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Link Between Genetics and PCOS: A Brief Review

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Review Article

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ABSTRACT

Polycystic Ovarian Syndrome is a genetically induced disease associated with hormonal imbalance. It is a condition that affects one in 10 women of reproductive age. It has become one of the complicated diseases due to poor diagnosis which in turn results in delaying clarification of its genetics, aetiology, clinical associations and assessment of treatment. In this review article the link between genetics and PCOS will be discussed.

INTRODUCTION

In a recent study relating to the link between the genetical factor and Pcos a survey was done in which around 1500 women from all over the world suffering from Pcos were chosen. The genes of these pcod affected women were compared with the genes of normal women [1]. The major difference which they found was the genes for reproductive hormones from the pituitary gland, and the receptors of those hormones in the ovaries. Later they came to a conclusion that pituitary gland was not the only genetic factor involved but a part of other genetic risk variants. Researchers have also discovered that constant ailment in either a mother or father can make unfavourable conditions in the womb that are connected with the advancement of polycystic ovarian disorder (PCOS) in their daughters [2-7]. In another study, scientists found that siblings of ladies with PCOS and insulin resistance are themselves at more risk of creating insulin resistance or diabetes, proposing that elements connected with the condition can be passed down to children and in addition to their daughters.

GENETICAL INTERACTIONS

Environmental factors mainly along with genes interact to provoke the phenotype biochemical parameters, including insulin levels or hyperandrogenemia, seem to be highly inheritable, suggesting that some clinical signs, symptoms, or biochemical parameters of PCOS could be transmitted.

Genetic investigations of PCOS can be divided into chromosomal/human leukocyte antigen (HLA) research, Karyotypes had been the primary genetic gear used inside while examining of PCOS. There have been remoted case reviews or small collection reporting polyploidies 23 and aneuploidies specifically X chromosomal aneuploidies. Those consist of XX/XXX and XX/XO mosaics.24,25 large cytogenetic series of PCOS sufferers, however, have found regular karyotypes [8-15].

A relation between PCOS with the X chromosome aneuploidies and polyploidies in addition to other cytogenetic abnormalities has been confirmed. The concept behind this research is that at least in few cases PCOS is caused due to X chromosomal factors which causes an abnormal follicular apparatus i.e. (ovarian cyst are derived from follocular apparatus before or after ovulation) and also a large deletion of the long arm of chromosome 11 was seen in some cases of PCOS [16].

Different studies have determined a genetic susceptibility to PCOS. It was shown that polycystic ovaries and hyperandrogenemia are present in 50% of sisters of affected women [17-25]. Both linkage and association studies have advised that PCOS may be defined by the interaction of a small range of key genes with

environmental, especially dietary factors [26-38]. Hyperandrogenaemia is genetically determined and the end result of familial studies indicates hyperandrogenism clusters as a dominant genetic trait.
The steroid synthesis gene CYP11a, coding for P450 cholesterol side chain cleavage and the insulin gene regulatory region may be involved [15,22,38-45].

Some of the research studies were done by undergoing the ultrasould tests. Hague and colleagues used high-resolution ultrasonography inorder to identify polycystic ovaries in women who had complains of menstrual disturbances, hyperandrogenic phenomena, drastic weight gain, and infertility. The ultrasonic appearance of the ovaries was considered to be a more sensitive diagnostic marker than either symptoms or biochemical markers. Segregation ratios were in excess of those expected in an autosomal dominant mendelian inheritance [45-49].

The major found criteria for the linkup between pcos and genetics was seen in women with diabetic background. The mother with diabetic history showed that the risk of pcos was found to be more in their daughters.

CONCLUSION

The significance of genetic and environmental elements within the etiology of PCOS is unclear. Modern-day awareness has focussed on importance of the genetics elements, due to the fact that molecular genetic techniques can now be employed to evaluate the contributions of person genes in complex genetic problems. Both autosomal and X-related dominant modes of inheritance were advocated to explain the found familial clustering of instances of PCOS. Lack of a sensitive diagnostic marker has formerly made it hard to follow segregation of the syndrome in families. Ovarian ultrasound enables definition of the phenotype more accurately than can be realizing by consideration of symptoms or biochemical parameters of the syndrome alone, and can thus be used to more accurately assign affected status.

