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Analysis of Genetic Spectrum in Polycystic Ovary Syndrome: A Review

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ABSTRACT:
Polycystic ovary syndrome (PCOS) is increase in an alarming rate since 1935. According to WHO the prevalence rate of PCOS is 3.4% worldwide. Hyperandrogenism, chronic anovulation, small cysts and increase in size of the ovary are the most common diagnostic feature for PCOS. Beside the environmental factors PCOS is highly associated with genetic back up of an individual. So, Different genetic pathways like steroid hormone synthesis , ovarian and adrenal steroidogenesis, gonadotropin action, insulin action and secretion, energy homeostasis , chronic inflammation pathways plays most important role in PCOS progression. Furthermore several report suggested that, some other genes like plasminogen activator inhibitor-1 (PAI-1), HSD3B2 , 17α-hydroxysteroid dehydrogenases, dopamine receptor, IGF107, aldosterone synthetase , paraoxonase, glycogen synthetase, resistin, apoprotein E are also involved in PCOS progression. From different case report it is established that epilepsy and diabetes condition are the two main regulators for PCOS progression. Whereas, epigenetic mechanism is also involved in the pathogenesis of PCOS. Some of the therapeutics is also available for treatment of PCOS but not ensure proper cure. Long-term treatment for PCOS, increases the risk of developing metabolic and cardiovascular abnormalities. So the main aim of this review is to reveal all aspects of genetics mechanism related to PCOS for better understanding of the disease. As well as established a profile of regulatory marker gene for early diagnosis and to develop a better treatment protocol.

Keywords: PCOS, IGF107, Androgen receptor gene, Serum Sex Hormone-Binding Globulin (SHBG), Follistatin coding gene.

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is also termed as Stein-Leventhal syndrome after its discovery in 1935 by Stein and Leventhal. This syndrome is characterized by hyperandrogenism, chronic anovulation, small cysts (diameter ranging between 2 and 9 mm) in one or both ovary and increase in size of the ovary exceeds 10 ml^3 (Evans et al., 1958, Azziz et al., 2004, Stein et al., 1935,). According to World health organization (WHO) the prevalence of PCOS affected 3.4% woman in worldwide and in India the prevalence percentage is near about 10. PCOS previously considered as disorder of adult

women but recently different reports suggested that PCOS is a lifelong syndrome. National Institutes of Health (NIH) estimated 4–10% of women suffer from PCOS at their reproductive age (Azziz et al., 2004). On the other hand according to Rotterdam diagnostic criteria PCOS can be vary among adolescents is near about 3-26% (Hashemipour et al., 2004, Driscoll et al., 2003, Kamangar et al., 2015,). However, the prevalence in children is still unknown. The PCOS follows multifactorial and polygenic or oligogenic inheritance patern. The environmental factors associated with PCOS, include environmental toxins, diet and nutrition, socioeconomic status, and geography (Merkin Sharon Stein et al., 2016,). High carbohydrate intake often affects body weight which is an indicator of PCOS (DiSarra et al., 2013). The physical variations such as the availability of safe drinking water, sources of available food, derivatives, dietary patterns, and supplements are the potential influencer of PCOS (Lim et al., 2013). A high prevalence of PCOD among 1st degree relatives is the indication of genetic inheritation (Franks et al., 1997, Amato et al., 2004). Different genetic pathways like steroid hormone synthesis (Androgen receptor gene, Serum Sex Hormone-Binding Globulin), ovarian and adrenal steroidogenesis (CYP11a gene CYP21 gene CYP17 Gene CYP19 gene), gonadotropin action and regulation (LH-subunit gene Follistatin coding gene), insulin action and secretion (Calpain), energy homeostasis (Leptin receptor gene), chronic inflammation(TNF-α gene) plays most important role in PCOS progression. Whereas some other genes involved in PCOS progression are plasminogen activator inhibitor-1 (PAI-1), HSD3B2 (Nayak et al., 1998), 17α-hydroxysteroid dehydrogenases (Moghrabi et al., 1998), dopamine receptor (Kahsar-Miller et al., 1999), IGF107, aldosterone synthetase (Zhao et al., 2003), paraoxonase (Rajkhowa et al., 1996), glycogen synthetase (Urbanek et al., 2003), resistin (Heinonen et al., 2001), apoprotein E (Sreenan et al., 2001), but the association were either controversial or without clear conclusions.

