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Unilateral Opercular Polymicrogyria in a Girl with 22q13 Deletion Syndrome

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Abstract

The 22q13 deletion syndrome, also known as Phelan-McDermid Syndrome (PMS), is a chromosomal microdeletion syndrome characterized by neonatal hypotonia, normal growth, profound developmental delay, absent or delayed speech, and minor dysmorphic features. Almost all of the 22q13 deletions published so far have been described as terminal. It is believed that the SHANK3 gene is the major candidate gene for the neurologic features of the syndrome.

Neuroradiological findings in PMS include arachnoid cyst, delayed myelination, frontal lobe hypoplasia, hypogenesis of corpus callosum and ventriculomegaly.

We describe a 3-year-old girl with severe developmental delay and right opercular polymicrogyria associated with 22q13.2 – 22q13.33 deletion.

Keywords: 22q13 deletion syndrome; Polymicrogyria; Phelan-McDermid syndrome; Cortical brain malformations

Introduction

Phelan-McDermid syndrome (OMIM# 606232), also known as the 22q13 deletion syndrome, is a chromosomal microdeletion syndrome characterized by neonatal hypotonia, normal growth, developmental delay, absent or delayed speech, and minor dysmorphic features [19].

PMS typically results from the loss of the distal long arm of chromosome 22 that may result from: (1) terminal or interstitial deletion of chromosome 22, (2) an unbalanced translocation that may be inherited or de novo, (3) or from other structural rearrangements [19].

The minimal critical region responsible for the monosomy 22q13 phenotype include the genes SH3 and multiple ankyrin repeat domains 3 (SHANK3, * 606230), acrosin (ACR, *102480), and RAB, member of RAS oncogene family-like 2B (RABL2B, *605413). In particular the haploinsufficiency for the SHANK3 gene is considered the main responsible for neurological symptoms associated with PMS [30].

Major features of the syndrome include neonatal hypotonia, moderate to severe intellectual impairment, severe or absent expressive language delay, and normal growth. Common facial characteristics include dolicocephaly, flat midface, wide brow, wide nasal bridge, deep-set eyes, full cheeks, puffy eyelids, long eyelashes, and bulbous nose. Large fleshy hands, dysplastic toenails, sacral dimple, and large poorly formed ears are frequently observed. Behavior is autistic-like with impaired communication, reduced social interaction, poor eye contact, anxiety, and self-stimulatory con- duct [19].

The differential diagnosis includes syndromes associated with hypotonia, developmental delay, speech delay and / or autistic-like behavior (Prader-Willi, Angelman, Williams, Smith-Magenis, Sotos, Opitz-Caveggia, Fragile X, trico-rhino-phalangeal joint, velo-cardio-facial, autism spectrum disorders and cerebral palsy) [20].

Neuroradiological findings associated with PMS include abnormal signal of White Matter (WM), hypogenesis of Corpus Callosum (CC), ventriculomegaly and posterior fossa or cerebellar abnormalities [2]. To date no cortical brain malformations have been described in PMS patients.

Here we report a girl with 8.4Mb deletion in chromosomal region 22q13.2 – 22q13.33, psychomotor delay, mild dysmorphic features and brain Magnetic Resonance Imaging (MRI) showing right opercular polymicrogyria and right retro-cerebellar cyst.

Case report

A 3 years old caucasian female came to our observation at six months of age for generalized hypotonia and delayed motor milestones. The parents were healthy and nonconsanguineous. Both pathological familiar histories were negative. She was born from an uneventful pregnancy at term by spontaneous vaginal delivery. Her birth weight was 2.700 Kg (10-25 centile), birth length was 49 cm (25 centile) and cranial circumference was 33 cm (10-25 centile).

At the time of the first observation the neurological exam showed generalized hypotonia, poor feeding, reduced osteotendinous reflexes and weakness. Mild psychomotor delay was present with lack of head control, reduced visual attention and impossibility to grasp objects. Craniofacial features were dolichocephaly, wide brow, deep set eyes, puffy eyelids, bulbous nose and long thick eyelashes, large ears, prominent and pointed chin. She was given indication to perform motor physiotherapy but she presented low benefits. At 12 months of age, the child could not keep sitting position, she did not maintain erect posture and walk with support and she did not use any single words. She showed poor interest and reduced interaction with object and people. Physical exam showed persistent facial dimorphisms while head circumference was normal.

