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REVIEW

Genetics Poly Cystic Ovary Syndrome

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Abstract

Background: Polycystic ovarian syndrome is a complicated hereditary disorder which does not have the specific reason and 6-10% of women at fertility age are involved. In another word, we can say that this syndrome is a familial hereditary syndrome which developed with the combination of environmental and genetic factors. Polycystic ovarian syndrome (PCOS) is related to cardiovascular diseases and has psychological and neurological effects on life quality as well as uterine and breast cancers. The main criteria for the diagnosis of the polycystic ovarian syndrome are chronic anovulation and hyperandrogenism and the sub-criteria are insulin resistance, hirsutism and obesity onset at menarche age, anovulation alternatively is associated with increased testosterone level and DHEA-S. The cause of polycystic ovarian syndrome (PCO) is unknown, but it could be the result of complex genetic factors which are evident at puberty onset, also hereditary and non-hereditary factors could be the cause of polycystic ovarian syndrome (PCO) phenotype. In many women with the polycystic ovarian syndrome, the insulin level is high. It seems that high levels of insulin increase androgens production. High levels of androgens can cause acne, supernumerary hair growth, weight gain, and ovulation problem. **Conclusion:** Early diagnosis and treatment of polycystic ovarian syndrome could help to reduce long-term complications such as diabetes type II, high blood pressure, heart disease, and stroke.

Keywords: Polymorphism- polycystic ovarian syndrome (PCOS)- hyperandrogenism

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Introduction

Polycystic Ovary Syndrome PCOS; (Poly Cystic Ovary Syndrome) is the most common endocrine disorder among women. This syndrome is a common prevalence of premenopausal women, ranging from 7-15% of the world's population. The disease or syndrome was defined by two doctors called Leventah & Stein in 1935 [1].

The polycystic ovary is a syndrome with a wide spectrum of clinical, biochemical, and ultrasound impairments. At one end, these are merely polycystic ovarian ultrasonography, including ovarian enlargement of greater than 9 ml, the presence of 2-8 mm cysts to 10 or more in There is a surface and increased stroma density, and at the other end there are clinical signs such as oligomenorrhoea (prolonged periods of menstruation), increased blood androgens, hirsutism (thickening of the body's hair) and lack of ovulation [2].

Another important complication of polycystic ovary syndrome is infertility. Research shows that the cause of ovulation is 83% of the infertile couples of the polycystic ovary syndrome, and 44% of the polycystic ovaries with ovulatory episodes have been reported in 56% of the couples who have infertility with unknown reasons. In fact, PCOS also increases the risk of metabolic syndrome MS; (Metabolic Syndrome) [4-5], type 2 diabetes (6.7.8.9.10), and possibly cardiovascular disease [5-11-12-13-14-15-16].

Clinical symptoms

Polycystic ovary syndrome has widespread clinical symptoms, but patients usually refer to doctors due to three disorders: menstruation irregularities, infertility, and symptoms associated with increased androgenic mercury hirsutism and acne [17].

Patients with PCOS are at risk for other diseases such

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as obesity, hyperinsulinemia, hyperandrogenemia, insulin resistance, and dyslipidemia, including cardiovascular and thrombotic diseases, which have attracted physiologist's attention and required special medical attention [19-20].

Regarding the effect of obesity on the polycystic ovarian syndrome, it appears that continuous exercise along with a healthy diet increase health [21]. Food can interact with the molecular mechanisms and the balance between physiological functions in the body. The focus is on the genomics of nutrition in the interaction between food ingredients and active bioactive components and the neurogenic and neutro-genomics genome. Genetic diversity is known as an effective factor in the balance between human populations and may also be influenced by daily needs and may increase the possibility of personal nutrition helping to prevent diseases and improve health [22].

Understanding the etiology or PCOS etiologies is difficult. Research shows that in PCOS, a number of endocrine disorders are mutating and exacerbating. These disorders include violations in the functioning of the hypothalamus-pituitary axis, ovarian function, and adrenal function. In fact, PCOS with the abnormal discharge of gonadotropins (LH) and FSH (follicle stimulating hormone), increased ovarian steroid secretion and associated insulin resistance [23].

