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Curating genes at 20p13 to identify candidate genes for terminal microdeletions

Terminal 20p13 delesyonlarına aday genleri tanımlamak

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Abstract

Purpose: Microdeletions are well-known drivers of genetic disorders. Generally, a few genes are identified as driver genes for the observed phenotypes in microdeletion carriers. In this study, we interrogated the 20p13 terminal region to identify candidate gene(s) primarily for the neurodevelopmental disorders in individuals with 20p13 terminal microdeletions.

Materials and methods: Publicly available information on gene functions, gene expressions, gene-disease relationships, and populational genomic data are used to identify genes within the terminal 2.5 Mb region of 20p13 that are tolerant or intolerant to deletions and loss-of-function variants.

Results: CSNK2A1 has the highest intolerance metrics to both deletion and loss-of-function variation among the 40 protein-coding genes within the terminal 2.5 Mb at 20p13, followed by SNPH when the rest of the genes are also evaluated by their gene functions and expression patterns.

Conclusion: We propose that CSNK2A1 is the main driver gene for the neurodevelopmental disorder/ intellectual disability phenotypes in individuals with microdeletions encompassing genes within the terminal 2.5 Mb at 20p13 region.

Keywords: CSNK2A1, microarray, SNPH, NGS.

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Öz

Amaç: Mikrodelesyonların genetik sendromlara yol açtığı bilinmektedir. Genellikle bir veya iki gen, gözlenen fenotiplerin ana nedeni olarak öne çıkarılır. Bu çalışmada, 20p13 mikrodelesyonu olan bireylerdeki fenotiplere yol açan major genleri tanımlamak amacıyla 20p13 terminal bölgesini araştırdık.

Gereç ve yöntem: 20p13'ün terminal 2.5 Mb bölgesi içinde delesyonlara toleranslı ve toleranssız genleri belirlemek amacıyla gen fonksiyonları, gen ekspresyonu ve gen–hastalık ilişkisi bilgileri ile delesyonlar ve fonksiyon kaybı varyantlarına ilişkin popülasyon verileri kullanılmıştır.

Bulgular: CSNK2A1 20p13'ün terminal 2.5 Mb bölgesi içinde yer alan 40 protein-kodlayan gen arasında en yüksek intolerans skorlarına sahip gendir ve onu SNPH takip etmektedir.

Sonuç: 20p13'ün terminal 2.5 Mb bölgesi içindeki genleri kapsayan mikrodelesyonlara sahip bireylerde görülen nörogelişimsel ve davranışsal bozukluk fenotiplerinin ana sürücü geninin CSNK2A1 olduğunu öne sürüyoruz.

Anahtar kelimeler: CSNK2A1, SNPH, mikrodizin, NGS.

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Introduction

Microdeletions and microduplications are well-established causes of genetic disorders. The widespread utilization of chromosomal microarray methodologies has facilitated the identification of candidate gene(s) that could be the main driver of clinical manifestations observed in individuals with variably sized copy number variants (CNVs). Detection rate of single nucleotide variants (SNVs) and monogenic disease discoveries have exponentially increased with the advent of next-generation sequencing (NGS) technologies and helped families to find valuable medical management resources. In contrast, many individuals with microdeletion/microduplication syndromes diagnosed with past chromosomal microarray (CMA) methodologies might miss a chance to benefit from later recognized and published gene-specific guidelines should the same gene also be the main driver of the microdeletion/microduplication syndrome phenotype. Thus, retrospective analysis of chromosomal microarray data can still make valuable contributions, such as expanding the variant spectrum associated with certain gene-disease syndromes, and also help with the medical management of individuals with microdeletion/microduplication syndromes.

CSNK2A1-related Okur-Chung Neurodevelopmental Syndrome (OCNDS) [MIM#617062] is an autosomal dominant non-specific neurodevelopmental disorder [1], for which missense variants primarily located in critical domains and residues account for about 80-90% of the reported variant spectrum [2]. Although a few loss-of-function variants are reported in the literature and in ClinVar, additional studies affirming the damaging effect of loss-of-function and haploinsufficiency variants are still lacking.