To investigate the etiology of her psychomotor delay a brain MRI was performed that revealed thin corpum callosum, right retrocerebellar cyst, mild frontal cortical atrophy and right opercular polymicrogyria (Fig1). Awake and sleeps electroencephalograms EEG were recorded and showed focal spikes in right temporal region. Chromosomal microarray analysis (Agilent Human Genome CGH Microarray Edition 1.5.2.0 – ADM-2 algorithm) was done, which revealed a terminal 8.4Mb deletion in chromosomal region 22q13.2 – 22q13.33 (positions chr22: 42,817,697– 51,219,009) and a 2.4Mb microduplication in region 22q13.1 – 22q13.2 (positions chr22: 39,106,714 - 41,497,969). Both chromosomal rearrangements were confirmed by FISH (fluorescence in situ hybridization) analysis that also detected a ring structure of chromosome 22. The same study of both parents demonstrated the de novo origin of abnormalities.

At present the girl is three years of age, she is unable to walk independently, and she has severely delayed speech, poor eye contact, and stereotypic movements and decreased socialization consistent with autism spectrum disorders (Fig.2). Until today she has not been affected by seizures.

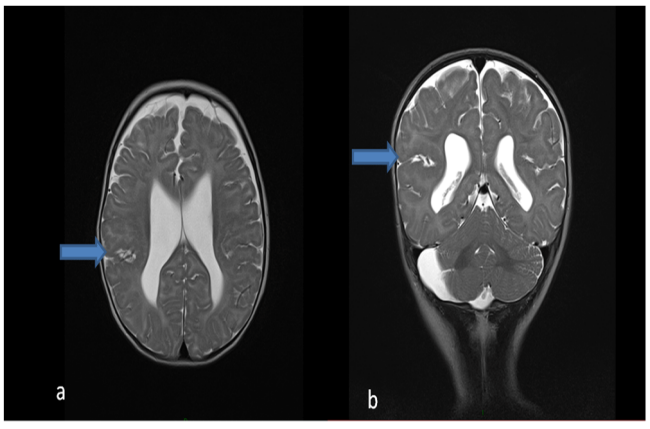

Figure 1: Brain MRI of the girl at 12 months of age. a) axial, T2-weighted –TSE image: opercular right polymicrogyria, mild frontal cortical atrophy. b) coronal, T2-weighted-TSE image: right retrocerebellar cyst and right opercular polymicrogyria.

Discussion

Central Nervous System (CNS) involvement is a major feature in 22q13 deletion syndrome and mainly include moderate to profound intellectual disability, severely delayed or absent speech, hypotonia, and autism spectrum disorders or autistic traits. Other neurological symptoms described in PMS are seizures, motor deficits and brain malformations [3].

Haploinsufficiency of SHANK3 gene is considered the main responsible for neurological manifestations associated with PMS, although other gene may play a minor role [5, 29]. If SHANK3 is responsible for most of the neurological abnormalities in these patients, this would imply that deletion of the region proximal to SHANK3 might have a mild phenotype that could be masked by the terminal deletion of SHANK3. Almost all of the 22q13 deletions published have been described as terminal [15, 30, 16, 12, 14, 20]. However, there are several cases identified in the literature that have been described as 22q13 interstitial deletion and that presented a phenotype similar to the 22q13 terminal deletion syndrome [27, 24, 8, 29]. These observations suggest that the etiology for the neurological features must also be due to genes located proximal to SHANK3. These genes would also be deleted in many patients with 22q13 terminal deletions, and therefore adding to their phenotype [29].

Possible involvement of other gene is also supported by brain MRI finding in patients with PMS. Recently [2] reported the brain MRI findings of 10 patients with deletion 22q13 that showed cerebellar vermis hypoplasia (CBVH), enlarged posterior fossa or both in 8/10 patients without features of cerebellar atrophy, and confirm prior reports of thin corpus callosum and ventriculomegaly. In particular the three individuals with the most severe CBVH or mega cisterna magna phenotypes have intermediate deletions. Surprisingly, the two individuals with the largest deletions have normal posterior fossa size and either normal vermis or mild CBVH, while the two individuals with the smallest deletions have normal vermis size and mildly enlarged posterior fossa. This genotype-phenotype study suggested that the 22q13 deletion phenotype includes abnormal posterior fossa structures that are unlikely to be attributed to SHANK3 disruption.

Other genes in the region, including Plexin B2 (PLXNB2, * 604293) and Mitogen-activated protein kinase 8 interacting protein 2 (MAPK8IP2, * 607755), display brain expression patterns and mouse mutant phenotypes critical for proper cerebellar development and have been hypothesized to be strong candidates for cerebellar phenotypes [2].

