Journal of Molecular and Genetic Medicine

Kumar et al., J Mol Genet Med 2014, 8:2
DOI: 10.4172/1747-0862.1000107

Review Article Open Access

Past, Present and Future of Insulin Gene and its Related Genes in Relation to Polycystic Ovary Syndrome

Amar Nagesh Kumar[1*], Jupalle Nagiah Naidu[2], Uppala Stayanarayana[3] and Medabalmi Anitha[4]

[1]*Research Scholar, Department of Biochemistry, Narayana Medical College, Dr NTRUHS, Nellore, Andhra Pradesh, India*

[2]*Professor and Head, Department of Biochemistry, Narayana Medical College, Nellore, Andhra Pradesh, India*

[3]*Research Director and Professor, Department of Biochemistry, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences, Chinnavutapalli, Gannavarm, Andhra Pradesh, India*

[4]*Professor and Head, Department of Obstetrics and Gynecology, Narayana Medical College, Nellore, Andhra Pradesh, India*

[*]Corresponding author: Amar Nagesh Kumar , Research Scholar, Department of Biochemistry, Narayana Medical College, Dr NTRUHS, Andhra Pradesh, India, Tel: +91-9493593750; E-mail: amarnageshkumar@gmail.com

Received date: 28 February 2014, **Accepted date**: 10 April 2014, **Published date**: 10 May 2014

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Abstract

Polycystic ovary syndrome is the most common endocrinal disorder and is associated with infertility. Insulin resistance is a key component in the pathogenesis of PCOS and the predisposition to Type 2 diabetes mellitus. The existing literature supports a strong basis of PCOS clusters in families. However, due to the genetic and phenotypic heterogeneity of PCOS and the lack of large cohort studies and identification of specific contributing genes to date have yielded only few conclusive results. Although several loci have been proposed as PCOS genes including CYP11A, the insulin gene, and a region near the insulin receptor, the strongest case can be made for the region near the insulin receptor gene. Insulin receptor substrates proteins (IRS) are critical for insulin mediated signal transduction in insulin target tissues. Several studies have shown that IRS-1 Gly972Arg polymorphism might be the factor causing susceptibility to Type 2 diabetes mellitus (T2DM) and are associated with phenotypic features of PCOS. In this article we reviewed the current status of the genetic analysis of insulin (INS), insulin receptor (INSR), insulin receptor substrate (IRS) in relation to polycystic ovary syndrome, an infertility disorder in females.

Keywords: Insulin genetics; Infertility; Polycystic ovary syndrome; Insulin receptor; IRS

Introduction

Infertility is defined as the inability to conceive after one year of regular unprotected intercourse and accounts for one in six newly married couples. In many infertility cases, the diagnosis is simply unexplained because a variety of reasons like lack of ovulation, mechanical stoppage, sperm deficiencies and parental age etc. It is difficult to assess accurately the overall magnitude of the contribution of genetics to infertility. Nevertheless, specific genotypes and karyotypes have been associated with infertility phenotypes and studies of specific genes in humans and model systems shed light on the nature of the polygenic and multifactorial basis of infertility. The genetic causes of infertility are varied and include chromosomal abnormalities, single gene disorders and phenotypes with multifactorial inheritance. Some genetic factors influence males specifically, whereas others affect both males and females. For example, chromosome translocations affect both males and females, whereas Klinefelter syndrome and the subsequent infertility phenotype caused by it are specific to males [1]. Polycystic ovary syndrome (PCOS), premature ovarian failure (POF) and endometriosis are known conditions causing infertility in the female. Recent evidences show a significant genetic association with these conditions. This article is mainly focused on genetics of insulin, insulin receptor and IRS gene polymorphisms and their association with POCS.