In this study, we evaluated the available clinical and molecular evidence in support of *CSNK2A1* being the main driver gene for the neurodevelopmental disorders and neurobehavioral issues in individuals harboring microdeletions within the terminal 2.5 Mb region of the short arm of chromosome 20 (20p13).

Materials and methods

No previously unpublished private health information was used for this study. Constraint metrics of probability of loss-of-function intolerance (pLI), probability of haploinsufficiency (HI) intolerance (pHaplo), loss-of-function observed/expected upper bound fraction (LOEUF), and selection coefficient of heterozygous loss-of-function variants (sHet) for the genes located within chr20:1-2,500,000 base pairs (bp) (terminal 2.5 Mb) according to human genome assembly version 38 (hg38) were obtained from DECIPHER and gnomAD v4.1.0 databases [3, 4]. As these metrics are routinely used in the clinical and molecular genetics practice, detailed information on these metrics can be found on the respective websites and references cited therein. Briefly, genes can get scores between 0 to 1 for pLI and pHaplo metrics; a gene with a pLI value >0.9 and a pHaplo value ≥0.86 is regarded as LoF and HI intolerant, respectively, and the analysis was primarily performed based on these two metrics [5, 6]. LOEUF and sHet values are used as auxiliary metrics; while sHet follows the same logic as pLI and pHaplo, LOEUF does not have a maximum upper boundary value, but a LOEUF score closer to 0 increases the confidence level of a gene being loss-of-function intolerant. Intracategory color coding of the values is utilized to show intolerance with color red and tolerance with color green in Figure 1.

A manual literature review was performed by clinical and laboratory geneticists to identify studies reporting microdeletions within the terminal 2.5 Mb region at 20p13 encompassing *CSNK2A1* along with other genes. Structural variants and copy number variants datasets of gnomAD SVs v4.1.0 and CNVs v4.1.0 were also cross-checked to determine whether there were any gene-encompassing deletions within that region common in the population. A representative schematic of the reported deletions and encompassed genes in Figure 2 was generated by using the UCSC genome browser [7]. The Human Protein Atlas (proteinatlas.org) website was checked for gene expression information.