REFERENCES

1. Cooper HE, et al. Hereditary factors in the Stein-Leventhal syndrome. Am J Obstet Gynecol. (1968)100: 371-387.
2. Amato P, et al. The genetics of polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol.(2005)18: 707-718.
3. Wilroy RS Jr, et al. Hyperthecosis: an inheritable formof polycystic ovarian disease. Birth Defects:Original Article Series. (1975)11: 81-85.
4. Givens JR. Familial polycystic ovarian disease. Endocrinol Metab Clin N Am. (1988)17: 771-783.
5. Franks S, et al. The genetic basis of polycystic ovary syndrome. Hum Reprod. (1997)12: 2641-2648.
6. Jahanfar S and Eden JA. Genetic and non-genetic theories on the etiology of polycystic ovary syndrome. Gynecol Endocrinol. (1996)10: 357-364.
7. Unluturk U, et al. The geneticbasis of the polycystic ovary syndrome: a literature review including discussion of PPAR-γ PPAR Res. (2007)1-23.
8. Franks S, et al. Pathogenesis of polycystic ovary syndrome: evidence for a genetically determined disorder of ovarian androgen production. Hum Fertil. (2000)3: 77-79.
9. Gharani N, et al. Association of the steroid synthesis gene CYP11a with polycystic ovary syndrome and hyperandrogenism. Hum Mol Gen. (1997)6: 397-402.
10. Diamanti-Kandarakis E, et al. Microsatellite polymorphism (tttta)n at -528 base pairs of gene CYP11α influences hyperandrogenemia in patients with polycystic ovary syndrome. Fertil Steril. (2000) 4: 735-741.
11. Wang Y, et al. Microsatellite polymorphism of (tttta) n in the promoter of CYP11a gene in Chinese women with polycystic ovary syndrome. Zhonghua Yi Xue Za Zhi. (2005)85: 3396-3400.
12. Gaasenbeek M, et al. Large-scale analysis of the relationship between CYP11A promoter variation, polycystic ovarian syndrome, and serum testosterone. J Clinl Endocrino Metab. (2004)89: 2408-2413.
13. Tan L and Zhu G. Relationship between the microsatellite polymorphism of CYP11a gene and the pathogenesis of hyperandrogenism of polycystic ovary syndrome in Chinese. Chin J Med Gen. (2005) 22: 216-218.
14. Escobar-Morreale H, et al. Ovarian suppression with triptorelin and adrenal stimulation with adrenocorticotropin in functional hyperadrogenism: role of adrenal and ovarian cytochrome P450cα Fertil Steri. (1994)62: 521-530.
15. Azziz R, et al. Adrenal androgen excess in women: lack of a role for 17-hydroxylase and 17,20-lyase dysregulation. J Clin Endocrinol Metab. (1995)80: 400-405.
16. Witchel SF and Aston CE. The role of heterozygosity for CYP21 in the polycystic ovary syndrome. J Pediatr Endocrinol Metab. (2000)13: 1315-1317.
17. Witchel SF, et al. Hyperandrogenism and manifesting heterozygotes for 21-hydroxylase deficiency. Biochem Mol Med. (1997) 62: 151-158.
18. Escobar-Morreale HF, et al. The presence of the 21-hydroxylase deficiency carrier status in hirsute women: phenotypegenotype correlations. Fertil Steril. (1999)72: 629-638.

