The genetic determinants of cerebral palsy

A thesis submitted for the degree of Doctor of Philosophy (PhD) to the University of Adelaide

By

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Statement of Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Gai Lisette McMichael

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HUGO Gene Nomenclature gene symbol and gene name

ADD3 – Adducin 3 (Gamma)

AGAP1 – ArfGAP with GTPase Domain, Ankyrin Repeat and PH Domain 1

AHI1 – Abelson Helper Integration Site 1

ANKRD15 – KN Motif And Ankyrin Repeat Domains 1 (KANK1)

AP-4 – AP-4 Complex

AP4B1 – Adaptor-related Protein Complex 4, β1 subunit

AP4E1 – Adaptor-related Protein Complex 4, ε1 subunit

AP4M1 – Adaptor-related Protein Complex 4, μ1 subunit

AP4S1 – Adaptor-related Protein Complex 4, σ1 subunit

CDK17 – Cyclin-Dependent Kinase 17

CD99L2 – CD99 Molecule-Like 2

CEP290 – Centrosomal Protein 290KDa

COPS3 – COP9 Signalosome Subunit 3

CTNND2 – Catenin (Cadherin-Associated Protein), Delta 2

CUL4B – Cullin 4B

ENPP4 – Ectonucleotide Pyrophosphatase/Phosphodiesterase 4 (Putative)

FLNB – Filamin B (Beta)

GAD1 – Glutamate Decarboxylase 1

GCH1 – GTP Cyclohydrolase 1

HSPA4 – Heat Shock 70kDa Protein 4

HSPG2 – Heparan Sulfate Proteoglycan 2

ITPR1 – Inositol 1,4,5-Trisphosphate Receptor, Type 1

JHDM1D – Lysine (K)-Specific Demethylase 7A

KANK1 – KN Motif And Ankyrin Repeat Domains 1 (ANKRD15)

HUGO Gene Nomenclature gene symbol and gene name (continued)

KDM5C – Lysine (K)-Specific Demethylase 5C

KCNC3 – Voltage-Gated Potassium Channel Subunit Kv3.3

L1CAM – L1 Cell Adhesion Molecule

LTN1 – Listerin E3 Ubiquitin Protein Ligase 1

MAOA – Monoamine Oxidase A

MAOB – Monoamine Oxidase B

MAST1 – Microtubule Associated Serine/Threonine Kinase 1

MCPH1 – Microcephalin 1

MED17 – Mediator Complex Subunit 17

MEF2C – Myocyte Enhancer Factor 2C

MIIP – Migration and Invasion Inhibitory Protein

MUM1L1 – Melanoma Associated Antigen (Mutated) 1-Like 1

MYH14 – Myosin, Heavy Chain 14, Non-Muscle

NAA35 – N(Alpha)-Acetyltransferase 35, NatC Auxiliary Subunit

NEMF – Nuclear Export Mediator Factor

NPHP1 – Nephronophthisis 1 (Juvenile)

NKX2-1 – NK2 Homeobox 1

PAK3 – P21 Protein (Cdc42/Rac)-Activated Kinase 3

PACRG – PARK2 Co-Regulated

PARK2 – Parkin RBR E3 Ubiquitin Protein Ligase

PAX5 – Paired Box 5

PLAC4 – Placenta-Specific 4

PLP1 – Proteolipid Protein 1

PCDH11X – Protocadherin 11 X-Linked

HUGO Gene Nomenclature gene symbol and gene name (continued)

RFX2 – Factor X, 2 (Influences HLA Class II Expression)

SCN2A – Sodium Channel, Voltage Gated, Type II Alpha Subunit

SCN8A – Sodium Channel, Voltage Gated, Type VIII Alpha Subunit

SLC11A2 – Solute Carrier Family 11 (Proton-Coupled Divalent Metal Ion Transporter), Member 2

SPAST – Spastin

SPR – Sepiapterin Reductase (7,8-Dihydrobiopterin:NADP+ Oxidoreductase)