HGNC symbol	Coordinates (hg38)	pLI	pHaplo	LOEUF	sHet	Inheritance	OMIM/ClinGen Disease
DEFB125	chr20:87250-97094	0.34	0.67	1.53	0.007	-	-
DEFB126	chr20:142590-145751	0.27	0.66	1.7	0.004	-	-
DEFB127	chr20:157454-159163	0.15	-	1.7	0.083	-	-
DEFB128	chr20:187853-189711	0.31	-	1.59	0.068	-	-
DEFB129	chr20:227258-229886	0.22	-	1.48	0.005	-	-
DEFB132	chr20:257724-261096	0	0.76	1.95	0.083	-	-
C20orf96	chr20:270863-290778	0	0.71	1.31	-	-	-
ZCCHC3	chr20:297570-300321	0	0.71	1.96	-	-	-
SOX12	chr20:325552-330224	0.08	0.95	0.89	-	-	-
NRSN2	chr20:346705-359660	0	0.47	1.56	0.007	-	-
TRIB3	chr20:362835-397564	0	0.63	1.67	0.007	-	-
RBCK1	chr20:407498-432139	0	0.94	0.89	0.028	AR	Polyglucosan body myopathy 1 with or without immunodeficiency [AR; MIM#615895]
TBC1D20	chr20:423596-462566	1	0.99	0.47	0.203	AR	Warburg micro syndrome 4 [AR; MIM#615663]
CSNK2A1	chr20:472498-543835	1	0.99	0.27	0.321	AD	Okur-Chung neurodevelopmental syndrome [AD; MIM#617062]
TCF15	chr20:604257-610309	0	0.96	1.96	-	-	-
SRXN1	chr20:646615-653378	0	0.63	1.78	0.02	-	-
SCRT2	chr20:661596-675802	0.04	0.99	1.95	-	-	-
SLC52A3	chr20:758695-776015	0	0.43	1.01	0.007	AR	Brown-Vialetto-Van Laere syndrome 1 [AR; MIM#211530] | ?Fazio-Londe disease [AR; MIM#211500]
FAM110A	chr20:833715-857463	0	0.6	1.57	-	-	-
ANGPT4	chr20:869900-916334	0	0.79	1.19	0.007	-	-
RSPO4	chr20:958452-1002372	0	0.77	1.33	0.008	AR	Anonychia congenita [AR; MIM#206800]
TMEM74B	chr20:1180561-1186842	0	0.94	1.68	0.008	-	-
PSMF1	chr20:1113240-1189415	0	0.92	1.38	0.006	-	-
C20orf202	chr20:1203454-1209076	0.01	0.49	1.69	-	-	-
RAD21L1	chr20:1226027-1296421	0	0.68	1.21	-	-	-
SNPH	chr20:1266269-1309328	0.98	0.93	0.5	0.171	-	-
SDCBP2	chr20:1309909-1329211	0	0.7	1.32	-	-	-
FKBP1A	chr20:1368977-1393164	0.09	0.8	1.15	0.092	-	-
NSFL1C	chr20:1442162-1473842	0.92	0.62	0.55	0.073	-	-
SIRPB2	chr20:1470741-1491587	0	0.4	0.95	0.016	-	-
SIRPD	chr20:1534251-1557705	0	0.31	1.61	0.013	-	-
SIRPB1	chr20:1561385-1620061	0	0.29	1.19	0.005	-	-
SIRPG	chr20:1629152-1657779	0	0.27	1.36	-	-	-
SIRPA	chr20:1892726-1940592	1	0.87	0.31	0.073	-	-
PDYN	chr20:1978757-1994285	0.49	0.69	0.77	0.005	AD	Spinocerebellar ataxia 23 [AD; MIM#610245]
STK35	chr20:2101767-2177038	0.01	0.69	0.77	0.162	-	-
TGM3	chr20:2296001-2341079	0	0.75	0.9	0.027	AR	?Uncombable hair syndrome 2 [AR; MIM#617251]
TGM6	chr20:2380901-2432753	0	-	1.13	0.004	AD	Spinocerebellar ataxia 35 [AD; MIM#613908]
SNRPB	chr20:2461634-2470884	1	0.94	0.32	0.025	AD	Cerebrocostomandibular syndrome [AD; MIM#117650]
ZNF343	chr20:2481817-2525028	0	0.75	1.2	-	-	-

Figure 1. Constraint metrics and clinical information on genes located within terminal 2.5 Mb region at 20p13

The genes are sorted by their chromosomal coordinates and constraint metrics are colored by scale based on their tolerance predictions Red = 1; highly intolerant, Green = 0; tolerant, Yellow-Orange = Inconclusive. Further information on the constraint metrics can be found in the Materials and Methods section

