5 Zusammenfassung

Geistige Behinderung ist eine äußerst heterogene Erkrankung. Schwere Formen dieser Erkrankung, charakterisiert durch einen IQ geringer als 50, haben hauptsächlich genetische Ursachen, wobei viele durch einen Defekt in einem einzigen Gen verursacht werden. In letzter Zeit ist der Nachweis einiger dieser genetischen Defekte, hauptsächlich auf dem X Chromosom, gelungen. Trotzdem bleibt die molekulare Ursache von X-chromosomal gekoppelter geistiger Behinderung (XLMR) in vielen Fällen immer noch ungeklärt. Hingegen hat die Identifizierung von autosomalen Genen, die eine Rolle bei der Entwicklung von kognitiven Fähigkeiten spielen, gerade erst begonnen. Das Ziel der vorliegenden Arbeit war es einen Beitrag zur Erweiterung des Verständnisses der molekularbiologischen Ursachen von geistiger Behinderung zu leisten. Diese Erkrankung ist immer noch eines der größten ungelösten Probleme der klinischen Genetik und ein wichtiger Aspekt der Gesundheitsvorsorge.

Als Ursache für X-chromosomale nicht-syndromale geistige Behinderung (NS-XLMR) sind bereits mehrere Gene identifiziert worden. Dennoch legt die geringe Mutationshäufigkeit in den bislang identifizierten Genen bei Familien mit NS-XLMR nahe, daß ungefähr 30 bis 100 weitere NS-XLMR Gene existieren (Ropers et al., 2003). Kürzlich konnte durch die Analyse von Kopplungsdaten verschiedener Familien gezeigt werden, daß ungefähr 30% der genetischen Defekte auf dem proximalen Arm des X-Chromosoms lokalisiert sind (Ropers et al., 2003). Im Rahmen der vorliegenden Arbeit wurde eine systematische Analyse von gehirnspezifisch exprimierten Genen, die in dieser Region des X-Chromosoms lokalisiert sind, durchgeführt. Diese Untersuchungen zeigten, daß Mutationen in den X-chromosomalen Genen *FTSJ1* und *PQBP1* bei männlichen Patienten zu geistiger Behinderung führen. Ebenso konnte gezeigt werden, daß die unterschiedlichen Mutationen in den verschiedenen Familien mit der Erkrankung kosegregiert.

Die Funktion des humanen FTSJ1 Proteins ist bislang nicht beschrieben worden. Dennoch läßt der Vergleich mit den entsprechenden paralogen Genen in der Hefe und dem orthologen Gen in *E. coli* die Schlußfolgerung zu, daß das humane FTSJ1 ebenfalls eine S-Adenosyl-L-Methionin abhängige Methyltransferase ist.

Darüber hinaus konnte im Rahmen der vorliegenden Arbeit mittels Komplementationsstudien mit dem humanen FTSJ1 in den entsprechenden Hefedeletionsstämmen gezeigt werden, daß FTSJ1 eine tRNA-Methyltransferase ist. Somit scheint FTSJ1 eine Rolle in dem fundamentalen Prozeß der Translation von Proteinen zu spielen. Im Gegensatz dazu ist der Phänotyp der Patienten mit Mutationen in FTSJ1 relativ mild ausgeprägt, und obwohl FTSJ1 ubiquitär exprimiert wird, scheint die Expression während der embryonalen Entwicklung des Gehirns besonders kritisch zu sein. Diese Annahme wird durch eine verstärkte Expression in fötalen Gehirngeweben unterstützt. Darüber hinaus ist es wahrscheinlich, daß das Gehirn auf Defekte in der Translationsmaschinerie sensibler als andere Körperorgane reagiert. Eine weitere Möglichkeit wäre, daß ein anderes Protein teilweise die Funktion von FTSJ1 übernehmen könnte. Eine *in vitro* Untersuchung des Methylierungsstatus der entsprechenden tRNAs wäre eine Möglichkeit um diese Fragen zu klären.

