BMJ Case Reports

TITLE OF CASE

Incidental finding of a *BRCA2* variant following whole genome sequencing to molecularly diagnose bilateral congenital cataracts

SUMMARY

A male patient in his 20s with a history of bilateral congenital cataracts and nystagmus presented to the genetic eye disease clinic at Moorfields Eye Hospital to enquire about genetic testing for family decision-making and access to pre-implantation genetic testing. He had a history of lensectomy with best-corrected visual acuities of LogMAR 0.60 and 1.00 in the right and left eye. Whole genome sequencing (WGS) was conducted, which included targeted analysis of a panel of 115 lens-related genes and incidental findings, for which patients are unable to opt out. Genetic testing identified the causative variant c.134T>C (p.Leu45Pro) in the *CRYGC* gene. A pathogenic variant in *BRCA2* was also identified as a secondary finding. This was unexpected given the absence of a strong family history of breast or ovarian cancer. This case illustrates the importance of genetic counselling and informing patients about the implications of incidental findings that arise from WGS.

BACKGROUND

Congenital cataracts refer to opacification of the crystalline lens that is present from birth, and can significantly impair visual acuity and normal development of the visual system.[1] Wu et al. estimated the global prevalence to be 4.24 per 10,000,[2] with 20- 40,000 children born with bilateral congenital cataracts leading to blindness annually.[3-5] Congenital cataracts can be idiopathic, a result of genetic mutations, or secondary to intrauterine infections.[6] Hereditary congenital cataracts represent 22.3% of congenital cataracts and are associated with variants in several genes, with 115 included in the current United Kingdom National Health Service (NHS) Genomic Test Directory cataract panel, and are most commonly inherited in an autosomal dominant pattern.[2, 6, 7] They can be an isolated finding, seen in conjunction with other ocular pathologies, or as part of multi-system diseases.[7] Deprivation amblyopia can result from congenital cataracts; therefore, surgical management is recommended within six weeks of birth.[8] This visual deprivation can also impact fixation resulting in nystagmus that can remain following cataract removal as manifest latent nystagmus.[9, 10] Complications seen following surgery include secondary glaucoma, ocular hypertension, and posterior capsule opacification.[11, 12]

Whole genome sequencing (WGS) is offered by the NHS in the diagnosis of inherited conditions, whereas, previously, targeted gene panels were used to screen a predetermined set of genes known to be associated

with the specific condition being investigated.[13, 14] This offers more comprehensive diagnostic testing, but confers the risk of incidental findings.[15] The use of WGS to identify variants associated with congenital cataracts can empower patients to make decisions in family planning. Preimplantation genetic testing for monogenic disorders (PGT-M) following *in vitro* fertilisation (IVF) is available for those with certain genetic diagnoses, including several genes associated with congenital cataracts.[16]

CASE PRESENTATION

A male patient in his late 20s with a history of bilateral congenital cataracts and intermittent manifest nystagmus presented to the genetic eye disease clinic at Moorfields Eye Hospital NHS Foundation Trust for genetic counselling regarding future family planning. He had a history of bilateral lens aspiration (lensectomies) in the first few months of life and a best-corrected visual acuity of 0.60 LogMAR in the right eye and 1.00 LogMAR in the left, and a family history of congenital cataracts. The patient and both of his parents consented to have WGS performed to investigate the molecular cause of the congenital cataract. The informed consent process included counselling about possible incidental or secondary findings. Blood samples were taken from all three individuals.

INVESTIGATIONS *If relevant*

DNA from the patient and both of his parents was sent for WGS (Illumina) and variants were analysed and classified, as directed by the NHS National Genomic Test Directory. Analysis was restricted to variants within a panel of 115 known congenital cataract genes, tiered *de novo* variants, and variants prioritised by Exomiser. Variants which met the American College of Medical Genetics (ACMG) classification guidelines for ‘pathogenic’ or ‘likely pathogenic’ were fed back to the referring clinician, after a multi-disciplinary discussion.[17-20]

DIFFERENTIAL DIAGNOSIS *If relevant*

N/A

TREATMENT *If relevant*

N/A

OUTCOME AND FOLLOW-UP

Trio WGS identified heterozygosity for the likely pathogenic missense variant c.134T>C (p.Leu45Pro) in the *CRYGC* gene, which segregates with the affected parent. *CRYGC* encodes gamma-C-crystallin, expressed in the lens. This variant has been classified as likely pathogenic by ACMG guidelines (PM2_moderate; PS4_moderate; PP3_supporting; PM1_moderate; PS3_moderate).[20] It has been reported previously in individuals with congenital cataracts. [21, 22] Cataract 2, multiple types (OMIM 604307) is a known outcome of *CRYGC*, with an autosomal dominant inheritance pattern.[23, 24]

Pathogenic variants in *CRYGC* are associated with congenital cataracts and several other eye pathologies including nystagmus, as seen in this patient, peripupillary iris atrophy and microcornea.[23, 24] Congenital cataract is a clinically and genetically heterogenous disease, occurring in isolation in 70%, with other ocular co-morbidities in 15% and as a syndromic feature in 15%. Molecular diagnostic rates range between 50% to 90%, with variants in genes encoding crystallins, including the *CRYGC* gene, accounting for 50% of non-syndromic hereditary cataract.[4, 13] There is a 50% chance that this variant will be inherited by each of the patient's offspring. PGT-M can be used to prevent the transmission of the gene to future offspring.[25]

WGS also identified an inherited autosomal dominant heterozygous pathogenic deletion variant c.6757_6758del (p.Leu2253Phefs*7) in the *BRCA2* gene present. Variants in *BRCA2* are associated with breast and ovarian cancer and this finding therefore has implications for the patient and his family both in terms of personal risk and risk of passing this gene on to future generations. Given the autosomal dominant inheritance pattern there is a 50% chance that each of his full siblings also carry this variant and a 50% chance of passing the variant on to any future offspring. PGT-M is available for *BRCA2* variants, so IVF embryos can also be analysed for this variant prior to implantation.[26] PGT-M and egg or sperm donation can be used to prevent transmission of the variant to offspring; amniocentesis and chorionic villus sampling can be done to diagnose prenatally and enables decisions to be made about terminations; adoption is another route for those worried about vertical transmission.