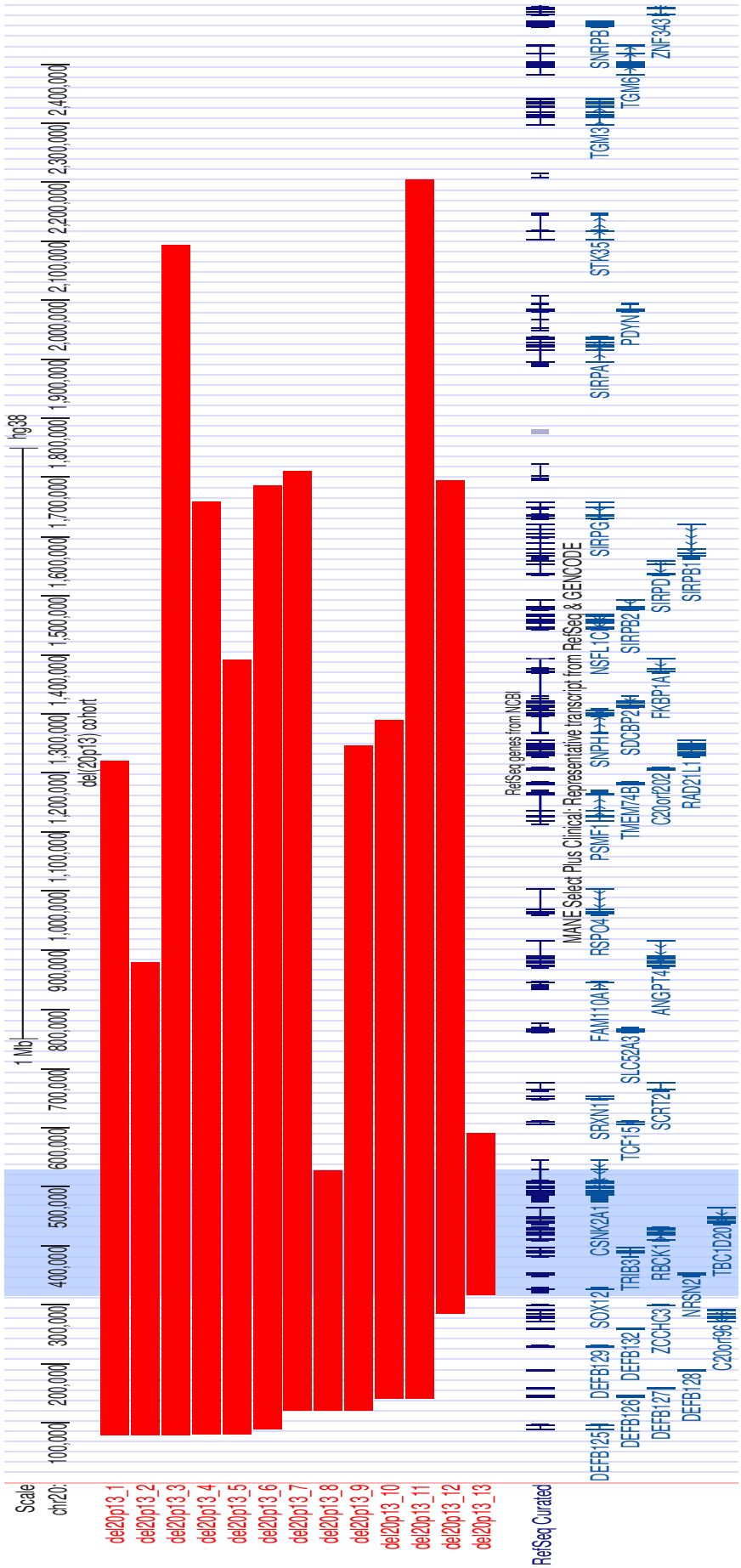

Figure 2. UCSC genome track visualization of reported chr20p13 microdeletions

Blue-highlighted region indicated minimally overlapping region. Below are the gene symbols with their length, orientation, and exon/intron structures

Results

There are a total of 40 protein-coding genes located between chr20:1-2,500,000bp coordinates. While six genes were LoF intolerant, eleven genes were HI intolerant, and of these, only five genes were both LoF and HI intolerant (Figure 1).