Some other association based study report shows that, PCOS is interrelated with epilepsy. (Herzog et al., 2006)According to bilo et al. a report shows 26% of PCOS women with epilepsy disorder due to the use of Valproic acid treatment for epilepsy.(Betts et al., 2003). In case of diabetes (both Type 1 and Type 2) the insulin signaling pathway including phosphatidylinositol 3-kinase and protein kinase B signaling plays an important role in PCOD progression, as these pathways regulates blood glucose level, obesity, androgen secretion and follicular development. (Qingqiang et al., 2019) Epigenetic mechanism also considered as one of the most important cause of PCOS pathogenesis. It is reported that DNA methylation and alteration in miRNAs expression in blood, serum, adipose tissue, granulose cells and theca cells promote the PCOS progression.(Francisca Concha et al., 2000) It is also reported that, in a dehydroepiandrosterone (DHEA)-induced mouse model, Demethylation of the luteinizing hormone receptor (*LHR*) gene promote PCOS (Zhu JQ et.al. 2010) . So the typical clinical features include hirsutism, irregular menses, chronic anovulation, and infertility. Impaired hypothalamic–pituitary feedback, LH hypersecretion, premature granulose cell luteinization, aberrant oocyte maturation, and premature arrest of activated primary follicles shows close association with hyperandrogenism. (Palomba et al., 2017). Thus all of the above features may act as clinical marker for the identification of PCOD. In this context the main aim of this review is to discuss the cause, effect and treatment in all aspects for better understanding of the disease.

PREVALENCE:

World health organization (WHO) reported that PCOS affected 3.4% woman in worldwide and the frequency may vary from 2.2% to 26% [34.] Whereas in India, there is no concrete data about the

prevalence of PCOS but some study reported that, the prevalence percentage is near about 10% (R.Vidya Bharathia et al., 2000). Furthermore, the Prevalence of PCOS is 9.13% in Andhra Pradesh, 12.2% in Mumbai, 3.7% in Lucknow. (Nidhi et al., 2011) It is reported that the incidence rate is high in urban area compared to rural population due to the lack of awareness or no exposure to junk foods, pollution and other endocrine disruptors. Moreover rural girls do not use labour saving devices for household work or vehicles for transport, thus this physical exercise helping to maintain a good BMI (R.Vidya Bharathia et al., 2000). Furthermore, it is reported that 20% of the rural symptomatic population are not yet visited to the concerned physician. Among the rural symptomatic population 11% expressed hirsutism and 69.5% had oligomenorrhea, left of the population undiagnosed. On the contrary around 6.37% urban populations are symptomatic to PCOS. In the urban symptomatic population 19.6% reported to have hirsutism and 59.8% experience oligomenorrhea.

CAUSE

Intricate association in both the genetic and environmental factors helps in promotion of polycystic ovary syndrome (PCOS), but exactly causes of PCOS still not proper clear. Some genetic studies have pointed PCOS as Autosomal dominant inheritance.(Cooper et al., 1968)while others showed that it was more likely that the syndrome is a complex trait with oligogenic basis. (Jahanfar et al. 1996) Two possible approaches are used to identify a genetic locus for PCOS genes: (i) association studies where a predisposing allele is expected to be found more frequently in the affected population than the normal individuals and (ii) linkage studies where the probands and their families are investigated to determine if particular genomic landmarks are distributed independently or in linkage with the phenotype.46Many genes presented altered expression suggesting thus that the genetic abnormality in PCOS affects signal transduction ruling steroidogenesis, steroid hormones action, gonadotrophin action and regulation, insulin action and secretion, energy homeostasis, chronic inflammation and others.(N Prapas et al., 2002) Besides a genetic inheritance some experiments in animal models reported that differential expression of chemical and hormones in mother's womb promote the PCOS progression.

The main TWO hormonal scenarios play critical role in PCOS

1. High amounts of androgens (including testosterone)
2. Insulin resistance (impaired sugar tolerance)

The above 2 factors influences and amplifyingeach other function. Thus, Genetics, environment and lifestyle are some of the major factors that can influence these different hormonal scenarios.