Increasing the amount of LH leads to an increase in the production of androgens [24]. Increasing the secretion of androgens is one of the most important characteristics of the ovaries in PCOS. In this case, the ovaries produce a significant amount of testosterone, androstenedione, and dehydroupiandrosterone (DHES), but serum testosterone is more common [23].

To diagnose PCOS, the following disorders should be rejected

CAH; (Congenital Adrenal Hyperplasia), Cushing's syndrome, and androgenetic secretion tumors. PCOS can affect some people's quality of life despite changes such as obesity, infertility, anorexia and nervousness, pelvic pain and depression [26].

Potential reasons for this syndrome are still uncertain. In this syndrome, the inappropriate secretion of gonadotropins is noted, in particular, the increased secretion of LH [26-27]. Major disadvantages of this syndrome are insulin resistance, hyperandrogenism, and changes in the dynamics of gonadotropins. The inadequate FSH secretion seems to be the most likely cause of inability Ovulation [28].

The diagnostic criteria for polycystic ovary syndrome also apply to adolescents. Although clinical manifestations of adult and adolescent women are said to be similar, lack of ovulation and hyperandrogenism, which contribute to the definition of this syndrome, is not always an adequate feature in adolescents with polycystic ovary syndrome, and 59% of the cycle menstruation up to 3 years after menarche in normal girls is not ovulation [29].

Data on the prevalence of PCOS vary due to the lack of an accepted and global diagnostic benchmark. In the United States, according to the National Institute for Growth and Wellbeing NIH; (National Institutes of Health) in 1990, Hyperandrogenism or Hyperandrogenemia and Ovulation Disorder without Non-Classic Hyperplasia Adrenals are diagnostic criteria for the disease. While these criteria in Europe, are/include the presence of ovaries full of cysts in ultrasound with one or more symptoms such as oligomenorrhoea, hyperandrogenism, obesity, testosterone elevation or serum LH [30]. Since there are different diagnostic criteria in different parts of the world, the spread of this disease has reported between 17 and 22% [31-32].

Metabolic Features

Glucose Intolerance

For the first time in 1980, it was shown that PCOS and obese women showed a significant increase in plasma glucose and venlaulin compared to non-PCOS and non-obese women [33.34]. 20% of these women are suffering from glucose tolerance IGT; (Impaird Glucose Tolerance) or type 2 diabetes [35]. Obesity and increased age increase the risk of abnormal glucose tolerance [8]. A family relationship between PCOS and diabetes GDM; (Gestational Diabetes Mellitus) and an increased prevalence of type 1 and type 2 diabetes are seen among PCOS women [36.37.38.39].

Insulin Resistance

Insulin is a polypeptide hormone secreted from pancreatic beta cells, which plays a major role in glucose homeostasis. Tissues are the target of insulin (liver, muscle, and fat). Stimulating insulin leads to consumption of peripheral glucose in muscle and fat tissue, protein synthesis, cell growth, and differentiation. Insulin increases glycogen storage and inhibits glycogenogenesis, glycogenolysis in the liver, as well as lipolysis [40]. Disruption of insulin secretion and function in PCOS women, seen as amenorrhea or non-ovulation, is more than that of regular women [41].

Obesity, fatty centers in the body and muscle volume all have independent and distinct effects on insulin sensitivity [42]. PCOS women do not show insulin resistance without obesity [43-44-45]. Evidence has shown that insulin sensitivity associated with abdominal obesity is correlated with PCOS [46].

Insulin Function

Insulin is activated after binding to the receptor, and in PCOS women, a defect occurs after this connection. Insulin, itself, acts as gonadotropin in the normal ovary, but in physiological conditions, it is likely to interact with paracrine ovarian factors such as insulin-like growth factor IGF; (Insulin Like Growth Factor) [47-48].