Polycystic Ovary Syndrome is one of the most common endocrinopathies in women of reproductive age group. Due to increasing stress and present day's sedentary lifestyle, the prevalence of PCOS has now increased among the adolescent females [2]. PCOS is a significant women health problem because it targets the women during her golden productive age (education/work). Its wide spectrum of manifestations like oligomenorrhoea, cosmetic deformities like hirsutism, alopecia, obesity [3], the impending fear of infertility and anxiety about the future metabolic complications has a remarkable impact over the psychology [4] of the young women. This can definitely limit their self-efficacy, which indirectly affects the nation's productivity. Further, Polycystic ovary disease is associated with a wide spectrum of morbidity [5] including cardiovascular abnormalities, Type 2 diabetes mellitus (T2DM), dyslipidemia, and risk for malignancies. Many environmental, ethnical, clinical, and genetic causes have been attributed for its etiopathology. Yet, this problem demands further investigations about its genetic background that may help in understanding the disease much better which in turn opens new gateways for diagnosis and treatment.

Insulin resistance and POCS

Insulin resistance (IR) is now known to be intrinsic to this disorder, present in approximately 50-70% of these women and is independent of obesity contributing to its pathogenesis [6-8]. Women with PCOS are frequently obese which contributes to extrinsic component of insulin resistance. It is known that insulin resistance progresses towards the development of compensatory hyperinsulinemia, which drives hyperandrogenemia in these women [8,9]. Excess androgen levels lead to menstrual disturbances, development of ovarian cysts, hirsutism and other related disorders. Insulin resistance also increases

the risk for development of glucose intolerance, Type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia and cardiovascular abnormalities in these women [7,8,10].

Insulin (INS) gene polymorphism in PCOS

The pancreatic β-cell dysfunction in PCOS women appears to have a genetic predisposition. The minisatellite variations (Variable Number of Tandem Repeats, VNTR) upstream of the insulin gene locus (INS) regulates insulin expression. Insulin which is produced in β-cells of pancreas, affects multiple organ systems in the body. In the reproductive system, it stimulates ovaries to produce and secrete androgens, enhances ovarian growth, and inhibits apoptosis in the ovarian follicles, which may cause cyst formation [9,11]. Because insulin resistance, hyperinsulinaemia, and β-cell dysfunction are common features of PCOS, insulin, and the other members of insulin-signaling pathway have been considered to be candidates for PCOS [12]. A Variable Number of Tandem Repeats (VNTR) polymorphism located in the 5' regulatory element of the insulin gene INS, affects its transcriptional regulation, and is associated with hyperinsulinemia, fasting insulin levels, susceptibility to T2DM, birth weight, and childhood obesity and juvenile obesity [10].

Role of INS in PCOS was first demonstrated by Waterworth et al. [13] indicating linkage in 17 families and preferential transmission of longer (class III) alleles at this locus from fathers of PCOS patients. The same result was reported by Michelmore [14]. Ferk found significant association between class III VNTR alleles and PCOS in 117 cases and 108 healthy controls from Slovenia [15]. However, these findings have not been replicated consistently; including studies with much larger data sets and different ethnic backgrounds [16-19] and therefore, contribution of INS to the etiology of PCOS is still in controversial.

Insulin receptor (INSR)

The insulin receptor (INSR) has long been considered a strong candidate gene for PCOS as mutations in INSR result in hyperandrogenemia [20]. INSR is still being studied widely in order to elucidate its potential role in PCOS. The tyrosine kinase domain of INSR (exons 17-21) is of particular interest, as mutations in this domain are associated with moderate hyperinsulinaemia and insulin resistance [21]. A silent C-to-T substitution at His1058 position (designated His1085 in dbSNP) was previously shown to be associated with PCOS in a study of 99 cases and 136 controls [22]. However, replication of this association has been highly variable. Two studies found increased frequency of His1058 T allele in PCOS patients from China and India [23,24]; whereas few other studies did not see a significant association in Korean and Turkish PCOS patients [25-27], although it should be noted that all these studies lacked power due to small sample sizes. To overcome this limitation, Ioannidis in 2010 combined the data from these studies for a meta-analysis of the His1058 C/T polymorphism in a total of 795 cases and 576 controls, and estimated the combined odds ratio (OR) of 1.28 (95% confidence interval (CI) 0.88-1.85), which suggests that His1058 variation is likely not a major contributor to the etiology of PCOS [28].

