Incidental Findings During Testing For Core Disorders; What Is The Clinical Approach?

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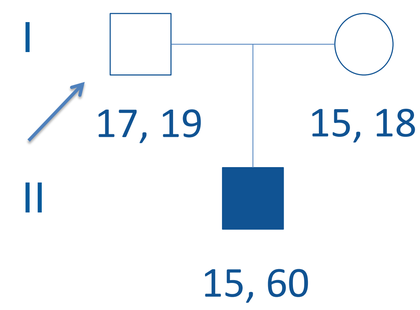
Introduction

The challenges of reporting incidental findings has been considered and discussed in depth in relation to whole genome/exome sequencing data, whilst genetic testing and counselling for the core rare disease disorders is perceived as being relatively straightforward. We present several cases that highlight the challenges faced by laboratories and clinicians when incidental findings are found during testing for such conditions.

Case 1: Huntington disease

- Proband II1 aged 27 diagnosed with juvenile HD
- Father I1 referred for presymptomatic testing at age 50. Normal CAG result, no alleles in common with son
- Repeat sample from I1 confirmed the previous normal result and excluded sampling and analytical errors
- Mother I2 tested and a normal PST report issued; excludes maternal transmission

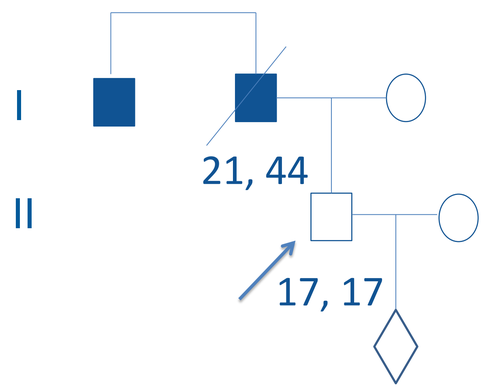
Clinical /Lab Approach: Initial results for I1 were discussed with Clinical Genetics prior to issuing a standard negative PST report. I1 was counselled at point of testing that he was likely to have a small expansion given juvenile onset in his son. I1 was counselled that an expansion had not been detected and therefore he will not develop HD
Mother I2 attended the results clinic with I1 and a sample was taken from her for predictive testing. Their body language during the session suggested that they were expecting this outcome. They were given several opportunities to question the result but did not follow this up.



Case 2: Huntington disease

- Father I2 given a molecular diagnosis of HD in 2000
- Son II1 was referred for presymptomatic testing; his partner was pregnant at the time. Normal CAG result; CAG/CCG repeat assay gave heterozygous normal result (17, 20) but no alleles in common with father
- Repeat sample from II1 confirmed previous normal result and excluded sampling/laboratory error

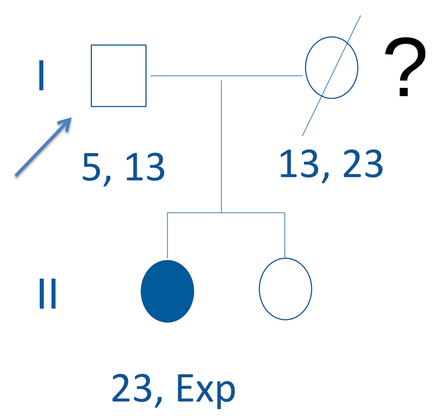
Clinical /Lab Approach: We confirmed the pedigree and control samples we were using to be correct. Result given out without highlighting issue of non-paternity. II1 and his partner were overjoyed as both II1 and the pregnancy were no longer at risk.



Case 3: Myotonic Dystrophy (DM1) – International referral

- Proband II1 referred with a clinical diagnosis – no clinical information provided
- Father I1 subsequently referred for confirmation of diagnosis (no clinical information provided) - normal CTG result
- Possible explanations: Alternative diagnosis in I1; non-paternity
- A repeat sample from I1 confirmed the previous result
- II2 received for carrier (presymptomatic) testing – analysis put on hold whilst further information requested
- Sample from I2 was received which was unexpected as referral information indicated she was deceased. Normal result excluded maternal transmission
- Fresh blood from I1 received by international lab, who performed identity testing. This excluded sampling/laboratory error and confirmed that I1 is not the biological father of II1

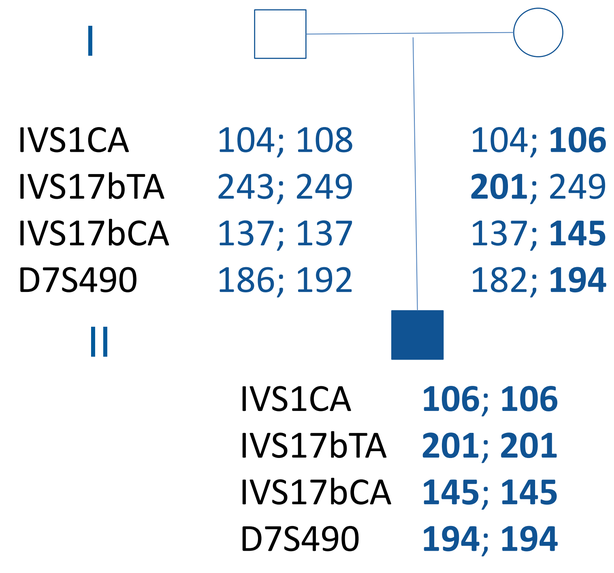
Clinical /Lab Approach: The referral information received was poor and attempts to clarify familial relationships and clinical indicators were hampered by language problems and differences in clinical and laboratory protocols between the two centres. Counselling protocols were also unclear so the report for I2 stated that the expansion in II1 had been paternally inherited but that testing of other siblings (including II2) could only be undertaken on a case by case basis.



Case 4: Russell Silver Syndrome

- Proband II1 referred for Russell Silver testing. 11p15.5 MLPA was normal.
- MatUPD7 investigations undertaken by microsatellite marker analysis of 7q (methodology at the time)
- Results indicated matUPD7 consistent with a diagnosis of Russell Silver syndrome
- Subsequent validation of a UPD7-UPD14 MLPA kit using this sample as a positive control was not supportive of matUPD7
- This result was confirmed independently by another diagnostic lab
- Identity analysis indicated that there was clearly no paternal contribution at 7/14 loci

Clinical /Lab Approach: Results were discussed with the clinical genetics team following UPD7 /14 MLPA result. Repeat samples from the child and parents for identity testing were requested by Clinical Genetics. An amended report was issued detailing the most recent results and revoking the molecular diagnosis. In the meantime the family have moved and therefore contact was made with their current clinician. Further samples and a diagnosis are pending.



Conclusion

All 4 cases highlight that clinicians and laboratories are reliant on receiving accurate clinical and pedigree information. When unexpected results arise all possible explanations for these should be investigated. These cases highlight that good clinical and laboratory interactions and communication is vital to this process. A case by case approach is essential in ensuring that the clinical question is answered in the most sensitive manner.