Insulin appears to have a modest effect on FSH in normal ovarian cells and, In fact, increases the effect on LH, and also affects the production of progesterone and E2 in the normal ovary. The ovary in the PCOS is susceptible to insulin effects. Insulin and FSH have synergistic effects on the production of E2 and granular cells in PCOS, but in most cases, normal ovulation is observed. Insulin is seen

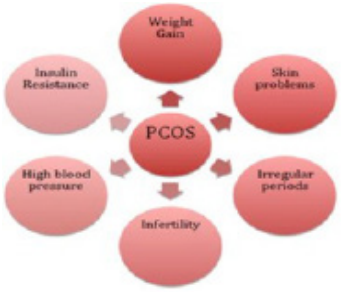

Figure 1. Clinical Manifestations of Polycystic Ovary Syndrome [18]

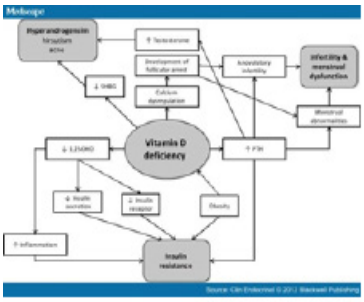

Figure 3. Vitamin D Deficiency Mechanism and Its Effect on Different Parts [62]

in high levels of androgen production by ovarian wall cells in PCOS over normal ovaries [49].

Hyper Androgenism & Insulin Resistance

High resistance to insulin in this syndrome is usually associated with hyperandrogenic conditions occurring in the premenopausal age. Hyperandrogenic is due to hyperinsulinemia since insulin has a variety of effects on steroidogenesis in humans. Insulin causes hyperandrogenic ovarian and polycystic ovary changes, that are susceptible to high androgen secretion [50].

The role of vitamin D and calcium in the polycystic ovary syndrome

Some evidence suggests that vitamin D deficiency may contribute to the pathogenesis of insulin resistance and metabolic syndrome in PCOS [51-52].

Vitamin D deficiency is common in women with polycystic ovary syndrome (PCOS) and 67-85% of women with PCOS have 25-hydroxyvitamin D (HD 250) concentrations (20 ml/ng). Vitamin D deficiency exacerbates PCOS symptoms. Low levels of HD 250 are associated with insulin resistance, irregularities, and ovulation, low probability of pregnancy, premature fever, hyperandrogenism, obesity and risk factors for cardiovascular disease. Vitamin D deficiency plays an important role in the severity of PCOS [53].

Vitamin D has been shown to affect PCOS by transcribing genes and regulating hormone regulation of insulin metabolism and fertility regulation [54].

Vitamin D deficiency increases PTH, which regulates serum calcium levels and vitamin D. increased PTH

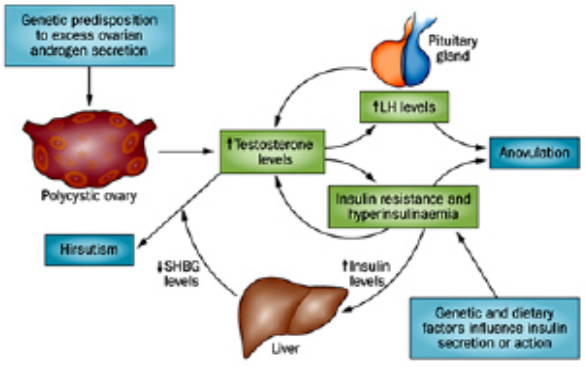

Figure 2. The mechanism of Hormonal Effect on Polycystic Ovary Syndrome [25].

associated with PCOS, which results in infertility and increased testosterone [55].

The 2001 Zborowski study showed that PCOS patients are also exposed to osteoporosis, which can be due to insulin function in calcium intake and the effect of homocysteine [56].

Several studies show that elevated levels of parathyroid hormone (PTH) result in high blood pressure following a reduction in serum calcium. Therefore, calcium intake can prevent hypertension and subsequently cardiovascular disease [57-58].

In a study by Yacob on PCOS patients, vitamin D deficiency was observed in these patients despite the abnormality of the extracellular calcium concentration; following a decrease in vitamin D, a decrease in intracellular calcium serum concentrations, as well as abnormal oocyte function, is seen [59].

With numerous studies on animals, the role of calcium in the evolution of the oocyte has also been identified, but its effect is unknown and researchers have investigated the need for the effectiveness of calcium and vitamin D on human ovulation, and especially in PCOS cases [60-61].

Genetic role in polycystic ovary syndrome

The genetic basis of polycystic ovary syndrome (PCOS) (Stein-Leventhal) was proposed by Cooper and colleagues in 1968 [63].

