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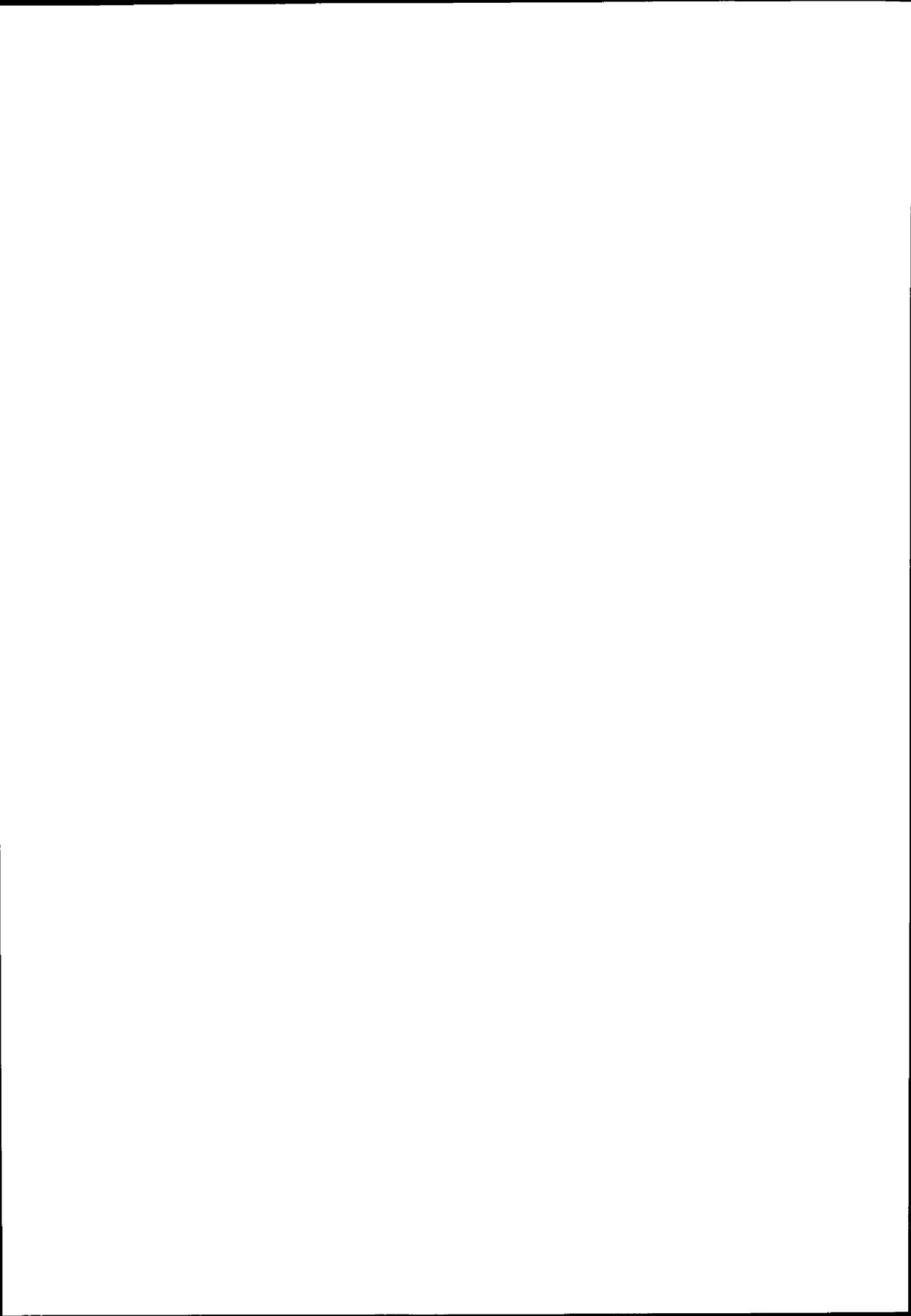
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Chapter 1

General Introduction  
and  
Outline of the Thesis



Many physicians will know what it means to care for a patient with a developmental delay. An exemplary and true story of a patient in the present study is Valerio.