The identified variant occurs in one of the three *BRCA2* ovarian cancer cluster regions (OCCR). Pathogenic variants present in the OCCR are associated with a greater risk of ovarian compared to breast cancers.[27] The patient did not have a strong family history of breast or ovarian cancer; this secondary finding was therefore unexpected. No consanguinity was present in his family; the only consistent history was a close relative who was diagnosed and passed away from breast cancer in their 50s, which was insufficient to arouse suspicion of a potential *BRCA2* variant. To determine the likelihood of a patient having a pathogenic variant in *BRCA1* or *BRCA2*, the Manchester scoring system was developed, which considers family history of cancer diagnoses alongside age at diagnosis and tumour histology.[28-30] In order to meet NHS criteria

for BRCA1/BRCA2 screening, a Manchester combined score of 15 is required, conferring a 10% risk of a variant being present in *BRCA1* or *BRCA2*, whereas this patient's combined score was four.[28-30]

The patient and family were referred to the clinical genetics service for counselling on lifetime risk, genetic testing and treatment options if results are positive for the variant.[31] Further management following positive diagnosis include increased screening for breast cancer, prophylactic treatment, such as mastectomy, and family planning.

DISCUSSION *Include a very brief review of similar published cases*

Pathogenic *BRCA* variants are most commonly associated with breast and ovarian cancer, but have also been associated with several other cancers including gastric, pancreatic and prostate.[32, 33] Cumulative risk of breast cancer in females was estimated to be 60% at 70 and 72.5% at 85 in *BRCA1* carriers and 55% at 70 and 58.3% at 85 in *BRCA2* carriers. Cumulative risk of ovarian cancer was estimated at 59% at 70 and 65.6% at 85 in *BRCA1* carriers and 16.5% at 70 and 14.8% at 85 in *BRCA2* carriers.[32, 34] Carriers are managed with increased screening and prophylactic risk reductive surgeries including mastectomy and oophorectomy.[34-37] The risk and management of *BRCA* carriers highlights the significance of a positive *BRCA* diagnosis.

Previous case reports have been published describing incidental findings. A report of a patient with features of autistic spectrum disorder (ASD), who underwent WGS to identify a genetic cause for his ASD, was published in 2020. Thirteen variants were found, one of which was a loss-of-function variant in *ANOS1*, which is the most common gene implicated in Kallman syndrome, characterised by hypogonadotropic hypogonadism, resulting in delayed puberty and infertility, with anosmia.[38] Another report, published in 2022, describes a patient investigated for a genetic cause of drug-resistant epilepsy and intellectual disability, who was subsequently found to have variants in *BRCA1* and *BRCA2*.[39] Incidental findings can enable risk reducing interventions to be made, however, they also risk overtreatment of patients and unwarranted distress. The gravity of these implications warrants scrupulous counselling.

In the Genomics England 100,000 Genomes Project, a project founded in 2012 to sequence the genomes of NHS patients with cancer and rare diseases to provide further insight into the role of genetics in disease, consent included the option for each participant to choose whether incidental findings should be relayed following WGS, whereas for patients undergoing WGS under the NHS, there is no option to refrain from receiving off-panel incidental findings.[40-43] This discrepancy emphasises the need for explicit and thorough counselling to ensure that patients appreciate the potential consequences of secondary findings in

WGS. Furthermore, variation in penetrance and phenotypic variability depending on the affected gene requires expert advice. Consent for WGS and interpretation of subsequent results involves complex considerations, and it is therefore advisable that it is undertaken by those with relevant genetics knowledge and experience, such as a genetic counsellor.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- WGS has the potential to identify secondary findings when investigating causal variants of known genetic diseases.
- Incidental findings have implications for the patient's family and future generations, which should be discussed with the patient prior to investigation.
- A full pedigree should be taken to appreciate the inheritance of these genetic variants and to use in the review of additional findings.

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FIGURE/VIDEO CAPTIONS

NA

PATIENT'S PERSPECTIVE

Being informed about this incidental finding was unexpected but was helpful to know. I had specifically requested to be informed about any additional findings that might be identified by WGS. The referral to the Moorfields Genetics Service from the Ophthalmology Department was done smoothly and the specialist input received enabled me to get a good understanding of the process of WGS. The benefits and risks were explained clearly, and the ocular conditions detailed comprehensively.

I understand that the *BRCA* variant results in a high dispensation to certain cancer and I'd like to get a clearer picture as to what options I have to mitigate the risk. I never expected this to be a life changing diagnosis for me and feel that it hasn't really changed my life knowing that I have this variant. I do feel that for those with more life-changing diagnoses it is good to ensure that good communication is maintained throughout the process and where delays in receiving results may occur, an explanation as to why these delays are occurring is conveyed to alleviate any anxiety.

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