UKCGG-National Cancer Genetics MDT meeting: 21st Sept 2023

ATM heterozygotes lead by Nottingham Clinical Genetics Service

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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	**3 cases of ATM heterozygote mothers from the National paediatric AT clinic showing the spectrum of population, moderate and high risk assessments for breast cancer screening**	Presented by: Dr Mohnish Suri (MS) Nottingham Clinical Genetics Service Mohnish.suri@nuh.nhs.uk
	Actions/Outcome: ACMG guideline hopefully being published in the next year. This is likely to need an additional UK statement to provide enough clarity for these cases. MS to provide a list of his variants from the AT clinic to try and compile a list of those reported on R208 and R430 and guidance re breast screening for more common variants. To set up UKCGG working group for a UKCGG guideline.	
Case 2	**39-year-old with breast cancer with ATM PV found on R208, no BC FH. Canrisk estimate for contralateral breast cancer risk 34%**	Presented by: Lara Hawkes Oxford clinical genetics department lara.hawkes@ouh.nhs.uk
	Actions/Outcome: see case 3	
Case 3	**36 year old woman Multifocal left breast cancer with LN metastases – diagnosed aged 36 Grade 2 ER+ PR+ HER2- FH: BC in paternal grandmother diagnosed in her 50's Mainstreamed R208 - ATM c.824del p.(Leu275*) - pathogenic truncating. Contralateral breast cancer risk 42%**	Presented by: Rachel Harrison Nottingham Clinical Genetics Service Rachel.harrison@nuh.nhs.uk
	Actions/Outcome: Case 2 and 3 are very similar. Highlighted the high estimated contralateral cancer risk predicted by Canrisk in women with ATM PV and young breast cancer. The Yadav data 2023 was discussed which found "ATM PV carriers did not have significantly increased CBC risk". It was highlighted that their data had a maximum follow up time of 20yr but with small numbers having longer follow-up. In these women, CanRisk estimates show the risk increasing in comparison to the control population after 15-20yrs. Other centres were offering RRM to ATM PV carriers who are assessed to be at high risk of breast cancer or of a contralateral breast cancer but are counselling carefully to emphasise caution about current data. Other centres were not altering radiotherapy regimes for ATM PV carriers as there is very little to suggest this	

	causes a significant increase in contralateral breast cancer risk.	
Case 4	**Early detection of breast cancer found in a 30 year old ATM heterozygote through VHR screening after a PST. Strong FH of breast cancer. CanRisk calculation predicted very high risk of breast cancer, 58.5% until 80. The woman's risk between ages 40 and 50 of having breast cancer is 17.2%.**	Presented by: Louise Izatt Guy's clinical genetics louise.izatt@nhs.net
	Actions/Outcome: Highlighted a case where ATM heterozygote had a very high risk of breast cancer and how VHR screening allowed early diagnosis of a breast cancer. The patient wished to highlight how little information was available for ATM heterozygotes and wished for a support group similar to PALB2. She had opted for bilateral mastectomy which had a significant impact particularly as a young woman in relation to breast feeding children.	
Case 5	**ATM high penetrance family with 7x cases of breast cancer and a case of AT. One young bilateral breast cancer case didn't carry the familial ATM PV.**	Presented by: Jackie Cook Sheffield Clinical Genetics Jackie.cook8@nhs.net
	Actions/Outcome: ATM detected from FH of AT, but the family also had a significant FH of breast cancer. Genetic analysis in more than one affected woman had not detected any other breast cancer predisposition gene variants. Highlighted that other genetic factors must be modifying risk in this family.	
Case 6	**ATM variant classification query for PST ATM - c.8418+5_8418+8del**	Presented by: Rachel Harrison Nottingham Clinical Genetics Rachel.harrison@nuh.nhs.uk
	Actions/Outcome: Patient presented with FH of prostate and breast cancer. Variant detected in brother with prostate cancer who had private genetic testing. Intronic ATM variant leading to in-frame deletion of one exon within the kinase domain of AT. Highlighted that some ATM variants fall outside the classification process suggested by the Dorling paper. Recognised as pathogenic in AT but hard to classify in relation to cancer risk. Functional data available from AT patients attending the Nottingham paediatric AT clinic activity demonstrate that this variant leads to small amounts of ATM protein production but this has no kinase activity. Discussion of classification difficulties for the laboratory to determine if we can offer PST for cancer risk. Canrisk shows BC risk of just >17% if PST is negative, despite only paternal grandmother having breast cancer in her 50s. Other centres would refer for breast screening in this situation, although not eligible from FH alone. Some commented that they would not routinely use Canrisk in this way.	
Case 7	**2 cases of breast cancer in ATM heterozygotes. The question about ongoing screening was raised. Hard to access actual risk of a second breast cancer as CanRisk only calculates risk in contralateral side but both these women had only had WLE and therefore had a lot of remaining tissue on the affected side.**	Presented by: Claire Searle and Esther Horton Nottingham clinical genetics claire.searle@nuh.nhs.uk
	Actions/Outcome: No one commented re appropriate screening	

Relevant publications/resources

Topic	Link
Dorling et al 2022	Dorling et al. - 2022 - Breast cancer risks as:
Dorling et al NEJM 2021	https://pubmed.ncbi.nlm.nih.gov/33471991/

Expert Speaker Talk

Practical aspects of assessing non- truncating ATM variants-

Anna Wilsdon The slides can be accessed at: [hyperlink]

Talk Summary:

Overview of AT and ATM heterozygotes and cancer risk.