The door of the office in the outward clinic swings open and a slender, pubertal boy with a notably small head and thick glasses held by a large nose enters the room. He looks at the doctor and quickly sits down in the corner of the room, as far away from the desk as possible. His parents follow him, and start with apologizing for the delay caused by his behaviour, immediately adding that Valerio has been that difficult to handle for a few months. In the meantime the boy looks around, observing first the doctor and then me, a researcher attending the outpatient clinic for some time. When our eyes meet he winks at me, smiling mischievously. At that moment, the mother quickly adds, "And to put it mildly, he is obsessed by the female race..." So at least part of the endocrine system functions all right. However, in Valerio whose IQ is estimated around 35, most things are not normal, as his intellectual functioning influences every aspect of his life to a great extent: his way of communicating, how he can take care of himself, how he gets along with others, where he lives, which sports he does, etc. So his mental retardation is not something he *has*, rather it is who and what he *is*.

During the consultation, the parents mention, "...it would be so much easier for us to cope with his behaviour and make decisions for him about his future, for living and working, if only we knew what causes this delay in him". Although his clinical history (progressive choreoretinopathy and renal failure) and phenotype (microcephaly, typical face, and peripheral lymphedema) give many clues, a diagnosis has proven too difficult, even after a huge number of additional investigations. This has been a great disappointment for his parents. For 3 years the parents have denied all further diagnostic tests. During this consultation, however, they ask again, "to make sure that his medical check-ups are well-timed, and not to forget to mention new things that might be important for him." The doctor informs them about the recent advent of subtelomeric FISH analysis, quickly adding that it is still unclear what the yield of this investigation will be, to prevent raising false hopes. To our surprise, mother's eyes fill with tears, "Oh, suppose you would find anything, and only in him and not us, then it might become clear that we did not have an increased risk for the same thing happening in another child....". Father adds that a second child has always been their dream, but they have never dared to take the risk, and now they do not have the age for more children anymore. "In fact, I think I hope that you'll find that we did have an increased risk, so we will learn that we did not refrain from more children in vain." At the end of the consultation, Valerio once again spoils me with a full wink.

Although the work in the present thesis has been driven in part by scientific curiosity, the care for children such as Valerio with a developmental delay and the contact with their parents and other relatives have been even more important factors. The goals for the present work are:

1. To provide more insight in the present knowledge of the yield of aetiologic studies in mental retardation (MR). To attain this, a systematic review of all peer-reviewed literature published world-wide during the last 35 years was performed. All papers were studied dealing with the yield of 6 diagnostic techniques: dysmorphic examinations, neurologic examinations, cytogenetic investigation, neuroradiology, metabolic studies, and cytogenetic/molecular studies for the fragile X syndrome. The first part of this study, which includes the study design and results on cytogenetic investigations in MR, is reported in **Chapter 2**.
2. To gain insight into the results of aetiologic diagnostic studies in the children with MR investigated in the Department of Paediatrics in the AMC. We prospectively studied the yield of the diagnostic investigations performed in a cohort of children with unexplained MR consecutively referred to a specialised outpatient clinic of the subdepartment 'Genetic/Congenital disorders' of our Paediatric Department. This is described in **Chapter 3**.
3. Of all diagnostic investigations, screening for subtelomeric rearrangements has received much attention in recent years, and it has been suggested that subtelomeric deletions may well provide the explanation for a large percentage of idiopathic MR cases. This constituted the third part of our study. We screened first in a pilot study a small and biased group of patients, likely to have a chromosome anomaly, and subsequently performed a prospective screening study of a large unbiased cohort of children with developmental delay. This is described in **Chapters 4.1 and 5**.
4. One of the anomalies detected in the pilot screening for subtelomeric rearrangements was a 14qter terminal microdeletion. We aimed to assess the value of a more careful study of a single patient with a microdeletion. We studied the phenotype of this patient, the genotype through cytogenetic and molecular studies, and compared the results with those from other cases with similar 14q terminal deletions described in the literature. This is described in **Chapter 4.2**.
5. Within the group of patients with MR in general, there are specific subgroups that may show specific result(s) if diagnostic studies were performed. We studied one of these subgroups, t.i. a group of individuals with retardation and autism. For practical reasons no children but young adults were studied, all living in the same institute for the mentally retarded. This is described in **Chapter 6**.
6. During the study of children with unexplained MR (described in Chapter 3), it appeared that uniform scoring and classification of abnormal physical features was extremely difficult. As

this uniformity is paramount to studying not only the present groups of patients, but also patient populations with various other disorders, we constructed a nomenclature for errors of morphogenesis detectable on surface examination, and a uniform Classification List. This is described in **Chapter 7**.

7. The results of studies described in the earlier chapters, and speculations on future directions, are discussed in **Chapter 8**.