In this paper we report a girl with unilateral polymicrogyria and 8.4 Mb deletions in chromosomal region 22q13.2 – 22q13.33 presenting with generalized hypotonia, psychomotor delay and behavioral disorders. To the best of our knowledge this is the first case of brain cortical malformation described in a patient with 22q13 deletion syndrome. As the majority of the cases previously described the reported girl presented a terminal deletion

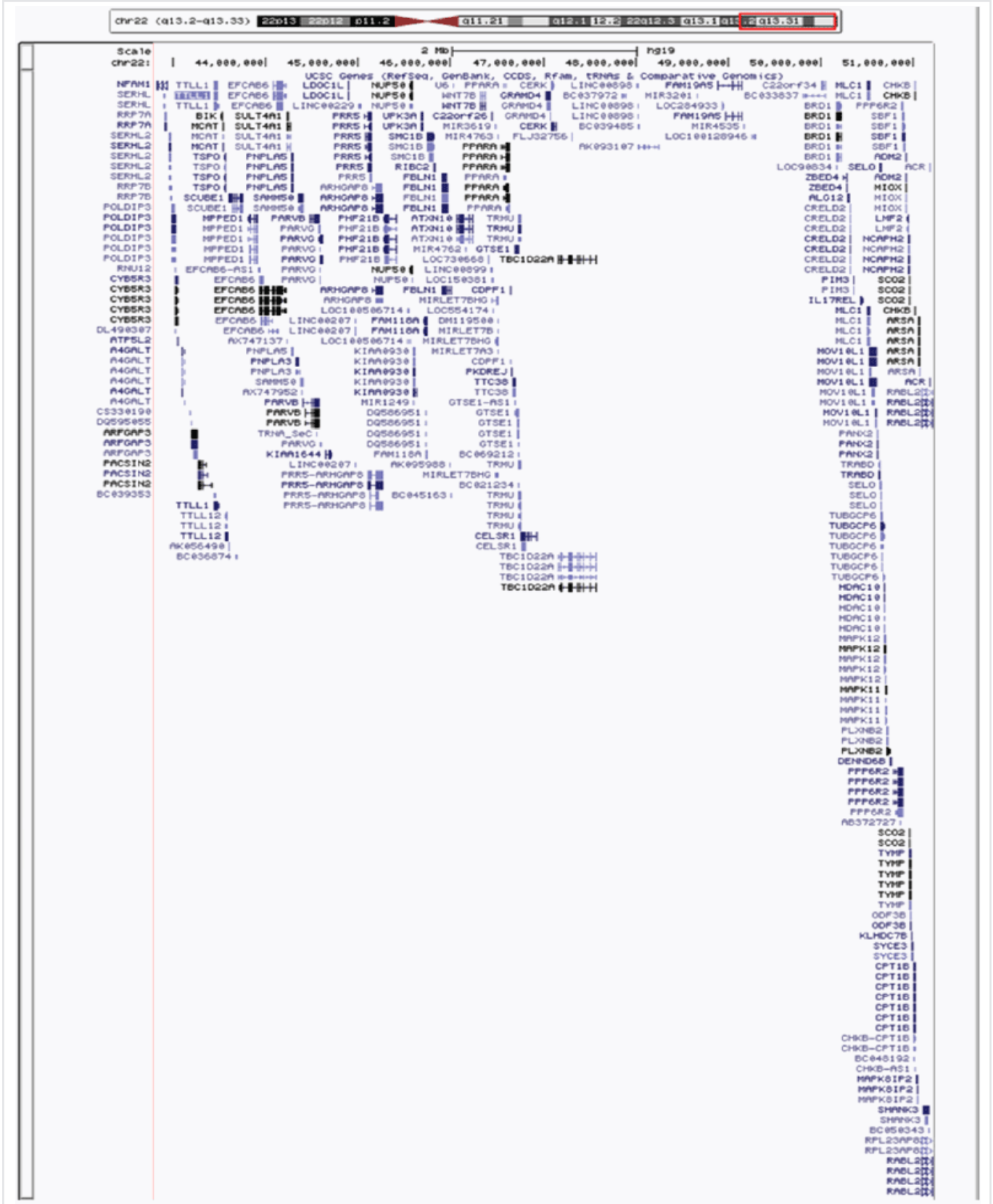

Figure 2: Girl at a) birth; b) 6 months of age; c) 3 years and 8 months of age. Generalized hypotonia (a). Craniofacial features were dolichocephaly, wide brow, deep set eyes, puffy eyelids, bulbous nose and long thick eyelashes, large ears, prominent and pointed chin (a,b, c).

of considerable extension involving several genes including SHANK3 [15, 30, 16, 12, 14, 20]. Because none of the previously reported cases of haploinsufficiency of SHANK3 were associated with a cortical brain disorder is improbably that this gene is involved in this kind of structural abnormalities. As suggested by other authors, it is feasible that more proximal genes could be responsible for brain structural defects and consequent neurological symptoms observed in the 22q13 deletion syndrome [26; 2]. The deleted area in our patient contains several known genes (158 genes) with different functions (Fig.3), so it becomes difficult to pinpoint the suspect of the origin of polymicrogyria to one of them. In particular the 22q13.2 – 22q13.33 region has a high concentration of genes whose products are expressed in CNS (Table 1).