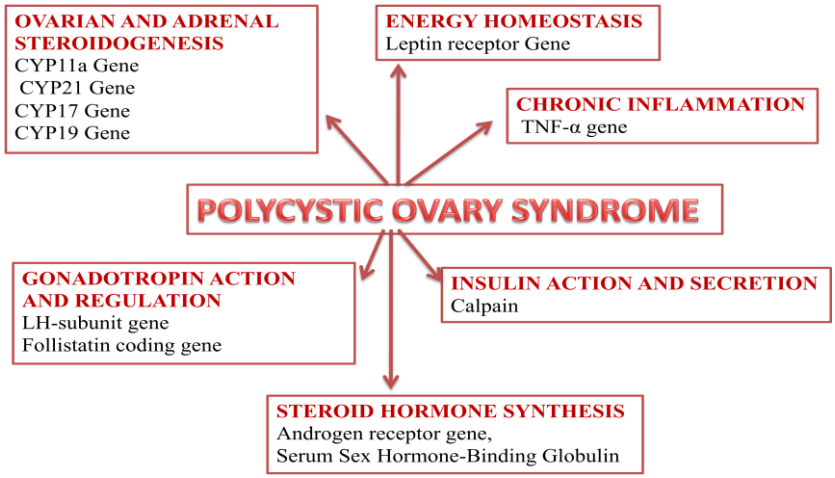

Fig: Some Important Genes Involved in PCOS Progression

Genes involved in steroid hormone synthesis:

Androgen receptor gene: It encoded by AR gene. (Lubahn et al., 1988) decreased number of CAG repeats present in transactivation domain with an increased androgen receptor activity could explain some of the PCOS phenotype exhibiting the normal serum androgen levels and hyperandrogenism symptoms (Mifsud et al., 2000)

Serum Sex Hormone-Binding Globulin (SHBG): levels are commonly low in patients with hyperandrogenism, especially in association with PCOS. (Ogeveen et al. 2001) A pentanucleotide repeat polymorphism, at the promoter of SHBG gene has been described to influence the transcriptional activity of SHBG gene. A significant association was found between this polymorphism and PCOS51. (Cousin et al., 2004)

Genes involved in ovarian and adrenal steroidogenesis:

CYP11a gene: conversion of cholesterol into progesterone, catalyzed by the P450 cytochrome side chain cleavage enzyme encoded by this gene. (Franks et al., 2003)CYP11A gene showed a significant association between serum testosterone levels and the alleles of the CYP11a with a 5 untranslated region (UTR) consisting of repeats of a (tttta) n pentanucleotide, a variable number tandem repeat (VNTR) polymorphism (Gharani et al., 1997). Two other case-control studies (Diamanti-Kandarakis et al., 2000, Wang et al., 2005), confirmed these findings in support of the encouraging evidence for the association between CYP11a and PCOS.

CYP21 gene: The conversion of 17-hydroxyprogesterone into 11-deoxycortisol which is catalyzed by the 21-hydroxylase enzyme encoded by CYP21. Adrenal hyperplasia and increased serum 17-hydroxyprogesterone levels are correlated with its deficiency. It is a common finding among women with functional hyperandrogenism or PCOS an increased serum 17-hydroxyprogesterone response to ACTH stimulation (Escobar-Morreale et al., 1994, Azziz et al., 1995) .Thus, patients having both heterozygote CYP21 mutations and clinical symptoms shows a PCOS-like phenotype (Witchel et al., 2000).

CYP17 Gene: The conversion of pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, and of these steroids into dehydrohepiandrosterone (DHEA) and 4-Androstendione (4) is catalyzed by the P450c17 enzyme & This enzyme has both 17-hydroxylase and 17,20-lyase activities and is encoded by CYP17 located at 10q24.3 Picado-(Leonard et al., 1987). It was reported increased P450c17 expression and enzymatic activity in ovarian theca cells from women with PCOS as well as increased transactivation of the CYP17 promoter (Escobar-Morreale et al., 1997).

CYP19 gene: P450aromatase is encoded by CYP19 located at 15p21.1 (Chen et al., 1988) Aromatase deficiency has been reported in a number of hyperandrogenic patients (Harada et al., 1992, Ito Y et al., 1993) It has been observed that granulosa cells obtained from medium-sized follicles of women with PCOS have little aromatase activity(Erickson et al., 1979).