Das zweite X-chromosomale Gen, das in mutierter Form geistige Behinderung verursacht und im Rahmen der vorliegenden Arbeit untersucht worden ist, ist *PQBP1*. Die molekularbiologische Analyse der RNA von Patienten mit Mutationen in *PQBP1* hat ergeben, daß die überwiegende Anzahl der Transkriptvarianten über den sogenannten *nonsense mediated mRNA* (NMD) Mechanismus abgebaut werden. Diese Ergebnisse weisen darauf hin, daß der pathologische Phänotyp wahrscheinlich durch einen Funktionsverlust der überwiegenden Anzahl der PQBP1 Proteinvarianten verursacht wird. Möglicherweise wird der pathologische Phänotyp durch eine Kombination aus Funktionsverlust und modifizierter Funktion der mutierten, stabilen PQBP1 Proteinvarianten verursacht. Im Rahmen der vorliegenden Arbeit wurde die zelluläre Lokalisation der mutierten PQBP1 Proteine im Vergleich zur zellulären Lokalisation der Wildtyp PQBP1 Hauptproteinvariante untersucht. Die beobachtete, veränderte zelluläre Lokalisation der mutierten Proteine unterstützt die Hypothese von einer veränderten Funktion verglichen mit dem Wildtyp Protein. Mehrere Interaktionspartner sind bereits für PQBP1 beschrieben worden, und einige dieser Interaktionspartner weisen auf eine Rolle von PQBP1 beim Spleißen von mRNA hin. Die präzise Aufgabe, die PQBP1 bei diesem Prozeß übernimmt, ist jedoch noch nicht erforscht. Weitere Analysen der unterschiedlichen Interaktionspartner von PQBP1 und deren Zusammenspiel mit PQBP1 müssen demnach noch eingehender untersucht werden. Des weiteren ist

es ziemlich wahrscheinlich, daß die unterschiedlichen PQBP1 Proteinvarianten verschiedene Aufgaben innerhalb der Zelle übernehmen, die entweder durch dessen Funktionsverlust oder aber durch eine veränderte Funktion der mutierten Proteinvarianten gestört werden. Weitere funktionelle Analysen sind notwendig, um ein besseres Verständnis der zellulären Prozesse zu erlangen, an denen PQBP1 beteiligt ist.

Der zweite Schwerpunkt der vorliegenden Arbeit lag bei der Identifizierung von autosomalen Genen, die eine Rolle bei der Entwicklung von kognitiven Fähigkeiten spielen. Die zytogenetische Analyse der DNA von Patienten mit geistiger Behinderung, die Träger einer balancierten, reziproken Translokation sind, können zur Identifikation von Kandidatengenen führen, die im oder in der Nähe des chromosomalen Bruchpunktes liegen.

Im Rahmen der vorliegenden Arbeit wurde eine solche molekulare Untersuchung der DNA einer weiblichen Patientin mit Rett Syndrom durchgeführt. Dabei wurde *NTNG1* als Kandidatengen identifiziert und mittels RT-PCR Experimenten gezeigt, daß eine Transkriptvariante dieses Gens durch die chromosomale Umstrukturierung unterbrochen wird und in reduzierter Menge vorliegt. Diese Transkriptvariante kodiert für eine Glykosylphosphatidylinositol (GPI) verankerte Proteinvariante von NTNG1. Alle Proteinvarianten von NTNG1 agieren als Axonleitmoleküle und sind für das Wachstum und die Ausrichtung von thalamokortikalen Axonen (TCAs) wichtig. Die TCAs wiederum sind für die Weiterleitung von Signalen aus dem Thalamus in den Kortex verantwortlich. Die Reduzierung einer NTNG1 Proteinvariante bei der Patientin führt möglicherweise zu einem verminderten Wachstum bzw. zu einer Fehlverschaltung solcher TCAs. Eine solche Entwicklungsstörung wäre eine mögliche Erklärung für die kognitiven Defizite der Patientin, und würde die Hypothese unterstützen, daß NTNG1 eine Rolle bei der Pathogenese des Rett Syndroms spielen könnte. Weitere *in vitro* Experimente mit neuronalen Zellen müßten zeigen, daß das Wachstum von TCAs, verursacht durch Haploinsuffizienz einer Variante von NTNG1, gestört wird. Darüber hinaus könnte *NTNG1*, auf Grund der phänotypischen Überlappung des Rett Syndroms und der geistigen Behinderung, ein autosomales Kandidatengen für geistige Behinderung sein.

