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The frequency of the m.1555A>G (*MTRNR1*) variant in UK patients with suspected mitochondrial deafness

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The m.1555A>G variant has been identified as a cause of hearing loss both in non-syndromic familial cases and sporadic cases associated aminoglycoside usage [1]. Variant testing is used both in the diagnosis of hearing loss of unknown origin and in cases of prospective aminoglycoside use.

Targeted mutation analysis of m.1555A>G in the UK is provided by the UK Genetic Testing Network (UKGTN) in five accredited laboratories: Oxford (Oxford Medical Genetics Laboratories), Birmingham (Inherited Metabolic Disease unit), London (UCLH Queen Square and Great Ormond Street Hospital, GOSH) and Newcastle upon Tyne (NHS Highly Specialised Mitochondrial Service). The mitochondrial genome, encompassing the *MTRNR1* gene, is also sequenced in the diagnosis of suspected mitochondrial disease by the laboratories in Newcastle and UCLH. We surveyed these centres and recorded 3979 specific test requests in addition to 1336 complete mitochondrial genomes (including the *MTRNR1* gene). A review of the clinical referrals revealed that this included testing in patients with hearing loss of unknown origin, patients for prospective aminoglycoside treatment and patients with undetermined neurological phenotypes suspected to have a pathogenic mtDNA mutation.

In total we recorded 20 positive test results within the 5-year survey period (20/5315, 0.37%, 95% CI = 0.21-0.53). Mitochondrial genome sequencing in patients with suspected mtDNA

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disease (e.g. neonatal leukodystrophy and lactic acidosis and hence not specifically for hearing impairment) detected 4 positive diagnoses (4/1336, 0.3% 95% CI= 0.1-0.59). This is as expected similar to the background population frequency (Fisher's exact $p = 0.735$).

Of the mutation specific tests the number of positive tests (16/3979, 0.4% 95% CI= 0.2-0.6) appears to be higher than the published background population incidence for the variant (0.21% 95% CI = 0.03- 0.39) but is not statistically different (Fisher's exact $p = 0.19$) [2]. All positive results in the hearing loss group were detected at GOSH ($n=12$) (Table 1) and the number of positive tests in this group (12/2147, 0.56%, 95% CI= 0.24-0.88) is also not significantly higher than the background population frequency (Fisher exact $p = 0.06$). This is surprising as we would expect a higher positive rate in these patients referred with hearing loss (i.e. a selected group with a relatively greater risk for the variant).

On the basis of our results, we propose that m.1555A>G testing could be potentially misleading in patients with hearing loss of unknown origin without maternal family history or aminoglycoside usage. Falsely concluding that the deafness is caused by m.1555A>G will prevent further investigations to identify the underlying cause, could lead to erroneous genetic counselling, and perhaps the inappropriate application of mitochondrial replacement therapy.

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Table 1

Summary of specific testing for the m.1555A>G mutation undertaken at UKGTN laboratories

Testing centre	Number of m. 1555A>G tests for hearing loss (1)	Number of tests for prospective aminoglycoside use (2)	Total number of tests for m. 1555A>G (1+2)	Hearing loss positives (3)	Non hearing loss positives (3)	Number of complete mitochondrial genomes sequenced	Number of positive tests (4)	Total positive tests (3+4)
Oxford	270	83	353	0	0	0	0	0
Newcastle	212	226	438	1	0	713	3	4
London (UCLH)	35	0	35	0	0	623	1	1
London (GOSH)	1434	1523	2957	11	4	0	0	15
Birmingham	196	0	196	0	0	0	0	0
Total	2147	1832	3979	12	4	1336	4	20