Genes involved in gonadotropin action and regulation:

LH-subunit gene: The gene encoding the -subunit of LH which is responsible for LH specificity, has been explored in PCOS patients. (Unluturk et al., 2007). Point mutation in the variant H molecules (v-LH) (Yamada et.al. 2007) increased invitro activity and decreased in-vivo life. Occurance of this mutation in normal or any PCOS patient is not different (Haavisto et.al. 1995). Subgroup analysis of this study revealed that obese PCOS patients had a higher frequency of the heterozygous v-LH

compared with obese controls (Unluturk et.al. 2007 Rajkhowa et.al. 1995). Overall, the functional role of the v-LHs is unclear but it seems not to be crucial in PCOS pathogenesis or female infertility.

Follistatin coding gene: Overexpression of follistatin in transgenic mice resulted in suppression of serum levels of FSH and arrested ovarian folliculogenesis (Guo Q et.al. 1998). Therefore overwhelming activin neutralization due to increased follistatin reduces FSH concentrations, arrests follicular maturation, augments androgen production, and impairs insulin release. Because all of these changes are typical features of PCOS. (Legro RS et al., 1998, follistatin gene has been explored as a candidate gene in PCOS.

Genes involved in insulin action and secretion:

The insulin gene: There is a linkage and association between INS VNTR polymorphism in the families with affected member of PCOS. In a recent study (Dilek et al., 2005) reported a higher frequency of the Gly972Arg polymorphism for IRS-1 in women with PCOS. Findings could be considered a rough indicator of the relationship between the IRS-1 genotype and the insulin resistance phenotype of PCOS.

Calpain: Calpain-10 is a cysteine protease that participates in insulin secretion and action (Sreenan et.al. 2005) and genetic studies have shown that variation in the gene (CAPN10) encoding calpain- 10 is associated with type-2 diabetes (Horikawa et al., 2000). There was an effort to determine whether variation in the CAPN10 is associated with quantitative traits related to the pathogenesis of PCOS and type-2 diabetes (Ehrmann et al., 2002). It was found association between the 112/121 haplotype of this gene and higher insulin levels in African-American women and an increased risk of PCOS in both African-American and white women. (Ehrmann et al., 2002).

Genes involved in energy homeostasis:

As a large proportion of women with PCOS are overweight, obese and extremely obese some genes of the most popular adipocytokines have been showed as candidate genes in the pathogenesis of PCOS.

Leptin receptor gene: Two polymorphism in exon2 and intron2 results in obesity, insulin resistance and the risk of developing type-2 diabetes (Menzaghi et al., 2002). Panidis et al, investigated the possible association of the T45G adiponectin gene polymorphisms with PCOS (Panidis et.al. 2004). A significant difference was observed between the groups when genotypes GG and TG were assessed together (Xita et al., 2005). It was also showed that the carriers of the G allele had a tendency for lower serum adiponectin levels in PCOS group (Xita et al., 2005). Concluding, the adiponectin gene do not have role in the pathogenesis of PCOS, rather seem to shows the severity of the syndrome, at least concerning the metabolic problems and to have a role in the phenotypic variability of PCOS.

Genes involved in chronic inflammation:

TNF-α gene: The polymorphisms in the TNF-α gene do not seem to have a key role in the etiology of PCOS. In one study the carriers of the mutation 308 A alleles showed increased androgen and 17-hydroxyprogesterone levels before and after GnRH stimulation (Escobar-Morreale et al., 2001). These data may indicate the hypothesis that TNF-α gene polymorphism might be a modifying factor for phenotypic features.

plasminogen activator inhibitor-1 (PAI-1): Women with PCOS also present an increased activity of PAI-1 (Legro et al., 2003).

In addition to the genes mentioned above, many different genes such as HSD3B2 (Nayak et al., 1998), 17α-hydroxysteroid dehydrogenases (Moghrabi et al., 1998), dopamine receptor (Legro et al., 1995 Kahsar-Miller et al., 1999), IGF107, aldosterone synthetase (Zhao et al., 2003), paraoxonase (Rajkhowa et al., 1996), glycogen synthetase (Urbanek et al., 2003), resistin (Heinonen et al., 2001), apoprotein E (Sreenan et al., 2001) have been studied. Results were either controversial or without clear conclusions.

