

Medical genetics: advances in brief

Non-invasive perinatal necropsy by magnetic resonance imaging

Brookes JAS, Hall-Craggs MA, Sams VR, Lees WR. *Lancet* 1996;348:1139-41.

Necropsy is only carried out in about 45% of perinatal deaths in the UK. There are several reasons for this, one of the major ones being the low level of acceptance of necropsy by parents for personal or religious reasons. Brookes and colleagues examined 20 fetuses by both post mortem scanning and necropsy and compared the diagnostic information obtained. In two fetuses necropsy provided more important diagnostic information than MRI. One of these was a fetus with cystomegaly and bladder wall hypertrophy which was not detected on MRI. In the other case there was ventriculomegaly diagnosed both at necropsy and on MRI, but only detailed histological examination showed the periaqueductal haemorrhage which caused it. This finding would have had importance in the genetic counselling of the family. In eight of the fetuses, comparable information was obtained by the two investigations. In eight, more detail was obtained by the necropsy but the MRI gave similar diagnostic results. In four cases, the MRI gave more information, particularly with respect to central nervous system structures. The fetal brain is very friable, even after preservation, and MRI scanning allows examination without disturbance. Musculoskeletal structures and cartilage were well seen in MRI scans. Two cases of hip dysplasia were diagnosed in this series; necropsy does not usually examine for this routinely. MRI scanning was also successful at showing body fluid abnormalities. The evidence presented suggests that in 90% of cases comparable diagnostic information is obtained by MRI as from necropsy. For many parents, MRI may prove acceptable where necropsy does not. Important information for genetic counselling could be obtained by using this novel approach to post mortem diagnosis.

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Support for the prion hypothesis for inheritance of a phenotypic trait in yeast

Patino M, Liu J-J, Glover JR, Lindquist S. *Science* 1996;273:622-6.

The discovery that prion proteins are implicated in the pathogenesis of a number of neurodegenerative disorders (for example, Creutzfeldt-Jakob disease) has forever altered the notion that nucleic acids are always to be found at the heart of infectious agents. This report may now alter the assumptions inherent in our analysis of heritable phenotypes. The [PSI⁺] factor in yeast behaves as a dominant, cytoplasmically inherited genetic element but is unlinked to any known nucleic acid. It results in increased translational read through of all three nonsense codons and can be monitored by omnipotent suppression of nonsense mutations. A number of experimental methods are used to show that [PSI⁺] represents the inheritance of a self-perpetuating alteration in the conformation of the nuclear encoded protein Sup35, a subunit of the translation release factor that causes ribosomes to terminate translation at nonsense codons. While mutations in Sup35 can cause omnipotent nonsense suppression, the mutant phenotypes, unlike [PSI⁺], exhibit Mendelian inheritance. Transient overexpression, however, of Sup35, or just its NH₂-terminal domain, can induce de novo heritable [PSI⁺] elements. Furthermore, transient overexpression of the chaperone Hsp104 can restore translational fidelity, heritably converting cells from [PSI⁺] to [PSI⁻]. The discovery of such a mechanism in yeast makes it likely that elusive epigenetic phenomena in other organisms may well prove to depend on the maintenance of alternative protein conformations. Finally, because the inheritance of [PSI⁺] elements depends on Hsp104, which may be induced by environmental stress, this phenomenon represents a plausible mechanism for the inheritance of an acquired characteristic.

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Familial transmission of the FMR1 CGG repeat

Nolin SL, Lewis FA III, Ye LL, et al. *Am J Hum Genet* 1996;59:1252-61.

The fragile X mutation is an amplification of a CGG triplet repeat which is inherited in an unstable fashion once it has expanded above a certain size. Normal subjects have 10 to 15 copies of the triplet repeat, and male and female carriers with a "premutation" have 56 to 200 repeats. These carriers are usually phenotypically normal and do not express the fragile site cytogenetically. Affected subjects with the full mutation have >200 repeats, as well as methylation of an associated CpG island, which results in the absence of FMR1 mRNA expression. An improved understanding of the stability of the CGG repeat in fragile X families is particularly important for genetic counsellors, so that they can try and give families some idea about the range of possible outcomes in future generations. In this study, the change in allele size was measured in 191 fragile X families, and 33 families with repeats in the "grey" zone (that is, 40 to 60). Expansion of the fragile X chromosome to the full mutation was seen in 13% of offspring from premutation mothers with 56 to 59 repeats, 21% of those with 60 to 69 repeats, 58% of those with 70 to 79 repeats, 73% of those with 80 to 89 repeats, and 97% of those with 90 to 199 repeats. For premutation fathers, 62% of their daughters had a larger repeat number, 22% a smaller repeat number, and in 16% the number was unchanged. Daughters only had a smaller repeat number if their father had ≥80 repeats (40% of such daughters had a smaller repeat size than their father). There appears to be a familial clustering of similar repeat numbers in the offspring of both males and females carrying the premutation, suggesting that there may be an additional factor, independent of parental repeat size, that influences CGG repeat instability. Instability in the grey zone allele transmissions was observed in 25% of those with 40 to 49 CGGs, but in <8% of those with 50 to 60 CGGs, but in <8% of pure CGGs (>34) are not always unstably transmitted. Overall, while the absolute size of the triplet repeat is clearly important in determining what happens when the fragile X gene is transmitted, there must be other unidentified factors which are also important.

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