Although the etiology of this syndrome is still unclear, genetics play an important role in the pathogenesis of the syndrome. In recent decades, much research has been done on accompanying studies of pathogenicity of genes in relation to reproductive hormones, insulin receptors and chronic inflammation [64].

The family history of PCOS and its accompanying features in the study on twins have shown that genetic factors play an important role in the pathogenesis of this disease. In addition, two more symptoms of the disease can be found in families. While the differences in the symptoms of the disease may reflect the different expression or the same effect of the genes [65-66], heterozygosity and the absence of a specific clinical and biochemical diagnostic criterion for PCO has made it difficult to diagnose [67].

PCO Gene Position Identification Methods

There is a basic and practical dilemma for identifying the position of PCOs:

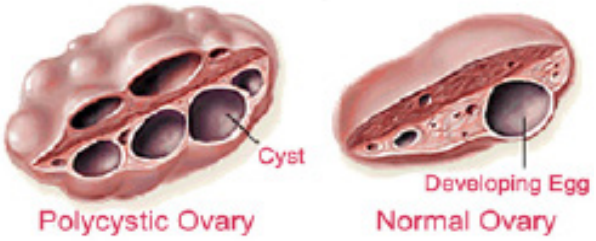

Figure 4. Is a View of a Full Cyst Ovary and a Natural Ovary [68]

1) Association studies where the predisposing allele has the highest frequency in the population of patients than normal people.

2) Linkage studies where Proband and their relatives are designated for a particular genetic status, independent or associated with their phenotypes [69].

Candidate genes include sex hormone genes and regulatory genes, insulin sensitivity, type 2 diabetes, cardiovascular disease [70], insulin genes, insulin receptor, and calapain-10 (36). Studies have shown that the combination of the CALAPINE-10 gene with the PCOS phenotype is well documented [71].

The single-nucleotide polymorphism of C/T in exon 17 dimetiosine kinase from the insulin receptor gene (INSR) in this syndrome is shown by the final effects of autophosphorylation from the insulin receptor gene in PCOS women [72-73].

In a study by Hyejin Lee and colleagues on Korean women with polycystic ovary syndrome through GWA in 2014, a new genome with a genomic significance and seven related sites were identified in PCOS. The best relationship was observed in chromosome 8, on 8q24.2 (rs10505648, OR./52, p = 5.46 * 10-8), the corresponding signals were identified at the following positions: 4q35.2, 16p13.3, 4p12, 3q26.33, 9q21.32, 11p13 and 1p22 (P = 5.72 * 10-6-6.43 * 10-5)

The strongest signals were in the KHDRBS3 upstream region, which is associated with telomerase function and leads to PCOS and clinical symptoms associated with the syndrome [74].

Evidence suggests that genetic effects include the PCOS family classification, and increased frequency of symptoms such as hyperandrogenism and type 2 diabetes in the first-degree relatives of women with PCOS [65-70].

According to these results, genetic effect defines a risk of PCOS of about 65% [75].

Recently, genetic link studies on PCOS have become widespread [76]. Several genetic studies have been conducted on PCOS [77.78.79].

GWA studies provide the possibility of analyzing a large number of variables at the same time, as a result of identifying new genes. The first GWA studies were conducted in a group of people with PCOS in China, and the design of the varieties in three positions (2p16.3, 2p21 and 9q33.3) were identified [80].

A secondary GWA in a larger group of Chinese patients with PCOS has identified the design of varieties in eight positions for PCO: 2p16.3, 9q22.32, 11q22.1, 12q13.2, 12q14.3, 16q12.1, 19p13.3 and 20q13.2 [81].

Although several genetic factors, including mutations and polymorphisms, are risk factors for PCOS [82], genetic patterns and molecular genetic mechanisms have not been well documented to confirm the potential factors of this syndrome [83].

Autosomal or predominant x-dependent inheritance patterns should be considered. However, PCOS inheritance is often multifactorial, such as type 2 diabetes or cardiovascular diseases [84].

Environmental factors such as obesity or sluggishness affecting the insulin, insulin sensitivity, or function, alter the clinical and biochemical manifestations of people with genetic predisposition to PCOS [44-46].

Telomerase enzyme and its relationship with polycystic ovary syndrome.

