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PRISCILA MEDEIROS

BOTUCATU – SP

2021

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Aplicabilidade de redes PPI em Biologia de sistemas no contexto da síndrome de Williams-Beuren

PRISCILA MEDEIROS

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COORIENTADOR: Dr. Bruno Faulin Gamba

Tese apresentada ao Instituto de Biociências, Campus Botucatu, UNESP, para obtenção do título de Doutor no Programa de Pós-Graduação em Ciências Biológicas (Genética).

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Palavras-chave: 7q11.23; Genética; PPI; Redes de interação proteína-proteína; Síndrome de Williams-Beuren.

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“É tão difícil a gente caminhar
Quando uma estrada não está mais lá
E ter que construir o próprio chão
Com as incertezas que tiver
Em cada curva pra lá e pra cá
Qualquer desvio pode transformar
A ponta de um universo em explosão
Coisa com o futuro que vier
E tudo que foi dor num dia
No outro dia será dia de continuar
Caminhado sobre o sol
Até o amor se reinventar
Vida que a gente aprende
Tudo o que acontece de ruim é para melhorar!”

Tudo o Que Acontece de Ruim É Para Melhorar – PAULINHO MOSKA

RESUMO

MEDEIROS, P. **Aplicabilidade de redes PPI em Biologia de sistemas no contexto da síndrome de Williams-Beuren**. 2021, p.15-120. Tese de doutorado – Instituto de Biociências de Botucatu, Universidade Estadual Paulista "Júlio de Mesquita Filho"

Uma microdeleção hemizigótica de 1,5Mb a 1,8Mb na região do braço longo do cromossomo 7 (7q11.23) ocasiona uma doença genética rara multigênica. Faces típicas, doenças cardiovasculares, alterações do tecido conjuntivo combinados com déficit de aprendizado e crescimento, personalidade e perfil cognitivo característicos representam o conjunto de sinais clínicos que caracteriza a síndrome de Williams-Beuren (SWB). Embora a técnica da FISH permita o diagnóstico citomolecular da síndrome, a existência de deleções de tamanhos típicos e atípicos, as quais não são evidenciadas pela FISH, acarreta em diferentes genes afetados. Por isso, o objetivo deste estudo foi investigar e caracterizar a microdeleção mediante análise por CMA (do inglês *Chromosome Microarray Analysis*) e analisar o impacto desta através de uma abordagem *in silico* utilizando redes de interação entre proteínas (PPI). Dentre os 14 indivíduos recrutados e avaliados no estudo, apenas um apresentou uma FISH negativa. Clinicamente, todos os participantes exibiram características da SWB com escore acima de 3. Uma deleção típica de 1,367,201Kb foi confirmada e caracterizada por CMA em 13 participantes do estudo e o impacto desta foi analisado em duas redes biológicas, uma representando a rede de um indivíduo sem alterações (GN) e outra representando o indivíduo acometido (PN). As proteínas codificadas pelos genes deletados foram extraídos da rede GN para simular a rede PPI do indivíduo com a deleção (PN). Análises topológicas de ambas redes foram analisadas, assim como nas redes no contexto de comunidades. Os resultados não mostraram diferenças significativas entre as redes. Pela análise de enriquecimento com termos ontológicos relacionados a processos biológicos, foi possível identificar as regiões onde houve enriquecimento dentro de cada comunidade, bem como identificar quais proteínas e termos ontológicos são compartilhados. Com isso, foi possível analisar diferenças entre as redes após a deleção e apontar diferentes proteínas até então não correlacionadas à síndrome. Embora a abordagem *in silico* utilizada neste estudo não tenha apresentando diferenças estatísticas, a utilização de estudos com redes biológicas além de trazer novas descobertas para o estudo da SWB, pode também ser uma ferramenta importante para esclarecer a variabilidade fenotípica e fisiopatologia da doença.

Palavras-chaves: genética, síndrome de Williams-Beuren; redes de interação proteína-proteína; região 7q11.23; SWB; PPI.

ABSTRACT

MEDEIROS, P. **Applicability of PPI networks in systems Biology in the context of Williams-Beuren syndrome**. 2021, p.15-120. Doctoral Thesis - Instituto de Biociencias de Botucatu, Universidade Estadual Paulista "Julio de Mesquita Filho"

