Review

Genetic construction between polycystic ovarian syndrome and type 2 diabetes

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ABSTRACT

Polycystic ovarian syndrome (PCOS) in reproductive-aged women is identified to be one of the endocrine disorders. This heterogeneous disorder is categorized through oligo-anovulation and hyperandrogenemia. National institutes of health and Rotterdam criterions were used to diagnose PCOS women. Type 2 Diabetes (T2D) is one of the complications in PCOS which is connected through insulin resistance (IR), which is a condition in which liver, muscles and fat infrequently respond to the hormones, and this leads to extreme IR and consequently leads to T2D disease. PCOS is inherited by the autosomal dominant mode of inheritance and may also with the different intricate patterns. Till now, many studies have been performed in PCOS with the genes identified by T2D and till now no studies have shown the similar genetic association and pathophysiology between both the diseases. So, the current review aims to investigate the genetic relation between PCOS and T2D and why both the diseases cannot be reverted. In this review, published data were screened with the T2D related genes and single nucleotide polymorphisms in PCOS women. The case-control, hospital-based and *meta*-analysis molecular studies disclosed both positive and negative connotations. Genetically, no relationship has been established between PCOS and T2D. Maximum studies have shown as PCOS women had developed T2D later in life because as a risk-factor, but none of the studies documented T2D women having developed PCOS as a risk factor. Apart from this, the disease PCOS is developed in women with reproductive age and T2D develops in both the men and women during adulthood. This review concludes as there is a genetic relation only in between PCOS and T2D, but not with T2D to PCOS and further it cannot be explicitly reverted from T2D to PCOS.

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1. Introduction

Polycystic ovarian syndrome (PCOS; OMIM-184700) is distressing reproductive women with documented endocrine disorders (Amisi and Ciccozzi, 2020). PCOS is a multifactorial, heterogeneous,

and life-long disorder that affects the hormone levels in women (Parker et al., 2020). Pre-menopausal women with 5–10% are affected by PCOS (Rondanelli et al., 2020). The history of PCOS was initially defined in 1935 by Stein and Leventhal as a combination of hirsutism, amenorrhea, infertility, distended ovaries, obesity and chronic anovulation (Stein, 1935). World Health Organization (WHO) formerly included PCOS with sclerotic ovary-Stein-Leventhal syndromes, till 10th revision of International Classification of Diseases in 1990 (Organization, 1992). Based on the symptoms, unapproved medical agency drugs were used to treat women with PCOS (Rojas et al., 2014). One of the major complications for PCOS is insulin resistance (IR); powerfully associated with diabetes and cardiovascular diseases (CVD) and these diseases are detected between 35 and 80% of PCOS women (Amisi et al., 2013). Based on NIH and Rotterdam criterias the PCOS prevalence ranged between 6 and 20% in the global population. PCOS women will be suffering from short and long-term complications such as reproductive, and physiological disorders (Ma et al., 2019). Rotterdam criteria method was used to diagnose PCOS women through the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (Alsibyani et al., 2017). The Rotterdam criteria encompass numerous phenotypes based on the presence of two–three findings of polycystic ovaries on ultrasound, irregular menses and hyperandrogenism (ESHRE TR, Fertility A-SPCWGJ, 2004). The Rotterdam definition is the currently accepted classification for PCOS, supported by scientific societies and health authorities worldwide. As per the accepted definition of PCOS, any women can be diagnosed based on clinical characteristics; for example, ovulatory dysfunction, polycystic ovaries, biochemical, clinical hyperandrogenism (Revised, 2003). Contribution of PCOS diagnostic criteria was an ultrasonographic picture of PCO, hyperandrogenism (clinical/laboratory) and oligo or anovulation (Menshawy et al., 2019) (Table 1). PCOS is categorized with genetic and environmental interaction mechanisms (Hepsen et al., 2019). Irregular menstruation, infertility, ovulation disorder, acne and hirsutism are known as an essential clinical manifestation in PCOS women. Additionally, PCOS will establish an enlarged occurrence of hyperinsulinemia, obesity, IR, T2D and impaired glucose tolerance (IGT) (Shi et al., 2019). High fat, low-fibre diet, consumption of alcohol, smoking, and sedentary lifestyles can contribute to the onset of PCOS. Healthy habits, including an active lifestyle, and an adequate diet without toxic substances can help prevent PCOS. Presence of polycystic-ovaries is recurrently appearing in PCOS women due to the accretion of ovarian follicles at various phases of atresia (Dewailly et al., 2013). Womens and their family members express irrational concerns for potential malignancy of cysts (Azziz, 2014). Aetiology of PCOS disease is inadequate till now. However, women are generally unprotected enormously for traumatic with regular physical activity, poor protein and high carbohydrate diet fat along with long periods of famine and infection (Escobar-Morreale, 2018;14(5):). PCOS may reflect a trade-off imposed by the need to survive the lean times by being energy-efficient ("thrifty genotype"), but in many times, the thrifty genotype can favor the development of PCOS. Symptoms of PCOS vary significantly among women of different ethnicity. The basic PCOS symptoms are obesity, hyperandrogenism, IR and chronic oligo-anovulation. Symptoms of CVD and T2D were disposes (Tiongco et al., 2019). Transformed gonadotrophin secretion increases LH-FSH ratios, inadequate FSH stimulation of ovaries (De Leo et al., 2016). Hyperinsulinism may be endogenous or exogenous. Endogenous includes T2D, gestational diabetes, obesity, IR, insulinomas, whereas exogenous reflects insulin dependent or type 1 diabetes. Women with extreme IR and obesity will not progress for PCOS (Li et al., 2013).

