Genetics in juvenile idiopathic arthritis

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CHAPTER 9

FUTURE PLANS

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Increasing the size of the JIA cohort

Although it is not the most scientific challenging goal, it is of utmost importance for the power of the following studies (for example candidate gene studies or genotyping by Immunochip) to increase the size of the JIA cohort by collaborating with more European rheumatology referral centers. It has been discussed that only the three subtypes that have a phenotypic overlap, should be included with a similar genetic/ geographic background. Not only information about the subtype, but also detailed information about the course of disease and use of medication should be gathered. Collaborating with other JIA cohorts will increase the number of patients, however independent cohorts should still remain in order to allow for replication of the associations found.

Functional studies

The associations with JIA that have been revealed in this thesis are located either in loci with an unknown function (ANKRD55), or in loci with more than one gene which could be involved (in locus TRAF1/C5 the genes *TRAF1* or *C5* and in locus 4q27 the genes *IL2* or *IL21*) and in loci/genes that are more likely to be directly involved in the pathogenesis or progression of JIA (VTCN1, CD226, CD28, PTPTN22, TNFA). Of all of these associations, the functional (non-synonymous) variant in PTPN22 seems the most obvious one of which the function should have shortly become clarified. However, after some years the functional consequences of PTPN22 (1858T) are still under investigation.[1;2] This illustrates the difficulty in translating a genetic association to a functional difference that is related to disease or disease severity.

Because of also its association with the course of disease and therefor its clinical relevance, the functional consequences of the different genetic variations in VTCN1 should also be studied. In different studies, several polymorphisms in this gene are associated with the susceptibility of JIA. These seem to be indirect associations, with the causal variant not yet known. Because as yet no change in coding for amino-acids is known, a 3D image of an altered protein, to provide more insight in the consequences of such a different amino acid, cannot be prepared. However, the polymorphic gene can be expressed differently, thus the gene expression of the different genetic variations should also be studied, especially because a higher expression has been related to a more progressive disease in certain types of cancer. Because B7-H4 (the gene product of *VTNC1*) has an inhibitory effect on T-cells, the effect of the different VTCN1-gene products on T-cell stimulation should be studied by means of T-cell proliferation assays and levels of cytokine production. This should be done in healthy persons to rule out the influence of disease activity. Bypassing

the more subtle changes in function and ignoring the association of certain genetic variations, one might consider applying agonists or antagonists and evaluating the outcome of this extreme intervention, for example in collagen induced arthritis. More insight in the altered function of VTCN1 in patients with a more remitting course could be a lead point for developing drugs interfering in the VTCN1-pathway. Not only in the case of VTCN1, but also of the other genes/ loci associated with JIA, functional consequences should be studied by means of expression studies, measuring levels of gene product and levels of proteins involved in the pathway of concern and in more functional studies such as proliferation assays.

Increasing the investigated pathways

In the work presented in this thesis the focus has been on replication of the genetic associations known in JIA and other autoimmune disease and investigating some genes that are part of a number of pathways that could be involved in JIA. Because ours is a new cohort of Caucasian JIA patients, reproduction in such an independent cohort is important for reinforcing the already known associations. At the same time replication of these associations shows that our cohort is comparable to others in the generation of similar results. The following step will then be to expand the number of pathways to be investigated. For example, the IL17/ IL23/ IL12/ IFN-gamma pathway also plays a major role in JIA. Associations of genes involved in this pathway and the susceptibility to and the severity of JIA should be studied. This could be done by means of a candidate gene study because of the limited number of genes involved.
However more pathways involved in autoimmunity can be studied simultaneous by an Immunochip assay and this should be considered. The SNPs incorporated on the immunochip are dense selected tagging SNPs in specific genetic loci.

Genome wide association study

In addition to studying selected genes or pathway, a study without prior hypothesis can be undertaken. In a genome wide association study (GWAS), polymorphisms throughout the entire genome may thus be identified. The advantage is that unexpected loci can be revealed. The disadvantage is the large number of patients that are needed (partly because of the low effect sizes that are expected). In JIA such a study has been undertake twice. Surprising associations were revealed. In the first GWAS the associations with VTCN1 were brought to light and the second revealed 3q13 as a novel susceptibility locus that needs to be investigated in more detail to identify an associated gene.

Pharmacogenetics

To develop more insight in determinants of the response to treatment, genetic associations in genes involved in the specific pathways should be investigated. The pharmacogenetics of the MTX pathway has already been discussed. Nowadays treatment with anti-TNF has a big part in treating ongoing disease. Genes involved in the TNF-pathway should also be investigated in relation to response (comparing allele frequencies between responders and non-responders). Ideally the response to drugs that are being developed based on genetic findings (such as might be the case in PTPN22 or VTCN1), should be studied in relation to the varying genetic background of a patient.

Predictive model for the course of disease and response to treatment

Nevertheless, the most important still is the individual patient, which should be treated in the best possible way. In this thesis many parameters have been raised and discussed that could be part of a predictive model for the course of disease in the individual patient. These parameters are either clinical parameters (such as the subtype of JIA), or genetic factors (such as VTCN1, or additional genes that will be tested in future studies), but may also be biomarkers resulting from future functional studies. Similar models should be developed concerning the response to treatment (MTX or anti-TNF), similarly involving clinical and genetic parameters and possible biomarkers.

Association with specific characteristics of JIA

Many patients with predominantly oligoarticular JIA develop JIA-associated uveitis. Because this type of uveitis has few clinical symptoms, a stringent follow-up of eye-involvement is required. Genetic associations with JIA-associated uveitis could be helpful in predicting uveitis. Genetic variations that are associated with the progression of uveitis are of clinical relevance for patients with uveitis. However creating a study patient group with JIA-associated uveitis of sufficient size is already challenging, therefore to include sufficient patients to compare mild uveitis patients with progressive uveitis patients seems hardly feasible.

REFERENCES

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