19. Glintborg D, et al. Significantly higher adrenocorticotropinstimulated cortisol and 17-hydroxyprogesterone levels in 337 consecutive, premenopausal, caucasian, hirsute patients compared with healthy controls. J Clil Endocrinol Metab. (2005)90: 1347-1353.
20. Picado-Leonard J and Miller WL. Cloning and sequence of the human gene for P450c17 (steroid 17α-hydroxylase/ 17,20lyase): similarity with the gene for P450. DNA. (1987)6: 439-448.
21. Escobar-Morreale HF, et al. Lack of an ovarian function influence on the increased adrenal androgen secretion present in women with functional ovarian hyperandrogenism. Fertil Steril. (1997)67: 654-662.
22. Wickenheisser JK, et al. Differential activity of the cytochrome P450 17α-hydroxylase and steroidogenic acute regulatory protein gene promoters in normal and polycystic ovary syndrome theca cells. J Clin Endocrinol Metab. (2000)85: 2304-2311.
23. Wickenheisser JK, et al. Increased cytochrorne P450 17α-hydroxylase promoter function in theca cells isolated from patients with polycystic ovary syndrome involves nuclear factor-1. Mol Endocrinol. (2004)18: 588-605.
24. Wickenheisser JK, et al. Dysregulation of cytochrome P450 17α-hydroxylase messenger ribonucleic acid stability in theca cells isolated from women with polycystic ovary syndrome. J Clin Endocrinol Metabol. (2005)90: 1720-1727.
25. Carey AH, et al. Polycystic ovaries and premature male pattern baldness are associated with one allele of the steroid metabolism gene CY. Hum Mol Gen. (1994)3: 1873-1876.
26. Gharani N, et al. 5'polymorphism of the CYP17 gene is not associated with serum testosterone levels in women with polycystic ovaries. J Clin Endocrinol Metab. (1996)81: 4174.
27. Techatraisak K, et al. . Frequency of a polymorphism in the regulatory region of the 17α-hydroxylase-17,20-lyase (CYP17) gene in hyperandrogenic states. Clin Endocrinol. (1997)46: 131-134.
28. Witchel SF, et al. 17α-hydroxylase/17,20-lyase dysregulation is not caused by mutations in the coding regions of CY. J Pediatr Adol Gynecol. (1998)11:133-137.
29. Kahsar-Miller M, et al. Role of a CYP17 polymorphism in the regulation of circulating dehydroepiandrosterone sulfate levels in women with polycystic ovary syndrome. Fertil Steril. (2004)82: 973-975.
30. Simpson ER, et al. Aromatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. Endocrine Rev. (1994)15: 342-355.
31. Chen S, et al. Human aromatase: cDNA cloning, Southern blot analysis, and assignment of the gene to chromosome 15. DNA. (1988)7: 27-38.
32. Dalia P, et al. Substituting Poly and Mono-unsaturated Fat for Dietary Carbohydrate Reduces Hyperinsulinemia in Women with Polycystic Ovary Syndrome. J Nutr Food Sci. (2015)5:429.
33. Dipanshu S and Chakravorty R. Genetic Polymorphism in the Vitamin D Receptor Gene and 25-Hydroxyvitamin D Serum Levels in East Indian Women with Polycystic Ovary Syndrome. J Mol Biomark Diagn. (2015)6:247.
34. Sandhu H and Kuburas R. Insulin Resistance in Women with Polycystic Ovary Syndrome: Optimising treatment by Implementing an in vitro Insulin Resistance Organ Culture Model. Clinics Mother Child Health. (2015)12: e107.
35. Phy JL, et al. Low Starch/Low Dairy Diet Results in Successful Treatment of Obesity and Co-Morbidities Linked to Polycystic Ovary Syndrome (PCOS). J Obes Weight Loss Ther. (2015)5:259.
36. Jain S, et al. A Genetic Polymorphism of CYP1A1 (T6235C) Gene as a Risk Factor for Polycystic Ovary Syndrome. Andrology. (2015)4:129. doi:10.4172/2167-0250.1000129
37. Jain M, Jain S, Pandey P, et al. Genetic Polymorphism of CYP1A1 (T6235C) Gene as a Risk Factor for Polycystic Ovary Syndrome. Gynecol Obstet. (Sunnyvale) (2015)5:263.
38. Unfer V, et al. Polycystic Ovary Syndrome: Features, Diagnostic Criteria and Treatments. Endocrinol Metab Synd. (2014)3:136.
39. Zahid N. Role of Anti-Mullerian Hormone (AMH) in Polycystic Ovary Syndrome (PCOS)? A Mini Review. Reprod Syst Sex Disord. (2014)3:143.
40. Huang D, et al. Low Frequency Electro-Acupuncture and Physical Exercise Induces Menstruation in a Young Woman with Amenorrhea Related to Polycystic Ovary Syndrome: A Case Report. Altern Integr Med. (2014)3:166.
41. Kumar AN, et al. Past, Present and Future of Insulin Gene and Its Related Genes In Relation To Polycystic Ovary Syndrome. J Mol Genet Med. (2014) 8:107.
42. Vine DF, et al. Insulin and Testosterone are Associated with Elevated Intestinal Secretion of Lipids and Lipoproteins in a Rodent Model of the Metabolic and Polycystic Ovary Syndrome. J Diabetes Metab. (2014)5:391.
43. Sahin AE, et al. Positive Effects of Acupuncture on Menstrual Irregularity and Infertility in a Patient with Polycystic Ovary Syndrome. Fam Med Med Sci Res. (2014)3:121.
44. Neves EM, et al. Polycystic Ovary Syndrome: Correlation between Phenotypes and Metabolic Syndrome. J Steroids Hormon Sci. (2014)5:132.
45. Julia VJ, et al. Prevalence of Gestational Diabetes Mellitus in Patients with Polycystic Ovary Syndrome. J Diabetes Metab. (2014)5: 354
46. Laganà AS and Pizzo A. Know your Enemy: The Rationale of Using Inositol in the Treatment of Polycystic Ovary Syndrome. Endocrinol Metab Synd. (2013)2: e121.