2. Genetics of PCOS

The PCOS disease is a heterogeneous disorder with unidentified aetiology. PCOS is known to be inherited genetically with the autosomal dominant manner and 50% of chances are documented of inheritance from mother to daughter. The disease PCOS is connected with the development of obesity and IR; further finally leads to T2D (Pelanis et al., 2017). The genetic evidence was documented with the presence of chronic disease either in any of the parents can create unfavorable conditions in wombs associated with the prone of PCOS in their female children (Legro RSJTAjom. 1995). Autosomal dominant transmission may link-up with single gene defect, but PCOS is known as polygenic pathology. It may happen due to one of the possible angles are specific gene in any families may have a predominant effect and stimulates the phenotypic manifestation (De Leo et al., 2016). The PCOS women will show the higher values in both the testosterone and androgen hormonal levels and further it contributes to the unbalanced menstruation, acne, weight gain, which leads to obesity and infertility (Ollila et al., 2017). Women with PCOS suffer from the symptoms of excess androgen, reproductive dysfunction and metabolic complications; which involves IR, compensatory hyperinsulinemias associated with IGT, GDM, T2D, NAFLD and CVD (Rodgers et al., 2019). In PCOS women, the existence of genetic (gene) abnormalities has been widely discovered. Numerous genes have been connected with PCOS, which plays a role in disease developing through the appearance of mutations or polymorphisms (Fratantonio et al., 2005) (Table 2). Accurate genetic variants have not been docu-

Table 2
List of T2D genes/SNPs associated in molecular studies of PCOS (Reddy et al., 2016).

S. No	T2D Genes	SNP/rs number
1	TCF7L2	rs7903146
2	TCF7L2	rs11196205
3	TCF7L2	rs12255372
4	IGFBP2	rs4402960
5	IGFBP2	rs1470579
6	HHEX	rs11111875
7	HHEX	rs7923837
8	CDKAL1	rs7754840
9	CDKAL1	rs7756992
10	CALPAIN 10	rs3792267
11	CALPAIN 10	rs5030952
12	SLC30A8	rs13266634
13	CDKN2A/B	rs10811661
14	IRS1	rs1801278
15	PPARG	rs1801282

Table 1
Diagnostic criteria of PCOS women (Spritzer and Metabologia., 2014).

Consensus criteria's	Features	Features
NIH Consensus-1990	• Clinical or biochemical hyperandrogenism	• Oligo amenorrhea, anovulation
Rotterdam Consensus-2003	• Clinical or biochemical hyperandrogenism	• Oligo amenorrhea, anovulation
		• Appearance of Polycystic ovaries on ultrasound
AEPCOS definition-2006	• Clinical or biochemical hyperandrogenism	• Oligo amenorrhea, anovulation
		• Appearance of Polycystic ovaries on ultrasound

