Commentary: Retinitis pigmentosa in Laurence–Moon–Bardet–Biedl syndrome: Genomic sequencing, gene therapy, and gene editing

Being a rare inherited retinal dystrophy, retinitis pigmentosa (RP) in Laurence–Moon–Bardet–Biedl syndrome (LMBBS) is typically described in case series and reports. In the current study,[1] the authors describe a detailed big data analysis of patients with RP which helps document the degree and progeression of vision loss in affected patients. It also helps depict in detail, associated systemic and ocular co-morbidities.

Genetic testing in such patients helps significantly. The advantages are threefold. First, we are able to share the likely course and progression of vision loss to patients by comparing them with people reported to have similar mutations. Second, the inheritance pattern can be informed and discussed with patients, which helps in family planning. Last but not the least, knowing the mutation helps us discuss potential ongoing gene therapy clinical trials and therapies in development, if available, for the same mutation.

That said, in a busy retina practice, often explaining the advantages of the same and discussing the nuances around it may not always be possible. Further, the genomic sequencing technology is financially formidable for most patients, restricting its applicability at present.

LMBBS is caused by mutations in the *BBS* gene (*BBS1–BBS21*), which account for 80% of cases with a clinical diagnosis of Bardet Biedl Syndrome (BBS).[2] The *BBS1* gene, which is the most commonly affected, is responsible for cilia formation in photoreceptors. The impact of *BBS* gene mutations is seen in ciliated cells. Therefore, photoreceptor changes accompany hearing loss and renal, gonadal, and intellectual dysfunction.

Advances in gene therapy have received US Food and Drug Administration (FDA) approval for retinal dystrophy caused by *RPE65* gene mutations (voretigene neparvovec), and clinical trials are in progress for various other mutations causing RP. However, targeting the *BBS* gene mutations via gene therapy has been found to be complex due to the structural stoichiometry of the BBSome protein.[3]

Gene editing using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) received the Nobel Prize in 2020. This promising new technique allows for editing the mutation. The CRISPR effector molecules consist of a guide RNA and Cas9 protein. The guide RNA identifies the target DNA to be edited, and the Cas9 protein cleaves the DNA, following which DNA repair mechanisms take place, which can insert the desired DNA bases, thereby correcting the mutation.[4] The technique can, however, cause DNA editing at other areas of the genome, called off-target effects. To mitigate this, CRISPR base editing and prime editing have been developed.[5] The technology holds promise and is currently in clinical trials for mutations in the *CEP290* gene causing RP, the Brilliance Trial.[6] The role of CRISPR is yet to be explored in *BBS* gene mutations and perhaps could form a prudent area to explore in the future.

To conclude, LMBBS is an important syndrome affecting multiple organs and tissues, the retina being one of them. Such descriptive studies driven by big data analytics help elucidate clinical characteristics of rare inherited retinal dystrophies. In future, an associated relevant genetic analysis of the causative mutations will help describe the mutational landscape in our country and plan therapies for the same.

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