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An Analysis of LMNA variants associated with PCOS

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ABSTRACT

Polycystic Ovarian Syndrome (PCOS) is a disease commonly characterized by the excessive production of male hormones, androgens, the growth of fluid filled cysts within the ovaries called and difficulty ovulating. PCOS affects an estimated 8-13% of women worldwide and is the foremost cause of infertility and anovulation (World Health Organization). This study's purpose is to identify and assess the pathogenicity of LMNA variants associated with PCOS. Some genetic mutations responsible for PCOS have been reported. However, studies regarding *LMNA* and its specific role in causing PCOS have been inconclusive. Simple Mendelian inheritance patterns cannot be applied to the pathogenesis of this disease as both genetic and environmental factors are to be considered. ClinVar, was used to identify the *LMNA* as a gene associated with PCOS and its two variants, single nucleotide missense mutations, p.Arg455Cys and p.Arg482Trp. The LMNA gene codes for a lamin A/C protein, a scaffold protein, that is vital for maintaining structural integrity, cell signaling and more specifically chain elongation. Pathogenic mutations in LMNA are known to alter the expression of certain tissues. The *LMNA* gene is expressed in most somatic tissues including the ovaries. Computational tools PolyPhen and Sift were used to determine pathogenicity of the two variants. PolyPhen predicted both mutations to likely be damaging while SIFT predicted the p.Arg455Cys variant to be tolerated and the p.Arg455Cys to be damaging. The pathogenicity of these mutations suggests that functionality of the lamina A/C protein was affected, potentially affecting gene expression and DNA replication within the ovaries. Previous studies have suggested pathogenic mutations in LMNA to be associated with PCOS as they have been widely implicated in insulin resistance, a phenomenon often observed in those with PCOS. However, a conclusive result has not been reached. This study contributes to the existing research regarding implications of the *LMNA*

INTRODUCTION

Polycystic Ovarian Syndrome

Endocrine disorder commonly characterized by the excessive production of male hormones, androgens by the ovaries and/or adrenal glands. This overproduction of androgens may result in excess body hair, facial hair, acne, weight gain and infertility.

Progesterone and estrogen levels may be insufficient to regulate the release of the Gonadotropin Releasing Hormone (GnRH) causing an increase in levels of the Luteinizing Stimulating Hormone (LSH). This results in an imbalance of FSH to LSH which is responsible for the abnormal growth of follicles and hypersecretion of androgens (Harada, 2022, p.2).

This disease affects an estimated 8-13% of women worldwide and is the foremost cause of infertility and anovulation (WHO).

Insulin Resistance is often seen, result of hyperandrogenism. Condition prevents the body from using Insulin, hormone necessary for uptake of glucose by cells, the main source of energy in the body. While Insulin is produced it begins to build up. Since, is not being used the body produces more insulin in attempt to maintain blood sugar levels. This excess of insulin, hyperinsulinemia results in further hyperandrogenism — the two conditions worsen in a feedback loop worsening symptoms of PCOS.

Growth of fluid filled cysts within the ovaries (follicles) containing immature eggs not released during ovulation.

METHODS

ClinVar was used to explore and identify *LMNA* variants (single nucleotide missense mutations) associated with PCOS and evaluate the conserved domains.

Computational tools PolyPhen and SIFT were used to predict the pathogenicity and impact on protein function of the two single nucleotide missense mutations.

SWISS Model was used to obtain 3D protein homology.

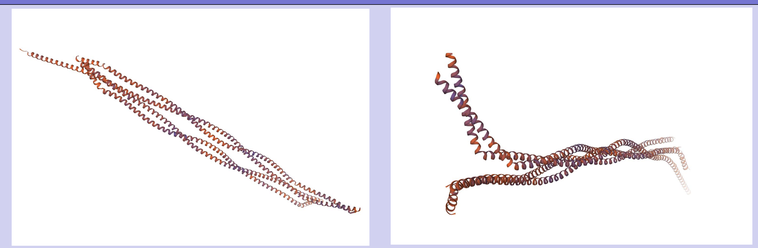
Literature review was conducted to learn more about the *LMNA* gene, PCOS and how the two are related.

RESULTS

About the LMNA gene

Codes for the Lamin A/C protein which :
- Maintains structural integrity of cell form (a part of the nuclear lamina)
- Acts as scaffold for regulatory proteins that oversee DNA synthesis, cell cycle and gene expression
- Mutations in this protein have been linked to laminopathies, the pathogenic damage and alteration of somatic tissues.
- Is highly conserved in the tail region which contains IgG fold necessary for binding an elongation factor needed for chain elongation, formation of a polypeptide chain, in DNA replication