As of December 2025, only four genes (*CSNK2A1*, *PDYN*, *TGM6*, and *SNRPB*) are associated with or implicated in autosomal dominant disorders, while five genes (*RBCK1*, *TBC1D20*, *SLC52A3*, *RSPO4*, and *TGM3*) are associated with or implicated in autosomal recessive conditions in OMIM (omim.org) or ClinGen (clinicalgenome.org). Among autosomal dominant disorders, early-onset neurodevelopmental delay is prominent only in *CSNK2A1*-related OCNDS. *PDYN* and *TGM6* are both implicated in adult-onset spinocerebellar ataxia phenotypes. *SNRPB* is associated with autosomal dominant Cerebrocostomandibular syndrome, an ultra-rare multiple congenital anomaly disorder characterized by branchial arch-derivative and thoracic malformations including micrognathia, cleft palate, feeding and airway difficulties, narrow chest, and striking posterior rib gaps, which distinguish this condition. Neurodevelopment is usually normal in affected individuals but can be impaired due to perinatal hypoxia sequelae. Only *CSNK2A1* and *SNRPB* have high pLI and pHaplo values, and HI or LoF variants of *SNRPB* were postulated to be perinatally lethal [8], while *PDYN* and *TGM6* have moderate-low pLI and pHaplo values, consistent with the missense variants being predominantly reported so far [9-11]. Of the five genes associated with or implicated in autosomal recessive conditions, all but one have low pLI, consistent with their molecular mechanism being biallelic loss-of-function. Although *TBC1D20* has high pLI and pHaplo values, no affected status has been reported to date in the carrier parents of individuals with Warburg micro syndrome [12-14].

Only *SNPH*, *NSFL1C*, and *SIRPA* genes have high pLI values among the remaining 31 protein-coding genes that have yet to be implicated in any human disorders. *SNPH* is a 6-exon gene, is highly expressed in the brain, and encodes syntaphilin, a membrane-associated protein that inhibits SNARE complex formation by binding free syntaxin-1. While there are no human reports yet, mice knock-out models showed abnormal mitochondrial physiology, abnormal neuron physiology, microcephaly, and growth restriction [15]. *NSFL1C* is a 9-exon gene, ubiquitously expressed, and encodes an ATPase known to be involved in transport vesicle/target membrane fusion and fusions between membrane compartments. There are no animal phenotype models yet. *SIRPA* is an 8-exon gene, highly expressed in neutrophils and mononuclear phagocytes in all tissues, with the highest expression in the brain, and encodes an immunoglobulin-like cell surface receptor for CD47. It mediates negative regulation of phagocytosis, mast cell activation, and dendritic cell activation and may play a key role in intracellular signaling during synaptogenesis and in synaptic function. Mice knockout models showed immune system abnormalities and abnormal synaptic morphologies [16, 17]. While an additional five genes (*SOX12*, *TCF15*, *SCRT2*, *TMEM74B*, and *PSMF1*) have pHaplo value ≥0.86, all of those genes have very low pLI values. Except for *PSMF1*, which is a 7-exon gene, the remaining four genes are 1-3 exon genes.

A total of seven publications reporting 13 microdeletions within the terminal 2.5 Mb region at 20p13 with sizes ranging from ~273 Kb to ~2.06 Mb were retrieved from the literature [18-24]. One publication reporting a prenatal detection of ~318 Kb deletion at 20p13 was excluded due to the absence of postnatal phenotype [25]. The molecular and clinical details of reported individuals with 20p13 microdeletions are provided in Table 1 and a schematic representation of the deleted segments is provided in Figure 2.

Table 1. Clinical and molecular characteristics of individuals with microdeletions at 20p13
(https://dergipark.org.tr/tr/download/article-file/1850985)

The ages of reported individuals ranged from 9 months old to 30 years-old. All individuals were reported to have neurodevelopmental disorders affecting both the motor and speech domains and neurobehavioral challenges as their primary phenotype. They also have variable nonspecific distinctive facial features, and many had short stature or failure to thrive. Other miscellaneous clinical findings and symptoms that are not uncommon in individuals with nonspecific neurodevelopmental disorders were also reported in some individuals. While some individuals had additional molecular findings, further analysis of those findings concluded that they were not clinically significant variants based on gene contents, functions of the genes, and additional variation frequency information.