Interestingly some of them encode for protein that are involved in microtubule cellular dynamics. (PACSIN2, TUBGCP6, GTSE1, TTLL1, TTLL12, FBLN1).

Tubulin genes (i.e TUBA1A, TUBB2B, TUBB3, and TUBA8) encode for proteins playing a key role in several cellular processes crucial for cortical development during neuronal migration, in cortical laminar organization, and in neuronal guidance of the radial glia. Mutations in the tubulin genes mostly affect the formation of tubulin heterodimers and result in different disorders. The associated phenotypic spectrum encompasses a wide range of brain malformations, all reflecting axon guidance disturbances (abnormal fascicles and axon tracts, abnormalities of the internal capsule and corpus callosum, hypoplasia of the brainstem and corticospinal tracts), and migration or post-migration defects (abnormal cortex and hippocampal lamination) [25]. In particular disorders of microtubule complex represent one of the most known causes of polymicrogyria (TUBA8, TUBB2B, TUBA1A) [7]. Furthermore, several environmental and other genetic factors have been hypothesized to be responsible for the disorder. Environmental causes of polymicrogyria include infections during pregnancy and intrauterine ischemia [28]. Genetic causes of polymicrogyria include deletions or rearrangements of chromosomic material involving several genes (Table 2) [1, 4, 6, 7, 11, 13, 17, 21, 22, 23].

Referencesg them, TUBA8 that encodes a member of the alpha tubulin protein family is localized on chromosome 22 but more proximally to deletion in our girl. Polymicrogyria has been described in patients with 22q11.2 deletion syndrome (OMIM# 192430), or velocardiofacial (VCF) syndrome [10].

In conclusion no association between polymicrogyria and genes responsible for 22q13 deletion syndrome has been previously reported. To the best of our knowledge this is the first case in literature suggesting a link between the two conditions and it widens the spectrum of brain malformations associated with 22q13 deletion syndrome, including neurological migration and cortical organization disorders.

Although the pathogenesis of PMG in 22q13 deletion syndrome is unknown, we can speculate that, the haploinsuficiency of a gene in the deleted region and with expression in the foetal brain (i.e. those encoding for microtubular components) could damage the brain cortical development. As previous authors have suggested, another possible mechanism leading to PMG could involve (asymmetric) hypoperfusion of the embryonic brain, caused by haploinsufficiency of a gene expressed in foetal vascular brain tissue [9].

Further clinical and experimental studies and animal models could contribute to clarify the role of PMS genes in the pathogenesis of PMG.

The reported case also suggests to pediatricians, child neurologists and clinical geneticists to consider testing for 22q13 deletion in patients with PMH of unknown origin, conversely in children with 22q13 deletion syndrome a brain MRI should be performed to look for cortical brain disorders.