Figure 1.
3D Swiss Model Lamin A/C Protein homology



Prediction of Pathogenicity : PolyPhen and Sift

LMNA Variant 1: Arg455Cys

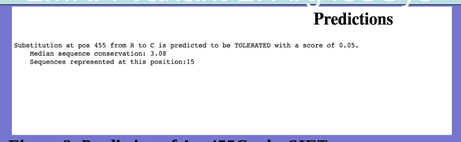


Figure 2. Prediction of Arg455Cys by SIFT
- SIFT predicted the single nucleotide missense mutation occurring at position 455 from Arginine to Cysteine to be tolerated with a score of 0.05

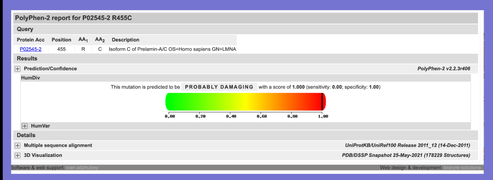


Figure 4. Prediction of Arg455Cys by PolyPhen
- PolyPhen predicted the single nucleotide missense mutation occurring at position 455 from Arginine to Cysteine to be possibly damaging with a score of 1.000

LMNA Variant 2: Arg482Trp

Figure 3. Prediction of Arg482Trp by SIFT
- SIFT predicted the single nucleotide missense mutation occurring at position 482 from Arginine to Tryptophan to AFFECT PROTEIN FUNCTION with a score of 0.00

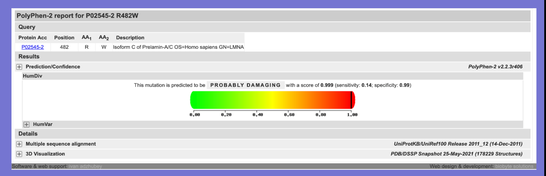


Figure 5. Prediction of Arg482Trp by PolyPhen
- PolyPhen predicted the single nucleotide missense mutation occurring at position 482 from Arginine to Tryptophan to be possibly damaging with a score of 0.999

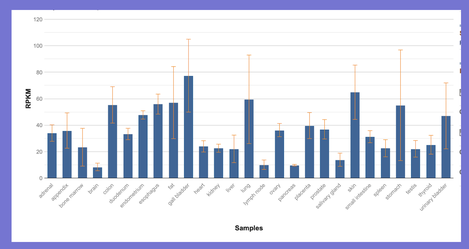


Figure 6. Expression of Lamin A/C protein in various tissues.
- This gene has high expression in several somatic tissues including the : gallbladder, stomach, and skin. It is expressed proficiently in the ovaries.

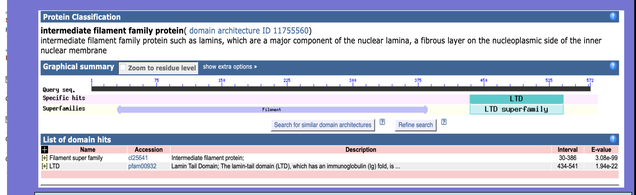


Figure 7. Conserved Domain of Lamin A/C protein

The Lamin A/C protein is highly conserved in the intermediate filament region and the tail region which contains an IgG fold important for the binding of an elongation factor (proliferating cell nuclear antigen). This factor is needed for chain elongation in the formation of a polypeptide chain during DNA replication.

DISCUSSION AND CONCLUSION

- Previous studies have hypothesized that variants of the LMNA gene are associated with PCOS (Bauer et al., 2023, p. A879). Mutations in this gene have been implicated in Familial partial lipodystrophy type 2 (FPLD2), a disease characterized by Insulin Resistance and issues with lipid storage. Pathogenic *LMNA variants* known to cause FPLD2 are found in the highly conserved, intermediate filament region of the lamin A/C protein. In one study, researchers sequenced the LMNA gene in 602 women with PCOS and 125 reproductively healthy women. Seven missense variants were identified in 8 cases and zero in the reproductive healthy controls. This study concluded that *LMNA* variants are to be further established as a mechanism in the pathogenesis of PCOS (Bauer et al., 2023, p. A890).

- In another such study, researchers re-sequenced three regions of the Lamin A/C protein, including the coding region, in 43 women with a phenotypic presentation of PCOS similar to FPLD2 (Urbanek et al., 2009). They identified 56 variants and tested for association between the variants and PCOS. They found no significant evidence for association of the variants with PCOS (Urbanek et al., 2009). However, this study was done exclusively on women of European descent. And genetic variants in Lamin A/C are not common in Caucasian women with PCOS. Further research should be done on a test group with greater racial diversity.

- As PCOS and FPLD2 share the common characteristic of Insulin Resistance it is may be hypothesized that pathogenic mutations in the *LMNA* gene are play a role in Insulin resistance.

- Insulin Resistance is linked to increased androgen secretion which leads to hyperandrogenism, the defining characteristic of PCOS.

- This research contributes to the existing data regarding implications of the *LMNA* gene in PCOS. This work is important because there are several widely known genes that play a role in the pathogenesis of PCOS. However, little data exists on the role of less frequent genes such as *LMNA.* The identification of mutations in this gene could expand treatment and understanding of PCOS in those with this genotype.

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