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Summary

Variation in intellectual ability is normally distributed and partly caused by genetic variation. We wanted to test the hypothesis that mild intellectual disability (IQ 70-50) is at the lower end of this distribution and often has a multifactorial cause, whereas moderate to severe (IQ>50) and/or syndromic intellectual disability often has a monogenetic cause by studying *SNAP25* and *AUTS2*. Keeping patients informed about all advances in knowledge and diagnostic techniques in a clinical setting is challenging. We hope to contribute to improvement on that area by two different studies: first our study on recontacting the patients and their families and second our detailed clinical overview of the *AUTS2* syndrome phenotype.

To demonstrate the multifactorial model for mild intellectual disability we compared the risk allele frequency of SNP rs363050 in *SNAP25* in cases with mild intellectual disability to controls with a higher than average IQ in Chapter 2. This SNP was already associated with variation in cognitive ability in general by Gosso et al. We show that there is a significantly higher number of minor alleles (G) (the risk allele) for this SNP in cases versus controls. The *SNAP25* gene has an important function in modulation of neurotransmitter release and is thought to have a role in learning and memory by its involvement in hippocampal long-term potentiation of neurons. The rs363050 SNP is in high linkage disequilibrium with two SNP's in intron 2 of *SNAP 25* that are located in a predicted transcription binding site.

In chapter 3 we describe a new intellectual disability syndrome, now named *AUTS2* syndrome (autosomal dominant mental retardation-26 (MRD26, OMIM nr. # 615834). Array analysis of 49,684 individuals with intellectual disability and/or multiple congenital malformations revealed 24 exon deletions in *AUTS2*, but no exonic deletions were found in 16,784 controls. The frequency of exonic deletions that we found was 1 in 2,000 cases, comparable with some of the recurrent deletions such as the 10q23 deletion (*NRG3* [MIM 605533] and deletions causing Sotos syndrome (MIM 117550) described by Cooper et al. (2011)

The syndrome is recognizable by microcephaly, feeding problems, hypotonia evolving to hypertonia and in some patients also mild dysmorphic features like micrognathia can be identified. The more severe phenotype in patients with C-terminal deletions has led to further analysis of the gene structure, conservation and alternative transcripts. This revealed an alternative transcription start site in exon 9 (a highly conserved area of the gene) that is transcribed in human brain. Translation of this alternative transcript would lead to a protein only containing the C-terminal part of *AUTS2*. Zebrafish studies confirmed the importance of this part of the protein for at least the dysmorphological part of the phenotype as the microcephaly and smaller jaw size in zebrafish treated with *auts2* morpholino's could be rescued with the human short transcript starting in exon 9.

In chapter 4 we describe the first *AUTS2* syndrome patient with a mutation at the nucleotide level picked up by Whole Exome Sequencing. This adult male has a 2-nucleotide deletion in exon 7 of *AUTS2* and is compared to an adult male patient with an exon 6 deletion. Both patients show many similarities that can be categorized as full blown *AUTS2* syndrome. As the mutations in both men do not affect the shorter 3' transcript starting in exon 9, we conclude that in humans there is no rescue of the phenotype by this transcript.

Chapter 5 is dedicated to the further evaluation of the clinical phenotype of *AUTS2* syndrome. Thirteen cases, all clinically analysed by the same physician, helped to further delineate the phenotype of *AUTS2* syndrome and confirmed the observation that haploinsufficiency of the long transcript of *AUTS2* is causing *AUTS2* syndrome, and that there is no rescue by the shorter transcript. Common clinical features of *AUTS2* syndrome are: mild to moderate intellectual disability with speech delay and stammering, hypotonia at a young age sometimes evolving to hypertonia and tight heel cords later in life, feeding problems until childhood age, microcephaly, low weight and stature between p1 and p25. Birth defects or general health problems are rare. A behavioural phenotype emerged, showing hyperactive and hypersocial behaviour in childhood and rather shy, drawn back behaviour in adulthood. Classical autism is rare but stereotypic movements and obsessive behaviour is frequently seen, while social interaction is less affected.

In chapter 6 we describe a pilot study on recontacting parents of patients with intellectual disability to inform them about new diagnostic techniques (array Comparative Genome Hybridization and Whole Exome Sequencing, WES). This pilot showed that recontacting is time consuming especially if there is no database with patients suitable for recontacting. The yield of recontacting is rather low but seems higher when contact is made by phone. The parental attitude towards recontacting in general is very positive as is the feeling about the recontacting, although an ascertainment bias cannot be excluded.

Some concluding remarks are described in chapter 7. The biological pathways important for cognitive ability and disability are largely overlapping. There are many different processes interacting with each other involved in normal and abnormal brain function. Next to that, many different cognitive traits are influenced by the same genetic factors that are in line with the large correlation between different cognitive traits when tested in IQ tests. These observations support Pearson's idea of a 'general intelligence factor's called g. and the 'Generalist genes theory' of Plomin.

From humans with *AUTS2* syndrome, zebrafish and mouse knockdown or knockout experiments we learned that the *AUTS2* protein has an important function in neuronal development by transcription regulation through histone modification and neuronal migration, and by its effect on the cytoskeleton and dendrite growth. Defects of the *AUTS2* gene cause the above described *AUTS2* syndrome.

Recontacting parents of patient's with intellectual disability to inform them about new diagnostic possibilities was appreciated. It can be debated who is responsible for recontacting and there are practical barriers that need to be overcome before a general introduction into clinical practice. Next to this 'mainstreaming of genomic medicine' might be another way to get the up to date information to the patients in an efficient way.

Future research on genes in 'cognition pathways' that effect intellectual ability and disability would be valuable. As is research on symptomatic treatment for *AUTS2* syndrome, on variants of unknown significance in *AUTS2*, on the phenotype of patients with whole gene duplications of *AUTS2* and on patients with large deletions or duplications of *AUTS2* and the Williams Beuren syndrome region. We suggest an expert network with national or international registration to improve information on rare syndromes. Further studies on recontacting mainly focusing on cost effectiveness and the emotional burden are necessary before introducing it into general clinical genetics practice.