SPTBN2 – Spectrin, beta, non-erythrocytic 2

SSPO – SCO-Spondin

SYNGAP1 – Synaptic Ras GTPase Activating Protein 1

TBC1D24 – TBC1 Domain Family, Member 24

TENM1 – Teneurin Transmembrane Protein 1

TGM6 – Transglutaminase 6

TUBA1A – Tubulin, Alpha 1a

UBE3A – Ubiquitin Protein Ligase E3A

UBQLN3 – Ubiquilin 3

WDR45 – WD Repeat Domain 45

WIPI2 – WD Repeat Domain, Phosphoinositide Interacting 2

ZC4H2 – Zinc Finger, C4H2 Domain Containing

ZNF674 – Zinc Finger Protein 674

Abbreviations

ACD – Acid citrate dextrose

AMC – Arthrogryposis multiplex congenita

ASD – Autism spectrum disorder

ATLAS – SNP

BCM – Baylor College of Medicine

BHC – Benign Hereditary Chorea

BWA – Burrows-Wheeler Aligner

CADD – Combined Annotation-Dependent Depletion

CGH – Comparative Genomic Hybridisation

ChIP – Chromatin immunoprecipitation

CNVs – Copy Number Variants

CNS – Central nervous system

CP – Cerebral palsy

DNA – Deoxyribonucleic acid

EDTA – Ethylenediaminetetraacetic acid

EVS – Exome Variant Server

ExAC – Exome Aggregation Consortium

GA – General anaesthetic

GABA – Gamma-aminobutyric acid

GATK – Genome Analysis Toolkit

GERP – Genomic Evolutionary Rate Profiling

GMFCS – Gross Motor Function Classification System

GRA – Genetic Repositories Australia

HGMD – Human Genome Mutation Database

Abbreviations (continued)

HGSC – Human Genome Sequencing Center

HSP – Hereditary Spastic Paraplegia

ID – Intellectual disability

IQ – Intelligence quotient

IUGR – Intrauterine growth restriction

IVF – *In vitro* fertilization

IVH – Intraventricular haemorrhage

LCLs – Lymphoblastoid cell lines

LM-PCR – Ligation mediated-polymerase chain reaction

LOF – Loss of function

MAF – Minor allele frequency

MIM – Mendelian Inheritance in Man

MPS – Massively parallel sequencing

mRNA – Messenger ribonucleic acid

miRNA – Micro ribonucleic acid

MRI – Magnetic resonance imaging

ncRNA –Non-coding ribonucleic acid

NGS – Next generation sequencing

NHLBI – National Heart, Lung, and Blood Institute

OMIM – Online Mendelian Inheritance in Man

OR – Odds ratio

PCR – Polymerase chain reaction

PE – Paired-end

PMD – Pelizaeus-Merzbacher disease

Abbreviations (continued)

POSU – Pregnancy Outcome in South Australia

PVL – Periventricular leukomalacia

RNA – Ribonucleic acid

rRNA – Ribosomal ribonucleic acid

tRNA – Transfer ribonucleic acid

RVIS – Residual Variation Intolerance Score

SHRs – Standardized hospitalisation ratios

SIFT – Scale-invariant feature transform

SNPs – Single nucleotide polymorphisms

SPG4 – Spastic paraplegia 4

UCSC – University of California, Santa Cruz Genome Browser

UTRs – Untranslated regions

WES – Whole-exome sequencing

WGS – Whole-genome sequencing

XLID – X-linked intellectual disability

URLs

Allen Human Brain Atlas – www.brainspan.org/

Australian Bureau of Statistics – www.abs.gov.au

BCM-HGSC protocol – https://hgsc.bcm.edu/ sites/default/files/documents/ Illumina_

Barcoded_PairedEnd_Capture_Library_Preparation.pdf Barcoded Paired-End Capture

Library Preparation.pdf

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/2013/04/ ACPR/

dbSNP – http://www.ncbi.nlm.nih.gov/projects/SNP/

Ensembl – www.ensembl.org/

EVS – http://evs.gs.washington.edu/ EVS/

ExAC database – exac.broadinstitute.org/

OMIM – www.omim.org/

Partek – http://www.partek.com/

RefSeq – www.ncbi.nlm.nih.gov/refseq/

1000 Genomes – http://browser.1000genomes.org/index.html

UCSC – https://genome.ucsc.edu/