Zum Abschluß läßt sich festhalten, daß im Rahmen der vorliegenden Arbeit sowohl autosomale als auch X-chromosomale Gene mit unterschiedlichen

Funktionen in Zusammenhang mit geistiger Behinderung gebracht werden konnten. Die Identifizierung von zwei neuen Genen für NS-XLMR, *FTSJ1* und *PQBP1*, bestätigen, daß es sich bei geistiger Behinderung um eine sehr heterogene Erkrankung handelt. Keines der beiden Proteine interagiert mit bereits beschriebenen Genprodukten, die in mutierter Form XLMR verusachen, oder agiert in deren Signaltransduktionswegen.

Vorgänge wie Axonleitung, vermittelt durch NTNG1, tRNA Methylierung, vermittelt durch FTSJ1 und Spleißen von mRNA, vermittelt durch PQBP1 scheinen wichtige Prozesse bei der Entwicklung des Gehirns zu sein.

Die Identifizierung von Genen, die für kognitive Fähigkeiten verantwortlich sind, stellen somit einen guten Ausgangspunkt dar, um ein besseres Verständnis der molekularen Mechanismen zu erlangen, die der Funktion des Gehirns zu Grunde liegen.

6 Summary

Mental retardation is a very heterogeneous disorder. Severe forms, defined by an IQ of <50, have predominantly genetic causes, and many are due to defects in single genes. Recently progress has been made in the identification of the relevant gene defects, most notably on the human X-chromosome. However, most of the underlying molecular causes of X-linked mental retardation have still to be identified, and the search for autosomal genes that play a role in mental retardation is in its infancy. The aim of this study was to contribute to the molecular understanding of mental retardation, which is the largest unsolved problem in clinical genetics and a very important healthcare issue.

Several genes involved in nonspecific X-linked mental retardation (NS-XLMR) have been identified by genetic analysis so far. However, the low mutation frequency in these NS-XLMR genes in families with X-linked inheritance of MR indicates that still 30-100 NS-XLMR genes have yet to be detected (Ropers et al., 2003). Recently, it has been shown by analysis of linkage data from several families that approximately 30% of these genetic defects cluster on the proximal Xp (Ropers et al., 2003). Within the framework of this study, a systematic mutation screen of brain-expressed genes from this region was designed and performed. This analysis revealed that mutations in the X-chromosomal genes *FTSJ1* and *PQBP1* definitively result in mental retardation in male patients. For each gene, mutations cosegregated with the disorder in several families.

The function of human FTSJ1 has not been investigated; however, studies on related yeast and *E. coli* proteins suggest that it functions as a S-Adenosyl-L-Methionine-dependent methyltransferase. Within the framework of this study, rescue experiments with human FTSJ1 in yeast deletion strains verified its role as a methyltransferase. Moreover, these results suggested that FTSJ1 functions specifically as a t-RNA methyltransferase. Which implies a role for FTSJ1 in protein translation. Although FTSJ1 is ubiquitously expressed, the phenotype of patients with mutations in this gene is relatively mild. Probably the activity of FTSJ1 is most critical during brain development; this is supported by its high expression in fetal brain. Moreover brain structures could be more sensitive than other organs to defects in the translational machinery. Another possibility is that another protein could partially compensate the loss of function of FTSJ1. Further

functional studies, investigating the methylation sites of particular tRNAs might help clarify these questions.

The second X-chromosomal gene involved in mental retardation and investigated in this work is *PQBP1*. Molecular analysis of RNA derived from patients with mutations in *PQBP1* showed that the majority of normal splice variants of *PQBP1* are degraded by NMD. Indicating that the disorder likely arises from a loss of function of the majority of the PQBP1 proteins, perhaps together with a modified PQBP1 function resulting from the remaining stable transcripts. These stable mutant proteins were investigated within the framework of this study, and the fact that they exhibit a modified cellular localization with respect to the wild type proteins supports this hypothesis. Various interaction partners for PQBP1 have been described, and it seems that PQBP1 is involved in RNA splicing. The precise role of PQBP1 in this process is still unclear and has to be investigated by more precise analysis of the relationships between PQBP1 and its interaction partners. Furthermore, it is likely that the different PQBP1 proteins fulfill numerous different functions that may be affected by the abnormal proteins present in affected individuals. Further studies aim to explore these functional questions. The second focus of this work was the identification of autosomal genes that might play a role in cognitive function. The cytogenetic and subsequent molecular analysis of DNA from mentally retarded patients carrying balanced chromosomal rearrangements can lead to the identification of candidate disease genes lying at or near the breakpoints.