47. Uckuyu A, et al. The Fluctuation in the Heart Rate Variability Throughout Ovulation Induction Cycle: Is the Case Different in Polycystic Ovary Syndrome? Gynecol Obstet. (2013)3: 172.
48. Karaca I, et al. Treatment of Premenstrual Syndrome with Progesterone in Women with Polycystic Ovary Syndrome. Gynecol Obstet. (2013)3: 151.
35. Jakimiuk AJ, et al. Aromatase mRNA expression in individual follicles from polycystic ovaries. MolHum Reprod. (1998)4: 1-8.
36. Petry CJ, et al. Association of aromatase (CYP 19) gene variation with features of hyperandrogenism in two populations of young women. Hum Reprod. (2005)20: 1837-1843.
37. Petry CJ, et al. Associations between common variation in the aromatase gene promoter region and testosterone concentrations in two young female populations. J Ster Biochem Mo Biol. (2006)98: 199-206.
38. Lubahn DB, et al. Cloning of human androgen receptor complementaryDNA and localization to the X chromomose. Science. (1988)240: 327-330.
39. Carson-Jurica et al. (Steroid receptor family: structure and functions.Endocrine Rev. (1990)11:201-220.
40. Chamberlain NL, et al. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res. (1994)22: 3181-3186.
41. Giovannucci E, et al. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. Proceedings of the National Academy of Sciences of the United States of America. (1997) 94:3320–3323.
42. Tut TG, et al. Long polyglutamine tracts in the androgen receptor are associated with reduced trans-activation, impaired sperm production, and male infertility. J Clin Endocrinol Metab. (1997)82:3777–3782.
43. Dowsing AT, et al. Linkage between male infertility and trinucleotide repeat expansion in the androgenreceptor gene. Lancet. (1999)354:640-643.
44. Mifsud A, et al. Androgen receptor gene CAG trinucleotide repeats in anovulatory infertility and polycystic ovaries. J Clin Endocrinol Metab. (2000)85:3484–3488.
45. Urbanek M, et al. Thirty-seven candidate genes for polycystic ovary syndrome: strongest evidence for linkage is with follistatin. Proceedings of the NationalAcademy of Sciences of the United States of America. (1999)96:8573-8578.
46. Hickey T, et al. The androgen receptor CAG repeat polymorphism and X-chromosome inactivation in Australian Caucasian women with infertility related to polycystic ovary syndrome. J Clin Endocrinol Metab. (2002)87:161–165.
47. Pugeat M, et al. Clinical utility of sex hormone-binding globulin measurement. Horm Res. (1996)45:148–155.
48. Selby C. Sex hormone binding globulin: origin, function and clinical significance. An Clin Biochem.(1990)27:532-541.
49. Berube D, et al. Localization of the human sex hormone-binding globulin gene (SHBG) to the short arm of chromosome 17 (17p12→p13) Cytogenet Cell Genet.(1990)54:65-67.