A hemizygous deletion of 1.5Mb to 1.8Mb in the long arm region of chromosome 7 (7q11.23) causes a rare multigenic genetic disorder. Typical faces, cardiovascular disease, connective tissue abnormalities combined with learning and growth deficits, a characteristic personality and cognitive profile represent the set of clinical signs that characterize Williams-Beuren syndrome (SWB). Although the FISH technique allows the diagnosis, a correct genotype-phenotype correlation is necessary since, due to the existence of typical or atypical deletions, different genes can be affected. To this end, the aim of this study was to investigate and characterize microdeletion by Chromosome Microarray Analysis (CMA) and analyze its impact through an in silico approach using protein-protein interaction networks (PPI). Among the fourteen recruited and evaluated individuals, only one had a negative FISH. Clinically, all individuals exhibited WBS characteristics with score higher than 3. A typical deletion of 1,367,201Kb in thirteen individuals was confirmed and characterized by CMA and its impact was analyzed in two biological networks, one representing the network of an unchanged individual (GN) and the other representing the affected individual (PN). The proteins encoded by the deleted genes were extracted from the GN network to simulate the PPI network of the individual with the deletion (PN). Topological analyses of both networks were analyzed, as well as networks in the context of communities. The results exhibited no significant differences among the networks. By analyzing enrichment with ontological terms related to biological processes, it was possible to identify the regions where enrichment occurred within each community, as well as to identify which proteins and ontological terms are shared. By doing so, it was possible to analyze differences between the networks after the deletion and to point out different proteins not previously correlated to the syndrome. Although the in silico approach used in this study did not show statistical differences, the use of studies with biological networks, besides bringing new discoveries for the study of WBS, can also be an important tool to clarify the phenotypic variability and pathophysiology of the disease.

Keywords: genetics; Williams-Beuren syndrome; protein-protein interaction networks; region 7q11.23; WBS; PPI.

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LISTA DE ABREVIATURAS

AAP - Academia Americana de Pediatria

ADNPM - artraso no desenvolvimento neuropsicomotor

AGSW - Associação Goiana da Síndrome de Williams

ATR - proteína quinase relacionada com Ataxia Telanxiectasia e Rad3

AVC - acidente vascular cerebral

BA – rede do tipo Albert-László Barabási

Betweenness - medidas de centralidade

CEP - Comitê de Ética em Pesquisa

CGD (*chronic granulomatous disease*) - doença granulomatosa crônica

CGH array (*comparative genomic hybridization array*) - hibridização genômica comparativa de microarranjos

CL - cutis laxa

CMA (*chromosomal microarray analysis*) - análise cromossômica por microarranjos

CNVs (*copy number variation*) - variações no número de cópias

DECIPHER - *Database of Chromosomal Imbalance and Phenotype in Human using Ensembl Resources*

DI - deficiência intelectual

DGV - *Database Genomic Variants*

E - aresta

EAo - estenose aórtica

EAP - estenose da artéria pulmonar

EASV - estenose aórtica supravalvar

FISH - hibridação *in situ* por fluorescência

G - grafo

GH - hormônio de crescimento

GN (*global network*) - rede global

GOs - termos ontológicos

hiPSC - células-tronco pluripotentes induzidas humanas

ISCN - *International System for Human Cytogenetic Nomenclature*

k (*degree*) - grau ou conectividade de um nó

KEGG - *Kyoto Encyclopedia of Genes and Genomes*

LCR (*low copy repeats*) - baixo número de cópias

lincRNA (*long intergenic non-coding RNA*) - lncRNA intergênico

lncRNA (*long non-coding RNA*) - ncRNA longo

miRNA - microRNAs

MLPA (*multiplex ligation-dependent probe amplification*) - amplificação multiplex de sondas dependentes de ligação

NAHR (*non allelic homologous recombination*) - recombinação entre homólogos não alélicos

NCBI - N*ational Center for Biotechnology Information*

ncRNA (*non-coding RNA*) - pequenos RNAs não codificantes

NGS (*next generation sequencing*) - sequenciamento de nova geração

NHEJ - união de extremidades não homólogas

NPC - células progenitoras neurais

OMIM - *Online Mendelian Inheritance in Man*

PCR - reação em cadeia da polimerase

piRNA (*piwi-interacting rna*) - RNAs interagindo com proteínas Piwi

PN (*patient network*) - rede do paciente

PPI - interação proteína-proteína

QI - quociente de inteligência

qPCR - PCR em tempo real

RCSWB - região crítica da SWB

RT (*reverse transcriptase*) - RT-qPCR

SAFE - análise espacial de enriquecimento funcional

SD (*segmental duplications*) - duplicações segmentais

SNC - sistema nervoso central

snoRNA (*small nucleolar RNA*) - RNAs nucleolares

SVAS - estenose supravalvar da aorta

SWB - síndrome de Williams-Beuren

TCLE - Termo de Consentimento Livre e Esclarecido

TE (*transposable elemento*) - elementos transponíveis

TEA - transtorno do espectro autista

UCSC *Genome Browser*

UFG - Universidade Federal de Goiânia

UniProt - *Universal Protein*

V - vértices ou nós

WEKA - *Waikato Environment for Knowledge Analysis*

WES (*Whole Exome Sequencing*) - sequenciamento de exoma

WGS (*Whole Genome Sequencing*) - sequenciamento do genoma todo

7dup - duplicação da região 7q11.23

<k> - média de *degree*

ρ - coeficiente de Pearson

SUMÁRIO

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