UKCGG-National Cancer Genetics MDT meeting: 17 August 2023

Mixed Cases- lead by West Midlands Regional Genetics Service (Birmingham)

Meeting contact: Dr Kai Ren Ong, kairen.ong@nhs.net

Thank you to everyone who attended this session. Below is a summary of the presented cases and relevant publications and resources to refer to.

Presented Cases

Case 1	**Breast cancer with CHEK2 mutation.** Compound heterozygous CHEK2 variants. Breast cancer at 31yo. Also KRIT1 variant (unrelated). Family based in Holland. No other breast cancers in family that we know of. **Query: Consensus on screening recommendations/surgical management?**	Presented by: David Walker Birmingham david.walker6@nhs.net
	Actions/Outcome: - CHEK2 clinical practice resource ACMG now published. Biallelic cases mentioned in paper. Higher risk, difficult to quantify. MRI can be considered – nationally there are discussions with the VHR screening group. Can't do individualised risk scores for this through CanRisk yet. - https://www.gimjournal.org/article/S1098-3600(23)00883-3/fulltext - No one spoke against with the option of bilateral mastectomy, if surgeon/patient opt for this, and it was generally agreed this would be a reasonable approach, otherwise, MRI screening	
Case 2	**Colonic adenocarcinoma at 53yo.** Wider FH unconfirmed. Initial tumour result – IHC isolated loss of PMS2. MSI +ve. **Query: Should we check tumour for PMS2 variant – as if present alongside another PMS2 may support reclassification**	Presented by: Alys Kennedy & Eamonn Kirk Wales
	Actions/Outcome: - Would support tissue testing - Concern that further FFPE testing (which includes more genes) may confuse the issue - Doing FFPE testing could find two other variants (pathogenic) present in the tumour which may give an answer and make this variant irrelevant - Confirm the brain tumours, check IHC. Consider CMMRD?	

Case 3	**Lynch cases** 1. Endometrial cancer. No variants detected MHS 6 loss on IHC twice. MSI testing – equivocal. IHC on sisters colorectal CRC and Mother's CRC – normal. Repeated tissue testing – confirmed MSH6 loss in tumour. Query: With CRC FH – would be moderate risk. Advice sought re: gynae risk/management	Presented by: Aoife O'Shaughnessey-Kirwan Dublin
	Actions/Outcome: - Recent UKCGG meeting on management of "Lynch like cases" (unexplained mismatch repair deficiency), no consensus on criteria that can identify a group that can be discounted as Lynch syndrome - Not a strong Lynch FH, especially with the normal IHC in other bowel cancers - Consensus would be bowel screening as per FH and no recommendation for RR gynae surgery for sisters.	
Case 4	**Endometrial cancer at 60** MSH6 one pathogenic and one VUS identified in tumour tissue (neither is in germline). Paternal FH not known No CRC otherwise in family	Presented by: Aoife O'Shaughnessey-Kirwan
	Actions/Outcome: 1. Appear to be somatic changes which likely explain the MSH6 IHC loss 2. Her generation not affected at all by bowel cancer – reassuring that Lynch is not very likely 3. Would not recommend Gynae intervention for other relatives 4. Lynch bowel screening not indicated here	
Case 5	**Peutz Jegher polyp query** 38yo presented with small bowel intussessption. 3x PJS polyps. No mucocutaneous pigmentation. No other PJS features. No significant FH No STK11 in germline STK11 c.358G>T somatic driver variant at VAF 2% found in one polyp and same variant at a 6% VAF in another polyp (this is two separate polyps as per histopath) **Query – any additional testing? is the STK11 somatic variant significant? Could this be low level mosaicism?**	Presented by: Dr Lucy Bownass Bristol
	Actions/Outcome: - Mosaicism rare in PJS but documented in a few cases in the literature, usually found in blood - Not unreasonable to offer testing to son at 11/12yo and examine for pigmentation. If negative can be reassuring to him - Repeat colonoscopy planned in 3 years already, this is clearly reasonable	

	- Would be interesting to review in UKCGG MDT meeting in a few years after repeat colonoscopy - No other testing needed	
Case 6	**SMARCA4 variant** 28yo female. Mod ID & dysmorphism – not typical of Coffin-Siris syndrome. No tumours in the past. Attends specialiast school. Lives with her parents. Mental age of 7/8yo child. No capacity. She would be able to lie still and have an USS if indicated. Microarray normal. 100K nil reported. Reanalysis by Manchester lab of 100K result – de novo deletion of coding exons 11 and 12 of SMARCA4. Classified as a VUS. Predicted to result in an in-frame deletion. **Query – what is the risk of SCCOHT? ATRT? What cancer screening is warranted? Pelvic USS – normal June 2023.**	Presented by: Dr Kate Chandler Manchester
	Actions/Outcome: - Leora Witkowski – seen inframe exon 16-17 in another patient with SCCHOT. This deletion would take out the BRK domain as opposed to exon 16-17 deletion which would take out helicase ATP-binding domain where most of the damaging missense variants have been seen. - if it is really a VUS we wouldn't recommend any intervention. But if we can't be certain it's a VUS, then risk reducing surgery (RRS) should probably be discussed. Small cell ovarian cancer is aggressive, poor survival. Not concerned about ATRT/MRT, has already lived through her risk for this. If she developed SCCHOT – intense chemotherapy and likely wouldn't tolerate. Prior to ACMG criteria this may well have been considered pathogenic. - generally, if we found an ovarian cancer VUS, wouldn't recommend RRS. If this is a "hot" VUS then wouldn't be unreasonable to recommend RRS. Would need an ethics type panel to decide in her best interest. - Also need to consider how she would tolerate early menopausal symptoms and treatment or surveillance for the side effects (e.g. bone density scans etc.) - Presenter stated that the patient's parents would probably rather opt for RRS than to put her through treatment for an aggressive cancer. She won't be having her own family, which may support RRS. - Broad agreement in summary - to offer RRS, but needs a panel/best interests meeting. Will need to mention that the classification may change in the future..	
Case 7	SMARCA4 variant Rhabdoid tumour predisposition gene Proband is 6yo girl, neuroblastoma. Pathogenic variant in SMARCA4. Paternally inherited. 3 paternal half-siblings offered testing	Presented by: Dr Farah Kanani Farah.kanani@nhs.net Birmingham
	Actions/outcome – this is essentially an incidental finding. Contact Leora Witkowski and confirm that she thinks this is pathogenic. Some 3' splicing variants may not be pathogenic. If it is pathogenic –wouldn't be concerned about father in terms of rhabdoid or other risks. Main issue is for children, especially 2 daughters (and the child with neuroblastoma) and	

	SCCHOT risk. There is likely to be a risk of SCCHOT in this family if this is definitely pathogenic and the need to discuss consideration of risk reducing surgery in daughters. Signpost to support group in US (www.smallcellovarian.org). Intensive screening protocol for rhabdoid tumours is not advocated as the risk is still low.

Relevant publications/resources

Topic	Link
CHEK2 guidelines	https://www.gimjournal.org/article/S1098-3600(23)00883-3/fulltext

Next meeting details

Date	Thursday 21st September
Time	12:30 pm-1:45 pm
Theme	Management of ATM carriers and interesting ATM cases
Leading centre	Nottingham
Contact for cases	clairesearle@nhs.net

Please send any questions or ideas for future meetings to Helen Hanson (helen.hanson@stgeorges.nhs.uk)