mented until now in PCOS. However, single-gene mutation gives rise to the phenotypes of PCOS (Govind et al., 1999). Right now, universally no genes have been accepted as an important aetiology in PCOS. Association and linkage studies were used to identify the genetic locus for PCOS genes. A predisposing allele is assumed to be found more frequently in the exaggerated population in an association studies; whereas in linkage analysis studies, probands with their families were explored to determine genomic landmarks are distributed separately or non-separately with linkage of phenotype. Limited number of genes have been connected with PCOS through chronic inflammation, steroid hormone actions, energy homeostasis, insulin action, insulin secretion, gonadotrophin regulation, gonadotrophin action, ovarian and adrenal steroidogenesis (Prapas et al., 2009). PCOS and genetics have been involved with candidate genes and single nucleotide polymorphisms (SNPs). PCOS is connected with 241 genetic variants (Joseph et al., 2016). The single nucleotide may lead to the defect in the transcriptional activity of a particular gene and this leads to PCOS disease. The strongest associated genes with PCOS are *FTO, AR, CAPN10, CYP450, INS*, and *FSHR* (Ajmal and Khan, 2019). Identified variants by genome-wide association studies (GWAS for T2D are *CDKAL1, FTO, HHEX, KCNJ11, SLC30A8* and *TCF7L2* genes have not been documented to have significant association in PCOS studies (Ewens et al., 2011; Kim et al., 2012; Saxena and Welt, 2013). The role of GWAS is to aspect for a relation between disease and common genetic SNP without any predefined hypothesis.

A misconception was linked up with GWAS is that they document the precise genes; but in certainty, it documents the associated marker in the ethnic population (Hiam et al., 2019). GWAS has been carried out in Han Chinese and European ancestry women and reproduced identifying 16 loci (Chen et al., 2011; Shi et al., 2012; Hayes et al., 2015; Day et al., 2015). Meta-analysis studies performed in PCOS with molecular case-control studies have been documented with both positive and negative factors (Cheng et al., 2019; Li et al., 2020; Liang et al., 2019; Liao et al., 2018; Liu et al., 2017; Liu and Fat, 2017; Niu et al., ; Pabalan et al., 2016; Park et al., 2019; Tiongco et al., 2019; Zhu et al., 2019; Zou et al., 2019). Day et al. (Day et al., 2018) from his large *meta*-analysis and GWAS studies; identified three novel loci such as *PLGRKT*; *ZBTB16* and *MAPRE1* and also replication of 11 loci previously documented. There are enormous case-control studies performed in PCOS women with the molecular analysis. However, large number of studies were linked up with documented SNPs for T2D were also performed in PCOS women in different ethnic populations (Cheng et al., 2019; Li et al., 2020; Park et al., 2019; Tiongco et al., 2019; Zhu et al., 2019; Batarfi et al., 2019; Dakshinamoorthy et al., 2020; Huang and Wang, 20202020; Olt et al., 2019; Raihan et al., 2019; Saeed et al., 2019; Santos et al., 20192019). GWAS or candidate genes related with T2D risk mutations duplicate in adequately powered studies may also converse the risk in PCOS and limited positively associated studies were also documented (Ewens et al., 2011; Barber et al., 2007; Barber et al., 2007; Barber et al., 2008; Li et al., 2011; Wang et al., 2010).

3. Connection between PCOS and T2D

T2D is known to be chronic and multifactorial disorders connected strongly with the family histories of T2D, obesity, other metabolic diseases (Khan et al., 2014). PCOS is recognized as a common disorder in women characterized by hyperandrogenemia and oligo-anovulation (Maas et al., 2016). Based on the International Diabetes Federation, PCOS is established as a non-modifiable risk factor associated with T2D (Sathyapalan and Atkin, 2011). IR is known to be the common factor for the connection between PCOS and T2D. In PCOS, the pathogenesis of IR is