Back to Valerio. During the period following Valerio's visit, the lab technician and I work hard at optimising the Multiprobe<sup>T</sup> FISH technique, applied for screening the chromosome ends for the presence of possible abnormalities in our patients with unexplained MR. The day comes when the slides with Valerio's chromosomes are placed under the microscope. Could it be true? It appears that a fluorescent signal is missing on the long arm of chromosome 2! This indicates a possible deletion of this region. And indeed, further studies (separate FISH analysis with the same probe) confirm the findings. To make sure the finding is significant, samples of both parents are tested. Unfortunately, father shows the same deletion, indicating the rearrangement to be a benign variation, which indeed has previously been reported in the literature. Although we did already warn his parents that we are unsure of the meaning of the 2qter deletion in their son, we still hear the disappointment in their voices when they are told that it is "only" a variation of normal. Mother does add, "...at least we now know one more thing which it is isn't. Please keep us informed, doctor, if any other new diagnostic means are developed". Father quickly interrupts, "But we'll only do such a test, if it is not too much for Valerio. He has spent enough time in hospitals and labs!"

And we will certainly do our best.

## Definition and classification

The most widely accepted definition of mental retardation clearly implies that it is not something which you *have*, rather it is what and whom you *are*: "Mental retardation is characterized by significantly subaverage intellectual functioning, existing concurrently with related limitations in two or more of the following applicable adaptive skills: communication, self-care, home living, social skills, community use, self direction, health and safety, functional academics, leisure and work. MR manifests before the age of 18."<sup>1</sup> Although there exist many different systems for classifying MR based on severity, the categorisation according to the World Health Organization classification<sup>2</sup> and DSM-IV criteria<sup>3</sup> were applied throughout the present thesis: profound (IQ=0-20); severe (IQ=21-35); moderate (IQ=36-50); mild (IQ=51-70); borderline (IQ=71-85).

## Importance of an aetiologic diagnosis

Establishing an aetiologic diagnosis in the individual with MR is usually a challenge for the practitioner, as the spectrum of possible underlying disorders is enormous and the range of available laboratory investigations extensive. Demonstrated by the story of Valerio, a successful pursuit of this challenge is of fundamental importance however, as understanding the pathogenesis of MR has immediate implications with respect to prognosis, management and recurrence risks.<sup>4,5</sup> Identification of the cause may furthermore provide relief to parents and other family members, and empowers them to make better informed choices for their affected relative.<sup>4</sup>

## Prevalence

Surprisingly little is known about the causes of a so frequently occurring and so disabling disorder.<sup>1</sup> Most studies on frequency of MR report cross-sectional prevalence rates, which is a function of incidence and duration. In MR length of survival substitutes for duration; for mild MR (IQ 50-70) prevalence is estimated 3-4 per 1,000 and for severe MR (IQ<50) 3-5-4 per 1,000.<sup>5</sup> If feeble-minded individuals, or those with borderline MR (IQ 70-85), would also be taken into account, prevalence would be considerably higher, i.e. 2.5-3 per 100 inhabitants. In MR there is a male predominance of 1.6:1,<sup>5</sup> which underlines the importance of X-linked genes in the aetiology of MR.

## Studies on aetiology of mental retardation in patient groups

Despite a large number of studies focussed on aetiology, many causes of MR remain hidden: Aetiologic diagnoses are usually identified in less than half of the patients,<sup>7,8</sup> and the reported frequencies of causal groups are remarkably variable:<sup>6,9</sup> Exogeneous causes (teratogens, infections, trauma) vary from 18.6% to 44.5%, genetic causes (chromosomal, Mendelian) from

17.4% to 47.1%.<sup>5,6,8,10</sup> These variations have been explained by differences in setting, assessment and classification of MR, severity of MR, patient selection criteria, definition of the term 'aetiologic diagnosis', and study protocols.

## The evaluation of the patient with mental retardation

There is no universally accepted consensus for a study protocol, and clinicians have been shown to differ widely in the way they investigate patients with developmental delay. Major factors influencing clinical practice include a lack of consensus in the medical literature, and personal experience causing a biased, non-evidence based approach to investigations.<sup>6,8,10,11</sup> As Opitz has stated, "The pathogenetic/causal biology of MR is forbiddingly complex and encompasses hundreds, perhaps several thousands of different entities. This realization frequently produces a virtual panic in the attending personnel...",<sup>12</sup> and too often results in a diagnostic work-up which can be unnecessarily complex, invasive, expensive, and a burden for the affected person.

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