Review of previous literature beginning with Moslemi et al 2021, who confirmed the association of ATM variants and breast cancer (OR 1.67). The highest risk from a missense variant was seen with V2424G, which has previously been classified as high risk. There were then two papers published by the same group, which began to clarify the risk of breast cancer with missense variants. The first was in 2021 (Dorling et al 2021) which compared approximately 60 000 women with breast cancer and 53 000 controls. Protein truncating variants are associated with breast cancer (moderate risk), and the association was strongest in ER-positive tumours. The estimated absolute risks by 80 years of age was around 20% (OR was 2.1) for individuals with ATM PTVs.

The paper also confirmed that rare missense variants in ATM are associated with breast cancer. The overall OR was 1.06 (95%CI 1-1.13). The increased risk was associated with variants in the FAT and protein kinase (phosphatidylinositol 3-kinase and 4 kinase) domains. Individuals with heterozygous variants have a higher risk of breast cancer than individuals with homozygous ATM variants. The highest risk was seen in people of Asian ethnicity compared to European (conflicting results in other studies).

The second paper from the same group as above (Dorling 2022) considered the same cohort and investigated the role of missense variants and how we can risk stratify them further. CADD is the best predictor of deleteriousness for ATM (version 1.4). Rare missense variants in the top quintile of CADD scores, and in the FAT or kinase domains have a higher risk. The authors state that the risk approaches that of PTVs.

In Nottingham we see carrier mothers of children with AT. It is challenging to determine

their risk. They are being risk stratified by calculating the CADD score and confirming the domain the variant falls in. Those that meet the criteria of being in a significant domain with a high enough CADD score will be assessed via CanRisk. If they do not meet the criteria, the screening recommendations are based on an assessment of family history.

We then considered some practical examples of use of the Dorling 2022 paper to assess missense variants including CADD score and looking at domains. Important issues to consider is the variable domain borders (consider using Uniprot or Lau et al) and variable versions of CADD (consider using v1.4 as per the paper).

There are many uncertainties and limitations and it is difficult to be sure how much of the increased risk is due to a restricted number of variants. This also creates inequality, as missense variants in ATM are not reported on the breast cancer panel testing currently. Further research is required.

Moslemi M, Moradi Y, Dehghanbanadaki H, Afkhami H, Khaledi M, Sedighimehr N, Fathi J, Sohrabi E. The association between ATM variants and risk of breast cancer: a systematic review and meta-analysis. BMC Cancer. 2021 Jan 5;21(1):27. doi: 10.1186/s12885-020-07749-6. PMID: 33402103; PMCID: PMC7786920.

Breast Cancer Association Consortium; Dorling L, Carvalho S, Allen J, González-Neira A, Luccarini C, Wahlström C, Pooley KA, Parsons MT, Fortuno C, Wang Q, Bolla MK, Dennis J, Keeman R, Alonso MR, Álvarez N, Herraez B, Fernandez V, Núñez-Torres R, Osorio A, Valcich J, Li M, Törngren T, Harrington PA, Baynes C, Conroy DM, Decker B, Fachal L, Mavaddat N, Ahearn T, Aittomäki K, Antonenkova NN, Arnold N, Arveux P, Ausems MGEM, Auvinen P, Becher H, Beckmann MW, Behrens S, Bermisheva M, Białkowska K, Blomqvist C, Bogdanova NV, Bogdanova-Markov N, Bojesen SE, Bonanni B, Børresen-Dale AL, Brauch H, Bremer M, Briceno I, Brüning T, Burwinkel B, Cameron DA, Camp NJ, Campbell A, Carracedo A, Castelao JE, Cessna MH, Chanock SJ, Christiansen H, Collée JM, Cordina-Duverger E, Cornelissen S, Czene K, Dörk T, Ekici AB, Engel C, Eriksson M, Fasching PA, Figueroa J, Flyger H, Försti A, Gabrielson M, Gago-Dominguez M, Georgoulias V, Gil F, Giles GG, Glendon G, Garcia EBG, Alnæs GIG, Guénel P, Hadjisavvas A, Haeberle L, Hahnen E, Hall P, Hamann U, Harkness EF, Hartikainen JM, Hartman M, He W, Heemskerk-Gerritsen BAM, Hillemanns P, Hogervorst FBL, Hollestelle A, Ho WK, Hooning MJ, Howell A, Humphreys K, Idris F, Jakubowska A, Jung A, Kapoor PM, Kerin MJ, Khusnutdinova E, Kim SW, Ko YD, Kosma VM, Kristensen VN, Kyriacou K, Lakeman IMM, Lee JW, Lee MH, Li J, Lindblom A, Lo WY, Loizidou MA, Lophatananon A, Lubiński J, MacInnis RJ, Madsen MJ, Mannermaa A, Manoochehri M, Manoukian S, Margolin S, Martinez ME, Maurer T, Mavroudis D, McLean C, Meindl A, Mensenkamp AR, Michailidou K, Miller N, Mohd Taib NA, Muir K, Mulligan AM, Nevanlinna H, Newman WG, Nordestgaard BG, Ng PS, Oosterwijk JC, Park SK, Park-Simon TW, Perez JIA, Peterlongo P, Porteous DJ, Prajzendanc K, Prokofyeva D, Radice P, Rashid MU, Rhenius V, Rookus MA, Rüdiger T, Saloustros E, Sawyer EJ, Schmutzler RK, Schneeweiss A, Schürmann P, Shah M, Sohn C, Southey MC, Surowy H, Suvanto M, Thanasitthichai S, Tomlinson I, Torres D, Truong T, Tzardi M, Valova Y, van Asperen CJ, Van Dam RM, van den Ouweland AMW, van der Kolk LE, van Veen EM, Wendt C, Williams JA, Yang XR, Yoon SY, Zamora MP, Evans DG, de la Hoya M, Simard J, Antoniou AC, Borg Å, Andrulis IL, Chang-Claude J, García-Closas M, Chenevix-Trench G, Milne RL, Pharoah PDP, Schmidt MK, Spurdle AB, Vreeswijk MPG, Benitez J, Dunning AM, Kvist A, Teo SH, Devilee P, Easton DF. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021 Feb 4;384(5):428-439. doi: 10.1056/NEJMoa1913948. Epub 2021 Jan 20. PMID: 33471991; PMCID: PMC7611105.