known to be multifactorial inheritance; while the family histories of IR, as well as obesity, were seeming to be highly prevalent in affected women (Christopoulos et al., 2008). Apart from this, both the parent's family and self-histories are inheriting the disease to their children and converting as a family disease. Excluding this, PCOS and T2D are connected by sharing standard features and thus, genetic susceptibility factors were associated with both the pathologies (Ben-Salem et al., 2014). Both the men and women in first-degree relatives of affected PCOS women will increase the risks of IR, obesity and T2D. Affecting the mode of inheritance remains to be unknown. IR is known for the protest in lean and obese women with PCOS (Silva et al., 2015). Peppard et al (Peppard et al., 2001) studies also confirmed from Virginia hospitals as PCOS occurs recurrently in premenopausal women with T2D. Pancreatic β-cell dysfunction is another factor associated with PCOS and T2D (Day et al., 2018). T2D associated genes have a substantially significant role in PCOS disease (Reddy et al., 2016;144 (3):). Nominally positive family histories of PCOS is considered as a risk factor for PCOS expansion in women. There is a piece of evidence showing that a family history of T2D, as a reflection of genetic risk is associated with an increased risk of the progression of T2D in PCOS women; with T2D and obesity-associated genes and genetic polymorphisms were connected to hyperandrogenism which have been associated with PCOS phenotype; suggesting an important genetic background (Lerchbaum et al., women. 2014). PCOS is intensified with obesity and along with significant reproductive, metabolic and psychological features; incorporating T2D (Hiam et al., 2019). In 1921, Achard et al. (Achard, 1921) observed the beard women with diabetes and from then T2D has been linked up with PCOS (Achard, 1921). One of the probable mechanisms is proposed as hyperandrogenemia which might contribute to IR in PCOS and which may promote hyperandrogenism. It is not mandatory to develop IR in all the PCOS women. One of the standard connections between IR and PCOS is related to obesity; which will further associate with the molecular mechanism. However, the pathogenesis of PCOS is varied in both obese and non-obese women. The PCOS in obese patients plays a central role with IR and hyperinsulinemia (Poretsky et al., 1990; Meirow et al., 1995). PCOS women can also increase the risk of gestational diabetes (GDM) during pregnancy, which is further connected with T2D (Lo et al., 2017). GDM is defined as carbohydrate intolerance during pregnancy and is documented as metabolic disorder in the pregnant women (Khan et al., 2019). Involvement of small cysts forming in ovaries are known as PCOS and there is also similar relation between PCOS and GDM which was known as PCOS and T2D (Pan et al.,). PCOS and GDM can cause significant morbidity because both of them were allied to increase the incidence of pregnancy induced hypertension, pre-eclampsia and neonatal hypoglycemia. Both these disorders were associated with IR, weight gain and genetic factors (Mustaniemi et al., 2018). PCOS converses a considerable risk of T2D and GDM in reproductive ages. Ran-

Table 3
List of obesity genes associated with PCOS (Ewens et al., 2011).

S. No	Obesity Genes	SNP/rs number
1	FTO	rs1421085; rs17817449; rs8050136; rs9939609; rs9930506
2	GNPDA2	rs10938397
3	INSIG2	rs7566605; rs2161829
4	KCTD15	rs11084753
5	MC4R	rs17782313; rs12970134
6	MTCH2	rs10838738
7	NEGR1	rs2815752
8	SH2B1	rs7498665
9	TMEM18	rs6548238

domly, 20% of PCOS women develops T2D creating IGT as common irregularity (El Hayek et al., 2016). Clinical trials had also verified abnormal glucose tolerance which leads toT2D in PCOS women (Peppard et al., 2001). The individual family histories of T2D and obesity will increase the prevalence of both diseases in PCOS women; majorly, family history of obesity contributes the development of T2D in PCOS women (Dunaif, 1999).

4. Connection between obesity and PCOS

PCOS is one of the hormonal abnormalities which appear in reproductive-age women. By the combined combination of IR and obesity, the disease PCOS is developed in the women. Obesity is a common connection between PCOS women and randomly 40–80% of women tends to be overweight/obese/morbid-obese. The association between obesity and PCOS leads to a spiteful circle. Obesity clearly modifies PCOS phenotype specifically, metabolically and it diminishes response to infertility treatments. Familial aggregation of PCOS sturdily recommends a genetic susceptibility of PCOS disorder (Sam SJOm., 2007; Legro,; Wang et al.,). There are limited SNPs are connected with obesity and PCOS in the global population which was shown in Table 3.

5. Conclusion

PCOS disease is developed only in the reproductive-aged women; whereas, T2D will occur in both genders. However, Cannarella et al, (Cannarella et al., 2018) studies confirmed the PCOS symptoms was observed in male subjects. From this review work, the author concludes as PCOS is connected by IR and other metabolic diseases, but genetically there was no link established. Even though PCOS women can develop T2D; which is one of the risk factors but diagnosed T2D women cannot develop PCOS. Obesity and GDM are the central-factors in the reproductive-aged women to confirm as PCOS in later in life because PCOS is not only defined as reproductive pathology but also as systemic conditions. Till now its etiopathology is still not completely understood. Several pathways have been linked with PCOS and known to be a multifactorial disease. Modification in the metabolic pathway with the defects in the gene leads to the evolution of both PCOS and ovary dysfunction. However, genetic studies showed all the possible associations with the common genetic markers in both PCOS and T2D.

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