Studies have shown that KHDRBS3 gene expression is related to the regulation of telomerase activity in human colon cancer [85].

Telomerase is an enzyme that plays a role in maintaining the length of telomere [86]. Telomere length is inherited and is regulated by a variety of environmental and genetic factors [87].

The short telomerase (?? telomeres or telomerase?) causes chromosomal instability and this condition increases the level of genetic mutations and chromosomal abnormalities. Several studies have shown the role of telomeric length in cancers [88], cardiovascular diseases [89], diabetes [90], and infectious diseases [91]. It turned out that telomere length is associated with PCOS too. Short-acting telomeres disrupt insulin secretion, signaling pathways, mitochondrial function and Ca + 2 metabolisms [92.93].

Different characteristics of PCOs, including high androgens, abnormal obesity, and insulin resistance, can lead to telomere shortening; short telomeres affect reproductive and metabolic reproduction and worsen the abnormal metabolic structures [94].

In another study using the original GWA on polycystic ovary syndrome, 11 vulnerabilities were identified in Chinese people. Some of the risk positions that were identified in Chinese people, most often in the early GwA, have also been observed in European populations. The effect of secondary GWA status in European subjects was to determine whether variants similar to PCOS are found in individuals of different races or not. The result of this study was that 4 vulnerabilities in polycystic ovarian syndrome, as seen in Chinese GWA studies, are linked to PCOS in European populations, and the identification of these sites plays an important role in etiology Polycystic ovary syndrome is common in all races [95].

The first extended genome-related study has identified three sites of polycystic ovary syndrome including THADA, LHCGR, and DENND1A regions [78]. THADA and DENND1A variants were also observed in European subjects (96.97).

In the GWA II studies, eight new sites were identified in Dutch, including areas (FSHR, C9orf3 INSR, HMGA2, YAP1, RAB5B / SUOX, TOX3 SUMO1P1) [81].

Table 1. Genotype Panel of Selected Gene [100] (Candidate Gene)

Marker locus	Gene symbol	Candidate gene	(cM)*	Chromosomal location
Steroid hormone				
AR	AR	Androgen receptor	0	Xq11.2
D15S519	CYP11A	cytochrome P450 side-chain cleavage.E	0	15q23–24
D15S520	CYP11A	cytochrome P450 side-chain cleavage.E	0	15q23–24
D10S192	CYP17	cytochrome P450 17α-hydroxylase/17,20-desmolase	<1	10q24.3
CYP19	CYP19	CYP19-cytochrome P450 aromatase	0	15q21
D17S934	HSD17B1	17 β-hydroxysteroid dehydrogenase, type I	<2	17q11–21
HSD17B2	HSD17B2	17 β-hydroxysteroid dehydrogenase, type II	0	16q24.2
D9S1809	HSD17B3	17 β-hydroxysteroid dehydrogenase, typeIII	<1	9q22
D1S514	HSD3B1+ 2	3 β-hydroxysteroid dehydrogenase typeI,II	<1	1p31.1
D8S1821	STAR	Steroidogenic acute regulatory protein	<2	8p11.2
Gonadotropin action				
D12S347	ACTR1	Activin receptor 1	<1	12q13.12
D2S2335	ACTR2A	Activin receptor 2A	<1	2q22.2
D3S1298	ACTR2B	Activin receptor 2B	<1	3p22.2
D5S474	FS	Follistatin	<2	5p14
D5S623	FS	Follistatin	<1	5p14
D5S822	FS	Follistatin	<1	5p14
D2S163	INHA	Inhibin A	<1	2q33.34
INHBA	INHBA	Inhibin β-A	0	7p13–15
D2S293	INHBB	Inhibin β-B	2	2cen–2q13
D12S1691	INHC	Inhibin C	<1	12q13
D17S1353	SHBG	Sex hormone binding globulin	<1	17p13.2
D2S1352	LHCGR	Luteinizing hormone/choriogonadotropin R	<2	2p21
D2S1352	FSHR†	Follicle-stimulating hormone receptor	<2	2p21
D18S474	MADH4	Mothers against decapentaplegic homolog4	<1	18q21
Obesity and energy regulation				
D18S64	MC4R	Melanocortin 4 receptor	<3	18q21.32
D7S1875	OB	Leptin	0.2	7q31.3–32.1
D1S198	OBR	Leptin receptor	0.5	1p31
D2S131	POMC	Pro-opiomelanocortin	<1	2p23
D11S911	UCP2+3	Uncoupling protein 2+3	<4	11q13
Insulin action				
IGF1	IGF1	Insulin-like growth factor I	0	12q22–23
IGF1R	IGF1R	Insulin-like growth factor I receptor	0	15q25–26
D7S519	IGFBP1+3	Insulin-like growth factor binding protein 1 + 3	1	7p13–7p12
HphI site	INS VNTR	Insulin gene VNTR	0	11p15.5
INSR	INSR	Insulin receptor	0	19p13.3
D19S216	INSR	Insulin receptor	4.2	19p13.3
D19S905	INSR	Insulin receptor	0	19p13.3
D19S884	INSR	Insulin receptor	1.2	19p13.3
D19S922	INSR	Insulin receptor	1.2	19p13.3
D19S391	INSR	Insulin receptor	3.6	19p13.2
D19S865	INSR	Insulin receptor	7.2	19p13.2
D19S906	INSR	Insulin receptor	11	19p13.2
D19S840	INSR	Insulin receptor	14	19p13.2
D19S212	INSL3	Leydig insulin-like protein 3	<1	19p13.1
D19S410	INSL3	Leydig insulin-like protein 3	<1	19p13.1
IRS1	IRS1	Insulin receptor substrate 1	0	2q36–37
D3S1263	PPARG	Peroxisome proliferator-activated receptor-γ	<0.2	3p25–24.2

