Structural analysis of age-related macular degeneration associated Retinol binding protein-4 in complex with small molecule ligands

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INTRODUCTION

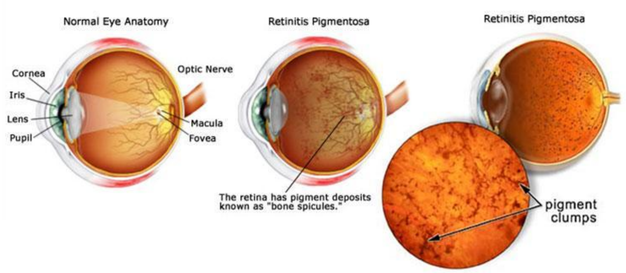
The retina is located at the back of the eye and made up of millions of light sensitive cells called **photoreceptors(PR)**.Behind the photoreceptor cells a simple layer of cuboidal cells that are strategically situated are called **retinal pigment epithelial cells(RPE)**.The relationship between RPE and PR cells is crucial to sight, this is evident from basic and clinical studies demonstrating that primarily dysfunctioning of the RPE can result in visual cell death and blindness. RPE cells carryout many functions including the conversion and storage of retinoid, the absorption of scattered light and RPE-PR apposition. Genes carry instructions for making proteins needed in the cells within the retina, called the photoreceptors.When genes mutate, some mutations result in harmful changes. These harmful changes or mutations can be different. Some mutations result in the genes not to make required protein, hence limiting the cell function.Some mutations result in the production of proteins that is toxic to the cell. Sometimes a abnormal protein is produced that doesn't function properly in all these scenarios.The photoreceptor cells take the damage which inevitably leads to retina pigmentosa.The retina is unable to function properly and struggles to process and transmit sight information to the brain. The most common retinal dystrophy is the group of condition called **retinitis pigmentosa**(figure-1)

The prevalence of retinitis pigmentosa is estimated to be between 1 in 3500 to 1 in 4000 individuals.Retinitis pigmentosa is a group of inherited eye disease that affects the light sensitive part of the eye.There's is no cure, but treatment for age-related macular degeneraion(AMD) may slow the disease and reduce the severe loss of vision. Mostly used treatments are **Anti-angiogenic drugs, Laser treatment, Photodynamic laser therapy**. RP may be caused by mutation in any of at least 50 genes. RPE65 was the first RPE gene reported in human retinal dystrophy.

EXPERIMENTALS

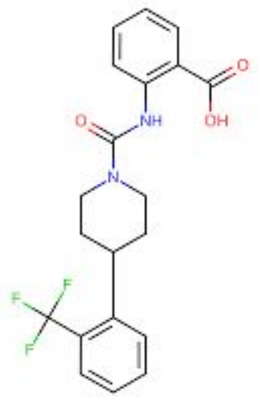
In order to understand the overall structure of retinal binding protein-4(RBP-4) of the retina pigmentatosa,3-dimensional analysis of its structure was performed using computational biology tools. Structure of RBP-4 was downloaded from the protein data bank (PDB ID: 6QBA). The analysis includes evaluation of the secondary structure (alpha-helix and beta strands) followed by hydrogen bonding analysis using PYMOL software. A small molecules binding site are identified.

Retinol binding protein-4(RBP4) is a transporter protein for retinol. It is synthesized in the liver and circulates in the blood stream bound to retinol in a complex with transthyretin. RBP4 is a drug target for ophthalmology research due to its role in vision.



Retina pigmentosa(finger1)

6QBA STRUCTURE



Crystal structure of RBP4

RESULTS & DISCUSSION

The structure of retinol-binding protein-4 (PDB ID: 6QBA) contain 2 chains which are a-chain & b-chain. Where both chains contain alpha-helix and beta-stands. Where a-chain consists of 2 alpha helix & 9 beta strands and b-chain consists of 2 alpha helix & 5 beta strands. Followed by structural analysis, 5 small molecules (LIGAND) are present in the structure which are 2T1;PEG;IMD;ZN;ACT. For 2T1,PEG,IMD,ACT ligands we found they are polar contacts attached and they are no polar contacts attached for ZN ligand.

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