The minimally overlapping region of the 13 deletions is ~211 Kb (chr20:316800-527968) and encompasses *SOX12*, *NRSN2*, *TRIB3*, *RBCK1*, *TBC1D20*, and *CSNK2A1.* Individual del20p13_13 has the smallest deletion of ~273 Kb in size, encompassing the same genes as in the minimally overlapping region. The concurrent duplication at 8q12.1 did not involve any significant genes. The clinical picture of individual del20p13_13 is consistent with the one reported in individuals with *CSNK2A1*-related OCNDS due to SNVs [26]. Furthermore, four more individuals (del20p13_1, del20p13_2, del20p13_8, and del20p13_9) had deletions between chr20:1-1,250,000 coordinates, wherein *CSNK2A1* and *TBC1D20* are the only genes with high pLI values. While there are six additional genes with high pHaplo values, all of them have very low pLI values (Figure 1).

Individual del20p13_11 has the largest deletion of ~2.06 Mb in size, encompassing 35-protein-coding genes including all the above-discussed genes with high pLI and/or pHaplo except for *SNRPB*. The clinical picture of this individual was comparable to the one of individual del20p13_13 and also individuals with *CSNK2A1*-related OCNDS due to SNVs. None of the individuals with terminal 20p13 microdeletions was reported to have clinical findings more specific to other disorders related to certain genes within the deleted intervals, such as cataracts/microphthalmia/microcornea (*TBC1D20*), immunodeficiency (*RBCK1*), cardiomyopathy (*RBCK1*), ataxia (*PYDN*, *TGM6*), uncombable hair (*TGM3*), or anonychia (*RSPO4*).

Discussion

Widespread utilization of NGS technologies such as whole exome (WES) and genome (WGS) sequencing has expanded our understanding and knowledge about genetic disorders, particularly the ones primarily caused by SNVs and small insertion/deletions (Indels). Consequently, more genetic disorders are being discovered to be caused by SNVs and indels, and some are eponymized, almost every week. Not only do these methodologies enable a faster diagnosis, but they also provide high reliability by interrogating the vast majority of the exome/genome and excluding other potential genetic causes of the manifesting clinical findings of tested individuals. Additionally, the information gathered from large-scale population databases utilizing WES/WGS also strengthens the credibility of novel gene-disease relationship assertions by way of introducing gene-specific evolutionary constraint metrics of pLI and pHaplo. Although these metrics are predominantly used in every gene-disease relationship assertion and curation nowadays, they can also guide us in mining the literature for not well-studied microdeletion/microduplication syndromes.

Our analyses indicate that *CSNK2A1* is the main driver gene for neurodevelopmental disorders and neurobehavioral phenotypes in individuals with 20p13 microdeletions encompassing the most terminal 1,250,000 bp (1.25 Mb), and it is the major contributor in individuals with 20p13 microdeletions encompassing the most terminal 2.5 Mb interval. The latter conclusion is due to the presence of additional genes also with high pLI that have yet to be implicated in human disorders. In particular, *SNPH* could also be a candidate gene for a novel neurodevelopmental disorder with or without autism spectrum disorder by looking at gene function, expression levels in the brain, and mice knockout studies [15]. One reason that *SNPH* has yet to be implicated in a human disorder might be that its LOEUF and sHet metrics are not highly complementary to its high pLI score. While an important metric, there are still loss-of-function carriers of genes with high pLI in the population databases such as gnomAD v4.1.0. LOEUF and sHet are the metrics that provide a more conservative confidence interval for LoF intolerance evaluations. Furthermore, there are discrepancies between pLI and pHaplo metrics in five genes (*SOX12*,

TCF15, *SCRT2*, *TMEM74B*, *PSMF1*) where pLI values indicate a LoF tolerance and pHaplo values indicate HI intolerance (Figure 1). Similar to *SNPH*, neither LOEUF nor sHet metrics are providing support for LoF intolerance in any of those six genes. *RBCK1* also has low pLI and high pHaplo values along with weak LOEUF and sHet values, and it is associated with an autosomal recessive Polyglucosan body myopathy disorder. Similarly, other genes with high pLI and/or pHaplo values, i.e., *NSFL1C* and *SIRPA*, also have weak LOEUF and sHet values, which might be the explanation for not having been implicated in early-onset neurodevelopment and neurobehavior affecting human disorders yet.