Dorling L, Carvalho S, Allen J, Parsons MT, Fortuno C, González-Neira A, Heijl SM, Adank MA, Ahearn TU, Andrulis IL, Auvinen P, Becher H, Beckmann MW, Behrens S, Bermisheva M, Bogdanova NV, Bojesen SE, Bolla MK, Bremer M, Briceno I, Camp NJ, Campbell A, Castelao JE, Chang-Claude J, Chanock SJ, Chenevix-Trench G; NBCS Collaborators; Collée JM, Czene K, Dennis J, Dörk T, Eriksson M, Evans DG, Fasching PA, Figueroa J, Flyger H, Gabrielson M, Gago-Dominguez M, García-Closas M, Giles GG, Glendon G, Guénel P, Gündert M, Hadjisavvas A, Hahnen E, Hall P, Hamann U, Harkness EF, Hartman M, Hogervorst FBL, Hollestelle A, Hoppe R, Howell A; kConFab Investigators; SGBCC Investigators; Jakubowska A, Jung A, Khusnutdinova E, Kim SW, Ko YD, Kristensen VN, Lakeman IMM, Li J, Lindblom A, Loizidou MA, Lophatananon A, Lubiński J, Luccarini C, Madsen MJ, Mannermaa A, Manoochehri M, Margolin S, Mavroudis D, Milne RL, Mohd Taib NA, Muir K, Nevanlinna H, Newman WG, Oosterwijk JC, Park SK, Peterlongo P, Radice P, Saloustros E, Sawyer EJ, Schmutzler RK, Shah M, Sim X, Southey MC, Surowy H, Suvanto M, Tomlinson I, Torres D, Truong T, van Asperen CJ, Waltes R, Wang Q, Yang XR, Pharoah PDP, Schmidt MK, Benitez J, Vroling B, Dunning AM, Teo SH, Kvist A, de la Hoya M, Devilee P, Spurdle AB, Vreeswijk MPG, Easton DF. Breast cancer risks associated with missense variants in breast cancer susceptibility genes. Genome Med. 2022 May 18;14(1):51. doi: 10.1186/s13073-022-01052-8. PMID: 35585550; PMCID: PMC9116026.

Lau WC, Li Y, Liu Z, Gao Y, Zhang Q, Huen MS. Structure of the human dimeric ATM kinase. Cell Cycle. 2016;15(8):1117-24. doi: 10.1080/15384101.2016.1158362. PMID: 27097373; PMCID: PMC4889239.

Meeting Summary

Acceptance of the need for more data to accurately advice ATM heterozygotes re cancer risk and screening

ACMG guideline hopefully being published in the next year re reporting ATM variants. This is likely to need an additional UK statement to provide enough clarity for these cases such as those presented. Consideration could be given to developing a 'white list' of missense variants to be reported. Dr Suri to provide a list of the common ATM variants from the paediatric clinic to help with this.

Agreed the need to set up UKCGG working group for a UKCGG guideline re ATM

Next meeting details

Date	Thursday 16th November
Time	12:30 pm-1:45 pm
Theme	Mixed Cases
Leading centre	Exeter
Contact for cases	helen.hanson6@nhs.net

Please send any questions or ideas for future meetings to Helen Hanson (helen.hanson6@nhs.net)