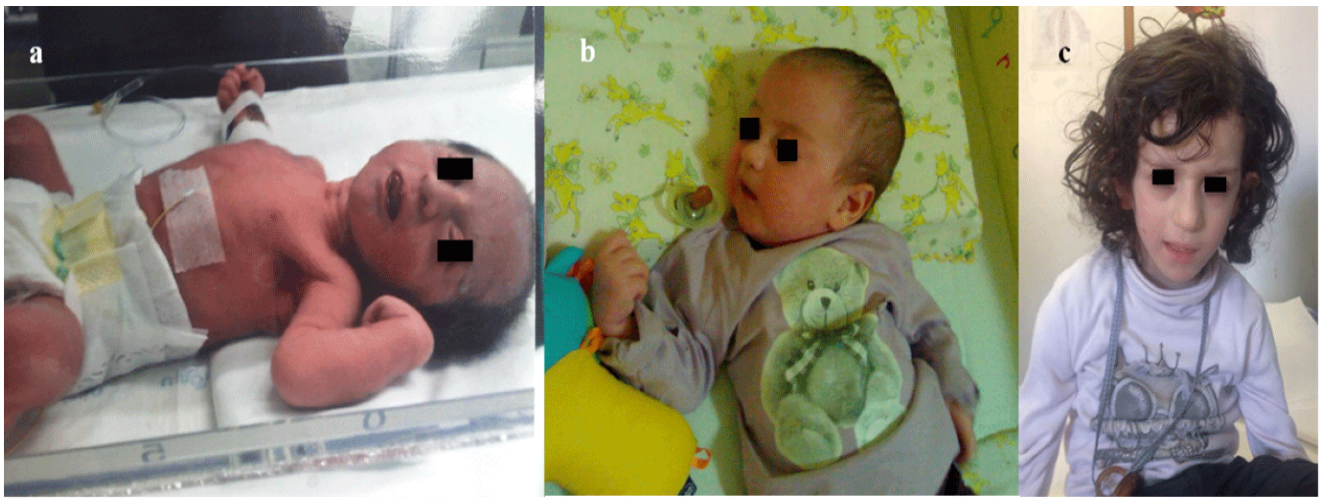

Figure 3: 22q13.1 – 22q13.2 region deletion (positions chr22: 39,106,714 - 41,497,969) and included genes.

Table 1: Genes localized in the 22q13.1 – 22q13.2 region (positions chr22: 39,106,714 - 41,497,969) with brain expression patterns.

NAME	DESCRIPTION	LOCATION	MIM
PACSIN2	Protein kinase C and casein kinase substrate in neurons 2 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (43265772..43411184, complement)	604960
TUBGCP6	Tubulin, gamma complex associated protein 6 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (50656118..50683453, complement)	610053
MAPK8IP2	Mitogen-activated protein kinase 8 interacting protein 2 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (51039131..51049979)	607755
MLC1	Megalencephalicleukoencephalopathy with subcortical cysts 1 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (50497820..50524358, complement)	605908
ZBED4	Zinc finger, BED-type containing 4 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (50247497..50283726)	612552
WNT7B	Wingless-type MMTV integration site family, member 7B [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (46316246..46373008, complement)	601967
ATXN10	Ataxin 10 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (46067678..46241187)	611150
PLXNB2	Plexin B2 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (50713408..50746062, complement)	604293
GTSE1	G-2 and S-phase expressed 1 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (46692638..46729596)	607477
TTLL1	Tubulin tyrosine ligase-like family, member 1 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (43435522..43485434, complement)	608955
TTLL12	Tubulin tyrosine ligase-like family, member 12 [Homo sapiens (human)]	Chromosome 22, NC_000022.10 (43562628..43583137, complement)	

Table 2: Known genes responsible for polymicrogyria.

NAME	DESCRIPTION	LOCATION	MIM
BOP	Polymicrogyria, bilateral occipital [Homo sapiens(human)]	Chromosome 6	612691
BFPP	Polymicrogyria, bilateral frontoparietal [Homo sapiens(human)]	Chromosome 16	606854
BPP	Polymicrogyria, bilateral perisylvian [Homo sapiens(human)]		300388

PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [Homo sapiens (human)]	Chromosome 3	171834
GPR56	G protein-coupled receptor 56 [Homo sapiens (human)]	Chromosome 16	604110
OCLN	Occludin [Homo sapiens (human)]	Chromosome 5	602876
PIK3R2	Phosphoinositide-3-kinase, regulatory subunit 2 (beta) [Homo sapiens (human)]	Chromosome 19	603157
AKT3	V-akt murine thymoma viral oncogene homolog 3 [Homo sapiens (human)]	Chromosome 1	611223
TUBA8	Tubulin, alpha 8 [Homo sapiens (human)]	Chromosome 22	605742
TUBB2B	Tubulin, beta 2B class IIb [Homo sapiens (human)]	Chromosome 6	612850
RTTN	Rotatin [Homo sapiens (human)]	Chromosome 18	610436
TUBA1A	Tubulin, alpha 1a [Homo sapiens (human)]	Chromosome 12	602529
Pmp	Prion protein [Mus musculus (house mouse)]	Chromosome 2	
PAX6	Paired box 6 [Homo sapiens (human)]	Chromosome 11	607108
FH	Fumarate hydratase [Homo sapiens (human)]	Chromosome 1	136850
TUB2	Tub2p [Saccharomyces cerevisiae S288c]	Chromosome 6	
WDR62	WD repeat domain 62 [Homo sapiens (human)]	Chromosome 19	613583
SRPX2	Sushi-repeat containing protein, X-linked 2 [Homo sapiens (human)]	Chromosome X	300642
Gpr56	G protein-coupled receptor 56 [Mus musculus (house mouse)]	Chromosome 8	

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Disclosure

Conflicts of interest: none

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