In this study, through such molecular characterization of DNA from a female Rett syndrome patient carrying a balanced translocation between chromosomes 1 and 7, the candidate gene *NTNG1* was identified. One transcript variant of the *NTNG1* gene is disrupted, and semi-quantitative RT-PCR experiments on a cell line from the patient showed that transcripts from this particular variant are reduced compared to controls. This transcript variant encodes a GPI anchored protein variant of NTNG1. All protein variants of NTNG1 act as axon guidance cues and are important for positioning thalamocortical axons (TCA). Thalamocortical axons are critical for transducing signals from the thalamus to the cortex. A dosage-dependent incorrect wiring of TCAs could explain the cognitive defects in this patient and thereby supports a role for NTNG1 in Rett Syndrome. Moreover, given the phenotypic overlap between this disorder and mental retardation, these results

bring the *NTNG1* gene to the forefront as an autosomal candidate mental retardation gene. Taken together, the results of this work demonstrated the presence of two novel NS-XLMR genes. Furthermore, detection of disease-causing mutations in *FTSJ1* and *PQBP1* confirmed the genetic heterogeneity of mental retardation in that neither one nor the other protein is involved in pathways or interactions with previously described genes involved in XLMR. Interestingly, both proteins are involved in basic cellular processes. FTSJ1 acts as a tRNA methyltransferase involved in translation, and PQBP1 seems to participate in mRNA splicing.

Finally, the identification of genes involved in cognitive function provides a starting point for gaining a better understanding of the molecular mechanisms critical for brain function. In this study, both autosomal and X-linked genes with diverse functions could be linked to mental retardation, implicating processes including axon guidance, RNA methylation, and regulation of mRNA splicing in the development of the brain, and thereby providing novel insights into the molecular aspects of cognition.

7 Literatur

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8 Abkürzungsverzeichnis

Abb.	Abbildung
APS	Ammoniumpersulfat
AS	Aminosäure
ATP	Adenosintriphosphat
Bp	Basenpaare
BSA	Rinderserum Albumin
bzw.	beziehungsweise
°C	Grad Celsius
cDNA	complementary DNA (engl.), komplementäre DNA
Ci	Curie
Cpm	counts per minute (engl.), Zählungen pro Minute
DABCO	1,4-diazobicyclo-2,2,2-octan
DAPI	4í-6-Diamidino-2-phenylindol
dATP	desoxy-Adenosintriphosphat
dCTP	desoxy-Cytidintriphosphat
DEPC	Diethylpyrocarbonat
dGTP	desoxy-Guanosintriphosphat
DHPLC	denaturing high-performance liquid chromatography
DMEM	Dulbecco´s Modified Eagle Medium
DMSO	Dimethylsulfoxid
DNA	desoxyribonucleic acid (engl.), Desoxyribonukleinsäure
dNTP	Desoxyribonukleosid-5í-triphosphat
DTT	Dithiothreithol
E. coli	*Escherichia coli*
EDTA	Ethylendiamintetraacetat
EST	Expressed Sequence Tag
EtBr	Ethidiumbromid
g	Gramm
HEPES	4-(2-Hydroxyethyl)-piperazin-1-ethansulfonsäure
IPTG	Isopropyl-£]-D-Thiogalactopyranosid
Kb	Kilobasen

kDa	kilo Dalton
l	Liter
LB	Luria-Bertani
m	milli
M	molar
µ	mikro
MOPS	3-Morpholinopropansulfonsäure
MR	mental retardation (engl.) geistige Behinderung
MRNA	messenger RNA (engl.), Boten-RNA
n	nano
NMD	nonsense mediated mRNA decay (engl.), Nonsense vermittelter mRNA-Abbau
NS-MRX	non-syndromic X-linked mental ratardation (engl.) nicht-syndromale geistige Behinderung
OD	optische Dichte
OLB	oligo labeling buffer (engl.), Oligo-Markierungspuffer
PCR	polymerase chain reaction (engl.), Polymerase-Kettenreaktion
RTT	Rett Syndrom
RT-PCR	Reverse Transkriptions-PCR
RNA	ribonucleic acid (engl.), Ribonukleinsäure
s.	siehe
S. cerevisiae	*Saccharomyces cerevisiae*: Bäckerhefe
SDS	sodium dodecylsulfate (engl.), Natriumdodecylsulfat
Tab.	Tabelle
Taq	Thermus aquaticus
tRNA	transfer-RNA
XLMR	X-linked mental retardation (engl.) X-chromosomal gekopppelte geistige Behinderung
ZNS	Zentrales Nervensystem