Recent studies suggest that DENND1 mRNA and protein in ovarian cells increase in polycystic ovarian syndrome and androgen biosynthesis enhance [98], taking into account the GWA's position in Chinese subjects.

The LHCGR promoter region in granulosa cells has been subjected to hypomethylation in women with PCOS, leading to increased transcription of LHCGR [99].

37 selected genes from 4 metabolic pathways are involved in the etiology of this syndrome and are restricted to 33 chromosomal regions. These regions have been discovered by determining the 45 genotypes of the continuous polymorphic site with 37 selected genes [100].

Discussion

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Although PCOS does not show Mendelian hereditary patterns, it identifies the role of genetic factors in its formation. A large number of candidate genes have a function, with the phenotypes of the syndrome, with positive and negative results, accompanied or consistent [100].

Govind et al. (1999) identified the genetic basis of the syndrome in 29 countries with PCOS and 10 healthy women. The results of this study clearly show the prevalence of autosomal dominant inheritance with male evaluation (baldness of the head) and positive ultrasound scan at postmenopausal age, a positive history of postmenopausal women. Also, no ultrasound manifestations and familial history of PCOS were observed in normal women group, and these results indicate that the phenotype of the disease has a genetic basis [101].

A comprehensive study of Urbanek et al in 1994, identified the PCOS-related genetic linkage in a group of 367 families, including individuals typical of the syndrome in European regions [102].

In 2003, Gonzalez and colleagues examined the combination of SNP (SNP19-SNP63-SNP43-SNP44) of the calpain-10 gene, suggesting that SNP44 was associated with PCOS in Spanish women [71-103].

A study by Talbott E and colleagues suggests that a new position has been identified in PCOS. Several genes involved in this disorder are associated with dyslipidemia, endometriosis, insulin resistance, and inflammatory signals [14].

The use of genetics in the field of medicine has made remarkable progress in recent years. When genetic knowledge, as well as other knowledge, is used in a suitable way, it can play an important role in contributing to the health of humans. The new developments and achievements of this knowledge are only accepted when they are in line with ethical standards, respecting autonomy, individual and social justice, the beliefs and laws of particular nations and different human societies [104].

In Conclusion, according to a review of the PCO and the genetic mechanism involved in the disease, it should be noted that there may be a link between these factors and the disease process, which confirms this to prevent the progression of the disease to further study in this area. Further studies are needed in this field due to, as well as considering that the role of the genetic and environmental factors that lead to the development of PCOS and their interaction with each other is still not well-known. The better understanding of these factors and reactions can help to more effectively diagnose and develop new therapies.

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