</td>
<td>SPRY1 (hSPRY1)</td>
<td>protein sprouty homolog 1; Sprouty RTK signaling antagonist 1</td>
<td>Induce atrial remodeling and fibrosis</td>
<td>miR-21</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>upregulation of miR-21</td>
<td></td>
<td>Zhang et al (2018), Wang et al (2018)</td>
<td>69,70</td>
<td>Chen et al (2019)</td>
</tr>
<tr>
<td>sRAGE</td>
<td>Soluble RAGE (sRAGE)</td>
<td></td>
<td>acts as a decoy receptor for AGEs and may prevent inflammation</td>
<td></td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>Low levels of sRAGE</td>
<td></td>
<td>Vohná et al (2011)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>tight junction pathways</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td>Tumor necrosis factor attenuate insulin resistance</td>
<td>miR-452</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>downregulation of miR-452</td>
<td>Khalyfa et al (2016)</td>
<td>27</td>
<td></td>
<td>Chen et al (2019)</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>TNF (DIF, TNF-alpha, TNFA, TNFSF2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>TNF (DIF, TNF-alpha, TNFA, TNFSF2)</td>
<td>summary of table 3</td>
<td>P0</td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>increased level of TNF-α</td>
<td>Gur et al (2016)</td>
<td>table 3</td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>TNF (DIF, TNF-alpha, TNFA, TNFSF2)</td>
<td>increased</td>
<td></td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>increased nuclear factor-k β, TNF-α, and IL-8</td>
<td>Gur et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSPAN17</td>
<td>TSPAN17 (FBX23, FBXO23, TM4SF17)</td>
<td>Tetraspanin 17</td>
<td>miR-378a-3p predicts blood pressure decreases to CPAP treatment; multiple targets, including TSPAN17. Overexpression of miR-378a-3p decreased the expression of TSPAN17, promoted apoptosis and decreased proliferation, migration and invasion.</td>
<td></td>
<td>PO</td>
<td>Sleep apnea</td>
<td>IHR</td>
<td>Up-regulated miR-378a-3p</td>
<td>Guo et al (2019)</td>
<td>60</td>
<td>Chen et al (2019) and Torre et al (2015)</td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Txrd2</td>
<td>TXNRD2 (TR, TR3, TRXR2)</td>
<td>Thioredoxin reductase 2</td>
<td>- AOE genes were analyzed (Sod1, Sod2, Cat, Txrd2, [Prdx4], Gpx2) [typo in review article read trdx4, amended from original article]</td>
<td>PO Sleep apnea</td>
<td>IH</td>
<td></td>
<td>reduced expression of Txrd2; increased DNA methylation of Txrd2</td>
<td></td>
<td>Nanduri et al (2017)</td>
<td>Nanduri et al. (19)</td>
<td>Perikleous et al (2018)</td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Genetested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
<td>------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>---------------</td>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Wnt1</td>
<td>WNT1 (INT1)</td>
<td>Wnt family member 1</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>H3Ac reduced</td>
<td>F1</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Decreased acetylation of H3</td>
<td>Yang et al (2012)</td>
<td>Yang et al., 2012a,b</td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>Wnt1</td>
<td>WNT1 (INT1)</td>
<td>Wnt family member 1</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>H3K9me increased</td>
<td>F1 (D7)</td>
<td>Diabetes</td>
<td>Metabolic syndrome</td>
<td>Increased methylation of H3K9 over Wnt1</td>
<td>Yang et al (2012)</td>
<td>Yang et al., 2012a,b</td>
<td>Park et al (2017)</td>
</tr>
<tr>
<td>Wnt1</td>
<td>WNT1 (INT1)</td>
<td>Wnt family member 1</td>
<td>Overnutrition in test subject; mark found in adult offspring</td>
<td>H4Ac reduced</td>
<td>Diabetes</td>
<td>metabolic syndrome</td>
<td>Wnt1 H4Ac reduced</td>
<td>Yang et al (2012)</td>
<td>Yang et al., 2012a,b</td>
<td>Park et al (2017)</td>
<td></td>
</tr>
<tr>
<td>YKL-40</td>
<td>CHI3L1 (GP39, YKL40)</td>
<td>(human cartilage glycoprotein) Chitinase 3 like 1</td>
<td>increased</td>
<td></td>
<td></td>
<td>Sleep apnea</td>
<td>OSA</td>
<td>YKL-40 (human cartilage glycoprotein) increased</td>
<td>Gur et al (2016)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<p>|  |  |  |  | miR-107 | Diabetes | Diabetes | | | Khurana et al (2019) |
|  |  |  |  | miR-122 | Diabetes | Diabetes | | | Khurana et al (2019) |
|  |  |  |  | miR-124 | Diabetes | Diabetes | | | Khurana et al (2019) |
|  |  |  |  | miR-126 | Diabetes | Diabetes | | | Khurana et al (2019) |</p>
<table>
<thead>
<tr>
<th>Gene</th>
<th>Description, Alias(es)</th>
<th>Protein</th>
<th>notes</th>
<th>RNA or Histone</th>
<th>Gen. tested</th>
<th>Associated condition described in paper as</th>
<th>Specific epigenetic mark</th>
<th>original paper</th>
<th>review paper reference</th>
<th>review paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-133</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>miR-134</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>miR-143</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>low levels of miR-143</td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>miR-145</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>miR-146a</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>miR-15a</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>miR-17-5p</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>miR-181a</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>miR-21</td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in original paper as</td>
<td>Specific epigenetic mark</td>
<td>review paper reference</td>
<td>review paper</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>--------------------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>miR-26b</td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>diabetes</td>
<td>increase in miR-26b</td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-29</td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>diabetes</td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-335</td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes and obesity</td>
<td>low levels of miR-335</td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-33a/b</td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>diabetes</td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-34a</td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>diabetes</td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein</td>
<td>notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>miR-503</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
</tr>
<tr>
<td>miR-543</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
</tr>
<tr>
<td>miR-7</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
</tr>
<tr>
<td>miR-9</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
</tr>
<tr>
<td>miR-93</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
</tr>
<tr>
<td>miR-96</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Khurana et al (2019)</td>
</tr>
<tr>
<td>Gene</td>
<td>Description, Alias(es)</td>
<td>Protein notes</td>
<td>RNA or Histone</td>
<td>Gen. tested</td>
<td>Associated condition</td>
<td>described in paper as</td>
<td>Specific epigenetic mark</td>
<td>original paper</td>
<td>review paper reference</td>
<td>review paper</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>AGE (Advanced Glycation End products)</td>
<td>higher sugar causes AGE causes Foxo4 ^Bcl2II; AGE probably increases lysine acetylation of Foxo4, necessary for binding and transcription of Bcl2II</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>Elevated AGIs activate FOXO4 transcription factor</td>
<td>Chuang et al (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>OSA</td>
<td>reduced nitrite and nitrate</td>
<td></td>
<td></td>
<td>Gur et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>