9 Publikationen

Kalscheuer VM, **Freude K**, Musante L, Jensen LR, Yntema HG, Gecz J, Sefiani A, Hoffmann K, Moser B, Haas S, Gurok U, Haesler S, Aranda B, Nshedjan A, Tzschach A, Hartmann N, Roloff TC, Shoichet S, Hagens O, Tao J, Van Bokhoven H, Turner G, Chelly J, Moraine C, Fryns JP, Nuber U, Hoeltzenbein M, Scharff C, Scherthan H, Lenzner S, Hamel BC, Schweiger S, Ropers HH (2003) Mutations in the polyglutamine binding protein 1 gene cause X-linked mental retardation. Nat Genet 35:313-3

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10 Lebenslauf

Nachname:	Freude
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Geburtsort:	Berlin
Familienstand:	ledig
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Schulbildung:

1980-1986	Grunewald-Grundschule Berlin
1986-1990	Orientierungsstufe Walther-Rathenau-Gymnasium, Berlin
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Universitätsausbildung:

1994	Humboldt-Universität Berlin LA Sonderschulpädagogik Germanistik
1995-2001	Freie Universität Berlin Biologie **Diplom**
2001	**Diplomarbeit** am Robert Koch Institut in der Arbeitsgruppe von Herrn Prof. Appel unter der Anleitung von Frau Dr. Lewin, Berlin Thema: Klonierung von DNA-Fragmenten aus schnellwachsenden Bakterien in das langsamwachsende *Mycobacterium bovis* BCG zur Charakterisierung des Wachstumsverhaltens

2001-2005	**Doktorarbeit** am Max-Planck Institut für molekulare Genetik in der Abteilung von Herrn Prof. Dr. Ropers unter der Anleitung von Frau Dr. Kalscheuer, Berlin Thema: Identifizierung, molekulare Analyse und funktionelle Charakterisierung von Genen die an neuronaler Entwicklung und geistiger Behinderung beteiligt sind
Seit Februar 2005	PostDoc im Institut für Zell- und Entwicklungsbiologie an der University of California, Irvine, USA, in der Abteilung von Frau Dr. Sander.

Nebentätigkeiten:

1998-2002	Tutorin im FB Mikrobiologie Freie Universität Berlin
1998-2003	Schulhelfer an der Hans-Fallada-Grundschule Berlin

Fortbildungen und Konferenzen:

07.2001	European Society of Mycobacteriology (ESM) Annual Meeting, Berlin
04.2003	European School of Genetic Medicine, Bertinoro (Italien)“16th Course in Medical Genetics”
10.2003	German Society for Human Genetics (GFH) Annual Medical Genetics Conference, Marburg **Poster Presentation**: “A female patient with Rett Syndrome carrying a *de novo* t(1;7)(p22;q32) balanced translocation”
11.2003	American Society of Human Genetics (ASHG) Annual Meeting, Los Angeles (USA) **Vortrag**: “A new player in X-linked mental retardation”

04.2004	Human Genome Meeting (HGM), Berlin (Germany) **Vortrag**: “FTSJ1: A novel player in X-linked mental retardation”
06.2004	European Society of Human Genetics (ESHG) Annual Meeting, München **Poster Presentation**: “FTSJ1: a novel player in X-linked mental retardation”

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12 Erklärung

Hiermit erkläre ich, Kristine Karla Freude, daß ich die vorliegende Arbeit selbständig verfaßt und keine anderen als der angegebenen Quellen als Hilfsmittel benutzt habe.

Berlin, den

Hiermit erkläre ich, Kristine Karla Freude, daß die vorliegende Arbeit in dieser oder ähnlicher Form an keiner anderen Hochschule zur Promotion eingereicht wurde; des weiteren erkläre ich, daß bisher kein Promotionsversuch an einer anderen Universität erfolgt ist.

Berlin, den

13 Anhang

- pGEMTeasy
- pCMVtag3A
- pBudCE4
- pYES2
- pAE