

## Abstract 12

### GENES FOR AUTOSOMAL RECESSIVE MENTAL RETARDATION IN OUTBRED FAMILIES

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Due to the extreme clinical and genetic heterogeneity of mental retardation (MR), unravelling the genetic basis of MR has proven to be difficult. In particular, identifying the genetic basis of autosomal recessive MR (AR-MR) has been challenging. Although AR-MR is estimated to affect approximately 25% of all patients with non-syndromic MR, today only a handful of AR-MR genes (*PRSS12*, *CRBN*, *CC2D1A*, *TUSC3* and *GRIK2*) and AR-MR loci (*MRT1-12*) have been identified. This has been established mostly by use of homozygosity mapping in large consanguineous families with multiple affected individuals. The disadvantage of this strategy is that these families show large stretches of homozygosity, commonly encompassing hundreds of genes. Therefore, the identification of causative genes for AR-MR, has been difficult. To improve our chances of success, we are studying outbred families with affected sib-pairs. Our hypothesis is, that even in outbred populations such as the Dutch population, individual patients with monogenic AR-MR will be homozygous for a single mutation in a gene residing in a homozygous stretch due to identical ancestors. We have collected clinical data, DNA and cell-lines of 30 families with brother-sister or sister-sister pairs, and are collecting additional families. So far 10 families have been analysed on the Affymetrix 250K SNP array to detect homozygous deletions and to study genotypes simultaneously. On average we found 17 homozygous stretches larger than 1 Mb per family containing on average 250 genes (ranging from 65-450 genes per family). From these regions, we have selected candidate genes that will be sequenced in the next step of this study. Our approach of studying outbred rather than inbred families should result in much fewer and shorter stretches of homozygosity than inbred families and seems a promising first step in the localisation and identification of genes for recessive MR.

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