TREATMENT

The purpose of therapy for PCOS is to reduce hyperandrogenism in order to improve hirsutism and acne, restore regular ovulatory cycles, and correct the metabolic syndrome features. Adolescents with PCOS tend to be troubled most by the cosmetic effects of PCOS, such as acne, hirsutism, and/or acanthosis nigricans. Their treatment must address these issues as well as take into account the long-term consequences, such as the risk of developing metabolic and cardiovascular abnormalities.(Katerina et al., 2003).

Modification of lifestyle: The most preferred and effective method of treatment for obese adolescents with PCOS is lifestyle modification; however, it is also the hardest for patients to comply with and achieve. Weight loss improves practically every parameter of PCOS. Healthy diet and regular exercise are the most beneficial therapies in treating PCOS symptoms and preventing future complications. Minimal weight loss of 2–7% of body weight reduces androgen levels and improves ovulatory function in many patients with PCOS. (Huber-Buchholz et.al. 1999, Hoeger et.al. 2004)

Hormonal therapy: Estrogen-progestin combination therapy is the predominant treatment for reduction of hyperandrogenism and imorovement of hirsutism and acne as well as menstrual irregularities. The estrogenic component suppresses LH and thus androgen production from the ovary, and enhances production of SHBG, thereby reducing free plasma testosterone. (Katerina et.al. 2003) Various progestins are utilized in oral contraceptive pills (OCPs), with some progestins having more androgenic activity than others. Norgestimate, desogestrel and gestodene are considered to have low androgenic potential, whereas levonorgestrel and norgestrel have high androgenic activity. Nevertheless, most pediatric endocrinologist prefer to use OCPs with low androgenic potential such as Demulcent 1/50 (useful in obese patients, who require higher doses of estrogen), Ortho-Tri-Cyclen (FDA approved for treatment of acne in women) or Yasmin , which contains drospirenone. (Spironolactone- related anti-mineral corticoid with antiandrogenic activity). OCP therapy should continue until gynecological maturity is reached or substantial weight loss has been achieved. Treatment can then be withheld for a few months to assess the function of the pituitary-gonadal axis and recovery of spontaneous periods. (Buggs et al., 2005)

Antiandrogens: Antiandrogens are usually required to substantially improve the hirsutism score as They act as competitive antagonists of steroid binding to the androgen receptor and reverse the androgen-induced transformation of vellus to terminal hair. Antiandrogens have only effect on the metabolic abnormalities associated with PCOS. (Deplewski et al., 2000) **Cyproterone acetate** is a progestin with antiandrogenic activity. It competitively inhibits binding of testosterone and 5-dihydrotestosterone (DHT) to the androgen receptor. **Spironolactone**, an aldosterone antagonist, has multiple antiandrogenic effects. It inhibits ovarian and adrenal androgen production, blockage of DHT binding to skin androgen receptors & elevation of SHBG levels, increased testosterone clearance from the body, and decreased 5 -reductase activity.(Spritzer et.al. 2000)**Flutamide,** a potent nonsteroidal

antiandrogen, is very effective in treatment of hirsutism. (Falsetti et.al. 1999) However, it has a minimal indication in the adolescent patient because of its potential dose-dependent hepatotoxicity and high cost.

Glucocorticoids: A modest dose (5–7.5 mg of prednisone) given at reduces the secretion of adrenal androgens more than that of cortisol and minimizes the sequelae of glucocorticoid therapy. The aim is to suppress DHEAS below the adult range but not completely. (Buggs et.al. 2005)

Cosmetic Treatment: Cosmetic and dermatologic treatment including depilation, destruction of the dermal papilla with electrolysis or laser. This last-mentioned technique is painful and expensive, and thus practical only for treatment of limited areas. The newest addition to the topical armamentarium is eflornithine hydrochloride 13.9% which has been recently approved for the treatment of hirsutism . (Balfour et.al. 2001)