Lee [25] sequenced the exons of INSR in 24 healthy Korean women to survey all coding variation present in the general population; 9 SNPs identified from the resequencing study were then genotyped in 134 Korean women with PCOS and 100 body mass index (BMI) matched controls. They found no significant associations, except with a novel SNP, rs2252673, for which, the minor T allele confers a modest protective effect to the carriers [26]. In contrast, Goodarzi et al. [29] selected "tag-SNPs" in the INSR gene (along with 38 other genes in insulin signaling pathway), based on Caucasian subjects in Hap Map project which aims to capture >80% of all genetic variation in this population. They utilized a two-step strategy, where they first genotyped all the selected SNPs in a discovery cohort of 275 cases and 171 controls, and then proceeded to genotype the SNPs with the strongest associations in a replication cohort of 526 cases and 3585 controls. At the discovery stage, 4 SNPs in INSR showed significant association with PCOS; however, only one of them, rs2252673, was found to be associated with PCOS in the replication cohort [29] supporting the findings of Lee [26].

IRS gene

Insulin receptor substrates proteins (IRS) are critical for insulin mediated signal transduction in insulin target tissues. Several studies have shown that two common polymorphisms in IRS particularly Gly972Arg (rs1801278) in IRS-1 and Gly1057Asp (rs1805097) in IRS-2 have been shown to influence the susceptibility to T2DM and are associated with phenotypic features of PCOS [30-36].

IRS1 - *Gly972Arg* polymorphism

A significant association between the IRS-1 Arg972 allele and PCOS was first reported by Sir Petermann in the Chilean population [37]. Meta-analysis by Ioannidis of eleven studies (889 cases, 1303 controls) yielded a significant association for IRS-1 Gly972Arg polymorphism concerning the Gly/Arg *vs.* Gly/Gly genotype with the risk of developing PCOS [28]. However, some articles reported associations of Gly972Arg and Gly1057Asp polymorphisms with PCOS, but the results of these studies were conflicting. Recent four researches in the association between IRS-1 Gly972Arg polymorphism and PCOS still had different conclusions [38-41]. Very recent meta-analysis by Ruan Y in 2012 concluded that IRS-1 Gly972Arg polymorphism is associated with PCOS, and this variation might be considered as a risk factor for PCOS further this study also concluded that no significant association was detected between IRS-2 Gly1057Asp polymorphism and PCOS [12].

Future genetic research in PCOS

Although a considerable progress has been made in identifying PCOS susceptibility genes in the last decade, this progress has been much slower in comparison to mapping studies of some of the other complex human traits, such as T2DM and obesity [12]. Still a number of strong PCOS susceptibility candidate genes are under scrutiny and with just started genome wide association studies, we are still far from fully understanding all the genetic contributions to this disorder. Contribution of many of the studied genes remains controversial or inconclusive, owing to lack of consistent replication. Several possible reasons are there for the variation in reporting different conclusion. This is because, as PCOS is complex in nature and great variability in its diagnosis, there is a large phenotypic heterogeneity across different studies. Majority of the studies are considerably underpowered due to small sample sizes (i.e. <300 affected women), which can lead to false positive and false negative associations. Many candidate gene studies assessed the effects of only few variants in each gene, rather than surveying the variation in the entire gene [42].

With the recent advancements in techniques and availability of new cost-effective analytical methods, research in genetics is rapidly moving towards a much more exciting era. Particularly, development of next-generation sequencing (NGS) methods has revolutionized the field by offering wide range of applications available to researchers. This will also influence the approaches commonly used in PCOS research like targeted and/or whole-genome resequencing studies may replace the current SNP based association studies, which will circumvent the problem of incomplete coverage of genes, as this has been a downfall in nearly all association studies to date. In addition, genome sequencing will enable genotyping the rare variants. The contribution of rare variants to complex diseases is currently not well understood and still under debate, as the SNP selection in many association studies are targeted for common variants.

Conclusion

Subphenotyping of PCOS women according to their insulin resistant status and also development of novel therapeutic approaches to overcome the defect of present treatment modalities may provide further insights to understand the molecular mechanism of insulin resistance in polycystic ovary syndrome. Finally we would like to conclude that with remarkable advancements in gene sequencing technology today, and development of new analytical methods, there is a lot to look forward in the coming years for delineation of genetic risk factors in PCOS.

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