HI and LoF are regarded as equal mechanisms in practice and are used interchangeably even though the underlying mutation types differ. While in theory, loss-of-function variants can show some leakage, in practice this probability is negligible until otherwise demonstrated, as evidenced by both HI and LoF variants causing the same phenotypic spectrum in the vast majority of affected individuals with many genetic disorders. Although microdeletions, hence HI of the genes, were investigated here, pLI was still used as the pivotal point to propose candidate genes since pHaplo was calculated from large copy number variation data detected via chromosomal microarray studies, and it might not be as sensitive as pLI in predicting intolerance to structural and/or functional loss of one gene copy due to a significant difference in resolution of methodologies [6]. For example, passenger genes in microdeletion/microduplication events can still get high pHaplo values due to their positional proximity to the breakpoints and CNV occurrence mechanism. Nevertheless, *CSNK2A1* has the highest values for main (LoF and HI) and auxiliary (LOEUF and sHet) intolerance metrics.

The chr20:1-2,500,000 bp interval was chosen for two reasons. First, the most proximal breakpoint of the published literature was at chr20:2,205,209 in individual del20p13_11. Secondly, *SNRPN* is the next downstream gene with high pLI and pHaplo values and autosomal dominant gene-disease relationship and it is located just upstream to the chr20:2,500,000 breakpoint. However, this border is arbitrary and can be extended to chr20:2,860,000 bp as there is still not another gene with high pLI within the chr20:2,500,000-2,860,000 interval.

Even though candidate gene identification from chromosomal microarray studies is not performed and published in the literature as commonly as it used to be, we believe there is still important knowledge in the literature, and their investigations are still important for the families and geneticists. For example, *SOX12* and *NRSN2* were proposed as the candidate genes by a very important publication on terminal 20p13 microdeletions in 2013, before CSNK2A1 was implicated in a neurodevelopmental disorder and constraint metrics became available [19]. Both genes have very low pLI values, and while *SOX12* had a high pHaplo value, its LOEUF value also indicates LoF or HI variants are probably tolerable. In addition to consolidating the previous efforts, our study may also provide further scientific evidence for LoF and HI variants of *CSNK2A1* also being pathogenic for OCNDS and help with decision-making for future diagnoses.

There are limitations to this study. First, the analysis is limited to the current scientific knowledge, which is evolving and may unravel novel gene-disease relationships in the future. However, ever since the abovementioned constraint metrics were introduced and improved, they aided novel gene-disease relationship discoveries by showing high correlation with reported variant type(s) and gene functions. Secondly, although the method employed here has long been utilized in the field to identify minimally overlapping regions and candidate genes, the synergistic effect of co-deletion of HI/LoF-intolerant and HI/LoF-tolerant genes along with the possible difference between the positional effect of a larger CNV and gene-only deletion variants cannot be excluded. Lastly, as inherent to the chromosomal microarray-based studies, the presence of additional molecular diagnoses due to SNVs cannot be excluded in these individuals without also testing them with NGS methodologies. Thus, larger studies comparing the single gene deletion variants detected by NGS methodologies and microdeletions detected by chromosomal microarray-only methodologies in affected individuals are

warranted to affirm our findings. In addition, further genotype-phenotype studies comparing the phenotype spectrum and disease severity among missense, LoF, single-gene deletion, and multi-gene deletion variant carriers are also warranted to understand underlying molecular and biological differences and similarities.

In conclusion, in this study we interrogated the terminal 20p13 region to identify the most plausible candidate genes that might drive the neurodevelopmental and neurobehavioral disorders in 20p13 microdeletion carriers. Among the 40 protein-coding genes within the target interval of 2.5 Mb, *CSNK2A1* stands out as the main contributor to the observed phenotypes in affected individuals with deletions encompassing the first 1.25 Mb terminal region and would be the major contributor in affected individuals with deletions encompassing the first 2.5 Mb terminal region.

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