Insulin Sensitizers: Metformin acts primarily by inhibiting hepatic glucose output and increasing insulin sensitivity in peripheral tissues. (Kirpichnikov et al., 2002) Insulin levels decrease and results in a decrease in the levels of androgens and LH. As beneficial as metformin can be for adult women with PCOS, it appears even more effective in adolescents with this condition. Hyperinsulinemia and hyperandrogenism improve just as much as in adults, but there is an even higher rate at normalizing menses and decreasing hirsutism score in teenagers and young adults. (Arslanian et al., 2002, Loverro et al., 2002, Ibanez et al., 2000). Metformin treatment was also found to correct anovulatory cycles and induce ovulation and regular periods in nonobese teenagers with PCOS (Ibanez et al., 20001). The recommended starting dose is 500 mg with dinner, to be increased by 500 mg weekly, as tolerated, to a maximum dose of 2,000 mg daily, divided into 2 doses for better tolerance in the larger doses. Patients need to be aware that it is not a weight-loss drug; however, it can enhance weight loss by suppressing appetite (Ibanez et al., 2004). Thiazolidinediones are another class of insulin-sensitizing medications that are potentially effective in treatment of PCOS. They act by improving insulin action and glucose utilization at the level of liver, skeletal muscle and adipose tissue, and they have a modest effect on hepatic glucose production. Pioglitazone has been shown to improve androgen and lipid profiles as well as insulin secretion and sensitivity in obese PCOS women. (Romualdi et al., 2003)

DISCUSSION

Poly Cystic Ovary Syndrome (PCOS) is a hormonal disorder common among woman of reproductive age. Woman with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels (hyperandrogenism). The ovaries may develop numerous small collection of fluid sacs (follicles) causing anovulation. PCOS can be hereditary or linked to the development of other medical conditions such as insulin resistance, Type 2 diabetes, high cholesterol, high blood pressure and heart disease. Symptoms include irregular periods, infertility, excessive hair growth (hirsutism) usually on the face, chest, back or buttocks, weight gain and acne. The hormonal imbalance of insulin and androgen (eg. testosterone) are the main signs of PCOS. While androgen causes male characteristics in human body, insulin regulates the level of glucose in the blood. PCOS cause 'insulin resistance', where body cells stop responding to glucose i.e., blocks the entry of glucose into the cells, increasing blood sugar. Because the insulin is not working effectively, the body reacts by producing more insulin. Higher level of insulin increases the production of androgens, such as testosterone, in the ovaries. Androgen is a 'male-hormone' but a small amount is also present in female. However in PCOD, there is increased level of androgen causing hyperandrogenism. Level of follicle stimulating hormone in PCOS appears to be low while the LH levels are elevated which contribute to poor egg development and inability to ovulate.

PCOS shows an autosomal dominant mode of inheritance and has oligogenic complexity. PCOS is thought to occur due to defeat/malfunctioning of (1) Ovarian Androgen biosynthesis and action [CYP11A, CYP21, CYP17, AR gene, SHBG gene], (2) Insulin secretion and action [INSR gene, INS gene, IRS 1, CAPN10 gene etc], (3) Gonadotropin release, regulation and action [LH gene,LH receptor gene, FST gene etc], (4) Energy Homeostasis (lepton receptor gene) & (5) Chronic inflammation (TNF alpha gene). Genetic polymorphisms are potentially associated with the risk of PCOS. Several genes like Adiponectin(APN), Calpain 10, CYP1A1, hOGG1, INSR on polymorphism leads to the condition of PCOS. Treatment include the intake of fertility drugs, birth control pills to regulate the menstrual cycle, oral contraceptives, anti- anfrogens, anti-diabetic drugs like Metformin and stains to control high cholesterol. Lifestyle changes, healthy diet, exercise and self care also helps in reducing the chances of PCOS.

CONCLUSION:

Polycystic ovary disease (PCOD) also polycystic ovary syndrome (PCOS) is a very common condition affecting reproductive age group woman. A number of factors results in PCOD. Exact cause of PCOS is still unknown. Polymorphism of many genes can leads the PCOD or its phenotypes but none of them is direct cause of it. Various treatments are also associated with the disorder but none of exactly cures PCOD. In recently there are lots of trial examinations occurring in women with PCOS. But it is just only start. As it can result in long term consequences in human health like diabetes, cardiovascular diseases and cancer, So identification and proper treatment with full guidelines is needed very much.

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